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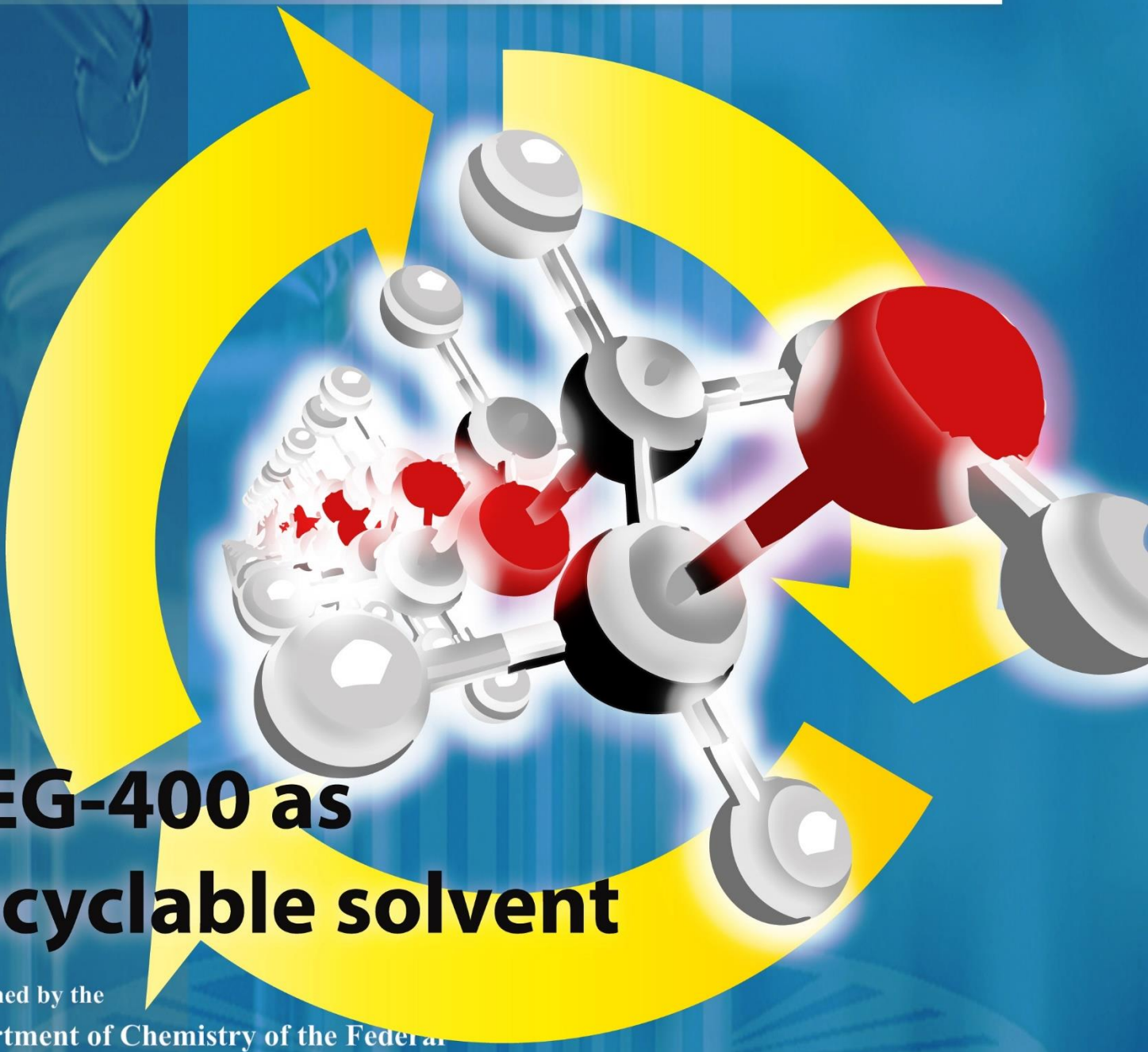

PEG-400 as recyclable solvent

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Orbital
The Electronic Journal of Chemistry

Editorial

Four years of crusade!

Orbital - The Electronic Journal of Chemistry is celebrating fourth year of existence. A great work has been devoted to preserve a scientific journal of international reputation. This work was not always without mistakes or any trouble. However, these very adversities stimulate additional efforts in order to overcome our errors and, continuing with our serious proposal of editing a journal which scientists from all over the world can submit online their original works manuscripts to be published in peer review and open-access style.

Beginning this year, Orbital was classified by the Chemistry Coordination Area on the B5 rank of CAPES Qualis (Brazil) and, leveled as B4 by Coordination Areas of Materials and Engineering II. These important details demonstrate that Orbital is progressively attaining the acknowledgment of the Brazilian scientific community. The recognition by CAPES Qualis is crucial as the system evaluates the generation of knowledge in the Brazilian universities and the method by which this same knowledge disseminated to society. Not all these were possible without endeavoring of editors and volunteer assistance of advisors from several national and international institutions.

Recently, the young Professors Kleber Thiago de Oliveira (UFSCAR), Grégoire Demetz (USP-RP) and Amilcar Machulek Júnior (UFMS) have joined us to share the idea and philosophy of Orbital by accepting our invitation to be associated editors. The tasks and challenges are enormous and, we are sure that new participants will support us on the way to achieve indexation in new Databases systems as SCOPUS, ISI and Scielo. Consequently, the international success of this electronic journal will be assured.

We sincerely hope that in the academic Brazilian scenario Orbital can figure as a solid bridge to interchange real creative science that is happening in various locations around the world.

Quatro anos de luta!

A revista Orbital está comemorando seu quarto ano de existência. Um grande esforço tem sido dedicado para cumprir nosso objetivo de torná-la uma revista científica de reputação internacional. Todo o trabalho devotado não foi sempre sem erros nem problemas. No entanto, as próprias adversidades serviram de estímulos adicionais para superarmos nossas falhas e continuarmos nossa proposta séria de editar um jornal onde cientistas de todo o mundo possam submeter seus trabalhos originais para serem publicados em um processo de revisão

por pares e de acesso livre.

No início deste ano, a revista Orbital foi classificada com QUALIS B5 pela Coordenação da área de Química da CAPES (Brasil). Nas áreas de avaliação de Materiais e Engenharia II a revista recebeu a classificação B4. Este fato importante demonstra que a revista Orbital está progressivamente conquistando o reconhecimento da comunidade científica brasileira. A classificação pela área de Química da CAPES é de extrema importância, uma vez que este sistema avalia a geração de conhecimento nas universidades brasileiras e a maneira que este conhecimento é difundido na sociedade. Nada disto seria possível sem o empenho dos editores e consultores voluntários de várias instituições nacionais e internacionais.

Recentemente, os jovens professores Kleber Thiago de Oliveira (UFSCAR), Grégoire Demets (USP-RP) e Amilcar Machulek Júnior (UFMS) juntaram-se a nós para compartilhar da ideia e filosofia da orbital aceitando nosso convite para serem editores associados. As tarefas e os desafios são enormes e temos certeza de que esses novos membros da revista irão nos apoiar no caminho para alcançar a indexação em bases de dados como SCOPUS, ISI e Scielo. Consequentemente, o sucesso internacional da revista eletrônica estará assegurado.

Esperamos sinceramente, que no cenário acadêmico brasileiro, a revista Orbital possa figurar como uma ponte sólida para o intercâmbio de uma ciência realmente criativa que está acontecendo em vários locais ao redor do mundo.

Adilson Beatriz (UFMS)
Editor, Orbital

Dênis Pires de Lima (UFMS)
Associate Editor, Orbital

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Full Paper

Approach towards cost effective practical method for synthesis of 1-(substituted phenyl)-3-methyl propane 1,3-dione

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ABSTRACT: *A simple, convenient and high yielding method for the synthesis of 1-(substituted phenyl)-3-methyl propane 1,3-dione from substituted acetophenones have been developed. This method provides several advantages such as shorter reaction time, high yields (78-90%) and simple work-up procedure.*

Keywords: *acetophenones; ethyl alcohol; sodium metal; ethylacetate; propane-1,3-dione*

Introduction

1,3-Dione constitutes an important class of compounds. 1-(Substituted phenyl)-3-phenyl propane-1,3-diones are important compounds [1] of natural occurrence and are used as an intermediates for synthesis of flavones [2], coumaran-3-ones [3], isoxazoles [4], pyrimidines [5], pyrazolines [6] and 1,5-benzodiazepines which have broad spectrum of pharmacological activities [7], β-diketone unit exhibit anti-inflammatory and antimitotic activities [8-11]. The most well known methods [12] for synthesis of 1,3-dicarbonyl compounds are acylation of ketone and Claisen condensation reaction. Acylation of ketone method involves use of acid chlorides or acid anhydrides, BF_3 and acetophenone. Reaction is carried out in a three naked round bottom flask, at a low temperature. Sodium acetate is added to decompose difluride complex and solution is steam distilled to yield 1,3-dicarbonyl compound and further purified using copper salt.

Claisen condensation method involves the use of absolute ethanol and strong base such as sodium ethoxide in dry xylene/dry ether and acetophenone to yield carbanion.

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Carbanion react with ester to yield required 1,3-diketone. Both methods involve organic solvents, toxic reagents and special designed apparatus. Symmetrical and unsymmetrical 1,3-dicarbonyl compounds are prepared by these methods. 1-(Substituted phenyl)-3-phenyl propane-1,3-dione are synthesized from alpha aryloxyacetophenone [13], dibromostryl ketone [14].

1-(Substituted phenyl)-3-methylpropane-1,3-dione [15, 16] synthesized using metallic sodium and substituted acetophenones in absolute ethanol and reacting with ethyl acetate using solvent dry ether. Uekawa et al. [17] have prepared number of beta-diketones using ethyl acetate and selected methyl ketone using sodium methoxide base and diethyl ether solvent and reaction mixture is stirred for 48 h at room temperature. Zhen and Lin [18] reported synthesis of symmetrical beta-ketones by reacting substituted imidazolium salt with bis-Grignard reagent. Pond et al. [19] have synthesized bis-beta ketones, i.e. 3,3-(pyridine-2,6-diyl) bis-1-phenylpropane-1,3-dione monohydrate) and 3,3'(pyridine-2,6 diyl/bis pyridine-2yl) propane-1,3-dione by Claisen condensation of the appropriate ketone and dimethyl pyridine-2,6-dicarboxlate ester. 1-(2-Hydroxy-phenylpropane-1,3-dione) is synthesized by modified Baker-Venketraman transformation using microwave irradiation [20]; solid phase Baker-Venketraman rearrangement under solvent-free condition [21]. An efficient acetylation of the multiple anions of poly-beta-carbonyl compound is reported by Timothy et al. [22].

All these reported methods for synthesis of 1,3-diketones involves costly inflammable solvents, costly and hazardous toxic reagents, specific setup of apparatus and longer time period. In present communication, we report an efficient and simple procedure for the synthesis of 1-(substituted phenyl)-3-phenylpropane-1,3-diones.

Material and Methods

All melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on Perkin-Elmer 157 and Shimadzu spectrometer. ^{1}H NMR was recorded on Aveanue-300 MHz instrument using $CDCl_3$ as solvent and TMS as internal standard. The mass spectra were recorded on VG 7070H spectrometer using ionization energy of 70ev. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer. The reactions were monitored on TLC and the spots were located in iodine chamber.

Typical procedure for synthesis of 1-(substituted phenyl)-3-methyl propane-1,3-dione. (2a-j)

Substituted acetophenones (0.01 mol) was dissolved in absolute ethanol (20 mL). Small pieces of sodium metal (0.011 mol) was added to it and stirred for 20 min. to obtain semisolid mass. Ethanol (5 mL) was added to obtain clear solution and ethyl

acetate (0.012 mol) was added drop wise with stirring within 10 min; stirring was continued for 20 min. and then acidified with acetic acid. The solid thus obtained was filtered and crystallized from ethyl alcohol.

Spectral and analytical data of 1-(Substituted phenyl)-3-methylpropane-1,3-diones

3 (a) 1-[(2-hydroxy-3,5-dichloro phenyl)]-3-methyl propane 1,3-dione: IR ν_{max} cm^{-1}: 3450 (OH), 3048 (=CH), 1640 (C=O), 1608, 1510 (C=C Aromatic). ^1H NMR: δ 2.04 (s, 3H, CH_3), 7.58 and 7.30 (s, 1H, Ar-H), 6.45 (s, 0.40 =CH), 12.40 (s, 1H, OH), 13.71 (s, .62, OH enol). Anal. Calcd. for $C_{10}H_8O_3Cl_2$: C, 48.61; H, 3.26; X (Cl), 28.70. Found: C, 48.60; H, 3.21; X (Cl), 28.28.

3 (b) 1-[(2-methoxy-3,5-diiodo phenyl)]-3-methyl propane 1,3-dione: IR ν_{max} cm^{-1}: 3051 (=CH), 1647 (C=O), 1610, 1510, 1435 (C=C Aromatic). ^1H NMR: δ 2.33 (s, 1H, CH_3), 6.42 (s, 0.5 =CH), 7.34 (s, 1H, 6 Ar-H), 7.69 (s, 4 Ar-H), 12.75 (s, 1H, OH enol). Anal. Calcd. for $C_{11}H_{10}O_3I_2$: C, 29.76; H, 2.27; X (I), 57.16. Found: C, 29.59; H, 2.20; X (I), 57.30.

3 (c) 1-[(4'-hydroxy-3,5-diiodo phenyl)]-3-methyl propane-1,3-dione: IR ν_{max} cm^{-1}: 3420 (OH), 3040 (=CH), 1640 (C=O), 1605, 1510, 1430 (C=C Aromatic). ^1H NMR: δ 2.35 (s, 1H, CH_3), 6.50 (s, 0.34 =CH), 7.80 (s, 1H, 2 Ar-H), 8.04 (s, 1H, 6 Ar-H), 8.32 (s, 1H, 4 OH), 12.46 (s, 0.65 OH enol). Anal. Calcd. for $C_{10}H_8O_3I_2$: C, 29.93; H, 1.88; X (I), 59.03. Found: C, 30.09; H, 1.97; X (I), 58.93.

3 (d) 1-[(2-hydroxy-3-iodo-5-chloro phenyl)]-3-methyl propane-1,3-dione: IR ν_{max} cm^{-1}: 3430 (OH), 3058 (=CH), 1645 (C=O), 1625, 1520 (C=C Aromatic). ^1H NMR: δ 2.20 (s, 1H, CH_3), 7.67 and 7.69 (s, 1H, Ar-H), 6.75 (s, 0.36, =CH), 12.60 (s, 1H, 2 x OH), 13.9 (s, 1H, OH enol). Anal. Calcd. for $C_{10}H_8O_3ClI$: C, 27.90; H, 1.86; X (Cl + I), 47.96. Found: C, 27.88; H, 1.86; X (Cl + I), 47.87.

3 (e) 1-[(2-hydroxy-3,5-diiodo phenyl)]-3-methyl propane-1,3-dione: IR ν_{max} cm^{-1}: 3430 (OH), 3070 (=CH), 1651 (C=O), 1552, 1422(C=C Aromatic). ^1H NMR: δ 2.25 (s, 1H, CH_3), 4.82 (s, 1H, OH), 6.57 (s, 0.38, =CH), 8.09 (s, 1H, Ar-H), 12.51 (s, 1H, 2 x OH), 13.60 (s, 0.60, OH enol). MS m/z: 446 (M^+), 440, 413, 405, 361, 329, 307, 176, 154, 107, 95. Anal. Calcd. for $C_{10}H_8O_3I_2$: C, 27.93; H, 1.88; X (I), 59.03. Found: C, 27.90; H, 1.88; X (I), 58.84.

3 (f) 1-[(2-hydroxy-3-bromo-5-methyl phenyl)]-3-methyl propane-1,3-dione: IR ν_{max} cm^{-1}: 3455 (OH), 3070 (=CH), 1650 (C=O),1600, 1510, 1460 (C=C Aromatic). ^1H NMR: δ 2.75 (s, 1H, CH_3), 8 and 8.06 (s, 1H, Ar-H), 6.5 (s, .35, =CH), 12.28 (s, 1H, 2 x OH), 13.50 (s, 1H, OH). Anal. Calcd. for $C_{11}H_{11}O_3Br$: C, 48.73; H, 4.09; X (Br), 29.47. Found: C, 48.71; H, 4.09; X (Br), 29.21.

3 (g) 1-[(2-hydroxy-3-bromo-5-chloro phenyl)]-3-methyl propane-1,3-dione: IR ν_{max} cm^{-1}: 3460 (OH), 3072 (=CH), 1635 (C=O),1610, 1420 (C=C Aromatic). ^1H NMR: δ 2.60 (s, 1H, CH_3), 8.10 and 8.12 (s, 1H, Ar-H), 6.60 (s, 0.36, =CH), 12.60 (s, 1H, 2 x OH), 14.52 (s, 0.63, OH enol). Anal. Calcd. for $C_{10}H_8O_3ClBr$: C, 41.20; H, 2.77; X (Cl + Br), 39.57. Found: C, 41.20; H, 2.76; X (Cl + Br), 39.96.

3 (h) 1-[(2,4-dihydroxy-3,5-dibromo phenyl)]-3-methyl propane-1,3-dione: IR ν_{max} cm^{-1}: 3450(OH), 3065 (=CH), 1630 (C=O),1600, 1520, 1440 (C=C Aromatic). ^1H NMR: δ 2.37 (s, 1H, CH_3), 6.55 (s, 0.35 =CH), 7.63 (s, 1H, 6 Ar-H), 8.42 (s, 1H, 4 OH), 12.83 (s, 1H, 2 OH), 13.03 (s, 0.62, OH enol). EIMS: m/z 352 (M^+), 310, 295, 237, 157, 77, 53. Anal. Calcd. for $C_{10}H_8O_4Br$: C, 34.12; H, 2.29; X (Br), 45.40. Found: C, 34.23; H, 2.37; X (Br), 45.53.

3 (i) 1-[(2,4-dihydroxy-3,5-diiodo phenyl)]-3-methyl propane-1,3-dione: IR ν_{max} cm^{-1}: 3372 (OH), 3068 (=CH), 1651 (C=O), 1552, 1499 (C=C Aromatic). ^1H NMR: δ 2.40 (s, 1H, CH_3), 6.61 (s, 0.36 =CH), 7.66 (s, 1H, 6 Ar-H), 8.35 (s, 1H, 4 OH), 12.94 (s, 1H, 2 OH), 13.05 (s, 0.61 OH enol). **EIMS**: m/z 446 (M^+), 413, 405, 391, 361, 329, 307, 176, 154, 107, 95. Anal. Calcd. for $C_{10}H_8O_4I_2$: C, 26.93; H, 1.81; X (I), 56.91. Found: C, 27.04; H, 1.73; X (I), 57.03.

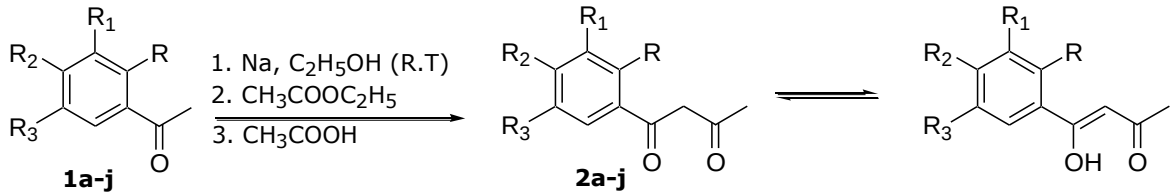
3 (j) 1-[(2,4-dihydroxy-3,5-dichloro phenyl)]-3-methyl propane-1,3-dione: IR ν_{max} cm^{-1}: 3452 (OH), 3072 (=CH), 1647 (C=O), 1608, 1500, 1434 (C=C Aromatic). ^1H NMR: δ 2.60 (s, 1H, CH_3), 6.55 (s, 0.36 =CH), 7.70 (s, 1H, Ar-H), 12.45 (s, 2H, OH), 13.35 (s, 0.65 OH enol). Anal. Calcd. for $C_{10}H_8O_4Cl_2$: C, 45.80; H, 3.05; X (Cl), 26.95. Found: C, 45.80; H, 2.98; X (Cl), 26.48.

Results and Discussion

Substituted acetophenones were dissolved in absolute ethanol and clean small pieces of sodium metal added and stirred for 20 minutes at room temperature. Acetophenones react with sodium metal and semisolid mass forms. Little more of absolute ethanol added to dissolve excess of sodium metal. Calculated amount of ethyl acetate added to the clear reaction solution and stirred for 10 minutes and then acidified with acetic acid up to the pH 5.5. Solid separated out. Separated solid filtered and crystallized from ethanol to gave 1-(substituted phenyl)-3-methyl propane-1,3-diones (Table 1). Structure of newly synthesized compounds confirmed by IR, ^1HNMR and Mass. IR spectra of compounds (**2a-j**) gave a broad band at 3450 cm^{-1} due to OH and a specific band appears at 3040-3068 cm^{-1} due to =CH. ^1H NMR gave signal at δ 6.4-6.6 due to =CH.

Reported methods involve the use of acetophenones and sodium hydride in ethanol or sodium metal and dry xylene. Further reported methods requires special

designed apparatus, dry ether/xylene as a solvent. We have used only absolute ethanol, sodium and acetophenone to give carbanion which react with ethyl acetate to yield 1,3-diketones, hence method is a cost effective.



1a-j **2a-j**

Scheme 1. Synthesis of 1-(substituted phenyl)-3-methyl propane-1,3-dione.

Table 1. Synthesis of 1-(substituted phenyl)-3-methyl propane-1,3-dione

Compound	R	R_1	R_2	R_3	Crystal appearances	M.P (^{0}C)	Yield (%)
2a	OH	Cl	H	Cl	Colourless	78	75
2b	OCH_3	I	H	I	Colourless	170	82
2c	H	I	OH	I	Pale Yellow	156	85
2d	OH	I	H	Cl	Pale Yellow	100	80
2e	OH	I	H	I	Pale Yellow	91	87
2f	OH	Br	H	CH3	Colourless	75	81
2g	OH	Br	H	Cl	Colourless	96	86
2h	OH	Br	OH	Br	Yellow	163	90
2i	OH	I	OH	I	Pale Yellow	179	80
2j	OH	Cl	OH	Cl	Colourless	159	84

This modified method is quick, simple, cost effective, work up is easy, reaction completed within one hr. giving 75-90 % yield. No need of toxic, hazardous reagent such as HF, dry ether, typical set up of apparatus. Utilization of non-toxic hazardous chemicals, time saving and less cost can be a partial green synthetic strategy.

Conclusion

In summary we have developed a simple, efficient and easy methodology for synthesis of 1-(substituted phenyl)-3-methyl propane-1,3-dione. The notable merits offered by this methodology are mild reaction condition, simple procedure, cleaner reaction, short reaction time and excellent yields of products (75-90%).

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Full Paper

An efficient and rapid synthesis of some novel 1,3-diaryl, diazenyl, 2-propen-1-one using PEG-400 as recyclable solvent and their *in vitro* antimicrobial evaluation

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ABSTRACT: *In the present communication, a series of some novel hetero 1,3-diaryl, diazenyl 2-propen-1-one (azochalcone) by using PEG as a green reaction medium. The reaction gives shorter reaction time, excellent yield and inexpensive. All the synthesized products were characterized by the spectroscopic and analytical measurement. Furthermore, all the synthesized compounds were screened for their in vitro antimicrobial activity.*

Keywords: *azochalcones; PEG-400; antimicrobial activity*

Introduction

In this work, we report the synthesis and biological activity of some novel azochalcone. Chalcones (1,3-diaryl, diazenyl-2-propen-1-ones) constitute an important class of natural products belonging to the flavonoid family. The organic compound containing azochalcone (1,3-diaryl, diazenyl-2-propen-1-ones) has wide application in medicinal chemistry and which has been possess wide spectrum of biological activities, including antibacterial, antifungal, anti-inflammatory, antitumor, antimutagenic [1, 2, 3], antihypertensive [4], antifidant [5], antioxidant [6]. Chalcones are also precursors in the synthesis of many biologically important heterocycles such as benzothiazepines [7], as pyrazolines [8], 1,4-diketones [9]. Due to their wide spectrum biological activity and used in as starting materials in the synthesis of a series of heterocyclic compound like

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isoxazoles, quinolinones, thiadiazines, benzofuranones and flavones [10, 11]. Some of chalcone derivatives have been found to inhibit several important enzymes in cellular systems, such as xanthine oxidase [12] and protein tyrosine kinase [13, 14]. Their simple structure and ease of preparation make chalcones as an attractive scaffold for structure-activity relationship (SAR) and a wide number of substituted chalcones have been synthesized to evaluate the effect of various functional groups on biological activity [15]. Hence the synthesis of such chalcones has more interest in organic as well as medicinal chemistry. To avoid the use of volatile organic solvent can minimize the generation of waste, which is requirement of one of the principles of green chemistry [16, 17]. Recently PEG is found to be interesting solvent system.

In continuation to synthesis we have planned to synthesis of series of novel hetero azochalcones by applying the principle of green chemistry [18]. PEG is an environmentally benign reaction solvent, it is non- toxic, inexpensive, potentially recyclable and water soluble, which facilities it's removed from the action product. All the products were newly synthesized and characterized by their spectral analysis

Material and Methods

The title compounds were synthesized by Claisen-Schmidt condensation [20] using PEG-400 as green reaction solvent. All the melting points were uncorrected and determined in an open capillary tube. 2-butyl-4-chloro-5-formyl-imidazole was purchased from Sigma-Aldrich (India), 2-amino-4-(4-chlorophenyl)-thiazole and 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxyaldehyde were prepared by the reported method [19]. Completion of the reaction was monitored by thin layer chromatography on precoated sheets of silica gel-G (Merck, Germany) using iodine vapors for detection, IR spectra were recorded in KBr on a Shimadzu spectrometer (Japan). ^{1}H NMR spectra were recorded in DMSO-*d6* with an Avance spectrometer 300-MHz frequency using TMS as an internal standard. Mass spectra were recorded on an EI-Shimadzu QP 2010 PLUS GC-MS system (Shimadzu, Japan). Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer. The synthetic pathway is presented in Scheme 1 and physicochemical data for the synthesized compounds are given Table 1.

General procedure for the synthesis 1-(substituted phenyl) diazenyl) phenyl)-2-propen-1-one

An equimolar mixture of substituted azo-acetophenone **1** (1 mmol), heteroaromatic aldehyde **2** (1 mmol) and KOH (2 mmol) was stirred in PEG-400 (10 mL) at 40-50 °C for 1 hour. After completion of the reaction (monitored by TLC), the crude mixture was worked up in ice-cold water (100 mL). The product which separated out was filtered and dried which on further recrystalized from acetic acid or ethanol, filtrate was

evaporated to remove water leaving PEG behind. The same PEG was utilized to synthesize further chalcones.

Spectroscopic data of synthesized derivatives:

*3-(2-butyl-5-chloro-1H-imidazol-4-yl)-1-(4-(5-chloro-2-hydroxyphenyl) diazenyl) phenyl)-2-propen-1-one (**3a**):* IR (KBr): 3335 (-NH), 3159 (-OH), 1650 (>C=O), 1595 (-C=N), 712 (-C-Cl). ^{1}H NMR (DMSO-*d6*), δ: 0.94 (s, 3H, -CH_3), 1.30 (m, 2H, -CH_2), 1.65 (m, 2H, -CH_2), 2.78 (t, 2H, -CH_2), 7.02-7.95 (m, 7H, Ar-H, -CH=CH-), 8.06 (s, 1H, -NH, D_2O exchangeable), 11.60 (s, 1H, -OH, D_2O exchangeable). M.S. (m/z): 442 [M^+]. Anal. Calcd for $C_{22}H_{20}Cl_2N_4O_2$ C, 59.60; H, 4.55; N, 12.64 %. Found: C, 59.69; H, 4.64; N, 12.75 %.

*3-(2-butyl-5-chloro-1H-imidazol-4-yl)-1-(4-(5-fluoro-2-hydroxyphenyl) diazenyl)phenyl)-2-propen-1-one (**3b**)*: IR (KBr): 3338 (-NH), 3145 (-OH), 1652 (>C=O), 1598 (-C=N). ^{1}H NMR (DMSO-*d6*), δ: 0.93 (s, 3H, -CH_3), 1.32 (m, 2H, -CH_2), 1.62 (m, 2H, -CH_2), 2.72 (t, 2H, -CH_2), 7.02-7.90 (m, 7H, Ar-H, -CH=CH-), 8.16 (s, 1H, -NH, D_2O exchangeable), 11.80 (s, 1H,-OH, D_2O exchangeable). M.S. (m/z): 426 [M^+]. Anal. Calcd for $C_{22}H_{20}ClFN_4O_2$ C, 61.90; H, 4.72; N, 13.12 %. Found: C, 61.76; H, 4.64; N, 13.15 %.

*3-(2-butyl-5-chloro-1H-imidazol-4-yl)-1-(4-(5-bromo-2-hydroxyphenyl) diazenyl) phenyl)-2-propen-1-one (**3c**)*: IR (KBr): 3332 (-NH), 3140 (-OH), 1645 (>C=O), 1592 (-C=N). ^{1}H NMR (DMSO-*d6*), δ: 0.90 (s, 3H, -CH_3), 1.34 (m, 2H, -CH_2), 1.60 (m, 2H, -CH_2), 2.74 (t, 2H, -CH_2), 7.02-8.15 (m, 7H, Ar-H, -CH=CH-), 8.14 (s, 1H, -NH, D_2O exchangeable), 11.60 (s, 1H, -OH, D_2O exchangeable). M.S. (m/z): 489 [M^+]. Anal. Calcd for $C_{22}H_{20}BrClN_4O_2$ C, 54.17; H, 4.13; N, 11.49 %. Found: C, 54.20, H, 4.14; N, 11.40%.

*3-(2-butyl-5-chloro-1H-imidazol-4-yl)-1-(4-(3,5-dichloro-2-hydroxyphenyl) diazenyl) phenyl)-2-propen-1-one (**3d**):* IR (KBr): 3330 (-NH), 3145 (-OH), 1648 (>C=O), 1596 (-C=N). ^{1}H NMR (DMSO-*d6*), δ: 0.96 (s, 3H, -CH_3), 1.36 (m, 2H, -CH_2), 1.65 (m, 2H, -CH_2), 2.72 (t, 2H, -CH_2), 7.02-7.85 (m, 6H, Ar-H, -CH=CH-), 8.24 (s, 1H, -NH), 11.72 (s, 1H, -OH)ppm; M.S. (m/z): 476[M^+]. Anal. Calcd for $C_{22}H_{19}Cl_3N_4O_2$ C, 55.31; H, 4.01; N, 11.73%. Found: C, 55.20, H, 4.16; N, 11.70%.

*3-(2-amino-4-(4-chlorophenyl)thiazol-5-yl)-1-(4-(5-chloro-2-hydroxyphenyl) diazenyl) phenyl)-2-propen-1-one (**3e**):* IR (KBr): 3298 (-NH_2), 3130 (-OH), 1630 (>C=O), 1586 (-C=N). ^{1}H NMR (DMSO-*d6*), δ: 7.10-8.25 (m, 13H, Ar-H+ -CH=CH-), 8.34 (s, 2H, -NH_2), 11.84 (s, 1H, -OH, D_2O exchangeable). M.S. (m/z): 495[M^+]. Anal. Calcd for $C_{24}H_{16}Cl_2N_4O_2S$ C, 58.19; H, 3.29; N, 11.31%. Found: C, 58.28, H, 3.16; N, 11.20%.

*3-(2-amino-4-(4-chlorophenyl)thiazol-5-yl)-1-(4-(3,5-dichloro-hydroxyphenyl) diazenyl) phenyl)-2-propen-1-one (**3f**):* IR (KBr): 3310 (-NH_2), 3160 (-OH), 1640 (>C=O), 1595 (-

C=N). ^{1}H NMR (DMSO-*d6*), δ: 7.08-8.10 (m, 12H, Ar-H+ -CH=CH-), 8.20 (t, 2H, -NH_2), 11.78 (s, 1H, -OH, D_2O exchangeable). M.S. (m/z): 530 [M^+]. Anal. Calcd for $C_{24}H_{15}Cl_3N_4O_2S$ C, 54.41; H, 2.85; N, 10.57%. Found: C, 54.32, H, 2.74; N, 10.45%.

*3-(2-amino-4-(4-chlorophenyl)thiazol-5-yl)-1-(4-(5-fluoro-hydroxyphenyl) diazenyl) phenyl)-2-propen-1-one (**3g**):* IR (KBr): 3290 (-NH_2), 3132 (-OH), 1636 (>C=O), 1590 (-C=N). ^{1}H NMR (DMSO-*d6*), δ: 7.10-8.25 (m, 11H, Ar-H+ -CH=CH-), 8.30 (s, 2H, -NH_2), 11.90 (s, 1H, -OH, D_2O exchangeable). M.S. (m/z): 478 [M^+]. Anal. Calcd for $C_{24}H_{16}ClFN_4O_2S$ C, 60.19; H, 3.37; N, 11.70%. Found: C, 60.25, H, 3.26; N, 11.82%.

*3-(2-amino-4-(4-chlorophenyl)thiazol-5-yl)-1-(4-(5-bromo-2 hydroxyphenyl) diazenyl) phenyl)-2-propen-1-one (**3h**):* IR (KBr): 3340 (-NH_2), 3178 (-OH), 1665 (>C=O), 1590 (-C=N). ^{1}H NMR (DMSO-*d6*), δ: 7.12-8.15 (m, 13H, Ar-H+ -CH=CH-), 8.24 (s, 2H, -NH_2), 11.60 (s, 1H, -OH, D_2O exchangeable). M.S. (m/z): 539[M^+]. Anal. Calcd for $C_{24}H_{16}BrClN_4O_2S$ C, 53.40; H, 2.99; N, 10.38%. Found: C, 53.28, H, 2.86; N, 10.42%.

*1-(4-(5-chloro-2-hydroxyphenyl)diazenyl)phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-propen-1-one (**3i**):* IR (KBr): 3158 (-OH), 1652 (>C=O), 1595 (-C=N). ^{1}H NMR (DMSO-*d6*), δ: 2.34 (s, 3H, CH_3), 7.12-8.35 (m, 12H, Ar-H+ -CH=CH-), 11.67 (s, 1H, -OH). M.S. (m/z): 476 [M^+]. Anal. Calcd for $C_{25}H_{18}Cl_2N_4O_2$ C, 62.90; H, 3.80; N, 11.74%. Found: C, 62.78, H, 3.86; N, 11.82%.

*1-(4-(5-chloro-2-hydroxyphenyl)diazenyl)phenyl)-3-(5-fluoro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-propen-1-one (**3j**):* IR (KBr): 3162 (-OH), 1645 (>C=O), 1589 (-C=N). ^{1}H NMR (DMSO-*d6*), δ: 2.32 (s, 3H, CH_3), 7.10-8.32 (m, 12H, Ar-H+ -CH=CH-), 11.76 (s, 1H,-OH, D_2O exchangeable). M.S. (m/z): 460 [M^+]. Anal. Calcd for $C_{25}H_{18}ClFN_4O_2$ C, 65.15; H, 3.94; N, 12.16%. Found: C, 65.18, H, 3.85; N, 12.24%.

*1-(4-(5-chloro-2-hydroxyphenyl)diazenyl)phenyl)-3-(5-bromo-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-propen-1-one (**3k**):* IR (KBr): 3178 (-OH), 1665 (>C=O), 1592 (-C=N), 776 (-C-Cl). ^{1}H NMR (DMSO-*d6*), δ: 2.30 (s, 3H, CH_3), 7.10-8.32 (m, 14H, Ar-H+ -CH=CH-), 11.58 (s, 1H, -OH, D_2O exchangeable). M.S. (m/z): 522 [M^+]. Anal. Calcd for $C_{25}H_{18}BrClN_4O_2$ C, 57.55; H, 3.48; N, 10.74%. Found: C, 57.44, H, 3.42; N, 10.65%.

*1-(4-(5-chloro-2-hydroxyphenyl)diazenyl)phenyl)-3-(3,5-dichloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-propen-1-one (**3l**):* IR (KBr): 3160 (-OH), 1678 (>C=O), 1605 (-C=N), 776 (-C-Cl). ^{1}H NMR (DMSO-*d6*), δ: 2.35 (s, 3H, CH_3), 7.12-8.06 (m, 13H, Ar-H+ -CH=CH-), 11.70 (s, 1H, -OH, D_2O exchangeable). M.S. (m/z): 510 [M^+]. Anal. Calcd for $C_{25}H_{17}Cl_3N_4O_2$ C, 58.67; H, 3.35; N, 10.95%. Found: C, 58.62, H, 3.29; N, 10.88%.

Antimicrobial activity

The antimicrobial activities of the synthesized compounds **3(a-l)** were determined by agar diffusion method [21-22]. The compounds were evaluated for antibacterial

activity against bacteria *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus* and *Bacillus subtillis.* The culture strains of bacteria were maintained on a nutrient agar slant at 37 ± 2°C for 24–48 hrs. Antifungal activity was studied against *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum* and *Fusarium moneliforme*. The results were compared with penicillin and nystatin. All the culture strains of fungi were maintained on a potato dextrose agar (PDA) slant at 27 ± 2 °C for 24–28 h, until sporulation. Spores were transferred into 5 mL of sterile distilled water containing 1% Tween-80 (to suspend the spores properly). The spores were counted with a haemocytometer (106 CFU mL^{-1}). Sterile PDA plates containing 2% agar were prepared; 0.1 mL of each fungal spore suspension was spread on each plate and incubated at 27 ± 2°C for 12 h. After incubation, a hole was made using a sterile cork borer and each agar well was filled with 0.1 mL azo-chalcone solution of 50, 100 and 250 mg mL^{-1} separately to get the minimum inhibitory concentration (*MIC*) value of azo-chalcones. Dimethyl sulphoxide (DMSO) was used as a solvent for chalcones and as well as a control, while distilled water used as solvent for standard drugs. The plates were kept in refrigerator for 20 minutes for diffusion and then incubated at 27 ± 2 °C for 24–28 h in an incubator. After incubation, the zone of inhibition of compounds was measured in mm and standard and minimum inhibitory concentrations *MICs*) were noted. The results of antimicrobial studies are given in Table 2 was measured in mm standard and minimum inhibitory concentrations (*MICs*) were noted.

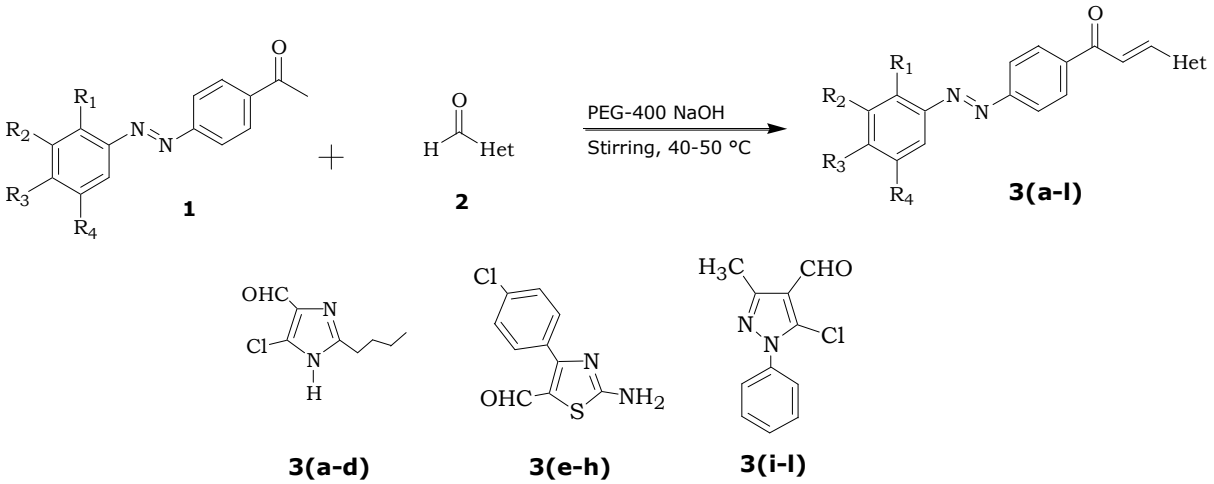
Results and Discussion

Synthesis

The Claisen-Schmidt condensation is an important C-C bond formation for the synthesis of 1,3-diaryl, diazenyl -2-propen-1-ones (azochalcones). It is generally carried out by the use synthesis of 1,3-diaryl, diazenyl-2-propen-1-ones (azochalcones). It is generally carried out by the use of strong bases such as NaOH or KOH in polar solvents (MeOH or DMF). The aim of the present study was to develop an efficient protocol using PEG-400 as a recyclable reaction solvent. To obtain 1,3-diaryl, diazenyl-2-propen-1-ones with good to excellent yields in a short span of time without formation of any side product.

First, we attempted condensation of 1-(4-(5-chloro-2-hydroxyphenyl) diazenyl) phenyl) ethanone with 2-butyl-4-chloro-5-formyl-imidazole using PEG-400 as a reaction solvent under alkaline condition. The reaction was completed within 1 h and the corresponding product was obtained in 95 % yield. Encouraged by the results, we turned our attention to a variety of azo-acetophenones and hetero aldehydes. In all cases, the reaction proceeds efficiently with high yields at 40-50 °C using PEG-400 as an alternative reaction solvent.

Scheme 1



IR spectra of azo-chalcones showed characteristic bands at 1640–1680 cm^{-1} due to >C=O stretching vibration. Lowering of normal >C=O frequency was observed due to the presence of -C=C stretching in chalcones. ^{1}H NMR spectra of the compounds showed characteristic doublet signals at δ 7.3 and 7.8 ppm due to alkenes α,β-protons, respectively. However, these doublets coalesced with aromatic protons. The phenolic proton (2'-OH) was observed as a singlet at δ 11–12.0 ppm, due to hydrogen bonding with the adjacent carbonyl group, while other aromatic and aliphatic protons were found at expected regions. The mass spectra of compounds **3a-l** showed molecular ion peaks corresponding to their molecular formula. Besides the molecular ion peak [M^+], the compounds showed [M^{+1}] (isotopic abundances), which confirmed the presence of halogen groups in respective compounds. The base peak was seen at *m/z* 43, corresponding to the CH_3C=O moiety.

Table1. Physico-chemical data of synthesized azo-chalcone derivatives **3(a-l)**

Entry	Comp. No.	R1	R2	R3	R4	Yield in %	M. P. (°C)
1	3a	OH	H	H	Cl	94%	125-128
2	3b	OH	H	H	F	92%	118-120
3	3c	OH	H	H	Br	91%	132-134
4	3d	OH	Cl	H	Cl	93%	148-150
5	3e	OH	H	H	Cl	89%	138-140
6	3f	OH	Cl	H	Cl	90%	114-116
7	3g	OH	H	H	F	94%	120-122
8	3h	OH	H	H	Br	92%	128-133
9	3i	OH	H	H	Cl	90%	135-138
10	3j	OH	H	H	F	88%	158-160
11	3k	OH	H	H	Br	87%	165-167
12	3l	OH	Cl	H	Cl	91%	150-153

Antimicrobial activity

All the synthesized compounds were tested for their *in vitro* antimicrobial activity. The results are given in Table 2. Compounds **3b**, **3d**, **3f**, **3g** and **3j** showed good activity

against all tested bacteria at concentration of 50 mg mL^{-1}. Compounds **3d** and **3g** showed a maximum zone of inhibition (20 mm) against *B. subtillis* compared to penicillin. Compounds **3b, 3d** and **3j** showed an effective zone of inhibition (18–20 mm) against *S. aureus* in comparison with the standard. Compounds **3a**, **3c**, **3e**, **3h**, **3i,3k** and **3l** were found to be less active against the tested bacterial strains (*MIC* = 100 mg mL^{-1}). Antifungal screening data showed that most of the compounds were active against all fungi. Compounds **3b**, **3d**, **3e**, **3g and 3j** showed effective activity against all fungal strains at *MIC* of 50 mg mL^{-1}. Compound **3j** showed comparable activity against *Aspergillus niger* to standard drug, but compounds **3e,** and **3g** displayed an even stronger zone of inhibition (19–22 mm) against all the tested fungi. On the other hand, compounds **3h**, **3i, 3k** and **3l** were found to be inactive against *fusarium moneliforme.* When structure and activity relationships (SAR) are investigated, we can inform from the results that halogen at the fluoro and dichloro at R_4 and R_2 position might be responsible for antibacterial and antifungal activity.

Table 2. Antibacterial activity of synthesized compounds

Compound	Zone of inhibition, mm (MIC µg/mL) Value							
	Bacteria				Fungi			
	Ec	St	Sa	Bs	An	Af	Pc	Fm
3a	12(100)	---	15(100)	13(100)	11(100)	13(100)	12(100)	14(100)
3b	15(50)	18(50)	19(50)	19(50)	18(50)	20(50)	18(50)	15(50)
3c	10(100)	12(100)	---	14(100)	9(100)	13(100)	---	16(100)
3d	17(50)	16(50)	19(50)	20(50)	18(50)	19(50)	18(50)	19(50)
3e	12(100)	13(100)	12(100)	15(100)	19(50)	17(50)	19(50)	19(50)
3f	17(50)	18(50)	14(50)	16(50)	16(50)	18(50)	16(50)	16(50)
3g	16(50)	20(50)	18(50)	20(50)	19(50)	20(50)	22(50)	20(50)
3h	12(100)	----	13(100)	10(100)	16(100)	----	14(100)	18(100)
3i	10(100)	12(100)	9(100)	13(100)	15(100)	----	16(100)	15(100)
3j	10(100)	12(100)	18(50)	16(50)	20(50)	20(50)	19(50)	22(50)
3k	-----	13(100)	12(100)	14(100)	16(100)	10(100)	10(100)	12(100)
3l	15(100)	12(50)	24(50)	24(50)	NA	NA	NA	NA
Penicillin	22(50)	22(50)	24(50)	24(50)	NA	NA	NA	NA
Nystatin	NA	NA	NA	NA	20(50)	22(50)	24(50)	24(50)

Solvents: DMSO, water : *Ec –Escherichia coli, St –Salmonella typhi*, Sa- *Staphylococcus aureus , Bs –Bacillus subtillis, An – Aspergillus niger, Af – Aspergillus flavus, Fm – Fusarium moneliforme, Pc – Penicillium chrysogenum,* (-) – MIC ≥ 100 µg L^{-1}, NA –not applicable.

Conclusion

In conclusion, our protocol is a practical approach which uses PEG as a commercially available, low-cost, recyclable non-ionic solvent. In most cases, the reaction proceeded smoothly to produce the corresponding 1,3-diaryl,diazenyl-2-propen-1-ones. The reaction was clean and the products were obtained in excellent yields without formation of any side products. The substituted chalcone derivatives **(3b),** (**3d**), (**3f**), **(3g)** and (**3j)** having revealed significant antibacterial and antifungal activity. Compound (**3j)** showed comparable activity against *Aspergillus niger.* Considering the results obtained from antibacterial and antifungal tests together, it is noteworthy that the

tested compounds were found more active towards fungi than bacteria. Hence it is concluded that there is enough scope for further study in the developing these as good lead compounds.

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Full Paper

Kinetics studies of oxidation of niacinamide by alkaline potassium permanganate

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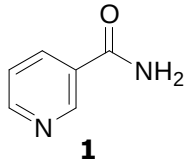
ABSTRACT: *The oxidation of niacinamide in alkaline media is carried out using potassium permanganate as an oxidizing agent. The reaction was monitored using UV-Visible spectrophotometer at 525 nm. It was found to be zero order with respect to oxidant,, fractional order with respect to hydrogen ion concentration and first order with respect to substrate. The thermodynamic parameters were determined. The average ($\Delta G^{\#}$) was found to be 87.60 KJ/mol. The values $\Delta S^{\#}$ was found to be -0.2132 KJ/mole and energy of activation was found to be 23.95 KJ/mole. A suitable mechanism is proposed based on the experimental conditions.*

Keywords: *kinetic study; mechanistic proposals; niacinamide; permanganetic oxidation*

Introduction

Niacinamide is also called as nicotinamide (**1**). Chemically, it is 3-pyridinecarboxamide. It is used as vitamin B3 and it gets hydrolyzed to the acid in digestive tract of non ruminants.



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The physical properties of this compound are given in the Table 1. The nicotinic acid (**2**) protect from oxidative stress injury in endothelial cells by inhibition of poly (ADP-ribose) polymerase and from NAD depletion. This in turn protects energetic allowing maintaining cellular ATP. Niacianamide is a component of coenzyme

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nicotinamide adenine dinucleotide (NAD^+), which is found in all living cells. NAD^+ undergoes redox reaction. It accepts an electron and converted into NADH, which can be used as a reducing agent to donate electrons. Although lot of literature is available on the reaction between NAD and other substances, the oxidation kinetics of niacin using permanganate is not studied so for. Therefore, we decided to undertake kinetic study of the nicianamide.

Table 1. Physical properties of niacianamide

Name of property	Value
Mol. Formula	$C_6H_6N_2O$
Mol. Weight	122.13 g/mol
R.I	1.466
Density	1.400 g/cm^3
M.P.	128-131 ^oC
Boiling point	150-160 ^0C
Flash Point	182 ^oC
solubility	Water soluble

Material and Methods

The reactions were allowed to occur in glass stopper Erlenmeyer flask of corning make. These flasks were suspended in a water bath with a temperature sensitivity of 0.1 ^oC. The reaction mixture except substrate was prepared by taking all reaction ingredients. The temperature pre-equilibrated solution of substrate was added into the reaction mixture and the time of initiation of the reaction was recorded when half of the contents of pipette were released. The reaction mixtures were shaken and aliquot (1 mL) was taken out at different time intervals and absorbance of remaining $KMnO_4$ was noted at $\lambda_{max.}$ = 525 nm. The reaction rates were calculated by drawing pseudo first order plot, [substrate]> [$KMnO_4$] condition. Good straight lines were obtained and pseudo first rate constant were calculated in the usual manner.

Product Analysis

Known volume of 0.1 M substrate and 0.01M $KMnO_4$ in 1 M H_2SO_4 solution were taken in 250 mL beaker and kept the reaction mixture for 4-5 days for completion of the reaction. The diethyl ether was added into the reaction mixture and then it was shaken for an hour before separating two layers ether and water by employing separating funnel. The etheral layer was taken on the watch glass; latter was left for some time for evaporation of ether. The residue left on the watch glass was air drying before identification. The solid mass was identified by M. P. and IR Spectra.

The IR spectra of NCA and the product obtained were compared. It gives values for:

IR (KBr , Cm-1) 3360 ( symmetrical streching) , 1690 ( streching)

The product obtained was nicianicacid with melting point 235 ^{O}C and shows IR frequencies:

IR (KBr , Cm-1) 3026 (—OH streching) , 1700 ( streching)

Results and Discussion

Dependence of permanganate concentration

To study the effect of dependence of permanganate concentration, the concentration of $KMnO_4$ was varied from $1x10^{-4}$ to $9x10^{-4}$ M, keeping constant concentration of other reaction ingredients such as substrate and acid. Since reaction has been studied under pseudo first order condition a plot of log [MnO_4^-] verses time was made and pseudo first order rate constants were calculated. These results are given in the Table 2 it is clear that pseudo first rate constant do not change with change in concentration of permanganate confirming the first order dependence with respect to oxidant.

Table 2. First order rate constant

Entry	[NCA]	[$KMnO_4$]	[NaOH]	k(s^{-1})
1	$1x10^{-3}$	1 $x10^{-4}$	1	0.0064
2	$1x10^{-3}$	2 $x10^{-4}$	1	0.0113
3	$1x10^{-3}$	3 $x10^{-4}$	1	0.0081
4	$1x10^{-3}$	4 $x10^{-4}$	1	0.0197
5	$1x10^{-3}$	5 $x10^{-4}$	1	0.0219
6	$1x10^{-3}$	6 $x10^{-4}$	1	0.0263
7	$1x10^{-3}$	7 $x10^{-4}$	1	0.0264
8	$1x10^{-3}$	8 $x10^{-4}$	1	0.0279
9	$1x10^{-3}$	9 $x10^{-4}$	1	0.0198

The least square method was used to find out co-relation between logk_{obs} and log [oxidation] which shows good co-relation (r = 0.889) and order (0.67) which can be taken as approximately one.

Dependence of substrate concentration

The concentration of substrate was varied from $1x10^{-3}$ to $9x10^{-3}$ M and fixed concentration of [MnO_4^-] = $1x10^{-4}$ M and [H_2SO_4] = 1 M The pseudo first order rate constant were calculated (Table 3) in this variation were plotted against concentration of substrate, a straight line passing through origin was obtained. This shows that order with respect to substrate is also one.

Dependence of base concentration

The hydroxyl ion concentration dependence was studied by employing NaOH at fixed [MnO_4^-] and [substrate], respectively. The pseudo first order plot was made and the plot of these rate constant against [OH^-] shows fractional order with respect to acid.

Since rate decrease with increase in [OH^-] ion, the deprotonated species of oxidant or substrate must involve in the reaction mechanism. The results are given in the Table 4.

Table 3. First order rate constant

Entry	[NCA]	[$KMnO_4$]	[NaOH]	k(s^{-1})
1	1 x10^{-3}	1x10^{-4}	0.5	0.0051
2	2 x10^{-3}	1x10^{-4}	0.5	0.0058
3	3 x10^{-3}	1x10^{-4}	0.5	0.0063
4	4 x10^{-3}	1x10^{-4}	0.5	0.0026
5	5 x10^{-3}	1x10^{-4}	0.5	0.019
6	6 x10^{-3}	1x10^{-4}	0.5	0.0088
7	7 x10^{-3}	1x10^{-4}	0.5	0.033
8	8 x10^{-3}	1x10^{-4}	0.5	0.0043
9	9 x10^{-3}	1x10^{-4}	0.5	0.0024

Table 4. First order rate constant

Entry	[NCA]	[$KMnO_4$]	[NaOH]	k(s^{-1})
1	1x10^{-3}	1x10^{-4}	0.1	0.0052
2	1x10^{-3}	1x10^{-4}	0.2	0.0061
3	1x10^{-3}	1x10^{-4}	0.3	0.0195
4	1x10^{-3}	1x10^{-4}	0.4	0.05
5	1x10^{-3}	1x10^{-4}	0.5	0.0082
6	1x10^{-3}	1x10^{-4}	0.6	0.0046
7	1x10^{-3}	1x10^{-4}	0.7	0.0064
8	1x10^{-3}	1x10^{-4}	0.8	0.0046
9	1x10^{-3}	1x10^{-4}	0.9	0.0057

Table 5. Effect of added salt on first order rate constant

Conc. of salt mol.L^{-1}	Rate constants (S^{-1})								
	KCl	KBr	KI	K_2SO_4	$CaCl_2$	$Ca(NO_3)_2$	$MgCl_2$	$AlCl_3$	$Al(NO_3)_3$
1x10^{-2}	0.0237	0.0522	0.038	0.0386	0.0293	0.0214	-	0.054	0.0231
2x10^{-2}	0.0252	0.0271	0.0302	0.0272	0.0302	0.0412	0.0077	0.0081	0.0427
3x10^{-2}	0.0338	0.0229	0.0327	0.0259	0.032	0.0274	0.0061	0.0556	0.0337
4x10^{-2}	0.0259	0.0288	0.0334	0.015	0.0293	0.0356	0.0141	0.0426	0.0304
5x10^{-2}	0.0255	0.0263	0.03	0.0291	0.0372	0.0312	0.0162	0.0508	0.0322
6x10^{-2}	0.04	0.0131	0.0358	0.029	0.0271	0.046	0.0365	0.0406	0.0396
7x10^{-2}	0.029	0.0263	0.0293	0.0307	0.0246	0.0348	0.0278	0.0334	0.0419
8x10^{-2}	0.0403	0.0226	0.0292	0.0336	0.0361	0.0321	0.0259	0.0283	0.0443
9x10^{-2}	0.0299	0.0259	0.0334	0.0234	0.0314	0.0584	0.0069	0.0112	0.0309

Effect of added salt

The effect of added salt was studied by varying concentration of salts from 1x10^{-2} M to 9x10^{-2} M and keeping [NCA] = 1x10^{-3} M and [$KMnO_4$] = 1x10^{-4} M constant. The salts added are $AlCl_3$, $Al(NO_3)_3$, $CaCl_2$, $Ca(NO_3)_2$, $MgCl_2$, KBr, KCl, KI and K_2SO_4. There was no regular trend observed for any of the added salts (Table 5). But, among these salts the rate constant for oxidation of NCA in presence of all salt was more and the trend

will be:

$$KI < KBr < KCl < K_2SO_4 < Ca(NO_3)_2 < CaCl_2 < MgCl_2 < Al(NO_3)_3 < AlCl_3$$

Effect of temperature

The effect of temperature was also studied keeping constant concentration of all other reaction ingredients such as [MnO_4^-], [substrate] and [OH] (Table 6). The temperature variation was at 25 to 60 °C. The energy of activation was calculated by plotting graph between logk verses 1/T, a straight line was obtained. The entropy of activation also calculated in the usual manner by employing bimolecular rate equation:

$$k = \frac{k_B T}{h} e^{\frac{-\Delta E_a^{\#}}{RT}} e^{\frac{\Delta S^{\#}}{R}}$$

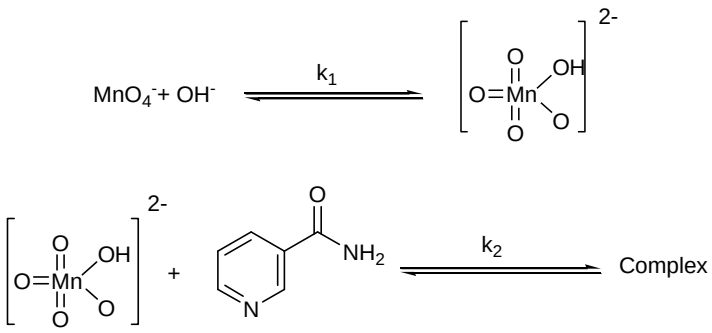
A plot of ($\Delta H^{\#}$) verses ($\Delta S^{\#}$) is linear with slope $\beta = 0.00308$.

Table 6. Thermodynamic parameter. Activation energy E_a = 33.0756732 $KJmol^{-1}$

Entry	Temp.(K)	$\Delta H^{\#}$ (J/mol)	$\Delta S^{\#}$ (J/mol)	$\Delta G^{\#}$ (J/mol)
1	293	30.639671	-0.1782287	82.8606807
2	298	30.598101	-0.1794198	84.0652058
3	303	30.556531	-0.1804919	85.2455698
4	308	30.514961	-0.1807436	86.1839813
5	313	30.473391	-0.1814894	87.2945876
6	318	30.431821	-0.1787859	87.2857401
7	323	30.390251	-0.1797682	88.4553669
8	328	30.348681	-0.1801432	89.4356572

Kinetics and mechanism

The reaction is first order with respect to $KMnO_4$; further the values of k_{obs} are independent of the initial concentration of MnO_4^-. The order of reaction with respect to substrate is less than one. The plot between 1/[substrate] against $1/k_{obs}$ is linear (least square method, r = -0.3566) with an intercept on the rate ordinate. Thus the reaction exhibits Michalis-Menten type kinetics with respect to substrate. Thus, indicate the following overall mechanism and rate law:



$$\text{Complex} \xrightarrow{k} \text{Products}$$

$$[MnO_4^-]_T = [MnO_4^-] + \left[O{=}\underset{\displaystyle O}{\overset{\displaystyle O}{\overset{\displaystyle \|}{\underset{\displaystyle \|}{Mn}}}}(OH)(O) \right]^{2-}$$

$$= [MnO_4^-] + k_1 [MnO_4^-] [OH^-]$$

$$= [MnO_4^-] \{1 + k1 [OH^-]\}$$

$$\text{Rate} = \frac{k\, k_2 [MnO_4^-] [NCA]}{1 + k1 [OH^-]}$$

$$\frac{\text{Rate}}{[MnO_4^-] [NCA]} = \frac{k\, k_2}{1 + k_1 [OH^-]}$$

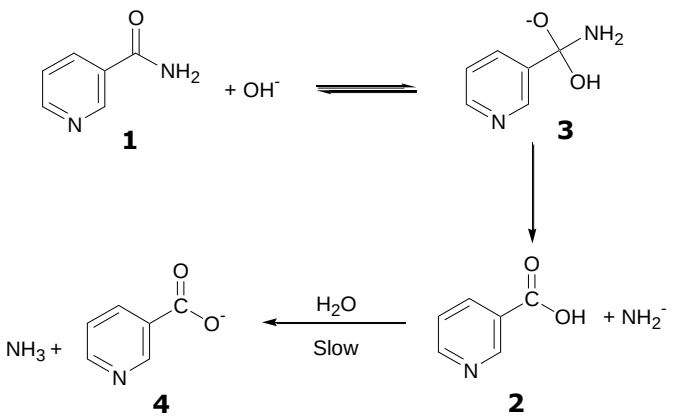
$$k_{obs} = \frac{k\, k_2}{1 + k_1 [OH^-]}$$

$$\frac{1}{k_{obs}} = \frac{1}{k\, k_2} + \frac{k_1}{k\, k_2} [OH^-]$$

The mechanism by which any multivalent oxidant like manganese oxidize, as well as the medium used for oxidation. It is a well known fact that in strong alkaline medium, the stable reduction product $MnO_4.OH^-$ [2] species. This was further supported by Michalis-Menten type of graph. It was observed that, the solution changes from violet to blue and then to light green. The formation of blue color may be due to mixing of violet color of permanganate and green color of manganate [3].

Mechanism of oxidation of niacianamide can be given as presented in Scheme 1.

Scheme 1



Conclusion

The oxidation of niacinamide in alkaline media is carried out using potassium permanganate as an oxidizing agent. The reaction was monitored using UV-Visible spectrophotometer at 525 nm. It was found to be zero order with respect to oxidant, fractional order with respect to hydrogen ion concentration and first order with respect to substrate.

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Full Paper

An atom efficiency, solvent-free synthesis of some new heterocyclic imines and antibacterial activity

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ABSTRACT: *A solvent-free condensation of substituted aryl amines with indole-3-aldehyde in presence of catalytic amount of acetic acid at room temperature in combination with grinding to yield new series of heterocyclic imines (Schiff bases). The simple reaction procedure, short reaction time, no need of organic solvent and high yields make this protocol practical and economically attractive.*

Keywords: *heterocyclic imines; indole-3-aldehyde; solvent-free; grinding*

Introduction

In recent years, there has been a growing interest in the synthesis of bioactive compounds in organic chemistry [1]. One important class of these compounds are imines. For these compounds various biological activities such as insecticidal, anticonvulsant, antifeedant, antituberculosis and antibacterial properties have been reported [2]. On the other hand indole nucleus has wide applications in medicinal chemistry. It is also reported that, indole nucleus is one of the most ubiquitous scaffolds found in natural products, pharmaceuticals, functional materials and agrochemicals [3]. Several indole derivatives that occur in nature possess pharmacological activity. These include the hapalindole alkaloids, which exhibit significant antibacterial and antimycotic activity. Other examples of indole alkaloids are uleine, aspidospermidine, ibophyllidine alkaloids, brevicolline and numerous tryptamine derivatives which exhibit broad spectrum of activities [4].

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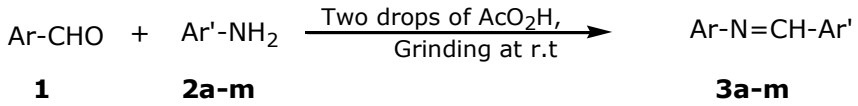
Schiff bases are well known because of their wide applications and are useful intermediates in organic synthesis [5]. Schiff bases were commonly synthesized by the reaction of aryl amines with aryl aldehydes or acetophenones [6] using organic solvent. Recently various modified synthetic protocols have gained popularity, which including environmentally benign solvents such (water or supercritical CO_2), recyclable reaction medium (PPG), and solvent-free conditions [7]. These reaction media and solvent-free conditions increasingly used in organic synthesis because it generates products in good yields. Thus utilization of non-toxic chemicals, renewable materials and solvent-free conditions are the key issues of green synthetic strategy. Due to wide range of pharmacological activity and application of solvent-free organic synthesis, promote us towards the synthesis of some new series of heterocyclic imines by the condensation of substituted aryl amines with indole-3-aldehyde under solvent-free environment using grindstone technique.

Material and Methods

Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. ^{1}H NMR spectra were recorded on a Gemini 300 MH_Z instrument in $CDCl_3$ as solvent and TMS as an internal standard. The mass spectra were recorded on EI SHIMADZU-GC-MS spectrometer. Elemental analysis was performed on a Perkin-Elmer 240 CHN elemental analyzer.

***General Procedure for synthesis of heterocyclic imines* 3a-m**

Scheme 1



A mixture of indole-3-aldehyde **1** (0.01 mol) and aryl amines **2** (0.01 mol) was thoroughly ground with a pestle in an open mortar at room temperature for 2-3 min. The catalytic amount of acetic acid was added to this reaction mixture and grinding continued for several min (Table 2). On completion of reaction as monitored by TLC, the pale yellow coloured solid was separated out. The obtained solid was diluted with cold water and isolated by simple Buchner filtration and recrystallized from ethanol to give the imines **3a-m**. The physical data of newly synthesized compounds are reported in Table 1.

*(2-Bromo-4-fluoro-phenyl)-(1H-indol-3-ylmethylene)-amine (**3a**):* Pale Yellow. IR (KBr): 3345 (NH), 1620 (C=N), 1450, 1575 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 6.92 (s, 1H, NH), 8.89 (s, 1H, *Azomethine proton*), 7.18-8.14 (m, 8H, Ar-H). ^{13}CNMR ($CDCl_3$), δ: 163.41 (C *of Azomethine*), 160.88 (C *of* Ar-F), 132.56 (2C *of* Ar-C), 115-122 (8C *of* Ar-H), 124.37 (C *of* Ar-Br), 106 (C *of* Ar-C), 127.78 (C *of* Ar-C). MS (m/z): 317 (M^+). Anal.

Calcd. for $C_{15}H_{10}N_2BrF$: C, 56.78; H, 3.15; X (F+Br), 31.23. Found: C, 56.74; H, 3.12; X (F+Br), 31.18.

*(1H-Indol-3-ylmethylene)-(2-iodo-4-nitro-phenyl)-amine (**3b**):* Pale Yellow. IR (KBr): 3358 (NH), 1622 (C=N), 1445, 1578 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$), δ: 6.90 (s, 1H, NH), 8.85 (s, 1H, *Azomethine proton*), 7.18-8.14 (m, 8H, Ar-H). $^{13}CNMR$ ($CDCl_3$), δ: 163.52 (C *of Azomethine*), 157.68 (C *of* Ar-C), 150.87 (C *of* Ar-NO_2), 138.73 (C *of* Ar-C), 112-129 (8C *of* Ar-H), 127.21 (C *of* Ar-C), 104.26 (C *of* Ar-C), 89.24 (C *of* Ar-I). MS (m/z): 391 (M^+). Anal. Calcd. for$C_{15}H_{10}N_3O_2I$: C, 46.03; H, 2.55; X (I), 32.48. Found: C, 46.10; H, 2.51; X (I), 32.53.

*(1H-Indol-3-ylmethylene)-(2,4,6-tribromo-phenyl)-amine (**3c**)*: Pale Yellow. IR (KBr): 3352 (NH), 1618 (C=N), 1448, 1571 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$), δ: 6.92 (s, 1H, NH), 8.87 (s, 1H, *Azomethine proton*), 7.12-8.23 (m, 7H, Ar-H). $^{13}CNMR$ ($CDCl_3$), δ: 163.58 (C *of Azomethine*), 156.27 (C *of* Ar-C), 137.63 (C *of* Ar-C) 112-135 (7C *of* Ar-H), 129.50 (C *of* Ar-C) 127.87 (C *of* Ar-Br), 122.39 (2C *of* Ar-Br), 104.20 (C *of* Ar-C). MS (m/z): 457 (M^+). Anal. Calcd. $C_{15}H_9N_2Br_3$: C, 39.38; H, 1.96; X (Br), 52.51. Found: C, 39.42; H, 1.93; X (Br), 52.55.

*(4-Bromo-2-methyl-5-nitro-phenyl)-(1H-indol-3-ylmethylene)-amine (**3d**)*: Pale Yellow. IR (KBr): 3355 (NH), 1624 (C=N), 1454, 1578 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$), δ: 2.39 (s, 3H, CH_3), 6.91 (s, 1H, NH), 8.88 (s, 1H, *Azomethine proton*), 7.19-8.12 (m, 7H, Ar-H). $^{13}CNMR$ ($CDCl_3$), δ: 163.56 (C *of Azomethine*), 150.64 (C *of* Ar-NO_2), 147.52 (C *of* Ar-C), 140.13 (C *of* Ar-C), 137.85 (C *of* Ar-C) 112-136 (7C *of* Ar-H), 127.79 (C *of* Ar-C), 120.98 ((C *of* Ar-Br), 104.41(C *of* Ar-C), 12.75 (C, *of* CH_3).

*(5-Bromo-2,4-dimethyl-phenyl)-(1H-indol-3-ylmethylene)-amine (**3e**):* Pale Yellow. IR (KBr): 3348 (NH), 1617 (C=N), 1450, 1572 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$), δ: 2.35 (s, 6H, *two* CH_3) 6.89 (s, 1H, NH), 8.91 (s, 1H, *Azomethine proton*), 7.14-8.16 (m, 7H, Ar-H). $^{13}CNMR$ ($CDCl_3$), δ: 163.48 (C *of Azomethine*), 144.23 (C, Ar-C), 135.22 (2C *of* Ar-CH_3), 132.69 (2C *of* Ar-C), 115-126 (7C *of* Ar-H), 124.38 (C, *of* Ar-Br), 104.31 (C, Ar-C), 12.81 (2C, *of two* CH_3). MS (m/z): 327 (M^+). Anal. Calcd. for $C_{17}H_{15}N_2Br$: C, 62.38; H, 4.58; X (Br), 24.46. Found: C, 62.42; H, 4.56; X (Br), 24.51.

*(2-Bromo-3,5-dichloro-phenyl)-(1H-indol-3-ylmethylene)-amine (**3f**)*: Pale Yellow. IR (KBr): 3342 (NH), 1622 (C=N), 1453, 1573 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$), δ: 6.90 (s, 1H, NH), 8.93 (s, 1H, *Azomethine proton*), 7.20-8.24 (m, 7H, Ar-H). $^{13}CNMR$ ($CDCl_3$), δ: 163.52 (C *of Azomethine*), 145.27 (C, *of* Ar-C), 138.89 (2C *of* Ar-Cl), 134.73 (C *of* Ar-C), 127.92 (C *of* Ar-C), 124.45 (C, *of* Ar-Br), 112-128 (7C *of* Ar-H), 104.63 (C *of* Ar-C). MS (m/z): 368 (M^+). Anal. Calcd. for $C_{15}H_9N_3Cl_2Br$: C, 48.91; H, 2.44; X (Cl+Br), 40.76. Found: C, 48.96; H, 2.41; X (Cl+Br), 40.81.

*(3-Chloro-5-iodo-phenyl)-(1H-indol-3-ylmethylene)-amine (**3g**):* Pale Yellow. IR (KBr): 3350 (NH), 1621 (C=N), 1445, 1576 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 6.90 (s, 1H, NH), 8.86 (s, 1H, *Azomethine proton*), 7.18-8.15 (m, 8H, Ar-H). $^{13}CNMR$ ($CDCl_3$), δ: 163.52 (C *of Azomethine*), 146.13 (C, *of* Ar-C), 138.67 (C *of* Ar-Cl), 134.81 (C *of* Ar-C), 127.86 (C *of* Ar-C), 110-130 (8C *of* Ar-H), 104.73 (C, *of* Ar-C), 90.27 (C *of* Ar-I). MS (m/z): 380.5 (M^+). Anal. Calcd. for $C_{15}H_{10}N_2ICl$: C, 47.30; H, 2.62; X (I+Cl), 42.70. Found: C, 47.24; H, 2.65; X (I+Cl), 42.75.

*(4-Bromo-phenyl)-(1H-indol-3-ylmethylene)-amine (**3h**):* Pale Yellow. IR (KBr): 3354 (NH), 1618 (C=N), 1449, 1571 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 6.92 (s, 1H, NH), 8.89 (s, 1H, *Azomethine proton*), 7.13-8.18 (m, 9H, Ar-H). $^{13}CNMR$ ($CDCl_3$), δ: 163.59 (C *of Azomethine*), 148.24 (C, *of* Ar-C), 111-136 (9C *of* Ar-H), 127.80 (C *of* Ar-C), 130.27 (C *of* Ar-C), 120.68 (C *of* Ar-Br), 104.29 (C *of* Ar-C). MS (m/z): 299 (M^+). Anal. Calcd. for $C_{15}H_{11}N_2Br$: C, 60.20; H, 3.67; X (Br), 26.75. Found: C, 60.23; H, 3.65; X (Br), 26.78.

*(2-Bromo-phenyl)-(1H-indol-3-ylmethylene)-amine (**3i**):* Pale Yellow. IR (KBr): 3348 (NH), 1621 (C=N), 1450, 1568 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 6.91 (s, 1H, NH), 8.88 (s, 1H, *Azomethine proton*), 7.15-8.14 (m, 9H, Ar-H). $^{13}CNMR$ ($CDCl_3$), δ: 163.61 (C *of Azomethine*), 148.21 (C, *of* Ar-C), 111-133 (9C *of* Ar-H), 128.56 (C *of* Ar-C), 130.23 (C *of* Ar-C), 155.96 (C *of* Ar-Br), 104.37 (C *of* Ar-C). MS (m/z): 299 (M^+). Anal. Calcd. for $C_{15}H_{11}N_2Br$: C, 60.20; H, 3.67; X (Br), 26.75. Found: C, 60.16; H, 3.62; X (Br), 26.81.

*(6-Chloro-benzothiazol-2-yl)-(1H-indol-3-ylmethylene)-amine (**3j**):* Pale Yellow. IR (KBr): 3346 (NH), 1620 (C=N), 1448, 1570 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 6.92 (s, 1H, NH), 8.90 (s, 1H, *Azomethine proton*), 7.16-8.12 (m, 8H, Ar-H). $^{13}CNMR$ ($CDCl_3$), δ: 163.41 (C *of Azomethine*), 156.45 (C, Ar-C *of benzothiazol ring*), 148.57 (C, Ar-C), 138.23 (C, Ar-C), 135.14 (C *of* Ar-Cl), 132.77 (2C *of* Ar-C), 112-128 (8C *of* Ar-H), 104.38 (C, Ar-C). MS (m/z): 311 (M^+). Anal. Calcd. for $C_{16}H_{10}N_3SCl$: C, 61.73; H, 3.21. Found: C, 61.67; H, 3.19.

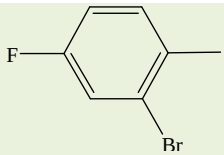
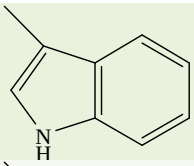
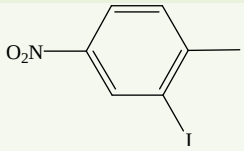
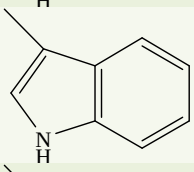
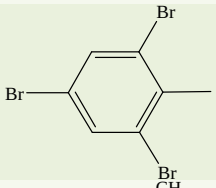
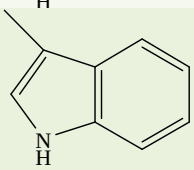
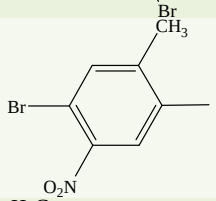
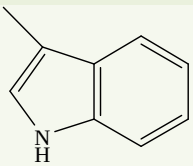
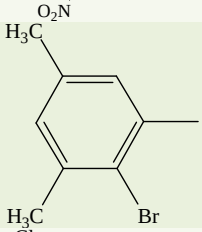
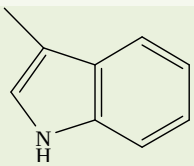
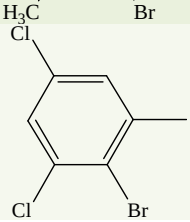
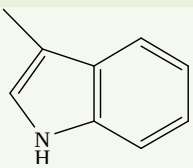
*2-[(1H-Indol-3-ylmethylene)-amino]-1,4,5,7-tetrahydro-purin-6-one (**3k**)*: Pale Yellow. IR (KBr): 3348 (NH), 1668 (C=O), 1622 (C=N), 1446, 1568 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 2.53 (d, 1H), 3.72 (d, 1H), 6.90 (s, 1H, NH), 7.18 (s, 2H, NH), 8.88 (s, 1H, *Azomethine proton*), 7.26-8.12 (m, 6H, Ar-H). $^{13}CNMR$ ($CDCl_3$), δ: 181.58 (C *of* C=O), 163.46 (C *of Azomethine*), 158.34 (C, *of purin ring*), 155.49 (C *of purin ring*), 132.71 (2C *of* Ar-C), 112-123 (5C *of* Ar-H), 104.47 (C, Ar-C), 78.24 (C, CH of purin ring), 56.69 (C, CH of purin ring). MS (m/z): 280 (M^+). Anal. Calcd. for $C_{14}H_{12}N_6O$: C, 60.0; H, 5.0. Found: C, 59.96; H, 4.98.

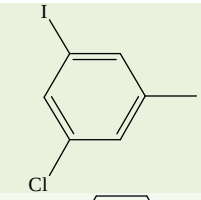
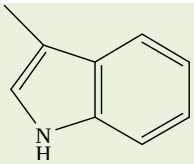
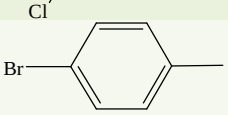
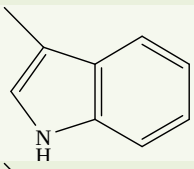
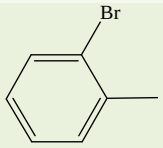
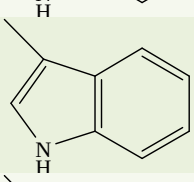
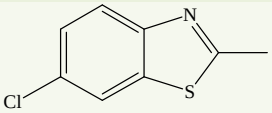
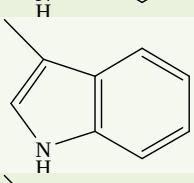
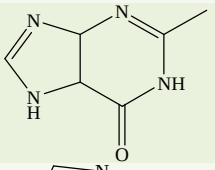
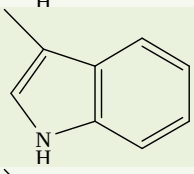
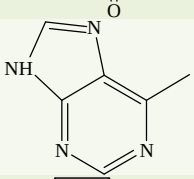
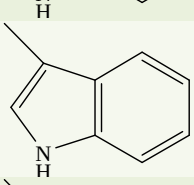
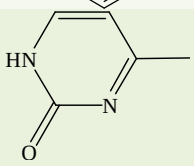
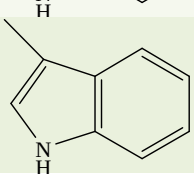
*(1H-Indol-3-ylmethylene)-(9H-purin-6-yl)-amine (**3l**)*: Pale Yellow. IR (KBr):

3350 (NH), 1619 (C=N), 1448, 1571 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 6.88 (s, 2H, NH), 8.86 (s, 1H, *Azomethine proton*), 7.18-8.10 (m, 7H, Ar-H), $^{13}CNMR$ ($CDCl_3$), δ: 163.46 (C *of Azomethine*), 158.23 (C, *of purin ring*), 155.42 (C *of purin ring*), 149.45 (C, *of purin ring*), 148.78 (C, Ar-H), 144.23 (C, Ar-C), 132.71 (2C *of* Ar-C), 114-125 (5C *of* Ar-H), 104.52 (C, Ar-C). MS (m/z): 262. Anal. Calcd. for $C_{14}H_{10}N_6$: C, 64.12; H, 3.81. Found: C, 64.15; H, 3.85.

*4-[(1H-Indol-3-ylmethylene)-amino]-1H-pyrimidin-2-one (**3m**):* Pale Yellow. IR (KBr): 3347 (NH), 1670 (C=O), 1618, (C=N), 1452, 1570 (C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 6.85 (s, 2H, NH), 8.92 (s, 1H, *Azomethine proton*), 7.18-8.10 (m, 7H, Ar-H). $^{13}CNMR$ ($CDCl_3$), δ: 179.6 (C=O), 163.52 (C *of Azomethine*), 158.37 (C *of pyrimidine ring*), 132.67 (2C *of* Ar-C), 128.22 (C, CH-*pyrimidine*) 112-127 (5C *of* Ar-H), 104.47 (C, Ar-C), 96.87 (C, CH-*pyrimidine*). MS (m/z): 238 (M^+). Anal. Calcd. for $C_{13}H_{10}N_4O$: C, 65.54; H, 4.20. Found: C, 65.59; H, 4.23.

Table 1. Physical data of some new heterocyclic imines **3a-m**

Product	Ar′	Ar	M.P. (^{0}C)
3a			140-142
3b			110-113
3c			125-128
3d			160-163
3e			102-105
3f			95-97

3g			120-123
3h			128-131
3i			137-140
3j			170-173
3k			210-212
3l			220-223
3m			153-155

Antimicrobial assay

The antibacterial activities of the synthesized compounds (**3a-m**) were determined by agar well diffusion method [8]. The compounds were evaluated for antibacterial activity against gram-positive bacteria *Bacillus subtilis* [MTCC 2063], *Staphylococcus aureus* [MTCC 2901] and gram-negative bacteria *Escherichia coli* [MTCC 1652] and *Salmonella typhi* were procured from Institute of Microbial Technology (IMTech), Chandigarh, India. The antibiotic penicillin (25 µg) used as reference drug for antibacterial activity, respectively. Dimethyl sulphoxide (1%, DMSO) used a control without compound.

The culture strains of bacteria were maintained on nutrient agar slant at 37 ± 0.5 ^{0}C for 24 h. The antibacterial activity was evaluated using nutrient agar plate seeded with 0.1 mL of respective bacterial culture strain suspension prepared in sterile saline (0.85%) of 10^{5} CFU/mL dilutions. The wells of 6 mm diameter were filled with 0.1 mL of

compound solution at fixed concentration 25 µg/mL separately for each bacterial strain. All plates were incubated at 37 ± 0.5 ^{0}C for 24 h. Zone of inhibition were noted in mm at Table 3.

Results and Discussion

Synthesis

In continuation of earlier research program [9]**,** here we wish to report for first time a typical condensation between substituted aryl amines **2a-m** and indole-3-aldehyde (**1**) at room temperature with combination of grinding to afford heterocyclic imines (Scheme-**1**). In grindstone technique reaction occurs through generation of local heat by grinding of crystal of substrate and reagent by mortar and pestle. Reactions are initiated by grinding with transfer of very small amount of energy through friction. In some cases, the mixture and reagent turn to glassy material. Such reactions are simple to handle, reduce pollution, comparatively cheaper to operate and may be regarded as more economical and ecologically favorable procedure in chemistry.

In order to optimize the capability and efficiency of present method, we carried out above reaction by conventional method using ethanol as reaction solvent (Table 2). We found that solid state reaction occur more efficiently and more selectively than does the solution reaction. Since molecules in the crystal are arranged tightly and regularly. Thus, in grindstone technique reaction occurs efficiently in terms of clean reaction conditions, operationally simple, short reaction time giving quantitative yields of product and environmentally and ecofriendly. In view of these observations we turned our attention towards various substituted aryl amines. In all cases, reaction proceeds smoothly in high yields using grindstone technique.

Table 2. Comparison of grinding technique with conventional method in condensation of substituted aryl amines with indole-3-aldehyde

Entry	Grinding (r.t.)[a]		Ethanol reflux[b]	
	Time (min)	Yield (%)[c]	Time (h)	Yield (%)[c]
3a	08	85	2.30	65
3b	10	88	3.10	68
3c	08	86	2.40	66
3d	09	89	3.00	68
3e	11	85	3.00	67
3f	10	90	2.50	70
3g	08	83	2.10	63
3h	06	85	1.00	67
3i	09	88	2.30	70
3j	12	84	3.30	66
3k	08	90	2.30	72
3l	10	91	2.40	73
3m	07	86	1.00	68

[a] Reaction carried out at room temperature.
[b] Reaction in solvent media.
[c] Yield of isolated product

Structure of newly synthesized compounds were established on the basis of their spectroscopic data, were IR spectra of condensed products **3** display disappearance of band at 1710 due to C=O of indole-3-aldehyde and appearance of band at 1620 cm^{-1} due to C=N formed. The ^{1}H NMR spectra showed the presence of azomethine proton at range 8.86-8.92 ppm.

Antimicrobial screening

The results of antimicrobial screening data are shown in Table 3. The compounds **3c** and **3f** showed effective activity against *Bacillus subtilis* and *Staphylococcus aureus* in comparison with standard drug. Compounds **3f** showed near to par activity against *Salmonella typhi.* Only compounds **3k** and **3m** showed potent activity against *Bacillus subtilis* and on the other hand the remaining compounds of the series showed moderate antibacterial activity against all tested microbes. The compounds **3b**, **3e**, **3h** and **3i** were inactive towards the growth of inhibition against *Bacillus subtilis, Escherichia coli and Salmonella typhi.*

Table 3. Antimicrobial activity of synthesized compounds (**3a-m**)

Product	A	B	C	D
3a	17	19	15	21
3b	14	18	17	--
3c	24	26	23	20
3d	19	21	16	18
3e	13	17	--	15
3f	25	26	22	24
3g	13	16	15	12
3h	--	12	10	--
3i	14	10	16	--
3j	20	22	18	14
3k	24	22	19	17
3l	16	24	20	16
3m	23	15	18	21
Standard drug	**26**	**26**	**26**	**26**

Zone of inhibitions are expressed in mm.
A = *Bacillus subtilis*, B = *Staphylococcus aureus,* C = *Escherichia coli,* D = *Salmonella typhi,* Standard drug = Penicillin.

Conclusion

In summary, we have synthesized novel heterocyclic imines by condensation of substituted aryl amines under solvent-free grinding technique. This method often lead to a remarkable decrease in reaction times, simplicity of operation, increased yield, easier workup and matches with green chemistry protocols. The preliminary *in vitro* antimicrobial screening the efficiency of compounds **3c** and **3f** in gram positive bacteria, to the compound **3l** to *Staphylococcus aureus* only and compound **3f** the antimicrobial activity against *Salmonella typhi* only.

Acknowledgments

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[1] (a) Clearq, E. de in: Jonnson (Ed.), Advance in antiviral drug, vol. 1, Jai. Greenwich, 1993; (b) Thomas, G. Medicinal Chemistry, John Wiley and Sons Ltda. 2000; (c) Doerge, R. F. In: Wilson and Gisvolds, Textbook of Organic Medicinal and Pharmaceutical Chemistry, 8th ed. J. B. Lippncott company, 1982; (d) Negwer, M.; Scharnow, H-G. *Organic-Chemical Drugs and Their Synonyms, 8th Edition.* Wiley-vcly. Weinheim, 2001; (e) Katzung, B .G. Basic Clinical Pharmacology, 8th ed. MCG-Hill, 2001; (f) O'neil, M. J.; Smith, A.; Heckelman, T. E.; Dudavari, F. Merck Index, an Encyclopedia of chemicals, Drug and biological, 13th ed. Merck, Whitehouse station, NG, 2001.

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Full Paper

Symmetrical molecules from reaction of β-cyclohexanediones with acetylenedicarboxylic acid in aqueous medium

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ABSTRACT *In an attempt to obtain Michael adducts in aqueous medium, 1,3-cyclohexanedione (**1**) or dimedone (**2**) and acetylenedicarboxylic acid monopotassium (**3**) were dissolved in water and heated to reflux. Under these conditions, two products were isolated from the reaction mixture between **1** and **3**: 2-[1-(2,6-dioxocyclohexyl)ethyl]-1,3-cyclohexanedione (**6**) and a xanthenedione (**7**), which corresponds to the cyclization of **6**. The reaction between **2** and **3** gave only the 2-[1-(4,4-dimethyl-2,6-dioxocyclohexyl)ethyl]-5,5-dimethyl-1,3-cyclohexanedione (**8**).*

Keywords: *xanthenediones; cyclohexanediones; symmetrical molecules; Michael addition*

Introduction

Organic reactions in aqueous medium present several potential advantages [1], since water, as a solvent, is cheap, is not detrimental to the environment, and is not toxic. Moreover, isolation of organic products from the reaction mixture can be accomplished by simple phase separation [2]. Recently, various carbon-carbon bond-forming reactions in aqueous medium have been reported, e.g: (i) Diels-Alder reactions [3], (ii) Michael additions [4], (iii) Claisen rearrangements [5], (iv) Barbier-type allylations [6], and (v) aldol reactions (Mukaiyama) [7].

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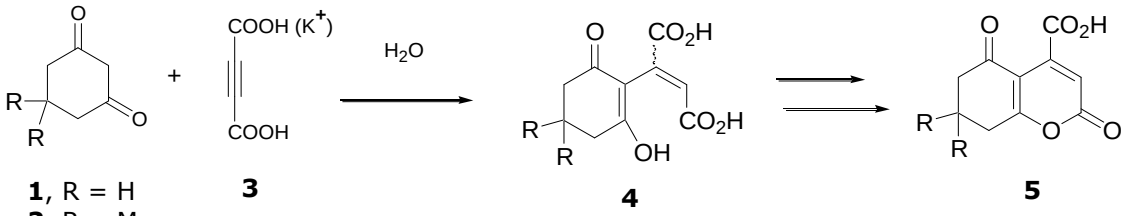
Our research was focused on the synthesis of polyfunctional scaffolds (such as **4** and **5** (Scheme 1) [8], by means of the Michael addition reaction of cyclic β-dicarbonyl compounds such as **1** (1,3-cyclohexanedione) or **2** (dimedone), and acetylenedicarboxylic acid (**3**) in aqueous medium.

The reaction of 1,3-diketones (**1** or **2**) with acetylenedicarboxilic acid salt (**3**) in water led, unexpectedly, to the formation of symmetrical molecules by a one-pot, tandem process comprised of Michael addition, decarboxylation, cyclization and elimination.



1, R = H
2, R = Me

3

4

5

Scheme 1. Hypothetical Michael addition reaction.

This unexpected but interesting result prompted us to report it, along with a possible reaction mechanism, which is discussed below.

Material and Methods

General

^{1}H and ^{13}C NMR spectra were obtained using a Bruker AVANCE DPX-300 spectrometer and were recorded at 300 and 75 MHz respectively. IR spectrum was obtained using a Perkin Elmer model 783. UV absorption spectroscopy was performed with a Hitachi U-3000 spectrophotometer. All reagents and chemicals were obtained from Acros Organic Company and were used as received unless otherwise noted.

Typical procedure

A mixture of β-diketone (**1** or **2**, 10 mmol) and salt **3** (3.5 mmol) in water (15 mL) was stirred for 3 h under reflux, and the reaction was monitored by TLC. The mixture was then extracted with $CHCl_3$ (3 x 20 mL), the combined organic layers dried over $MgSO_4$ (10 min), filtered, and evaporated. Flash chromatography (silica gel) using ethyl acetate/hexane (3:2) gave the products **6** and **7**. Compound **8** was isolated in similar fashion.

2-[1-(2,6-dioxocyclohexyl)ethyl]-1,3-cyclohexanedione (**6**). Yield: 5%, solid. UV (chloroform): 258 nm; IR: ν_{max} (KBr): 3418, 2971, 1580, and 1456; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.42 (d, J= 7.4 Hz, 3H); 1.80 – 1.88 (m, 4H); 2.20 – 2.48 (m, 8H); 4.06 (q, J= 7.4 Hz, 1H); 12.09 (sl, 1H); 12.88 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz,) δ (ppm):

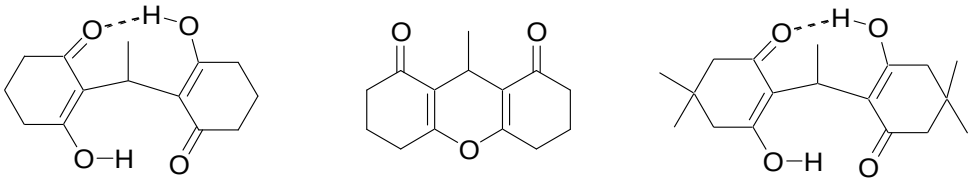
15.9 (CH_3): 19.8 (CH_2); 23.9 (CH); 32.2 (CH_2); 33.3 (CH_2); 118.8 (C); 190.9 (C); 191.1 (C=O).

9-methyl-2,3,4,5,6,7,8,9-octahydro-1H-1,8-xanthenedione (**7**): Yield: 30%, solid, m.p: 53-55°C. UV (chloroform): 243 and 296 nm; IR ν_{max} (KBr): 3412; 2958, 1647, 1616, 1458, 1372 and 1177. ^{1}H-NMR ($CDCl_3$, 300 MHz,) δ (ppm): 1.03 (d, J= 6.5 Hz, 3H); 1.97 – 2.03 (m, 4H); 2.31 – 2.88 (m, 8H); 3.62 (q, J= 6.5 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 20.4 (CH_3); 20.8 (CH_2); 22.1 (CH_2); 27.0 (CH); 37.0 (CH_2); 117.9 (C); 164.3 (C); 197.3 (C=O). MS m/z (relative intensity, %) 232 [M+] (4.0); 218 (15.2); 217 (100); 175 (4.8); 105 (5.7); 91 (9.3).

2-[1-(4,4-dimethyl-2,6-dioxocyclohexyl)ethyl]-5,5-dimethyl-1,3-cyclohexanedione (**8**): Yield: 15%, solid, m.p: 139-141°C UV (chloroform): 260 nm. IR ν_{max} (KBr): 3303, 3263, 2963, 1671, 1489, 1170. ^{1}H-NMR: ($CDCl_3$, 300 MHz) δ (ppm): 1.03 (s, 12H); 1.45 (d, J= 7.4 Hz, 3H); 1.98 – 2.67 (m, 8H); 4.07 (q, J= 7.4 Hz,1H); 12.45 (s,1H). ^{13}C-NMR: ($CDCl_3$, 75 MHz) δ (ppm): 15.6 (CH_3); 23.5 (CH); 26.4 (C); 29.6 (CH_3); 31.1 (CH_2); 46.9 (CH_2); 117.6 (C); 189.4 (C); 189.6 (C=O).

Results and Discussion

Upon heating to reflux temperature, various polar products were formed (TLC); two major products were isolated by flash chromatography, and their structure determined by ^{1}H- and ^{13}C- NMR. The less polar material was identified as being compound (**6**) the more polar, was identified as the xanthenedione (**7**), which corresponds to the cyclization of **6** followed by dehydration (Figure 1). The preparation of these compounds has been reported in the literature, but they were obtained by different methods [9].



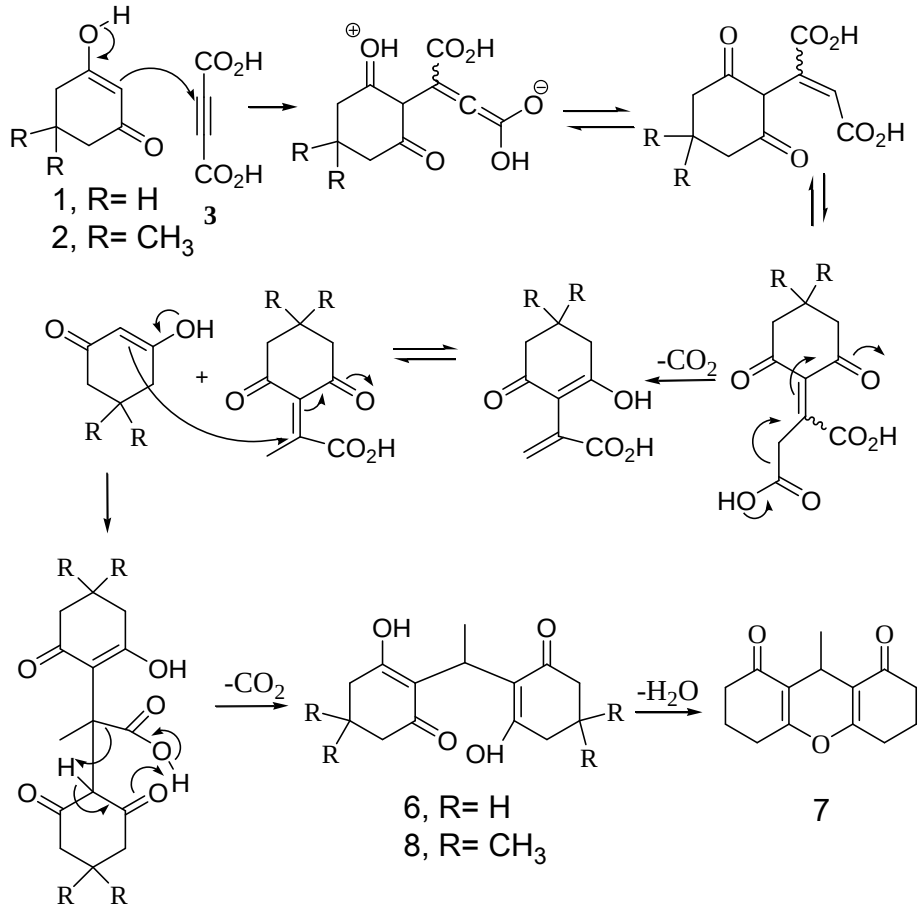
6 **7** **8**

Figure 1. Structures of the symmetrical molecules.

Dimedone (**2**) was also subjected to the same reaction conditions with **3**, but, in this case, only compound **8** was observed. Compound **1** is very soluble in the reaction medium and decomposes quite extensively under these conditions, leading to lower yields. Compound **2** is partially soluble in the reaction medium and reacts with **3** giving poor yields of **8**; however, a large amount of unreacted starting material is recovered. Also, no cyclization product derived from **8** was detected, as observed in the reaction of

1. Horning and Horning [9] report that the cyclization of **8** is achieved by treatment with an 8:2 mixture of methanol and water, under reflux, in the presence of dilute HCl. We propose the following mechanism to explain our observations (Scheme 2).

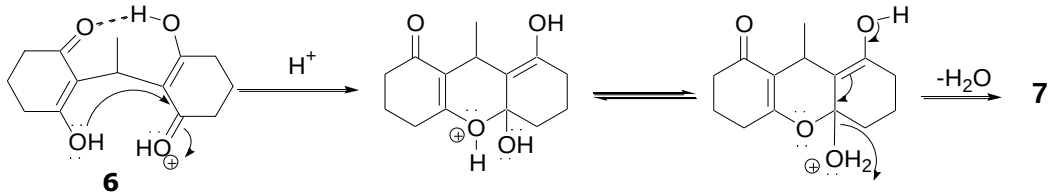
Enols are notoriously soft nucleophiles (neutral), which react with α,β-unsaturated carbonyl compounds preferentially *via* conjugate addition. Since the enol form is favored in 1,3-dicarbonyl compounds, the conjugate addition may take place in neutral or slightly acidic environment [10]. It is plausible that the reaction is initiated by Michael addition followed by fast proton exchange and decarboxylation. Thus, the enol tautomerizes and undergoes a new Michael addition with 1,3-diketone, leading to a tetrahedral intermediate that collapses with loss of CO_2 to give compounds **6** or **8**. Cyclization followed by dehydration leads to the formation of **7**.



Scheme 2. Mechanism proposed to formation of the compounds **6-8**.

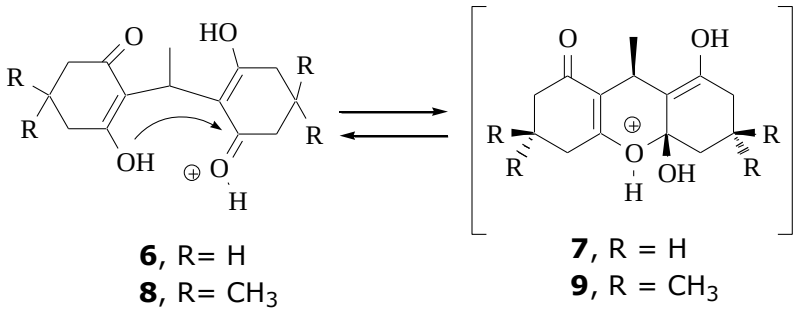
Conversion of **6** → **7** (Scheme 3) occurs under mild conditions and can be observed by repeatedly taking NMR measurements of a solution of **6** in $CDCl_3$ on the course of a few days, where one can observe the gradual disappearance of signals attributed to **6**, concurrent with the appearance of peaks related to **7**. Due to the slight acidic character of $CDCl_3$ [11], we believe this conversion can be rationalized by the

mechanism below.



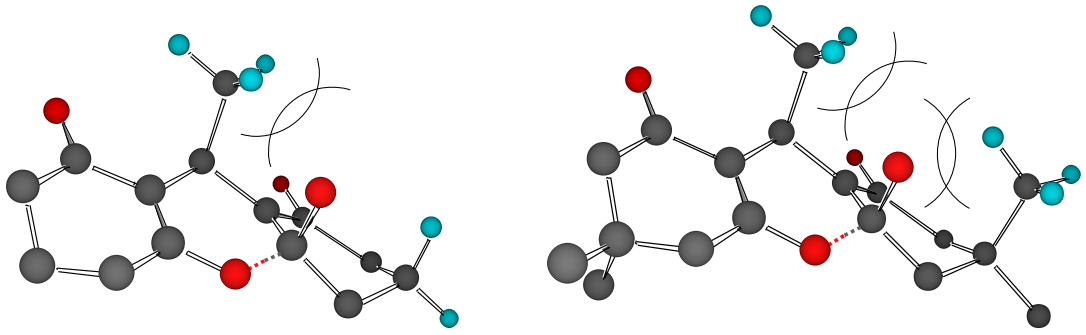
Scheme 3. Mechanism proposed to formation of compound **7** in $CDCl_3$.

The difference in reactivity between **6** and **8** (Scheme 4) was rationalized based on the fact that, in the transition state that leads to intermediate **9**, an adverse 1,3-diaxial interaction between the developing tertiary alcohol (formed prior to the elimination reaction) and one of the methyl groups of dimedone considerably raises the activation energy required to convert **8** into the corresponding cyclized product. The cartoon structures **A** and **B** (Scheme 4) illustrate our proposal [12]. Although in both cases it is possible to recognize that there is some steric blocking between the tertiary hydroxyl and the methyl group at the linker, it is seen that the extra steric interference in **B** plays a role in the rate of this reaction. It is then tempting to predict that deletion of the methyl group at the linker would lead to a faster rate of cyclization than that observed for compound **6**.



6, R= H
8, R= CH_3

7, R = H
9, R = CH_3



A B

Scheme 4. 1,3-diaxial interactions between the budding tertiary alcohol (formed prior to the elimination reaction) and one of the methyl groups of dimedone (cartoon B).

Conclusion

We have presented an unexpected sequence of reactions in aqueous medium that led to formation of compounds possessing a symmetrical framework. Acetylenodicarboxylic acid has played the role of a synthetic equivalent of acetaldehyde towards reaction with a dicarbonyl compound. These results illustrate an unusual mechanistic pathway.

Acknowledgments

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[12] Models were generated using the Chem3D implementation of MM2 (CambridgeSoft; SN 251657); whenever possible, transition state geometries were calculated using the Chem3D implementation of MOPAC, at the PM3 level of theory. The structures of charged intermediates were built using MM2, followed by energy minimization using MOPAC, at the PM3 level of theory; charges were simulated using the Mulliken model.

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Short Communication

A descrição matemática do comportamento eletroquímico durante o processo da sobreoxidação anódica dos polímeros condutores no meio muito ácido

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ABSTRACT: *The electrochemical behavior of the system with the anodic overoxidation of conducting polymers was described mathematically. The balance equation system describing it was analyzed using the linear stability theory and bifurcation analysis. The stable steady-state conditions and oscillatory instability conditions were found.*

Keywords: *conductive polymers; polypyrrole; polythiophene; overoxidation; oxidative degradation*

Os polímeros condutores são uma das classes de compostos mais investigados nas últimas 4 décadas e continuam atraindo o interesse de vários grupos de pesquisas [1-6]. Eles podem ser usados em aparelhos eletroquímicos, em sensores e biossensores, microcondensadores, elétrodos para finalidades diferentes.

Porém, os polímeros não podem ser usados sob potenciais anódicos altos, já que o processo da degradação eletroquímica irreversível começa a se realizar. A instabilidade do revestimento polimérico se manifesta nas instabilidades eletroquímicas que sobrevêm ao se sobreoxidar o polímero. Se o potencial da sobreoxidação do polímero for inferior ao da polimerização do monômero, poder-se-á afirmar a presença do "paradoxo de politiofeno" [2, 3], que se vê na semelhança dos espectros de infra-vermelho (IV) dos politiofenos e polibitiofenos eletrossintetizados e sobreoxidados. É por isso que não se usa a copolimerização de pirrol com tiofeno [1, 2]. A instabilidade do revestimento polimérico pode causar a instabilidade eletroquímica neste processo.

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Em meio ácido, o comportamento neste sistema se torna mais complicado, porque a reação da sobreoxidação do polímero é pH-dependente. Os prótons se formam durante a sobreoxidação como produto lateral [4]; então, o processo da formação deles (conforme o esquema "Prótons + PC → PCS + Mais prótons") é autodeterminado. O pH da solução diminui durante a reação (como mesmo na eletropolimerização). Os prótons a se formar atacam o sistema conjugado (quebrado) do polímero condutor sobreoxidado, para formar os produtos da menor condução da corrente.

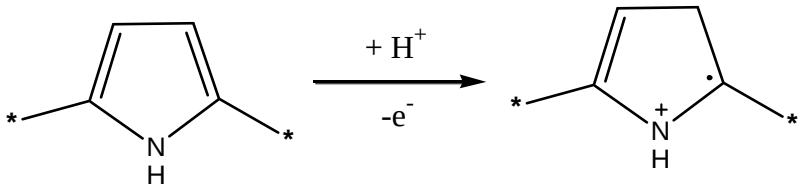
Para determinar as causas possíveis das instabilidades eletroquímicas sobrevindas durante este processo e o mecanismo de aparecimento delas, nós construímos um modelo matemático capaz de descrever adequadamente os processos eletroquímicos neste sistema e o investigamos através da teoria da instabilidade linear e análise de bifurcações.

O SISTEMA E O MODELO

O mecanismo da sobreoxidação dos polímeros condutores dos compostos heterocíclicos de 5 membros

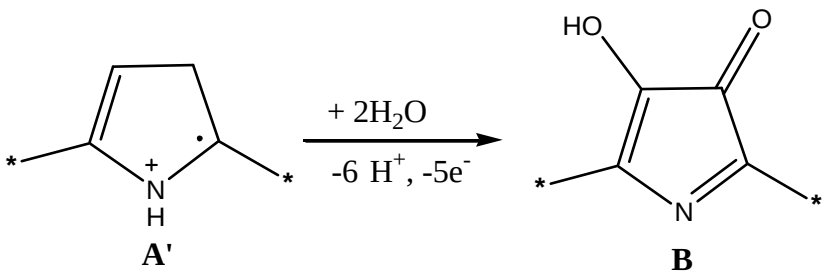
Conforme descrito por Ansari [4], o polímero condutor A, sobreoxidando-se e sofrendo o ataque de prótons forma o radical-cátion A' (o mecanismo é mostrado para o anel heterocíclico que age neste processo para o caso de pirrol), Esquema 1.

Esquema 1



O radical-cátion **A'** depois se oxida reagindo com água da solução e eliminando os prótons. A molécula sobreoxidada **B** já não possui o sistema conjugado (ele é quebrado por não ser coplanar) e a condutividade do polímero diminui irreversivelmente..

Esquema 2



A propósito, podemos referir ao fato histórico da primeira polimerização química

do pirrol, feita em 1916, na presença do peróxido do hidrogênio [5] (o polímero sintetizado chamava-se "o pirrol preto" e possuia pouca condutividade, já que seu sistema conjugado foi descontinuado pelos ataques de prótons).

Neste artigo, vamos descrever o comportamento deste sistema no modo potenciostático, por ser mais usado nos processos da síntese de polímeros condutores [6].

A descrição matemática do processo da sobreoxidação do revestimento polimérico

Para descrever matematicamente os processos neste sistema no modo potenciostático, podemos introduzir duas variáveis:

Θ_d - o grau da formação do composto B a partir da superfície do eletrodo completamente coberta pelo composto A.

h - a concentração de prótons na camada pré-superficial.

Suposições

Para simplificar o modelo matemático deste processo, suponhamos que o líquido se está intensamente agitado (para menosprezar a influência do fluxo da convecção), o eletrólito de suporte está em excesso, pois podemos menosprezar a influência do fluxo da migração. A distribuição concentracional de prótons na camada de difusão é suposta a ser lineal e a espessura da camada constante e igual a δ.

O polímero sobreoxidado

Se forma a partir do polímero condutor normal (A) quando ele se sobreoxida e muda a sua estrutura reagindo com os prótons. A equação do balanço do polímero sobreoxidado pode ser descrito como:

$$\frac{d\Theta_d}{dt} = G_{\max}^{-1}(v_1 - v_2) \equiv F_1$$

Sendo v_1 a velocidade da sobreoxidação do polímero, v_2 a velocidade da reação do polímero sobreoxidado com os prótons e G_{max} a concentração superficial máxima do polímero sobreoxidado.

Os prótons

Entram na camada pré-superficial difundindo-se nela. A quantidade de prótons também aumenta durante a sobreoxidação do polímero condutor (pH-dependente). Eles são consumidos reagindo-se com o polímero sobreoxidado. A equação do balanço de prótons então poderá ser descrita como:

$$\frac{dh}{dt} = \frac{2}{\delta}\left(\frac{D}{\delta}(h_i - h) + v_1 - v_2\right) \equiv F_2$$

Sendo h_i a concentração de prótons no interior da solução, D o coeficiente da difusão.

Para simplificar a investigação pelo modelo matemático do processo, supomos que as reações de prótons são de ordem um.

As velocidades da sobreoxidação eletroquímica e da reação do polímero sobreoxidado com prótons são:

$$v_1 = k_1(1-\theta_d)h\exp\left(-\frac{zF}{RT}\phi_0\right);\ v_2 = k_2\theta_d h$$

Sendo k_1 e k_2 as constantes das reações da sobreoxidação e reação do polímero sobreoxidado com prótons, z a quantidade dos elétrons transferidos, F o número de Faraday, R a constante universal de gases, T a temperatura absoluta, φ_0 o salto do potencial relativamente ao potencial da carga zero. Para investigar o comportamento oscilatório deste sistema, é preciso investigar as equações do balanço juntos.

O comportamento eletroquímico deste sistema será descrito usando a teoria da estabilidade linear. A matriz funcional de Jacobi, cujos membros são calculados para o estado estacionário, se vê como:

$$J = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}$$

Sendo

$$a_{11} = \frac{\partial F_1}{\partial \theta_d} = -\frac{h}{G_{\max}}\left(k_1\exp\left(-\frac{zF}{RT}\phi_0\right) + k_2\right);\qquad a_{12} = \frac{\partial F_1}{\partial h} = \frac{1}{G_{\max}}\left(k_1(1-\theta_d)\exp\left(-\frac{zF}{RT}\phi_0\right) - k_2\theta_d\right);$$

$$a_{21} = \frac{\partial F_2}{\partial \theta_d} = -\frac{2h}{\delta}\left(k_1\exp\left(-\frac{zF}{RT}\phi_0\right) + k_2\right)\quad a_{22} = \frac{\partial F_1}{\partial h} = \frac{2}{\delta}\left(k_1(1-\theta_d)\exp\left(-\frac{zF}{RT}\phi_0\right) - k_2\theta_d - \frac{D}{\delta}\right)$$

A condição do estado estacionário estável para um sistema bidimensional de equações pode ser descrita como Tr J<0, Det J >0. Sento TrJ = a_{11} + a_{22} e Det J = $a_{11}a_{22}$-$a_{21}a_{12}$.

Se introduzir as variáveis $k_1\exp\left(-\frac{zF}{RT}\phi_0\right) + k_2 = g$ e

$k_1(1-\theta_d)\exp\left(-\frac{zF}{RT}\phi_0\right)-k_2\theta_d = f$, podem facilmente ver que g é sempre positivo, a_{11} então é sempre negativo, como também a_{21}.

Pode-se ver então que Det $J = -\frac{2fgh}{G_{max}\delta}+\frac{2Dgh}{G_{max}\delta^2}+\frac{2fgh}{G_{max}\delta}=\frac{2Dgh}{G_{max}\delta^2}>0$

durante o processo. Isso exclui a possibilidade da instabilidade monotônica neste sistema, cujas condições para um sistema de duas dimensões são Tr J<0, Det J = 0 durante a reação.

A condição da instabilidade oscilatória pode ser descrita como Tr J = 0, Det J>0. Ela requer a presença das parcelas positivas nos elementos da diagonal principal da matriz de Jacobi. A parcela a_{22} contém a parcela $k_1(1-\theta_d)\exp\left(-\frac{zF}{RT}\phi_0\right)$ podendo ser positiva por causa da formação autocatalítica de prótons durante a reação da sobreoxidação. O requerimento de TrJ=0 nos dará a condição explícita da instabilidade oscilatória.

$$f=\frac{hg\delta}{2G_{max}}+\frac{D}{\delta}$$

Conclusão

1. O sistema eletroquímico da sobreoxidação dos polímeros condutores no meio muito ácido foi investigado matematicamente. Seu modelo matemático foi investigado através da teoria da estabilidade linear e da análise de bifurcações.

2. A condição do estado estacionário se implementa na vasta região dos parâmetros. A instabilidade monotônica é impossível durante a reação.

3. A condição explícita da instabilidade oscilatória também foi achada através dos cálculos, sendo a formação autodeterminada de prótons a causa dela.

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