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Short Communication

Unexpected Formation of Bis(hydrazinecarboximidamide) via Ultrasound Promoted Rearrangement of Epoxy Ketone

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Abstract: An efficient synthesis of aromatic pyrazoles via cyclocondensation of epoxy chalcones with hydrazine is reported. When aminoguanidine hydrochloride is the dinucleophilic specie the reaction leads to a mixture of amidino pyrazole and a minor amount (15%) of an interesting co-product identified as 2,2'-(1,3-diphenylpropane-1,2-diylidene)bis(hydrazinecarboximidamide) dihydrochloride by X-ray diffraction and NMR. A plausible mechanism for the co-product formation via rearrangement of the epoxy chalcone into 1,2-diketone followed by the condensation with aminoguanidine reaction is proposed.

Keywords: α,β-epoxy ketones; pyrazoles; ultrasound; unexpected reaction

1. INTRODUCTION

Pyrazole derivatives are important scaffolds due to their wide applicability in medicinal chemistry, agrochemistry and material chemistry [1, 2]. Therefore, numerous synthetic methods for the preparation of pyrazoles have been developed in the last years. Conventional synthetic approaches involve formation of C-N and C-C bonds via intermolecular [3+2] cycloadditions between 1,3-dipoles and dipolarophiles [3] or formation of two C-N bonds by the condensation between hydrazine derivatives and 1,3-dicarbonyl compounds or their 1,3-dielectrophilic equivalents [4]. Although each method has its utilities and advantages, the reaction of α,β-unsaturated ketones **I** with hydrazines is the most useful approach for the preparation of 1,3,5-trissubstituted pyrazole derivatives due to the work up simplicity, availability of starting materials and great regioselectivity (Figure 1). However, the product of such reaction is an enantiomeric mixture of pyrazolines **II**. In order to obtain 1,3,5-trissubstituted pyrazoles from **I**, it is necessary an oxidation step to convert the pyrazolines **II** into the corresponding aromatic pyrazoles **III** [5]. Another way of preparing aromatic pyrazoles starting from α,β-unsaturated ketones without loss of regioselectivity requires the oxidation of the C=C double bond of chalcones **I** forming α,β-epoxy ketones **IV** followed by the condensation/dehydration steps [6]. The course of these reactions may be defined by using acidic or basic catalysis. Generally, neutral conditions and basic catalysts lead to the formation of 3,5-diaryl-4-hydroxy-4,5-dihydro-1*H*-pyrazoles **V** [7] whereas the presence of acidic medium favors the dehydration of intermediates **V** leading to the pyrazoles **III** [8].

As a part of our ongoing research on the clean ultrasound-promoted synthesis and bioactivity of pyrazole derivatives [9-12] we explored the reactions between epoxy chalcones and hydrazines aiming the scope enlargement for more complex hydrazines as well as the development of cleaner synthetic methods. In this direction, we report here the catalyst-free preparation of a series of aromatic pyrazoles by the

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reaction between epoxy chalcones and hydrazines. We also describe the unprecedented formation of a bis(hydrazinecarboximidamide) from the reaction between epoxy chalcones and aminoguanidine hydrochloride as well as its structural determination by X ray diffraction and NMR.

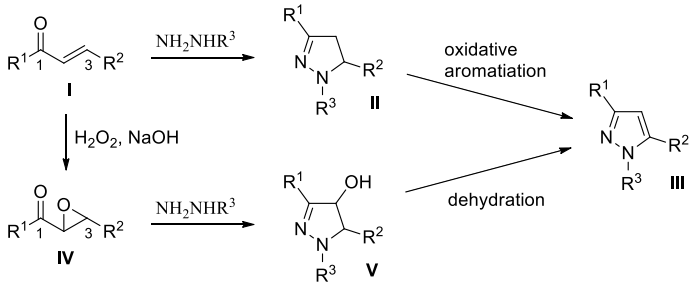


Figure 1. General routes for the synthesis of aromatic pyrazoles starting from chalcones.

2. MATERIAL AND METHODS

2.1 General

Phenyl(3-aryloxiran-2-yl)methanones (epoxy chalcones) **1a-f** were prepared by us following reported procedures [13]. All the chemicals were used without purification as purchased from commercial suppliers. The sonicated reactions were carried out with a microtip probe connected to a 500 W Sonics Vibracell ultrasonic processor operating at 20 kHz at 20% of the maximum power output. Reaction progresses were monitored by thin layer chromatography (TLC) or gas chromatography (GC). Melting point values were determined in open capillary on an Instrutherm DF-3600 II apparatus and are uncorrected. Infrared spectra (IR) were acquired on a JASCO-4100 spectrophotometer as KBr pellets. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired on a Bruker Avance III HD instrument (300 MHz for ^{1}H and 75 MHz for ^{13}C) in 5 mm sample tubes at 298 K in dimethyl sulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as internal reference standard. Low-resolution mass spectra were obtained on a Varian 210 MS connected to a Varian 431 GC. The GC was equipped with a split-splitless injector, cross-linked to a Varian Factor Four™ capillary column (30 m × 0.25 mm), and helium was used as the carrier gas. A Bruker CCD X8 Kappa APEX II diffractometer outfitted with a graphite monochromator and Mo-Kα radiation (λ = 0.71073 Å) was used to collect X-ray data for structural analysis. CCDC 1536540 contains the supplementary for **4a**. Additional Material containing the spectra and selected crystallographic data of the synthesized compounds is available free of charge at http://www.orbital.ufms.br/index.php/Chemistry as a PDF file.

2.2 General procedure for the ultrasound-promoted synthesis of 5-aryl-3-phenyl-1*H*-pyrazoles (2a-f)

Hydrazine hydrate (0.1 g, 2 mmol) was added to a 50 mL vial containing a solution of phenyl(3-aryloxiran-2-yl)methanone **1a-f** (1 mmol) in ethanol (20 mL). The mixture was sonicated for 45 minutes and the resulting solution was cooled overnight in a refrigerator. The solid material which precipitated was filtered off, washed with cold water and dried in a desiccator to give the pure products **2a-f**. The authenticity of compounds **2a-f** was established by comparing their melting points with data reported in literature [6,14-16] as well as by means of their IR and low-resolution mass spectra.

*2.2.1 3,5-Diphenyl-1H-pyrazole (**2a**) CAS number [1145-01-3]*: whitish solid; yield 97%; mp 199-201°C (lit. 199-200°C) [6]; LRMS: *m/z* (%) 220 (100), 117 (7.5), 77 (15); IR (KBr): ν (cm^{-1}) 3290, 3137, 1349, 1264, 1041, 759, 689.

*2.2.2 3-Phenyl-5-(4-tolyl)-1H-pyrazole (**2b**) CAS number [30152-31-9]*: whitish solid; yield 93%; mp 181-183°C (lit. 179-181°C) [14]; LRMS: *m/z* (%) 334 (100), 130 (12.5), 77 (15); IR (KBr): ν (cm^{-1}) 3264, 3112, 1041, 816, 686.

*2.2.3 3-Phenyl-5-(4-methoxyphenyl)-1H-pyrazole (**2c**) CAS number [32664-28-1]*: whitish solid; yield 95%; mp 171-173°C (lit. 167-169°C) [6]; LRMS: *m/z* (%) 250 (100), 178 (10), 77 (9); IR (KBr): ν (cm^{-1}) 3264, 3060, 2842, 2704, 1041, 822, 670.

*2.2.4 3-Phenyl-5-(4-chlorophenyl)-1H-pyrazole (**2d**) CAS number [30152-32-0]*: yellowish solid; yield 91%; mp 220-222°C (lit. 218-220°C) [14]; LRMS:

m/z (%) 254 (100), 198 (10), 89 (9); IR (KBr): ν (cm^{-1}) 3257, 3081, 1493, 1041, 816, 670.

*2.2.5 3-Phenyl-5-(4-trifluoromethylphenyl)-1H-pyrazole (**2e**) CAS number [773858-14-3]*: whitish solid; yield 97%; mp 228-230°C (lit. 142-144°C) [15]; LRMS: *m/z* (%) 288 (100), 77 (7); IR (KBr): ν (cm^{-1}) 3272, 3103, 1668, 1326, 1107, 831, 685.

*2.2.6 3-Phenyl-5-(4-nitrophenyl)-1H-pyrazole (**2f**) CAS number [1233238-15-7]*: yellowish solid; yield 89%; mp 264-266°C (lit. 281°C) [16]; LRMS: *m/z* (%) 265 (100), 235 (25), 165 (7.5), 89 (12.5).

2.3 General procedure for the ultrasound-promoted reaction between phenyl(3-phenyloxiran-2-yl)methanone 1a and aminoguanidine hydrochloride

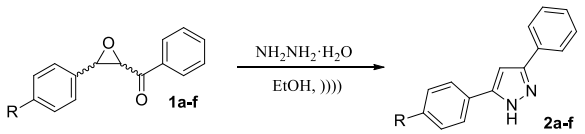
To a 50 mL vial containing a solution of the phenyl(3-phenyloxiran-2-yl)methanone **1a** (0.11 g, 0.5 mmol) and aminoguanidine hydrochloride (0.16 g, 1.5 mmol) in ethanol (20 mL) was added HCl (2 mL). The reaction mixture was sonicated for 45 min. The solvent was removed under vacuum. Methanol was added to the resulting crude material and the insoluble solid was filtered off, washed with cold methanol and dried in a desiccator. Analysis of the NMR spectra and X-ray structure of the isolated material revealed that the obtained product possessed the structure of 2,2'-(1,3-diphenylpropane-1,2-diylidene)bis(hydrazinecarboximidamide) dihydrochloride **4a**. Methanol was evaporated from the filtered solution, the resulting solid was neutralized with 10% KOH and filtered. After washing with cold water the solid was dried in a desiccator. GC-MS analysis revealed two peaks with similar retention times and low-resolution mass spectra in accordance with the structure of the 3,5-diphenyl-1*H*-pyrazole-1-carboximidamide **3a**. The pyrazole was obtained in yield of 79%.

*2.3.1 2,2'-(1,3-Diphenylpropane-1,2-diylidene)bis(hydrazinecarboximidamide) dihydrochloride (**4a**)*: yellowish solid; yield 15%; mp 208-210°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.68 (sa, 3H, NH), 7.53-7.44 (m, 3H, Ar), 7.39-7.36 (m, 2H, Ar), 7.29-7.25 (m, 2H, Ar), 7.19-7.10 (m, 3H, Ar), 7.52 (sa, 3H, NH), 4.40 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.8, 155.8, 153.0, 151.6, 138.1, 131.7, 129.1, 128.8, 128.6, 128.6, 128.3, 125.9, 30.4.

*2.3.2 3,5-Diphenyl-1H-pyrazole-1-carboximidamide (**3a**)*: whitish solid; yield 79%; LRMS: *m/z* (%) 262 (100), 192 (63), 191 (55), 189 (14), 165 (15), 115 (15), 89 (7).

3. RESULTS AND DISCUSSION

The synthetic way has started with the preparation of a series of chalcones which were converted into the corresponding epoxy chalcones by oxidation of the olefinic portions, using the known H_2O_2/NaOH oxidative system, in the presence of ultrasonic irradiation [13]. Next, we investigated the ultrasound-promoted reactions of epoxy chalcones with hydrazine monohydrate in order to verify the possibility of obtaining aromatic pyrazoles without acid catalysis or detection of the intermediates 4-hydroxy-4,5-dihydro-1*H*-pyrazoles. Thus, epoxy chalcones **1a-f** were dispersed in ethanol and treated with hydrazine monohydrate. The pyrazoles **2a-f** were obtained in yields up to 89% after sonication during 40 minutes (Scheme 1).



Scheme 1

The molecular structures of compounds **2a-f** were confirmed by comparing melting points with those reported in literature, IR spectroscopy and low-resolution mass spectrometry. Yields and melting points of the compounds **2a-f** are shown in the Table 1.

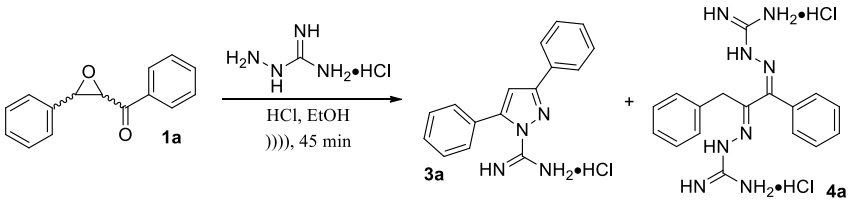
Table 1. Yields and melting points of the 5-aryl-3-phenyl-1*H*-pyrazoles (**2a-f**).

Compound	R	Yield (%)[a]	MP (°C)
2a	H	97	199-201 (199-200) [6]
2b	Me	93	181-183 (179-181) [14]
2c	OMe	95	171-173 (167-169) [6]
2d	Cl	91	220-222 (218-220) [14]
2e	CF_3	97	228-230 (142-144) [15]
2f	NO_2	89	264-266 (281) [16]

[a]Isolated yields.

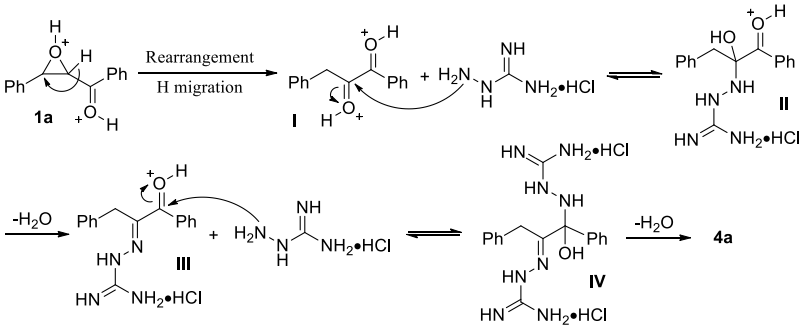
We have also investigated the reaction of epoxy chalcone with aminoguanidine hydrochloride aiming the preparation of 1-amidino pyrazoles, employing the same methodology described above.

As the acid free condition was not effective for converting starting material in the desired product, we added increasing amounts of HCl. Reaction was carried on under ultrasonic conditions. The solvent was removed under vacuum when starting material was not detected by TLC anymore (typically 45 min). GC-MS analysis of the crude residue showed the presence of the desired pyrazole together with an additional peak. Fortunately, this component was separated from the pyrazole by selective solubilization in methanol followed by filtration. Analysis of the NMR spectra and X-ray structure of the isolated material revealed that the obtained product possessed the structure of 2,2'-(1,3-diphenylpropane-1,2-diylidene)bis(hydrazinecarboximidamide) dihydrochloride **4a** (Scheme 2). Further treatment of the methanol solution gave the diphenyl-1*H*-pyrazole-1-carboximidamide **3a** in 79% of yield.



Scheme 2

Due to the novelty of the result for such reactions we searched in the literature a rationalization for the unexpected formation of the bis(hydrazinecarboximidamide). The elucidation came to the light when we found that epoxy chalcones rearrange to 1,2-diketones in concentrated HCl [17]. Indeed, the rearrangement of epoxy chalcones in the presence of acids usually gives mixture of 1,2- and 1,3-diketones by hydride or acyl migration, respectively. Therefore, we propose that the formation of compound **4a** started with the rearrangement of the epoxy chalcone **1a** to the 1,2-diketone **I** which undergo a double acid catalyzed condensation with two equivalents of aminoguanidine hydrochloride according to the mechanism shown in the Scheme 3.



Scheme 3

3.1 X-Ray structural determination

The molecular crystal structure of the compound **4a** was solved using direct methods in the SHELXS program [18]. The final structure was refined using SHELXL [18], in which anisotropic displacement parameters were applied to all non-hydrogen atoms. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. Additional structural information is provided in Table 2.

The structure of the compound **4a** is shown in Figure 2. It shows protonated amidino-nitrogen atoms resulting in a delocalized positive charge in C17 and C18, according to the symmetric bond lengths between C17-N7 = 1.318(2) Å, C17-N8 = 1.314(2) Å and C18-N3 = 1.315(2) Å, C18-N4 = 1.309(3). The charge-balance is achieved by two chloride anions. The Cl(3) has multiplicity equal to 1.0 while the Cl(1)

and Cl(2) have multiplicity equal to 0.5 that totalize two negative charges. A pair of imine C−N double bonds is evident due to the distance of 1.280(2) Å between N1-C14 and N3-C13. Selected crystallographic data for **4a** are shown in the Supplementary Material.

Table 2. Crystallographic data and refinement parameters for **4a**.

Molecular Formula	$C_{17}H_{24}Cl_2N_8O$
Fw [g mol^{-1}]	427.34
T [*K*]	293(2)
Crystal system	Monoclinic
Space group	*C*2/*c*
a [Å]	27.0071(7)
b [Å]	14.7352(4)
c [Å]	10.6471(3)
β [°]	91.5060(10)
V [Å^3]	4235.6(2)
Z	8
$\rho_{calcd.}$ [g cm^{-3}]	1.340
μ [mm^{-1}]	0.332
F(000)	1792
Crystal size [mm]	0.481 x 0.421 x 0.259
θ range [°]	1.57 - 27.19
Limiting indices (*h, k, l*)	$-34 \leq h \leq 34$; $-18 \leq k \leq 18$; $-13 \leq l \leq 13$
Reflections collected	31920
Reflections unique [R_{int}]	4690 [R(int) = 0.0198]
Completeness to θ_{max} [%]	99.4
Absorption correction	Gaussian
Min. and max. Transmission	0.852 and 0.918
Data / restraints / parameters	4690 / 1 / 255
Goodness-of-fit on F^2	1.018
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0429, wR_2 = 0.1160
R indices (all data)	R_1 = 0.0510, wR_2 = 0.1236
Largest diff. peak and hole (e Å^{-3})	0.481 and -0.362

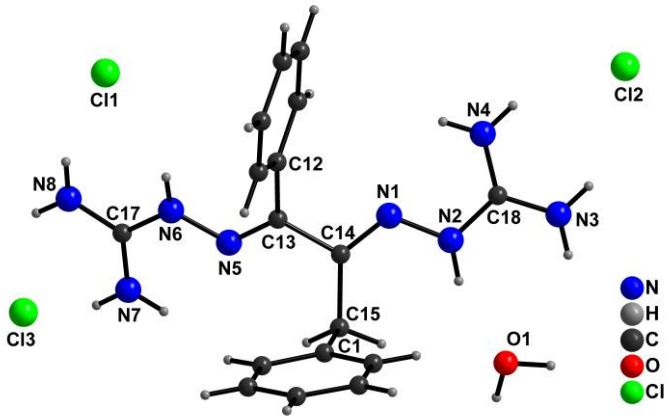


Figure 2. Molecular structure of 2,2'-(1,3-diphenylpropane-1,2-diylidene)bis(hydrazinecarboximidamide) dihydrochloride monohydrate (**4a**).

4. CONCLUSION

In conclusion, a very fast and simple catalyst-free procedure for obtaining aromatic pyrazoles starting from epoxy chalcones was stablished. Pyrazoles bearing both electron-withdrawing and

electron-donating groups were equally synthesized in high yields under green conditions such as ultrasonic irradiation and use of ethanol as reaction medium, which is a bio-renewable product of low toxicity to human health and relatively non-hazardous to the environment. When reactions between epoxy chalcones and aminoguanidine hydrochloride were conducted in the presence of HCl, an interesting unreported co-product was obtained besides the expected amidino pyrazole. The proposed mechanism for the formation of the unexpected bis(hydrazinecarboximidamide) opened a way to explore the viability of using aminoguanidine as an organocatalyst for converting epoxy chalcones into 1,2-diketones. Moreover, the structure of the bis(hydrazinecarboximidamide) was fully elucidated by means of X-ray diffraction and NMR.

5. ACKNOWLEDMENTS

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