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SHORT COMMUNICATION

Optimization of Conditions for the Synthesis and Oxidation of 5,8-Dimethoxy-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one into Novel 2-Methylisoquinoline-1,5,8(2*H*)-trione

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Abstract:

Due to stability issue of isoquinolone's, their *N*-methylation is a challenging task, achieved the synthesis of *N*-methylated 2-methylisoquinoline-1,5,8(2*H*)-trione using readily available precursor 2-(2,5-dimethoxyphenyl) ethanamine *via* multistep strategy, finally oxidation of 5,8-dimethoxy-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one with ceric ammonium nitrate (CAN) lead to target isoquinolone in good yield, further oxidation conditions in final step were optimized using different catalyst ratio, reaction time, and temperature conditions.

Keywords: catalyst ratio; ceric ammonium nitrate; isoquinolone's; *N*-methylation; oxidation

1. Introduction

Kibdelones and isokibdelones are the subgroups of hexacyclic tetrahydroxanthone a family of polyketides natural products [1] isolated from rare Australian actinomycete genus, Kibdelosporangium sp. [2; 3] due to their action as antiproliferative agent and anticancer activities [4], their total synthesis, and their structural fragments i.e isoquinolines [5], isoquinolones [6] and their derivatives [7] synthesis got wide attention [1, 4, 6, 8, 15] these molecular fragments are part of many natural products structure [16], due to which these moieties are used as precursor in the total synthesis of biologically active molecules [17, 18]. It has been observed isoquinolones are not very stable; due to which their *N*-methylation through conventional alkylation methods is a challenging task [16]. Different procedures are reported for the synthesis of a wide variety of derivatives [1, 4, 13] i.e. Avendano *et al*. used Yoshizaki's procedure [19] for *N*-methylation along with CAN as oxidizing agent [20] to synthesis isoquinoline-2,5,8(2*H*)-trione [21]. Our novel target isoquinolone *i.e*. 2-methylisoquinoline-1,5,8(2*H*)-trione is an important structural fragment of kibdelones and isokibdelones [11], one of its derivative **Figure 1** is used to synthesis Kibdelones [4, 17].

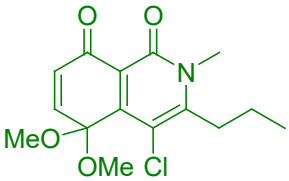

Figure 1. Isoquinolone derivative used to synthesis Kibdelones (type A-C) [4, 17]

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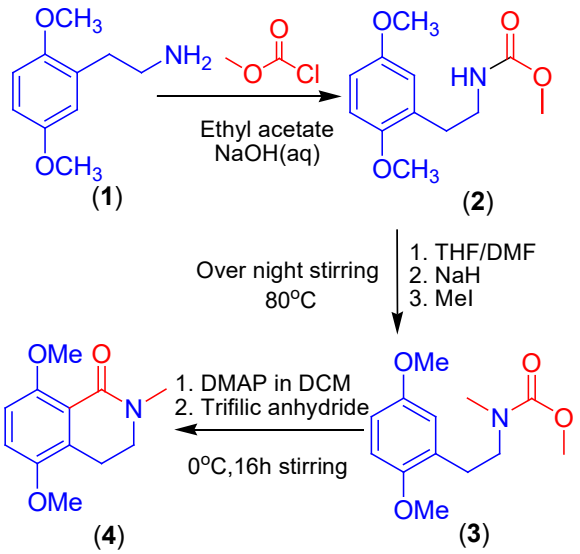
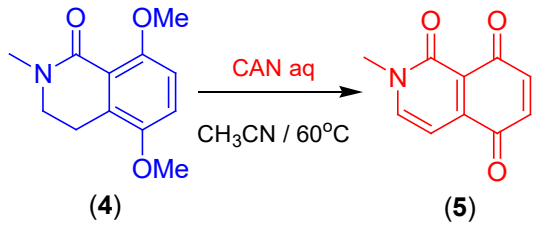
2. Results and Discussion

Keeping in view the synthetic significance of novel methylisoquinoline-1,5,8(2*H*)-trione, here we reported successfully optimized conditions for the synthesis and oxidation of 5,8-dimethoxy-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one into our target molecule as shown in Scheme 1 – 2 and Table 1. The most significant aspect of this synthesis is the introduction of a double bond between position 3 and 4 carbon atoms in heterocyclic part of isoquinolone for further substitution or extension on this site to synthesis our target Kibdelones in near future.



Scheme 1. Synthesis of dihydroisoquinolin-1(2H)-one (**4**)



Scheme 2. Oxidation of dihydroisoquinolin-1(2H)-one into isoquinoline-1,5,8(2*H*)-trione (**5**)

3. Material and Methods

Reagents and Chemicals were used as supplied by the vendor after checking their purity through TLC and melting point, while solvents were purified and dried where required. All reactions were carried out under the nitrogen environment following the standard synthetic procedure in cleaned and dried glassware's, and the magnetic bar was used for stirring. Completion of reaction was monitored with TLC observation technique. HRMS's are recorded on micrOTOF-Q by Bruker Daltonics. NMR spectra were taken on a Bruker-400MHz instrument used $CDCl_3$ as a solvent. Chemical shifts are reported in parts per million.

Table 1. Optimization of oxidation conditions in Scheme 2.

Reactant (4): CAN	Reaction time hrs	Temp.	Yield % age
1:1	1	rt	No reaction
1:1	1	60 °C	27.5%
1:1	1/2	80 °C	Decompose
1:2	2	rt	No reaction
1:2	2	60 °C	31%
1:2	2	70 °C	Decompose
1:3	1/2 -1	60 °C	40.3%
1:4	1 - 3	0 °C	No reaction
1:4	1	60 °C	86.7%
1:4	2	70 °C	Decompose
1:5	1	60 °C	54.5%

Methyl 2,5-dimethoxyphenethylcarbamate (***2***): 2,5-dimethoxyethylamine (2.9 mM, 370 µL) was added in a mixture of 8 ml ethyl acetate and 8 ml aqueous solution of NaOH (1 M) in 25 ml round bottom flask under nitrogen then added methyl chloroformate (2.2 mM, 225 µL) dropwise. The mixture stirred at room temperature for 45 min, then washed with water to get the desire product **2**. Off white solid, yield 74 %, ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 6.78(dd, CH), 6.73 (m, CH), 6.71(obsc., CH), 4.89(s, br, NH), 3.78(s, OCH_3), 3.75(s, OCH_3), 3.64(s, br, OCH_3), 3.40(dt, CH_2), 2.79(t, CH_2), ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2(CO), 153.7(C), 151.9(C), 128.6(C), 117.0(CH), 112.0(CH), 111.4(CH), 56.0(OCH_3), 55.8(OCH_3), 52.0 (OCH_3), 41.3(CH_2), 30.9(CH_2),. HRMS (EI) calcd. for $C_{12}H_{17}NO_4$, 239.1158. Found: 239.1152.

Methyl 2,5-dimethoxyphenethyl (methyl) carbamate (***3***): After purification, compound **2** (0.84 mM) was dissolved in 4 mL THF and DMF (10:1) solution, in this solution NaH (0.07 g, 2.9 mM) was added under nitrogen followed by dropwise

addition of MeI (175 µL, 2.9 mM). After 10 min of stirring at room temp, the reaction (reactants were) was heated at 80 °C for about 12h. On completion of reaction, slightly more THF was added and then the mixture was filtered. The solvent evaporated under reduced pressure. The crude product was dissolved in ethyl acetate and dried with $Na_2S_2O_3$ and $MgSO_4$. After drying the solvent was removed under reduced pressure got product **3** as a yellow oil. Yield 96 %, ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 6.77(d, *J* = 9.2, CH), 6.73(d, *J* = 2.7, CH), 6.71(dd, *J* = 9.2, 2.7, CH), 3.79(s, OCH_3), 3.75(s, OCH_3), 3.68(s, br, OCH_3), 3.42(br. s, CH_2), 2.86(br. s, CH_3), 2.82(br. s, CH_2),^{13}C NMR (100 MHz, $CDCl_3$) δ157.2 (CO), 153.7(C), 151.9(C), 128.6(C), 117.0(CH), 112.0(CH), 111.4(CH), 56.0(OCH_3), 55.8(OCH_3), 52.0(OCH_3), 41.3(CH_2), 30.9(CH_2),. HRMS (EI) calcd. For $C_{13}H_{19}NO_4$, 253.1314. Found: 253.1309.

5,8-dimethoxy-2-methyl-3,4-dihydroisoquinolin-1(2H)-one (***4***): Compound **3** (50 mg, 0.19 mM) was further dissolved in 5 ml of dichloromethane with DMAP (72.3mg, 0.59 mM) at 0 °C under nitrogen. Added trifilic anhydride (171 µL) drop-wise in the round bottom flask over a period of 15 min, then stirred reaction mixture for 16h at room temperature. Then added 8 ml water and adjusted pH at 8 with aq. $NaHCO_3$. 30mL DCM (10 mL volume, three times) was used to extract compound **4** from the aqueous layer which was washed with brine, dried with $MgSO_4$, concentrated with a rotary evaporator, and purified with column chromatography using EtOAc : Hexane (4:1) as mobile phase. Light Brown solid, yield 85 %, ^{1}HNMR (400 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 6.94(d, *J* = 9.1, CH), 6.82(d, *J* = 9.1, CH), 3.85(s, OCH_3), 3.80(s, OCH_3), 3.48(t, *J* =6.3, CH_2), 3.16(br. s, CH_3), 2.91(t, *J* =6.3, CH_2), ^{13}CNMR (100 MHz, $CDCl_3$) δ 164.7(CO), 153.8(C), 149.1(C), 129.6(C), 118.7(C), 114.7(CH), 111.1(CH), 56.3(OCH_3), 56.1(OCH_3), 47.8(CH_2), 35.3(CH_3), 22.3(CH_2). HRMS (EI) calcd. for $C_{12}H_{15}NO_3$, 221.1052. Found: 221.1057.

2-methylisoquinoline-1,5,8(2H)-trione (***5***): Compound **4** (50 mg, 0.23mM) was dissolved in 6 mL of CH_3CN in a round bottom flask. Ceric ammonium nitrate (CAN) (0.82mM) was dissolved in 6ml of distilled water and added drop wise in reaction mixture. Stirred for 30 min at room temperature and then stirred at 60 °C for one hour, compound **5** was extracted from reaction mixture using DCM five times. Crude product **5** was further purified through column chromatography on silica gel using EtOAc as mobile phase. Pale orange solid, yield 86.7 %, ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm, *J* Hz) δ7.81 (d,*J* = 6.8, CH),6.77 (d, *J* = 6.8, CH), 6.89 (d, *J* = 6.8, CH), 3.67 (s, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ185.2 (CO),183.0 (CO), 158.8 (CO), 145.3 (CH), 143.1 (C), 140.8 (CH), 135.1 (CH), 118.9(C), 100.6 (CH), 39.1(CH_3). HRMS (EI) calcd. for $C_{10}H_7NO_3$, 189.0426. Found:189.0431.

4. Conclusions

In conclusion, we use readily available 2,5-dimethoxyethylamine to synthesize the *N*-methylated isoquinolone with a 52% overall yield in four-step-synthesis. With the yield target molecule can be used for further substitution to synthesize complex target molecule. During the optimization of reaction-conditions, we observed that 60 °C temperature and 1:4 of reactant and catalyst is the best ratio for a good yield of the target molecule (**5**).

Supporting Information

^{1}H-NMR, ^{13}C-NMR and HRMS Spectra (PDF) available in the supplementary material.

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