DABCO-Catalyzed Easy Access to Benzo[*d*]naphtho[2,3-*g*][1,3]-oxazocine‑8,13(6*H*,14*H*)‑diones in Aqueous Media

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ABSTRACT: *An eco-friendly, highly efficient, and tandem reaction between 2-hydroxy-1,4-naphthoquinone and quinolinium salts in the presence of DABCO, 1,4-diazabicyclo[2.2.2]octane, in aqueous medium is developed for the synthesis of functionalized polycyclic naphthooxazocines. The advantageous features of this operationally simple procedure along with good to excellent yields of products highlighted this method for the preparation of oxazocine. Moreover, the products obtained without the need to column chromatography. In order to reduce the hazards of chemicals and solvents, the reaction was conducted in the green solvent, water. All newly synthesized compounds were characterized by different methods involving IR, ^{1}H NMR, ^{13}C NMR spectroscopy.*

KEYWORDS: *Naphthooxazocines; DABCO; Aqueous media; Environmentally benign*.

INTRODUCTION

The privileged N, O-acetal heterobicyclic compounds with medium-sized rings are attractive molecules in both organic chemistry and biology [1, 2]. These frameworks have been widely found among diverse natural products such as Larutensine, Naucleamide E, Calycinumine B, and Spiramide A (Fig. 1) with antiproliferative, antimicrobial, anti-allergic, anti-inflammatory, and cytotoxic activity [3-7]. Moreover, benzoxazocine derivatives have been identified as a bioactive motif exhibiting various activities involving potential CNS, NK1 receptor antagonist,

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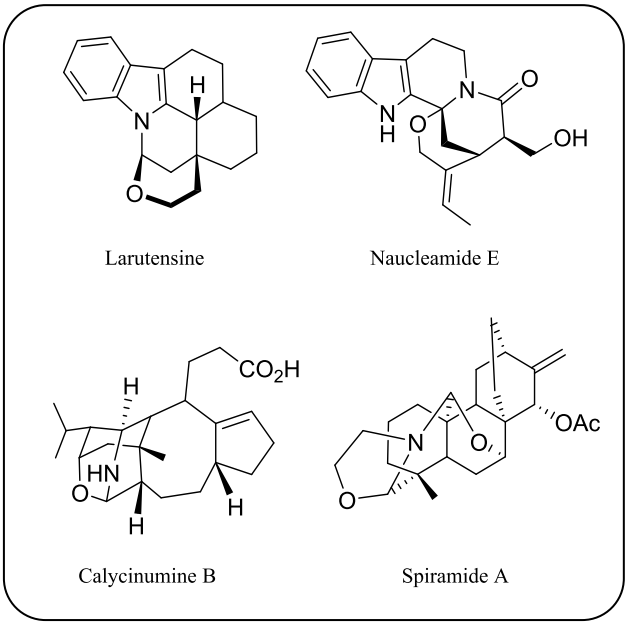


Fig. 1: Natural Products Containing oxazocine skeleton.

anti-thrombotic, anti hepatitis C and anti-inflammatory [8-13]. The synthesis of polycyclic molecules is relatively difficult regarding the unfavorable entropy, enthalpy and transannular interaction values, but due to their wide range of biological activities [14, 15] and substantial selectivity in their interactions with multiple enzymes and receptors [16, 17], there is a growing interest in the development of new methodologies for accessing these skeletons.

Many Synthetic approaches have been reported in the literature for the construction of these heterocycles [18-21]. The main protocol is based on the addition of nucleophilic reagents to quinolinium or isoquinolium salts, the bifunctional nucleophile acceptor, in the presence of base catalyses [22-29]. These reactions allow the formation of bridgehead oxazocine core in a tandem *C*-alkylation and intramolecular *O*-alkylation manner. The reaction of coumarins, enolizable ketones and non-hindered primary amines is another synthetic approach for the stereoselective synthesis of benzo[1,3]oxazocines [30, 31].

In new century, the synthesis of organic compounds in environmentally-friendly media has become the most important goal of scientists [32-38]. Water as a cheap, readily available, nontoxic and nonflammable solvent with unique properties (hydrogen bonding, and hydrophilic and hydrophobic interactions) compared to organic solvents, has been considered as an ideal green solvent [39-41]. As a part of our research interest in the synthesis of heterocyclic compounds [42-46], and in connection with our previous work on the synthesis of benzoxazocines [47], herein, we report the efficient and green approach for the synthesis of oxazocine derivatives from relatively simple starting materials via tandem reactions under mild reaction condition.

EXPERIMENTAL SECTION

General

All reagents and materials were procured from Merck, Aldrich and Fluka chemical companies and used as received. Thin-Layer Chromatography (TLC) was done on silica gel 60 F254 plates (Merck). FT-IR spectra of products were recorded by a Bruker, Equinox 55 spectrometer. All melting points were measured by a Buchi melting point B-540 B.V.CHI apparatus. A Bruker 500 MHz NMR instrument was used to record the ^{1}H NMR and ^{13}C NMR spectra using $CDCl_3$ as solvent. Mass spectra of the products were obtained with an Agilent technology (HP) 5973 Mass Selective Detector, operating at an ionization potential of 70 eV.

Typical procedure for the synthesis of compound 3a

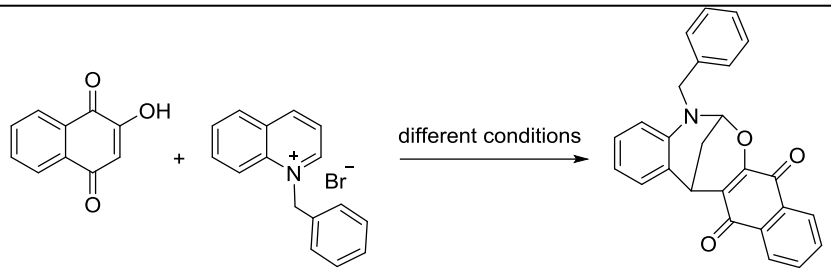
A mixture of 2-hydroxy-1,4-naphthoquinone (1 mmol), 1-benzylquinolin-1-ium bromide (1 mmol) and DABCO (10 mol%) in 7 mL H_2O were stirred at room temperature. Upon completion (nearly 2.5 h), the reaction mixture was allowed to cool, and the resulting precipitate was filtered and washed with lukewarm water. Then, the precipitate was recrystallized from EtOH to afford the desired products (**5a-g**) in 73-94% yield.

Spectroscopic data for new compounds

*5‑(3‑Methylbenzyl)‑5H‑6,14‑methanobenzo[d]naphtho [2,3‑g][1,3] oxazocine‑8,13(6H,14H)‑dione (**3d**)*

Yellow powder ; Mp: 171-173 °C; IR (KBr): ν/cm^{-1}= 3045, 2923, 2835, 1672, 1482, 1332, 1171, 1092 ; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.08 (d, J = 7 Hz, 1H), 7.82 – 7.77 (m, 2H), 7.75 (d, J = 7 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.21 – 7.18 (m, 3H), 7.12 (t, J = 7 Hz, 1H), 7.06 (t, J = 7 Hz, 2H), 6.66 (d, J = 7 Hz, 1H), 5.80-5.81 (m, 1H), 4.70 (d, J = 17 Hz, 1H), 4.53 (d, J = 17 Hz, 1H), 4.45-4.44 (m, 1H), 2.26-2.25 (m, 2H), 2.12 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 185.0 (CO), 182.6, 152.2, 147.4, 138.2, 135.5, 133.5, 133.5, 133.0, 131.6, 130.2, 129.12, 128.5, 127.8, 127.5, 127.5, 126.8, 126.5, 126.5, 125.8,

Table 1: Optimization of reaction conditions.



1 2a 3a

Entry	Catalyst	mol % of catalyst	Solvent	Conditions/temp(˚C)	Time (h)	Yield(%)[b]
1	K_2CO_3	5	H_2O	r.t	12	40
2	EtONa	5	H_2O	r.t	12	25
3	DABCO	5	H_2O	r.t	3	55
4	DABCO	5	H_2O	50	3	51
5	DABCO	5	Ethanol	r.t	3	28
6	DABCO	5	Ethanol	50	12	25
7	DABCO	5	H_2O:Ethanol (1:1)	r.t	3	37
8	**DABCO**	**10**	**H_2O**	**r.t**	**2.5**	**90**
9	DABCO	15	H_2O	r.t	3	82
10	DABCO	20	H_2O	r.t	3	71
11	DABCO	25	H_2O	r.t	3	53

Bold values indicate the best condition, chosen for derivatization

[a]*Reaction condition: 2-hydroxy-1,4-naphthoquinone (1 mmol), 1-benzylquinolin-1-iumbromide (1 mmol), and base (1 mmol) were stirred in water/ethanol/ethanol:water at room temperature/50 ˚C*

[b] *Isolated yield*

123.1, 118.5, 111.0, 84.8 (O*C*HN), 52.2 (N*C*H$_2$), 27.9, 21.1, 18.0 ppm; MS: *m/z* (%) = 407 (M^+, 28), 378 (32), 302 (19), 284 (54), 246 (22), 146 (10), 127 (36), 105 (100), 89 (45), 77 (25), 63 (34).

*5 ‑(4 ‑Chlorobenzyl) ‑5H ‑6,14 ‑methanobenzo[d]naphtho [2,3 ‑g][1,3]oxazocine ‑8,13(6H,14H) ‑dione (**3f**)*

Yellow powder; Mp: 157-158 °C; IR (KBr): ν/cm^{-1}= 3036, 2925, 2852, 1672, 1492, 1340, 1171, 1095; ^{1}H NMR ($CDCl_3$, 500 MHz): δ =8.09 (t, *J* = 7 Hz, 1H), 7.81-7.84 (m, 2H), 7.74 (d, *J* = 8 Hz, 1H), 7.31 –7.8 (m, 4H), 7.19 (d, *J* = 7 Hz, 1H), 7.12 (t, *J* = 7 Hz, 1H), 7.06 (t, *J* = 7 Hz, 1H), 6.68 (d, *J* = 8 Hz, 1H), 5.81-5.82 (m, 1H), 4.72 (d, *J* = 17 Hz, 1H), 4.54 (d, *J* = 17 Hz, 1H), 4.46-4.45 (m, 1H), 2.25-2.26 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 182.9, 180.1 (CO), 163.7, 153.9, 140.9, 136.0, 134.1 (2C), 133.1, 132.9, 131.9, 129.0 (2C), 128.7, 127.9, 127.6, 126.3, 126.2, 124.8, 124.4, 119.0, 111.2, 85.0 (O*C*HN), 52.4 (N*C*H$_2$), 26.5, 25.0 ppm; MS: *m/z* (%) = 429 ([M + 2]$^+$, 8), 427 (M^+, 5), 411 (27), 384 (12), 301 (35), 287 (34), 274 (20), 256 (44), 217 (30), 189 (22), 174 (46), 127 (39), 125 (100), 115 (20), 105 (54), 89 (40), 77 (57), 63 (24).

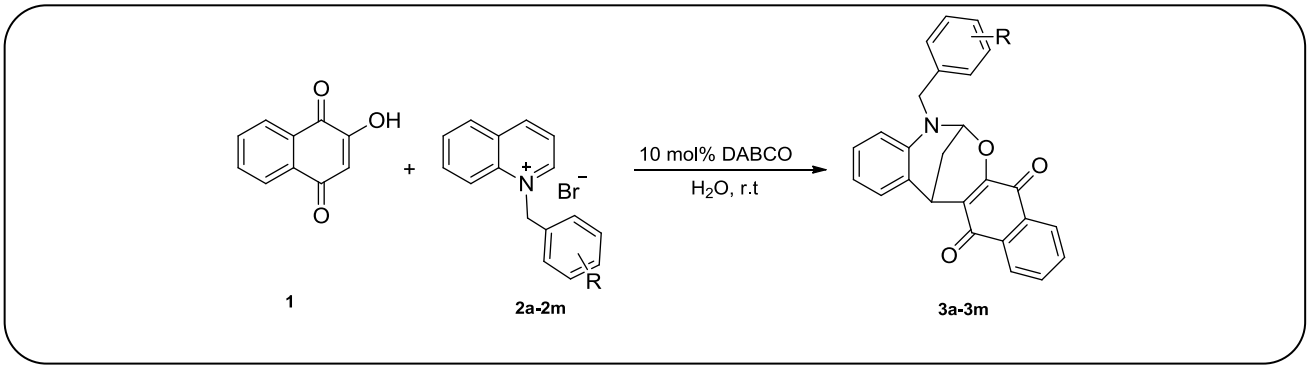
RESULTS AND DISCUSSION

As outlined in Table 1, we commenced our studies by probing various reaction conditions for the model reaction between 2-hydroxy-1,4-naphthoquinone (**1**) and 1-benzylquinolin-1-ium bromide (**2a**), prepared from quinoline and benzyl bromide [47]. In order to optimize the reaction condition, the model reaction was investigated in the presence of different reagents such as K_2CO_3, and CH_3CH_2ONa and DABCO (Table 1, entries 1-3). By choosing DABCO, The effect of solvent and temperature was examined (Table 1, entries 4-7). it was found that,

Table 2: Synthesis of benzo[d]naphtho[2,3-g][1,3]oxazocine-8,13(6H,14H)-diones 3a–3m.

Entry	Compound	Ar	Yield/%[a]	Time/h	M.p. (˚C)/[reported][b]
1	3a	C_6H_5	90	2.5	193 [193–195]
2	3b	4-$MeOC_6H_4$	74	3	184 [183–185]
3	3c	2-MeC_6H_4	63	3	174 [173–175]
4	3d	3-MeC_6H_4	65	2	171-173
5	3e	3-ClC_6H_4	69	2.5	160 [160–162]
6	3f	4-ClC_6H_4	83	2.5	157-158
7	3g	2,6-$Cl_2C_6H_3$	79	2	177 [176–178]
8	3h	2-BrC_6H_4	66	2.5	186 [184–185]
9	3i	3-BrC_6H_4	75	3.5	165 [164-166]
10	3j	4-Br C_6H_4	72	2	190 [191-193]
11	3k	2-$O_2NC_6H_4$	84	2.5	191 [190]
12	3l	3-$O_2NC_6H_4$	66	2	157 [155-157]
13	3m	4-$O_2NC_6H_4$	86	2	190 [189-191]

2-Hydroxy-1,4-naphthoquinone (1 mmol), quinolinium salts (1 mmol), and DABCO (10 mol %) were stirred in water at room temperature
[a] Isolated yields. [b] Reference [46]

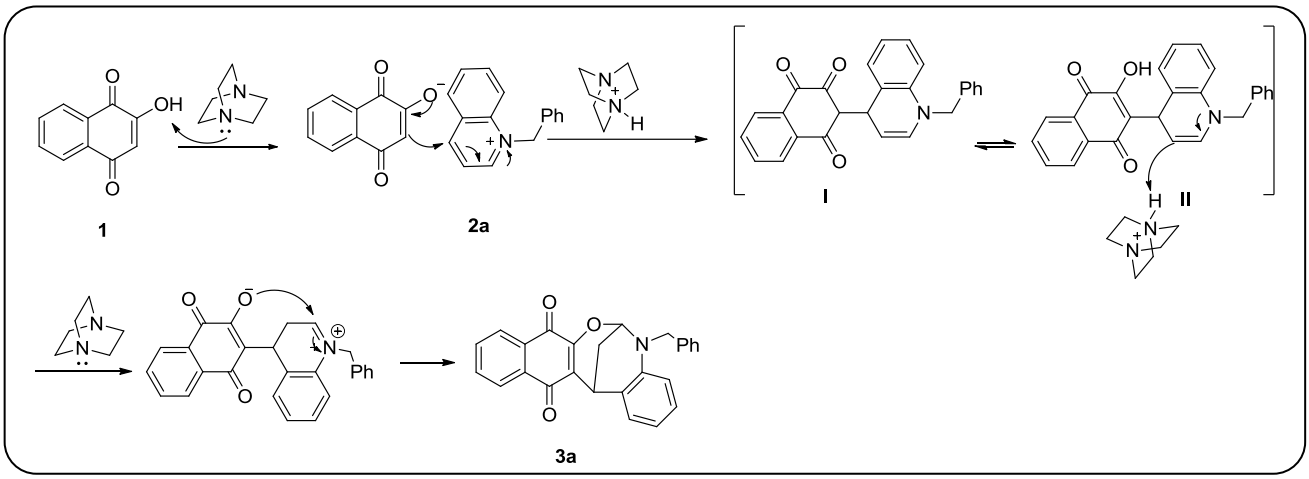


Scheme 1: Synthesis of benzo[d]naphtho[2,3-g][1,3]oxazocine-8,13(6H,14H)-diones using DABCO in water.

in the presence of 10 mol% of DABCO in aqueous medium at room temperature, the reaction proceeded well and the maximum yield of the desired product was obtained within 3 h. Higher amounts of DABCO did not improve the yield (Table 1, entries 9, 10 and 11). By employing the optimized reaction condition (Table 1, entry 8), the protocol was applied for the synthesis of various naphthooxazocines, derived from different 1-benzylquinolin-1-ium bromides. (Scheme 1)

This transformation showed good functional group tolerance which led to the synthesis of thirteen compounds (Table 2). The structures of all the naphthooxazocine derivatives (**3a–m**) were well characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometery. The IR spectrum of the model compound **3a** showed two stretching bands at 1676 and 1648 cm^{-1} related to carbonyl groups. In the ^{1}H NMR spectrum of **3a,** the multiplet in the region at 2.24–2.26 ppm and two distinct doublets at δ 4.71 and 4.95 ppm related to hydrogens of bridge methylene and benzylic moiety respectively, confirmed the proposed structure.

A suggested reaction mechanism for the formation of the product **3a** is shown in Scheme 2. First, 2-hydroxy-1,4-naphthoquinone **1** which is activated by the DABCO catalyst, undergoes a Michael type addition to the 1-benzylquinolin-1-ium bromide **2a**. Finally, intramolecular cyclization led to the desired product.



Scheme 2: Plausible mechanism for the synthesis of 3a.

CONCLUSIONS

In this paper, we have developed a green and efficient method for the synthesis of naphthooxazocine in high yields by employing DABCO as a cheap and ecofriendly catalyst. The advantages of this approach include the use of environmentally benign, mild condition, easy work-up procedure, and good to excellent product yields showcasing this method as an applicable tool for the construction of novel poly heterocyclic compounds.

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