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Facile, four-component, domino reactions for the regioselective synthesis of tetrahydrobenzo[*g*]quinolines

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ABSTRACT

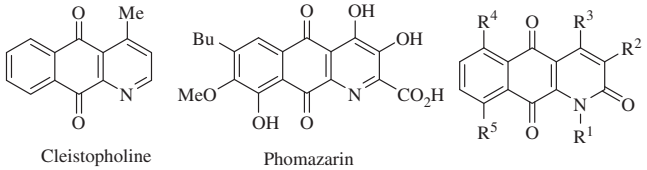
Facile, four-component domino reactions of 2-hydroxy-1,4-naphthaquinone, aromatic aldehydes, methyl/ethyl acetoacetate and ammonium acetate in ethanol under microwave irradiation at 100 °C afforded tetrahydrobenzo[g]quinoline-5,10-diones regioselectively in good yields. This transformation presumably proceeds via α,β-unsaturated triketone generation/Michael addition/regioselective annulation via intramolecular condensation domino sequence.

Designing new multicomponent reactions (MCRs) as well as improving known MCRs constitute a research area of immense interest in contemporary organic synthesis.[1] In contrast to classical multistep linear synthetic protocols, MCRs enable expedient and efficient assembly of molecules of structural complexity and diversity in one-pot operations with facile execution, high atom-economy and selectivity.[1b,1c,2,3] These reactions obviate the isolation and purification of intermediates and diminish waste generation, thereby enhancing the greenness of transformations. Consequently, MCRs have emerged as a powerful tool for delivering molecular libraries needed in combinatorial approaches for the assembly and lead identification of bioactive compounds.[4]

The benzo[g]quinoline-5,10-dione skeleton is an important structural motif prevalent in natural products with interesting biological properties (Fig. 1). For example, cleistopholine isolated from *cleistopholis patens*,[5] *oncodostigma monosperma*,[6] *meiogyne virgata polyalthia*[7] and *annona cherimolia*,[8] exhibits antimicrobial activity[9,10] and anticancer activity against several cell lines,[11] besides serving as intermediate in the synthesis of the antifungal agent, sampangine.[12] Phomazarin, isolated from the cultures of *phoma terrestris Hansen*,[13] shows in vitro cytotoxic activity.[14] Dielsiquinone and marcanines A-E, isolated from the stem bark of *goniothalamus marcanii craib*, also show cytotoxic activity.[15] Synthetic methods for the construction of tetrahydrobenzo[g]quinoline-5,10-dione derivatives include hetero Diels–Alder reaction,[16] annulation[17,18] and aza-Diels–Alder cycloaddition-rearrangement sequence.[19]

These methods suffer from one or more disadvantages such as requirement of expensive reagents, prolonged reaction time and low yield or selectivity. Consequently, now we report a convergent four-component domino protocol for the assembly of tetrahydrobenzo[g]quinoline-5,10-diones from 2-hydroxy-1,4-naphthaquinone, aromatic aldehydes, methyl/ethyl acetoacetate and ammonium acetate in ethanol (Scheme 1) in this Letter. This work stems from our recently embarked research on the synthesis of structurally diverse, novel heterocycles employing tandem/domino reactions[20] and/or their study of anti-tubercular activity.[21]

Initially, we investigated the reaction of 2-hydroxy-1,4-naphthaquinone, 4-chlorobenzaldehyde, ethyl acetoacetate and ammonium acetate in ethanol at room temperature. This reaction



Dielsiquinone, R^1, R^2 = H; R^3 = Me; R^4, R^5 = H
Marcanine A, R^1, R^2 = H; R^3 = Me; R^4, R^5 = H
Marcanine B, R^1 = H; R^2 = OMe; R^3 = Me; R^4, R^5 = H
Marcanine C, R^1 = H; R^2 = OMe; R^3 = CH_2OH; R^4, R^5 = H
Marcanine D, R^1 = H; R^2 = OMe; R^3 = Me; R^4 = OH; R^5 = H
Marcanine E, R^1 = Me; R^2 = OMe; R^3 = Me; R^4 = H; R^5 = OH

Figure 1. Structures of naturally occurring benzo[g]quinoline-5,10-diones.

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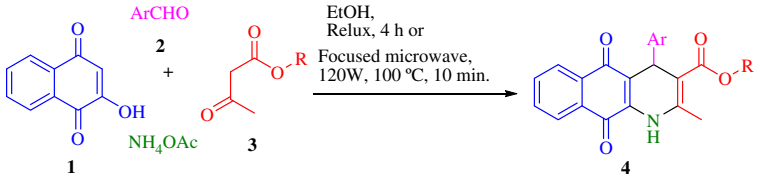


Scheme 1. Synthesis of tetrahydrobenzo[*g*]quinoline-5,10-diones **4**.

Table 1
Optimization of reaction conditions for synthesis of **4k**

Entry	Solvent	Conditions[a]	Catalyst (mol %)	Yield of **4k** (%)
1	EtOH	rt, 8 h	—[b]	0
2	EtOH	Thermal, 4 h	—[b]	78
3	EtOH	MW, 120 W, 10 min	—[b]	88
4	MeOH	MW, 120 W, 15 min	—[b]	60
5	Ethylene glycol	MW, 120 W, 10 min	—[b]	45
6	Glycerol	MW, 120 W, 20 min	—[b]	25
7	PEG-400	MW, 120 W, 10 min	—[b]	Trace
8	CH_3CN	MW, 130 W, 20 min	—[b]	65
9	Water	MW, 130 W, 15 min	—[b]	Trace
10	EtOH	MW, 120 W, 15 min	*p*-TsOH (100)	35
11	EtOH	MW, 120 W, 15 min	Sulfamic acid (100)	30
12	EtOH	MW, 120 W, 10 min	I_2 (10)	38
13	EtOH	MW, 120 W, 10 min	CAN (10)	40
14	EtOH	MW, 120 W, 10 min	$YbCl_3$ (50)	42
15	EtOH	MW, 120 W, 25 min	L-Proline (20)	55
16	EtOH	Thermal, 8 h	Ammonia and L-Proline[c]	0

[a] All reactions performed at 100 °C in presence of ammonium acetate.
[b] No catalyst other than ammonium acetate was employed.
[c] NH_3 and proline were used instead of NH_4OAc.

failed to occur and the starting materials remained unreacted (Table 1, entry 1). Hence this reaction mixture was subjected to heating under reflux, whereupon the reaction could be completed in 4 h affording **4k** in 78% yield (Table 1, entry 2). In view of the advantages associated with the use of microwave irradiation in performing reactions,[22,23] the above reaction was investigated under microwave irradiation at 120 W and 100 °C in EtOH. This reaction went to completion in 10 min affording a higher yield of **4k** (88%) (Table 1, entry 3) than the thermal reaction.

With a view to further optimizing the conditions for the reaction under microwave irradiation, the reaction was also investigated in methanol, ethylene glycol, glycerol, PEG-400, CH_3CN and water (Table 1, entries 4–9). All the alternative solvents used in place of ethanol resulted in lower yields of **4k**.

The reaction under microwave irradiation was further investigated in presence of Bronsted and Lewis acids, viz. *p*-TsOH, sulfamic acid, I_2, CAN, $YbCl_3$ and L-proline (Table 1, entries 10–16). The data in Table 1 disclose that (i) these acids diminish the yield and (ii) the reaction in the absence of the above Lewis or Bronsted acids affords better yields. It is pertinent to note that a large number of optimized procedures for the Hantzsch reaction[24] for the synthesis of multisubstituted 1,4-dihydropyridines (1,4-DHPs) employ catalysts such as triphenylphosphine,[25] molecular iodine,[26] Baker's yeast,[27] silica-supported acids,[28] ceric ammonium nitrate (CAN),[29] organocatalysts,[30] polymers[31] and metal triflates.[32] However, some of these methods suffer from limitations such as high reaction temperature, prolonged reaction time, incomplete conversion of reactants, expensive metal precursors or environmentally toxic catalysts. In contrast, the present Hantzsch-type reaction furnishes tetrahydrobenzo[*g*]quinoline-5,10-diones in very high yields, considering the number of steps involved, under metal-free conditions in presence of ammonium acetate, a soft Bronsted acid, which could serve as a reactant as well as a catalyst. The catalytic role of ammonium acetate in this reaction is evident from the fact that the reaction in presence of ammonia instead of ammonium acetate failed to occur.

Based on the above results, all subsequent reactions for the synthesis of **4** were performed under microwave irradiation (120 W, 100 °C for 10 min) in presence of ammonium acetate in EtOH. Under these optimized conditions, a study on the substrate scope and generality of the synthetic protocol was investigated by synthesizing a library of hitherto unreported methyl/ethyl 2-methyl-5,10-dioxo-4-aryl-1,4,5,10-tetrahydrobenzo[*g*]quinoline-3-carboxylates (**4**) (Scheme 1 and Table 2). Typically, a mixture of 2-hydroxy-1,4-naphthoquinone (**1**), aromatic aldehyde (**2**), methyl/ethyl acetoacetate (**3**) and NH_4OAc (1:1:1:2.5 mmol) in a sealed vial was irradiated

Table 2
Synthesis of compounds **4** via thermal and microwave irradiation reactions

Entry	Compd	Ar	R	Yield of **4** (%)[a,b]	
				Thermal	MW
1	**4a**	C_6H_5	Me	78	83
2	**4b**	4-MeC_6H_4	Me	79	85
3	**4c**	4-ClC_6H_4	Me	78	89
4	**4d**	3-BrC_6H_4	Me	80	88
5	**4e**	2-ClC_6H_4	Me	79	84
6	**4f**	2,4-$Cl_2C_6H_3$	Me	80	82
7	**4g**	1-Naphthyl	Me	76	82
8	**4h**	C_6H_5	Et	77	85
9	**4i**	4-MeC_6H_4	Et	75	84
10	**4j**	4-$Pr^iC_6H_4$	Et	72	80
11	**4k**	4-ClC_6H_4	Et	78	88
12	**4l**	3-BrC_6H_4	Et	79	87
13	**4m**	2-ClC_6H_4	Et	70	84
14	**4n**	2,4-$Cl_2C_6H_3$	Et	79	83
15	**4o**	4-$O_2NC_6H_4$	Et	80	86
16	**4p**	2-Thienyl	Et	71	80

[a] Isolated yield after purification by column chromatography.
[b] Thermal and microwave reactions performed for 4 h and 10 min, respectively.

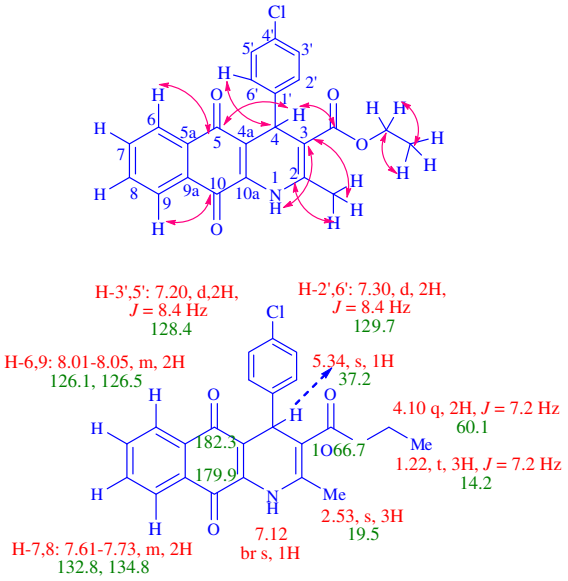


Figure 2. Selected HMBCs, ^{1}H- and ^{13}C- chemical shifts of **4k**.

in a focused microwave oven at 100 °C and 120 W for 10 min.[33] After completion of the reaction (TLC), the products **4** were isolated and purified by flash column chromatography. All the thermal reactions went to completion within 4 h. The data in Table 2 indicate that the reaction under microwave irradiation could be performed in higher yields conveniently in minutes than the thermal reaction.

The structure of **4** was assigned using one- and two-dimensional NMR spectroscopic data. The ^{1}H NMR spectrum of **4k** has a singlet at

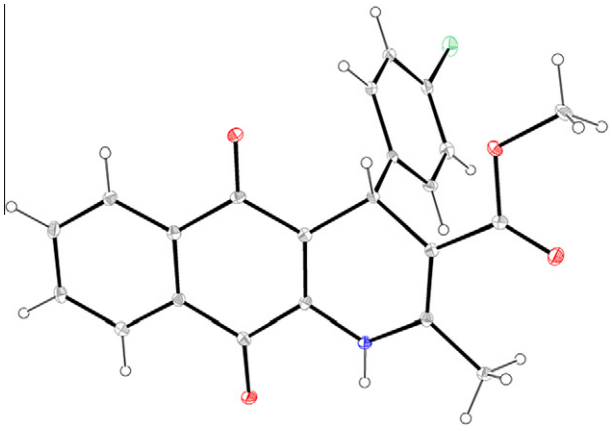
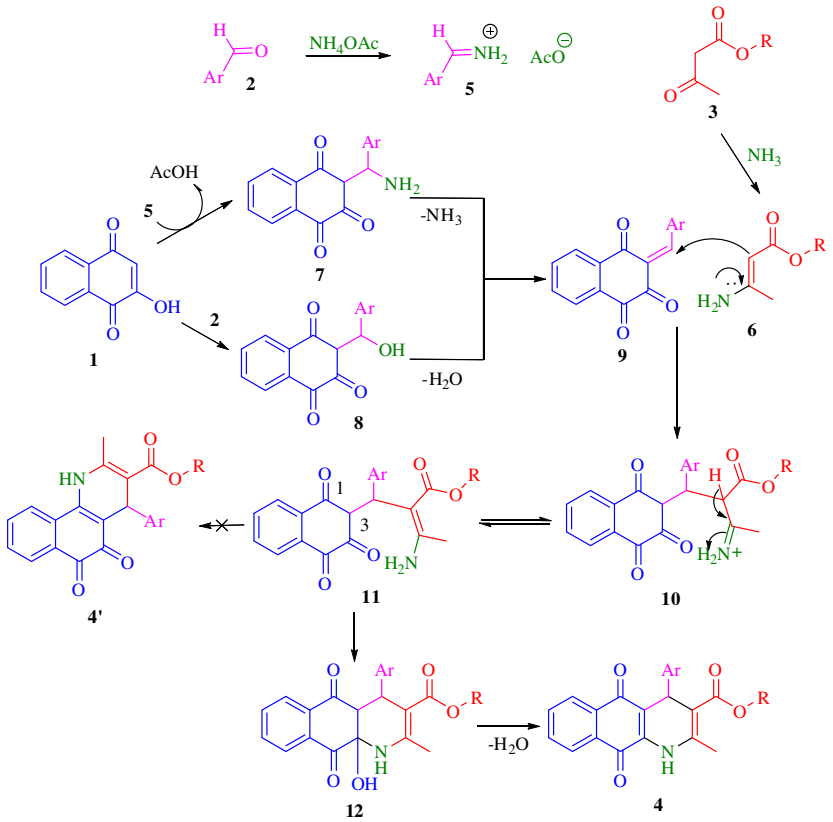


Figure 3. ORTEP diagram for **4c**.

5.34 ppm due to the H-4, which shows a C,H-COSY correlation with carbon signal at 37.2 ppm, due to C-4 and HMBCs with ester carbonyl at 166.7 ppm, C-10a at 143.8 ppm, C-2 at 144.1 ppm and C-5 at 182.3 ppm (Fig. 2). The CH_3 hydrogens of the 1,4-dihydropyridine ring occur as singlet at 2.53 ppm, which shows HMBCs with C-2 at 144.1 ppm and C-3 at 104.5 ppm. The multiplet in the chemical shift range of 8.01–8.05 ppm is assigned to H-6 and H-9. Another multiplet at 7.61–7.73 ppm is assigned to H-7 and H-8. The H-3′,5′ show a doublet at 7.20 ppm (J = 8.4 Hz), while the H-2′,6′ appear as a doublet at 7.30 ppm (J = 8.4 Hz). The NH proton appears as a br s at 7.12 ppm, which shows HMBC with C-3 at 104.5 ppm. An X-ray crystallographic study of a single crystal of **4c**[34] (Fig. 3) confirmed the structure deduced from NMR spectroscopic studies. A plausible mechanism for the formation of tetrahydrobenzo[*g*]quinolines (**4**)



Scheme 2. Probable domino sequence leading to **4**.

is depicted in Scheme 2. Presumably, the intermediate, 3-[1-arylmethylidene]-1,2,3,4-tetrahydro-1,2,4-naphthalenetriones (**9**), could arise via (i) the Mannich reaction of 2-hydroxy-1,4-naphthoquinone (**1**) with an iminium ion **5** generated from **2** and ammonium acetate, followed by elimination of ammonia, or (ii) the ammonium acetate-catalyzed reaction of **1** with aldehyde to afford aldol **8**, which could undergo dehydration. Michael addition of enamine **6**, generated from the reaction of β-ketoester with ammonia, available from the dissociation of ammonium acetate, to **9**, followed by regioselective intramolecular condensation affords solely **4** (Scheme 2). The regioisomer **4′** is not formed even in traces in this reaction. This is presumably due to the higher electrophilicity of the carbonyl at non-conjugating 3-position in intermediate **11** than the carbonyl at conjugating 1-position.

In conclusion, we have described an expedient and convergent four-component domino protocol for the regioselective synthesis of a library of tetrahydrobenzo[*g*]quinolines in excellent yields from readily available simple starting materials. The quinolinediones obtained in this study could also serve as valuable synthons for further elaboration into more complex heterocycles of biological relevance.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.102.

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33. *General procedure for synthesis of* **4**: Microwave irradiation method: A vial containing a mixture of 2-hydroxy-1,4-naphthoquinone (**1**) (1 mmol), aromatic aldehyde (1 mmol), methyl/ethyl acetoacetate (**3**) (1 mmol), and NH_4OAc (2.5 mmol) in ethanol (5 ml) was sealed and placed in a CEM Discover microwave oven. The vial was subjected to microwave irradiation, programed at 100 °C and 120 W. After a period of 3–5 min, the temperature reached a plateau, 100 °C, and remained constant. After completion of the reaction (10 min), the vial was cooled to room temperature and poured in to water (50 ml). The precipitated solid was filtered and and purified by column chromatography using a 7:1 petroleum ether-AcOEt mixture, to yield pure **4**.
Conventional heating method: A mixture of 2-hydroxy-1,4-naphthoquinone **1** (1 mmol), the suitable aromatic aldehyde (1 mmol), methyl/ethyl acetoacetate **3** (1 mmol), and NH_4OAc (2.5 mmol) in ethanol (12 ml) was heated to reflux in an oil bath for 4 h. After completion of the reaction (TLC), the reaction mass was poured into water (50 ml). The precipitated solid was filtered and purified by the column chromatography using a 7:1 petroleum ether-AcOEt mixture, to yield pure **4**.
Characterization data of compound **4k** *are given below.*
Ethyl 4-(4-chlorophenyl)-2-methyl-5,10-dioxo-1,4,5,10-tetrahydrobenzo[g] quinoline-3-carboxylate (**4k**): Isolated as red brown solid. Yield: 88%; mp = 209 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.22 (t, 3H, *J* = 7.2 Hz), 2.53 (s, 3H), 4.10 (q, 2H, *J* = 7.2 Hz), 5.34 (s, 1H), 7.12 (br s, 1H), 7.20 (d, 2H, *J* = 8.4 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 7.61–7.73 (m, 2H), 8.01–8.05 (m, 2H). ^{13}C NMR (75 MHz,

$CDCl_3$) δ_C: 14.2, 19.5, 37.2, 60.1, 104.5, 118.7, 126.1, 126.5, 128.4, 129.7, 130.1, 132.5, 132.8, 134.8, 136.8, 143.8, 144.1, 166.7, 179.9, 182.3. Anal. Calcd for $C_{23}H_{18}ClNO_4$: C, 67.73; H, 4.45; N, 3.43%. Found C, 67.81; H, 4.36; N, 3.49%.

34. Crystallographic data (excluding structure factors) for tetrahydrobenzo[*g*] quinoline-5,10-dione **4c** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 823746. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223-336033 or e-mail:deposit@ccdc.cam.ac.uk].