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A practical, green, and selective approach toward the synthesis of pharmacologically important quinone-containing heterocyclic systems using alumina-catalyzed Michael addition reaction

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Abstract

A convenient method for double Michael additions to quinone systems catalyzed by Al_2O_3, is reported. The advantages of this method include the use of a cheap and environment-friendly catalyst, a straightforward isolation of the pure product by filtration, high yields, and excellent selectivity, thus providing rapid access to useful building blocks for the preparation of biologically active quinones.

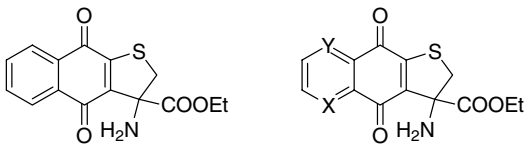
Keywords: Michael addition; Eco-friendly heterogeneous catalysts; Quinone-containing antitumoral drugs

Quinone-containing antitumor drugs such as doxorubicin, and mitoxantrone have been established as one of the most effective classes of anticancer agents in clinical use today, with broad application in the treatment of several leukemia and lymphomas as well as in combination chemotherapy of solid tumors. As a consequence, a large number of quinone derivatives and related compounds have been prepared, in the search for novel agents endowed with improved pharmacokinetic properties, potency or activity spectrum and lower side effects, and several of them have shown promise in clinical studies.

We have recently reported the synthesis and the in vitro antitumor activity of dihydrothieno[2,3-*b*]naphtho-4,9-dione (DTNQ) derivatives **1** and of their aza analogs dihydrothieno[2,3-*g* and 3,2-*g*]quinoline-4,9-diones (DTQQ) **2a** and **2b** (Fig. 1).[1]

The compounds were obtained by reacting a thiazolidine derivative **3** with naphthoquinone (**4**) or quinoline-5,8-dione (**5**) in the presence of silver carbonate and DBU as base, according to the method previously described by us (Scheme 1).[1a] The proposed reaction mechanism involves the 1,4-Michael addition of the thiol group arising from the opening of the thiazolidine ring followed by a second attack at the α,β-unsaturated system.[1b]

Although extensively used by us, this method suffers from poor reproducibility and from the use of expensive



1 **2a**: X = N, Y = CH **2b**: X = CH, Y = N

Fig. 1. DTNQ **1** and DTQQ **2a** and **2b.**

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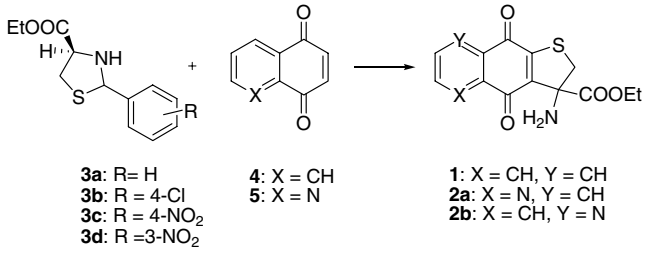

Scheme 1. Synthesis of DTNQ and DTQQ involving double Michael addition.

reagents. Moreover, the reaction with quinoline-5,8-dione **5** furnishes two isomers (**2a** and **2b)**, which are very difficult to separate. Therefore, our intention to further explore the structure–activity relationships (SARs) of this class of compounds made the development of a cheaper and more profitable approach to their synthesis highly desirable.

In this Letter, we report a practical, environment-friendly and selective new strategy for the preparation of DTNQ and DTQQ derivatives.

Both acid and basic catalysis conditions have been reported for the Michael reaction and several eco-friendly inorganic heterogeneous catalysts, such as alumina,[2] potassium fluoride supported on alumina,[3] zeolite,[4] montmorillonite K10[5], and silica[6] have been successfully employed to increase the efficiency and to maintain the 'greenness' in Michael additions to a variety of conjugated alkenes.

Thus, we first decided to set up a series of experiments to identify the fittest environment for our reaction. Indeed, we used a very straightforward protocol[7] and reacted naphthoquinone **4** and thiazolidine **3b** in the presence of $KF–Al_2O_3$, Al_2O_3 (basic catalysis), montmorillonite K10 or silica (acid catalysis).

The experimental results evidenced the catalytic efficacy of alumina in this reaction, whereas the acid catalysts montmorillonite K10 and silica caused a drop in purity and yield and the use of potassium fluoride supported on alumina resulted in an instantaneous degradation of the reaction mixture (Table 1, entries 1–4).

As the number of surface hydroxyl groups on alumina could vary its basicity,[8] we decided to fine-tune the reactivity of the catalyst and repeated the alumina-catalyzed reaction in the presence of different amounts of water.[9] The results obtained by increasing the amount of water were slightly inferior to the standard ones, whereas dry conditions were detrimental (Table 1, entries 4–6).

Then, we turned our attention to the nature of the solvent and to the catalyst requirements and tested the reaction in chloroform, acetonitrile, and ethanol as solvents (Table 1, entries 4, 7 and 8) and with different amounts of Al_2O_3 (Table 1, entries 4, 9 and 10). The combination of ethanol as a solvent and 50-fold excess (in weight) of the catalyst furnished better yields (58%) and high purity[10] ($\geqslant$95%) and was found as the optimum condition.

With the remarkable results on DTNQ derivatives in our hands, we subsequently focused our attention to the reaction of thiazolidine derivatives **3a–d** with quinoline-5,8-dione **5**. To the best of our knowledge, no previous examples of completely regioselective Michael addition of thiols on quinolinequinone derivatives were reported. So we were pleased to discover that, besides proceeding smoothly and with good yields, the reaction between quinoline-5,8-dione **5** and thiazolidine derivatives provided only isomer **2a** (Table 2).

The data presented herein are consistent with a mechanism involving a chelation-assisted selective addition of thiol. In fact, in the presence of aluminum ion functioning as a Lewis acid the electron-attracting power of the heterocyclic nitrogen atom is greatly increased by coordination with a positive ion. The reactivity of the 6-position is so strongly enhanced that this position is attacked almost exclusively.[11]

A selective procedure to DTQQ derivative **2b** is under development and will be described in due course.

In conclusion, a practical method for double Michael additions to quinone systems mediated by alumina has been developed.

Compared to the previously reported ones, the advantages of this method include the use of a cheap and environment-friendly catalyst, ease of product isolation by filtration, high yields and excellent selectivity, thus

Table 1
Reaction of naphthoquinone **4** with thiazolidine **3b** and various catalysts, solvents and different reaction conditions

Entry	Catalyst	Mass[b]	Solvent	Method[c]	Yield[d] (%)
1	K10[a]	50	EtOH	A	<5
2	Silica gel	50	EtOH	A	<2
3	$KF–Al_2O_3$	50	EtOH	A	—
4	Al_2O_3	50	EtOH	A	58
5	Al_2O_3	50	EtOH	B	55
6	Al_2O_3	50	EtOH	C	20
7	Al_2O_3	50	CH_3CN	A	45
8	Al_2O_3	50	$CHCl_3$	A	40
9	Al_2O_3	5	EtOH	A	7
10	Al_2O_3	30	EtOH	A	10

[a] Montmorillonite.
[b] Times fold in weight of catalyst, calculated with respect to thiazolidine.
[c] Reaction conditions: (A) commercially available aluminum oxide, basic, Brockmann activity 1 (Macherey–Nagel) and ACS grade solvents; (B) commercially available aluminum oxide and ACS grade solvents supplemented with 5% of water; (C) commercial aluminum oxide, heated at 220 °C for two days before use, and freshly distilled solvents.
[d] Isolated yield.

Table 2
Alumina-catalyzed reaction of quinoline-5,8-dione **5** with thiazolidines **3a–d**

Entry	R	Yield[a] ([c])	**2a/2b**[b] ([c])
1	**3a**	55 (22)	>99:1 (82:18)
2	**3b**	38 (8)	98:2 (75:25)
3	**3c**	34 (17)	95:5 (53:47)
4	**3d**	42 (—)	96:4 (—)

[a] Isolated yield.
[b] HPLC determination.
[c] Results obtained using the previously reported method (See Ref. 1b).

providing rapid access to DTNQ and DTQQ derivatives, important building blocks for the development of new antiproliferative quinones.

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References and notes

1. (a) Gomez-Monterrey, I.; Campiglia, P.; Mazzoni, O.; Novellino, E.; Diurno, M. V. *Tetrahedron Lett.* **2001**, *42*, 5755–5757; (b) Bolognese, A.; Correale, G.; Manfra, M.; Lavecchia, A.; Novellino, E.; Barone, V. *Tetrahedron* **2004**, *60*, 8189–8197; (c) Bolognese, A.; Correale, G.; Manfra, M.; Lavecchia, A.; Mazzoni, O.; Novellino, E.; La Colla, P.; Sanna, G.; Loddo, R. *J. Med. Chem.* **2004**, *47*, 849–858; (d) Gomez-Monterrey, I.; Santelli, G.; Campiglia, P.; Califano, D.; Falasconi, F.; Pisano, C.; Vesci, L.; Lama, T.; Grieco, P.; Novellino, E. *J. Med. Chem.* **2005**, *48*, 1152–1157; (e) Gomez-Monterrey, I.; Campiglia, P.; Carotenuto, A.; Califano, D.; Pisano, C.; Vesci, L.; Lama, T.; Bertamino, A.; Sala, M.; Mazzella di Bosco, A.; Grieco, P.; Novellino, E. *J. Med. Chem.* **2007**, *50*, 1787–1798.
2. Michaud, D.; Hamelin, J.; Texier-Boullet, F. *Tetrahedron* **2003**, *59*, 3323–3331.
3. (a) Basudeb, B.; Pralay, D.; Ismail, H. *Synlett* **2004**, *12*, 2224–2226; (b) Moghaddam, F.; Bardajee, G.; Chadorneshine Veranlou, R. *Synth. Commun.* **2005**, *35*, 2427–2433.
4. Kumarraja, M.; Pitchumani, K. *J. Mol. Catal. A-Chem.* **2006**, *256*, 138–142.
5. Sharma, G.; Kumar, R.; Chakraborti, A. K. *J. Mol. Catal. A-Chem.* **2007**, *263*, 143–148.
6. Firouzabadi, H.; Iranpoor, N.; Jafarpour, M.; Ghaderi, A. *J. Mol. Catal. A-Chem.* **2006**, *249*, 98–102.
7. *Typical experimental procedure for the reaction of naphthoquinone* **4** *or quinoline-5,8-dione* **5** *and thiazolidine derivatives* **3a–d** *with solid catalysts*. A solution of thiazolidine **3a** (1 equiv) in the proper solvent was added to a homogeneous mixture of naphthoquinone **4** (1.4 equiv) and the appropriate solid catalyst. The resulting mixture was stirred for 1.5 h and then filtered. The solid was carefully washed with methanol and the solvent evaporated under vacuum. The residue was dissolved in the minimum amount of chloroform and treated with 1 N HCl solution for 1 h. Then, diethylether and water were added and the organic phase was washed twice with 1 N HCl. The combined acid aqueous phases were neutralized with 10% $NaHCO_3$ solution and the free amine **1** (DTNQ) was then extracted with chloroform. The product was analyzed by HPLC.
8. Sponholtz, W. R.; Pagni, R. M.; Kabalka, G. W.; Green, J. F.; Tan, L. C. *J. Org. Chem.* **1991**, *56*, 5700–5703.
9. We set up three different experiments: (A) *standard* conditions: commercially available aluminum oxide, basic, Brockmann activity 1 (Macherey–Nagel) and ACS grade solvents; (B) *hydrated* conditions: commercially available aluminum oxide and ACS grade solvents supplemented with 5% of water; (C) *dry* conditions: commercial aluminum oxide, heated at 220 °C for two days before use, and freshly distilled solvents.
10. Purity was determined by analytical RP-HPLC performed on C18 column (Vydac 218TP152010) using a gradient of acetonitrile (40–70% acetonitrile in 30 min) in 0.1% aqueous TFA at 1 mL/min.
11. Pratt, Y. T. *J. Org. Chem.* **1962**, *27*, 3905–3910.