

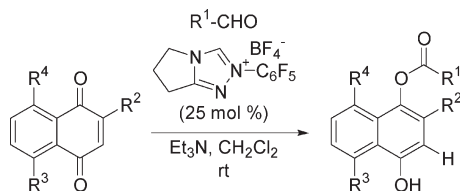
N-Heterocyclic Carbene-Catalyzed Monoacylation of 1,4-Naphthoquinones with Aldehydes

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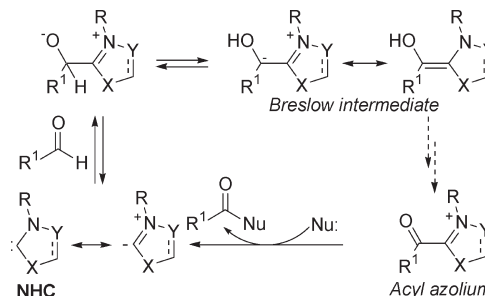
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The NHC-catalyzed conjugate hydroacylation of 1,4-naphthoquinones allows for the synthesis of monoacylated 1,4-dihydroxynaphthalene derivatives. These targets, difficult to prepare selectively by standard protocols, represent important intermediates in the elaboration of highly substituted 1,4-naphthoquinone derivatives, which constitute relevant pharmaceutical scaffolds. High regioselectivity has been observed in the hydroacylation reaction when starting from nonsymmetrical quinones.

N-Heterocyclic carbene (NHC) organocatalysis has become an increasingly popular field in recent times, as it permits a broad range of useful synthetic transformations.¹ The nucleophilic character of NHCs enables their addition to the carbonyl group of aldehydes, giving rise to the formation of

SCHEME 1



“Breslow intermediates”. These can evolve by several reaction pathways, which allows the synthesis of different types of compounds. Among these reaction pathways, the generation of acyl azolium intermediates deserves particular attention, as these species can behave as acylating reagents for carbon- and heteronucleophiles (Scheme 1).^{2,3}

Herein, we report (Scheme 2) the NHC-catalyzed reduction–acylation of 1,4-naphthoquinones (**1**) with aldehydes (**2**) to give the monoacylated 1,4-dihydroxynaphthalenes **4**. In particular, high regioselectivity has been observed when starting from nonsymmetrical 1,4-naphthoquinones.⁴ Compounds **4** are difficult to prepare selectively by conventional acylation reactions, and are useful intermediates in the synthesis of highly substituted 1,4-naphthoquinone derivatives, which constitute relevant pharmaceutical scaffolds.^{5,6}

We have recently undertaken the study of the addition of different reagents to quinones.⁷ In the search of a new type of acylation of quinones, we began the present study by screening several commercially available azolium salts as

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(2) For leading examples on the use of in situ generated NHC-derived acyl azolium species as acylating reagents, see ref 1. For some additional recent examples, see also: (a) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126. (b) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518. (c) Chiang, P.-C.; Kim, Y.; Bode, J. W. *Chem. Commun.* **2009**, 4566. (d) Wang, L.; Thai, K.; Gravel, M. *Org. Lett.* **2009**, *11*, 891. (e) Domingo, L. R.; Aurell, M. J.; Arnó, M. *Tetrahedron* **2009**, *65*, 3432. (f) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190 and references cited therein.

(3) For NHC-catalyzed acylations under oxidative conditions, see: (a) Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727. (b) Zeitler, K.; Rose, C. A. *J. Org. Chem.* **2009**, *74*, 1759. (c) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Tetrahedron* **2009**, *65*, 3102. (d) Maki, B. E.; Patterson, E. V.; Cramer, C. J.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 3942.

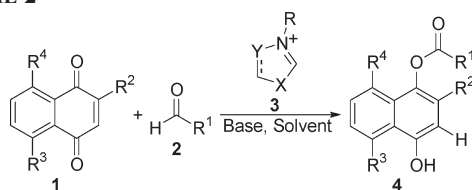
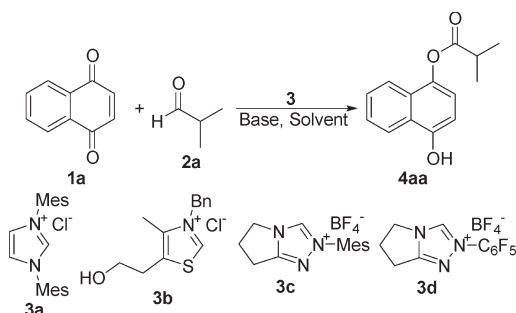
(4) For chemoselectivity in esterification reactions (perspective), see: Nahmany, M.; Melman, A. *Org. Biomol. Chem.* **2004**, *2*, 1563.

(5) See for example: (a) Mellidis, A. S.; Papageorgiou, V. P. *Tetrahedron Lett.* **1986**, *27*, 5881. (b) Deshpande, P. P.; Martin, O. R. *Tetrahedron Lett.* **1990**, *31*, 6613. (c) Hosoya, T.; Takashiro, E.; Yamamoto, Y.; Matsumoto, T.; Suzuki, K. *Heterocycles* **1996**, *42*, 397. (d) Nunes, R. L.; Bieber, L. W.; Longo, R. L. *J. Nat. Prod.* **1999**, *62*, 1643. (e) Ciuffreda, P.; Casati, S.; Santaniello, E. *Tetrahedron* **1999**, *56*, 317. (f) Qabaja, C.; Jones, G. B. *J. Org. Chem.* **2000**, *65*, 7187. (g) Kumamoto, T.; Aoyama, N.; Nakano, S.; Ishikawa, T.; Narimatsu, S. *Tetrahedron: Asymmetry* **2001**, *12*, 791. (h) de Frutos, O.; Atienza, C.; Echavarren, A. M. *Eur. J. Org. Chem.* **2001**, 163. (i) Foti, M. C.; Johnson, E. R.; Vinqvist, M. R.; Wright, J. S.; Barclay, L. R. C.; Ingold, K. U. *J. Org. Chem.* **2002**, *67*, 5190. (j) Wang, X.-Y.; Bu, X.-Z.; Liu, P.-Q.; Ma, L.; Xie, B.-F.; Liu, Z.-C.; Li, Y.-M.; Chan, A. S. C. *Synth. Commun.* **2006**, *36*, 2667. (k) Kimura, M.; Fukasaka, M.; Tamaru, Y. *Synthesis* **2006**, 3611. (l) Krohn, K.; Diederichs, J.; Riaz, M. *Tetrahedron* **2006**, *62*, 1223. (m) Suhara, Y.; Hirota, Y.; Nakagawa, K.; Kamao, M.; Tsugawa, N.; Okano, T. *Biorg. Med. Chem.* **2008**, *16*, 3108.

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SCHEME 2

TABLE 1. Optimization of Reaction Conditions^a

entry	3	base	solvent	yield of 4aa (%)
1	3a	Et ₃ N	CH ₂ Cl ₂	0
2	3b	Et ₃ N	CH ₂ Cl ₂	0
3 ^b	3b	DBU	DMF	0
4	3c	Et ₃ N	CH ₂ Cl ₂	0
5	3d	Et ₃ N	CH ₂ Cl ₂	80
6	3d	DBU	CH ₂ Cl ₂	0
7	3d	Et ₃ N	1,4-dioxane	70
8	3d	Et ₃ N	toluene	20
9	3d	Et ₃ N	DMF	20
10 ^c	3d	Et ₃ N	CH ₂ Cl ₂	60 ^d

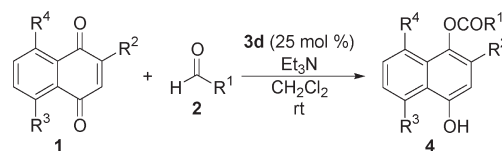
^aUnless otherwise stated, all reactions were performed with 0.1 mmol of quinones **1**, 1.25 equiv of aldehyde **2a**, 0.25 equiv of azolium salts **3**, and 1.0 equiv of base at rt. ^bReaction carried out at 50 °C. ^cReaction carried out with 0.12 equiv of **3d**. ^d10% of the diacylated product **5aa** was also isolated.

precatalysts for the reaction between 1,4-naphthoquinone (**1a**) and isobutyraldehyde (**2a**) (Table 1). Whereas no reaction was observed for imidazolium **3a**, thiazolium **3b**, or mesityltriazolium **3c** salts (entries 1–4), the use of the pentafluorophenyltriazolium salt **3d**⁸ catalyzed a conjugate hydroacylation reaction at rt to afford **4aa** in good yield (entry 5). Best results were obtained in CH₂Cl₂ as solvent as compared with other solvents of different polarities (entries 7–9).^{3d}

Under the optimized reaction conditions achieved (Table 1, entry 5), we examined a variety of aldehydes **2** in their reaction with naphthoquinone **1a** (Table 2, entries 1–6).

We observed that the reaction was general with respect to **2**, admitting aliphatic, alicyclic, aromatic, and unsaturated aldehydes. Also, the reaction was tolerant to the presence of *peri* substituents on the quinone system (Table 2, entry 7).

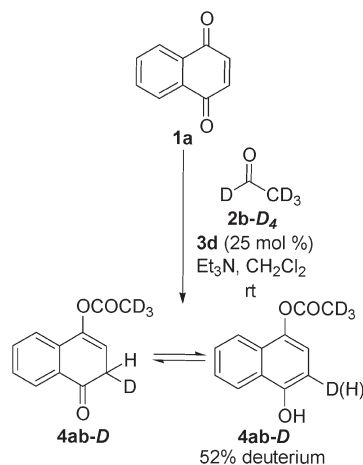
Several nonsymmetrically substituted naphthoquinones **1** were also examined to assess the scope of the reaction with regard to the regiochemistry (Table 2, entries 8–13).⁹ We observed that a single monoacylated compound **4** was formed in all cases. It is noteworthy that, in the case of the

TABLE 2. Scope of the Acylation Reaction^a

entry	1	2	R ¹	R ²	R ³	R ⁴	4 (yield, %) ^b
1	1a	2b	Me	H	H	H	4ab (75)
2	1a	2c	cyclopropyl	H	H	H	4ac (80)
3	1a	2d	<i>o</i> -Br-C ₆ H ₄	H	H	H	4ad (70)
4	1a	2e	CH=CHMe	H	H	H	4ae (80) ^c
5	1a	2f	CH=C(Me) ₂	H	H	H	4af (60)
6	1a	2g	CH=CHCH=CHMe	H	H	H	4ag (65)
7	1b	2a	ⁱ Pr	H	OMe	OMe	4ba (80)
8	1c	2a	ⁱ Pr	Me	H	H	4ca (75)
9	1c	2e	CH=CHMe	Me	H	H	4ce (70)
10	1d	2a	ⁱ Pr	H	OMe	H	4da (75)
11	1d	2d	<i>o</i> -Br-C ₆ H ₄	H	OMe	H	4dd (70)
12	1d	2e	CH=CHMe	H	OMe	H	4de (70)
13	1e	2a	ⁱ Pr	Ph	OMe	H	4ea (65)

^aAll reactions were performed with 0.1 mmol of quinones **1**, 1.25 equiv of aldehydes **2**, 0.25 equiv of **3e**, and 1.0 equiv of Et₃N in CH₂Cl₂ solution (0.3 mL) at rt. ^bIsolated yield after chromatography. ^c10% of the diacylated product **5ae** was also isolated.

SCHEME 3



C2-substituted quinones **1c** and **1e**, the most hindered acylated products **4** resulted from the reaction. In the case of quinone **1d**, high regioselectivity¹⁰ was observed in favor of the 4-hydroxy-5-methoxy-1-naphthyl esters **4**. In one case (Table 2, entry 4), the corresponding diacylated product **5ae** was also isolated.

With regard to the formulation of a plausible mechanism, we have observed that reaction of **1a** with deuterated acetaldehyde (**2b-D₄**) takes place with 52% deuterium incorporation at C3 of the product **1ab-D** (Scheme 3).

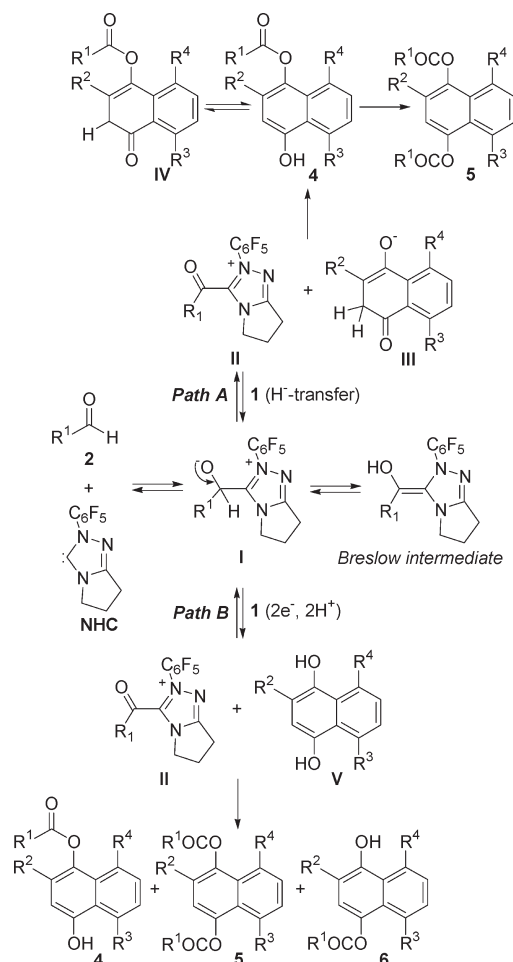
Our experimental results, in particular the obtention of the most hindered acylated hydroquinones **4** as major reaction products, are in agreement with a hydride transfer

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(9) The regiochemical assignment of compounds **4c–e** has been carried out by 1D-NOE, COSY, HMQC, and HMBC NMR experiments. See the Supporting Information for further details.

(10) For regioselective additions to quinone derivatives, see ref 7 and the following: (a) Kelly, T. R.; Gillard, J. W.; Goerner, R. N. Jr.; Lyding, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 5515. (b) Parker, K. A.; Sworin, M. E. *J. Org. Chem.* **1981**, *46*, 3218. (c) Kelly, T. R.; Parekh, N. D.; Trachtenberg, E. N. *J. Org. Chem.* **1982**, *47*, 5009. (d) Couladouros, E. A.; Plyta, Z. F.; Haroutounian, S. A. *J. Org. Chem.* **1997**, *92*, 6 and references cited therein.

SCHEME 4. Plausible Reaction Mechanism



mechanism from intermediate **I** (Scheme 4, path A).^{11,12} In the presence of 1,4-naphthoquinones **1**, which are well-known both for their redox properties and their ability to add nucleophiles in a conjugate fashion, 1,4-hydride transfer from **I** may take place giving rise to the acyl azolium **II** and intermediate **III**. Rapid acylation of **III** by **II** affords **IV**, which tautomerizes to **4**. Further acylation of **4** with **II** may occur to give the diacylated compounds **5** as minor reaction products. However, redox pathways are not to be excluded, and the hydride transfer step might take place intramolecularly from a cation-radical/anion-radical complex between **I** and the Breslow intermediate, leading to an ion pair complex.

(11) For the NHC-catalyzed hydroacylation reaction of non-enolizable 1,2-dicarbonyl compounds (benzil and aroylformates) with aromatic aldehydes, see: Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4558. No reaction was shown by other less electrophilic ketones such as fluorenone or aliphatic aldehydes.

(12) For the reduction of N=N bonds as a secondary reaction in the NHC-catalyzed reaction of α,β -unsaturated aldehydes with hydrazines, see: Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740.

Also, a SET mechanism in which the quinones were acting as oxidants of the Breslow intermediate³ (Scheme 4, Path B) could be operative. This would give rise to the acyl azolium intermediate **II** and the hydroquinone **V**. Acylation of **V** with **II** should have furnished the diacylated compounds **5** as major reaction products, together with the less hindered monoacylated products **6**, and the observed products **4** as minor components of the reaction mixture. However, this product distribution is not in agreement with our experimental results.

In summary, we have developed the NHC-catalyzed reduction–acylation of 1,4-naphthoquinones with aldehydes to afford monoacylated 1,4-dihydroxynaphthalene derivatives. This process takes place with high regioselectivity in agreement with a consecutive hydride transfer–electrophilic acylation mechanism. Further investigations for the use of other Michael acceptors in this catalytic reaction are in progress, and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of 4. With exclusion of air and humidity, 1,4-naphthoquinone **1** (0.1 mmol) was dissolved in CH_2Cl_2 (0.3 mL) in a screw-cap vial containing a magnetic stirring bar. The azolium catalyst **3** (0.025 mmol) was added, followed by 0.125 mmol of the aldehyde **2**, and Et_3N (0.1 mmol). The vial was capped under Ar. After 18 h of stirring at rt, the mixture was filtered through a pad of Celite, which was repeatedly rinsed with Et_2O . The solvent was evaporated under reduced pressure and the products were isolated by chromatography on silica gel with CH_2Cl_2 as eluent.

Isobutyric acid 4-hydroxynaphthalen-1-yl ester (4aa): ^1H RMN (CDCl_3 , 300 MHz) δ 8.00 (d, $^3J = 8.0$ Hz, 1H), 7.65 (d, $^3J = 8.0$ Hz, 1H), 7.45–7.32 (m, 2H), 6.83 (d, $^3J = 8.8$ Hz, 1H), 6.43 (d, $^3J = 8.8$ Hz, 1H), 6.13 (s, 1H), 2.91 (sept, $^3J = 6.7$ Hz, 1H), 1.36 (d, $^3J = 7.1$ Hz, 6H) ppm; ^{13}C RMN (CDCl_3 , 75.5 MHz) δ 176.8, 149.7, 139.8, 127.6, 126.8, 125.5, 125.2, 122.3, 120.8, 117.8, 107.9, 34.4, 19.2, 19.2 ppm; HRMS (EI) calcd for $\text{C}_{14}\text{H}_{14}\text{O}_3$ 230.0943 (M⁺), found 230.0944.

Isobutyric acid 4-isobutyroyloxynaphthalen-1-yl ester (5aa): ^1H RMN (CDCl_3 , 300 MHz) δ 7.83–7.76 (m, 2H), 7.50–7.44 (m, 2H), 7.19 (s, 2H), 2.93 (sept, $^3J = 6.7$ Hz, 2H), 1.37 (d, $^3J = 7.2$ Hz, 12H) ppm; ^{13}C -RMN (CDCl_3 , 75.5 MHz) δ 173.2, 173.2, 143.4, 143.4, 127.5, 127.5, 125.5, 125.5, 120.5, 120.5, 116.7, 116.7, 33.1, 33.1, 17.7, 17.7, 17.7, 17.7 ppm; HRMS (EI) calcd for $\text{C}_{18}\text{H}_{20}\text{O}_4$ 300.1362 (M⁺), found 300.1362.

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Supporting Information Available: Regiochemical assignments and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.