ORGANIC LETTERS

2006
Vol. 8, No. 18
3919−3922

[3+2] versus [4+2] Cycloadditions of Quinone Monoimide with Azadienes: A Lewis Acid-Free Access to 5-Amino-2,3-dihydrobenzofuranes

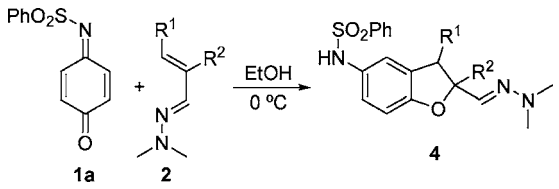
Thierry Lomberget,[†] Fabien Baragona,[†] Bernard Fenet,[‡] and Roland Barret*,[†]

Laboratoire de Chimie Thérapeutique, EA 3741, Ecosystèmes et Molécules Bioactives, Faculté de Pharmacie, Université Claude Bernard Lyon 1, 8 Avenue Rockefeller, 69373 Lyon Cedex 08, France, and Centre Commun de RMN, UMR 5012 CNRS, Université Claude Bernard Lyon 1, CPE, 43 Bd du 11 Novembre 1918, 69622 Villeurbanne Cedex, France

barret@sante.univ-lyon1.fr

Received May 15, 2006

ABSTRACT



The reaction between *p*-quinone monoimide 1a and various azadienes 2 is described in the absence of a Lewis acid promoter. When α,β-unsaturated hydrazones are substituted by proton or alkyl groups, 2,3-dihydrobenzofuranes 4, a motif that is present in numerous biologically active products, are obtained in moderate to excellent yields. The regio- and stereoselectivity of this reaction has been proved by a complete NMR study, including ^{1}H–^{15}N correlations.

Quinone imides, the aza analogues of quinones, exhibit a wide range of reactivity, based on a weak electrophilic pattern.[1] Among all, [4+2] and [3+2] cycloaddition reactions have been extensively studied and proved to be useful in organic synthesis. In the mid 90s, Engler's group described an elegant Lewis acid promoted [3+2]-type condensation between alkoxy *p*-quinone monoimides and a styrenic moiety, which allows the selective formation of either indolines or dihydrobenzofuranes.[2] Recently, Kerr and co-workers have exploited Diels−Alder reactions of sulfonylated *p*-benzoquinone monoimide with various carbodienes as the starting point for a versatile synthesis of 5-triflyloxyindoles.[3]

However, to our knowledge, no example of the reaction between a dienophile such as **1** has been described so far with α,β-unsaturated *N*,*N*-dimethylhydrazones **2** (Figure 1).[4]

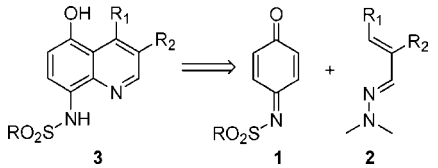


Figure 1. [4+2] cycloaddition strategy to compounds **3**.

This synthetic approach would allow an easy access to 3- and 4-substituted 8-sulfonamido-5-hydroxyquinolines **3**,

[†] Faculté de Pharmacie, Université Claude Bernard Lyon 1.
[‡] UMR 5012 CNRS, Université Claude Bernard Lyon 1.

(1) For a recent and exhaustive review on the chemistry of quinone imides, see: Nair, V.; Dhanya, R.; Rajesh, C.; Devipriya, S. *Synlett* **2005**, 2407.

(2) (a) Engler, T. A.; Chai, W.; Lynch, K. O. *Tetrahedron Lett.* **1995**, *36*, 7003. (b) Engler, T. A.; Chai, W.; LaTessa, K. O. *J. Org. Chem.* **1996**, *61*, 9297.

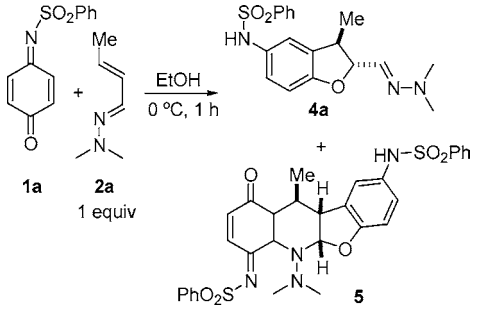
(3) England, D. B.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 6519.

10.1021/ol061184a CCC: $33.50
Published on Web 08/03/2006

regarding the leaving ability of the dimethylamino group of the Diels−Alder intermediate for a subsequent aromatization (Figure 1).[5]

We first investigated the reaction of quinone monoimide **1a** (R = Ph)[6] with 1 equiv of azadiene **2a** (R^1 = Me and R^2 = H) at 0 °C in absolute ethanol. A fast reaction occurred as shown by the total disappearance of **1a** (checked by TLC analysis) after a 1 h reaction time. To our surprise, neither the Diels−Alder adduct nor aminophenol **3** was detected in the crude mixture but we observed the formation of 5-sulfonamido-2,3-dihydrobenzofurane **4a** as the major product[7] (32% yield) together with tetracyclic compound **5** (24% yield) (Scheme 1).[8]

Scheme 1. [3+2] and [4+2] Cycloaddition Reactions between *p*-Quinone Monoimide **1a** and Azadiene **2a**



The latter compound was formed after a cascade sequence: a [4+2] cycloaddition reaction between **1a** and diene **2a** first occurred that led to the Diels−Alder adduct **6a** which, in turn, reacted with a second molecule of quinone imide **1a** according to a [3+2]-type reaction on the newly formed double bond (Figure 2).

Compound **5** slowly isomerizes to the corresponding aromatic aminophenol **7** in deuterated chloroform[9] and isomerizes more slowly in polar solvents such as acetone[10] or ethyl acetate. This tautomeric rearrangement is greatly

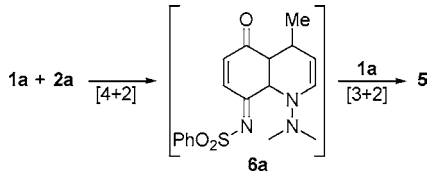
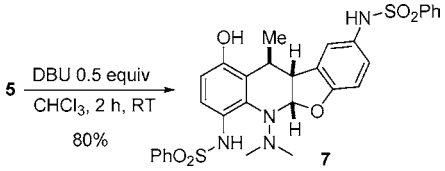


Figure 2. [4+2] + [3+2] cascade sequence to compound **5**.

accelerated by a basic treatment with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (Scheme 2). The relative stability of a

Scheme 2. Base-Promoted Tautomerization of **5** into **7**



keto form in **5** may be assumed by intramolecular interactions between the electron-deficient nitrogen atom of the sulfonamide and the electron-rich dimethylhydrazone one.

The structure of compound **7** was determined without ambiguity with the help of a single-crystal diffraction analysis which clearly shows the cis junction of the dihydrobenzofurane with the C_6 nitrogen-containing ring (Figure 3).

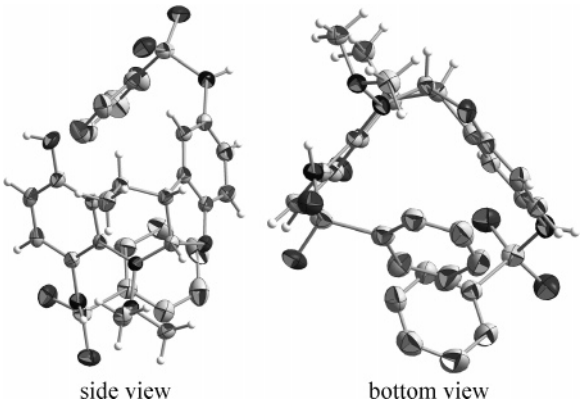


Figure 3. ORTEP view of the crystal structure of **7**. Ellipsoids are represented at the 40% probability level (hydrogens of the sulfonamides and acetone of crystallization removed for clarity).

Despite the numerous examples of elimination of the dimethylamino group in cyclic hydrazones,[4] the robustness of the two central nonaromatic rings toward the aromatization process is worth noting. This particularity could be explained by an intramolecular hydrogen bond[11] and interactions between the two sulfonamide functionalities in this folded and compact structure (Figure 3, bottom view).

(4) For examples of the synthetic utility of α,β-unsaturated *N*,*N*-dimethylhydrazones for the elaboration of nitrogen heterocycles, see: (a) Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261. (b) Waldner, A. *Helv. Chim. Acta* **1988**, *71*, 486. (c) For a review: Pautet, F.; Nebois, P.; Bouaziz, Z.; Fillion, H. *Heterocycles* **2001**, *54*, 1095.

(5) This strategy has been exploited in the quinone series for the preparation of various heterocycles: (a) Kitahara, Y.; Tamura, F.; Nishimura, M.; Kubo, A. *Tetrahedron* **1998**, *54*, 8421. (b) Pascual-Alfonso, E.; Avendaño, C.; Menéndez, J. C. *Synlett* **2000**, 205. (c) Alvarez, F.; Taleb, A.; Gentili, J.; Nebois, P.; Terreux, R.; Domard, M.; Thozet, A.; Merle, D.; Fillion, H.; Walchshofer, N. *Eur. J. Org. Chem.* **2005**, 1903.

(6) Adams, R.; Looker, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 1145.

(7) Formation of 5-hydroxy-2,3-dihydrobenzofurane during the reaction between azadiene **2a** and *p*-benzoquinone is reported in the literature but requires a stoichiometric amount of Lewis acid (1 equiv of BF_3) to proceed in a 38% yield (20 h reaction time, 23 °C): Echavarren, A. M. *J. Org. Chem.* **1990**, *55*, 4255.

(8) For an optimized synthesis of compound **5** involving its selective precipitation, see Supporting Information.

(9) Aged $CDCl_3$ generally contains acid traces which behave as a catalyst for the transformation of the keto compound **5** into the phenol **7**.

(10) A 11% conversion of **5** into **7** in acetone-d_6 was observed by ^{1}H NMR after a 22 h stay at 25 °C.

The construction of the dihydrobenzofurane ring in **5** as well as the formation of compound **4a** could be explained by the use of a polar protic solvent such as ethanol which must favor ionic intermediates that govern the [3+2]-type reaction.[12] The interest of our method is to avoid the use of a Lewis acid to promote the reaction, a reagent that is often not compatible with numerous protecting groups.[13]

The regioselectivity of this reaction (i.e., formation of dihydrobenzofurane **4a** rather than an indoline) and the trans stereochemistry of **4a** had been proved by a complete NMR analysis (Figure 4).

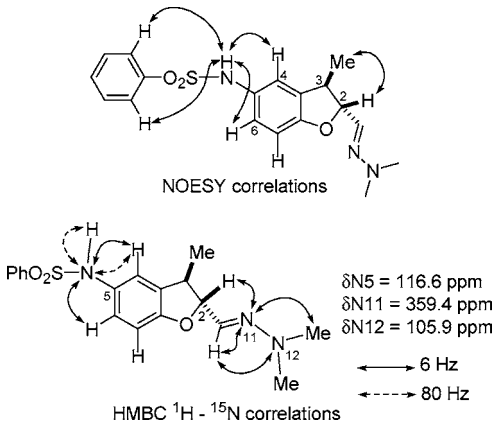


Figure 4. NMR study of compound **4a**.

NOESY correlations were observed between the sulfonamide proton and (a) the protons at the ortho position of the sulfonamide phenyl ring and (b) protons H4 and H6 of the dihydrobenzofurane ring.

An additional structural proof was provided by ^{1}H−^{15}N HMBC heteronuclear correlation experiments that were carried out on nonenriched compounds.[14] A first 2D experiment (optimized for J_{NH} = 6 Hz, plain arrows, Figure 4) showed: (a) attachment of the sulfonamide group at the 5-position, (b) a strong correlation between N11 and H2, and (c) a correlation between the hydrazone proton and N12 (external reference for ^{15}N NMR: liquid NH_3).

A second experiment (optimized for J_{NH} = 80 Hz, dashed arrows, Figure 4) was carried out to confirm the linkage between the broad exchangeable proton signal and N5 of the sulfonamide.

Concerning the stereochemistry of compound **4a**, the distance between the methyl group at the 3-position and H2 (Figure 4) was evaluated from the NOESY experiment to be 2.44 Å,[15] a distance that is not compatible with a cis configuration on the oxygen ring.

The formation of the dihydrobenzofurane (DHBF) **4a** appears very attractive and helpful for organic chemists because this structure is present in many natural products and biologically active compounds.[16] Moreover, there is actually a growing interest for this motif as shown by recent approaches for the building of dihydrobenzofurane derivatives.[17] The main synthetic interest of the method described herein consists of the dual incorporation of an amino substituent at the 5-position of the DHBF (for QSAR purposes) and the hydrazone moiety which could be transformed into various functionalities such as nitrile or aldehyde.

We then decided to optimize the reaction conditions to favor the formation of this oxygen-containing heterocyclic compound. To achieve this goal, we hypothesized that the stoichiometry and/or reagent concentration would play an important role. Indeed, we observed that the amount of the bisadduct **5** is maximum when a 1:1 molar ratio for the reagents was used[18] (Table 1, entry 1) whereas the proportion

Table 1. Optimization of the [3+2] Reaction Conditions

entry	equiv of **2a**	reaction conditions[a]/ time	molar ratio[b] **4a/5**
1	1	direct addition/1 h	63:37
2	2	direct addition/1 h	75:25
3	5	direct addition/1 h	86:14
4	5	slow addition (1 h)/30 min	93:7
5	5	slow addition (4 h)/30 min	100:0

[a] All the reactions were carried out in EtOH (0.01 M concentration for quinone monoimide **1a**) at 0 °C. See Supporting Information for a detailed protocol. [b] Determined by ^{1}H NMR on the crude mixture.

of the DHBF **4a** increased with the quantity of diene **2a** and, so, its concentration (Table 1, entries 2 and 3).

Finally, the formation of product **5** was completely avoided by slowly adding (syringe pump) an alcoholic solution of quinone imide onto a solution of azadiene (5-fold excess), a process which maintains a low concentration of the dieno-

(11) The distance between the sulfonamide proton and the NMe_2 nitrogen is 2.21 Å (measured on the X-ray crystal structure).

(12) Blanco, M. M.; Alonso, M. A.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **1996**, *52*, 5933.

(13) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999.

(14) For a review on the use of ^{15}N NMR spectroscopy at the natural abundance: Martin, G. E.; Hadden, C. E. *J. Nat. Prod.* **2000**, *63*, 543.

(15) Ämmälahti, E.; Bardet, M.; Molko, D.; Cadet, J. *J. Magn. Res., Ser. A* **1996**, *122*, 230.

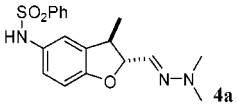
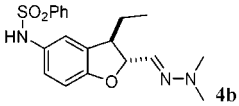
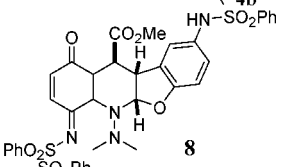
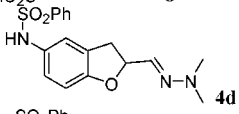
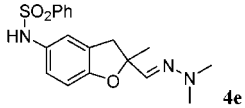
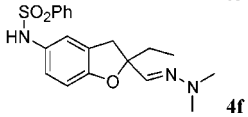
(16) For some examples: (a) anti-HIV pterocarpans: Engler, T. A.; LaTessa, K. O.; Iyengar, R.; Chai, W.; Agrios, K. *Bioorg. Med. Chem.* **1996**, *4*, 1755. (b) Antihypertensive Efaroxan: de Carvalho e Silveira, G. P.; Coelho, F. *Tetrahedron Lett.* **2005**, *46*, 6477 and references therein. (c) Melatoninergic agents: Sun, L.-Q.; Takaki, K.; Chen, J.; Bertenshaw, S.; Iben, L.; Mahle, C. D.; Ryan, E.; Wu, D.; Gao, Q.; Xu, C. *Bioorg. Med. Chem. Lett.* **2005**, *25*, 1345. (d) PPARα agonists: Shi, G. Q.; Dropinski, J. F.; Zhang, Y.; Santini, C.; Sahoo, S. P.; Berger, J. P.; MacNaul, K. L.; Zhou, G.; Agrawal, A.; Alvaro, R.; Cai, T.-q.; Hernandez, M.; Wright, S. D.; Moller, D. E.; Heck, J. V.; Meinke, P. T. *J. Med. Chem.* **2005**, *48*, 5589. (e) κ-opioid agonists: Chu, G.-H.; Gu, M.; Cassel, J. A.; Belanger, S.; Graczyk, T. M.; DeHaven, R. N.; Conway J.; Koblish, M.; Little, P. J.; Dehaven-Hudkins, D. L.; Dolle, R. E. *Bioorg. Med. Chem.* **2005**, *15*, 5114.

(17) For recent reports on the preparation of dihydrobenzofuranes, see: (a) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887. (b) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Marcos, C. *Chem.−Eur. J.* **2005**, *11*, 5397. (c) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778. (d) Grant, V. H.; Liu, B. *Tetrahedron Lett.* **2005**, *46*, 1237. (e) Lin, H.; Schall, A.; Reiser, O. *Synlett* **2005**, 2603.

(18) The use of a 2-fold excess of **1a** led to a more complex reaction mixture: this could be explained by the oxidizing properties of the quinoid compound **1a**.

phile in the reaction mixture (Table 1, entry 5). Compound **4a** was then prepared under these conditions with a 66% isolated yield (Table 2, entry 1).

Table 2. [3+2] Reaction of Quinone Monoimide **1a** with Various Azadienes **2a**−**f**

entry	azadiene	product[a]	isolated yields (%)
1	**2a** R^1 = Me R^2 = H	 **4a**	66
2	**2b** R^1 = Et R^2 = H	 **4b**	53
3	**2c** R^1 = CO_2Me R^2 = H	 **8**	32
4	**2d** R^1 = R^2 = H	 **4d**	73
5	**2e** R^1 = H R^2 = Me	 **4e**	93
6	**2f** R^1 = H R^2 = Et	 **4f**	90

[a] All the experiments were carried out in EtOH, at 0 °C, with quinone monoimide **1a** (0.01 M) and azadiene **2** (5 equiv). See Supporting Information for a typical experimental procedure.

With these optimal conditions in hand, we decided to study the scope of the reaction further by using other azadienes **2b**−**f**, bearing either electron-withdrawing or electron-donating substituents.[19]

By increasing the steric hindrance on the β-position of the azadiene with an ethyl group, DHBF **4b** was obtained with a slightly lower yield (Table 2, entry 2).

With azadiene **2c**, having an electron-withdrawing ester group at the β-position, we observed the exclusive formation of the Diels−Alder adduct **8** with a moderate 32% yield (Table 2, entry 3). The deactivation of the azadiene appears to inhibit the [3+2] process: the reaction now proceeds under a pure orbital control, independently of the reaction medium polarity.

Without any substituent on the α,β-unsaturated hydrazone **2d**, the reaction proceeded well and the DHBF **4d** was obtained with a 73% yield (Table 2, entry 4).

Finally, by using azadienes bearing electron-donating methyl or ethyl groups at the α-position, we can observe a significant improvement as the corresponding 2-methyl and 2-ethyl dihydrobenzofuranes **4e** and **4f** were obtained in excellent 93% and 90% yields, respectively (Table 2, entries 5 and 6). It is noteworthy that during these last two examples a quaternary center next to the oxygen atom was created, which renders our strategy of valuable interest.[20]

In conclusion, we have described the Lewis acid-free reaction between *p*-quinone monoimide and various azadienes as an access to substituted 2,3-dihydrobenzofuranes. We are currently investigating a diastereoselective approach of this widely spread heterocyclic structure, and this study will be reported in due course.

Acknowledgment. The authors would like to thank Dr. Erwann Jeanneau (Centre de Diffractométrie Henri Longchambon, Université Claude Bernard Lyon 1) for the X-ray diffraction analysis of compound **7**.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for compounds **4a**,**b**,**d**−**f**, **5**, **7**, and **8**. Crystallographic file (.cif) for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The reaction of **1a** with 5 equiv of cinnamaldehyde *N*,*N*-dimethylhydrazone (R^1 = Ph, R^2 = H) led to a complex mixture with only traces of the corresponding DHBF.

(20) For a review on the construction of enantioenriched quaternary stereocenters, see: Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369.