ORGANIC LETTERS

2005
Vol. 7, No. 7
1211−1214

One-Pot Multistep Synthesis of 4-Acetoxy-2-amino-3-arylbenzofurans from 1-Aryl-2-nitroethylenes and Cyclohexane-1,3-diones

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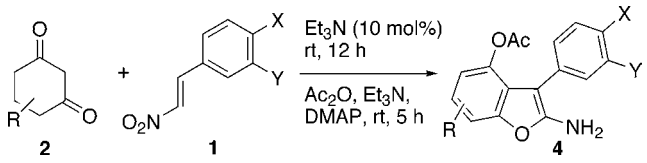
Received December 1, 2004

ABSTRACT



A novel method for synthesizing 4-acetoxy-2-amino-3-arylbenzofurans (4) from 1-aryl-2-nitroethylenes (1) and cyclohexane-1,3-diones (2) is described. The method features one-pot operation of a solution of 1 and 2 in THF with catalytic Et_3N (rt, 12 h) followed with Ac_2O, Et_3N, and DMAP (rt, 5 h), although the process consists of 13 elementary reactions.

The benzofuran framework is a core structure of many heterocyclic compounds of synthetic or pharmaceutical importance.[1] Because benzofurans elicit a broad spectrum of biological activities, a number of synthetic methods have been reported. Many of these synthetic routes employ substituted phenol derivatives as a starting material.[2,3] During the course of our studies on the synthetic potential of cyclohexane-1,3-diones,[4] we have discovered a novel domino process[5] consisting of 13 elementary reactions that commences with a Michael addition reaction between 1-aryl-2-nitroethylenes (**1**)[6] and cyclohexane-1,3-diones (**2**) to eventually afford 4-acetoxy-2-amino-3-arylbenzofuran derivatives (**4**) as outlined in Scheme 1.

Extremely simple reagents and conditions were used in this two-component coupling reaction. A solution of **1** and **2** in THF containing a catalytic amount of triethylamine (10 mol %) was stirred at room temperature for 12 h, which was expected to afford cyclic oxime intermediates (**3**).[7] To this mixture were added acetic anhydride (Ac_2O), triethylamine (Et_3N), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) at room

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(1) (a) Cagniant, P.; Cagniant, D. In *Advanced Heterocyclic Chemistry* Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1975; pp 337−482. (b) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. In *Pharmaceutical Substances*, 3rd ed.; Thieme: Stuttgart, 1999.

(2) For leading references, see: (a) Brady, W. T.; Giang, Y. F. *J. Org. Chem.* **1986**, *51*, 2145−2147. (b) Nicolaou, K. C.; Snyder, S. A.; Bigot, A.; Pfefferkon, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1093−1096; *Angew. Chem.* **2000**, *112*, 1135−1138. (c) Meshram, H. M.; Sekhar, K. C. Ganesh, Y. S. S. Yadav, J. S. *Synlett* **2000**, 1273−1274. (d) Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031−1032. (e) Katritzky, A. R.; Ji, Y.; Fang, Y.; Prakash, I. *J. Org. Chem.* **2001**, *66*, 5613−5615.

(3) For palladium-catalyzed synthesis of benzofurans from 2-alkynylphenol derivatives, see: (a) Larock, R. C.; Yum. E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270−3271 and references therein. (b) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280−9288. (c) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297−299. (d) Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365−2368.

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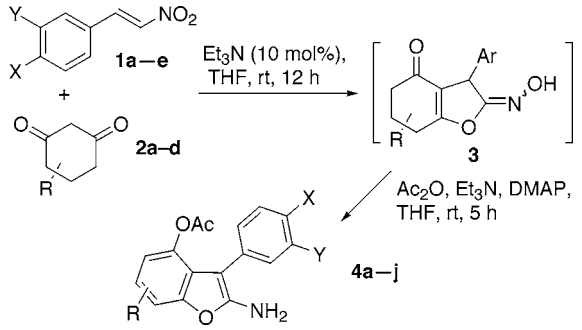
(5) For reviews of domino reactions, see: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131−163. (b) Waldmann, H. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, 1995; p 193.

(6) For the preparation of *trans*-1-aryl-2-nitroethylenes (**1**), see Supporting Information.

(7) Formation of cyclic oximes of this class was fragmentally reported; see: (a) Larson, H. O.; Oot, T.-C.; Siu, A. K. Q.; Hollenbeak, K. H.; Cue, F. L. *Tetrahedron* **1969**, *25*, 4005−4010. (b) Ansell, G. B.; Moore, D. W.; Nielsen, A. T. *Chem. Commun.* **1970**, 1602−1603.

10.1021/ol047540b CCC: $30.25
Published on Web 03/04/2005

Scheme 1. One-Pot Synthesis of 4-Acetoxy-2-amino-3-arylbenzofurans from 1-Aryl-2-nitroethylenes and Cyclohexane-1,3-diones



temperature. The resulting solution was stirred at that temperature for 5 h to give **4a**−**j** in acceptable yields.[8] The structures of **4a**−**j** were revealed by ^{1}H and ^{13}C NMR analysis. In addition, the NMR-based structures were confirmed by X-ray crystallographic analysis of **4b**[9] and **4c**[9] as representative examples (Figure 1). Results summarizing the

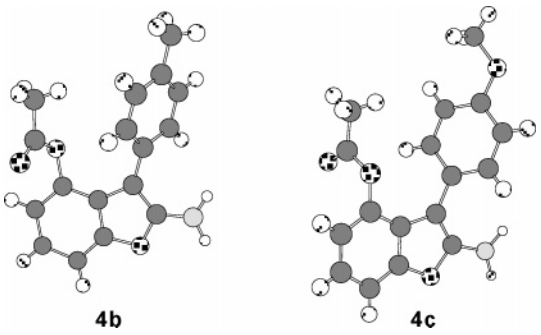


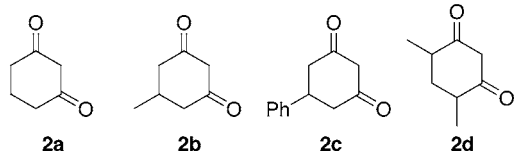
Figure 1. Chem 3D presentation of X-ray structures.

reactions between **1a**−**e** and symmetrical cyclohexane-1,3-diones (**2a**−**d**)[10] leading to 4-acetoxy-2-amino-3-arylbenzofurans (**4a**−**j**) are given in Table 1.

When an aryl substituent of **1** was replaced with an alkyl group, as in **1f**, the reaction product was **5** (27%) under identical reaction conditions (Scheme 2). In addition, the use of dimedone generated **6** (51%) (Scheme 2). Since the treatment of **3** with a combination of Ac_2O, Et_3N, and DMAP should effect acetylation of the oxime moiety, we were able to deduce a plausible pathway (Scheme 3) on the basis of

Table 1. 4-Acetoxy-2-amino-3-arylbenzofurans from Symmetrical Cyclohexane-1,3-diones[a]

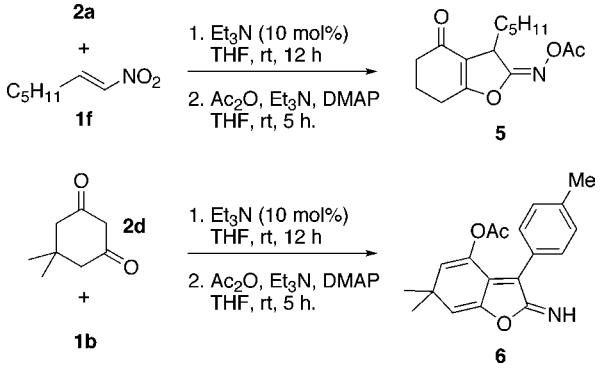
entry	nitroolefin	X	Y	dione	product (R)	yield (%)[b]
1	**1a**	H	H	**2a**	**4a** (H)	70
2	**1b**	Me	H	**2a**	**4b** (H)	61
3	**1c**	OMe	H	**2a**	**4c** (H)	56
4	**1d**	Br	H	**2a**	**4d** (H)	35
5	**1e**	H	NO_2	**2a**	**4e** (H)	23
6	**1b**	Me	H	**2b**	**4f** (6-Me)	62
7	**1d**	Br	H	**2b**	**4g** (6-Me)	40
8	**1b**	Me	H	**2c**	**4h** (6-Ph)	76
9	**1d**	Br	H	**2c**	**4i** (6-Ph)	51
10	**1b**	Me	H	**2d**	**4j** (5,7-Me_2)	57



[a] Conditions: (1) Et_3N (10 mol %), THF, rt, 12 h. (2) Ac_2O, Et_3N, DMAP, rt, 5 h. [b] For product isolated by SiO_2 column chromatography.

these two control experiments. This pathway involves 13 elementary reactions and can be outlined as follows: double conjugate additions (**2** + **1** → **7** → **8**), formation of **3** as a tautomer of the nitroso intermediate (**9**) produced from **8** by dehydration, acetylation of **3** triggering 1,8-elimination[11] of **11** (tautomer of **10**), resulting in the formation of α,β:γ,δ-unsaturated imine (**12**), and finally the aromatization from **12** facilitated by enolization to give **4** via acetylation of the phenolic hydroxy group.

Scheme 2



The formation of **5** (Scheme 2) clearly means that **10** must be tautomerized to **11** for the succeeding 1,8-elimination to be feasible. Increased acidity of the benzylic hydrogen is likely to be responsible for this reaction. This is apparently lacking in **5**. However, the isolation of **6** is indicative of the

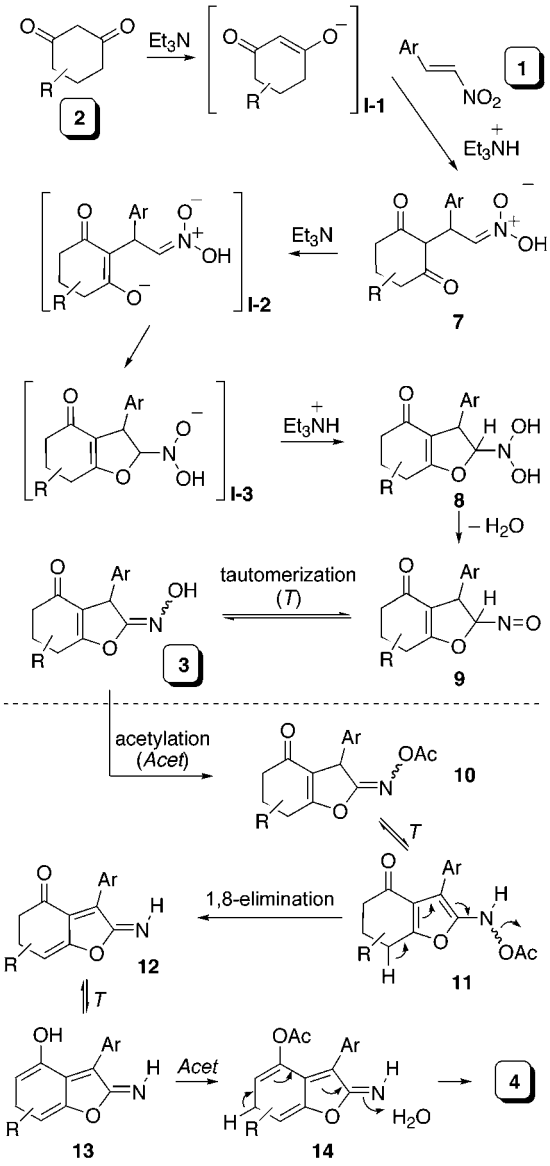
(8) For example, although the yield of **4e** was 23%, the average yield per step can be calculated to be 85% if the process involves eight intermediates as shown in Scheme 3.

(9) CCDC-251515 and -251516 contain the supplementary crystallographic data for this paper. These data can be obtained online free of charge (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK; fax (+44) 1223-336-033; e-mail deposit@ccdc.cam.ac.uk). For similar information, see Supporting Information (CIF).

(10) Among them, **2a**−**c** are commercially available: for the synthesis of **2d**, see ref 4.

(11) For a 1,8-elimination reaction, see: Klaus, R.; Koenig, T. *Tetrahedron Lett.* **1985**, *26*, 4835−4838.

Scheme 3. Plausible Mechanism



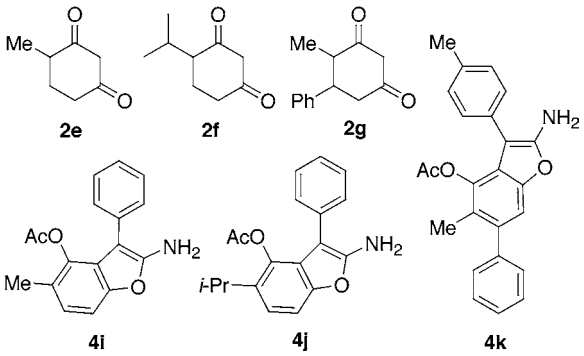
occurrence of an isoaromatization as the final step of this domino process.

We have recently developed a method for preparing substituted cyclohexane-1,3-diones from simple ketones and α,β-unsaturated esters.[4] Therefore, we have examined the regiochemistry of the second conjugate addition step by the internal heteronucleophile (**7** → **8** → **9** → **3**) by using unsymmetrical cyclohexane-1,3-diones such as **2f**−**h**.[4] However, substituents at the C(4) or C(5) positions of **2f**−**h** exhibited almost no control over this kind of regiochemistry for manipulating the furan framework, resulting in only marginal selectivity (Table 2).

To expand the structural diversity of **4**, we made some efforts to introduce substituents at C(2) of **4** other than the amino group.[12] We tried to directly replace the amino group of **4** with an acetoxy group and found a quite simple answer to the problem of realizing such a transformation, which is shown in Scheme 4. Upon treatment of **4a** or **4e**, as

Table 2. 2-Amino-3-arylbenzofurans from Unsymmetrical Cyclohexane-1,3-diones

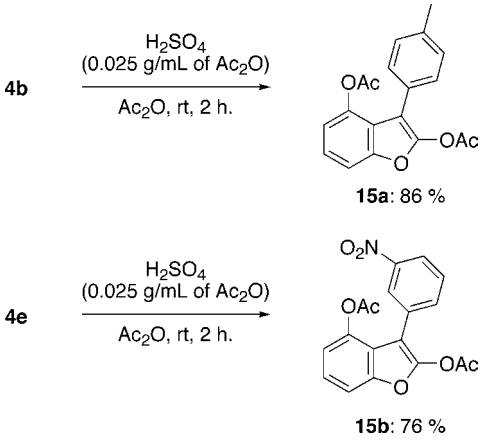
nitroolefin	diones	products [c]	yield % [a] (**4** + **4′**)	ratio [b] (**4** : **4′**)
1a (X = H)	**2e**	**4i** + **4′i**	51	3 : 1
	2f	**4j** + **4′j**	58	4 : 1
1b (X = Me)	**2g**	**4k**+ **4′k**	55	3 : 1



[a] For products isolated by SiO_2 column chromatography. [b] **4** and **4′** could not be separated by SiO_2 column chromatography, and the ratios were determined by ^1H NMR analysis. [c] **4′k** = 4-acetoxy-7-methyl isomer; **4′l** = 4-acetoxy-7-isopropyl isomer; **4′m** = 4-acetoxy-6-phenyl-7-methyl isomer.

representative cases, with acetic anhydride (60 times as much as **4**) in the presence of H_2SO_4 (ca. 1.5 times as much as **4**),

Scheme 4. Conversion of **4** to 2-Acetoxybenzofurans



they led to **15a** or **15b**, respectively, in good yields. The process probably involves the generation of an imidatonium ion intermediate through protonation at C(3) and the addition

(12) For benzofuran derivatives with an oxygen-linking substituent such as a alkoxycarbonyloxy group at C(2) and their synthetic implications, see: (a) Black, T. H.; Arrivo, S. M.; Schumm, J. S.; Knobeloch, J. M. *J. Chem. Soc., Chem. Commun.* **1986**, 1524−1525. (b) Black, T. H.; Arrivo, S. M.; Schumm, J. S.; Knobeloch, J. M. *J. Org. Chem.* **1987**, *52*, 5425−5430. (c) Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770−4773. (d) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921−3924. (e) Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031−1032.

of an acetoxy anion to such a reactive intermediate followed by Hoffman-type elimination to give C(2)-acetoxy product **15**, although the rationalization of the exact nature of this pathway must await further studies.

In conclusion, we have developed one-pot, multistep synthesis of 2-aminobenzofurans in which the union of 13 elementary reactions are proposed to play an important role. The synthesis simply involves treating a solution of **1** and **2** in THF with catalytic Et_3N, followed by conventional acetylation conditions (Ac_2O, Et_3N, and DMAP) at room temperature. The reaction scheme is so simple that **4** can be synthesized in multigram quantities if so desired. Furthermore, the availability of derivatives of **1** and **2** would make the present synthesis highly attractive in diversity-oriented organic synthesis.[13]

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We greatly appreciated Drs. N. Hamanaka and Y. Nagao, Ono Pharmaceutical Co., Ltd, for X-ray crystallographic analyses.

Supporting Information Available: Experimental procedures and spectroscopic data for **4a**−**m**, **5**, **6**, and **15a**,**b**; X-ray structural information for **4b** and **4c** in CIF format; and ^1H and ^{13}C NMR spectra for **4a**,**b**,**d**−**f**,**j**, **6**, and **15a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For example, see: (a) Mitchison, T. J. *Chem. Biol*. **1994**, *1*, 3−6. (b) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969. (c) Stavenger, R. A.; Schreiber, S. L. *Angew. Chem., Int. Ed*. **2001**, *40*, 3417−3421; *Angew. Chem.* **2001**, *113*, 3525−3529.