ORGANIC LETTERS

2005
Vol. 7, No. 23
5273−5276

A One-Pot Regiospecific Synthesis of Highly Functionalized 1,4-Benzodioxin Derivatives from an Electrochemically Induced Diels–Alder Reaction

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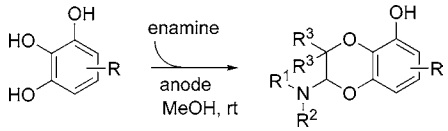
Received September 6, 2005

ABSTRACT



The anodic oxidation of pyrogallol derivatives produces chemically unstable *o*-quinone heterodienes, which are trapped in situ by enamine dienophiles through regiospecific inverse-electron-demand Diels–Alder reactions. The possibility of introducing variations in both cycloaddition partners gives rise to highly substituted 1,4-benzodioxin cycloadducts with up to five elements of diversity. The reactions proceed under mild conditions with a good efficiency. The methodology should be amenable to the assembly of libraries of biologically relevant heterocycles.

Various 1,4-benzodioxin derivatives have been shown to display very interesting pharmacological properties including anti-inflammatory, diuretic, anti-hyperglycemic, and calcium antagonistic activities.[1] Some of them are also antagonists of α-adrenergic receptors at the origin of anti-hypertensive properties, while others have affinities with serotonin receptors which are involved in nervous breakdown and schizophrenia.[2]

Among the different methods leading to the 1,4-benzodioxin scaffold, the Diels−Alder reaction may provide access to a wide molecular diversity through the variation of the structure of both cycloaddition partners. Despite this potential, the synthetic scope of this reaction is limited by the requirement of *o*-quinone heterodienes which are not readily accessible stable compounds. Most of the work has been generally restricted to specific *o*-quinone heterodienes, mainly to 4-*tert*-butyl *o*-quinone, Corey's reagent, *o*-chloranil, *o*-bromanil, and *o*-naphthoquinones.[3] To the best of our knowledge, only a few reports described the synthesis of 1,4-benzodioxin derivatives from in situ chemically generated unstable *o*-quinone, and the yield was somewhat low.[3j−l,4]

Electrochemically induced cycloadditions have proved to be a promising tool for organic chemistry.[5] Various unstable electrogenerated dienes[5e−g] or dienophiles[5h] have been successfully used in Diels−Alder reactions to afford the desired cycloadduct in high yield, with good stereocontrol.

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(1) Guillaumet, G. In *Comprehensive Heterocyclic Chemistry II*, 1st ed.; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 6, p 447.

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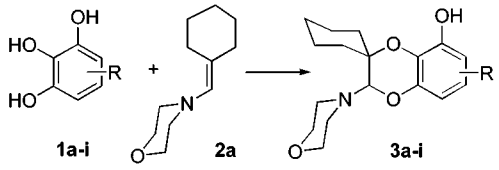
10.1021/ol052146e CCC: $30.25
Published on Web 10/20/2005

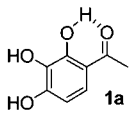
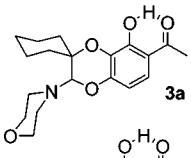
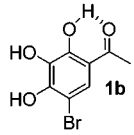
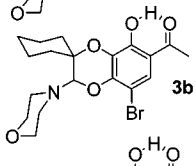
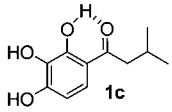
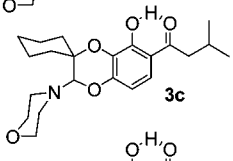
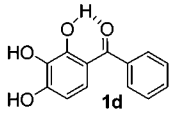
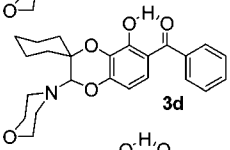
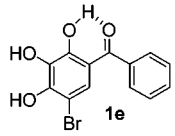
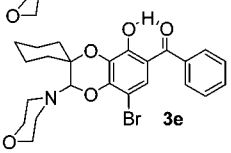
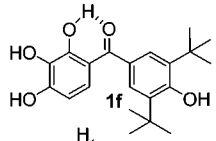
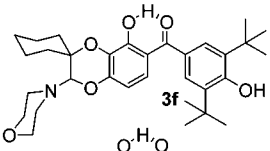
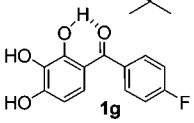
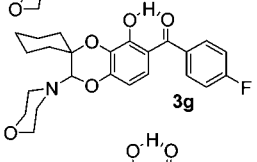
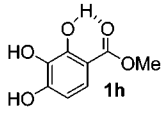
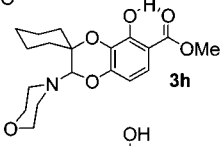
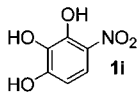
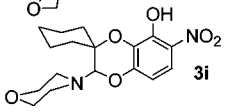
Recently, we described a cascade reaction traversing through an inverse-electron-demand Diels−Alder (IEDDA) reaction of an *o*-iminoquinone diene and a secondary alkylenamine dienophile, two chemically nonaccessible unstable entities.[6] Our electrochemical procedure, wherein both cycloaddition partners were generated in situ, at room temperature, under metal-free conditions, allowed the rapid construction of diverse 2-alkylamino-1,4-benzoxazine derivatives which proved to be potent neuroprotective agents in vitro and in vivo.[6d]

We report now the electrochemically induced *o*-quinone cycloaddition reaction with enamines, which gives rise to highly functionalized 1,4-benzodioxin derivatives, with complete regiochemical control. This reaction, which offers the opportunity to introduce diversity elements in both cycloaddition partners, should allow the easy synthesis of libraries of biologically relevant heterocycles.

We first performed optimization studies of the anodic controlled-potential electrolysis of pyrogallol derivatives using **1a** in the presence of 4-cyclohexylidenemethylmorpholine **2a**. We found that the optimum conditions required a mercury anode, methanol as the solvent, and tetraethylammonium hexafluorophosphate as the supporting electrolyte. One equivalent of **1a** and 5 equiv of enamine were a good reagent combination for the reaction. However, due to the instability of the electrogenerated 3,4-quinone heterodiene, compound **1a** was added in four equal portions to the electrolysis solution which contained the enamine dienophile. In the meantime, the anode potential was maintained at +50 mV vs SCE, which is at a potential for which **1a** could be oxidized to the corresponding 3,4-quinone form. Thus, the continuously low concentration of the electrogenerated *o*-quinone heterodiene, together with the large excess of enamine dienophile, should promote the cycloaddition reac-

Table 1. Variation of the Diene Part: Anodic Oxidation of Various Pyrogallol Derivatives **1a**−**i** and Trapping of the Electrogenerated *o*-Quinone Heterodiene by 4-Cyclohexylidenemethylmorpholine[a]



entry	substrate	product	yield%[b]
1	 **1a**	 **3a**	62
2	 **1b**	 **3b**	66
3	 **1c**	 **3c**	53
4	 **1d**	 **3d**	77
5	 **1e**	 **3e**	76
6	 **1f**	 **3f**	60
7	 **1g**	 **3g**	52
8	 **1h**	 **3h**	60
9	 **1i**	 **3i**	25

[a] Reagents and conditions: (**1a**−**i**) = 2 mM (added in four equal portions), (enamine) = 10 mM, MeOH, rt, Hg anode (E = + 50 mV vs SCE), 4 h; 1 equiv of morpholine was added to the bulk solution for producing the monoanionic species of **1a**−**i**, which is the sole form that can be oxidized to *o*-quinone. [b] Yields refer to chromatographically pure isolated products.

(3) See, for example: (a) Horspool, W. M.; Tedder, J. M.; Din, Z. U. *J. Chem. Soc. C* **1969**, 1692−1693. (b) Ansell, M. F.; Bignold, A. *J. Chem. Commun.* **1969**, 1096−1097. (c) Ansell, M. F.; Leslie, V. J. *J. Chem. Soc. C* **1971**, 1423−1426. (d) Friedrichsen, W.; Schröer, W.-D.; Schmidt, R. *Liebigs Ann. Chem.* **1976**, 793−819 and references therein. (e) Dondoni, A.; Fogagnolo, M.; Mastellari, A.; Pedrini, P.; Ugozzoli, F. *Tetrahedron Lett.* **1986**, *27*, 3915−3918. (f) Boger, D. L.; Weinreb, S. N. In *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987; pp 167−213. (g) Takada, M.; Oshima, R.; Yamauchi, Y.; Kumanotani, J.; Seno, M. *J. Org. Chem.* **1988**, *53*, 3073−3080. (h) Nair, V.; Kumar, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 443−447. (i) Nair, V.; Kumar, S. *Tetrahedron* **1996**, *52*, 4029−4040. (j) Nair, V.; Kumar, S. *Synlett* **1996**, 1143−1147 and references therein. (k) Nair, V.; Kumar, S. *Synth. Commun.* **1996**, 26, 217−224. (l) Nair, V.; Mathew, B.; Radhakrishnan, K. V.; Rath, N. P. *Tetrahedron* **1999**, *55*, 11017−11026. (m) Cameron, D. W.; Heisey, R. M. *Aust. J. Chem.* **2000**, *53*, 109−121.

(4) (a) Omote, Y.; Tomotake, A.; Kashima, C. *Tetrahedron Lett.* **1984**, *25*, 2993−2994. (b) Omote, Y.; Tomotake, A.; Kashima, C. *J. Heterocycl. Chem.* **1984**, *21*, 1841−1844. (c) Omote, Y.; Tomotake, A.; Kashima, C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 151−156. (d) Nair, V.; Kumar, S. *Indian J. Chem.* **1996**, *35B*, 5−7.

(5) For some examples, see: (a) Yoshida, J. I.; Sakaguchi, K.; Isoe, S. *J. Org. Chem.* **1988**, *53*, 2525−2533. (b) Inokuchi, T.; Tanigawa, S. I.; Torii, S. *J. Org. Chem.* **1990**, *55*, 3958−3961. (c) Gûrther, C. F.; Blechert, S.; Steckhan, E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1900−1901. (d) Peglow, T.; Blechert, S.; Steckhan, E. *Chem. Eur. J.* **1998**, *4*, 107−112. (e) Jinno, M.; Kitano, Y.; Tada, M.; Chiba, K. *Org. Lett.* **1999**, *1*, 435−437 and references therein. (f) Utley, J. H. P.; Ramesh, S.; Salvatella, X.; Szunerits, S.; Motevalli, M.; Nielsen, M. F. *J. Chem. Soc., Perkin Trans. 2* **2001**, 153−163. (g) Kise, N.; Mimura, R.; Ueda, N. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2693−2694. (h) Lorans, J.; Hurvois, J. P.; Moinet, C. *Acta Chem. Scand.* **1999**, *53*, 807−813.

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tion at the expense of the polymerization of the putative 3,4-quinone. Under these reaction conditions, compound **3a** was isolated in 62% yield as a single regioisomer (entry 1, Table 1).[7]

With a reliable set of conditions in hand, we probed the scope of the electrochemically induced cycloaddition reaction with different *o*-quinone heterodienes. Table 1 shows some examples of the molecular diversity that is accessible through this reaction, which is an IEDDA reaction between the electron-poor *o*-quinone heterodiene and the electron-rich enamine dienophile. This uncatalyzed cycloaddition reaction occurred at room temperature, within 4 h, with complete regioselectivity. The more electron-rich carbon atom of the enamine dienophile added to the 3-oxygen atom of the *o*-quinone heterodiene. Conclusive evidence of the structure of the regioisomer was provided by X-ray crystallographic analyses of the benzodioxin derivative **3h** (Figure 1).

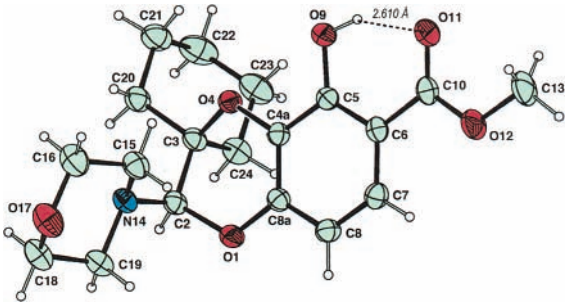
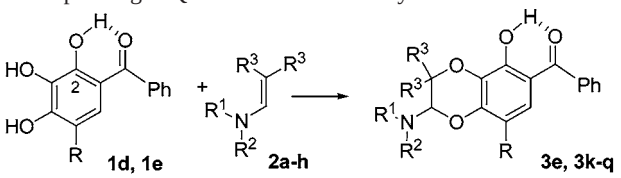


Figure 1. ORTEP view of **3h**. Displacement ellipsoids are drawn at the 30% probability level.[10]

Interestingly, bromosubstituted pyrogallol derivatives reacted effectively to furnish the desired cycloadduct in good yields (entries 2 and 5, Table 1).[8] In the specific case of pyrogallol derivatives bearing a benzophenone framework (entries 4−7), the scope of the cycloaddition reaction could be also extended by the attachment of substituents on the benzoyl moiety. As we suspected that electron-poor *o*-quinone heterodienes possessing electron-withdrawing groups on the benzoyl moiety should favor the IEDDA reaction with the electron-rich enamine, we focused on the introduction of electron-donating substituents. Surprisingly, the presence of electron-donating groups did not significantly interfere with the reaction since the yield of the cycloadduct only slightly decreased (entries 6 and 7). Anodic oxidation of 1-nitropyrogallol **1i** generated a highly unstable *o*-quinone heterodiene which, as a result of its concomitant decomposition to melanin-like polymers, failed to produce the corresponding cycloadduct **3i** in good yield (entry 9).

The regiospecificity of the reaction deserves special note because the regioselectivity of previously reported similar reactions was quite variable.[3,4] Furthermore, when the pyrogallol derivative **1d** was replaced by its corresponding 2-methoxy analogue **1j**, the electrochemically induced cy-

Table 2. Variation of the Dienophile Part: Anodic Oxidation of Pyrogallol Derivatives **1d** and **1e** and Trapping of the Corresponding *o*-Quinone Heterodiene by Different Enamines[a]



entry	enamine	product	yield%[b]
1	**2a**	**3e**	76
2	**2b**	**3k**	75
3	**2c**	**3l**	70
4	**2d**	**3m**	70
5	**2e**	**3n**	75
6	**2f**	**3o**	83[c]
7	**2g**	**3p**	35[d]
8	**2h**	**3q**	50

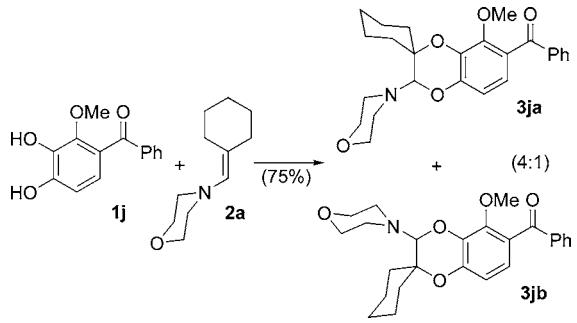
[a] Reagents and conditions: (**1d**, **1e**) = 2 mM (added in four equal portions), (enamine) = 10 mM, MeOH, rt, Hg anode ($E = +50$ mV vs SCE), 4 h; 1 equiv of morpholine was added to the bulk solution for producing the monoanionic species of **1d** or **1e**, which is the sole form that can be oxidized to *o*-quinone. [b] Yields refer to chromatographically pure isolated products. [c] Obtained as a mixture of two unassigned diastereoisomers. [d] 2-Hemiacetal was isolated as the byproduct in 20% yield.

(7) Various solvents and reaction conditions were screened, but none of changes led to an improvement of the yield of the reaction. Replacing the Hg anode by a Pt anode for instance lowered the yield to 50%.

(8) Bromosubstituted aromatic rings are particularly attractive in diversity-oriented synthesis because they can be easily transformed into differently substituted aromatics by cross-coupling reactions.

cloaddition reaction led to a 4:1 mixture of regioisomers **3ja** and **3jb** (75% combined, Scheme 1).[9] This result highlights

Scheme 1. Anodic Oxidation of the 2-Methoxy Analogue **1j** and in Situ Trapping of the *o*-Quinone Heterodiene by Enamine **2a**



the crucial role of the 2-hydroxyl group as the inducer of regiospecificity. This point merits thorough further investigation.

The structure of the enamine dienophile could be also very diverse (Table 2). As expected, alkylenamines with a pronounced electron-rich character produced the desired cycloadduct in high yield (entries 1−6), whereas the enamine **2h** that bore phenyl substituents resulted in somewhat lower yield (entry 8). Except for the cycloadduct **3p** (entry 7), no subsequent elimination of the alkylamino chain was observed, in contrast to what has been previously reported for similar reactions of enamines with *o*-quinones.[4c] This feature is of synthetic interest since the methodology we describe allows the easy synthesis of 2-alkylamino-1,4-benzodioxin derivatives.

In conclusion, we have reported a successful use of in situ generated *o*-quinone heterodienes for the regiospecific IEDDA reaction with enamines. The possibility of introducing variations in both cycloaddition partners afforded highly substituted 1,4-benzodioxin derivatives with up to five elements of diversity. Because it would be difficult to access them more rapidly, our electrochemical methodology proved to be particularly attractive for library development. Finally, as a result of their structural similarity with a series of 1,4-benzoxazine derivatives reported earlier,[6d] these new compounds could be considered as target structures for the design of novel neuroprotective agents.

Acknowledgment. We thank Prof. M.-B. Fleury for fruitful discussions and encouragement. D.X. thanks Paris 5 University and the MRT for a postdoctoral grant.

Supporting Information Available: Typical experimental procedures and full spectroscopic data for compounds **3a**−**q**, including ^{1}H and ^{13}C NMR spectra together with crystallographic files (CIF) for compound **3h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The reaction was performed under the same experimental conditions. However, as *o*-quinol **1j** was oxidizable at a slightly higher potential, the Hg anode, which has a low anodic decomposition potential, was replaced by a Pt anode.

(10) Crystallographic data for **3h**: prismatic colorless crystal of 0.75 × 0.40 × 0.30 mm; empirical formula $C_{19}H_{25}NO_6$, $M = 363.40$, $T = 293$ K, triclinic system, space group $P\bar{1}$, $Z = 4$, $a = 11.468(3)$, $b = 12.662(4)$, $c = 13.310(4)$ Å, $\alpha = 76.23(2)°$, $\beta = 80.61\ (2)°$, $\gamma = 89.87(2)°$, $V = 1850.7$ Å^3, $d_{calc} = 1.304$ g cm^{-3}, $F(000) = 776$, $\mu = 0.10$ mm^{-1}, λ(Mo Kα) = 0.71073 Å. There are two enantiomeric independent molecules in the asymmetric unit. 13 482 reflections measured of which 8462 unique, 478 parameters refined on F^2. Final $R1(F) = 0.0433$ calculated with the 5713 observed reflections as $I > 2\sigma(I)$, wR2(F^2) = 0.1156 (with all the 8462 data). Deposited CCDC no. 282558.