ORGANIC LETTERS

2009
Vol. 11, No. 23
5530−5533

Preparation of Zwitterionic Hydroquinone-Fused [1,4]Oxazinium Derivatives via a Photoinduced Intramolecular Dehydrogenative-Coupling Reaction

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Received October 12, 2009

ABSTRACT

A simple and efficient photochemical reaction can be performed to construct functionalized [1,4]oxazinium derivatives via a direct dehydrogenative coupling between sp^3- and sp^2-hybridized C-atoms, starting from easily accessible stable semiquinone radicals.

Heterocyclic compounds containing both N and O atoms are attractive structures for pharmaceutical and materials sciences. They constitute not only important structural units in many natural products and biologically active compounds but also highly versatile building blocks in synthetic organic chemistry.[1−3] Their synthesis has attracted the interest of organic chemists for decades, and several strategies based on transition-metal-catalyzed cross-coupling reactions have been reported. In practice, this approach requires that one or both molecular fragments are prefunctionalized.[1] Recently, some elegant methodologies involving the direct coupling between two C−H bonds through an overall cross-dehydrogenative coupling (CDC) in the presence of an oxidizing reagent have been reported, in order to eliminate this prerequisite in synthetic design.[4] From a further perspective, it is important to bear in mind that most reactions were still classified as being metal-catalyzed,[5] as well as oxygen- and water-sensitive; above all, sometimes expensive and toxic metals were used. In addition and more specifically, C−C

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(1) For reviews, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (c) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555–1564. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (e) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (f) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245. (g) Special issue on heterocycles: *Chem. Rev.* **2004**, *104*, 2125−2812. (h) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241.

(2) (a) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645–12647. (b) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332–5333. (c) Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 609–612. (d) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512–1522.

(3) (a) Jia, Y.-X.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636–1639. (b) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190–7191. (c) Liégault, B.; Fagnou, K. *Organometallics* **2008**, *27*, 4841–4843.

(4) (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335–344. (b) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278–6282. (c) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673. (d) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949–1952. (e) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175. (f) Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301–1304. (g) Li, B.; Tian, S.; Fang, Z.; Shi, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115–1118.

10.1021/ol902355b CCC: $xxxx
Published on Web 11/09/2009

bond-forming reactions involving a direct dehydrogenative coupling between sp^3- and sp^2-hybridized C-atoms are still quite rare.[3]

Herein, we report a simple and efficient photochemical reaction to construct functionalized [1,4]oxazinium derivatives (Figure 1) via an unprecedented intramolecular dehydrogenative coupling of a C(sp^3) center adjacent to an oxygen atom with a C(sp^2) center in positively charged heterocycles. This direct, powerful, and metal-free method for C−C bond formation is highly atom-economical and corresponds to the next generation of green chemical synthesis.[6] Moreover, such heterocyclic compounds are related to recently discovered antiinfective agents.[7]

Very recently, we have developed a facile and efficient protocol for the synthesis of stable semiquinone radicals of type **1** (Scheme 1).[8] This reaction is based on the concept of proton-coupled-electron-transfer (PCET) and involves the reaction of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) with an excess of pyridine in an alcohol ROH as solvent.

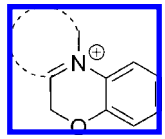
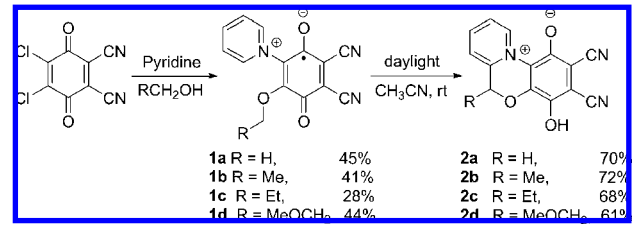


Figure 1. Representative core of [1,4]oxazinium derivatives.

It is noteworthy that these radicals show a substitution pattern which presents a hydrogen atom at the γ-position to the carbonyl group, an interesting aspect in view of the exploration of their photochemical reactivity. In this context, it is important to note that carbonyl compounds in the electronically excited state serve as versatile intermediates in countless reactions. Among them, one of the fundamental phototransformation of ketones that contain a hydrogen atom at the γ-position is the Norrish-type-II reaction.[9] In that reaction, a 1,5-H transfer is initiated by the photoexcited triplet state of the ketones via a six-membered cyclic transition state which normally leads to the formation of triplet 1,4-diradicals as intermediates. The present study seeks to test the analogous photochemical reaction based on a semiquinone radical platform which therefore potentially gives rise to the appearance of an excited radical intermediate.

Specifically, the stable zwitterionic semiquinone radicals **1a**−**d** were exposed to daylight, giving straightaway rise to

Scheme 1. Synthetic Route to **1** and **2**



2,3-dicyano-6-alkyl-1,4-dihydroxy-6*H*-pyrido[2,1-*c*][1,4]benzoxazinium inner salts[10] **2a**−**d** in 61−72% yields (Scheme 1).

A plausible mechanism to rationalize the formation of **2** is depicted in Scheme 2. Irradiation of **1** affords the excited phenoxyl radical **A** that exhibits a remarkably selective intramolecular 1,5-hydrogen-atom transfer analogous to a Norrish-type-II reaction. This gives rise to the 1-aryloxyalkyl radical **B**, which affords the heterocyclic products **2** via an homolytic aromatic substitution process involving cyclization to radical **C** followed by a rearomatization process.[11] Inter- and intramolecular radical addition to pyridinium salts are well documented.[12] The mechanism of the rearomatization step most probably involves oxygen from air as oxidizing agent.

Next, the reaction sequence starting from DDQ was extended to imidazole derivatives (Scheme 3). Treatment of DDQ with an excess of 1-methylimidazole in alcohol gave the air- and moisture-stable zwitterionic imidazolio-semiquinone π-radicals **3** as deep-red powders. Exposure of **3** to daylight led to the completely regioselective formation of **4**, consistent with the above-mentioned reaction mechanism. The molecular structures of the products **2a**−**d** and **4a**,**b** were unambiguously established by NMR and ESI-MS as well as confirmed by X-ray diffraction analysis in the cases of **2c** and **4a**.

The starting semiquinone radicals are soluble in DMF and DMSO, slightly soluble in CH_3CN and acetone, and not soluble in water. Indeed, all reactions were carried out with the corresponding semiquinone radicals in saturated CH_3CN solution. To test solvent effects, some of the reactions have been performed in DMF under higher concentration. However, it turned out that the yields of the corresponding photochemical products significantly decrease; for example, compound **2b** can only obtained in DMF with a yield of 29% (see the Supporting Information). Moreover, preliminary attempts to use other commercially available chlorinated

(5) For a recent metal-free photoinitiated cross-coupling reaction, see: De Carolis, M.; Protti, S.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1232–1236.

(6) Oelgemöller, M.; Jung, C.; Mattay, J. *Pure Appl. Chem.* **2007**, *79*, 1939–1947.

(7) Hubschwerlen, C.; Panchaud, P.; Specklin, J.-L. *PCT Int. Appl.* **2008**, 85.

(8) Yi, C.; Blum, C.; Liu, S.-X.; Keene, T. D.; Frei, G.; Neels, A.; Decurtins, S. *Org. Lett.* **2009**, *11*, 2261–2264.

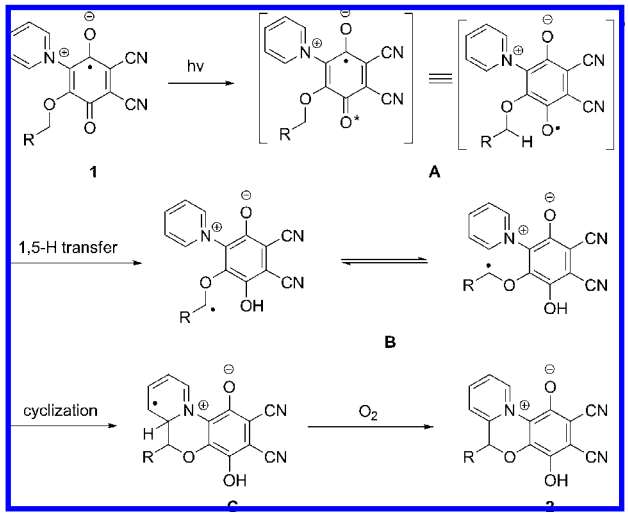
(9) For reviews, see: (a) Wagner, P. J.; Park, B.-S. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1991; Vol. 11, Chapter 4. (b) Wagner, P. J. In *CRC Handbook of Organic Photochemistry and Photobiology*; CRC: Boca Raton, FL, 1995.

(10) Bünzli-Trepp, U. *Systematic Nomenclature of Organic, Organometallic and Coordination Chemistry*; EPFL: Lausanne, 2007.

(11) (a) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002–6016. (b) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, *36*, 1803–1822.

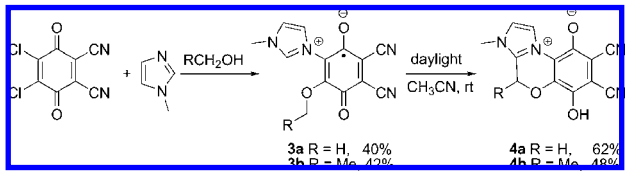
(12) (a) Minisci, F.; Fontana, F.; Pianese, G.; Yan, Y. M. *J. Org. Chem.* **1993**, *58*, 4207–4211. (b) Togo, H.; Hayashi, K.; Yokoyama, M. *Chem. Lett.* **1993**, *22*, 641–644. (c) Togo, H.; Hayashi, K.; Yokoyama, M. *Chem. Lett.* **1991**, *20*, 2063–2064. (d) Harrowven, D. C.; Sutton, B. *J. Prog. Heterocycl. Chem.* **2004**, *16*, 27–53. (e) Russell Bowman, W.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, *24*, 2747–2762.

Scheme 2. Proposed Reaction Mechanism for the Photoinduced Cross-Dehydrogenative Coupling Reaction



quinones such as tetrachlorobenzoquinone and dichloronaphthoquinone were not successful. Particularly promising noncommercially available chlorinated quinones bearing radical stabilizing groups such as esters, aryls, and amides have not yet been tested.

Scheme 3. Synthetic Route to **4**



Compound **2c** crystallizes in the form of red plates in a 1:1 enantiomeric mixture in the monoclinic space group *C*2/*c* and **4a** as yellow blocks as a methanol solvate in the triclinic space group $P\bar{1}$. The ORTEP views of both compounds are given in Figure 2. There are no exceptional geometrical features, and all bond lengths and angles are within the expected ranges; they compare well with reported structures of 1,4-benzoxazine skeletons.[13] The oxazine moieties adopt slightly twisted conformations.[14]

The electrochemical properties of compounds **2a**−**d** and **4a**,**b** in CH_3CN were investigated by cyclic voltammetry (Figure 3 and Table S1, Supporting Information). All of them show almost the same redox behavior. As shown in Figure 3, **2a** exhibits a reversible two-electron redox wave at 0.77 V vs Ag/AgCl for the oxidation of the hydroquinone

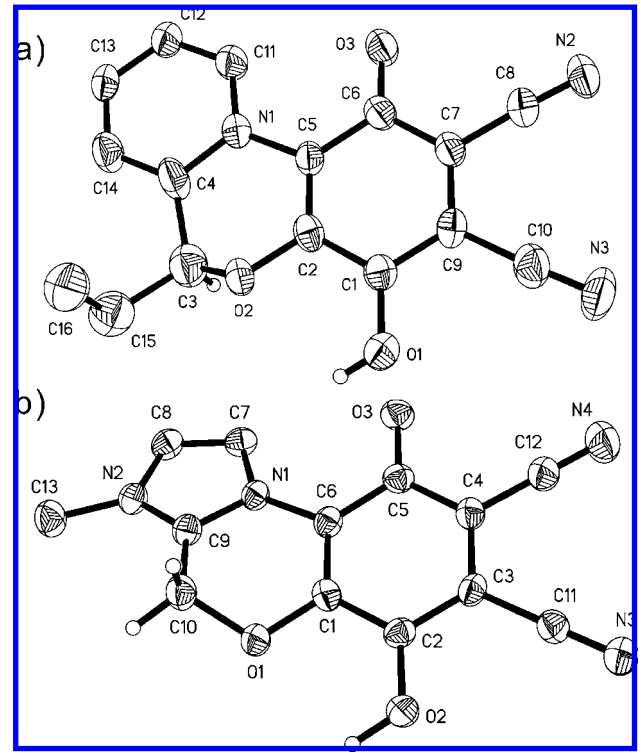


Figure 2. X-ray crystal structure of (a) **2c** (the (*R*)-enantiomer is shown). Selected bond lengths (Å): C1−O1 1.340(5), C1−C2 1.410(6), C2−O2 1.360(5), O2−C3 1.394(6), C3−C4 1.547(7), C4−N1 1.375(6), N1−C5 1.451(5), C2−C5 1.383(6), C5−C6 1.442(6), C6−O3 1.279(5), C6−C7 1.416(6), C7−C9 1.410(6). X-ray crystal structure of (b) **4a**. Selected bond lengths (Å): C2−O2 1.354(2), C1−C2 1.399(3), C1−O1 1.379(2), O1−C10 1.434(3), C10−C9 1.476(3), C9−N1 1.342(2), N1−C6 1.428(3), C1−C6 1.378(3), C6−C5 1.425(3), C5−O3 1.294(2), C5−C4 1.414(3), C4−C3 1.414(3), C3−C2 1.383(3). ORTEP: thermal ellipsoids set at the 50% probability level. Hydrogen atoms (partially) and solvents (in the case of **4a**) are omitted for clarity.

moiety.[15] This observation can be interpreted with an electron transfer−chemical reaction−electron transfer ECE mechanism[15] wherein the radical cation that is formed by the first electron transfer is deprotonated by the solvent itself. The chemical reversibility is indicative of the formation of a stable quinone cation. Moreover, compounds **2a**−**d** undergo two irreversible reduction processes, for example, **2a** at −0.92 and −1.19 V.

The electronic absorption spectra of compounds **1a**, **2a**, and **4a** are shown in Figure 4. Notably, the diagnostic absorption bands of the pyridiniosemiquinone π-radical **1a** at 340, 420, 445, 550, and 590 nm disappear upon its photoirradiation. Naturally, the colors of the photoproducts **2a** and **4a** are reflected in their absorption spectra. The intense absorption bands are characteristic for $\pi-\pi^*$ transitions, and specifically in the case of **2a**, the broad absorption band centered at 507 nm reflects a pronounced charge-transfer character (hydroquinone → pyridinium).

(13) Li, Z.-B.; He, X.-Y.; Dong, W.-L.; Liao, D.-D. *Acta Crystallogr.* **2009**, *E65*, o762.

(14) Rao, R. K.; Naidu, A. B.; Sekar, G. *Org. Lett.* **2009**, *11*, 1923–1926.

(15) (a) Costentin, C. *Chem. Rev.* **2008**, *108*, 2145–2179. (b) Quan, M.; Sanchez, D.; Wasylkiw, M. F.; Smith, D. K. *J. Am. Chem. Soc.* **2007**, *129*, 12847–12856. (c) Albrecht, M.; Schneider, O.; Schmidt, A. *Org. Biomol. Chem.* **2009**, *7*, 1445–1453.

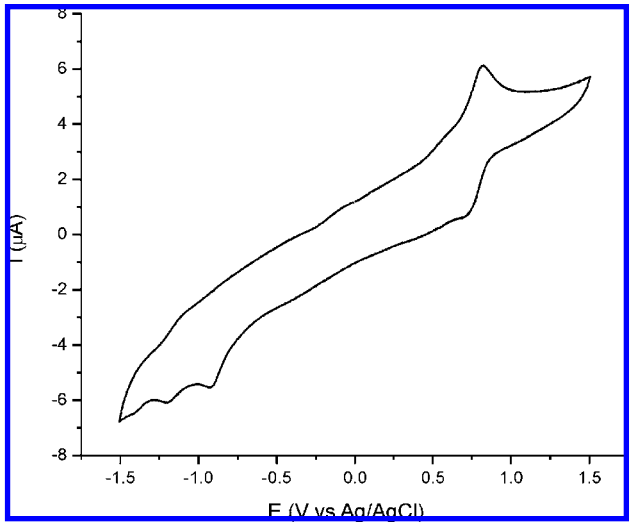


Figure 3. Cyclic voltammogram of **2a** (2×10^{-4} M) in CH_3CN, supporting electrolyte 0.1 M $(Bu_4N)PF_6$, scan rate 100 mV s^{-1}.

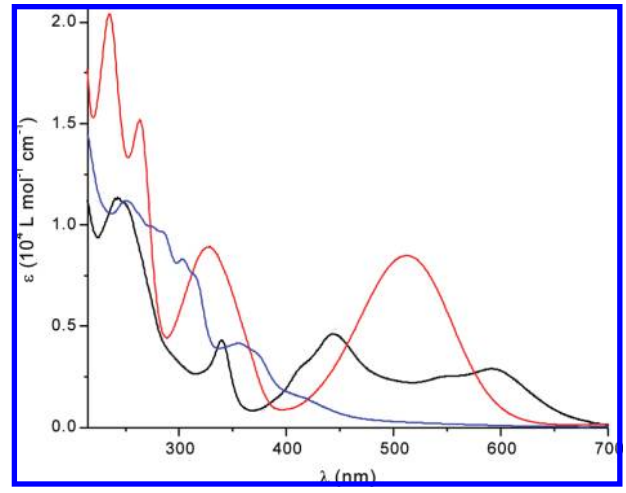


Figure 4. UV−vis absorption spectra of compounds **2a** (red curve), **4a** (blue curve), and the semiquinone radical **1a** (black curve) in CH_3CN.

In conclusion, we have discovered a unique and very simple protocol for the direct dehydrogenative cross-coupling of a C(sp^3) adjacent to an oxygen atom with a C(sp^2) belonging to a positively charged heterocycle. This cross-coupling reaction starts from stable semiquinone radicals that are very easily prepared in one step by a three-component coupling process involving DDQ, a basic aromatic compound such as pyridine or *N*-methylimidazole, and an alcohol. We have demonstrated that two of these components, the alcohol and the basic aromatic compound, can be varied. So far, the third component, DDQ, cannot be changed, but we believe that the presence of the two versatile cyanide groups offers many possibilities for post modification of the DDQ building block. The coupling process is run under air atmosphere and is triggered by daylight. It requires neither a metal catalyst nor an additional oxidant. This approach compares very favorably with the multistep procedures reported in the literature for the syntheses of biologically active 1,4-benzoxazine derivatives.[14,16] Beside the synthetic aspect of our results, we believe that the demonstration that an excited phenoxyl radical becomes reactive enough to perform C−H bond functionalization may have important consequences for the design of new processes involving excitation of stable radicals by irradiation. Further investigations toward the understanding of the detailed reaction mechanism as well as a more extensive determination of the synthetic scope are underway.

Acknowledgment. This work was supported by the Swiss National Science Foundation (Grant No. 200020-116003).

Supporting Information Available: General experimental details and characterization data for compounds **1**−**4**; CIF files for **2c** and **4a** (CCDC 730336 and 730337); NMR spectra of compounds **2** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902355B

(16) (a) Sainsbury, M. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Oxford: New York, 1984; Vol. 3. (b) Ilas, J.; Stefanic Anderluh, P.; Sollner Dolenc, M.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325–7348.