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Unexpected Reactivity of *o*-Nitrosophenol with RCH_2Br: C−H Bond Cleavage and Annulation to Benzoxazoles and Benzoxazines (R = Alkynyl)

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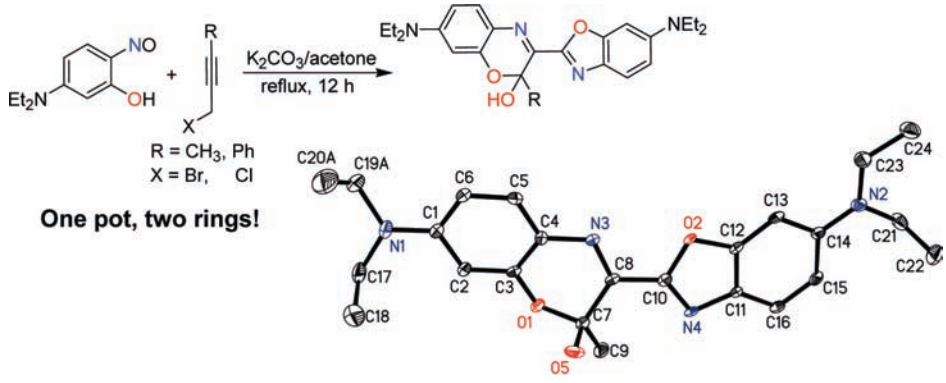
ABSTRACT



A one-pot reaction between two molecules of 5-diethylamino-2-nitrosophenol with one molecule of 2-butynyl bromide gave rise to a new heterocyclic compound (structure shown above) consisting of one benzoxazole and one benzoxazine ring. The reaction works equally well with 1-phenyl-3-chloro-1-propyne. It was also found that 5-diethylamino-2-nitrosophenol reacts with R-CH_2Br (R = aryl or vinyl) to give benzoxazoles with good functional group tolerance and high yield.

Nitroso compounds have potential as starting materials for synthesizing a wide range of heterocyclic compounds owing to their rich reactivity. Nitrosoarenes undergo cycloaddition to alkynes to give *N*-hydroxyindoles.[1] The nitroso-ene reaction is a mild and selective method for the direct allylic nitrogen functionalization of alkenes.[2] Not much other synthetic applications have been reported for *o*-nitrosophenol and its analogues except in the synthesis of dyes such as Nile blue, Nile red[3] and cyanine.[4] Reported herein are an unexpected new reaction pattern of *o*-nitrosophenol and its naphthalene analogue toward RCH_2Br forming oxazoles through C−H bond activation and annulation. Compounds with benzoxazole structural motifs are receiving much attention as therapeutic agents and optical-electronic materials.[5,6]

(1) Penoni, A.; Giovanni Palmisano, G.; Yi-Lei Zhao, Y.-L.; Kendall, N.; Houk, K. N.; Volkman, J.; Nicholas, K. M. *J. Am. Chem. Soc.* **2009**, *131*, 653–661.

(2) Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131–4146.

(3) For synthetic methods for Nile blue derivatives, see: (a) Jose, J.; Ueno, Y.; Burgess, K. *Chem.—Eur. J.* **2009**, *15*, 418–423. For synthetic methods for Nile Red derivatives, see: (b) Jose, J.; Burgess, K. *J. Org. Chem.* **2006**, *71*, 7835–7839.

(4) Shindy, H. A.; El-Maghraby, M. A.; Eissa, F. M. *Color. Technol.* **2008**, *124*, 159–164.

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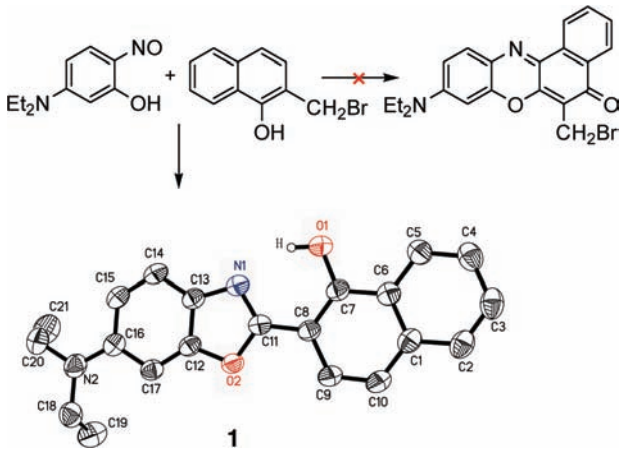
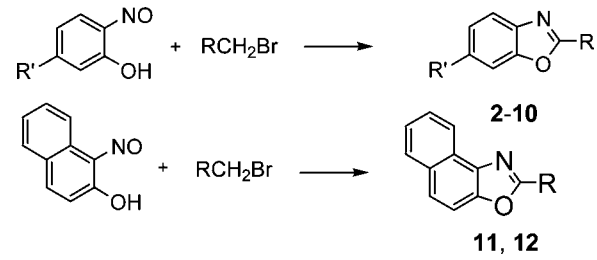
Scheme 1

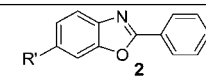
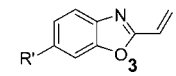
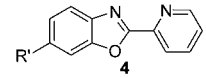
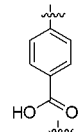
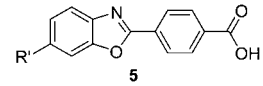
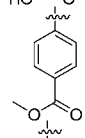
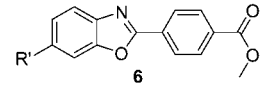
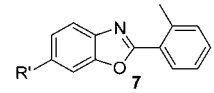
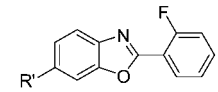
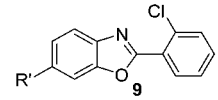
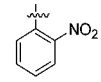
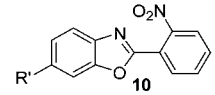
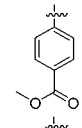
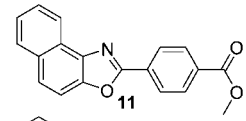
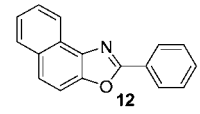


In an attempt to prepare fluorescence dye, a Nile red derivative with CH_2Br functionality via a known ring-closing reaction,[3] we did not obtain the expected red color product upon heating 5-diethylamino-2-nitrosophenol with 2-bromomethyl-1-naphthol in DMF. Instead, a bright yellow benzoxazole **1** was isolated in 85% yield (Scheme 1). The structure of **1** is solved by single-crystal X-ray diffraction. The bond length of the C═N (1.3019(19) Å) and C−O (1.3721(18) Å) of the oxazole falls within the normal range as predicted. The proton of the HO group is pointed toward the N for an intramolecular hydrogen bond. This is further corroborated by the short N(1) to O(1) distance of 2.626 Å. The two conjugated ring systems are nearly coplanar. The structure is consistent with collective spectral data. We further investigated the scope of the reaction with a number of RCH_2Br. In most cases, the reaction gave good to excellent yield as shown in Table 1. The R− group includes naphthyl, phenyl (entry 1), allyl (entry 2), and pyridyl (entry 3). However, the reaction did not work for 2-bromobutane. Apparently, a conjugated R− group is essential for the reaction. It is remarkable that the reaction has good functional group tolerance toward phenol (compound **1**), pyridine (entry 3), carboxylic acid (entry 4), ester (entry 5), halogen (entries 7, 8) and nitryl (entry 9). The electronic effects of the substituent on the aryl ring are negligible as both electron-donating (CH_3) and electron-withdrawing (F, Cl, NO_2) groups gave comparable yields (entries 6−9).

1-Nitroso-2-naphthol also reacts with RCH_2Br to give similar product (entries 10, 11). The annulation reaction can be carried out in aprotic solvents including DMF, THF, and acetone in the presence of either acid or base without much impact on the yield. We propose a working mechanism shown in Scheme 2. Phenol reacts with RCH_2Br to yield an aryl ether intermediate, which undergoes an intramolecular hydrogen atom transfer reaction to give an unobserved biradical intermediate. The intramolecular radical coupling closes the ring. Subsequently, dehydration leads to the final

Table 1. Synthesis of Benzoxazoles[a]



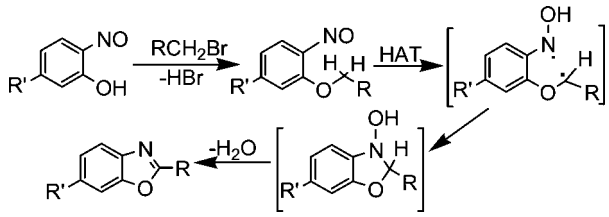
entry	R	product [R' = Et_2N]	isolated yield (%)
1		 **2**	87
2		 **3**	41
3		 **4**	73
4		 **5**	83
5		 **6**	80
6		 **7**	76
7		 **8**	71
8		 **9**	77
9		 **10**	70
10[b]		 **11**	78
11[b]		 **12**	81

[a] Typical conditions: THF, K_2CO_3, reflux, 6 h. [b] 1-Nitroso-2-naphthol was used.

(5) (a) Aiello, S.; Geoffrey Wells, G.; Stone, E. L.; Kadri, H.; Bazzi, R.; David, R.; Bell, D. R.; Malcolm, F. G.; Stevens, M. F. G.; Matthews, C. S.; Bradshaw, T. D.; Andrew, D.; Westwell, A. D. *J. Med. Chem.* **2008**, *51*, 5135–5139. (b) Razavi, H.; Palaninathan, S. K.; Powers, E. T.; Wiseman, R. L.; Purkey, H. E.; Mohamedmohaideen, N. N.; Deechongkit, S.; Chiang, K. P.; Dendle, M. T. A.; Sacchettini, J. C.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2758–2761.

(6) (a) Taki, M.; Wolford, J. L.; O'Halloran, T. V. *J. Am. Chem. Soc.* **2004**, *126*, 712–713. (b) Seo, J.; Kim, S.; Park, S. Y. *J. Am. Chem. Soc.* **2004**, *126*, 11154–11155. (c) Ohshima, A.; Momotake, A.; Nagahata, R.; Arai, T. *J. Phys. Chem. A* **2005**, *109*, 9731–9736.

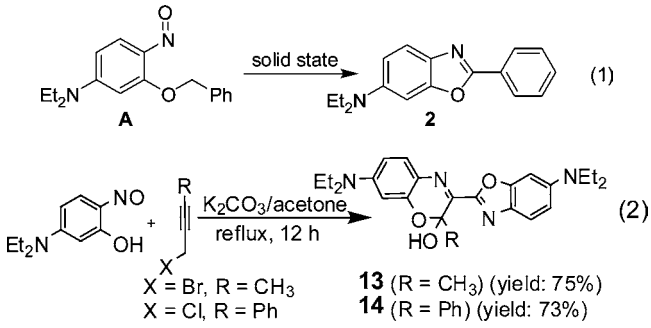
Scheme 2[a]



[a] (HAT = Hydrogen atom transfer).

product. Alkyl bromide could not work because the formed carbon radical does not gain stabilization through conjugation.

To gain some insight into the reaction, we prepared benzyl ether intermediate **A** and converted it to **2** cleaningly in solution or *even in the solid state* by heating to 65 °C (eq 1). Addition of a radical scavenger, Trolox, did not slow down the reaction. The purported intramolecular radical coupling could be too fast to be trapped by radical scavengers. We did not observe any reaction intermediates by the NMR spectrum, and addition of water did not slow down the reaction. This indicates that the elimination of water was an irreversible and fast reaction. It is thus likely that the hydrogen atom transfer is the rate-limiting step.



When we expanded the R-CH_2X to include alkynes such as $CH_3C{\equiv}CCH_2Br$ or $PhC{\equiv}CCH_2Cl$, we isolated new compounds **13** and **14** in good yield (eq 2). X-ray crystal structural analysis demonstrated that **13** contains benzoxazole and benzoxazine rings (Figure 1). There is a chiral carbon in C7, and the unit cell contains both optical isomers. We proposed a formation mechanism of **13** and **14** as shown in Scheme 3. The first *o*-nitrosophenol reacts with R-CH_2X to afford the benzoxazole. The alkynyl moiety in the benzoxazole intermediate reacts with a second *o*-nitrosophenol through Diels−Alder reaction to form a benzoxazine intermediate with OH on the nitrogen. Rearrangement of the HO group occurred under the basic reaction conditions to give

(7) (a) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411–6413. (b) Chen, Y.-X.; Qian, L.-F.; Zhang, W.; Han, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9330–9333. (c) Marsden, S. P.; McGonagle, A. E.; McKeever-Abbas, B. *Org. Lett.* **2008**, *10*, 2589–2591.

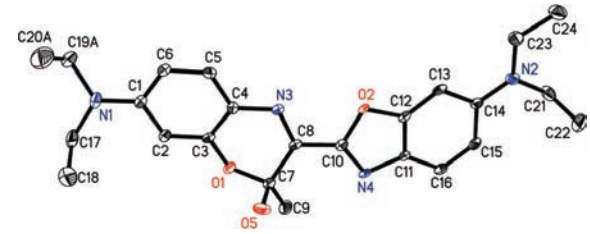
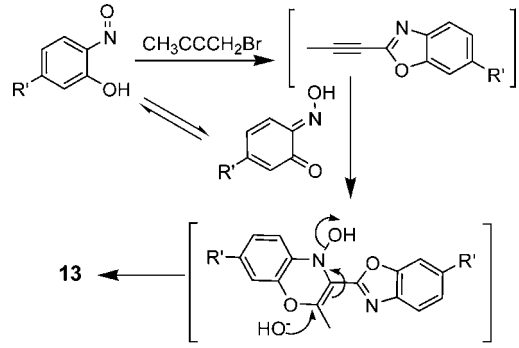


Figure 1. ORTEP drawing of one (S) of the two independent complexes (S and R) presented in the crystals of **13**.

13. We found that *o*-nitrosophenol did not react with $CH_3C{\equiv}CCH_2OH$ under the same conditions, indicating that an electron-withdrawing group on alkyne ("dienophile") is needed for the cyclization reaction to occur. 1-Nitroso-2-naphthol reacted with $PhCCCH_2Cl$ but gave low yield. The full scope of the R group of reaction **2** is being investigated.

Scheme 3



In summary, this is the first reported such reaction pattern of *o*-nitrosophenol with alkynes. Nitrosoarenes and alkynes underwent cycloaddition to form *N*-hydroxyindoles as the main products, and the hydroxyl group could be reduced by hydrogenation (H_2/Pd−C) to give indoles.[1] In our case, the presence of an *ortho*-phenol group alters the reaction pathway completely. The new reactions described herein are attractive synthetic methods because they occurred under mild conditions, with good functional group tolerance and without catalysts required as is the case in a few reported procedures.[7]

Acknowledgment. The authors thank the Science and Engineering Research Council (SERC) of the Agency for Science, Technology and Research (A*Star) of Singapore for financial support (Grant number: 072-101-0015).

Supporting Information Available: General procedures and characterization for representative compounds. CIF for **1** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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