Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 1958

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Chemical generation of *o*-quinone monoimines for the rapid construction of 1,4-benzoxazine derivatives†

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Received 4th October 2011, Accepted 5th January 2012
DOI: 10.1039/c2ob06681e

Highly reactive *o*-benzoquinone monoimines were chemically generated and successfully trapped with electron-rich olefins that led to the synthesis of hitherto unknown 1,4-benzoxazine derivatives. This unprecedented transformation was achieved by the oxidation of *o*-aminophenols bearing appropriate functionality on the arene residue with less expensive hypervalent iodine reagent in the presence of vinylic ethers or thioethers.

Quinone imines are powerful intermediates for organic synthesis and constitute potential precursors to a number of natural products.[1] The synthetic utility of these intermediates has not been extensively exploited since they are highly unstable; in particular *o*-benzoquinone monoimines are very prone to polymerization.[2] The difficulties encountered in handling *o*-benzoquinone monoimines are (i) the dimerization reaction with their precursors *i.e.*, *o*-aminophenols, leading to 2-aminophenoxazones[3] and (ii) formation of polymers.[4a] Hishida[4] and co-workers studied, spectrophotometrically, the reaction between *o*-benzoquinone monoimine and *o*-aminophenol and they obtained 2-aminophenoxazones and polymers as the reaction products. However to stabilize these transient intermediates and to diminish their reactivity and thereby prevent the decomposition, an imide functionality (*N*-acyl or *N*-benzoyl group) on these *o*-benzoquinone monoimines is necessary. Heine *et al.*[5] showed that *o*-benzoquinone monoimines are willing partners in hetero Diels–Alder reaction[6] by introducing an amide functionality and two chlorine atoms on the ring. Later pioneering work on *o*-azaquinones was done by Nicolaou *et al.*[7] and Fleury *et al.*[8]

Nicolaou and his co-workers synthesized *N*-acetyl *o*-azaquinone derivatives from easily accessible anilides and carried out intermolecular Diels–Alder cycloaddition. However, this reaction procedure is limited to *ortho*-substituted anilides and involves the use of excess amount of oxidizing reagent (Dess–Martin periodinane); the oxidation of *para*-substituted anilides leads to *p*-quinones. Lectka *et al.* demonstrated an enantioselective synthesis of 1,4-benzoxazones from *o*-quinone monoimides and chiral ketene enolates.[9] The demanding task in this area is controlling the reactivity of *o*-benzoquinone monoimine without introducing an amide functionality since the removal of an amide functional group requires harsh reaction conditions. Recently Fleury discovered an electrochemical method for the generation of *o*-benzoquinone monoimines,[8] where these reactive species oxidize primary aliphatic amines into enamines to participate in Diels–Alder reaction.

o-Quinone monoimines bearing electron-withdrawing groups in the ring residue, and *o*-quinone monoimides being electron-deficient in nature, react with electron-rich species.[7c,e,8e] These reactive intermediates participate as hetero dienes in inverse-electron demand Diels–Alder reaction with electron-rich dienophiles to furnish heterocyclic compounds of biological interest.[10] 3,4-Dihydro-2*H*-1,4-benzoxazine is a recurring structural motif in a number of natural products having important biological activities. Some of them are central nervous system depressants,[10h] antipsychotic agents,[10d,c] antagonists,[10f] and antibacterial agents,[10a,b] while others are potential drugs for treating neurodegenerative,[10e] cardiovascular,[10h] and diabetic disorders.[10g] Although, there are a variety of methods for the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazine[11] most of these methods involve multistep processes. However, the Diels–Alder reaction not only provides a single step pathway but also allows the construction of complex structures.[5,7–9] Unfortunately there has been only one electrochemical method reported for intermolecular Diels–Alder reaction of *o*-quinone monoimines with enamines.[8] In order to explore quinone monoimine chemistry many features of the reaction system need to be improved, including the use of less toxic, low-cost catalysts and reagents, and convenient and mild operating conditions. Herein we report a novel method for the generation of *o*-benzoquinone monoimines by using diacetoxyiodobenzene, a hypervalent iodine reagent,[12] and successfully trapping with vinyl ethers. To the best of our knowledge, this reaction is the first example of intermolecular inverse-electron demand Diels–Alder reaction of chemically generated *o*-quinone monoimines.

Inspired by the protocols harnessing the reactive *ortho*-benzoquinone monoketals[13] generated by oxidation of 2-methoxyphenols with hypervalent iodine reagents, we became interested in extending this strategy for the generation of *o*-quinone

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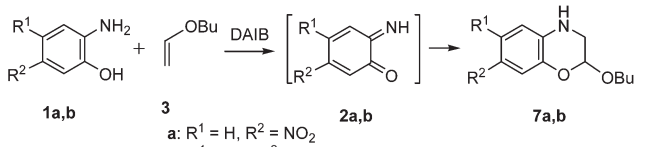
†Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, copies of ^{1}H NMR (500 MHz), crystallographic data (CIF) and computational details. CCDC reference number 815224. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob06681e

Table 1 Optimization of the Diels–Alder reaction of *in situ* generated *o*-quinone monoimines **2a** and **2b** with butyl vinyl ether[a]

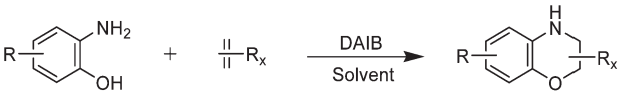


a: R^1 = H, R^2 = NO_2
b: R^1 = CN, R^2 = H

Entry	Solvent	Base	Temp.	Time	Product	Yield (%)[b]
1[c]	CH_2Cl_2	—	RT	1 h	**7a**	19
2[d]	CH_2Cl_2	—	RT	2 h	**7a**	21
3	CH_2Cl_2	—	RT	2 h	**7a**	40
4[e]	CH_2Cl_2	—	RT	2 h	**7a**	42
5	CH_2Cl_2	—	40 °C	3 h	**7a**	38
6	CH_2Cl_2	—	0 °C	3 h	**7a**	64
7	CH_2Cl_2	—	0 °C	6 h	**7a**	51
8	CH_2Cl_2	Et_3N	0 °C	6 h	**7a**	0
9	THF	Et_3N	0 °C	3 h	**7a**	0
10	THF	$KHCO_3$	0 °C	3 h	**7a**	0
11	CH_2Cl_2	—	0 °C	2 h	**7b** + *N*-Ac **7b**	53[f]
12	CH_2Cl_2	$KHCO_3$	0 °C	3 h	**7b**	52
13	THF	Et_3N	0 °C	3 h	**7b**	Trace
14	THF	$KHCO_3$	0 °C	3 h	**7b**	66

[a] Reactions were carried out with 5 equiv. of butyl vinyl ether and 1.2 equiv. of DAIB, unless otherwise mentioned. [b] Yield of isolated products. [c] 1 equiv. of DAIB was used. [d] 1 equiv. of butyl vinyl ether was used. [e] 1.5 equiv. of DAIB was used. [f] Combined yield.

Table 2 Cycloaddition of *o*-quinone monoimines with vinyl ethers and phenyl vinyl sulfide[a]



	o-Aminophenol				
Entry	**1**	R	Dienophile	Product	Yield (%)[b]
1	**1a**	5-NO_2	**3**	**7a**	64
2	**1a**	5-NO_2	**4**	**8a**	69
3	**1a**	5-NO_2	**5**	**9a**	52[c]
4	**1a**	5-NO_2	**6**	**10a**	78
5	**1b**	4-CN	**3**	**7b**	66
6	**1b**	4-CN	**4**	**8b**	68
7	**1b**	4-CN	**5**	**9b**	61[c]
8	**1b**	4-CN	**6**	**10b**	76
9	**1c**	4-CN, 6-OMe	**3**	**7c**	68
10	**1c**	4-CN, 6-OMe	**4**	**8c**	72
11	**1c**	4-CN, 6-OMe	**5**	**9c**	59[c]
12	**1c**	4-CN, 6-OMe	**6**	**10c**	71
13	**1d**	5-CN	**3**	**7d**	61
14	**1d**	5-CN	**4**	**8d**	63
15	**1d**	5-CN	**5**	**9d**	51[c]
16	**1d**	5-CN	**6**	**10d**	64
17	**1e**	4-COOMe	**3**	**7e**	66
18	**1e**	4-COOMe	**4**	**8e**	71
19	**1e**	4-COOMe	**5**	**9e**	56[c]
20	**1e**	4-COOMe	**6**	**10e**	75
21	**1f**	4-CF_3	**3**	**7f**	54
22	**1f**	4-CF_3	**4**	**8f**	60
23	**1f**	4-CF_3	**5**	**9f**	49[c]
24	**1f**	4-CF_3	**6**	**10f**	64

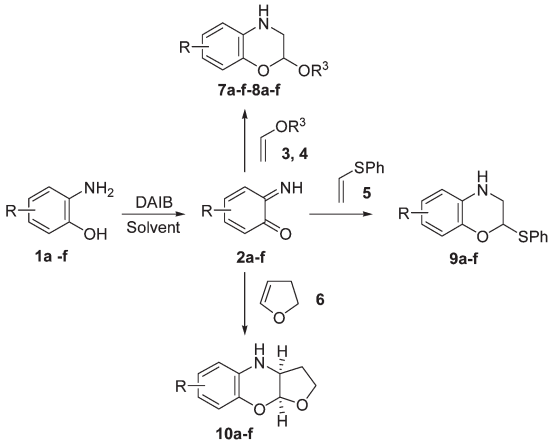
[a] All reactions were carried out with 5 equiv. of vinyl ether, entries 1–4 were carried out in CH_2Cl_2; and entries 5–24 were carried out in THF and in presence of $KHCO_3$. [b] Yield of isolated products. [c] Reactions were carried out with 2 equiv. of phenyl vinyl sulfide and slow addition of DAIB.

monoimines as electrophilic intermediates by oxidative dearomatization of *o*-aminophenols. Considering the stability of *o*-benzoquinone monoimides, we reasoned that electron-withdrawing group(s) on the arene moiety of the *o*-aminophenols would impart considerable stability to the corresponding oxidized *o*-benzoquinone monoimines. To test this hypothesis, 2-aminophenol was oxidized with diacetoxyiodobenzene (DAIB) in dichloromethane in the presence of butyl vinyl ether (**3**). However, no identifiable products were observed under these conditions.

Upon treatment of the parent 2-aminophenol with DAIB in the presence of butyl vinyl ether, neither 2-aminophenol nor any isolable product was observed from TLC analysis. It was presumed that *o*-quinone monoimine, if formed, could not undergo Diels–Alder reaction as it is not sufficiently electron-deficient to drive the reaction. Keeping the required electronic nature for the reactants of inverse-electron demand Diels–Alder reaction in mind and to amplify the probability of the heterodiene participating in the Diels–Alder event, we introduced a nitro group onto the aromatic ring of *o*-aminophenol. The oxidation of nitro-aminophenol **1a** was carried out with varying amounts of DAIB at different temperatures in the presence of butyl vinyl ether. The use of 1.2 equiv. of DAIB and 5 equiv. of butyl vinyl ether in dichloromethane at 0 °C afforded the benzoxazine derivative **7a** in 64% yield (Table 1, entry 6). The yield of the product can be further improved with an additional amount of enol ether (72% with 20 equiv.). The treatment of cyano-aminophenol **1b** with DAIB and butyl vinyl ether in the absence of base provided the desired product **7b** along with its *N*-acetylated derivative in a combined yield of 53% (Table 1, entry 11). We then probed the reactivity of 4-cyano-2-aminophenol (**1b**) under oxidative dearomatization Diels–Alder conditions in the presence of $KHCO_3$ to provide the heterocycle **7b** in similar yield (Table 1, entry 14).

With a consistent set of conditions in hand, we extended the protocol for the reactions of 5-nitro-2-aminophenol (**1a**) in the presence of electron-rich enol ethers such as ethyl vinyl ether (**4**), dihydrofuran (**6**), and phenyl vinyl sulfide (**5**) (Table 2). The reactions proceeded smoothly at 0 °C to furnish the benzoxazines **8a–10a** in good yields. However, the reaction of 4-nitro-2-aminophenol, under the same conditions, provided the corresponding products in moderate yields.

To determine the scope and to test the generality of this novel synthetic technology, a range of aminophenols **1b–1f** bearing different withdrawing groups at different positions of the arene moiety were probed (Scheme 1, Table 2). Since the reaction of **1b** with butyl vinyl ether furnished clean product in the presence of $KHCO_3$, the reactions of **1b–1f** were performed under the same conditions. The introduction of methoxy substituent in position-6 of cyano-aminophenol as shown in **1c** also exhibited very good reactivity in this methodology. These current conditions were also employed for 5-cyano derivative **1d** and as seen in Table 2, the reactivity of **2d** towards Diels–Alder



Scheme 1 [4 + 2] Cycloaddition of *o*-quinone monoimines **2a–f** with electron-rich dienophiles.

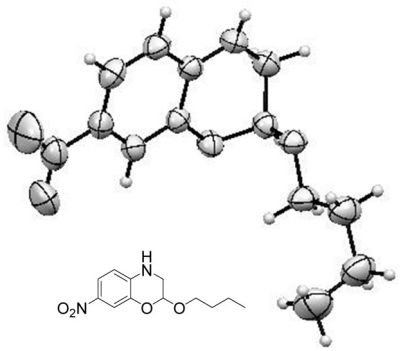


Fig. 1 Crystal structure of benzoxazine **7a**.

cycloaddition was found to be slightly reduced in comparison to its regio isomer **2b**. This remarkable protocol is also tolerant for functionalities such as 4-CO_2Me and 4-CF_3. The efficient reactivity of ester derivative **2e** is evident from Table 2. Surprisingly, the aminophenol with 3-CO_2Me substitution failed to give the corresponding cycloadducts under the reaction conditions. The yields of 1,4-benzoxazine derivatives shall be seen as overall yields of two steps *i.e.*, oxidation/Diels–Alder reaction. The yields are comparable with those of 1,4-benzoxazine derivatives derived from *o*-quinone monoimides/monoimines.[7,8]

The more electron-rich carbon atom of the dienophilic enol ether added to the nitrogen atom of the *o*-quinone monoimine. This can be attributed to the electron-deficiency on the nitrogen atom due to the presence of more electronegative oxygen atom at the other end of the heterodiene. The regiochemistry of benzoxazine derivative **7a** was confirmed by its single crystal X-ray analysis (Fig. 1).† To evaluate the origin of the regioselectivity observed in this study, we have computed the energies of the transition-state structures for the reaction between *o*-quinone monoimine **2b** and ethyl vinyl ether (**4**) by the B3LYP/6-31G(d) method. It was found that the transition-state structure of the product **8b** is favored by 7.7 kcal mol^{-1} over the transition-state structure of its regioisomer.

In summary, we have described a novel method for the chemical generation of *o*-quinone monoimines, which underwent [4 + 2] cycloaddition reaction with vinyl ethers and phenyl vinyl sulfide with complete regioselectivity, to afford *N*-unsubstituted-1,4-benzoxazine derivatives of diverse functionalities. Consequently these heterocycles could be considered as target structures for medicinal use since they have a 1,4-benzoxazine nucleus. The significant discovery of the current study is the incorporation of electron-withdrawing substituent on the aryl ring to disfavor polymerization and allow for the described intermolecular reaction to proceed. The present protocol demonstrated here may be helpful for expanding the horizons of *o*-quinone monoimine chemistry. Further studies are currently underway in this direction.

Acknowledgements

The authors thank Council for Scientific and Industrial Research [CSIR 01(2297)/09/EMR-II], New Delhi for financial support. We thank Prof V. R. Pedireddi, IIT Bhubaneswar for X-ray crystallographic assistance. N. B. thanks CSIR for a research fellowship.

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