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Sequential C–N and C–O Bond Formation in a Single Pot: Synthesis of 2*H*-Benzo[*b*][1,4]oxazines from 2,5-Dihydroxybenzaldehyde and Amino acid Precursors

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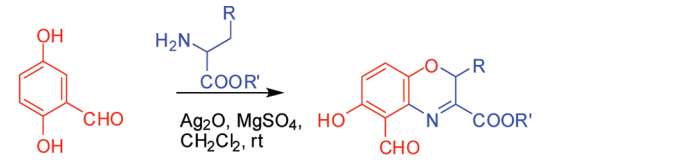
ABSTRACT



R= phenyl, *p*-BrC_6H_4, *p*-FC_6H_4, *p*-$CH_3C_6H_4$, *p*-$CH_3(CHCH_3)C_6H_4$, *p*-$OCH_3C_6H_4$, *p*-$OCOPhC_6H_4$, $OCH_2PhC_6H_4$, O-allyl, 3'-indolyl, 1-naphthyl

Functionalized β-aryl alanine ester derivatives were found to undergo rapid C–N and C–O bond formation with quinol carbonyl compounds to afford 2*H*-benzo[*b*][1,4]oxazines in good to excellent yields. This unprecedented finding reported herein offers a straightforward, highly efficient, and rapid method for the synthesis of 2*H*-benzo[*b*][1,4]oxazines.

2*H*-Benzo[*b*][1,4]oxazines have been part of molecular skeletons for the design of biologically active compounds, ranging from herbicides and fungicides to therapeutically useful drugs (Figure 1).[1] A few well-known methods reported for the synthesis of 2*H*-benzo[*b*][1,4]oxazines are cyclocondensation of aminophenols with suitable dihalo derivatives,[2] intramolecular copper-catalyzed O-arylation of β-aminoalcohols,[3] and epoxide opening of aminoalcohols followed by cyclocondensation.[4]

Alternative methods include alkylation of *o*-nitrophenol with haloester followed by reductive cyclization[5] and epoxide opening with *o*-halosulfonamides followed by cyclization.[6] More recently, the formation of aryl C–X bonds (X = N, O, S, etc.) by Ullmann coupling was successfully extended to the preparation of many such heterocycles.[7]

Oxidative dearomatization of phenols has been long perceived as an attractive tactic in the syntheses of complex natural products of various kinds. Several reports

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(3) Zhangqin Liu, Z.; Chen, Y. *Tetrahedron Lett.* **2009**, *50*, 3790.
(4) Brown, D. W.; Ninan, A.; Sainsbury, M. *Synthesis* **1997**, 895.
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(6) Albanese, D.; Landini, D.; Lupi, V.; Penso, M. *Ind. Eng. Chem. Res.* **2003**, *42*, 680.

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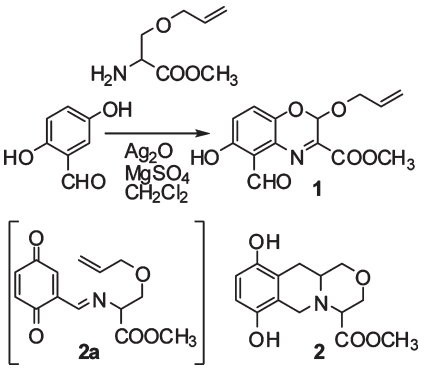
Scheme 1. Formation of 2*H*-Benzo[*b*][1,4]oxazines



previously highlighted oxidative dearomatization as a powerful strategy for the total synthesis of architecturally complex molecules wherein planar, aromatic scaffolds are converted to three-dimensional molecular architectures.[8]

Oxidative dearomatization has been previously adapted to nitrogen-tethered *ortho*-quinol acetates for azacyclization reactions for the synthesis of lycorine-type Amaryllidaceae alkaloids.[9]

In light of these classical and elaborated examples, the present report puts forward an application of oxidative dearomatization of 2,5-dihydroxy carbonyl compounds using silver oxide[10] for the synthesis of 2*H*-benzo[*b*]-[1,4]oxazines that provides an easy access to nitrogen–carbon (N–Cx) and oxygen–carbon (O–Cy) strategic bonds in a single operation.

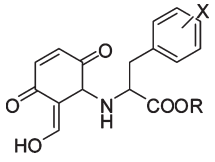
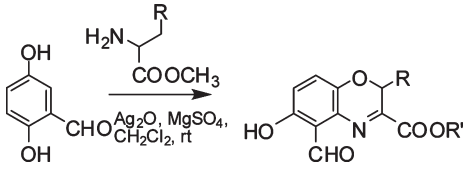
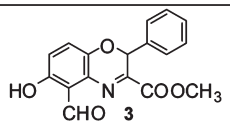
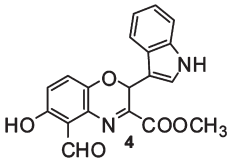
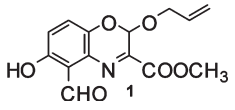


Figure 1. Representative structure of electrocyclization precursor.

In an experiment designed to synthesize the napthoxazine cycloadduct **2** by intramolecular Diels–Alder cyclization from an imine precursor **2a** of 2,5-dihydroxybenzaldehyde and a chirally pure phenylalanine ester derivative, we observed that racemic 2*H*-benzo[*b*][1,4]oxazine **1** was obtained as the only product, in good yields (Scheme 1). This new finding lead us to believe that an electrocyclization precursor possessing extended conjugation or a *β*-aryl substituent may be essential for the adjacent 1,4-benzoquinone system to cause benzylic oxidation, in a way that is similar to benzylic oxidations caused by DDQ (Figure 1).[11]

Table 1. Synthesis of 2*H*-Benzo[*b*][1,4]oxazines from Quinol and Natural Amino Acid Derivatives



entry	R	product	yield (%)
1	phenyl		75[a]
2	3'-indolyl		70
3	O-CH_2-CH=CH_2		52

[a] No reaction in acetonitrile and methanol. Reaction in THF with 4 equiv of silver oxide resulted in 10% yield; product obtained in 70% yield with THF and 2 equiv of silver oxide.

Thus similar reaction conditions were applied to esters of other natural amino acids which contain a *β*-aryl substituent like phenylalanine and tryptophan esters. We were pleased to obtain 2*H*-benzo[*b*][1,4]oxazines **3** and **4** in good to excellent yields in all the cases (Table 1). One of the 2*H*-benzo[*b*][1,4]oxazines, **4**, was isolated as a bright yellow solid that crystallized well, whose

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(8) (a) Liao, C. C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856. (b) Lin, K. C.; et al. *J. Org. Chem.* **2002**, *67*, 8157. (c) Gao, S.-Y.; Lin, Y.-L.; Rao, P. D.; Liao, C.-C. *Synlett* **2000**, 421. (d) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068. (e) Tsai, Y.-F.; Peddinti, R. K.; Liao, C.-C. *Chem. Commun.* **2000**, 475. (f) Nicolaou, K. C.; Vassilikogiannakis, G.; Simonsen, K. B.; Baran, P. S.; Zhong, Y.-L.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 3071.

(9) (a) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, *4*, 467. (b) Pouységu, L.; Avellan, A. V.; Quideau, S. *J. Org. Chem.* **2002**, *67*, 3425–3436. Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-V.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397.

(10) (a) Valderrama, J. A.; González, M. F.; Mahana, D. P.; Tapia, R. A.; Fillio, H.; Pautet, F.; Rodriguez, J. A.; Theoduloz, C.; Schmeda-Hirschmann, G. *Bioorg. Med. Chem.* **2006**, *14*, 5003. (b) Valderrama, J. A.; Colonelli, P.; González, M. F.; Rodriguez, J. A.; Theoduloz, C. *Bioorg. Med. Chem.* **2008**, *16*, 10172.

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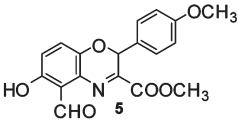
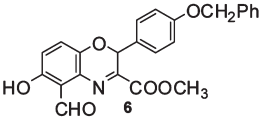
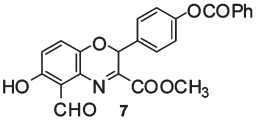
structure was unequivocally characterized by single crystal X-ray diffraction studies (see Supporting Information).

Table 2. Synthesis 2*H*-Benzo[*b*][1,4]oxazines from Quinol and Tyrosine Derivatives

entry	R	product	yield (%)
1	*p*-OH C_6H_4,	-	NR[a]
2	*p*-OCH_3 C_6H_4,	 **5**	92
3	*p*-$COCH_3$ C_6H_4,	-	NR
4	*p*- OCH_2Ph C_6H_4,	 **6**	10
5	*p*-OCOPh C_6H_4,	 **7**	50

[a] No reaction.

However tyrosine ester did not cyclize to a similar product (entry 1, Table 2). We have attributed this observation to oxidation of the hydroxyl moiety in tyrosine in the presence of silver oxide. Thus we chose to prepare different derivatives of tyrosine with electron-releasing and -withdrawing groups and to apply the same reaction conditions. Quantitative yields of 2*H*-benzo[*b*][1,4]oxazines were obtained from aminoester derivatives possessing electron-donating groups (entry 2, Table 2), and no such product was observed with the electron-withdrawing counterparts (entry 3, Table 2).

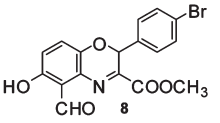
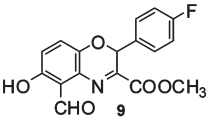
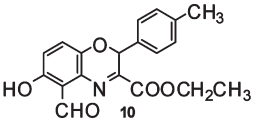
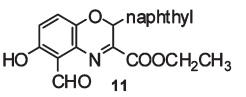
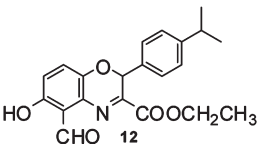
Therefore we presumed that the reaction mechanism is influenced by the electronic factors of the β-aryl ring which merits further validation. The initial cyclization studies using 4 equiv of silver oxide and dichloromethane as solvent provided the 2*H*-benzo[*b*][1,4]oxazines in good yields.

We then attempted further optimization of the reaction conditions using 2 equiv of silver oxide and CH_2Cl_2, which failed to afford products, except in the case of phenylalanine (footnote a, Table 1).

Further, methanol, acetonitrile, and THF too have either decreased the yield drastically or failed to afford products. Therefore, we continued using 4 equiv of silver oxide for the synthesis of 2*H*-benzo[*b*][1,4]oxazines. After these optimization studies, we then set out to validate our results using esters of a variety of unnatural amino acids to evaluate the scope of our strategy.

Thus, a range of unnatural racemic aminoesters with different electron-donating and -withdrawing groups were synthesized using the method reported in literature.[12] These unnatural racemic aminoesters were also subjected to similar reaction conditions, and the results are summarized in Table 3.

Table 3. Synthesis of 2*H*-Benzo[*b*][1,4]oxazines from Unnatural Amino Acid Derivatives

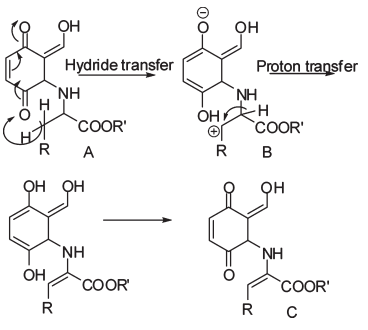
entry	R	product	yield (%)
1	*p*-Br C_6H_4,	 **8**	66
2	*p*-F C_6H_4,	 **9**	58
3	*p*-CH_3 C_6H_4,	 **10**	47[a]
4	1-naphthyl	 **11**	70%
5	*p*-$CH(CH_3)_2$ C_6H_4,	 **12**	72%

[a] 2 equiv of silver oxide in CH_2Cl_2 resulted in only a 10% yield. No reaction when R = *p*-$CF_3C_6H_4$, *p*-$NO_2C_6H_4$, and 4′-C_6H_4N.

The observations demonstrated a striking influence of electronic factors in the aryl moiety on this transformation. 2*H*-Benzo[*b*][1,4]oxazines were obtained in good yields from aminoesters containing electron-donating moieties (entries 1–5, Table 3). Aminoesters with *p*-CF_3 and

(12) (a) *Aldrichimica ACTA* **2001**, *34* (1), 1–14. (b) Lee, J.; Kim, S. Y.; Park, S.; Lim, J.-O.; Kim, J.-M.; Kang, M.; Lee, J.; Kang, S. U.; Choi, H.-K.; Jin, M.-K.; Welter, J. D.; Szabo, T.; Tran, R.; Pearce, L. V.; Toth, A.; Blumberg, P. M. *Bioorg. Med. Chem.* **2004**, *12*, 1055.

(13) Formation of intermediate **C** may be occurring *via* an initial rate-limiting hydride transfer involving **A** to give cation **B** which results in the formation of a double bond by proton transfer followed by further oxidation to give **C** as shown below.



p-NO_2 substituents on phenyl did not afford the desired 2*H*-benzo[*b*][1,4]oxazines, thus validating our assumption. We have further observed that 3-(4-pyridyl)alanine ester too did not result in the formation of 2*H*-benzo[*b*][1,4]-oxazines (footnote a, Table 3).

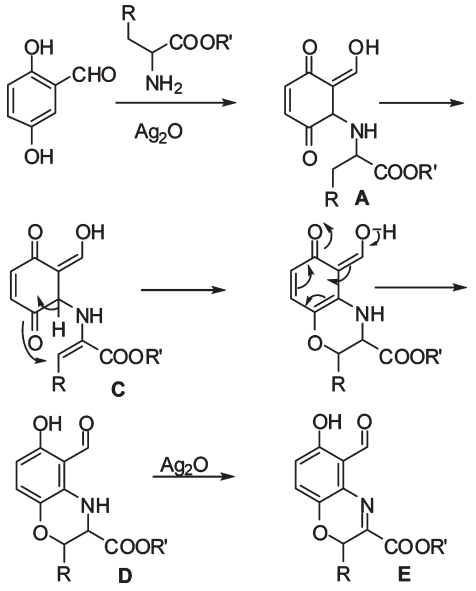


Figure 2. Plausible mechanism for oxidative dehydrogenation, C−N and C−O bond generation.

The most plausible mechanistic pathway delineated for the reaction to account for the formation of the product is shown in Figure 2. The initial event may be considered as the nucleophilic attack of amine in a Michael fashion on the transient enone to generate an intermediate **A**. Intermediate **A** may undergo benzylic oxidation leading to **C**.[13]

Subsequent electrocyclization of the latter and eventual rearomatization leads to **D** which further undergoes oxidation to final product **E** (Figure 2).

An electron-rich aryl group can significantly enhance the yield of 2*H*-benzo[*b*][1,4]oxazines by an apparent stabilization of benzylic cation **B** that may be destabilized by electron-withdrawing substituents on R.

In conclusion we have demonstrated a facile synthesis of 2*H*-benzo[*b*][1,4]oxazines by sequential generation of C−N, C−O bonds in a single pot *via* oxidative dearomatization of 2,5-dihydroxybenzaldehyde in the presence of functionalized amino acid derivatives. Further mechanistic studies of this reaction are underway.

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Supporting Information Available. Experimental procedures, characterization and copies of ^{1}H and ^{13}C NMR spectra for all new products, ORTEP diagram, and CIF for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.