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Preparation of α-Imino Aldehydes by [1,3]-Rearrangements of *O*-Alkenyl Oximes

Dimitra Kontokosta, Daniel S. Mueller, Heng-Yen Wang, and Laura L. Anderson*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607, United States

lauralin@uic.edu

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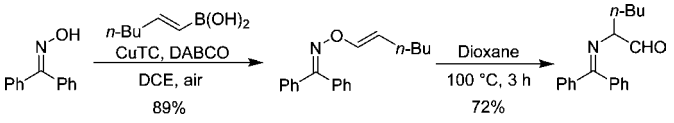
ABSTRACT



The synthesis of α-imino aldehydes has been achieved through the thermal [1,3]-rearrangement of *O*-alkenyl benzophenone oximes. A copper-mediated C−O bond coupling between benzophenone oxime and alkenyl boronic acids provides facile access to the required *O*-alkenyl oximes and a Horner−Wadsworth−Emmons olefination can be applied to the α-imino aldehyde products to give γ-imino-α,β-unsaturated esters. The scope of the method is described and mechanistic experiments are discussed.

α-Amino aldehydes are versatile intermediates in organic synthesis. These compounds undergo reductions and nucleophilic additions to form stereodefined amino alcohols, are converted to allylic amines or α,β-unsaturated γ-amino esters with olefination reagents, and act as dienophiles for hetero-Diels−Alder reactions.[1] Traditional methods for the preparation of α-amino aldehydes involve either the reduction of α-amino acid derivatives or the oxidation of 1,2-amino alcohols.[2] Enamine catalysis has also recently been shown to be highly effective for the α-amination of aldehydes with diazodicarboxylates (Scheme 1).[3] In contrast to these established methods, we wondered if α-amino aldehydes could be accessed from alkenyl boronic acids. This approach would effectively bypass the need for an aldehyde or carboxylic acid derivative and allow preparation of α-amino aldehydes from terminal alkynes through simple hydroboration.[4]

Recently, we discovered that acetophenone-derived *O*-alkenyl oximes undergo a [1,3]-rearrangement and cyclization sequence to form 2,3,5-trisubstituted pyrroles through an α-imino aldehyde intermediate.[5,6] We speculated that the use of a nonenolizable oxime under similar reaction conditions would prevent pyrrole formation and facilitate the development of alternative synthetic applications for this unique route to these reactive species. Herein we describe a procedure for the preparation of α-imino aldehydes from alkenyl boronic acids through a two-step sequence involving C−O bond coupling with benzophenone oxime followed by a [1,3]-rearrangement of the resulting *O*-alkenyl oxime ether (Scheme 1). A subsequent Horner−Wadsworth−Emmons (HWE) olefination has also been used to demonstrate the synthetic utility of the rearrangement-generated α-imino aldehydes for the preparation of γ-imino-α,β-unsaturated esters, and appropriate hydrolysis conditions have been determined to afford access to the

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(6) For an example of a [1,3]-rearrangement of an aryl ether of *N*-hydroxyphthalimide, see: Kikugawa, Y.; Tsuji, C.; Miyazawa, E.; Sakamoto, T. *Tetrahedron Lett.* **2001**, *42*, 2337.

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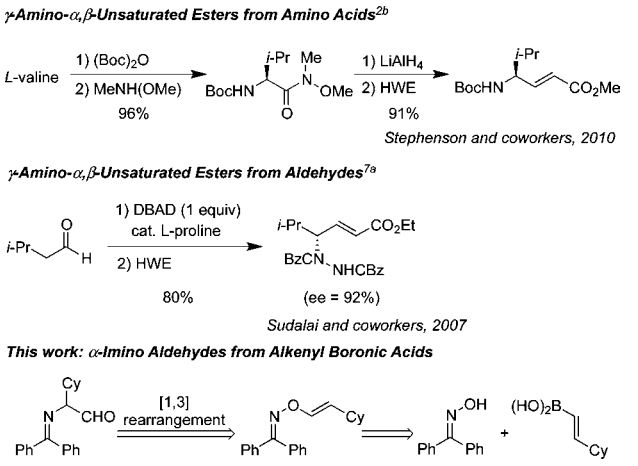
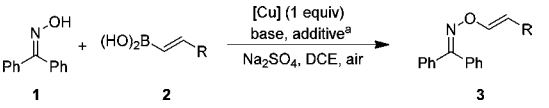
corresponding free amine.[7,8] This new method provides an alternative route for the preparation of α-amino aldehydes from alkenyl boronic acids that bypasses the need for a carbonyl functionalized precursor.

Scheme 1. Synthesis of α-Amino Aldehydes



The *O*-alkenyl oximes required for the targeted [1,3]-rearrangement were prepared by a Chan−Lam−Evans C−O bond coupling between benzophenone oxime **1** and alkenyl boronic acids **2**.[9,10] Propenyl oxime ether **3a** was first isolated from a $Cu(OAc)_2$-mediated reaction mixture, albeit in low yield due to competing hydrolysis of **1** (Table 1, entry 1). Preliminary optimization of this transformation included a survey of copper salts and amine bases which identified CuTC as the most effective coupling reagent and DABCO as the best choice of base (Table 1, entries 2−7). Surprisingly, the addition of silver salts to the coupling reaction mixture of **1** and 1-hexenylboronic acid **2b** had a dramatic effect on the yield of **3b**. The influence of these additives was highly dependent on the choice of counterion, but a control experiment suggested that the silver salts were

Table 1. Optimization of Cu-Mediated Oxime Ether Synthesis



entry	R	Cu salt	base	additive	**3**[b] (yield, %)
1	Me	$Cu(OAc)_2$	Py	none	**3a** (18)
2	Me	$Cu(OAc)_2$	NEt_3	none	**3a** (12)
3	Me	$Cu(OAc)_2$	DMAP	none	**3a** (28)
4	Me	$Cu(OAc)_2$	DABCO	none	**3a** (32)
5	Me	CuCl	DABCO	none	**3a** (29)
6	Me	$Cu(acac)_2$	DABCO	none	**3a** (nr)
7	Me	CuTC	DABCO	none	**3a** (51)
8	*n*-Bu	CuTC	DABCO	$AgBF_4$	**3b** (62)
9	*n*-Bu	CuTC	DABCO	AgOTf	**3b** (58)
10	*n*-Bu	CuOTf[c]	DABCO	none	**3b** (7)
11	*n*-Bu	CuTC	DABCO	$AgClO_4$	**3b** (70)
12	*n*-Bu	CuTC	DABCO	$AgClO_4$[d]	**3b** (39)
13	*n*-Bu	CuTC[c]	DABCO	$AgClO_4$[e]	**3b** (90)

[a] Reaction mixtures were prepared as 1:2:1:3:4:0.5 mixtures of **1**/**2**/[Cu]/base/Na_2SO_4/additive in DCE (0.1 M). [b] Percent yield determined by ^1H NMR spectroscopy using CH_2Br_2 as a reference. [c] $[CuOTf]_2 \cdot Tol$. [d] 0.2 equiv of $AgClO_4$ was used. [e] A second portion of **2b** was added after 1.5 h. TC = 2-thiophenecarboxylate.

not simply acting as counterion exchange reagents and AgOTf was ineffective in the absence of CuTC (Table 1, entries 8−11). $AgClO_4$ was identified as the best source of Ag(I) and was most effective when used at 50 mol % loading. Further tuning of the reaction conditions ultimately showed that addition of a second portion of 2 equiv of boronic acid **2b** after 1.5 h provided the highest yields of *O*-alkenyl oxime **3b** (Table 1, entry 13).[11] These optimal conditions were then used to explore the scope of the oxime ether synthesis.

A variety of *trans*-alkenylboronic acids undergo copper-mediated C−O bond coupling to form *O*-alkenyl benzophenone oximes **3**. As shown in Table 2, several alkenylboronic acids with linear and branched alkyl substituents were well-tolerated, including a bulky *tert*-butyl group and an α-substituted benzyl functionality (entries 1−9).[12] Cyclopropylvinylboronic acid **2i** was tested and provided the corresponding oxime ether **3i** without any evidence of ring-opened side products.[13] Alkenylboronic acids with both silyl- and benzyl-protected alcohol substituents also gave the desired alkenyl benzophenone oximes in high yields when the ether was one or more methylene units away from the olefin (Table 2, entries 10 and 11). We were pleased to discover that chloro-, ester-, and cyano-substituted alkenylboronic acids were similarly tolerant of the copper-mediated reaction conditions since these functionalities provide

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(8) For references on vinylogous amino acids, see: (a) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568. (b) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6570. (c) Mali, S. M.; Bandyopadhyay, A.; Jadhav, S. V.; Kumar, M. G.; Gopi, H. N. *Org. Biomol. Chem.* **2011**, *9*, 6566 and references within.

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(10) The corresponding pinacol boronic acids were ineffective reagents.

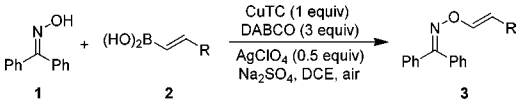
(11) Initial addition of 4 equiv of **2b** was less efficient.

(12) Styrenyl boronic acids gave primarily homocoupling products.

(13) (a) Kim, S.; Yoon, J.-Y., Novel Radical Traps. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001. (b) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151. (c) Halgren, T. A.; Roberts, J. D.; Horner, J. H.; Martinez, F. N.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **2000**, *122*, 2988. (d) Newcomb, M.; Chestney, D. L. *J. Am. Chem. Soc.* **1994**, *116*, 9753.

handles for further synthetic manipulation (Table 2, entries 12–14). The *O*-alkenyl benzophenone oximes prepared as described in Table 2 were subsequently tested for [1,3]-rearrangement reactivity to access a variety of α-imino aldehydes.

Table 2. Scope of *O*-Alkenyl Benzophenone Oxime Preparation



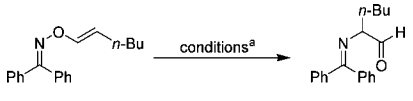
1 2 3

entry	R	3[a](yield, %)	entry	R	3[a](yield, %)
1	Me	**3a** (90)	8	−CH(Ar)(Et)	**3h** (69)
2	*n*-Bu	**3b** (89)	9	−cyclopropyl	**3i** (56)
3	*n*-Hex	**3c** (96)	10	$-CH_2OTBS$	**3j** (71)
4	*i*-Pr	**3d** (83)	11	$-(CH_2)_2OBn$	**3k** (82)
5	Cy	**3e** (84)	12	$-(CH_2)_4Cl$	**3l** (73)
6	*t*-Bu	**3f** (61)	13	$-(CH_2)_3CO_2Me$	**3m** (64)
7	Bn	**3g** (78)	14	$-(CH_2)_3CN$	**3n** (96)

[a] Percent isolated yields. Ar = *p*-*t*-Bu(C_6H_4).

When oxime ether **3b** was heated to 75 °C in dioxane-d_8, the corresponding α-imino aldehyde **4b** was observed by ^{1}H NMR spectroscopy (Table 3, entry 1). This product could be isolated as a crude oil but hydrolyzed in the presence of silica gel. Dioxane was initially selected as an appropriate medium for the rearrangement since it had previously been identified as the most effective solvent for the [1,3]-rearrangement and condensation of acetophenone-based *O*-alkenyl oximes to give the corresponding pyrroles.[5] As described in Table 3, a solvent screen showed that the preparation of **4b** was less efficient in aromatic and halogenated solvents, as well as THF (entries 2–4). Reaction time and temperature also played a dependent role on the efficiency of the transformation: faster rearrangements were achieved at higher temperatures and gave higher yields (Table 3, entries 5 and 6). The optimal conditions described in Table 3, entry 6, were

Table 3. Optimization of [1,3]-Rearrangement

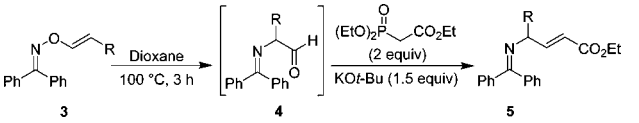


3b 4b

entry	solvent	time (h)	temp (°C)	yield[b] (%)
1	dioxane-d_8	3	75	67
2	toluene-d_8	3	75	38
3	DCE-d_4	3	75	62
4	THF-d_8	3	75	25
5	dioxane-d_8	8	50	19
6	dioxane-d_8	0.5	100	72

[a] 0.1 M solutions. [b] Percent yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Table 4. [1,3]-Rearrangement and Olefination



3 4 5

entry	R	4[a] (yield, %)	5[b] (yield, %)
1	Me	**4a** (56)	**5a** (52)
2	*n*-Bu	**4b** (72)	**5b** (69)
3	*n*-Hex	**4c** (62)	**5c** (66)
4	*i*-Pr	**4d** (63)	**5d** (54)
5	Cy	**4e** (72)	**5e** (70)
6	*t*-Bu	**4f** (64)	**5f** (64)
7	Bn	**4g** (66)	**5g** (63)
8	−CH(Ar)Et	**4h** (39)[c]	**5h** (26)[c]
9	cyclopropyl	**4i** (22)[d]	
10	$-(CH_2)_2OBn$	**4k** (56)	**5k** (51)
11	$-(CH_2)_4Cl$	**4l** (63)	**5l** (52)
12	$-(CH_2)_3CO_2Me$	**4m** (56)	**5m** (52)
13	$-(CH_2)_3CN$	**4n** (58)	**5n** (55)

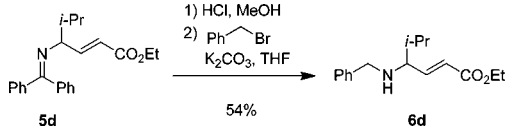
[a] Percent yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b] Percent isolated yield. [c] dr = 1:1. [d] No evidence of ring-opening was observed. Ar = *p*-*t*-Bu(C_6H_4).

ultimately chosen to screen the scope of the *O*-alkenyl benzophenone oxime [1,3]-rearrangement.

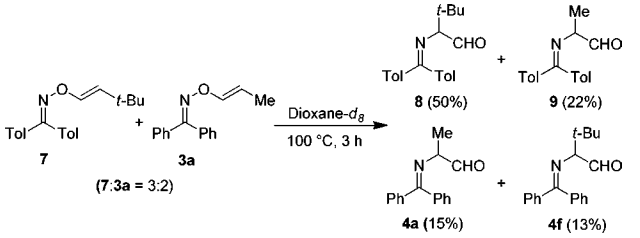
A variety of oxime ethers **3** were evaluated for both thermal [1,3]-rearrangements to give α-imino aldehydes **4** as well as a single flask, thermal rearrangement, and HWE olefination sequence to form isolable γ-imino-α,β-unsaturated esters **5**. These transformations were shown to be general for the majority of the *O*-alkenyl oximes described in Table 2, and the isolated yields of **5** correlate appropriately with the corresponding observed yields of **4**, determined by ^{1}H NMR spectroscopy. As shown in Table 4, *trans*-alkenyl oxime ethers with linear and branched alkyl substituents were well-tolerated for these transformations (entries 1–7). Chloro-, ester-, and cyano-functionalized substrates also provided the corresponding α-imino aldehydes and γ-imino-α,β-unsaturated esters in good yields (Table 4, entries 11–13). Surprisingly, only benzyl ether **3k** was efficiently converted to **4k** and **5k**, while silyl ether **3j** decomposed under the [1,3]-rearrangement conditions. Alkenyl oxime ether **3h** provided 1:1 diastereomeric mixtures of **4h** and **5h**, which implied that the stereochemistry of the rearrangement cannot be controlled by the alkenyl boronic acid substituent. Vinylcyclopropane-substituted oxime ether **3i** underwent a rearrangement to **4i** in low yield; however, the lack of any evidence of ring-opening suggests that the transformation is not proceeding by a radical pathway.[13] With a variety of γ-imino-α,β-unsaturated esters in hand, simple imine hydrolysis conditions were also determined to remove the imine protecting group and release the free amine for further manipulation (Scheme 2).

While the lack of any evidence of ring-opening for the rearrangement of **3i** suggests that the [1,3]-rearrangements

Scheme 2. Imine Hydrolysis and Protection



Scheme 3. Crossover Experiment



of *O*-alkenyl oximes do not proceed through a single-electron pathway, we were still interested in determining if the transformation was proceeding through a dissociative mechanism.[14−16] As shown in Scheme 3, a crossover experiment between oxime ethers **3a** and **7** provided four distinct products. This result suggests that the [1,3]-rearrangement can occur through solvent separated intermediates and may be proceeding through an ion-pair pathway.[15,17] To compare the enthalpy of activation for the [1,3]-rearrangement to reported N−O bond dissociation energies, first order rate constants for the rearrangement were determined at five points between 40 and 80 °C and used to form an Eyring plot. The following activation parameters were determined from these data: $\Delta H^{\ddagger}$ = 25.4 kcal/mol and $\Delta S^{\ddagger}$ = −0.8 eu.[18] While the experimental activation enthalpy value is lower than the reported N−O bond dissociation energy value for *O*-phenyl benzophenone oxime (34.9 kcal/mol), it suggests that the oxime ether N−O bond is significantly weakened during the rate-determining step of the [1,3]-rearrangement and supports the observation of crossover products through a dissociative mechanism.[19]

In summary, we have shown that α-imino aldehydes can be prepared directly from alkenylboronic acids through a copper-mediated C−O bond coupling with benzophenone oxime and a subsequent [1,3]-rearrangement. In analogy to other protected α-amino aldehydes, these products undergo HWE reactions to provide γ-imino-α,β-unsaturated esters that can be hydrolyzed to release the free amine. The [1,3]-rearrangement of *O*-alkenyl benzophenone oximes described above provides an alternative route to an important synthetic intermediate that avoids the use of amino acid starting materials or aldehyde precursors and provides access to α-imino aldehydes directly from alkynes via simple hydroboration.

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Supporting Information Available. Experimental procedures and compound characterization data. This information is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.