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Direct β-Acyloxylation of Enamines via PhIO-Mediated Intermolecular Oxidative C–O Bond Formation and Its Application to the Synthesis of Oxazoles

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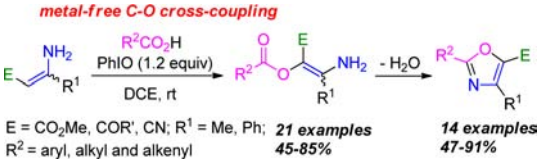
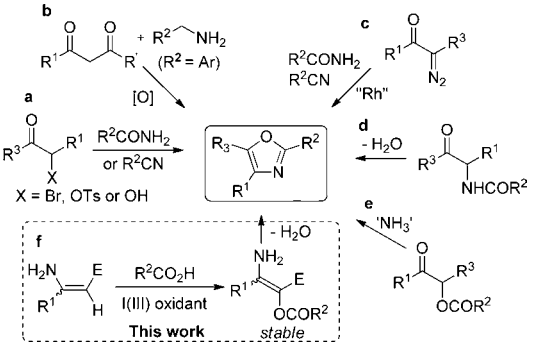
ABSTRACT



A direct β-acyloxylation of enamine compounds has been achieved by using iodosobenzene (PhIO) as an oxidant to realize the intermolecular oxidative C(sp^2)-O bond formation between enamines and various carboxylic acids, including N-protected amino acids. The transformation tolerates a wide range of functional groups and furnishes a variety of β-acyloxy enamines that can be conveniently converted to oxazole compounds via cyclodehydration.

Ketone derivatives are useful buliding blocks for the construction of the biologically important oxazole compounds. Generally, the formation of an oxazole ring involving ketone derivatives as the starting materials falls into one of the following categories: (1) The ketones substituted with a leaving group at the α-position reacts with acyl amides or nitriles (Scheme 1, path **a**).[1] (2) The tandem reactions between 1,3-dicarbonyl compounds with benzylamine derivatives under oxidative conditions, in which the benzylic carbon is incorporated into the oxazole ring (Scheme 1, path **b**).[2] (3) The reaction of α-diazocarbonyl compounds with amides or nitriles in the presence of Rh catalyst (Scheme 1, path **c**).[3] (4) The cyclodehydration of α-acylaminoketones, esters, or amides, which is also knonwn as Robinson-Gabriel oxazole synthesis[4] (Scheme 1, path **d**). (5) The reaction of α-acyloxy ketones[5] with ammounium acetate (Scheme 1, path **e**). In this last approach, the β-acyloxy enamines have been

Scheme 1. General Strategy for the Formation of Oxazoles from Ketone Derivatives



(1) For selected examples, see: (a) Batsila, C.; Kostakis, G.; Hadjiarapoglou, L. P. *Tetrahedron Lett.* **2002**, *43*, 5997. (b) Lee, J. C.; Choi, H. J.; Lee, Y. C. *Tetrahedron Lett.* **2003**, *44*, 123. (c) Herrera, A.; Martinez-Alvarez, R.; Ramiro, P.; Molero, D.; Almy, J. *J. Org. Chem.* **2006**, *71*, 3026. (d) Lee, J. C.; Seo, J.-W.; Baek, J. W. *Synth. Commun.* **2007**, *37*, 2159. (e) Ritson, D. J.; Spiteri, C.; Moses, J. E. *J. Org. Chem.* **2011**, *76*, 3519.

(2) For selected examples, see: (a) Wang, C.; Zhang, J.; Wang, S.; Fan, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 2338. (b) Xie, J.; Jiang, H.; Chenga, Y.; Zhu, C. *Chem. Commun.* **2012**, *48*, 979.

(3) For selected examples, see: (a) Shi, B.; Blake, A. J.; Campbell, I. B.; Judkinsb, B. D.; Moody, C. J. *Chem. Commun.* **2009**, *45*, 3291. (b) Shi, B.; Blake, A. J.; Lewis, W.; Campbell, I. B.; Judkins, B. D.; Moody, C. J. *J. Org. Chem.* **2010**, *75*, 152. (c) Linder, J.; Garner, T. P.; Williams, H. E. L.; Searle, M. S.; Moody, C. J. *J. Am. Chem. Soc.* **2011**, *133*, 1044. (d) Austeri, M.; Rix, D.; Zeghida, W.; Lacour, J. *Org. Lett.* **2011**, *13*, 1394.

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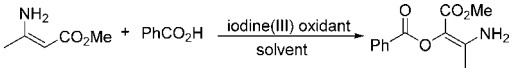
postulated to be the possible intermediate but was never separated to be confirmed.[5a] Although β-acyloxylated enamines are a class of compounds not yet been extensively studied, they can logically be envisaged to be useful building blocks for the synthesis of oxazoles through cyclodehydration. However, the synthesis of oxazoles from a "real" β-acyloxy enamines has not been thoroughly studied,[6] partially due to the fact that there are limited methods for the preparation of the N-unprotected β-acyloxy enamines. Literature survey shows that the existed approaches include only the phenyliodine(III) diacetate (PIDA)-mediated α-acyloxylation of β-monosubstituted enamines[6,7] and the enamination of α-acetoxylated dicarbonyl compound using ammonium acetate.[8] Unfortunately, neither of the above two strategies can provide a general or efficient synthesis of β-acyloxy enamines bearing versatile acyloxy moiety since the former methods are only applicable to the synthesis of β-acetoxy enamines, while the latter only describe one example of the formation β-acetoxy-β-enamino ester in a poor yield. Obviously, direct β-acyloxylation of the readily available enamine compounds through the oxidative intermolecular coupling with various carboxylic acids will be highly valuable and strongly desired. However, to the best of our knowledge, this strategy has been less studied and there is no report on the intermolecular oxidative coupling of an enamine compound with carboxylic acid;[9] even the powerful palladium-catalyzed oxidative cross-coupling has not touched on this transformation. As a continuation of our study on oxidative reactions mediated by hypervalent iodine reagents,[6,7b,10] we described herein a mild and convenient synthesis of β-acyloxy enamines using iodosobenzene (PhIO) as the oxidant, which has realized the direct oxidative C(sp^2)-O bond formation between enamine compounds with carboxylic acids. The application of the obtained β-acyloxy enamines to the synthesis of oxazoles was also established (Scheme 1, path **f**). Notably, the N-atom was introduced early by using enamines as starting materials and the carboxylic acids were installed into the enamines at a later stage in this process.

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

entry	oxidant (equiv)	solvent	time (h)	yield[b](%)
1	PIDA (1.2)	DCE	1	29
2	PIFA (1.2)	DCE	3	ND
3	$PhICl_2$ (1.2)	DCE	3	ND
4	PhIO (1.2)	DCE	1	75
5	PhIO (1.4)	DCE	1	59
6[c]	PhIO (1.2)	DCE	1	85
7[d]	PhIO (1.2)	DCE	1	79
8[e]	PhIO (1.2)	EtOAc	2	49
9[e]	PhIO (1.2)	toluene	1	34
10[e]	PhIO (1.2)	DMF	6	21
11[e]	PhIO (1.2)	acetonitrile	1	81

[a] All reactions were carried out by adding **2a** (0.5 mmol) to a mixture of **1a** (0.5 mmol) and oxidant (0.6 mmol) in solvent (2.5 mL) unless otherwise stated. [b] Isolated yields. [c] 1.2 equiv of **2a** was used. [d] 1.5 equiv of **2a** was used.

We have recently described a direct method for the synthesis of 2-(trifluoromethyl)oxazoles from β-monosubstituted enamines and phenyliodine(III) bistrifluoroacetate (PIFA),[6] in which the trifluoroacetoxylated enamine intermediate is postulated to be generated but too reactive to be separated and thus undergoes simultaneous condensation to give the cyclized oxazole product. Replacing PIFA with another readily available iodine(III) oxidant, i.e., PIDA gave the stable β-acetyloxy enamine intermediate, which could also cyclize to give 2-methyloxazole compound under reflux in AcOH.[6] In both cases, one of the ligands in the iodine(III) oxidant was incorporated into the final product. One can easily envisage that by changing the ligand of PIDA with another carboxylate moiety, various β-acyloxy enamines bearing different R^2 groups can be synthesized using the above strategy which thus provides an convenient route for the synthesis of 2-substituted oxazole compounds. However, the preparation of the analogs of PIDA with different ligands turns out to be a time-consuming and troublesome process. To get around, We rationalized that the reaction of the β-monosubstituted enamine with various carboxylic acid in the presence of an appropriate iodine(III) oxidant may very well undergo a similar pathway to give the desired β-acyloxy enamine products. If succeeded, such tranformation will stand out for its significant advantage of eliminating the participation of any transition metal while facilitating a direct intermolecular oxidative coupling of an enamine with carboxylic acid.

To begin with, enamine **1a** and benzoic acid were used as the model substrates to test the feasibility of this transformation. Subjecting 1.0 equiv of **1a** to a mixture of 1.0 equiv of benzoic acid and 1.2 equiv of PIDA in DCE at room

(4) For selected examples, see: (a) Morwick, T.; Hrapchak, M.; Turi, M. D.; Campbell, S. *Org. Lett.* **2002**, *4*, 2665. (b) Keni, M.; Tepe, J. J. *J. Org. Chem.* **2005**, *70*, 4211. (c) Li, W.; Lam, Y. *J. Comb. Chem.* **2005**, *7*, 644. (d) Biron, E.; Chatterjee, J.; Kessler, H. *Org. Lett.* **2006**, *8*, 2417. (e) Sanz-Cervera, J. F.; Blasco, R.; Piera, J.; Cynamon, M.; Ibáñez, I.; Murguía, M.; Fustero, S. *J. Org. Chem.* **2009**, *74*, 8988. (f) Thompson, M. J.; Adams, H.; Chen, B. *J. Org. Chem.* **2009**, *74*, 3856. (g) Clapham, B.; Spanka, C.; Janda, K. D. *Org. Lett.* **2001**, *3*, 2173.

(5) For selected examples, see: (a) Strzybny, P. P. E.; van Es, T.; Backeberg, O. G. *J. Org. Chem.* **1963**, *20*, 3381. (b) Huang, W.; Pei, J.; Chen, B.; Pei, W.; Ye, X. *Tetrahedron* **1996**, *52*, 10131.

(6) For our preliminary probe into the reaction, see: Zhao, F.; Liu, X.; Qi, R.; Zhang-Negrerie, D.; Huang, J.; Du, Y.; Zhao, K. *J. Org. Chem.* **2011**, *76*, 10338.

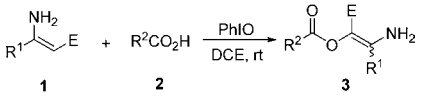
(7) For selected examples, see: (a) Zhang, P. F.; Chen, Z. C. *J. Chem. Res.-S* **2001**, 150. (b) Chen, Y.; Ju, T.; Wang, J.; Yu, W.; Du, Y.; Zhao, K. *Synlett* **2010**, 231.

(8) Zhao, Y.; Zhao, J.; Zhou, Y.; Lei, Z.; Li, L.; Zhang, H. *New J. Chem.* **2005**, *29*, 769.

(9) For selected examples describing the intramolecular and intermoleculatr condensation of carboxylic acids with ketones, ethers and alkenes catalyzed by iodine reagents, see: (a) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331. (b) Shi, E.; Shao, Y.; Chen, S.; Hu, H.; Liu, Z.; Zhang, J.; Wan, X. *Org. Lett.* **2012**, *14*, 3384. (c) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem.—Eur. J.* **2011**, *17*, 4085.

(10) (a) Du, Y.; Liu, R.; Linn, G.; Zhao, K. *Org. Lett.* **2006**, *8*, 5919. (b) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417. (c) Li, X.; Du, Y.; Liang, Z.; Li, X.; Pan, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2643. (d) Wang, J.; Yuan, Y.; Xiong, R.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2012**, *111*, 2210.

Table 2. Synthesis of β-Acyloxy Enamines from the PhIO-mediated Oxidative Coupling of Enamines with Carboxylic Acids[a]



1 2 3

entry	R^1	E	R^2	3	time (h)	yield[b] (%)
1	Me	CO_2Me	Ph	**3a**	1	85
2	Me	COMe	Ph	**3b**	1	80
3	Me	COPh	Ph	**3c**	1	62
4	Me	CN	Ph	**3d**	2	56
5	Ph	CO_2Me	Ph	**3e/3e′**	1	74[c]
6	Me	CO_2Me	*o*-Me-Ph	**3f**	2	72
7	Me	CO_2Me	*p*-MeO-Ph	**3g**	3	63
8	Me	CO_2Me	*p*-F-Ph	**3h**	1	80
9	Me	CO_2Me	*m*-NO_2–Ph	**3i**	1	65
10	Me	CO_2Me	2-thienyl	**3j**	6	55
11	Me	CO_2Me	2-furfuryl	**3k**	2	61
12	Me	CO_2Me	4-pyridinyl	**3l**	4	45
13	Me	CO_2Me	Me	**3m**	1	70
14	Me	CO_2Me	*n*-decanyl	**3n**	4	59
15	Me	CO_2Me	cyclopropyl	**3o**	1.5	67
16	Me	CO_2Me	*t*-Bu	**3p**	2	65
17[d]	Me	CO_2Me	PhCH=CH-	**3q**	1	67
18	Me	CO_2Me	$ClCH_2$-	**3r**	1	66
19[e]	Me	CO_2Me	EtO_2CCH=CH-	**3s**	1	76
20	Me	CO_2Me	$BocNHCH_2$-	**3t**	1	61[f]
21	Me	CO_2Bn	Ph	**3u**	1	71

[a] General conditions: PhIO (0.6 mmol), **2a** (0.6 mmol), **1a** (0.5 mmol) in DCE (2.5 mL), rt. [b] Isolated yields. [c] Mixture of two separable isomers (**3e**/**3e′** = 5/2). [d] Cinnamic acid was used. [e] Fumaric acid was used. [f] Mixture of two inseparable isomers (Z/E = 1/4).

temperature for 1 h afforded the desired cross-coupled product **3a** in 29% (Table 1, entry 1), along with the formation of other unidentified byproducts. No desired product was detected when PIDA was replaced with PIFA or $PhICl_2$ (Table 1, entries 2–3). To our delight, when PhIO was used as the oxidant, the reaction became very clean and the coupled product could be furnished in a satisfactory yield (Table 1, entry 4). Increasing the dosage of PhIO from 1.2 equiv to 1.4 equiv did not benefit the yield due to the obvious formation of more byproducts (Table 1, entry 5). However, when an excess of benzoic acid (1.2 equiv) was used, the yield was greatly improved to 85% (Table 1, entry 6). Attempt to further improve the yield by increasing the amount of the acid to 1.5 equiv was unsuccessful (Table 1, entry 7). Further solvent screening showed that other solvents including EtOAc, toluene and DMF were not desired for this reaction, while acetonitrile also gave a relatively good result (Table 1, entries 8–11).

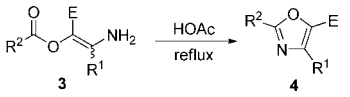
Under the most optimal conditions (Table 1, entry 6), various enamines and carboxylic acids were examined to probe the scope and generality of the method. The reaction of the enamines bearing other electron-withdrawing groups such as acyl or benzoyl groups with benzoic acid also provided the desired products (the presence of the carbonyl moiety keeps the products an *E* configuration due to the existence of an internal H-bond) in good yields (Table 2, entries 2–3). The reaction of an enamine bearing a cyano group needs much longer reaction time and the corresponding product was obtained in a relatively lower yield (Table 1, entry 4). When the methyl group in enamine **1a** was replaced with a bulky phenyl group, the coupled products were obtained as two separable isomers in an overall 74% yield (Table 2, entry 5).

Our next study was aimed at extending the scope of the reactants from, benzoic acid to a range of substituted benzoic acids. Results show that the presence of either electron-donating or electron-withdrawing substituents in the phenyl ring of the carboxylic acid does not influence the reaction to any significant extent as the desired products **3f**–**i** were all obtained in moderate to good yields (Table 2, entries 6–9). The phenyl group of the carboxylic acid can be further replaced with thienyl, furfuryl and pyridinyl rings (Table 2, entries 10–12). However, the yields achieved for these β-acyloxy enamines bearing heterocyclic moiety were relatively lower. Furthermore, the aliphatic carboxylic acids can also be applied to the method and the desired products that bear a methyl, decanyl, cyclopropyl or *tert*-butyl groups can be achieved (Table 2, entries 13–16). When the long-chained or bulkyl aliphatic acids were used, much more reaction time was required for the reaction to complete (Table 2, entries 14 and 16). Notably, other substituted carboxylic acids, such as cinnamic acid, chloroacetic acid, fumaric acid monoethyl ester and even N-protected amino acid could also be well tolerated in the process and the desired products could be furnished in moderate yields under the same conditions (Table 2, entries 17–20). Moreover, the E substituent in the substrate can also be extended to a benzyloxycarbonyl group (Table 2, entry 21), in which the benzyl group can be easily removed.

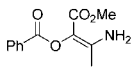
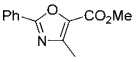
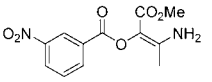
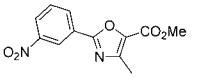
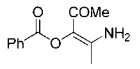
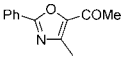
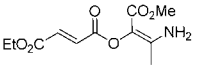
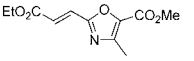
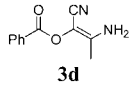
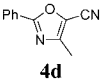
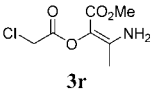
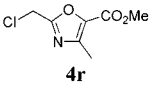
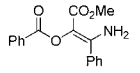
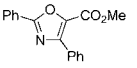
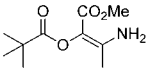
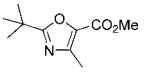
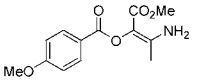
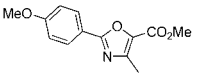
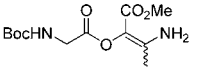
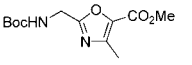
One important application of the obtained β-acyloxy enamines is the capacity to be transformed into various oxazole compounds via intramolecular condensation in boiling AcOH.[5,6] The results listed in Table 3 demonstrated that by heating at reflux temperature in AcOH, all the selected β-acyloxy enamines could be efficiently converted to the corresponding oxazoles in acceptable to excellent yields. All these reactions went to completion very fast (within 30 min) except for the case in entry 4 (Table 3), which needed relatively longer reaction time (1 h). It is worthy to note that the alkenyl, chloro and the protected amino functionality have no influence on the outcome of the reaction (Table 3, entries 7–10).

Furthermore, a one-pot sequence for synthesizing oxazoles directly from the readily available β-monosubstituted enamine **1a** and N-protected amino acids were examined. enamines intermediates in chlorobenzene, the reaction mixture was refluxed and the desired oxazole products could be obtained in moderate to good yields (Table 4). However, the reaction time was prolonged due to the sluggish dehydration process under the given conditions.[11] The presence of a biologically important oxazole ring as well as an amino residue of a biologically active amino acid might render this class of oxazoles some potential applications in pharmacuetical studies.

Table 3. Synthesis of Oxazoles via Intramolecular Condensation of β-Acyloxy Enamines[a]

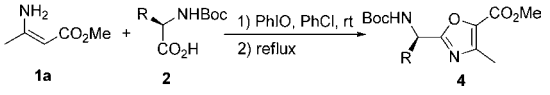


3 4

entry	substrate **3**	product **4**	yield (%)[b]	entry	substrate **3**	product **4**	yield (%)[b]
1	 **3a**	 **4a**	73	6	 **3i**	 **4i**	81
2	 **3b**	 **4b**	81	7	 **3s**	 **4s**	80
3	 **3d**	 **4d**	61	8	 **3r**	 **4r**	91
4	 **3e**	 **4e**	77	9	 **3p**	 **4p**	65
5[c]	 **3g**	 **4g**	47	10	 **3t**	 **4t**	75

[a] General conditions: **3** (0.5 mmol), AcOH (2.5 mL), reflux, 30 min unless otherwise stated. [b] Isolated yields. [c] The reaction time was 1 h.

Table 4. One-pot Synthesis of Oxazoles from Enamines and N-Protected Amino Acids[a]



1a **2** **4**

entry	**2**	R	**4**	time (h)	yield (%)[b,c]
1	**Boc-Gly**	H	**4t**	10	62
2	**Boc-L-Phe**	Ph	**4u**	8	65[d]
3	**Boc-L-Ala**	Me	**4v**	12	87[e]
4	**Boc-L-ILe**	*sec*-Bu	**4w**	10	75[d]

[a] General conditions: PhIO (0.6 mmol), **2** (0.5 mmol), **1a** (0.6 mmol) in PhCl (10 mL), rt and then reflux. [b] Isolated yields. [c] Calculated based on **2**. [d] No racemization occurred. [e] Partial racemization occurred, 84% ee.

Control experiments were carried out for understanding the mechanistic pathway. The enamine substrate **1a**, although underwent β-trifluoroacetoxylation and β-acetyloxylation with PIFA and PIDA, respectively, was found to be inert in the presence of PhIO based on the experimental fact that no reaction occurred when benzoic acid was not applied. While the reaction between PIDA and benzoic acid was found to undergo ligand replacement to give $PhI(OCOPh)_2$ intermediate.[12] On the basis of these results, we tentatively propose that the reaction adopts a sequence process involving the *in situ* generation of $PhI(OCOR)_2$ from the reaction of PhIO and carboxylic acid (RCO_2H), and the subsequent β-acyloxylation of enamines.[6]

In summary, we have developed an iodine(III)-mediated cross-coupling of enamines with various carboxylic acids through the intermolecular C(sp^2)-O bond formation. Advantages of the method include the readily availability of the starting materials, the mild reaction conditions and the much desired transition-metal-free feature. Moreover, the transformation can tolerate a wide range of functional groups and furnish a variety of β-acyloxy enamines that can be further cyclized to oxazole compounds, showing the value and practicality of this cross-coupling method.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(11) The reaction time could be shortened to 2 h if an excess of Boc-glycine was used; however, the yield of the desired oxazole **4u** was reduced to 59%.

(12) For evidence of such ligand replacement reactions, see: (a) Bell, R.; Morgan, K. J. *J. Chem. Soc.* **1960**, 1209. (b) Baker, G. P.; Mann, F. G.; Sheppard, M. N.; Tetlow, A. J. *J. Chem. Soc.* **1965**, 3721. (c) Leffler, J. E.; Ward, D. C.; Burduroglu, A. *J. Am. Chem. Soc.* **1972**, *94*, 5339.