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Tandem Migration–Carboalkoxylation of *o*-Isocyanophenyl Acetals Leading to Benzoxazoles

Takashi Okitsu, Kenta Nagase, Nobuhiko Nishio, and Akimori Wada*

Department of Organic Chemistry for Life Science, Kobe Pharmaceutical University, 4-19-1, Motoyamakita-machi, Higashinada-ku, Kobe 658-8558, Japan

a-wada@kobepharma-u.ac.jp

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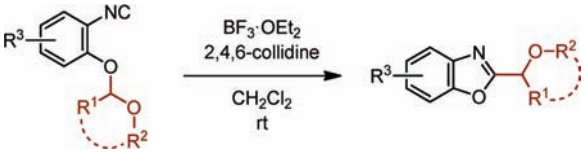
ABSTRACT



An efficient approach to benzoxazoles via tandem migration–carboalkoxylation of *o*-isocyanophenyl acetals has been developed. Both a Lewis acid and base are essential for this reaction, and the $BF_3 \cdot OEt_2$/2,4,6-collidine combination is the best choice for cooperative transformation.

Benzoxazoles are an important class of aromatic compounds and have been used for biologically active molecules and fluorescent sensors.[1] Because of their usefulness, numerous efficient methods for the synthesis of benzoxazoles have been developed, including the condensation of 2-aminophenols with carboxylic acid derivatives.[2] To date, transition-metal-catalyzed C–H functionalizations of benzoxazoles have been reported and those elegant and straightforward approaches can create C–C bonds directly, even sp^3 carbon centers.[3]

Recently, we have explored a versatile synthesis for benzofurans by iodocyclization of ethoxyethyl ethers to alkynes.[4] During the course of our studies into the iodine-mediated cyclization using isonitriles instead of alkynes as the substrates, we found that the reaction of isocyanophenyl acetal **1a** with bis(2,4,6-collidine)iodonium(I) hexafluorophosphate $[I(coll)_2PF_6]$ and $BF_3 \cdot OEt_2$ afforded 2-(α-alkoxyalkyl)benzoxazole **2a** in 79% yield and iodinated benzoxazole **3a** was not obtained (eq 1). Isonitrile compounds are often used for multicomponent reactions such as Ugi's four-component reaction and Passerini's three-component reaction,[5] and in general, they are transferred to amide groups through carboalkoxylations. Isonitriles are also converted to a component of heteroaromatic rings such as indoles,[6] benzofurans,[7] imidazoles,[8] and oxazoles.[9] While benzoxazoles can be prepared via carboalkoxylation of unstable *o*-isocyanophenols,[10] this variant accompanied by

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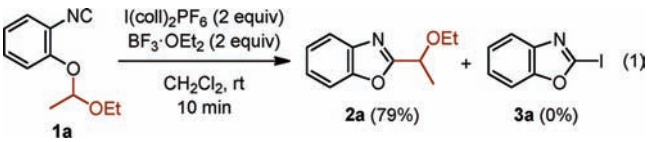
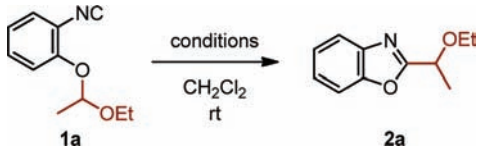
migration of the α-alkoxyalkyl group has not yet been established.[11] In the present communication, we describe our primary studies of this unprecedented reaction.



First, we investigated the suitable reaction conditions for the tandem migration–carboalkoxylation process of **1a** (Table 1). Based on the initial result in eq 1, we investigated which reagents were necessary for this reaction to proceed cleanly. Although each reagent alone was not sufficient (entries 1–3), to our surprise, the combination of $BF_3 \cdot OEt_2$/2,4,6-collidine promoted this process to give **2a** in good yields similar to eq 1 (entries 4–5). As both a Lewis acid and base were essential for our desired transformation, we next screened for the best combination. The use of pyridine, DMAP, or triethylamine as the Lewis base resulted in the recovery of **1a**, whereas the choice of 2, 6-lutidine or triphenylphosphine afforded **2a** in moderate yields (entries 6–10). TMSOTf/2,4,6-collidine conditions afforded no product at all, and **1a** was recovered (entry 11). Other Lewis acids were also examined, but more efficient candidates were not found (entries 12–13). The treatment with PPTS, a complex of a Lewis acid and base, resulted in a complex reaction with undesired byproducts (entry 14). Therefore, the optimized conditions were determined as shown in entry 5.

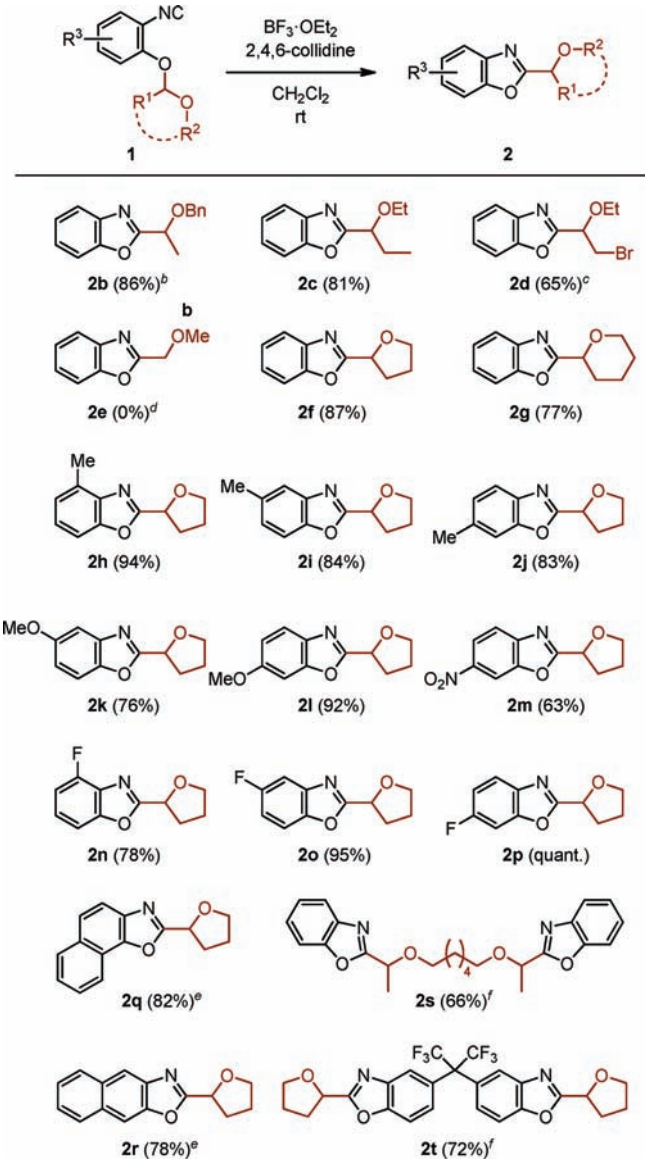
Table 1. Transformation of **1a**[a]



entry	conditions (equiv)	time (min)	**2a** (%)	**1a** (%)
1	$I(coll)_2PF_6$ (2)	15	0[b]	0
2	$BF_3 \cdot OEt_2$ (1)	10	30	0
3	2,4,6-collidine (2)	30	0	96
4	$BF_3 \cdot OEt_2$ (1), 2,4,6-collidine (1)	10	76	0
5	**$BF_3 \cdot OEt_2$ (1), 2,4,6-collidine (2)**	**10**	**81**	**0**
6	$BF_3 \cdot OEt_2$ (1), pyridine (2)	30	8	63
7	$BF_3 \cdot OEt_2$ (1), 2,6-lutidine (2)	10	78	0
8	$BF_3 \cdot OEt_2$ (1), DMAP (2)	60	16	41
9	$BF_3 \cdot OEt_2$ (1), Et_3N (2)	30	18	57
10	$BF_3 \cdot OEt_2$ (1), Ph_3P (2)	10	63	0
11	TMSOTf (1), 2,4,6-collidine (2)	60	0	100
12	$TiCl_4$ (1), 2,4,6-collidine (2)	10	35	0
13	$SnCl_4$ (1), 2,4,6-collidine (2)	10	48	0
14	PPTS (1)	90	8[c]	0

[a] Lewis acid was added to a solution of **1a** and Lewis base in CH_2Cl_2 (0.1 M) at rt. [b] Decomposed. [c] Reaction gradually became more complex.

Scheme 1. Tandem Migration–Carboalkoxylation of **1**[a]



[a] $BF_3 \cdot OEt_2$ (1 equiv) was added to a solution of **1** and 2,4,6-collidine (2 equiv) in CH_2Cl_2 (0.1 M) at rt. [b] $BF_3 \cdot OEt_2$ (2 equiv) and 2,4,6-collidine (2 equiv) were used. [c] $BF_3 \cdot OEt_2$ (4 equiv) and 2,4,6-collidine (6 equiv) were used. [d] No reaction. [e] $BF_3 \cdot OEt_2$ (1.5 equiv) and 2,4,6-collidine (2 equiv) were used. [f] $BF_3 \cdot OEt_2$ (2 equiv) and 2,4,6-collidine (4 equiv) were used.

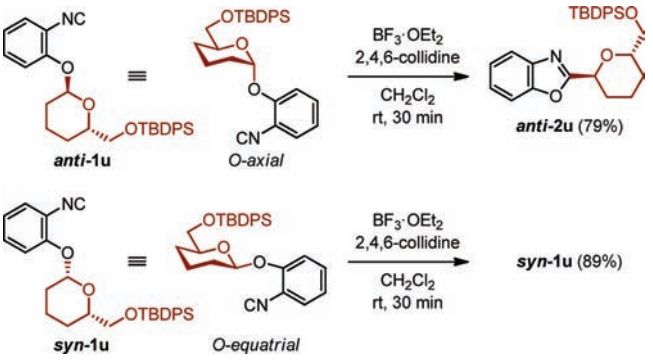
These results prompted us to apply this tandem migration–carboalkoxylation sequence to various acetal compounds (Scheme 1). Other acyclic acetal substrates **1b–c** were effective; however, bromo-substituted acetal **1d** required three times the quantity of reagents and a long

(11) For intramolecular carboalkoxylation of alkynes accompanied by migration of the acetal unit, see: (a) Nakamura, I.; Bajracharya, G. B.; Mizushima, Y.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4328–4331. (b) Nakamura, I.; Bajracharya, G. B.; Wu, H.; Oishi, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 15423–15430. (c) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022–15023. (d) Nakamura, I.; Chan, C. S.; Araki, T.; Terada, M.; Yamamoto, Y. *Adv. Synth. Catal.* **2009**, *351*, 1089–1100. (e) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025. (f) Fürstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760–4763.

reaction time (6 h). MOM (methoxymethyl) ether **1e** was sluggish probably due to its stereoelectronic effect. Cyclic acetals such as THF and THP ethers were also efficiently transformed into **2f**–**g** in high yields. The reactions were not affected by the alkyl (**1h**–**j**), methoxy (**1k**–**l**), nitro (**1m**), and fluoro (**1n**–**p**) substituents at any position of the aromatic ring. Bicyclic systems such as naphthalene derivatives **1q**–**r** gave corresponding naphthoxazoles **2q**–**r** in good yields. 1,6-Hexanediol-derived acetal **1s** and perfluoroalkyl-tethered bis-acetal **1t** could be applied to this process by using twice the quantity of reagents to obtain the respective double-cyclized products **2s** and **2t** in moderate yields.

To clarify the stereoelectronic effect of this tandem migration–carboalkoxylation process, we examined each diastereomer of THP ether **1u** (Scheme 2). The reaction of *anti*-**1u** gave the corresponding *anti*-**2u** as a single diastereomer in 79% yield. On the other hand, reaction of *syn*-**1u** did not proceed and starting material was recovered in 89% yield. These phenomena are attributed to the location of the phenolic oxygen of *anti*-**1u** in the axial position, and its C–O bond is easily cleaved due to the anomeric effect. In contrast, the positions of both substituents of the THP ring of *syn*-**1u** are constrained in the equatorial configuration.

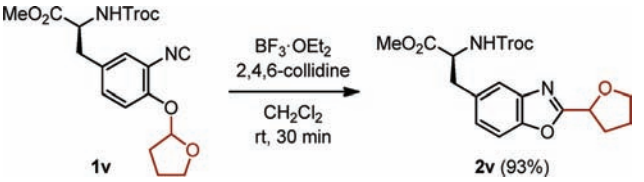
Scheme 2. Anomeric Effect



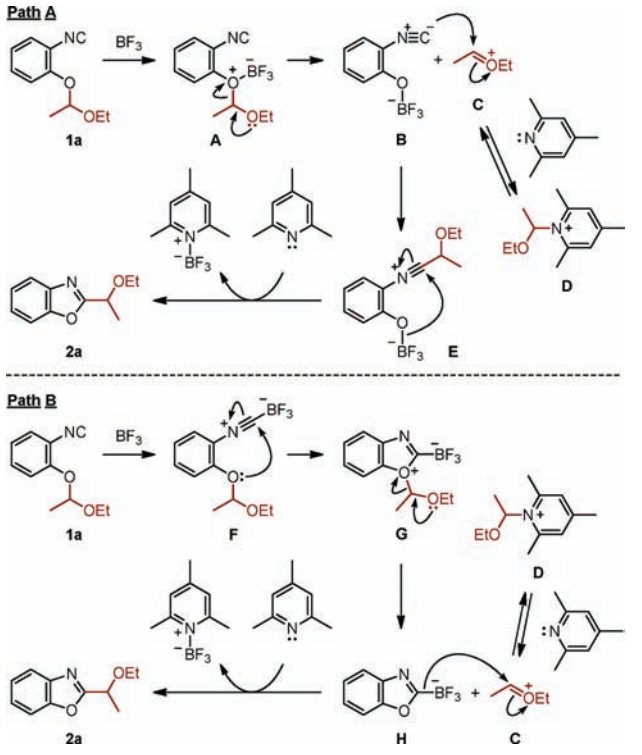
A valuable benefit in this tandem reaction is characterized by an application to a more highly functionalized molecule such as an amino acid (Scheme 3). Tyrosine-derived substrate **1v** was applicable to this transformation to afford novel α-amino acid derivative **2v** in high yield. It is worth noting that the $BF_3 \cdot OEt_2$/2,4,6-collidine system was so mild that several functionalities were tolerated, including a silyl group (**2u**), an ester, and even a carbamate (**2v**).

On the basis of the outcomes of these reactions, we proposed two reaction mechanisms for the tandem migration–carboalkoxylation (Scheme 4). For path A, after the phenolic oxygen of **1** binds to BF_3, the resulting intermediate **A** decomposes to isocyanophenoxide **B** and oxonium ion **C**. Then, nucleophilic attack of isonitrile **B** toward **C** forms reconstructed phenoxide **E**. Finally, the cyclization of intermediate **E** accompanies the elimination of BF_3 to

Scheme 3. Application to a More Complex Molecule



Scheme 4. Plausible Reaction Mechanism



afford benzoxazole **2**. In an alternative mechanism (path B), BF_3 would activate the isonitrile group. The acetal **F** would add to the carbon of the isonitrile to form a zwitterion **G**. The oxocarbenium ion **C** could then form by departure from the oxonium ion **G** followed by trapping by the carbanion **H** to afford **2**. 2,4,6-Collidine might play two important roles: (1) the stabilization of oxonium ion **C** as collidinium salt **D**[12] and (2) the facilitation of the cyclization step from **E**/**H** to **2** by the trapping of BF_3. Intermediates **B**/**H** and **D** were actually confirmed by ESIMS study of the reaction mixture of **1a** (see the Supporting Information).

In summary, we have developed a tandem migration carboalkoxylation of *o*-isocyanophenyl acetals. Since this

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reaction proceeds under the mild conditions of a $BF_3 \cdot OEt_2$/2,4,6-collidine system, a wide variety of 2-(α-alkoxyalkyl)-benzoxazoles can be prepared. Interestingly, a Lewis acid and base function cooperatively in this process. Further studies into the full scope of this transformation are ongoing.

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Supporting Information Available. Detailed experimental procedures and characterization data of compounds. Copies of ^1H and ^{13}C NMR spectra of all new compounds and ESIMS spectra of the reaction mixture. This material is available free of charge via the Internet at http://pubs.acs.org.