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Iodocyclization of olefinic amides with acetoxybenziodoxolone and NaI toward 4-iodomethylated benzoxazines

Yong Zhang,*[a] Junxue Bai[b] and Song Sun*[b]

[a] *Suzhou Industrial Park Institute of Services and Outsourcing, Suzhou, 215123 Jiangsu, P. R. China*
[b] *School of Petrochemical Engineering, Changzhou University, 213164 Changzhou, P. R. China.*
E-mail: zhangyong@siso.edu.cn; sunsong@cczu.edu.cn

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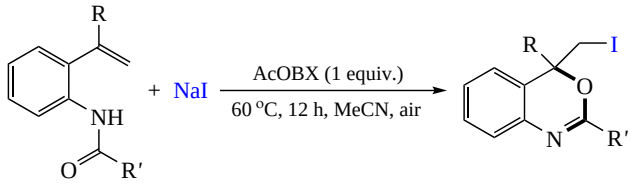
Iodocyclization of *N*-(2-alkenylphenyl)carboxamides with acetoxybenziodoxolone/NaI system gives 4-iodomethyl-4*H*-3,1-benzoxazines with high efficiency. The process is triggered by the oxidation of NaI with acetoxybenziodoxolone to afford iodine cation which is added to alkene moiety to form iodonium species, and the ultimate intramolecular nucleophilic addition generates the final products.



Keywords: iodonium ion, alkene difunctionalization, 3,1-benzoxazines, organoiodine compounds, cyclization.

Functionalized benzoxazines represent a class of useful skeleton widespread in a variety of pharmaceuticals and natural products with diverse biological activities.[1,2] Also they act as versatile building blocks for the construction of a range of bioactive molecules.[3,4] Considering their importance, much effort has been made to synthesized them [Figure 1(*a*)–(*c*)].[5] In this field, the intramolecular cyclization of olefinic amides with electrophiles *via* halonium ions is one of the most convenient methods for this purpose [Figure 1(*d*)].[6–8] For example, Xiao disclosed a visible-light promoted oxytrifluoromethylation of *N*-allylamides affording diverse CF_3-containing benzoxazines with good efficiency.[9] Ji demonstrated a Cu-catalyzed oxycyanomethylation of olefinic amides by the use of acetonitrile as the cyanomethyl radical source.[10] However, stoichiometric peroxide should be employed as an oxidant. To overcome these limitations, we recently disclosed a visible-light promoted radical difunctiona-lization of olefinic amides with bromoacetonitrile toward a series of functionalized benzoxazines.[11] Despite these

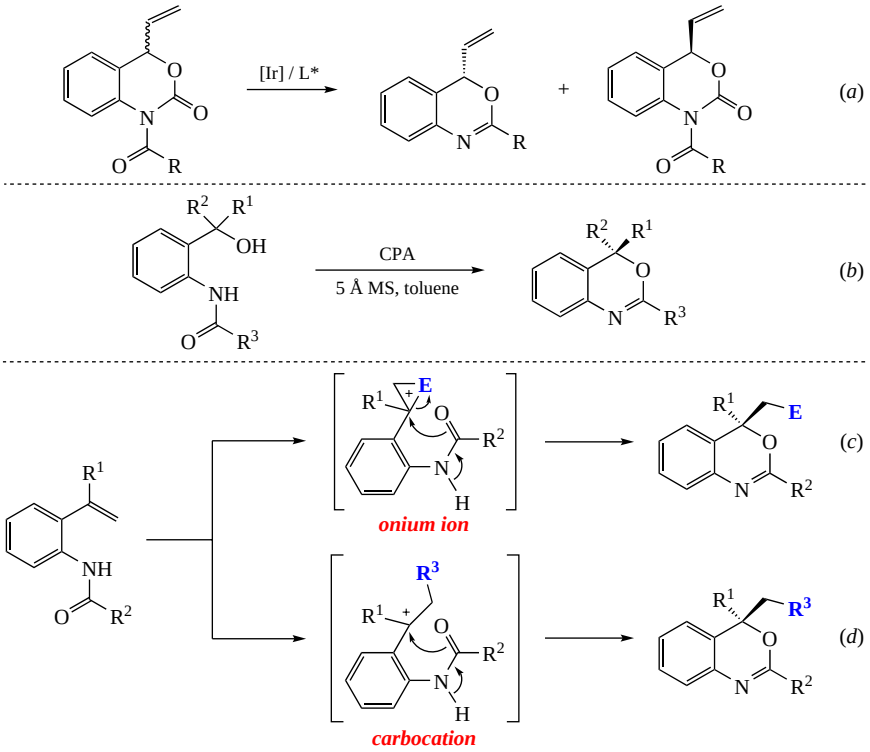
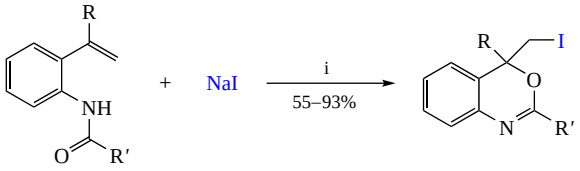


Figure 1 Representative examples of the synthesis of benzoxazines.



1a–s **2a–s**

a R = Me, R′ = Ph
b R = Me, R′ = 4-MeC_6H_4
c R = Me, R′ = 3-MeC_6H_4
d R = Me, R′ = 2-MeC_6H_4
e R = Me, R′ = 4-$MeOC_6H_4$
f R = Me, R′ = 4-$Me_2NC_6H_4$
g R = Me, R′ = 4-ClC_6H_4
h R = Me, R′ = 4-FC_6H_4
i R = Me, R′ = 2,6-$Cl_2C_6H_4$
j R = Me, R′ = 4-BrC_6H_4
k R = Me, R′ = 4-IC_6H_4
l R = Me, R′ = 4-$F_3CC_6H_4$
m R = Me, R′ = 1-naphthyl
n R = Me, R′ = 2-thienyl
o R = Me, R′ = 2-furyl
p R = Me, R′ = PhCH=CH
q R = R′ = Me
r R = Me, R′ = Cy
s R = R′ = Ph

Scheme 1 *Reagents and optimized conditions*: i, **1a–s** (0.2 mmol), acetoxybenziodoxolone (AcOBX) (0.25 mmol), NaI (0.25 mmol), K_2CO_3 (2 equiv., 0.4 mmol), MeCN (2.0 ml), 60 °C, under air, 12 h, sealed tube, unless otherwise noted.

Table 1 Optimization of the iodocyclization of *N*-[2-(prop-1-en-2-yl)-phenyl]benzamide **1a** into 4-iodomethyl-4-methyl-2-phenyl-4*H*-3,1-benzoxazine **2a**.[a]

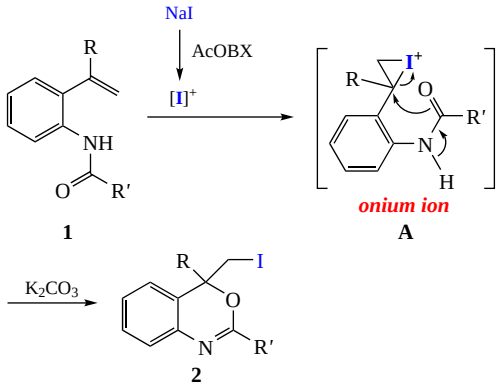
Entry	Base	Solvent	Yield of **2a** (%)[b]
1	K_2CO_3	1,4-dioxane	68
2	K_2CO_3	THF	65
3	K_2CO_3	MeCN	92 (0[c])
4	K_2CO_3	DMF	86
5	Na_2CO_3	MeCN	88
6	Cs_2CO_3	MeCN	85
7	Bu^{t}OK	MeCN	59
8	DBU	MeCN	45

[a] *Reaction conditions*: **1a** (0.2 mmol), AcOBX (0.25 mmol), NaI (0.25 mmol), base (2 equiv., 0.4 mmol), solvent (2.0 ml), 60 °C under air, 12 h, sealed tube. [b] Isolated yield. [c] Without NaI or AcOBX.

achievements, further development of more facile and efficient methods for the construction of functionalized benzoxazines from simple starting materials under mild reaction conditions is still in high desire.

On the other hand, the halogenation of alkenes has emerged as a facile route to construct new C–X bond, which provides handles for further functionalization.[12,13] In the field of halocyclization of olefinic amides, many works have been reported. For instance, Toste pioneered to describe the enantioselective bromocyclization of olefinic amides with tricationic brominating reagents leading to the brominated 4*H*-3,1-benzoxazines.[14] Wei reported on oxy-iodomethylation of olefinic amides with *N*-iodosuccinimide as the iodine source.[15] With our continuous interest in the difunctionalization of alkenes, herein we report a iodocyclization of olefinic amides to obtain 4-iodomethylated 3,1-benzoxazines using acetoxybenziodoxolone (AcOBX) and NaI as the combined iodine source.

To test our hypothesis, *N*-[2-(prop-1-en-2-yl)phenyl]benzamide **1a** (Scheme 1) was selected as the model substrate to react with NaI and AcOBX in the presence of 2 equiv. K_2CO_3 as the base at 60 °C in 1,4-dioxane. Delightedly, the desired product **2a** could be isolated in 68% yield (Table 1, entry 1). Based on this primary result, then some common solvents such as THF, MeCN, DMF were screened. It was found that all of them were suitable for the access to desired product **2a** while MeCN was the best (entry 3, yield 92%). Further screening the base revealed that Na_2CO_3 or Cs_2CO_3 gave the comparable results (entries 5, 6), however Bu^{t}OK and DBU were inferior to K_2CO_3 (entries 7, 8). When the reaction was conducted without NaI or AcOBX, none of **2a** could be isolated (see entry 3).



Scheme 2

With the optimized reaction conditions established, the substrate scope of olefinic amides was investigated (see Scheme 1).† Generally, all of the substrates reacted smoothly under the standard reaction conditions, leading to the desired oxy-iodomethylation products **2a–s** in good to excellent yields. Notably, all the substrates bearing different substituents on the phenyl rings at the *para*-position, regardless of their electron nature, could be transformed into the desired products **2a–l** in 75–93% yields. Typically, the steric hindrance had some effect on the reaction efficiency, as the amides with 2-methyl (**1d**) and 2,6-dichloro (**1i**) substituents gave the corresponding products **2d** and **2i** in 80 and 66% yields, respectively. Some reactive groups such as methyl (**2a**), chloro (**2g**), bromo (**2j**), iodo (**2k**) and styryl (**2p**) survived in this transformation, which provides possibilities for the further functionalization. To our delight, 1-naphthyl- (**1m**), 2-thienyl- (**1n**), 2-furyl- (**1o**) substituted analogues were also good candidates to afford the desired products **2m–o** in 66–82% yields. Subsequently, olefinic amides with *N*-acetyl (**1q**) and *N*-cyclohexylcarbonyl (**1r**) groups also reacted smoothly to give the products **1q** and **1r** in 90 and 83% yields, respectively. When *N*-[2-(1-phenylvinyl)phenyl-benzamide **1s** was involved in the reaction, the corresponding product **2s** was isolated in 55% yield.

According to the above results and some relative works,[15] the reaction may follow the pathway shown in Scheme 2. Initially, NaI is oxidized with AcOBX to generate the corresponding iodine cation I^+ which attacks the alkene moiety affording the iodonium species **A**. The subsequent intramolecular nucleophilic addition of the amide oxygen atom should lead to the final 4-iodomethylated benzoxazines **2**.

In summary, we have developed a procedure for the iodocyclization of olefinic amides with acetoxybenziodoxolone and NaI to synthesize a series of 4-iodomethylated 3,1-benzoxazines in good yields. This reaction features readily available materials and good functional group tolerance.

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† *General procedure for the synthesis of* **2a–s**. Under air, olefinic amide **1a–s** (0.2 mmol), NaI (0.25 mmol, 37.5 mg), acetoxybenziodoxolone (0.25 mmol, 76.3 mg), K_2CO_3 (0.3 mmol, 41.4 mg) and MeCN (2.0 ml) were added into a 20 ml Schlenk tube equipped with a Teflon cap. The solution was stirred at room temperature under air for about 12 h. Then, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel with petroleum ether–ethyl acetate as eluent to give the desired product **2a–s**.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.06.032.

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