Tetrahedron Letters 56 (2015) 1501–1504

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

$BF_3{\cdot}Et_2O$ catalyzed allylation of oxindoles with allyl trichloroacetimidate

Jiao Ma, Ling Zhou, Jie Chen *

Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710069, PR China

ARTICLE INFO

Article history:
Received 24 November 2014
Revised 15 January 2015
Accepted 23 January 2015
Available online 30 January 2015

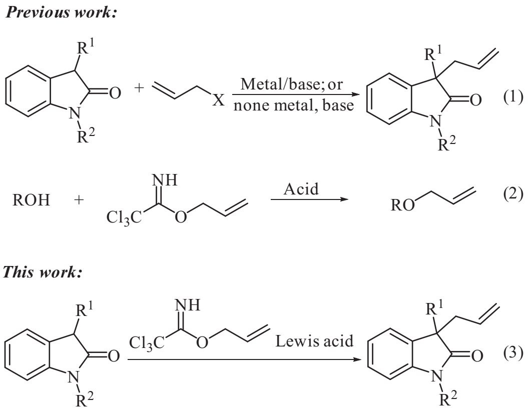
Keywords:
Allylation
Lewis acid
Catalysis
Allyl trichloroacetimidate
Oxindole

ABSTRACT

An efficient Lewis acid catalyzed allylation of 3-substituted oxindoles has been developed for the first time using allyl trichloroacetimidate as an electrophile under mild reaction conditions.

The 3,3′-disubstituted oxindole derivatives are structural motifs often found in a number of alkaloid natural products and pharmaceutically active compounds.[1,2] Therefore, many remarkable endevours have been made to develop general and efficient methods for the preparation of this structural motif.[3–9] Typically, synthesis of an all-carbon quaternary center at the C-3 of oxindole is attractive owing to its manifold bioactive properties and as the intermediate for the synthesis of other indole ring systems. To date, transition-metal-catalyzed allylic alkylation of 3-substituted oxindole has been shown to be the most efficient and synthetic useful method for the construction of quaternary carbon centers (Scheme 1, Eq. 1).[3,5] For example, Trost and co-workers developed Pd, Mo-catalyzed allylic alkylation of 3-substituted oxindoles.[6] On the other hand, organocatalytic allylic alkylation of 3-substituted oxindole has also been reported.[8,10] For example, Ooi and co-workers developed 1,2,3-triazoliums as cationic organic catalysts to realize asymmetric alkylation of 3-substituted oxindoles.[10] However, most of these reactions are performed under basic conditions.[3–11] Here we report the first Lewis acid catalyzed allylic alkylation of 3-substituted oxindoles by using allyl trichloroacetimidate as the electrophile (Scheme 1, Eq. 3).

Allyl trichloroacetimidate has been widely used as a convenient reagent for the O-allylation of hydroxyl groups under acidic conditions in oligosaccharide and natural products synthesis (Scheme 1, Eq. 2),[12] which is compatible with ester, imide, and acetal protecting groups. However, studies on the construction of C-allylation using this reagent are rare.[13] Inspired by the O-allylation reactions,[12] we envisage that a relative stable allylic carbocation ion intermediate may be generated from allyl trichloroacetimidate under acidic conditions, which may be captured by 3-substituted oxindoles to form a new carbon–carbon bond, leading to 3,3′-disubstituted oxindole derivatives bearing an allyl group.



Scheme 1. Allylation of oxindoles and alcohols.

To test this hypothesis, an acid catalyzed reaction of 1-methyl-3-benzylindolin-one (**1a**) with allyl trichloroacetimidate (**2**) was

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* Corresponding author.

http://dx.doi.org/10.1016/j.tetlet.2015.01.155
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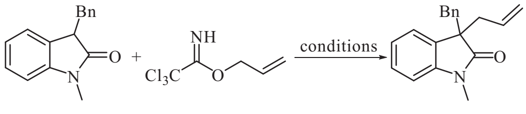
Table 1
Optimization of the reaction conditions[a]



1a 2 3a

Entry	**2** (equiv)	Acid (equiv)	Solvent	Yield[b] (%)
1	1.2	CF_3CO_2H (0.4)	DCM	3
2	1.2	CF_3SO_3H (0.4)	DCM	7
3	1.2	$BF_3{\cdot}Et_2O$ (0.4)	DCM	30
4	1.2	$AlCl_3$(0.4)	DCM	—
5	1.2	$Cu(CF_3SO_2)_2$ (0.4)	DCM	Trace
6	1.2	$BF_3{\cdot}Et_2O$ (0.4)	THF	—
7	1.2	$BF_3{\cdot}Et_2O$ (0.4)	Toluene	4
8	1.2	$BF_3{\cdot}Et_2O$ (0.4)	ACN	Trace
9[c]	1.2	$BF_3{\cdot}Et_2O$ (0.4)	DCM	31
10	2.0	$BF_3{\cdot}Et_2O$ (0.4)	DCM	58
11	3.0	$BF_3{\cdot}Et_2O$ (0.4)	DCM	61
12	2.0	$BF_3{\cdot}Et_2O$ (0.8)	DCM	57
13	2.0	$BF_3{\cdot}Et_2O$ (0.2)	DCM	44
14[d]	1.0 * 2	$BF_3{\cdot}Et_2O$ (0.4)	DCM	63
15[d]	1.0 * 3	$BF_3{\cdot}Et_2O$ (0.4)	DCM	75
16[d]	0.5 * 6	$BF_3{\cdot}Et_2O$ (0.4)	DCM	80

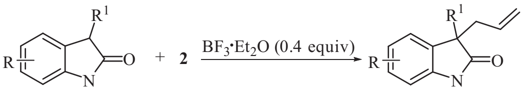
[a] Reactions were carried out with **1a** (0.20 mmol), catalyst and **2** in solvent (1.0 mL) at room temperature for 36 h.

[b] Isolated yield.

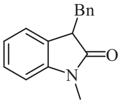
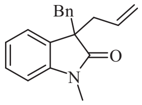
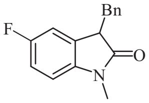
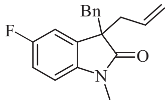
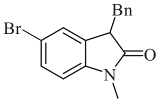
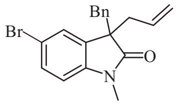
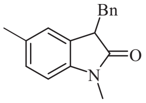
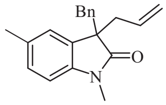
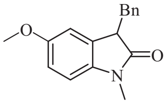
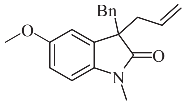
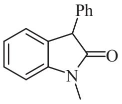
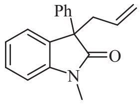
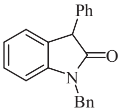
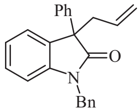
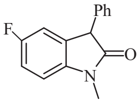
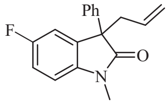
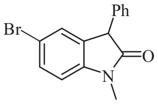
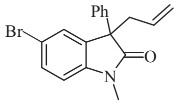
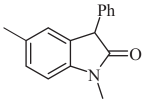
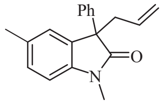
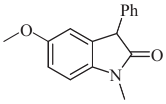
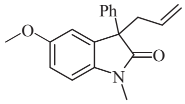
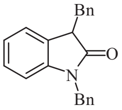
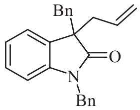
[c] Reaction time is 115 h.

[d] Compound **2** was added portionwise over a 5 h interval.

Table 2
Substrate scope of allylation of 3-substituted oxindoles[a]



1a-l 3a-l

Entry	Substrate	1	Product	3	Yield[b] (%)
1		**1a**		**3a**	81[c]
2		**1b**		**3b**	78
3		**1c**		**3c**	75
4		**1d**		**3d**	74
5		**1e**		**3e**	76
6		**1f**		**3f**	93
7		**1g**		**3g**	89
8		**1h**		**3h**	90
9		**1i**		**3i**	87
10		**1j**		**3j**	85
11		**1k**		**3k**	86
12		**1l**		**3l**	73

[a] Reactions were carried out with **1a–l** (0.20 mmol), $BF_3{\cdot}Et_2O$ (0.08 mmol, 0.4 equiv) and **2** (0.60 mmol, 3.0 equiv) in DCM (1.0 mL) at room temperature for 36 h.

[b] Isolated yield.

[c] 2.0 mmol scale.

examined (Table 1). As expected, the desired 3-allyl-3-benzyl-1-methylindolin-2-one (**3a**) was obtained. Treatment of **1a** with **2** in the presence of 0.4 equiv of trifluoromethanesulfonic acid in CH_2Cl_2 at room temperature gave **3a** in 7% yield (Table 1, entry 2). A variety of Lewis acids were evaluated in the model reaction (Table 1, entries 1–5), and $BF_3{\cdot}OEt_2$ was found to give the desired **3a** in 30% yield (Table 1, entry 3). Other Brønsted acids (H_3PO_4, H_2SO_4) and Lewis acids ($SnCl_4$, $FeCl_3$, $ZnCl_2$) all resulted in only a trace amount of product. Other solvents such as toluene, THF, and acetonitrile diminished the reaction clearly (Table 1, entries 6–8). Notably, the starting material **1a** was always recovered during the process. So the reaction time was prolonged, however, similar results were obtained (Table 1, entry 9). To our delight, the yields were clearly increased when 2.0 equiv of **2** was employed (Table 1, entry 10). The reason may be ascribed to the corresponding allylic carbocation intermediate being unstable. Indeed, using a large excess of **2** resulted in a higher yield (Table 1, entries 10, 11 vs entry 3). In contrast, no improvement was achieved by changing the catalyst amount (Table 1, entry 12 vs entry 10). Further optimization of the reaction conditions revealed that addition of 3.0 equiv of **2** by 6 times dramatically enhanced the yield to 80% (Table 1, entry 16).

Having identified the optimized conditions, we next examined this new method in a range of substrates with different substitution patterns. The results are summarized in Table 2. Overall, a variety of 3-allyl-3′-substituted oxindole derivatives were successfully prepared, and various substituents on the aromatic ring were found to be tolerable in this process. Substrates with electron-deficient or electron-rich substitutions at the aromatic ring offered good yields (Table 2, entries 2–5), indicating that the electron effect plays little role in this reaction. Reaction of 1,3-dimethylindolin-2-one with **2** under the optimal conditions gave the desired product in only 24% yield. It seemed that the reaction started from an acid catalyzed enolization of oxindole at 3-position, thus a 3-aryl substituted group will be beneficial to such a ketone-enol equilibrium through π–π conjugation. Then 3-phenyl substituted oxindole substrates were prepared and subjected to this reaction. Generally, the desired 3-allylation oxindole products were obtained with higher yields than those of 3-benzyl substituted oxindole substrates (Table 2, entries 6–11 vs entries 1–5). Similar to a previous observation, electron-deficient or electron-rich substituted 3-phenyl oxindole substrates all gave the desired ally-