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An efficient synthesis of cyclic urethanes from Boc-protected amino acids through a metal triflate-catalyzed intramolecular diazocarbonyl insertion reaction

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Abstract—A simple and efficient synthesis of cyclic urethanes and related oxazinanones **1a**–**l** from diazoketones **3a**–**l** is described. The transformation involves generation of carbenes by activation of diazo groups using metal triflates in intramolecular diazocarbonyl insertion reactions in high overall yields.

1. Introduction

Cyclic urethanes and related oxazinanones are important classes of compounds in organic, pharmaceutical, medical, agrochemical, and polymer chemistry,[1] which possess biologically significant properties such as anticonvulsants,[2] antibacterials,[3] antiepileptics,[4] and enzyme inhibitors.[5] They are also useful chemical intermediates for many industrial products such as fine chemicals, cosmetics, and pesticides.[6] A variety of routes for the synthesis of cyclic urethanes have been reported in the literature.[7] Most of these methods are based on the reactions of diamines or amino alcohols with several different reagents, that is, phosgene dialkyl carbonates or a mixture of carbon monoxide and oxygen through oxidative carbonylation. The generation of cyclic urethanes from aliphatic or aromatic amino alcohols are limited due to low yields, longer reaction times, stringent conditions, and use of expensive reagents. Recently, the Hanessian group[8] performed the generation of four-membered ketone ring as a major product and five-membered ketone ring, a six-membered oxazinanone as two side products through rhodium-catalyzed carbene insertion reaction. The Kubota group[9] reported the preparation of cyclic urethanes from amino alcohols and carbon dioxide using phosphorus (II) reagents and haloalkanes in high yield. The Pansare group[10] demonstrated that scandium triflate catalyzed diazocarbonyl insertions from intramolecular reactions of carbenoids with a carboxycarbonyl *N*-protecting group, followed by debenzylation in 61% yield. The Arai group[11] developed a route to cyclic urethanes and related oxazinanones using direct reaction of urea with diamines, amino alcohols, or amino phenols at 150 °C in the absence of a catalyst.

In the context of our medicinal chemistry program dealing with the development of new antimalarials, we required 1,3-oxazinane-2,5-diones and several amino ketones as important intermediates for the generation of novel cysteine protease inhibitors. We wish to report herein the synthesis of cyclic urethanes and related oxazinanones via metal triflate [$M(OTf)_3$] catalyzed intramolecular diazocarbonyl insertion reactions.

2. Results and discussion

Although a number of methods have been developed for the generation of urethanes and azetidinones through carbene insertion into the *N*–H bond of diazoketones,[10]

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practically all of the previous studies on Lewis acid or metal-mediated diazoketone insertion reactions involving heteroatom participation were restricted to the intramolecular mode. Recently, Hanessian and co-workers reported an intramolecular version, which offers an alternative to most methods for the synthesis of 4–6-membered ketones by addition of the carbonyl oxygen atom of the Boc protecting group.[8] To explore the scope and generality of this latter method, we investigated a series of *N*-Boc protected amino acids **2a–l** with different substituted moieties. The diazoketones **3a–l** were prepared from amino acids **2a–l** by reacting with freshly prepared diazomethane[12] in the presence of *N*-methylmorpholinepolystyrene and isobutyl chloroformate in excellent yields. Intramolecular *N*–H insertion of diazoketones **3a–l** was achieved by treatment with a catalytic amount of indium triflate to generate 4-substituted-1,3-oxazinane-2,5-diones **1a–l** in high yields (Scheme 1).[13] Most intramolecular ring cyclization reactions using indium triflate were completed in high yield. We found that *N*–H insertion of diazoketones **3a–l** containing aliphatic groups, aromatic groups, and heterocyclic groups readily generated 4-substituted 1,3-oxazinane-2,5-diones (**1a–l**, Table 1).

Table 1. Synthesis of various 4-substituted-1,3-oxazinane-2,5-diones (**1a–l**)[a] via $In(OTf)_3$ catalyzed *N*–H insertion reaction of functionalized diazoketones (**3a–l**)

Entry	R	Yield (%)[b]	Product
1	H	95	**1a**
2	Me	98	**1b**
3	Et	96	**1c**
4	*n*-Bu	96	**1d**
5	*c*-Propyl	95	**1e**
6	*c*-Hexyl	97	**1f**
7	Ph	93	**1g**
8	3,4-Difluorophenyl	94	**1h**
9	Bn	96	**1i**
10	CH_2–Bn	98	**1j**
11	3-Methylbenzothienyl	93	**1k**
12	*N*-BOM-imidazolyl[c]	90	**1l**

[a] The reaction was carried out using diazoketones (1.0 mmol) and indium triflate (0.03 equiv) in dichloromethane at 0 °C to rt for 30 min.
[b] Isolated yield.
[c] *N*-Benzyloxymethyl (BOM)-imidazolyl.

We investigated the catalytic activity of several activators such as $Sc(OTf)_3$, $In(OTf)_3$, $Cu(OTf)_2$, $Sn(OTf)_2$, $La(OTf)_3$, $Yb(OTf)_3$, $Mg(OTf)_2$, $Hg(OTf)_2$, and $Bi(OTf)_3$. Diazoketone **3j** was treated with a catalytic amount of metal triflate as an initial study (Table 2). Excellent results were obtained with diazoketone **3j** in the presence of 3 mol% of indium triflate in dry dichloromethane at 0 °C for 30 min (Table 2, entry 2). Practically, most of the other metal triflates showed a similar effect for the reaction while they suffered from drawbacks such as longer reaction times (Table 2, entry 1 and entries 3–9).

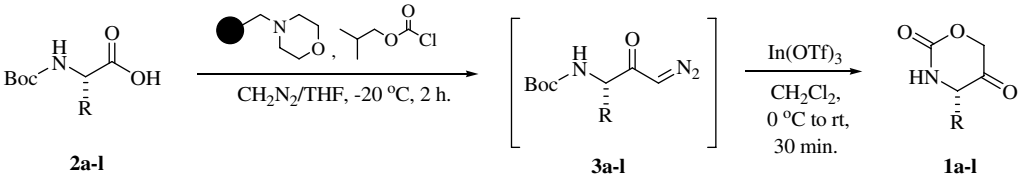
Table 2. Intramolecular diazocarbonyl insertion reaction of **3j** using various catalysts

Entry	Activator	Time (h)	Yield (%)[a]
1	$Sc(OTf)_3$	8	91
2	$In(OTf)_3$	0.5	98
3	$Cu(OTf)_2$	5	95
4	$Sn(OTf)_2$	4	93
5	$La(OTf)_3$	10	91
6	$Yb(OTf)_3$	10	96
7	$Mg(OTf)_2$	16	92
8	$Hg(OTf)_2$	16	90
9	$Bi(OTf)_3$	16	91

[a] Isolated yield.

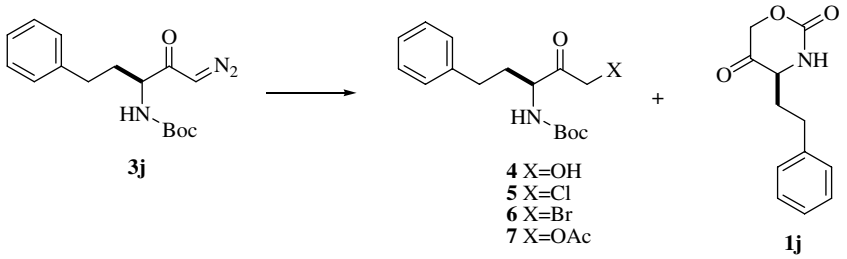
Our initial endeavors focused on the preparation of *N*-Boc ketones **4–7** as key fragments of cysteine protease inhibitors. We have performed the substitution reaction of diazoketone **3j** with several nucleophiles that is, hydroxide, halides, and acetates to generate *N*-Boc ketones **4–7** under mild reaction conditions (Table 3). The acylation reactions were tentatively examined in the presence of several acids such as sulfuric acid, hydrochloric acid, hydrobromic acid, peracetic acid, perchloric acid, periodic acid, and various bases (lithium hydroxide, sodium hydroxide, potassium hydroxide, and magnesium bromide). Interestingly, when the diazoketone **3j** was reacted under acidic conditions, the cyclic urethane **1j** was isolated (Table 3, entries 1–7), however when **3j** was treated with bases in THF/H_2O, primary alcohol **4** was generated as the single product (Table 3, entries 11–14). This fact implied that diazoketone **3j** can be activated preferentially under acidic media to generate the carbene, followed by removal of the *N*-Boc group, while under basic media, the unactivated diazogroup of **3j** was readily replaced by different nucleophiles leading to substituted *N*-Boc ketones **4–7** in low yields and with slow reaction rates.

In conclusion, we have reported that a catalytic amount of metal triflate efficiently catalyzes the intramolecular diazocarbonyl insertion reaction of activated diazoketones **3a–l** to generate cyclic urethanes and related six-membered oxazinanones **1a–l** in high yields. It was found that the cyclic urethanes were readily generated



Scheme 1.

Table 3. Diazoketone **3j** under various conditions



Entry	Reaction conditions	Solvent	Temperature (°C)	Time (h)	Product	Yield (%)[a]
1	0.25 M-H_2SO_4	THF/H_2O	rt	36	(**4** + **1j**)	(10 + 80)
2	1.0 M-HCl (aq)	CH_2Cl_2	rt	12	(**4** + **5** + **1j**)	(15 + 60 + 20)
3	$MeCO_3H$	CH_2Cl_2	rt	8	**1j**	5[b]
4	$HClO_4$	CH_2Cl_2	rt	1	**1j**	93
5	$HClO_4$	CH_2Cl_2	−78 to rt	2	(**4** + **1j**)	(10 + 85)
5	$HClO_4$	THF/H_2O	rt	12	(**4** + **1j**)	(15 + 80)
6	HIO_4	CH_2Cl_2	rt	2	**1j**	90
7	HIO_4	THF/H_2O	rt	12	(**4** + **1j**)	(12 + 85)
8	H_2O/AcOH	CH_2Cl_2	rt	2	(**4** + **7**)	(5 + 30)
9	HCl/AcOH	THF/Et_2O	0	0.2	**5**	95
10	HBr/AcOH	THF/Et_2O	0	0.2	**6**	93
11	LiOH	THF/H_2O	rt	24	**4**	5[b]
12	LiOH, H_2O_2	THF/H_2O	rt	16	**4**	5[b]
13	NaOH	THF/H_2O	rt	24	**4**	33
14	KOH	THF/H_2O	rt	24	**4**	30
15	$MgBr_2$, $MeNO_2$	Et_2O/CH_2Cl_2	rt	1	—	—[c]

[a] Isolated yield.
[b] Based on recovered starting material.
[c] No reaction.

in acidic media, and indium triflate was the most effective catalyst for generation of cyclic urethanes and related six-membered oxazinanones among all the tested metal triflates.

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13. General procedure for the preparation of 4-substituted-1,3-oxazinane-2,5-diones **1a**–**l**. To a stirred suspension of *N*-Boc amino alcohols **2a**–**2l** (2.0 mmol) in dry THF (10 mL) was slowly added *N*-methylmorpholinepolystyrene (0.5 g, 200–400 mesh) at −20 °C, followed by addition of isobutyl chloroformate (2.4 mmol). The mixture was stirred at −20 °C for 2 h and filtered. The resin was washed with anhydrous THF (2 mL). The filtrate was re-cooled to −20 °C under an argon atmosphere, and freshly prepared diazomethane[12] was added dropwise at the same temperature. The resulting reaction mixture was stirred for 1 h and then gradually warmed to room temperature. After elimination of excess diazomethane under argon gas, the organic phase was concentrated under reduced pressure to give diazoketone **3a**–**l**, which

was diluted with dry dichloromethane (10 mL) and treated with indium triflate (0.03 M equiv) at 0 °C. The mixture was warmed to room temperature for 30 min. The resulting reaction mixture was diluted with dichloromethane (10 mL/mmol). The organic layer was washed with satd aqueous NH_4Cl solution (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20–30% ethyl acetate/hexanes) to give 4-substituted 1,3-oxazinane-2,5-diones **1a**–**l**. Selected data: **1j**: white crystals, mp 122–123 °C. $R_f = 0.2$ (30% ethyl acetate in hexanes); $[\alpha]_D^{25}$ −34.04 (*c* 0.3, $CHCl_3$); IR (neat, NaCl) 3252, 3029, 2919, 1728, 1681, 1453, 1271, 1081, 878 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.20 (m, 6H), 4.60 (dd, $J = 17.5$, 17.5 Hz, 2H), 3.89 (t, $J = 7.0$ Hz, 1H), 2.81 (t, $J = 7.5$ Hz, 2H), 2.27–2.17 (m, 1H), 2.16–2.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.3, 155.3, 139.5, 128.6, 128.5, 126.5, 71.9, 58.7, 33.9, 31.1; HRMS calcd for $C_{12}H_{14}NO_3$: 220.0974 $[M+H]^+$, found: 220.1017.