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Indium triflate-catalyzed ring opening of aziridines with carboxylic acids

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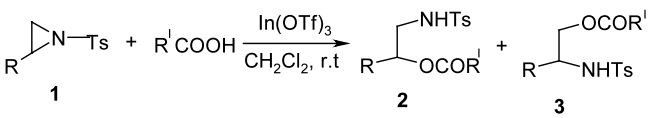
Abstract—Aziridines react smoothly with carboxylic acids in the presence of a catalytic amount of indium triflate at ambient temperature to afford the corresponding β-aminoacetates and benzoates in high yields with high regioselectivity. © 2002 Elsevier Science Ltd. All rights reserved.

Aziridines are versatile synthetic intermediates for the synthesis of many biologically interesting molecules such as amino acids,[1] heterocycles[2] and alkaloids.[3] They are well known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo regioselective ring opening reactions contributes largely to their synthetic value.[4–6] However, there are no reports on the regioselective ring opening of aziridines with carboxylic acids. Metal triflates are unique Lewis acids that are currently of great research interest.[7]

In this report we wish to highlight our results on the regioselective ring opening of aziridines with carboxylic acids using a catalytic amount of indium triflate. Thus, treatment of styrene-*N*-tosyl aziridine with acrylic acid in the presence of 5 mol% $In(OTf)_3$ at ambient temperature resulted in the formation of β-amino acrylate derivatives **2** and **3** in 90% yield (Scheme 1).

Similarly, aryl-*N*-tosyl aziridines reacted smoothly with carboxylic acids to afford the corresponding β-amino esters in high yields. Aryl-*N*-tosyl aziridines underwent cleavage by an acid with preferential attack at the benzylic position resulting in the formation of products **2** with a trace amount of **3** (Table 1, entries g–m). However, the treatment of alkyl-*N*-tosyl aziridines with carboxylic acids gave predominantly the ring-opened products **3** with a minor amount of **2** (entries n–p). The ratios of products **2** and **3** were determined from the ^{1}H NMR spectra of the crude products. A variety of carboxylic acids reacted well with aziridines to give the respective β-amino esters. In all cases, the reactions proceeded efficiently in high yields at ambient temperature. Furthermore, the treatment of cycloalkyl-*N*-tosyl aziridines with acids afforded the corresponding β-amino esters in high yields with high stereoselectivity (Scheme 2).



R= aryl, alkyl, naphthyl

R'= alkyl, acryl, styryl, phenyl, benzyl

Scheme 1.

In the case of cycloalkyl aziridines, the stereochemistry of the ring product **4e** was found to be *trans* from the coupling constants of the ring protons at δ 3.47 ppm (ddd, $J=6.0$, 8.0, and 8.0 Hz, 1H) for (NCH) in the ^{1}H NMR spectrum, similarly the peak at δ 4.89 ppm for (CHOCOR) showed a similar splitting pattern (ddd, $J=5.5$, 8.0, and 10.0 Hz, 1H). The method is clean and highly regioselective, affording β-amino esters in excellent yields. The reaction conditions are mild and no side products or decomposition of the products was observed. All the products were fully characterized by ^{1}H NMR, IR, ^{13}C NMR and mass spectroscopic data. Similar yields and selectivity were also obtained with 3 mol% scandium triflate under the present reaction conditions. However, in the absence of catalyst, the reaction did not yield any product even at reflux temperature. Finally, the catalyst was recovered from the aqueous layer on work-up and recycled in subse-

Keywords: indium reagents; aziridines; carboxylic acids; β-aminoacetates.

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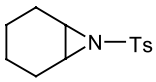
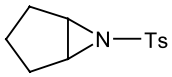
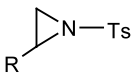
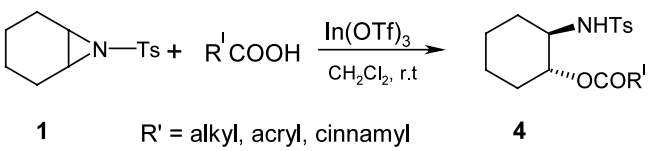
Table 1. $In(OTf)_3$-catalyzed ring opening of aziridines with carboxylic acids

Entry	Aziridine	Acid	Reaction time (h)	Yield[a] (%)	Ratio **2:3**
a		acetic acid	3.0	90	--
b	"	crotonic acid	2.0	92	--
c	"	acrylic acid	2.5	85	–
d		acetic acid	3.5	89	--
e	"	crotonic acid	2.5	92	--
f	"	cinnamic acid	3.0	85	--
					
g	R= C_6H_5	phenylacetic acid	3.0	90	92:8[b]
h	"	acetic acid	2.5	92	96:4[b]
i	R= 4-Me-C_6H_4	acrylic acid	3.0	88	97:3[b]
j	"	cinnamic acid	2.5	90	95:5[b]
k	"	benzoic acid	3.0	89	91:9[b]
l	R= 2-naphthyl	crotonic acid	4.0	87	94:7[b]
m	R= 4-Cl-C_6H_4	cinnamic acid	3.0	90	95:5[b]
n	R= cyclohexyl	acetic acid	4.0	89	7:93[c]
o	R= *n*-butyl	crotonic acid	3.5	90	10:90[c]
p	"	acetic acid	4.5	87	12:88[c]

[a]Isolated and unoptimized yield. [b]Ratio of products from internal attack *Vs* terminal attack
[c]Ratio of products from terminal attack *Vs* internal attack.



Scheme 2.

quent reactions with a gradual decrease in activity; for example, styrene-*N*-tosyl aziridine and acetic acid gave 92, 85 and 80% yields over three cycles. Several examples illustrating this novel and simple method for the synthesis of β-amino esters are summarized in Table 1.[8]

In conclusion, we have demonstrated a novel and efficient method for the preparation of β-amino esters from aziridines using a catalytic amount of indium triflate. The notable features of this method are high yields of products, short reaction times, mild reaction conditions, greater regioselectivity, cleaner reaction profiles, simplicity in operation and reusability of the catalyst, which makes it a useful and attractive process

for the synthesis of β-amino acetates, acrylates, propionates, butenoates and benzoates.

Acknowledgements

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8. *Experimental procedure*: A mixture of *N*-tosyl aziridine (5 mmol), acid (7 mmol) and indium triflate (5 mol%) or scandium triflate (3 mol%) in dichloromethane (10 mL) was stirred at ambient temperature for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water and extracted with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and the resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure β-amino ester. Spectroscopic data for product **4e**: 2-(4-methylphenylsulfonamido)cyclopentyl (*E*)-2-butenoate: ^{1}H NMR (400 MHz $CDCl_3$) δ: 1.18–1.27 (m, 2H), 1.33–1.45 (m, 2H), 1.70–1.77 (m, 2H), 1.83 (dd, 3H, $J=1.7$, 6.8 Hz), 2.40 (s, 3H), 3.47 (ddd, 1H, $J=6.0$, 8.0, 8.0 Hz), 4.89 (ddd, 1H, $J=5.5$, 8.0, 10.0, Hz), 5.42 (brs, 1H, NH), 5.66 (qd, 1H, $J=1.7$, 15.7 Hz), 6.86 (qd, 1H, $J=6.9$, 15.7 Hz), 7.25 (d, 2H, $J=8.0$ Hz), 7.70 (d, 2H, $J=8.0$ Hz). EIMS: m/z: 323 M^+.