Pergamon

Tetrahedron Letters 41 (2000) 6245–6248

TETRAHEDRON LETTERS

$InCl_3$ catalyzed reactions of ethyl diazoacetate with aldimines: a highly diastereoselective synthesis of *cis*-aziridine carboxylates

Saumitra Sengupta* and Somnath Mondal

Department of Chemistry, Jadavpur University, Calcutta 700 032, India

Received 3 May 2000; accepted 20 June 2000

Abstract

$InCl_3$ catalyzed reactions of ethyl diazoacetate with aldimines give aziridine carboxylates under mild conditions, low catalyst loading and with high *cis*-selectivity.

Keywords: $InCl_3$; diazoacetate; imines; aziridines.

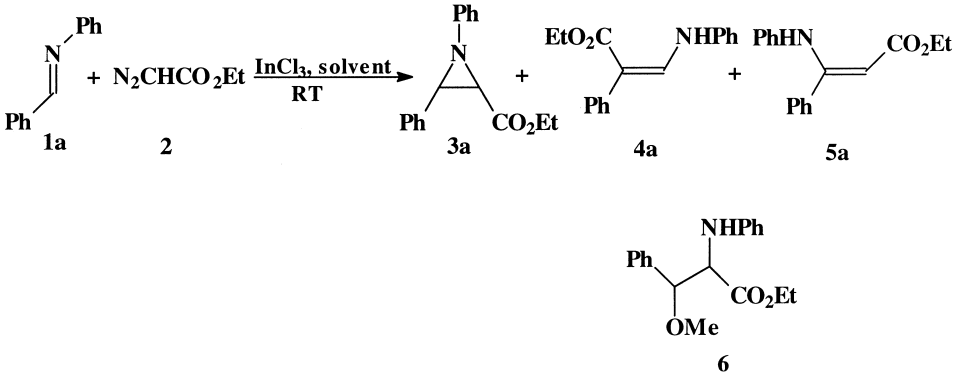
Aziridines are useful building blocks for the synthesis of many biologically active compounds such as amino alcohols, unnatural amino acids and nitrogenous heterocycles.[1] In view of this, stereoselective synthesis of aziridines continues to attract the attention of synthetic chemists. In 1995, a conceptually new synthesis of aziridines via catalyzed carbene-transfer reactions of α-diazoacetates with imines, appeared in the literature.[2] Although copper(II) salts were seminally used as catalysts for these reactions, the yields and/or diastereoselectivities of aziridine formation were somewhat unsatisfactory.[2] Subsequent improvements have been reported using $MeReO_3$ and Rh–clay catalysts which produced aziridine carboxylates with high *trans*-selectivity.[3] In a related development, recently, it has been shown that reactions of α-diazoacetates and imines can also be catalyzed by Lewis acids ($BF_3{\cdot}Et_2O$, $Zn(OTf)_2$, lanthanide triflates) to produce aziridine carboxylates, albeit in moderate yields.[4] Interestingly, a high degree of *cis*-selectivity has been observed in some of these Lewis acid catalyzed reactions.[4a,d] Although in its infancy, this Lewis acid catalyzed aziridine synthesis, by virtue of its operational simplicity, mild reaction conditions and the prospect of asymmetric indiction[4c,f] via the use of chirally modified Lewis acids, holds more promise than the metal-catalyzed route described above and hence, if properly developed, can lead to broader synthetic ramifications.

* Corresponding author. Fax: 91 33 4734266.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01042-X

$InCl_3$ has recently emerged as a versatile Lewis acid catalyst for a variety of organic reactions.[5] We have reported that $InCl_3$ is an excellent catalyst (vis-a-vis $BF_3{\cdot}Et_2O$ or $Rh_2(OAc)_4$) for a number of reactions of α-diazocarbonyl compounds,[6] which led us to investigate the efficacy of this Lewis acid in carbene-transfer reactions of α-diazoacetates with aldimines. Results of this study, which has indeed given rise to a highly diastereoselective synthesis of *cis*-aziridine carboxylates, are described here.

Model studies were carried out with the imine **1a** and ethyl diazoacetate (**2**) which revealed that $InCl_3$ catalyzed aziridine formation is quite sensitive to the reaction solvent, catalyst loading and the time of the reaction (Scheme 1, Table 1). Thus, the reaction of **1a** with **2**, when carried out with 10% $InCl_3$ in CH_2Cl_2 for 12 h at rt, produced only 23% of the aziridine **3a** together with 16% of the enamines **4a** and **5a** and other unidentified side products (entry 1). However, only the *cis*-isomer of **3a** was formed in this reaction, as evident from the ^1H NMR spectrum of the crude product mixture which showed a large coupling constant ($J = 6.9$ Hz) for the aziridine ring protons at δ 3.20 and 3.59 (ring protons of *trans*-**3a** appear at δ 3.20 and 3.80 with a smaller coupling constant, $J = 2$–3 Hz).[3,4a,c]



Scheme 1.

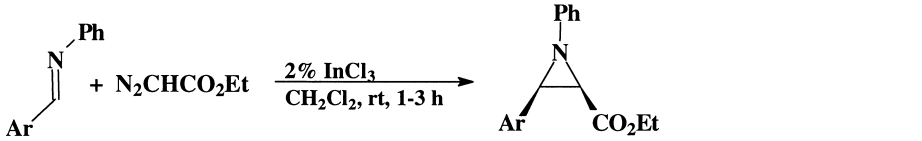
Table 1
$InCl_3$ catalyzed reactions of **1a** and **2** (Scheme 1)

Entry	$InCl_3$ (mol %)	Solvent	Reaction time (h)	3a/(4a+5a) (yield %)[a]	3a (*cis*/*trans*)
1	10	CH_2Cl_2	12	23/16	*cis* only
2	10	THF	12	–[b]	–
3	10	MeOH	12	16/44[c]	*cis* only
4	10	CH_2Cl_2	2	33/67	*cis* only
5	**2**	**CH_2Cl_2**	**2**	**56/44**	***cis* only**
6	2	Pet. ether	12	83/17	78/22

[a]by ^1H NMR (300 MHz);
[b]very slow reaction;
[c]14% of **6** is also produced.

Encouraged by this high *cis*-selectivity, we then looked for conditions that would improve the yield of aziridine formation. Lowering the reaction temperature (–10°C) or changing the solvent to THF, however, gave low conversions (entry 2). In MeOH at rt (entry 3), the yield of **3a** dropped even further and the proportions of enamines (**4a** and **5a**) increased together with the formation of a new side product **6** (14%). The latter was perhaps formed via $InCl_3$ mediated ring-opening of **3a** with MeOH, which led us to believe that $InCl_3$, while catalyzing the formation of the aziridine **3a**, was also instrumental in its decomposition through activation of the aziridine nitrogen. To minimize this, the reaction of **1a** and **2** was re-examined in CH_2Cl_2 with a lower catalyst loading (2% $InCl_3$) and a shorter reaction time (2 h) which indeed led to a much improved yield of **3a** (56%), again, exclusively as the *cis*-isomer (entry 5). Reactions carried out with 2% $InCl_3$ in petroleum ether, on the other hand, gave **3a** in high yield (83%) but as a 78/22 mixture of *cis*/*trans* isomers (entry 6). Similar loss of diastereoselectivity, albeit with higher chemical yields, has also been reported by others in their Lewis acid catalyzed aziridine formation in hydrocarbon solvents.[4c,d] However, as has been reported with other Lewis acid catalysts,[4] under no circumstances could we completely suppress the formation of the enamine side products (**4a**, **5a**) in this reaction.

For preparatory purposes, a number of *N*-arylidene anilines **1a–d** were reacted with **2** in presence of 2% $InCl_3$ in CH_2Cl_2 at rt for 1–3 h (entry 5, Table 1) which produced the corresponding aziridines **3a–d** together with the corresponding enamine by-products. The latter could be easily removed by silica-gel chromatography to give the pure aziridines **3a–d** in 45–65% yields (Scheme 2).[7] The isolated yields of these aziridines were always found to be somewhat lower than their NMR yields due to some unavoidable decomposition during silica-gel chromatography, but are, nevertheless, comparable to those obtained with other Lewis acid catalysts.[4] Most significantly, all the aziridines were produced either exclusively as the *cis*-isomer (**3a–c**) or with a high *cis*/*trans* ratio (**3d**). It may be noted that only lanthanide triflates[4a] and $BF_3{\cdot}Et_2O$[4d] have, until now, shown such high degrees of *cis*-selectivity in these reactions. In this work, imines derived from electron deficient or weakly electron rich aldehydes gave the best results, whereas those derived from strongly electron rich aldehydes, e.g. *p*-anisaldehyde, gave complex product mixtures having large amounts of the enamine side products. In another limitation, aldimines prepared from electron rich anilines, e.g. *p*-anisidine, when reacted with **2** in presence of 2% $InCl_3$ led to gradual darkening of the reaction mixture with no aziridine formation. Similar electronic effects have also been previously observed with other Lewis acids.[4d]



1a-d 2

3a: Ar = Ph (50%, *cis* only)
3b: = *p*-Cl-Ph (48%, *cis* only)
3c: = *p*-Me-Ph (45%, *cis* only)
3d: = *p*-NO_2-Ph (65%, *cis*/*trans* 80/20)

Scheme 2.

In summary, $InCl_3$ catalyzed reactions of ethyl diazoacetate with aldimines provide a highly diastereoselective synthetic route to *cis*-aziridine carboxylates under mild and operationally simple conditions (low catalyst loading, short reaction times). Improvements in the yields as well as

synthesis of enantiopure aziridines via use of chiral auxiliaries in these reactions are currently under investigation.

Acknowledgements

DST (SP/S1/G-14/97) and UGC (senior research fellowship to S.M.) are warmly thanked for financial support.

References

1. (a) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon Press: Oxford, 1996; Vol. 1A, p.1; (b) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599; (c) Kump, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, p. 469; (d) Taclwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 7, p. 47.
2. (a) Rasmussen, K. G.; Jorgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1401; (b) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676.
3. (a) Zhu, Z.; Espenson, J. H. *J. Org. Chem.* **1995**, *60*, 7090; (b) Zhu, Z.; Espenson, J. H. *J. Am. Chem. Soc.* **1996**, *118*, 9901; (c) Mohan, J. M.; Uphade, B. S.; Choudhary, V. R.; Ravindranathan, T.; Sudalai, A. *J. Chem. Soc., Chem. Commun.* **1997**, 1429.
4. (a) Xie, W.; Fang, J.; Li, J.; Wang, P. G. *Tetrahedron* **1999**, *55*, 12929; (b) Nagayama, S.; Kobayashi, S. *Chem. Lett.* **1998**, 685; (c) Rasmussen, K. G.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1287; (d) Casarrubios, L.; Perez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358; (e) Mayer, M. F.; Hossain, M. M. *J. Org. Chem.* **1998**, *63*, 6839; (f) Juhl, K.; Hazell, R. G.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2293; (g) Kubo, T.; Sakaguchi, S.; Ishii, Y. *J. Chem. Soc., Chem. Commun.* **2000**, 625.
5. Review: Ranu, B. C. *Eur. J. Org. Chem.* in press.
6. Sengupta, S.; Mondal, S. *Tetrahedron Lett.* **1999**, *40*, 8685.
7. The aziridines **3a–d** were characterized by matching their spectral (IR, NMR) data with those reported in the literature (Ref. 4). *Typical procedure*: ***cis*-Ethyl 1,3-diphenylaziridine-2-carboxylate (3a):** $InCl_3$ (0.003 g, 0.014 mmol) was added to a mixture of *N*-benzylidene aniline **1a** (0.11 g, 0.7 mmol) and ethyl diazoacetate **2** (0.07 g, 0.7 mmol) in CH_2Cl_2 (7 ml) and the mixture stirred at room temperature for 2 h. The solvent was then removed in vacuo and the residue purified by preparative thin layer chromatography on silica-gel (15% EtOAc in petroleum ether) to give **3a** (0.092 g, 56%) as a waxy solid; IR (KBr): 1750, 1600, 1540, 1370, 1190 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (t, 3H, $J=7.2$ Hz), 3.20 (d, 1H, $J=6.9$ Hz), 3.59 (d, 1H, $J=6.9$ Hz), 3.90–4.11 (m, AB, 2H), 7.06 (d, 2H, $J=8.7$ Hz), 7.20–7.38 (m, 6H), 7.51 (d, 2H, $J=6.8$ Hz).