Pergamon

Tetrahedron Letters 41 (2000) 9939–9942

TETRAHEDRON
LETTERS

Addition of silylated carbon nucleophiles to iminium and cyclic *N*-acyliminium ions promoted by $InCl_3$

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Received 29 September 2000; revised 16 October 2000; accepted 19 October 2000

Abstract

$InCl_3$ was used as Lewis acid in the addition of silyl enolates and allyltrimethylsilane to aromatic aldimines and cyclic *N*-acyliminium ions derived from 5-acetoxylactams affording β-aminocarbonyl systems and allyl adducts, respectively, in reasonable to good yields. The diastereofacial selectivity of cyclic *N*-acyliminium ions was investigated. © 2000 Elsevier Science Ltd. All rights reserved.

The Mannich reaction is a powerful tool in the construction of β-aminocarbonyl systems.[1–4] In the bimolecular version[1] of the classical Mannich reaction, the use of preformed or in situ generated iminium[5] or *N*-acyliminium ions[6,7] and carbon nucleophiles has greatly expanded the versatility of this methodology allowing the use of milder reaction conditions and the introduction of elements of regio- and stereoselective control.

The intensive research on new types of Lewis acids as activating agents, e.g. zirconium[8] and palladium[9] complexes and rare earth triflates,[10] in aldol-type Mannich reaction has enlarged the field of its applications.

Recently, the use of $InCl_3$ as a Lewis acid in a multicomponent aldol-type Mannich reaction in aqueous media[11,12] was reported. However, the aqueous media protocol lacks generality due to the lower solubility and/or stability of the reactants and products.

Despite the use of $InCl_3$ in a three-component Mannich reaction, to the best of our knowledge there has been no report on the employment of $InCl_3$ to promote the generation of iminium ions from aldimines and/or cyclic *N*-acyliminium ions to carry out the bimolecular aldol-type Mannich reaction.

This prompted us to disclose our preliminary results using $InCl_3$ as an activating agent of aromatic aldimines as well as to promote the generation of cyclic *N*-acyliminium ions and their reactions with silylated carbon nucleophiles in organic media.

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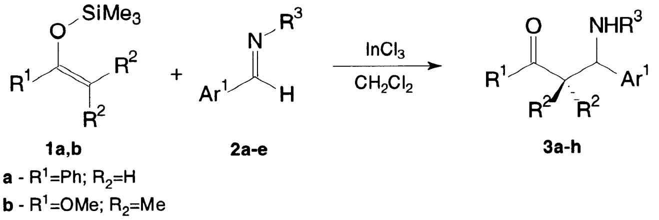
PII: S0040-4039(00)01828-1

Firstly, we investigated the use of catalytic amounts (10 mol%) of $InCl_3$ in the addition reaction of silyl enolates **1a**,**b** to aromatic aldimines **2a**–**e** in dichloromethane (Scheme 1) at 0°C for 1.5 h which afforded the corresponding secondary β-aminocarbonyl compounds **3a**–**h** in good yields (Table 1).



Scheme 1.

Table 1
Preparation of secondary β-aminocarbonyls **3a**–**h**

Entry	Silyl enolates **1a**,**b**		Aldimines **2a**–**e**		Product[a] (%)
	R^1	R^2	Ar^1	R^3	
1	Ph	H	Ph	Ph	**3a** (70)
2	Ph	H	Ph	*p*-Br–C_6H_4	**3b** (82)
3	Ph	H	*p*-Br–C_6H_4	Ph	**3c** (75)
4	MeO	Me	Ph	Ph	**3d** (85)
5	MeO	Me	Ph	*p*-Br–C_6H_4	**3e** (85)
6	MeO	Me	*p*-Br–C_6H_4	Ph	**3f** (80)
7	MeO	Me	Ph	CH_2Ph	**3g** (70)
8	MeO	Me	Ph	$^*CH(CH_3)Ph$	**3h** (75)[b]

[a] The spectroscopic data of all compounds are in agreement with the proposed structures.

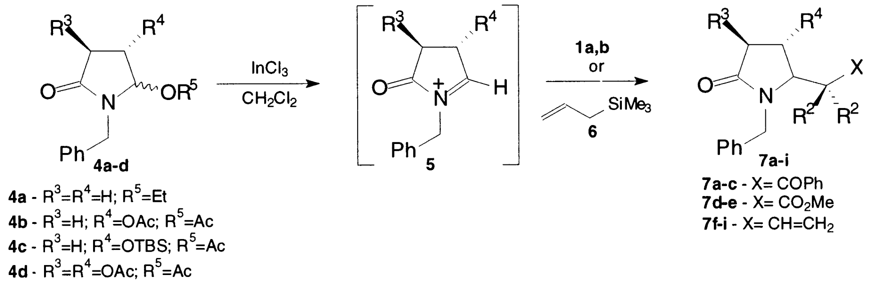
[b] The diastereoisomeric ratio was determined by GC of the crude mixture.

The reaction of chiral aldimine **2e** derived from (*S*)-phenylethylamine with **1b** (entry 8) produced β-aminoester **3h** in good yield as a 3:1 diastereoisomeric mixture and the relative stereochemistry of the major product was not determined.

Next, we observed that $InCl_3$ is able to promote the reaction of cyclic *N*-acyliminium ions precursors **4a**–**d** with nucleophiles **1a**,**b** and allyltrimethylsilane (**6**) (Scheme 2) under the same reaction conditions leading to 5-substituted lactams **7a**–**i** in reasonable to good yields (Table 2). In these cases, the best results were obtained using 60 mol% of $InCl_3$.

It should be noted that the formation of adducts **7** was not observed in the absence of $InCl_3$ and the utilization of the aqueous media protocol described by Loh[11] afforded the corresponding 5-hydroxylactam derivatives due to the preferential attack of water to the highly reactive *N*-acyliminium ion species **5** (Scheme 2).

The diastereoisomeric ratio was determined by GC analysis of the crude mixtures and the *trans* relative stereochemistry of the major product **7b** (entry 2) was established after analysis of the multiplicity and coupling constants of the H_4 and H_5 protons[7] and this was extended to the other related compounds: H_4 (Fig. 1, **A**) displays a doublet (^3J 6.9 Hz at δ 5.12) due to the unique coupling with the *cis* $H_3\beta$ proton.



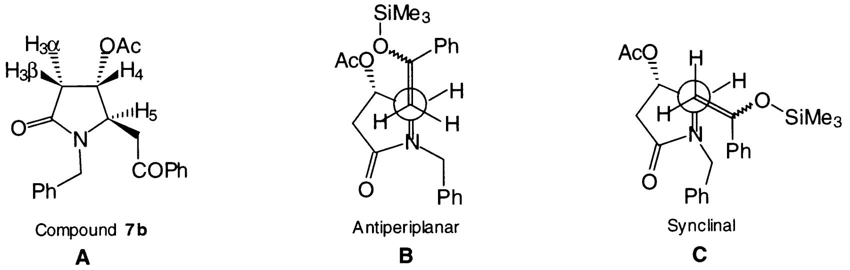
Scheme 2.

Table 2
Preparation of 5-substituted lactams **7a**–**i**

Entry	Nucleophile	5-Acetoxylactams **4a**–**d**			*Cis*/*trans*[a] (%)	Products[b]		
		R^3	R^4	R^5		R^2	X	(%)
1	**1a**	H	H	Et	–	H	COPh	**7a** (15)
2	**1a**	H	OAc	Ac	9:91	H	COPh	**7b** (65)
3	**1a**	OAc	OAc	Ac	25:75	H	COPh	**7c** (50)
4	**1b**	H	OAc	Ac	4:94	Me	CO_2Me	**7d** (80)
5	**1b**	OAc	OAc	Ac	2:98	Me	CO_2Me	**7e** (85)
6	**6**	H	H	Ac	–	H	$CH{=}CH_2$	**7f** (50)
7	**6**	H	OAc	Ac	25:75	H	$CH{=}CH_2$	**7g** (70)
8	**6**	H	OTBS	Ac	66:34	H	$CH{=}CH_2$	**7h** (65)
9	**6**	OAc	OAc	Ac	50:50	H	$CH{=}CH_2$	**7i** (50)

[a] The diastereoisomeric ratio was determined by GC of the crude mixture.

[b] The spectroscopic data of all compounds are in agreement with the proposed structures.



Compound **7b**
A

Antiperiplanar
B

Synclinal
C

Figure 1.

On the other hand, the observation of the H_5 proton as a triplet (^3J 6.3 Hz at δ 4.00) is due to the vicinal coupling with the two exocyclic α-carbonyl protons.

The preference for *trans* addition is in accordance with previous results[13] and is rationalized by the intervention of transition states **A** and **B** where the preferential approach of the nucleophile occurs at the opposite face of the acetoxy group in the cyclic *N*-acyliminium ion (Fig. 1, **B** and **C**).

Accordingly, an increase in the steric bulkiness of the nucleophilic carbon significantly improves the diastereoselection and preparatively useful results were observed for the reaction of the *N*-acyliminium ion derived from tartaric acid with silylketene acetal **1b** (entries 4 and 5) and from that derived from malic acid with silylenol ether **1a** (entry 2).

A representative procedure for the preparation of **7b** follows: 60 mol% of previously dried $InCl_3$ was suspended in 1 mL of dried CH_2Cl_2 in a flask adapted with an argon atmosphere and a magnetic stirrer at 0°C. A solution of **4b** (0.5 mmol) in CH_2Cl_2 (0.5 mL) was added in one portion. After 10 min, **1a** (0.75 mmol) was added dropwise over a 3 min period, and the reaction mixture was maintained at 0°C for 3 h. The reaction was terminated by the addition of a saturated solution of $NaHCO_3$ (1 mL). The mixture was diluted with CH_2Cl_2 (5 mL), the organic phase was separated, dried over $MgSO_4$ and the solvent was removed under vacuum. The crude mixture was purified by column chromatography on silica gel using hexane/ethyl acetate (75:25 v/v) to afford **7b** in 65% yield.

In conclusion, the use of $InCl_3$ as a catalyst in the bimolecular Mannich reaction is a viable methodology for synthesizing β-aminocarbonyl targets in moderate to good yields. The good diastereofacial selectivity observed with derivatives of malic and tartaric acid (entries 2, 4 and 5, Table 2) is promising and further studies are needed to disclose the structural features controlling the stereochemical outcome of the intermolecular addition of carbon nucleophiles to iminium and cyclic *N*-acyliminium ions. Studies on the simple diastereoselection using $InCl_3$ as an activator are currently under investigation.

Acknowledgements

This work was supported by grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq-grant 523069/95-2) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS-grant 96/50208-3). Professor Beatriz Tenius is acknowledged for her generous support. The authors acknowledge CAPES (R.Z.P), FAPERGS (M.N.G.) and CNPq (R.A.P.) for the fellowships.

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