Pergamon

Tetrahedron Letters, Vol. 38, No. 19, pp. 3465-3468, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00595-8

Indium-Trichloride Catalyzed Mukaiyama-Aldol Reaction in Water: Solubility, Aggregation and Internal Pressure Effect

Teck-Peng Loh,* Jian Pei, Kevin Siong-Ve Koh, Guo-Qiang Cao and Xu-Ran Li

Department of Chemistry, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260

Abstract: Studies on the effects of water and the binding characteristic of $InCl_3$ in the Mukaiyama-aldol reaction with an in depth mechanistic probe on the probable internal pressure and aggregation effects exerted in this media. © 1997 Elsevier Science Ltd.

The development of new Lewis acid-catalyzed C-C bond formation reactions in water has been an area of great interest among organic chemists. Accordingly, much effort has been focused on the development of new water stable Lewis acids, including most recently on the use of indium trichloride as an efficient catalyst for the catalysis of the Mukaiyama aldol reaction in water.[1] Initially, erractic results were obtained with varying yields observed by us and Kobayashi et al.[2] In this paper we describe the optimized conditions and the unusual contributory factors for carrying out a successful reaction in pure water.

It was found that the use of purified $InCl_3$ and freshly distilled silyl enol ethers were critical for this reaction as was the actual reaction procedure.[3]

To ascertain the role which water plays in this aldol reaction, we ran a series of reactions with benzaldehyde and trimethylsilyloxycyclohexene **1** exploring both solvent and the effects of different sequence of addition (Table 1). First (Expt. 1), we conducted the reaction by stirring $InCl_3$ and benzaldehyde in distilled water for 1/2h followed by silyl enol ether **1**. Second (Expt. 2), water and then silyl enol ether was added to neat prestirred $InCl_3$ and benzaldehyde. Third (Expt. 3), silyl enol ether and then water was added to neat prestirred $InCl_3$ and benzaldehyde and finally the control reaction was done in the absence of water. As table 1 shows, the first reaction (entry 1) gave little aldol product whilst with neat prestirring of $InCl_3$ and benzaldehyde they gave comparably high yields with the third reaction having a slight edge. The control reaction in the absence of water gave little product. Prestirring of neat aldehyde and $InCl_3$ for 1/2 h before addition of silyl enol ether and water as well as vigorous stirring, in that order, was neccessary for high yields.

The nil to low reactivity of the control reaction in the absence of water compared to the higher yields obtained with experiments 1, 2 and 3 illustrates the importance of water as solvent whereby the aggregation of these substrates by the internal pressure in this media becomes significant. Furthermore from the slightly higher diastereoselectivity of the aldol-adduct obtained from experiment 2 over experiment 1 or 3, in which water was added prior to the silyl enol ether, suggests more restricted co-ordination between $InCl_3$-benzaldehyde and the enolate in the water matrix.

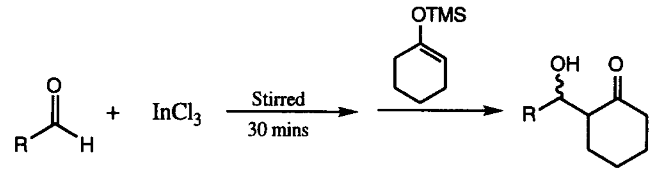
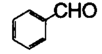
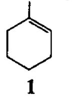
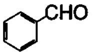
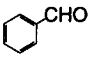
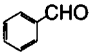
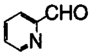
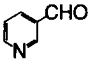


Table 1. Catalytic InCl_3 (20%)-Promoted Mukaiyama Aldol Reaction With **1** Using Differing Sequence of Addition[a]

Entry	Aldehyde	Silyl enol ether	Conditions[b]	*anti* / *syn*[c]	Yield[d] (%)
1		 **1**	InCl_3 (20 mol%), H_2O **1** (15 h),	48:52	51
2		**1**	InCl_3 (20 mol%), H_2O (15 h), **1**	61:39	74 (69)
3		**1**	InCl_3 (20 mol%), **1** H_2O (15 h)	52:48	79 (55)
4		**1**	InCl_3 (20 mol%), THF (15 h), **1**	50 / 50	80
5	$\text{HOOCCHO}\cdot\text{H}_2\text{O}$	**1**	InCl_3 (20 mol%), **1** H_2O (15 h)	56/44	80
6		**1**	InCl_3 (20 mol%), 1 H_2O (15 h)	40 / 60	82
7		**1**	InCl_3 (20 mol%), **1** H_2O (15 h)	54 / 46	76

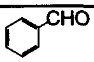
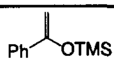
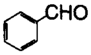
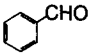
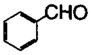
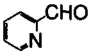
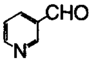
[a] All reactions were carried out on a 0.5-1 mmol scale. [b] Conditions: Sequence of addition as described. [c] The isomer ratio was determined by ^{1}H NMR. [d] Isolated yields. (In parenthesis) denote duplicate experiments.

When repeated with various aromatic and heteroaromatic aldehydes using the optimized reaction condition 3, all gave high yields as summarized in Tables 1.

This was repeated with 1-phenyl-1-trimethylsilyloxyethylene **2**. If the silyl enol ether **2** was added after the addition of water, we consistently obtained the desired aldol products in good isolated yields (82-89%) unlike entry 2 (Table 2) where the prior addition of water to aldehyde and InCl_3 seem to interfere with the subsequent 1-phenyl-1-trimethylsilyloxyethylene **2** reaction. The results are summarized in Tables 2.

To confirm that the reaction did not occur in the absence of water, silyl enol ether was added to the indium trichloride-benzaldehyde complex neat, and the reaction sampled at intervals. We observed no significant reaction when indium trichloride, benzaldehyde and silyl enol ether were added in the first 5 min, approximately 5% in 20 min or 10% in an hour, but the reaction did not go to completion as that with the optimized condition in 15 h as monitored by ^{1}H NMR.

Table 2. Catalytic $InCl_3$ (20%)-Promoted Mukaiyama Aldol Reaction With **2** Using Differing Sequence of Addition[a]

Entry	Aldehyde	Silyl enol ether	Conditions[b]	Yield[c] (%)
1		 **2**	$InCl_3$ (20 mol%), H_2O (15 h), **2**	10-80[#]
2		**2**	$InCl_3$ (20 mol%), **2** H_2O (15 h	89
3		**2**	$InCl_3$ (20 mol%), **2** H_2O (15 h)	89
4		**2**	$InCl_3$ (20 mol%), THF (15 h), **2**	80
5	$HOOCCHO{\cdot}H_2O$	**2**	$InCl_3$ (20 mol%), **2** H_2O (15 h)	81
6		**2**	$InCl_3$ (20 mol%), H_2O (15 h), **2**	87
7		**2**	$InCl_3$ (20 mol%), **2** H_2O (15 h)	83
8	$CH_3(CH_2)_3CHO$	**2**	$InCl_3$ (20 mol%), **2** H_2O (15 h)	66

[a] All reactions were carried out on a 0.5-1 mmol scale. [b] Conditions: Sequence of addition as described. [c] Isolated yields. [#] Erratic results obtained.

The necessity for the preassociation of Lewis acid with the aldehyde is illustrated in the NMR studies which shows a high degree of association of aldehyde with $InCl_3$ in D_2O. With the more water soluble 2-pyridine carboxaldehyde, this complexation is highly pronounced as shown in the shift of the aldehydic peak from δ 9.8 to δ 8.6 on addition of $InCl_3$ within 5 minutes. For comparison studies to observe the effects of prestirring $InCl_3$ with other aldehydes prior to reaction and otherwise. Benzaldehyde was chosen, as complexation is mainly localized about the aldehyde functionality, its high bulk, inherent lower reactivity and solubility in H_2O would present the worst case scenario for reaction in water. The addition of $InCl_3$ (100 mol %) to benzaldehyde in D_2O resulted in the shift of the aldehydic peaks from δ 9.97 (sharp) to give a sharp peak at δ 9.94 whilst prestirred $InCl_3$ and neat benzaldehyde gave twin peak at δ 9.94 and δ 9.87 in D_2O. The high resolution of these peaks in D_2O under these two conditions illustrate the different and high degree of complexation experienced on complexation. However neat prestirring of benzaldehyde with $InCl_3$ as opposed when water is first added would explain the erratic results if different addition sequence of the reagents were used (Table. 2, entry 1 and 2). So this would promote the solubility of the more water immiscible aldehydes for subsequent reaction with the respective silyl enol ether in water. *This is evidenced by the slightly milky solution experienced on addition of the enolate with precomplexation as opposed to a chalky suspension without prestirring of the $InCl_3$-benzaldehyde.* Hence it appears that the addition of all the reagents before the addition of water is critical for the success of this reaction.

The following points are essential for the success of the reaction for water-insoluble aldehydes. (1) Purified indium trichloride affected the reaction in higher yields. (2) Prestirring of indium trichloride and aldehyde for 1/2 h is critical for optimized yields. (3) Addition of silyl enol ether immediately followed by water is also important for getting high and reproducible yields. This is probably due to the fact that the aggregation of these substrates is enhanced by the internal pressure exerted by water but at the expense of stereoselectivity. In conjunction with the fact that the reaction with the addition of silyl enol ether to the neat complex (before addition of water) proceeded faster and in higher yields than the reverse addition, they both clearly show that water do exert a significant effect in the reaction. In effect, the addition of all the reagents together probably allows better aggregation of the organic compounds and whose enforced hydrophobic interactions exert internal pressure on these components as well as stabilising the activated polarised complex through hydrogen bonding, thus speeding up the overall reaction rate.[4]

Typical Procedure of the Mukaiyama Aldol Reactions in Water. To indium trichloride (22.1mg, 0.1 mmol) was added neat aldehyde (51μL, 0.5 mmol) and prestirred for about 1/2h, before addition of silyl enol ether (0.19 ml, 1 mmol), followed by water (5 ml). The mixture was vigourously stirred overnight for about 15 h at room temperature and then the product was extracted with dichloromethane. After the usual workup, the crude product was chromatographed on silica gel to give the pure adduct (70.1 mg, 69%). Indium trichloride was almost quantitatively recovered from water after removing water and could be reused.[1(d)]

We acknowledge the financial support for this project from the National University of Singapore (Grant RP 940633 and RP 950609).

References

1 (a) For pioneering work in organic reactions: Mukaiyama T.; Narasaka K.; Banno T. *Chem. Lett.* **1973**, 1011.; Mukaiyama, T.; Banno, T.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Water-promoted aldol reaction under pressure of silyl enol ethers with carbonyl compounds: Lubineau A. *J.Org.Chem.* **1986**, *51*, 2142: Lubineau A.; Meyer E. *Tetrahedron.* **1988**, *44*, 6065. (c) In aqueous reactions using Lanthanide triflates: Kobayashi S.; Hachiya I. *J.Org.Chem.* **1994**, *59*, 3590. Kobayashi S. *Chem.Lett.* **1991** 2187. (d) In pure water: Loh T.P.; Pei J.; Cao G.Q. *J.Chem.Soc. Chem. Commun.* **1996**, 1819.

2. Personal communication.

3. Predissolved $InCl_3$ was filtered through a Millex-GV13 Millipore filter and the water was subsequently removed under high vacuum with gentle heating to yield the purified form. 82% $InCl_3$ was recovered after purification of 98% from Aldrich.

4. (a) Franks F. 'In Watere, A Comprehensive Treatise'; Franks F.. Ed; Plenum. N.Y. (1975). (b). Tanford C.. 'In The Hydrophobic Effect'. Wiley. N.Y. (1980). (c) Breslow R., Rideout D.C. *J. Am.Chem. Soc.* 1980, **102**, 7816. (d) Grieco P.; Garner P.; He Z. *Tetrahedron.Lett.* **1983**, *24*, 1897.

(*Received in UK* 18 *March* 1997; *accepted* 26 *March* 1997)