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Indium- or Zinc-Mediated One-Pot Synthesis of Homoallylamines, β-Amino Esters, and β-Amino Nitriles

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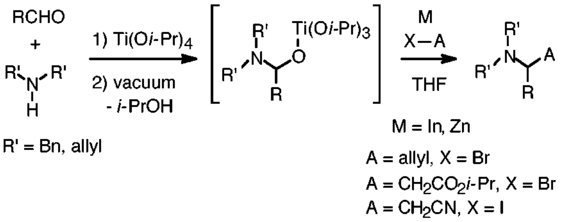
ABSTRACT



Homoallylamines, β-amino esters, and β-amino nitriles were obtained in a one-pot synthesis directly from an aldehyde and a secondary amine such as dibenzylamine or diallylamine. Their condensation with titanium(IV) isopropoxide generates an intermediate aminoalkoxy titanium complex. Further reaction in THF with nucleophilic organometallic species, generated in situ from indium or zinc and a reactive halide (allyl bromide, alkyl bromo- or iodoacetate, iodoacetonitrile), furnished the corresponding amines.

Nucleophilic addition to imines and iminium ions is a widely used reaction for the preparation of amines.[1] For example, homoallylamines are prepared by reaction of these nitrogen electrophiles with allylic nucleophiles such as allylsilanes, allylstannanes, and allylic organometallics, which can be generated in situ from a metal and an allylic halide. For this purpose, metallic indium was proved to be very successful.[2] Direct three-component syntheses of homoallylamines were also reported from an aldehyde, an amine (or an amide), and a Si, Sn, or Ge allylic organometallic.[3] However, this method requires the use of a presynthesized organometallic compound and of a suitable nitrogen component (e.g., aromatic amines). Recently, we reported indium-mediated reactions of iminium salts, generated in situ by protonation of enamines, leading to tertiary homoallylamines and β-amino esters.[4] In our search for other systems for generating iminium salts, our attention turned toward reductive amination of carbonyl compounds. Mattson et al.[5] and later Bhattacharyya et al.[6] reported the titanium(IV) isopropoxide-mediated reductive amination of carbonyl compounds. An aminoalkoxy titanium complex that is formed intermediately can be reduced by a hydride ($NaBH_3CN$ or $NaBH_4$) to an

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[1] For recent reviews, see: (a) Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 975−1006. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438.

[2] (a) Beuchet, P.; Le Marrec, N.; Mosset, P. *Tetrahedron Lett.* **1992**, *33*, 5959−5960. (b) Cintas, P. *Synlett* **1995**, 1087−1096.

[3] (a) Larsen, S. D.; Grieco, P. A.; Fobare, W. F. *J. Am. Chem. Soc.* **1986**, *108*, 3512−3513. (b) Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 1378−1380. (c) Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997−1000. (d) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun.* **1998**, 19−20. (e) Akiyama, T.; Iwai, J. *Synlett* **1998**, 273−274. (f) Masuyama, Y.; Tosa, J.; Kurusu, Y. *Chem. Commun.* **1999**, 1075−1076. (g) Masuyama, Y.; Iwai, J.; Onuma, Y.; Kagoshima, H. *Chem. Commun.* **1999**, 2191−2192.

[4] Tussa, L.; Lebreton, C.; Mosset, P. *Chem. Eur. J.* **1997**, *3*, 1064−1070.

[5] Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552−2554.

[6] (a) Bhattacharyya, S. *Tetrahedron Lett.* **1994**, *35*, 2401−2404. (b) Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928−4929. (c) Neidigh, K. A.; Avery, M. A.; Williamson, J. S.; Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2527−2531.

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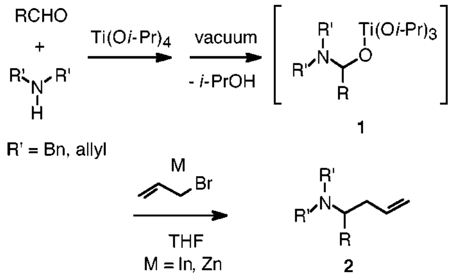
amine, either directly or via iminium ions. In this context, we surmised that these titanium complexes would also react with other nucleophiles. Indeed, as presented in this paper, reaction with in situ generated organometallic species from a metal (In, Zn) and a reactive halide (allyl bromide, alkyl bromoacetate, iodoacetonitrile) enabled the synthesis of homoallylamines, β-amino esters, and β-amino nitriles, often in good yields.

We devised a two-step, one-pot procedure. In the first step, various aldehydes were condensed with a secondary amine such as dibenzylamine or diallylamine in the presence of titanium(IV) isopropoxide (2−3 h at 40 °C) to afford an aminoalkoxy titanium complex **1** (Scheme 1).[7] Liberated 2-propanol was removed by application of vacuum.[8] In the second step, a solvent (anhydrous THF) was added followed by a metal (indium[9] or zinc[10] powder), and allyl bromide. After reaction (4 h at 30 °C) and workup, homoallylamines **2** were isolated generally in good yields (Table 1).[11] Indium and zinc proved to be equally efficient.

Scheme 1



Homoallylamines are precursors to β-amino acids and β-lactams. To avoid the need of transforming the terminal double bond into a carboxylic function, we studied the direct access to β-amino esters by a Reformatsky-type reaction, using α-halo esters instead of allyl bromide. Initial experiments were conducted with benzaldehyde, dibenzylamine, $Ti(O^iPr)_4$, and ethyl bromo- or iodoacetate. The expected β-amino ethyl ester was obtained with some contamination by the corresponding isopropyl ester resulting from $Ti(O^i\text{-}Pr)_4$-catalyzed transesterification.[12] This problem was circumvented using isopropyl bromoacetate (Scheme 2). Compared to the synthesis of **2**, the second step was found to be noticeably slower, requiring ca. 40 h at 40 °C. Under these conditions, good yields of the expected β-amino esters **3** were obtained for benzaldehyde and some *p*-substituted benzaldehydes (Table 2). However, with dibenzylamine, this reaction proved to be highly dependent on the aldehyde employed since very poor or no reaction was observed with

Scheme 2

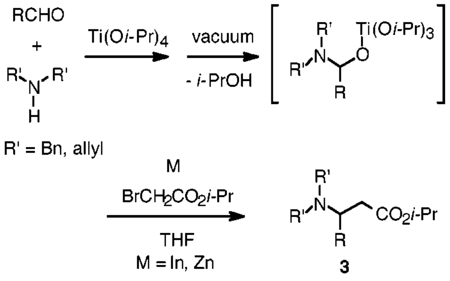


Table 1. Yields of Homoallylamines **2** for the Condensation of Aldehydes with Dibenzylamine or Diallylamine and Titanium(IV) Isopropoxide Followed by Reaction of Indium or Zinc and Allyl Bromide[a]

R	R′	M	**2**[b]
Ph	Bn	In	74
Ph	Bn	Zn	76
Ph	allyl	In	78
Ph	allyl	Zn	66
p-Br-C_6H_4	Bn	In	83
p-MeO-C_6H_4	Bn	In	62
c-C_6H_{11}	Bn	In	80
c-C_6H_{11}	Bn	Zn	81
i-Pr	Bn	In	64
i-Pr	Bn	Zn	66
Et_2CH	allyl	In	60
$PhCH_2CH_2$	Bn	In	58

[a] Reaction conditions: aldehyde (1 mmol), dibenzylamine (1.05 mmol), or diallylamine (1.25 mmol) and titanium(IV) isopropoxide (1.15 mmol), 2−3 h, 40 °C, vacuum, THF (1 mL), indium (0.8 mmol) or zinc (1.25 mmol), and allyl bromide (1.5 mmol), 4 h, 30 °C. [b] Isolated yield of **2** (%).

Table 2. Yields of β-Amino Esters **3** for the Condensation of Aldehydes with Dibenzylamine or Diallylamine and Titanium(IV) Isopropoxide Followed by Reaction of Indium or Zinc and Isopropyl Bromoacetate[a]

R	R′	M	**3**[b]
Ph	Bn	In	86
Ph	Bn	Zn	74
Ph	allyl	In	81
Ph	allyl	Zn	69
p-F-C_6H_4	Bn	In	73
p-Cl-C_6H_4	Bn	In	82
p-Cl-C_6H_4	allyl	In	79
p-MeO-C_6H_4	Bn	In	68
c-C_6H_{11}	allyl	In	62
c-C_6H_{11}	allyl	Zn	48
Et_2CH	allyl	In	19

[a] Reaction conditions: aldehyde (1 mmol), dibenzylamine (1.05 mmol) or diallylamine (1.25 mmol) and titanium(IV) isopropoxide (1.15 mmol), 2 h, 40 °C, vacuum, THF (1 mL), indium (0.8 mmol) or zinc (1.25 mmol), and isopropyl bromoacetate (1.25 mmol), 40 h, 40 °C, darkness. [b] Isolated yield of **3** (%).

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(7) This reaction was performed in the absence of a solvent. A slight excess of amine and $Ti(O^iPr)_4$ were used to ensure complete conversion of the aldehyde.

(8) This was visualized by immediate foaming. Omitting this operation resulted thereafter in far lower yields of **2**.

4-cyanobenzaldehyde and aliphatic aldehydes. This limitation was overcome when diallylamine was used and the reaction with aliphatic aldehydes such as cyclohexanecarboxaldehyde and 2-ethylbutyraldehyde afforded the compounds **3**. It was also noticed that, for this Reformatsky-type reaction, indium proved to give better yields than zinc.

Scheme 3

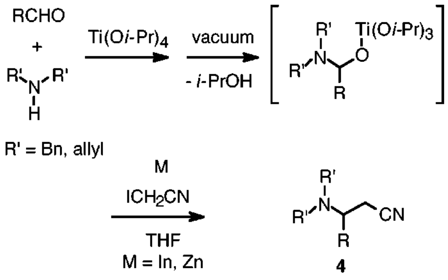

Table 3. Yields of β-Amino Nitriles **4** for the Condensation of Aldehydes with Dibenzylamine or Diallylamine and Titanium(IV) Isopropoxide Followed by Reaction of Indium or Zinc and Iodoacetonitrile[a]

R	R′	M	**4**[b]
Ph	Bn	In	62
Ph	Bn	Zn	45
Ph	allyl	In	50
p-Cl-C_6H_4	Bn	In	63
c-C_6H_{11}	allyl	In	48

[a] Reaction conditions: aldehyde (1 mmol), dibenzylamine (1.05 mmol) or diallylamine (1.25 mmol) and titanium(IV) isopropoxide (1.15 mmol), 2−3 h, 40 °C, vacuum, THF (1 mL), indium (0.8 mmol) or zinc (1.25 mmol), and iodoacetonitrile (1.2 mmol), 18−20 h, 40 °C, darkness. [b] Isolated yield of **4** (%).

Another reactive halide that was investigated was iodoacetonitrile (Scheme 3). Under similar conditions except for a shorter reaction time with the intermediate titanium complex (18−20 h at 40 °C), the expected β-amino nitriles **4** were obtained (Table 3). As for the reaction with a bromoacetate, the use of diallylamine enabled to get a successful reaction with an aliphatic aldehyde such as cyclohexanecarboxaldehyde. Finally, the compatibility of the nitrile function under these reaction conditions is noteworthy.

In conclusion, an efficient one-pot synthesis of homoallylamines, β-amino esters, and β-amino nitriles was found directly from an aldehyde and a secondary amine such as dibenzylamine or diallylamine. It relies on the generation in situ of iminium ions and of organometallic species, which allows us to avoid the use of presynthesized reagents and substrates. Furthermore, the introduction of cleavable groups on nitrogen should make these methodologies useful for organic synthesis. Their extension as well as the study of their stereocontrol is presently under active investigation.

Supporting Information Available: Representative procedures, characterization data, and representative spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) A 0.8 equiv portion of indium was used. That corresponds to a slight excess since 0.67 equiv is required for a stoichiometric reaction. Indium is trivalent and all three R groups of the intermediate indium sesquihalide, e.g., $R_3In_2Br_3$ are transferred in their reaction with iminium ions.[4] Use of 1 equiv of indium led to no significant increase of yields.

(10) A 1.25 equiv portion of zinc was used.

(11) More reactive secondary amines such as diethylamine, pyrrolidine, or morpholine also form the expected homoallylamine when an aromatic aldehyde is used but not in the case of enolizable aliphatic aldehydes probably due to formation of an enamine, Ti(O^{i}Pr)$_4$ therefore acting as a dehydrating agent.

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