

Lithium Perchlorate Mediated Three-Component Preparation of Primary Aminoesters

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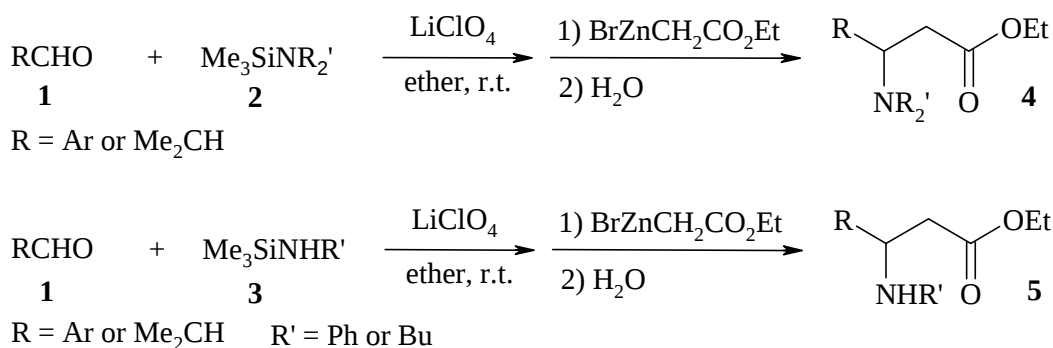
Abstract: A three-component reaction between an aldehyde, metallated hexamethyldisilazane and a functionalized organozinc compound proceeded smoothly in the presence of LiClO₄ in diethyl ether to afford primary amino esters in good yields.

Keywords: Primary aminoesters; Lithium perchlorate; Mannich reaction.

Introduction

Recently, we reported the lithium perchlorate mediated one pot three-component aminoalkylation of aldehydes, **1**, with (trimethylsilyl)dialkylamines, **2**, or *N*-(trimethylsilyl)-*N*-alkylamines **3**, and functionalized organozinc compounds, for the preparation of tertiary aminoesters, **4**, and secondary aminoesters, **5**, respectively (Scheme 1) [1,2].

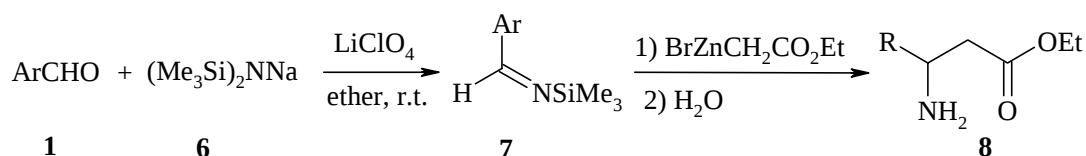
Scheme 1



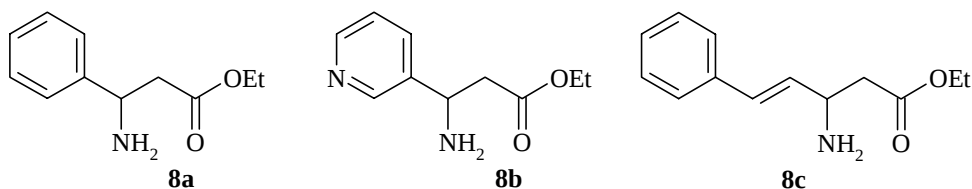
Results and Discussion

Alkylzinc reagents are generally unreactive toward aldehydes. For such reactions to proceed, special circumstances are required, involving either highly reactive organozinc reagents, such as α -zinc ester, or activation in the presence of Lewis acids [3]. In this paper, we would like to report that the reaction of aldehydes, **1**, with sodium or lithium hexamethyldisilazane, **6**, at r.t., in the presence of a 5M solution of lithium perchlorate in diethyl ether produces the imine **7**, *in situ*, in about 30 min. The subsequent reaction of **7** with the bromoalkylzinc ester $\text{BrZnCH}_2\text{COOEt}$ in diethyl ether at room temperature then afforded the corresponding primary aminoesters, **8**, in good yields (Scheme 2).

Scheme 2



The structures of the primary aminoesters prepared are shown below. When the reaction was carried out in diethyl ether or dichloromethane solution without using LiClO_4 , products **8** were produced in low yield after long reactions (*ca.* 40% of **7a** after stirring for 24 hours at r. t.).



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Experimental

General

Chemicals were purchased from Fluka and used as received, except for LiClO_4 , which was dried at 160°C and 10^{-1} Torr for 48 h. Ether was dried over Na/benzophenone under argon. IR spectra were taken on a Mattson 1000 Unicam FTIR, ^1H NMR spectra were recorded on Bruker AC 80 or Bruker 500 MHz Ultra ShieldTM instruments. All reactions were performed under argon.

Caution: Although we have not experienced any accidents while using LiClO₄, the authors advise that this reagent should always be dried in a hood equipped with a suitable lab-shield.

General Procedure for the Preparation of Primary Aminoesters 8:

Hexamethyldisilazane (3.5 mmol, 0.24 mL) was placed under argon in two-necked flask fitted with a condenser and a stirring bar. Diethyl ether (3 mL) and 3.7 mmol of sodium hydride (60-65%, after washing with light pet. ether) were added, and the mixture was stirred for about 30 min. Then 3 mL of a 5M solution of lithium perchlorate in diethyl ether and 2 mmol of aldehyde were added via syringe. After stirring for 30 min., the bromoalkylzinc ester, BrZnCH₂COOEt, (3.5 mmol) was added, and the mixture was stirred for an additional 2.0 hours. Water (10 mL) was then added and the product was extracted with dichloromethane (2x10 mL). The organic layer was separated and extracted with cold 0.5 M HCl solution. Neutralization with 2.0 M KOH solution gave the desired products. Further purification was done by preparative gas chromatography if needed. All products described had structures in accordance with their spectroscopic data.

Spectroscopic data

8a, oil, (65%), IR (neat), $\nu_{\max}$ 3538 (NH₂), 1730 (C=O) cm⁻¹; ¹H-NMR (CDCl₃): δ 1.20 (t, 3H, *J* 7.2 OCH₂CH₃), 2.00 (br. s, 2H, NH₂), 2.60 (d, 2H, *J* 6.7 CH₂CH), 4.10 (q, *J* 7.2, 2H, OCH₂CH₃), 5.10 (t, *J* 6.7, 1H, CH₂CH), 7.20 (s, 5H, Ar-H) [4].

8b, oil, (78%), IR (neat), $\nu_{\max}$ 3400 (NH₂), 1725 (C=O) cm⁻¹; ¹H-NMR (CDCl₃): δ 1.20 (t, 3H, *J* 7.1 OCH₂CH₃), 2.20 (br. s, 2H, NH₂), 2.60 (d, 2H, *J* 6.7 CH₂CH), 4.10 (q, *J* 7.1, 2H, OCH₂CH₃), 4.40 (t, *J* 6.7, 1H, CH₂CH), 7.10-7.30 (m, 1H, Ar-H), 7.60-7.80 (m, 1H, Ar-H), 8.40-8.60 (m, 2H, Ar-H).

8c, oil, (60%), IR (neat), $\nu_{\max}$ 3389 (NH₂), 1723 (C=O) cm⁻¹; ¹H-NMR (CDCl₃): δ 1.10 (t, 3H, *J* 7.4 OCH₂CH₃), 2.00 (br. s, 2H, NH₂), 2.70 (d, 2H, *J* 5.7 CH₂CH), 3.40 (m, 1H, CH₂CH), 4.10 (q, *J* 7.4, 2H, OCH₂CH₃), 6.20-6.60 (m, 2H, CH=CH), 7.10-7.45 (5H, Ar).

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Sample availability: available from the authors.