Monatshefte für Chemie 135, 309–312 (2004)
DOI 10.1007/s00706-003-0093-2

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Aminoalkylation with Aldehydes Mediated by Solid Lithium Perchlorate

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Received May 27, 2003; accepted (revised) June 24, 2003
Published online November 20, 2003

Summary. The solid $LiClO_4$-mediated one-pot reaction of aldehydes with secondary amines and C nucleophiles afforded the corresponding aminoalkylation products in high yields. Unlike the previous reported procedure, the aminoalkylation of aldehyde was achieved in the presence of only 0.5 equivalents of solid lithium perchlorate in dichloromethane as the solvent with good to high yields at room temperature.

Keywords. Aminoalkylation; Aldehyde; Solid Lithium Perchlorate; *Mannich* reaction.

Introduction

Direct aminoalkylation is interesting for synthetic organic chemistry and it has considerable importance for the synthesis of drugs, pesticides, and natural products. Dialkylamino esters and amines are widely used for their antispasmodic activity, as topical anesthetic, amongst other pharmaceutical uses, and as plant growth promoters [1–4]. The *Mannich* reaction is one of the most important multicomponent reactions in organic synthesis and biosynthesis [5]. The classical *Mannich* reaction is an aminoalkylation with formaldehydes involving three-components, an aldehyde, a secondary amine, and compounds with an active CH [6a]. Although, β-aminoketones (*Mannich* bases) can be obtained in good yields, the classical reaction has limited applications. Many attempts have been made to extend the *Mannich* reaction [6b]. In this context, *Mannich* products can be prepared by the addition of nucleophiles to the benzotriazole **1** or titanium derivatives of type **2** [7, 8], as well as addition of nucleophiles to *in situ* prepared iminium salts **3** from trimethylsilyldimethyl amine and an aldehyde in a concentrated ethereal $LiClO_4$ solution (*LPDE*) [9]. We have reported several transformations of the iminium salt **3** to different organic compounds on a 2 mmol scale (ca. 2.1 g solid $LiClO_4$ for each run) [10].

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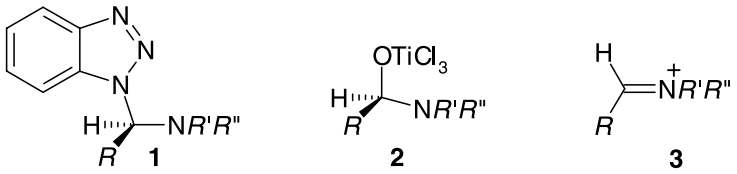


Formulae 1

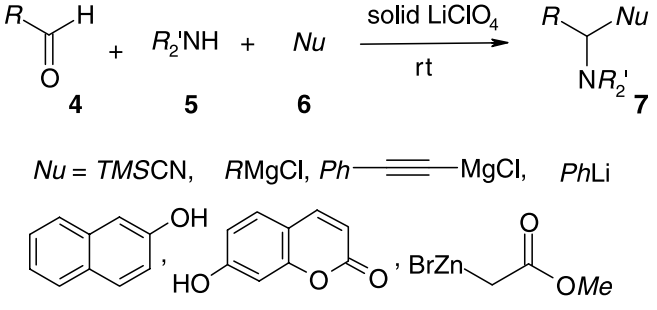
Although *LPDE* is a convenient medium to carry out reactions under neutral condition, drying lithium perchlorate and preparation of its concentrated solution in diethyl ether (*ca.* 5.0 *M*) is one disadvantage of this medium. On the other hand, due to the current challenge for developing easy to handle synthetic systems and in continuation of our interest on the applications of lithium perchlorate for various organic transformation, we herein describe a simple, general, and efficient protocol for the aminoalkylation with aldehydes with different types of nucleophiles using only about 0.08 g of solid $LiClO_4$, in a small amount of CH_2Cl_2.

Results and Discussion

Treatment of 1 equivalent of an aldehyde with 1.5 equivalents of a secondary amine and a nucleophile in the presence of about 0.5 equivalents of solid $LiClO_4$ produces the expected aminoalkylated product in high yield after a short time at room temperature (Scheme 1).

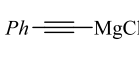
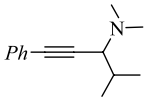
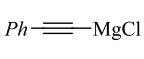
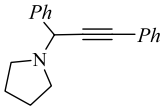
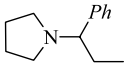
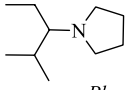
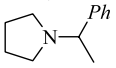
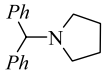
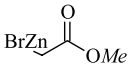
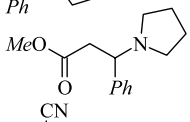
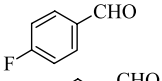
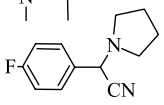
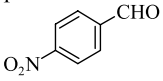
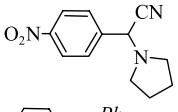
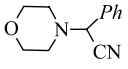
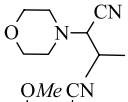
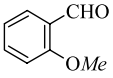
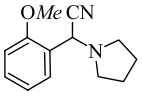
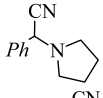
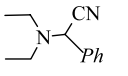
Several aldehydes, secondary amines, and nucleophiles were examined according to this procedure. The reaction time is different for each reaction due to the nucleophilicity of each nucleophile (Table 1). The aminoalkylation reaction did not occur without using solid $LiClO_4$. The three components coupling reactions preceeded smoothly and the corresponding aminoalkylated products were isolated in good to high yields with no by-products. In most cases the pure products were isolated without any further purification. The reaction can also proceed with 2-methylpropanal (an enolizable aldehyde) in relatively good yield. All compounds are known and they were characterized on the basis of their spectroscopic data (IR, NMR, MS) and by comparison with data reported in Ref. [10].

In conclusion we have presented a practical, efficient, and simple method for aminoalkylation with aldehydes using a small amount of solid lithium perchlorate (about 0.5 equiv.) in dichloromethane.



Scheme 1

Table 1. Aminoalkylation of aldehydes with different nucleophiles mediated by solid $LiClO_4$

Entry	Aldehyde	Amine	Nucleophile	Product		Time min	Yield[a] %
1					**7a**	60	85[b]
2	*Ph*CHO				**7b**	60	54
3	*Ph*CHO		*Et*MgCl		**7c**	45	79
4			*Et*MgCl		**7d**	80	63[b]
5	*Ph*CHO		*Me*MgI		**7e**	30	64
6	*Ph*CHO		*Ph*Li		**7f**	60	90
7	*Ph*CHO				**7g**	60	73
8			Me_3SiCN		**7h**	30	75[b]
9			Me_3SiCN		**7i**	20	70
10			Me_3SiCN		**7j**	15	90
11	*Ph*CHO		Me_3SiCN		**7k**	20	90
12			Me_3SiCN		**7l**	30	74[b]
13			Me_3SiCN		**7m**	20	86
14	*Ph*CHO		Me_3SiCN		**7n**	20	90
15	*Ph*CHO		Me_3SiCN		**7o**	20	68
16	*Ph*CHO				**7p**	90	80
17	*Ph*CHO				**7q**	180	71

[a] Isolated yields; [b] In this case 0.12 g of $LiClO_4$ were used

Experimental

NMR spectra were recorded on a Bruker ACF 500, IR spectra with a Perkin Elmer 1600 FTIR spectrometer. Column chromatography was performed on silica gel, Merck grade 60. CH_2Cl_2 was distilled before use. All reactions were performed under Ar. Anhydrous $LiClO_4$ and other chemicals were from Fluka or Merck. All compounds were characterized on the basis of spectroscopic data (IR, NMR, MS) and by comparison with data reported in Ref. [10].

General Procedure for the Aminoalkylation with Aldehydes Mediated by Solid $LiClO_4$

Lithium perchlorate (0.75 mmol, 0.08 g) was added to 5 cm^3 of dry CH_2Cl_2. After 2 min of stirring, 2 mmol of aldehyde were added and the mixture was stirred at rt for 5 min. A secondary amine (3.0 mmol) was added and the solution was stirred until the iminium salt was formed after about 5 min stirring at rt. Then 3 mmol of a nucleophile were added and the reaction mixture was stirred at rt for an appropriate time as indicated in Table 1 (In case of **7a**, **7b**, and **7g**, 4 mmol of nucleophile were added). After the reaction was completed, 10 cm^3 of CH_2Cl_2 and 20 cm^3 of H_2O were added and the organic layer was separated. The filtrate was washed with H_2O. The organic phase was separated, dried over $MgSO_4$, and the solvent was removed using a rotary evaporator. Further purification was carried out by column chromatography on basic alumina eluting with petroleum ether/ethyl acetate or by recrystalization. For products **7h–7o** no purification was needed, and the pure products were isolated after usual work up.

Acknowledgments

We thank "Volkswagen-Stiftung, Federal Republic of Germany" for financial support to purchase equipments and chemicals.

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