Three component aminoalkylation of aldehydes by functionalized organozinc compounds promoted by lithium perchlorate ($LiClO_4$)

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The one-pot synthesis of several *N*,*N*-dialkylamino esters is reported. Treatment of aldehydes 1 (aliphatic and aromatic) with (trimethylsilyl)dialkylamines 2, in the presence of $LiClO_4$ in diethyl ether presumably gives the intermediates 3. Reaction of these intermediates 3 with functionalized organozinc reagents, RZnBr, produces a variety of *N*,*N*-dialkylamino esters in a short time (about 1 h) and in good to moderate yields. The pure products are isolated by extraction with cold hydrochloric acid.

Introduction

N,*N*-Dialkylamino esters are widely used for their antispasmodic activity and as topical anaesthetics, amongst other pharmaceutical uses (such as treatment of hypertension and heart failure). They are also used as plant growth promoters (they enhance yields and increase production of useful compounds such as carotene), as plant growth regulators, as anti-inflammatories and as analgesics.[1–4] Usually these compounds are prepared by reaction of aminal and trimethylsilyl ketene acetals, by nucleophilic substitution of the corresponding halo esters, or by palladium catalysed reaction of a Schiff base with a Reformatsky reagent.[4–6] A convenient method for the preparation of these compounds is the aminoalkylation of aldehydes in the presence of a (trimethylsilyl)dialkylamine and a functionalized zinc reagent.

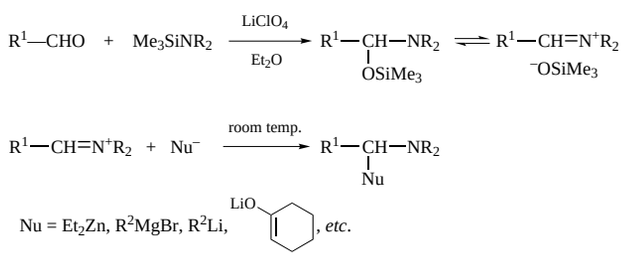
Generally alkylzinc reagents are unreactive towards aldehydes. For the reaction to proceed, special conditions are required, involving either highly reactive organozinc reagents (such as α-zinc esters), or activation in the presence of Lewis acids or bases (*e.g.* $BF_3{\cdot}Et_2O$, titanium tetrachloride). Thus, α-, β- or γ-bromozinc esters add to aldehydes in the presence of a Lewis acid catalyst to produce the corresponding hydroxy esters.[7–11]

Recently we reported the $LiClO_4$ mediated one-pot three component aminoalkylation of aldehydes with (trimethylsilyl)-dialkylamines, **2** and different nucleophiles, including diethylzinc.[12] In this paper we describe an efficient synthesis of amino esters, as well as functionalized alkylamines, using aldehydes **1** (enolizable or non-enolizable), (trimethylsilyl)dialkylamines **2**, α-, β- or γ-bromo- or iodo-zinc esters, as well as allylzinc bromide, chlorozinc acetylide and other functionalized organozinc reagents, at room temperature in a concentrated solution of lithium perchlorate in diethyl ether. The reaction allows aminoalkylation with good to moderate yields.

Hydroxy compounds are not formed due to the fast reaction of the aldehyde with the (trimethylsilyl)dialkylamine in concentrated lithium perchlorate solution, presumably to form an iminium salt. This salt is then much more reactive towards nucleophilic addition compared with the starting aldehyde (Scheme 1). Bromozinc esters themselves are unreactive towards benzaldehyde in 5 M $LiClO_4$ in diethyl ether.[13]

Results

Iminium salts are important intermediates in organic synthesis.[14] These salts may be produced *in situ* by the reaction of (trimethylsilyl)dialkylamines with various aliphatic or aromatic aldehydes, promoted by a 5 M solution of $LiClO_4$ in diethyl ether[12] (Scheme 1). Bromo- or iodo-zinc esters were prepared from the corresponding bromo esters of iodo esters with a Zn–Cu couple in THF or diethyl ether. Activation of the Zn–Cu couple with trimethylsilyl chloride (TMSCl) enhanced the formation of the bromoalkylzinc esters, $BrZn(CH_2)_nCO_2R$, especially when $n > 1$. These reagents were produced very slowly (or not at all) from bromo esters without using TMSCl for activation of the Zn–Cu couple. Reaction of α-, β- or γ-zinc esters with intermediates **3** in diethyl ether afforded the corresponding dialkylamino esters **4** at room temperature in good to moderate yields. The yields were higher when $BrZnCH_2CO_2R$ compounds were used. Other functionalized organozinc reagents, RZnBr, were produced in the same manner according to literature procedures,[15–18] and were reacted with intermediate **3**, to give the corresponding R-amines, Scheme 2. The results are shown in Table 1.



Scheme 1

Experimental

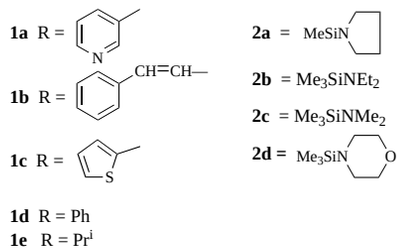
$LiClO_4$ (Fluka) was dried at 160 °C and 10^{-1} Torr (1 Torr = 133.322 Pa) for 48 h. Diethyl ether was dried over Na–benzophenone. IR spectra were taken on Matt Son 1000 Unicam FTIR and Beckman IR 4250 spectrometers. ^1H and ^{13}C NMR spectra were recorded on Bruker AC 80, AM 400 and AC 200 spectrometers. Mass spectra were obtained on a Finnigan MAT model 8430, a Varian MAT 311A or a Varian MAT 111 spectrometer. *J* Values are given in Hz. Compounds **4a**, **4d**, **4e**, **4j** and **4k** were prepared as previously reported.[4,5]

CAUTION: Although we did not have any accidents using lithium perchlorate ($LiClO_4$), the authors advise drying lithium perchlorate in a hood behind a suitable lab-shield.

General procedure for the preparation of bromozinc esters

Zinc–copper couple (3.3 mmol, 0.22 g) was placed in a two-necked flask fitted with a condenser and a stirring bar, under

Table 1 Product obtained from the reaction of functionalized zinc reagents *via* intermediate **3**



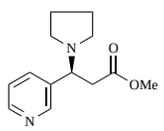
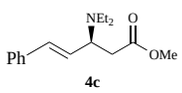
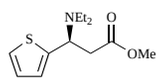
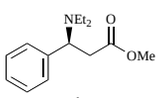
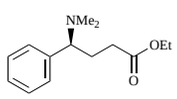
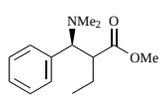
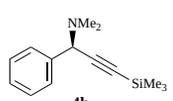
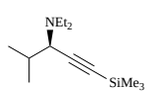
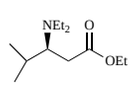
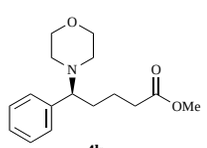
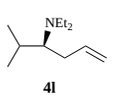
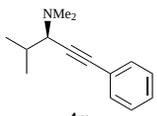
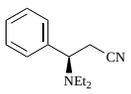
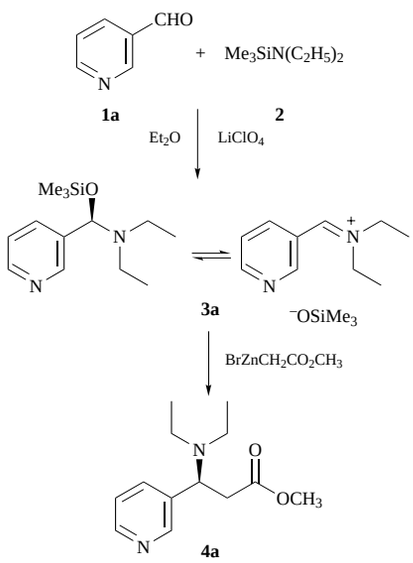
Aldehyde **1**	Amine **2**	RZnX	Product	Yield (%)
1a	**2a**	$BrZnCH_2CO_2Me$	 **4b**	71
1b	**2b**	$BrZnCH_2CO_2Me$	 **4c**	67
1c	**2b**	$BrZnCH_2CO_2Me$	 **4d**	73
1d	**2b**	$BrZnCH_2CO_2Me$	 **4e**	74
1d	**2c**	$BrZn(CH_2)_2CO_2Me$	 **4f**	59
1d	**2c**	$BrZnCH(Et)CO_2Me$	 **4g**	69
1d	**2c**	$ClZnC{\equiv}CSiMe$	 **4h**	77
1e	**2b**	$ClZnC{\equiv}CSiMe_3$	 **4i**	82
1e	**2b**	$BrZnCH_2CO_2Et$	 **4j**	52
1d	**2d**	$BrZn(CH_2)_3CO_2Me$	 **4k**	57
1e	**2b**	$BrZnCH_2CH{=}CH_2$	 **4l**	62

Table 1 (*Continued*)

	Aldehyde **1**	Amine **2**	RZnX	Product	Yield (%)
	1e	**2c**	ClZnC≡CPh	 **4m**	86
	1d	**2b**	$ClZnCH_2CN$	 **4n**	55



Scheme 2

argon. Dry diethyl ether or dry THF (3 ml) and trimethylsilyl chloride (0.05 ml) were added and the mixture was stirred for about 5 min. The appropriate bromo ester (3 mmol) was then added *via* syringe. After stirring for an additional 30 to 60 min, the solvent was removed under reduced pressure and the $BrZn(CH_2)_nCO_2R$ reagent was ready for the next step. Other functionalized bromo-, chloro- or iodo-zinc reagents were prepared according to the literature procedure.[16–18]

General procedure for the three compound aminoalkylation of aldehydes

The appropriate aldehyde (2.0 mmol) was placed in a two-necked flask fitted with a stirring bar under argon. $LiClO_4$ solution in diethyl ether (3–4 ml, 5 M) was added and the mixture was stirred for about 10 min. Then the (trimethylsilyl)-dialkylamine (3.5 mmol) was added and the mixture was stirred for an additional 30 min (or for aliphatic aldehydes, up to 1 h). The mixture was then added to the prepared $BrZn(CH_2)_nCO_2R$ reagent *via* a double needle syringe. After stirring for about 1 h at room temp., water (20 ml) and diethyl ether (20 ml) were added and the mixture filtered. The organic layer was separated and extracted with cold aqueous hydrochloric acid (3 × 20 ml, 0.2 M). Neutralization with a 2.0 M solution of KOH, gave the desired product.[19] Further purification, if required, was carried out by preparative gas chromatography. The structures of the new compounds were determined by ^1H and ^{13}C NMR spectroscopy, and by their mass spectra and/or elemental analyses.

Methyl 3-diethylamino-3-(pyridin-3-yl)propanoate 4a. 330 mg (70%); ν_{max}(film)/cm^{-1} 1737; δ_H 7.05–8.71 (m, 4H), 4.21 (dd, 1H, *J* 7.1, 8.4), 3.49 (s, 3H), 2.21–2.77 (m, 6H), 0.88 (t, 6H, *J* 7.4).

Methyl 3-(pyrrolidin-1-yl)-3-(pyridin-3-yl)propanoate 4b. 330 mg (71%); ν_{max}(film)/cm^{-1} 1727; δ_H 7.11–8.72 (m, 4H), 3.91 (s, 3H), 4.06–4.24 (m, 1H), 2.12–2.59 (m, 6H), 1.38–1.79 (m, 4H); δ_C 168.94 (CO), 150.00 (CH), 148.60 (CH), 136.18 (CH), 131.74 (C), 122.58 (CH), 82.71 (CH), 52.56 (CH_3), 49.07 (CH_2), 24.12 (CH_2), 23.17 (CH_2) (Calc. for $C_{13}H_{18}O_2N_2$: C, 66.64; H, 7.74. Found: C, 67.10; H, 8.06%).

Methyl 3-diethylamino-5-phenylpent-4-enoate 4c. 350 mg (67%); ν_{max}(film)/cm^{-1} 1734; δ_H 6.92–7.41 (m, 5H), 6.01–6.72 (m, 2H), 4.45–4.73 (m, 1H), 3.51 (s, 3H), 2.66–2.24 (m, 6H), 0.83 (t, 6H, *J* 7.4) (Calc. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87. Found: C, 73.25; H, 8.60%).

Methyl 3-diethylamino-3-(2-thienyl)propanoate 4d. 355 mg (73%); ν_{max}(film)/cm^{-1} 1724; δ_H 7.65–7.74 (m, 3H), 4.49 (dd, 1H, *J* 5.5, 9.8), 3.66 (s, 3H), 2.26–2.77 (m, 6H), 0.98 (t, 6H, *J* 7.3); δ_C 171.91 (CO), 148.55 (C), 136.03 (CH), 134.92 (CH), 128.18 (CH), 54.10 (CH), 51.32 (CH_3), 47.73 (CH_2), 43.75 (CH_2), 12.06 (CH_3).

Methyl 3-diethylamino-3-phenylpropanoate 4e. 345 mg (74%); ν_{max}(film)/cm^{-1} 1741; δ_H 7.19 (m, 5H), 4.12 (t, 1H, *J* 8.1), 3.55 (s, 3H), 2.78–2.10 (m, 6H), 0.91 (t, 6H, *J* 8.1); δ_C 172.41 (CO), 139.89 (C), 130.30 (CH), 128.09 (CH), 127.82 (CH), 60.37 (CH), 51.32 (CH_3), 43.27 (CH_2), 37.32 (CH_2), 13.36 (CH_3).

Ethyl 4-dimethylamino-4-phenylbutanoate 4f. 294 mg (59%); ν_{max}(film)/cm^{-1} 1734; δ_H 7.28 (m, 5H), 4.09 (q, 2H, *J* 7.2), 3.23 (dd, 1H, *J* 9.0, 5.3), 2.20 (s, 6H), 2.14 (m, 2H), 1.26 (m, 2H), 1.21 (t, 3H, *J* 7.2); δ_C 173.14 (CO), 137.88 (C), 128.90 (CH), 128.31 (CH), 128.10 (CH), 70.07 (CH_2), 60.16 (CH), 42.50 (CH_3), 31.04 (CH_2), 27.72 (CH_2), 14.12 (CH_3); *m*/*z* 134 (base peak, $C_6H_5CH{=}N^+Me_2$), 236 (M + 1) (Calc. for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99. Found: C, 71.12; H, 8.63%).

Methyl 3-dimethylamino-2-ethyl-3-phenylpropanoate 4g. 325 mg (69%); ν_{max}(film)/cm^{-1} 1730; δ_H 6.98–7.37 (m, 5H), 3.83 (m, 1H), 3.71 (s, 3H), 2.97 (dt, 1H, *J* 16.0, 4.5), 2.08 (s, 6H), 1.08–1.45 (m, 2H), 0.81 (dd, 3H, *J* 14.0, 6.8) (Calc. for $C_{14}H_{21}NO_2$: C, 71.59; H, 8.99. Found: C, 72.25; H, 8.62%).

3-Dimethylamino-3-phenyl-1-trimethylsilylprop-1-yne 4h. 356 mg (77%); ν_{max}(film)/cm^{-1} 2162; δ_H 7.27 (m, 5H), 4.42 (s, 1H), 2.04 (s, 6H), 0.07 (s, 9H); δ_C 140.61 (C), 128.21 (CH), 127.94 (CH), 127.36 (CH), 100.71 (C), 92.58 (C), 62.11 (CH), 41.15 (CH_3), 0.00 (CH_3) (Calc. for $C_{14}H_{21}NSi$, M^+ 231.1443. Found: *M*, 231.1461).

3-Diethylamino-4-methyl-1-trimethylsilylpent-1-yne 4i. 367 mg (82%); ν_{max}(film)/cm^{-1} 2159; δ_H 2.78 (d, 1H, *J* 9.9), 2.42 (m, 2H), 2.17 (m, 2H), 1.58 (m, 1H), 0.87 (d, 3H, *J* 6.7), 0.86 (t, 6H, *J* 7.3), 0.79 (d, 3H, *J* 6.5), 0.02 (s, 9H); δ_C 105.16 (C), 88.72 (C), 60.95 (CH), 44.72 (CH_2), 30.98 (CH), 20.62 (CH_3), 20.04 (CH_3), 13.68 (CH_3), 0.30 (CH_3); *m*/*z* 182 (base peak), 226 (M + 1) (Calc. for $C_{13}H_{27}NSi$: C, 69.26; H, 12.07; N, 6.21. Found: C, 69.61; H, 12.41; N, 6.18%).

Ethyl 3-diethylamino-4-methylpentanoate 4j. 224 mg (52%); ν_{max}(film)/cm^{-1} 1734; δ_H 4.11 (dq, 2H, *J* 1.0, 7.1), 2.63 (m, 1H), 2.52 (m, 2H), 2.41 (m, 2H), 2.43 (dd, 1H, *J* 5.9, 14.9), 2.24 (dd, 1H, *J* 6.6, 14.9), 1.62 (m, 1H), 1.25 (t, 3H, *J* 7.1), 1.01 (t, 6H, *J* 7.2), 0.96 (d, 3H, *J* 6.7), 0.86 (d, 3H, *J* 6.7); δ_C 174.09 (CO),

63.33 (CH_2), 60.11 (CH), 44.18 (CH_2), 33.97 (CH_2), 31.57 (CH), 21.05 (CH_3), 20.06 (CH_3), 14.66 (CH_3), 14.10 (CH_3); *m*/*z* 216 (M + 1), 128 (base peak, $Me_2CH{-}CH{=}N^+Et_2$).

Methyl 5-morpholino-5-phenylpentanoate 4k. (57%); ν_{max}(film)/cm^{-1} 1739; δ_H 7.32 (m, 5H), 4.10–4.28 (m, 1H), 3.58 (s, 3H), 3.57–3.8 (m, 4H), 2.14–2.79 (m, 6H), 0.78–1.28 (m, 4H).

4-Diethylamino-5-methylhex-1-ene 4l. 210 mg (62%); ν_{max}(film)/cm^{-1} 1641; δ_H 5.90 (m, 1H), 4.96 (m, 2H), 2.60 (m, 1H), 2.55 (m, 2H), 2.47 (m, 2H), 2.33 (m, 1H), 2.31 (m, 1H), 1.70 (m, 1H), 0.99 (t, 6H, *J* 7.3), 0.92 (d, 3H, *J* 6.9), 0.90 (d, 3H, *J* 6.9); δ_C 139.36 (CH), 114.67 (CH_2), 65.95 (CH), 44.62 (CH_2), 33.04 (CH), 31.07 (CH_2), 20.95 (CH_3), 20.76 (CH_3), 14.96 (CH_3); *m*/*z* 128 (base peak), $Me_2CH{-}CH{=}N^+Et_2$), 170 (M + 1) (Calc. for $C_{11}H_{23}N$, M^+, 169.1830. Found *M*, 169.1808).

3-Dimethylamino-4-methyl-1-phenylpent-1-yne 4m. (86%); ν_{max}(film)/cm^{-1} 1946 (weak), 1598; δ_H 7.44 (m, 2H), 7.29 (m, 3H), 3.03 (d, 1H, *J* 9.8), 2.32 (s, 6H), 1.85 (m, 1H), 1.11 (d, 3H, *J* 6.6), 1.02 (d, 3H, *J* 6.6); δ_C 131.72 (CH), 128.22 (CH), 127.75 (CH), 123.67 (C), 86.75 (C), 86.41 (C), 65.58 (CH), 41.76 (CH_3), 31.03 (CH), 20.60 (CH_3), 19.83 (CH_3) (Calc. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.69. Found: C, 83.23; H, 9.94; N, 7.36%).

3-Diethylamino-3-phenylpropanenitrile 4n. (55%); ν_{max}(film)/cm^{-1} 2192; δ_H 7.21 (m, 5H), 4.15 (dd, 1H, *J* 7.44, 5.68), 2.50–2.79 (m, 6H), 1.10 (t, 6H, *J* 7.05) (Calc. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97. Found: C, 77.42; H, 8.62%).

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