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A simple one-pot three-component reaction for preparation of secondary amines and amino esters mediated by lithium perchlorate

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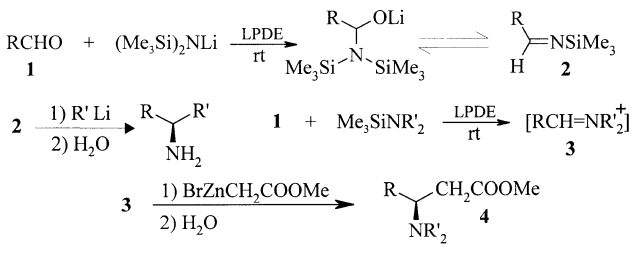
Abstract—The one-pot synthesis of several secondary amines and secondary amino esters are reported. Treatment of aldehydes (aliphatic or aromatic) with (trimethylsilyl)alkylamines, in the presence of 5 M lithium perchlorate in diethyl ether gives intermediate imines. Reaction of these intermediate imines with different nucleophiles and functionalized organozinc reagents, $BrZnCH_2COOR$, produce a variety of secondary amines and *N*-alkyl- or *N*-arylamino esters in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

The synthesis of secondary amines[1–9] and *N*-alkyl- or *N*-arylamino esters[10–14] are of great interest due to their wide use as plant growth regulators and plant growth promoters as well as other chemical and pharmaceutical activities. One approach to synthesize these compounds involves addition of organometallic reagents to imines, but the low electrophilicity of the imine has frequently hindered these reactions. The reactivity of the imines has been improved by complexation with Lewis acids, or by preparation of 'masked' imine derivatives.[15] Recently, it was reported that lanthanide triflates, tetrabutylammonium fluoride, and indium trichloride can be used as a catalyst for addition of nucleophiles to imines.[16]

Generally organozinc halides are useful organometallic intermediates and are widely used for organic synthesis. Their high functional group tolerance associated with their reactivity toward electrophiles makes them a unique class of nucleophilic reagents.[17]

Recently we reported a one-pot three component amino-alkylation of aldehydes with (trimethylsilyl)dialkyl amines or lithium hexamethyldisilazane and different nucleophiles such as organolithium, organomagnesium, organosilicon and functionalized organozinc compounds, in 5 M solution of lithium perchlorate in diethyl ether (LPDE), for the preparation of various tertiary and primary amines,[18–22] Scheme 1.

Substituted imines are important intermediates in organic synthesis. Substituted imines can be produced in situ by



Scheme 1.

reaction of *N*-alkyl(trimethylsilyl) amines with various aliphatic or aromatic aldehydes, promoted by 5 M solution of $LiClO_4$ in diethyl ether. Thus, aldehyde, **1** (enolizable or non-enolizable), *N*-alkyl(trimethylsilyl) amines, **5**, in 5 M ethereal leads to the formation of the intermediate imine **7**. The intermediate imine **7** can be detected in solution by ^{13}C NMR spectroscopy, or can be isolated from the solution after work-up. $BrZnCH_2COOMe$ was prepared from the corresponding bromoester with Zn–Cu couple in diethyl ether. Activation of the Zn–Cu couple with trimethylsilyl chloride enhanced the formation of bromoalkylzinc ester.[18] Reaction of bromoalkylzinc esters or other organolithium and organomagnesium reagents with intermediate **7** afforded the corresponding *N*-alkyl- or *N*-arylamino esters or secondary amines at room temperature in good yields, Scheme 2. The by-product β-lactam was not formed in this process.[15] The results are summarized in Table 1.

In conclusion, we have described a one-pot Mannich-type reaction of nucleophiles with in situ preformed imines in 5 M ethereal lithium perchlorate solution, which leads to the formation of substituted secondary amines or *N*-alkyl- or *N*-arylamino esters.

Keywords: secondary amines; aminoesters; lithium perchlorate.

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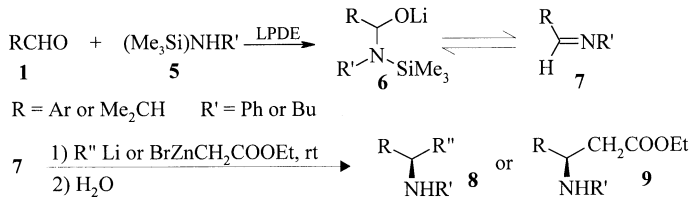
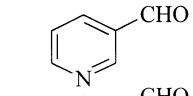
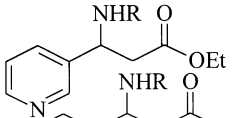
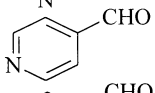
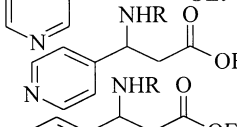
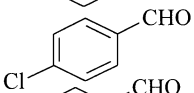
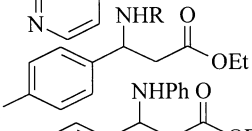
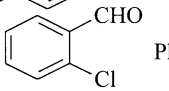
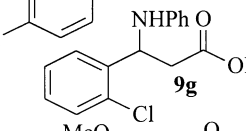
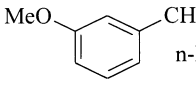
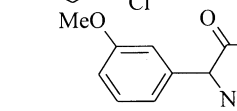
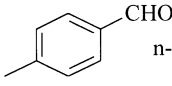
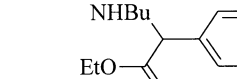
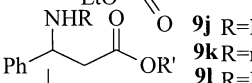
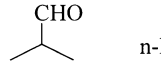
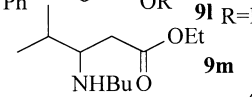
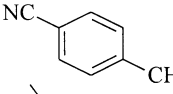
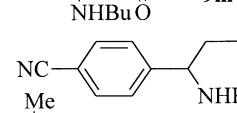
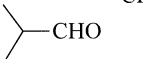
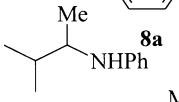
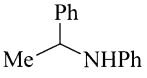
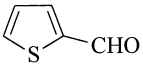
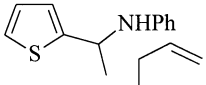
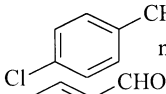
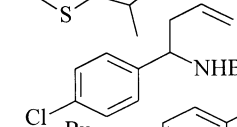
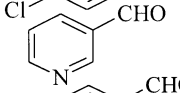
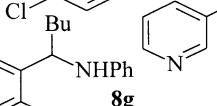
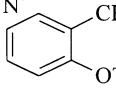


Scheme 2.

Table 1. Product obtained from the in situ performed reaction of imine with nucleophile

Aldehyde	Amine	Nucleophile	Product	%Yield[a]
	RNHTMS	$BrZnCH_2CO_2Et$		**9a** R=Ph 86 **9b** R=n-Bu 78
	RNHTMS	$BrZnCH_2CO_2Et$		**9c** R=Ph 84 **9d** R=n-Bu 76
	RNHTMS	$BrZnCH_2CO_2Et$		**9e** R=Ph 80 **9f** R=n-Bu 70
	PhNHTMS	$BrZnCH_2CO_2Et$		**9g** 80
	n-BuNHTM	$BrZnCH_2CO_2Et$		**9h** 78
	n-BuNHTM	$BrZnCH_2CO_2Et$		**9i** 60
PhCHO	RNHTMS	$BrZnCH_2CO_2R$		**9j** R=Ph, R'=Et 82 **9k** R=n-Bu, R'=Et 74 **9l** R=Ph , R'=Me 78
	n-BuNHTM	$BrZnCH_2CO_2Et$		**9m** 45
	PhNHTMS	$BrZnCH_2CO_2Et$		**9n** 86
	PhNHTM	Me Li		**8a** 74
PhCHO	PhNHTM	Me Li		**8b** 76
	RNHTMS	MeLi		**8d** R=Ph 66
	n-BuNHTM	AllylMgBr		**8e** 44
	PhNHTMS	MeLi		**8f** 86
	PhNHTMS	n-BuLi		**8g** 63

[a] Isolated yields.

1. Experimental

1.1. General

$LiClO_4$ (Fluka) was dried at 160°C and 10^{-1} Torr for 48 h. Diethyl ether was dried over Na/benzophenone under argon. IR spectra were taken on Matt Son 1000 Unicam FT-IR, ^1H and ^{13}C NMR spectra were recorded on Bruker AC 80 or Bruker 500 MHz Ultra Shield™. Mass spectra were obtained on Fisson 800 Trio, and GC-Mass HP 5973 MSD. All reactions were performed under argon. Most aldeyhdes were distilled before use. Chemicals were purchased from Fluka, Merck, and used as received.

Caution. Although we did not have any accident in using $LiClO_4$, the authors advise that lithium perchlorate is dried

in a hood using a suitable lab-shield. The etheral solution should be freshly prepared and not stored.

1.2. General procedure for preparation of substituted secondary amines or *N*-alkyl- or *N*-arylamino esters

The aldehyde (2 mmol) and 3 mL of 5 M $LiClO_4$ in diethyl ether were placed in a 50 mL flask under argon and stirred for 5 min. (Trimethylsilyl)alkyl amine (3 mmol) was then added via a syringe. After 30 min the solution of 5–6 mmol of nucleophile in diethyl ether was added and the mixture stirred at room temperature for 2 h. The best result was obtained when 6 mmol of nucleophile was used. Then water (20 mL) and diethyl ether (20 mL) were added. The organic phase was separated, dried with $MgSO_4$, and the solvent was removed in a rotary evaporator. The crude product was further purified by column chromatography on basic alumina. The products are characterized by comparison of their IR, NMR (^1H and ^{13}C) spectra with those of authentic samples. Yields refer to pure isolated products.

1.2.1. Ethyl 3-(*N*-phenylamino)-3-(pyridin-3-yl)propionate 9a. Yeild 86%; white solid, mp 73°C; IR (KBr), ν_{max} (KBr) 3246 (NH), 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.09 (t, 3H, J=7.2 Hz, OCH_2CH_3), 2.72 (d, 2H, J=6.3 Hz, CH_2CO), 4.10 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.80 (t, 1H, J=6.2 Hz, $CHCH_2$), 6.42–8.60 (m, 10H, Ar–H, NH); ^{13}C NMR ($CDCl_3$): δ 18.2 (CH_3), 42.0 (CH_2), 54.4 (CH), 62.3 (CH_2), 114.8 (CH), 118.1 (CH), 128.0 (CH), 133.8 (C), 139.8 (C), 147.1 (CH), 171.0 (C); MS *m/e* 270 (M^+, 18.3), 271 [$(M+1)^+$, 2.4], 183 (base peak, 100), 104 (7.0), 93 (5.4), 77 (9.8); (calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71. Found: C, 71.55; H, 7.03%).

1.2.2. Ethyl 3-(*N*-phenylamino)-3-(pyridin-4-yl)propionate 9c. Yield 84%; white solid, mp 84°C; IR (KBr), ν_{max} 3330 (NH), 1732 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.01 (t, 3H, J=7.25 Hz, OCH_2CH_3), 2.71 (d, 2H, J=7.2 Hz, CH_2CO), 3.98 (q, 2H, J=7.25 Hz, OCH_2CH_3), 4.70 (t, 1H, J=7.2 Hz, $CHCH_2$), 6.40–8.60 (m, 10H, Ar–H, NH); MS *m/e* 270 (M^+, 22.8), 271 [$(M+1)^+$, 4.3], 183 (base peak, 100), 104 (76.4), 93 (5.7), 77 (8.6).

1.2.3. Ethyl 3-(*N*-phenylamino)-3-(4-chlorophenyl)propionate 9e. Known.[23] Yield 80%; pale yellow solid; mp 92°C.

1.2.4. Ethyl 3-(*N*-butylamino)-3-(4-chlorophenyl)propionate 9f. Known.[23] Yield 70%; brownish oil.

1.2.5. Ethyl 3-(*N*-butylamino)-2-(4-chlorophenyl)propionate 9g. Known.[23] Yield 80%, Yellowish solid; mp 78°C.

1.2.6. Ethyl 3-(*N*-butylamino)-3-(3-methoxyphenyl)propionate 9h. Yield 78%; pale yellow oil; IR (thin film), ν_{max} 3330 (NH), 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.60–1.31 (m, 10H, $CH_2CH_2CH_3$, OCH_2CH_3), 1.62 (s, 1H, NH), 2.28 (t, 2H, J=6.8 Hz, CH_2N), 2.30–2.60 (m, 2H, $CHCH_2$), 3.70 (s, 3H, CH_3O), 3.86 (m, 1H, $CHCH_2$), 4.05 (q, 2H, J=7.2 Hz, OCH_2CH_3), 6.60–7.30 (m, 4H, Ar–H); MS *m/e* 279 (M^+, 3.7), 280 [$(M+1)^+$, 0.7], 236 (9.6), 222 (29.4), 207 (8.1), 192 (base peak, 100), 165 (30.1), 148 (16.9), 135 (13.2), 109 (5.8).[23]

1.2.7. Ethyl 3-(*N*-butylamino)-3-(4-methylphenyl)propionate 9i. Known.[24] Yield 60%; yellow oil; IR (thin film), ν_{max} 3390 (NH), 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.60–1.20 (m, 10H, $CH_2CH_2CH_3$, OCH_2CH_3), 2.2 (s, 3H, $ArCH_3$), 2.30–2.60 (m, 4H, $CHCH_2$, CH_2N), 3.55 (m, 1H, $CHCH_2$), 4.10 (q, 2H, J=6.7 Hz, OCH_2CH_3), 6.60–7.19 (m, 5H, Ar–H, NH).

1.2.8. Ethyl 3-(*N*-phenylamino)-3-phenylpropionate 9j. Yield 82%; white solid, mp 65°C; IR (KBr), ν_{max} 3246 (NH), 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.06 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.70 (d, 2H, J=6.7 Hz, CH_2CO), 4.12 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.71 (t, 1H, J=6.3 Hz, $CHCH_2$), 6.40–7.80 (m, 11H, Ar–*H*, N*H*); $^{13}CNMR$ ($CDCl_3$): δ 16.8 (CH_3), 43.1 (CH_2), 56.9 (CH), 61.5 (CH_2), 115.1 (CH), 117.8 (CH), 129.1 (CH), 130.1 (CH), 139.8 (C), 146.8 (C), 179.9 (C). MS *m/e* 269 (M^+, 18.8), 270 [$(M+1)^+$, 3.4], 182 (base peak, 100), 104 (12.3), 77 (13). (Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11. Found: C, 75.53; H, 6.76%).

1.2.9. Methyl 3-(*N*-butylamino)-3-phenylpropionate 9k. Yield 74%; viscose oil; IR (thin film), ν_{max} 3400 (NH), 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.61–1.30 (m,10H, $CH_2CH_2CH_3$, OCH_2CH_3), 2.34 (t, 2H, J=7.0 Hz, CH_2N), 2.58 (d, 2H, J=6.8 Hz, CH_2CO), 3.82 (m, 1H, $NCHCH_2$), 4.08 (q, 2H, J=7.2 Hz, OCH_2), 7.20 (braod s, 5H, Ar–H). MS *m/e* 249 (M^+, 1.4), 206 (17.4), 192 (27.5), 177 (15.9), 162 (base peak, 100), 135 (34.7), 105 (16.9), 91 (8.4).

1.2.10. Methyl 3-(*N*-phenylamino)-3-phenylpropionate 9l. Known.[25] Yield 78%; white solid, mp 106–107°C; IR (KBr), ν_{max} 3384 (NH), 1723 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.87 (d, 2H, J=6.9 Hz, CH_2CO), 3.70 (s, 3H, OCH_3), 4.71 (dd, 1H, J=6.9, 5.9 Hz, $CHCH_2$), 6.60–7.30 (m, 10H, Ar–H); MS, *m/e* 255 (M^+, 21), 256 [$(M+1)^+$, 3.9], 182 (base peak, 100), 121 (13.8), 104 (15.7), 77 (15.6).

1.2.11. Ethyl 3-(*N*-butylamino)-4-methylpentanoate 9m. Known.[25] Yield 45%; pale yellow oil.

1.2.12. Ethyl 3-(*N*-phenylamino)-3-(4-cyanophenyl)propionate 9n. Known.[26] Yield 86%; white solid, mp 112°C; IR (KBr), ν_{max} 3390 (NH), 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.10 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.72 (d, 2H, J=6.9 Hz, CH_2CO), 4.10 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.68 (t, 1H, J=6.9 Hz, $CHCH_2CO$) 6.40–7.80 (m, 10H, Ar–H, NH).

1.2.13. (*N*-Phenyl)-1,2-dimethylpropanamine 8a. Known, yield 74%; pale yellow oil.[28]

1.2.14. (*N*-Phenyl)-1-phenylethanamine 8b. Known.[27,30] Yield 76%; yellow oil; IR (thin film), ν_{max} 3361 (NH), 3030, 1607 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 (d, 3H, J=7.9 Hz, $NCHCH_3$), 3.55 (br. s, 1H, N*H*), 4.38 (q, 1H, J=7.9 Hz, $NCHCH_3$), 6.50–7.27 (m, 10H, Ar–*H*).

1.2.15. (*N*-Butyl)-1-phenylethanamine 8c. Known. Yield 71%; pale brown oil.[30]

1.2.16. (*N*-Phenyl)-1-(2-thienyl)ethanamine 8d. Known. Yield 76%; pale brown oil.[29]

1.2.17. (*N*-Phenyl)-α-2-propenyl-*p*-chlorobenzomethanamine 8e. Known. Yield 44%; yellow oil.[16b]

1.2.18. (*N*-Phenyl)-1-(pyridin-3-yl)ethanamine 8f. Yield 86%; pale orange solid, mp 68°C; IR (KBr), ν_{max} 3384 (NH), 3030, 1607 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.48 (d, 3H, J=7.2 Hz, NCHCH_3), 3.71 (br. s, 1H, NH), 4.46 (q, 1H, J=7.9 Hz, N$CH$$CH_3$), 6.40–7.70 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 24.5 (CH_3), 51.0 CH), 113.1 (CH), 114.8 (CH), 126.3 (CH), 128.9 (CH), 133.2 (CH), 134.6 (CH), 151.2 (C), 151.7 (CH), 156.9 (C); (calcd for $C_{13}H_{14}N_2$: C, 78.76; H, 7.12. Found: C, 71.98; H, 7.28%).

1.2.19. (*N*-Phenyl)-α-(*n*-butyl)-*o*-hydroxybenzomethanamine 8g. Yield 63%; yellow oil.[28]

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