Trimethylamine–Borane a Useful Reagent in the One-Pot Preparation of Carboxylic Esters from Carboxylic Acids

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The carboxylic esters **2a–h** ($R^1CO_2CH_2R^1$) and **4a–d** ($R^1CO_2CH_2R^2$) are synthesized from alkyl or aryl carboxylic acids, a one-pot reaction involving *in situ* reduction followed by esterification, both steps are mediated by trimethylamine–borane.

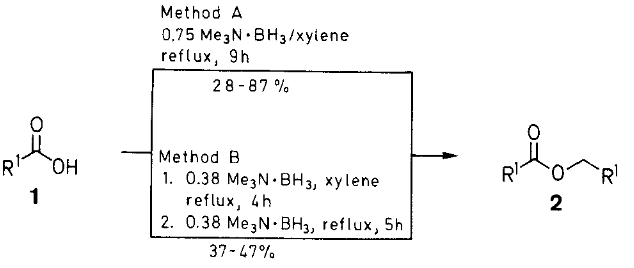
Following previous research[1] on the *N*-acylation or *N*-alkylation of amines by carboxylic acids and trimethylamine–borane, we have found that the last two reagents allow a one-pot synthesis of carboxylic esters. Thus, by refluxing a xylene solution of trimethylamine–borane, and the carboxylic acid **1** in molar ratio 1.5:2 (Method A) the formation of the corresponding ester **2** occurs in moderate to good yield (Table).

Conversion of **1** to **2** appears to be applicable both to aliphatic and aromatic carboxylic acids. Interestingly, based on the observed formation of ester **2b** and cinnamyl alcohol, the carbon–carbon double bond of the (*E*)-cinnamic acid is not affected (Table). It should be due to a reduction of the carboxylic group faster than alkene moiety hydroboration.

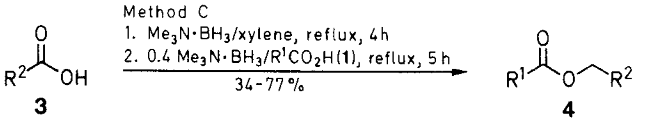
Moreover, the reaction proceeds in good yield with palmitic, 4-methoxybenzoic and 3,4-dimethoxybenzoic acid whereas with acids having an electron-withdrawing or weak electron-donating group R^1, high amounts of the corresponding alcohol together with low yields of the corresponding esters **2**, are obtained. In the latter case the yields may be slightly improved by varying the mode of addition of the trimethylamine–borane, namely 0.38 equivalents of trimethylamine–borane is added to a previously refluxed solution of trimethylamine–borane and carboxylic acid in molar ratio 0.38:1 (Method B).

These results can be interpreted assuming that the conversion of **1** to **2** proceeds by reduction of the carboxylic acid to the corresponding alcohol and its acylation via a triacyloxyborane species which is known to possess acylating properties.[2]

Esters of type **4** may also be prepared by a one-pot procedure provided that the principal two reactions mediated by trimethylamine–borane are: reduction of the carboxyl group of **3** to the corresponding alcohol and conversion of the carboxyl group of **1** to a triacyloxyborane species. This is achieved by refluxing a mixture obtained by addition of a xylene solution of trimethylamine–borane and carboxylic acid **1** in molar ratio 0.4:1 to a previously refluxed xylene solution of trimethylamine–borane and carboxylic acid **3** in molar ratio 1.1:1 (Method C).



1, 2	R^1	1, 2	R^1
a	$Me(CH_2)_{14}$	e	$4-MeOC_6H_4$
b	(*E*)-PhCH=CH	f	$4-O_2NC_6H_4$
c	Ph	g	$4-ClC_6H_4$
d	$4-MeC_6H_4$	h	$3,4-MeOC_6H_4$



4	R^1	R^2
a	Et	Ph
b	Et	$4-ClC_6H_4$
c	$Me(CH_2)_{14}$	$4-O_2NC_6H_4$
d	Ph	$4-ClC_6H_4$

By Method C the esters **4** are obtained in moderate to good yield, (Table) together with variable amounts of R^2CH_2OH. Furthermore, it is found that formation of the esters $R^2CO_2CH_2R^1$, $R^1CO_2CH_2R^1$ and $R^2CO_2CH_2R^2$ does not occurs.

Table. Carboxylic Esters **2a–h** and **4a–d** Prepared

Product	Method	Yield[a] (%)	mp[b] or bp/Torr (°C)	Molecular Formula or Lit. mp (°C), Lit. bp/Torr (°C)
2a	A	61 (22)	51–52	53–54[3]
2b	A	29 (10)	44–45	44–44.5[4]
2c	A	28 (25)	18–19	18–20[3]
2d	B	47 (5)	92/2	$C_{16}H_{16}O_2$ (240.3)
2e	A	84 (2)	47–48	47–49[5]
2f	B	37 (25)	169–171	169–170[6]
2g	A	35 (29)	70	70–72[7]
2h	A	87 (3)	94	$C_{18}H_{20}O_6$ (332.3)
4a	C	58 (25)	222/760	222[3]/760
4b	C	77 (19)	100/3	107/5[8]
4c	C	34 (29)	42–42.5	42–42.5[3]
4d	C	36 (53)	149/0.8	153/1[9]

[a] Yield of isolated pure product. Yield of isolated alcohol (R^1CH_2OH or R^2CH_2OH) are shown in parenthesis. The purity was checked by TLC analysis [silica gel, light petroleum/EtOAc (95/5) as eluent]. The products were identified by direct comparison with authentic samples and/or by their microanalytical data as well as by their IR and ^{1}H-NMR spectra.

[b] Uncorrected, measured with a Kofler apparatus.

In contrast to the currently available methods for the preparation of the esters **2** and **4** starting from carboxylic acids the above reported methods do not require the often laborious isolation of the intermediate alcohol. Moreover, taking into account that the esters **2** and **4** are easily separated from the contaminant alcohol and that the latter compound can be in turn esterified by known methods, the presently reported one-pot procedures to esters **2** and **4** by the commercially available trimethylamine–borane constitute a useful and convenient method.

Trimethylamine–borane was purchased from Fluka Chemical Col. Analytical TLC plates and silica gel (70–230 mesh) were purchased from Carlo Erba. Microanalyses were obtained using a Carlo Erba mod. 1106 analyser. IR spectra were obtained using a Perkin-Elmer 283 spectrophotometer. ^{1}H-NMR spectra were obtained using a Varian EM-390 instrument operating at 90 MHz.

Carboxylic Esters 2 and 4; General Procedures:

Method A: The carboxylic acid (**1**; 18.2 mmol) and trimethylamine–borane (0.98 g, 13.7 mmol) are refluxed in xylene (60 mL) with stirring and under N_2 for 9 h. The solvent is evaporated under reduced pressure to give a residue which is taken up in H_2O (30 mL) and the mixture made alkaline with aq 10% $NaHCO_3$. The mixture is extracted with $CHCl_3$ (2 × 30 mL), the organic layers are separated, dried (Na_2SO_4), and evaporated. The residual product is purified by column chromatography on silica gel (40 cm × 4 cm; 70–230 mesh) using light petroleum ether/EtOAc (9:1) as eluent.

4-Methylbenzyl 4-Toluate (**2d**); yield: 2.05 g (47%); bp 92°C/2 Torr.

$C_{16}H_{16}O_2$	calc.	C 79.97	H 6.71
(240.3)	found	80.10	6.58

IR (KBr): $\nu = 1720\ cm^{-1}$ (CO).

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.30$ (s, 6H, $2CH_3$), 5.26 (s, 2H, CH_2), 7.0–7.4 (m, 6H_{arom}), 7.8–8.0 (m, 2H_{arom}).

3,3-Dimethoxybenzyl 3,4-Dimethoxybenzoate (**2h**); yield: 5.25 g (87%); mp 94°C.

$C_{18}H_{20}O_6$	calc.	C 65.05	H 6.07
(332.3)	found	65.15	6.13

IR (KBr): $\nu = 1710\ cm^{-1}$ (CO).

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 3.80$ (s, 6H, $2OCH_3$), 3.84 (s, 6H, $2OCH_3$), 5.21 (s, 2H, CH_2), 6.8–7.1 (m, 4H_{arom}), 7.5–7.7 (m, 2H_{arom}).

Method B: The carboxylic acid (**1**; 18.2 mmol) and trimethylamine–borane (0.49 g, 6.9 mmol) are refluxed in xylene (60 mL) with stirring and under N_2 for 4 h. To the mixture further trimethylamine–borane (0.49 g, 6.9 mmol) is added and the heating is continued for additional 5 h. Workup is as in Method A.

Method C: The carboxylic acid (**3**; 9.1 mmol) and trimethylamine–borane (0.72 g, 10 mmol) are refluxed in xylene (60 mL) with stirring and under N_2 for 4 h.

To the mixture further trimethylamine–borane (0.27 g, 3.7 mmol) and the carboxylic acid (**1**; 9.1 mmol) are added and refluxing is continued for an additional 5 h. Workup is as in Method A.

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