Transformation of Amides into Esters by the Use of Chlorotrimethylsilane

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A mild transformation of various amides and imides into the corresponding esters and diesters in good yields by using chlorotrimethylsilane and alcohols at rt are described. Either primary, secondary, or tertiary amide or imide can be used in this transformation. Primary and secondary alcohols gave better yields than tertiary alcohols.

Keywords: Amides; Esters; Chlorotrimethylsilane; Transformation, Interconversion.

INTRODUCTION

Hydrogen halide generated *in situ* from TMSX and water is useful when HX is needed in requisite amounts and under dry reaction conditions. As a part of our program in studying the use of HX generated from TMSX,[1-3] we have found that amides can be transformed into esters in good yields. Usually, amides do not react with alcohols because the incoming alcohol nucleophile is a weaker base than the leaving group of the amide. So far, there are a few reports in the literature to bring about the transformation from amides to esters.[4-10] But, they normally involve using either gaseous HCl or strong acids at high temperature. The mild conversion of amides into esters by the use of acidic resins has been reported.[11] However, this process is specific for unsubstituted carboxamides. Thus, a new approach is still needed for this conversion. Herein, we report the scope of the transformation of various amides and imides into esters or diesters in good yields by a convenient approach as shown in Scheme I.

RESULTS AND DISCUSSION

A variety of esters obtained by the above procedure are summarized in Table 1. Thus, two equiv of alcohol and one equiv of amide were mixed first at room temperature, then the requisite amount of chlorotrimethylsilane added dropwise into the reaction mixture could give the desired esters in good to excellent yields. In this transformation, solvent is not required.

Attempts to use solvents like THF, CH_2Cl_2 and toluene resulted in poor yields even by prolonging the reaction time. No ortho-esters were found in this reaction as evidenced by ^{1}H-NMR and GC/MS analysis. Primary and secondary alcohols gave good to excellent yields. In the case of using more hindered alcohol such as *t*-butanol, we could recover only starting materials. Primary, secondary, or tertiary amide or imide can be used in this transformation. The opening of imide systems (entries 5, 6, and 7) afforded the corresponding dicarboxylic acid esters. Under the reaction conditions, a cyano group can also be transformed into ester groups to afford dialkyl malonate esters (entries 8 and 9). For entries from 4 to 9, two equiv of TMSCl and alcohol were used to generate the corresponding esters. Protonation of amides by HCl generated *in situ* from TMSCl and the alcohol followed by nucleophilic attack of another equiv of alcohol seemed to be a plausible mechanism for this transformation (Scheme II). Since the alcoholysis of amide or imide to form the esters was run under anhydrous conditions, this method can be easily applied to other moisture sensitive compounds.

In comparison with the previously reported method for the transformation of amides into the corresponding esters, our approach offers considerable advantages: (1) simplicity, (2) yields are good to excellent, (3) generate HCl gas *in situ* by the requisite amount of chlorotrimethylsilane, (4) the reaction was run at relatively low temperature, (5) can be easily

Scheme I Interconversion of amide into ester by the use of TMSCl

$$RCONR'_2 + TMSCl + 2\,R''OH \longrightarrow RCO_2R'' + \overset{+}{N}R'_2H_2\ Cl^- + TMSOR''$$

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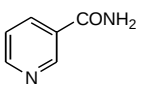
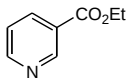
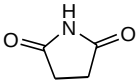
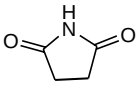
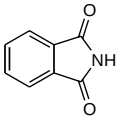
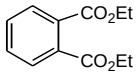
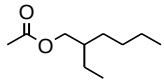
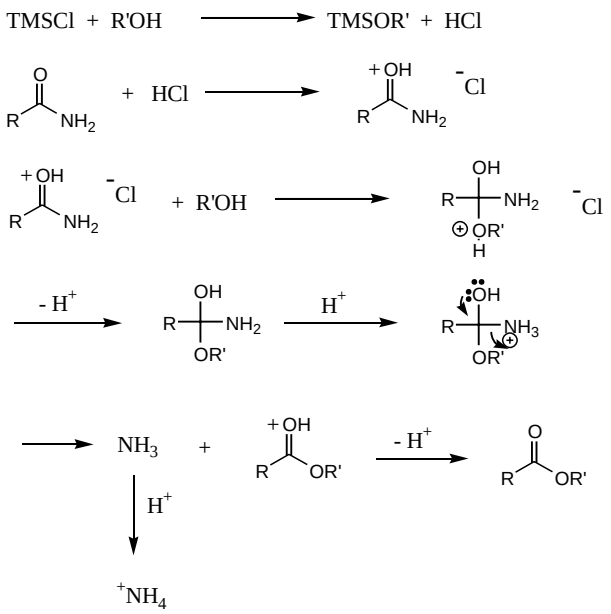
Table 1. Transformation of Amides into Esters by the Use of TMSCl and Alcohols

Entry	Amide	R″ =	Ester	Yield (%)[a]
1	$PhCONH_2$	Et-	$PhCO_2Et$	91
2	$PhCONH_2$	Me	$PhCO_2Me$	96
3	$PhCONH_2$	*i*-Pr-	$PhCO_2Pr$-*i*	73
4		Et-		86
5		Et-	$(EtO_2CCH_2)_2$	96
6		*i*-Pr-	$(i\text{-}PrO_2CCH_2)_2$	54
7		Et-		55
8	$NCCH_2CONH_2$	*i*-Pr-	$i\text{-}PrO_2CCH_2CO_2Pr$-i	76
9	$NCCH_2CONH_2$	Et-	$EtO_2CCH_2CO_2Et$	80
10	$PhCH_2CONH_2$	Et-	$PhCH_2CO_2Et$	76
11	$PhCH_2CONH_2$	*i*-Pr-	$PhCH_2CO_2Pr$-*i*	72
12	$PhCH(CH_3)CONH_2$	Et-	$PhCH(CH_3)CO_2Et$	71
13	$PhCH(CH_3)CONH_2$	*i*-Pr-	$PhCH(CH_3)CO_2$ Pr-*i*	69
14	$PhCONMe_2$	Et-	$PhCO_2Et$	60
15	$MeCONMe_2$	2-ethylhexyl		82

[a] Isolated yields with GC purity ≥ 98%. Products were characterized by comparison of their ^{1}H- and ^{13}C-NMR as well as MS spectra with those of known samples.[12-25]

Scheme II Plausible mechanism for the interconversion of amide into ester group



applied to the synthesis of various esters or diesters.

In conclusion, we have found a very mild and general method for the preparation of esters from amide in good to excellent yields by using two equiv of primary or secondary alcohols and the *in situ* generated HCl from chlorotrimethylsilane at room temperature.

EXPERIMENTAL SECTION

Amides, alcohols, and TMSCl were purchased from commercial companies. TLC was done on aluminum sheets with precoated silica gel 60 F_{254} (40 × 80 mm) from Merck. Purification by column chromatography was carried out with neutral silica gel 60 (70-230 mesh ASTM). The purity of each compound was judged by GC. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution on either a Bruker 300 MHz or 400 MHz instrument using TMS (0 ppm) and $CDCl_3$ (77.0 ppm) as internal standards. GLC analyses were performed on a Shimadzu GC-14A gas chromatograph, equipped

with a 2m × 3mm column packed with SE-30 (5% on Chromosorb W). GLC peak integrals were recorded by using a Shimadzu Chromatopac C-R3A integrator. MS spectra were determined on a Shimadzu QP-1000 spectrometer or Fisons MD800 GC/MS or VG 70-250S spectrometer. The products were characterized by comparison of their ^{1}H-NMR and ^{13}C-NMR as well as MS spectra with those of known samples.

General Procedure for the Transformation of Amides and Imides into the Corresponding Esters and Diesters by using Chlorotrimethylsilane and Alcohols

TMSCl (1.27 mL, 10 mmol) was added dropwise into the reaction mixture of benzamide (0.6 g, 5 mmol), and EtOH (2.34 mL, 40 mmol) in a dry flask under nitrogen atmosphere at room temperature. The reaction mixture was then heated to 40 °C for 5 h. Excess alcohol was distilled out under reduced pressure. After being cooled to room temperature, chloroform (15 mL) and hexane (15 mL) were added and the solution was filtered through a silica gel bed. The filtrate was concentrated at reduced pressure to afford ethyl benzoate in 91% yield and with GC purity ≥ 98%.

Selected ^{1}H-, ^{13}C-NMR, and MS spectral data of esters:

Ethyl benzoate:[12] MS (*m/z*) 150 (M^+), 122, 105, 77.

i-Propyl benzoate:[13] ^{1}H-NMR ($CDCl_3$, TMS) δ 1.38 (d, *J* = 6 Hz, 6H), 5.21-5.30 (m, 1H), 7.42 (t, *J* = 7 Hz, 2H), 7.54 (t, *J* = 7 Hz, 1H), 8.03 (d, *J* = 7 Hz, 2H) ppm; ^{13}C-NMR ($CDCl_3$, TMS) δ 21.93, 68.31, 128.23, 129.48, 131.05, 132.66, 166.11 ppm; MS (*m/z*) 164 (M^+), 123, 105.

Ethyl pyridine-3-carboxylate:[14] ^{1}H-NMR ($CDCl_3$, TMS) δ 1.42 (t, *J* = 7 Hz, 3H), 4.42 (q, *J* = 7 Hz, 2H), 7.39 (dd, *J* = 8, 5 Hz, 1H), 8.30 (d, *J* = 8 Hz, 1H), 8.77 (dd, *J* = 5, 2 Hz, 1H), 9.22 (d, *J* = 2 Hz, 1H) ppm; MS (*m/z*) 151 (M^+), 129, 106.

Diethyl butane-1,4-dioate:[15] ^{1}H-NMR ($CDCl_3$, TMS) δ 1.26 (t, *J* = 7 Hz, 6H), 2.62 (s, 4H), 4.15 (q, *J* = 7 Hz, 4H) ppm.

Di-i-propyl butane-1,4-dioate:[16] ^{1}H-NMR ($CDCl_3$, TMS) δ 1.22 (d, *J* = 7 Hz, 12H), 2.58 (s, 4H), 4.96-5.08 (m, 2H) ppm; MS (*m/z*) 202 (M^+), 143, 119, 101.

Diethyl phthalate:[17] ^{1}H-NMR ($CDCl_3$, TMS) δ 1.37 (t, *J* = 7 Hz, 6H), 4.37 (q, *J* = 7 Hz, 4H), 7.51-7.54 (m, 2H), 7.71-7.74 (m, 2H) ppm; MS (*m/z*) 222 (M^+), 177, 149.

Di-i-propyl malonate:[18] ^{1}H-NMR ($CDCl_3$, TMS) δ 1.26 (d, *J* = 7 Hz, 12H), 3.34 (s, 2H), 5.0-5.1 (m, 2H) ppm; MS (*m/z*) 173 (M^+ - Me), 129, 111, 104, 87.

Diethyl malonate:[19] ^{1}H-NMR ($CDCl_3$, TMS) δ 1.29 (t, *J* = 7 Hz, 6H), 3.37 (s, 2H), 4.22 (q, *J* = 7 Hz, 4H) ppm; MS (*m/z*) 160 (M^+), 133, 115, 88.

Ethyl 2-phenylacetate:[20] MS (*m/z*) 164 (M^+), 91.

i-Propyl 2-phenylacetate:[21] ^{1}H-NMR ($CDCl_3$, TMS) δ 1.22 (d, *J* = 6 Hz, 6H), 3.57 (s, 2H), 5.00 (m, 1H), 7.28 (m, 5H) ppm; ^{13}C-NMR ($CDCl_3$, TMS) δ 21.73, 41.70, 68.14, 126.91, 128.46, 129.15, 134.31, 171.11 ppm; MS (*m/z*) 178 (M^+), 91.

Ethyl 2-phenylpropanoate:[22] ^{1}H-NMR ($CDCl_3$, TMS) δ 1.20 (t, *J* = 7 Hz, 3H), 1.49 (d, *J* = 7 Hz, 3H), 3.68 (q, *J* = 7 Hz, 1H), 4.14 (q, *J* = 7 Hz, 2H), 7.28 (m, 5H) ppm; ^{13}C-NMR ($CDCl_3$, TMS) δ 14.09, 18.58, 45.55, 60.70, 127.02, 127.44, 128.55, 140.68, 174.54 ppm; MS (*m/z*) 178 (M^+), 105.

i-Propyl 2-phenylpropanoate:[23] ^{1}H-NMR ($CDCl_3$, TMS) δ 1.13 (d, *J* = 6 Hz, 3H), 1.21 (d, *J* = 6 Hz, 3H), 1.48 (d, *J* = 6 Hz, 3H), 3.66 (q, *J* = 6 Hz, 1H), 4.95-5.05 (m, 1H), 7.20-7.40 (m, 5H) ppm; ^{13}C-NMR ($CDCl_3$, TMS) δ 18.52, 21.53, 21.72, 45.74, 67.90, 126.93, 127.42, 128.49, 140.81, 174.05 ppm; MS (*m/z*) 192 (M^+), 105.

2-Ethylhexyl acetate:[24] ^{1}H-NMR ($CDCl_3$, TMS) δ 0.88-0.92 (m, 6H), 1.23-1.42 (m, 9H), 2.05 (s, 3H), 3.98 (d, *J* = 6 Hz, 2H) ppm; MS (*m/z*) 172 (M^+), 157, 154, 144, 112.

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