$AlCl_3$-Catalysed *trans* N-acylation of Acetanilides with α-Chloropropionyl Chloride†‡

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trans N-acylation of acetanilides with α-chloropropionyl chloride catalysed by $AlCl_3$ has been shown to occur efficiently, affording 2-chloro-*N*-phenylpropanamides in preparative yields.

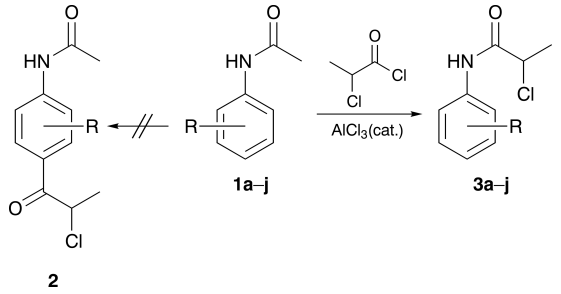
Friedel–Crafts acylation reactions of aromatic compounds with acid chlorides and anhydrides, catalysed by Lewis acids, have been extensively employed for the synthesis of aryl ketones.[1] There is growing interest in recent years in the synthesis of potential drug intermediates such as α-chloropropiophenones (**2**) as they can be readily rearranged, either photochemically[2] or by Lewis acids,[3] to α-arylpropionic acids, a class of non-steroidal and anti-inflammatory drugs.[4] In our continuing efforts to provide a practical route to Flurbiprofen, an important anti-inflammatory agent, we required *p*-amino substituted α-chloropropiophenone (**2**) as the starting material. Accordingly, when acetanilide **1** (R = H) was subjected to Friedel–Crafts acylation with α-chloropropionyl chloride in the presence of 1.1 mol of anhyd. $AlCl_3$, a polymeric material was obtained. However, when the $AlCl_3$ employed was catalytic (0.3 mol), the reaction proceeded exceedingly well to afford the *trans* N-acylated product **3** instead of the expected *p*-acylated one (**2**) (Scheme 1). In this context, it is pertinent to note that the only example of C-acylation of acetanilides was reported some time ago.[1]

trans N–acylation, in which one amide function is directly converted into another, is an important reaction, finding widespread application both in amino sugars[5] and in penicillin and cephalosporin derivatives.[6] However, a few methods of *trans* N-acylation with either acids or anhydrides at high temperatures have been reported using highly acidic catalysts such as trifluoroacetic acid–trifluoroacetic anhydride (TFAA),[6] TFAA–DBN[7] and $AlCl_3$.[8] The utility of zeolites as efficient catalysts has been recently reported by our group.[9] In view of the synthetic applications of α-chloroanilides, particularly in the synthesis of agrochemicals (as herbicides),[10] we wish to report a new catalytic method for the *trans* N-acylation of anilides with α-chloropropionyl chloride, catalysed by $AlCl_3$.

The results are summarized in Table 1. Evidently, the scope and generality of the reaction is wide; even the NO_2 group has increased the substrate reactivity (entry f). The low yield of product formation in the case of cyclohexylacetamide is due to the formation of many unidentified products.

Mechanistically, it may be reasoned that the acyl cation $MeCHClCO^+$ attacks the nitrogen of the amide preferentially to form the diacylated product **4**, which in turn equilibrates with the acetanilide, leading to the formation of the *trans* acylated product (Scheme 2). The overall low yield may be explained in terms of the reversible nature of the reaction.

These results thus establish the synthetic utility of the process toward the synthesis of a variety of *trans* N-acylated products in preparative yields in most of the examples studied. However, it may be mentioned that this method is unsatisfactory as far as aliphatic acetamides are concerned, *e.g.* cyclohexylacetamide (entry j).



Scheme 1

Experimental

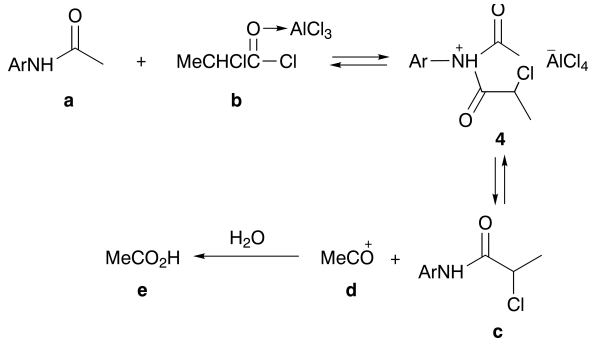
All mps are uncorrected. IR spectra were recorded on a Perkin Elmer Model 137E spectrometer. ^1H and ^{13}C NMR spectra (δ in ppm from TMS) were obtained on Varian 60 MHz, Varian FT/80A 80 MHz and Bruker FT 200 MHz spectrometers. Mass spectra were recorded on an automated Finnagan-MAT 1020C mass spectrometer.

General Procedure.—To a mixture of acetanilide (1.35 g, 10 mmol) and anhyd. $AlCl_3$ (400 mg, 3 mmol) in dichloroethane (20 ml) was added slowly α-chloropropionyl chloride (1.4 g, 11 mmol) in 5–10 min. The mixture was boiled under reflux for 16 h, cooled and decomposed with cold water. The organic layer was separated, washed with $NaHCO_3$ and H_2O and dried over anhyd. Na_2SO_4. The crude product was purified by column chromatography.

2-*Chloro*-N-*phenylpropanamide* (**3a**).—Mp 82–83 °C; ν_{max}/cm^{-1} (Nujol) 3280, 1680 (CONH), 1620, 1560, 1460, 1210, 1090, 1010, 850, 650; δ_H (80 MHz, $CDCl_3$) 1.88 (d, 3 H, CH_3 *J* 8 Hz,), 4.5 (q, 1 H, CHCl, *J* 7.5 Hz), 7.1–7.8 (m, 5 H, ArH); *m*/*z* 183 (M^+, 5%), 148 (3), 120 (100), 119 (65), 93 (85), 92 (84), 77 (19), 65 (8).

2-*Chloro*-N-(2-*methylphenyl*)*propanamide* (**3b**).—Mp 101–102 °C; ν_{max}/cm^{-1} (Nujol) 3260, 1660 (CONH), 1620, 1550, 1460, 1370, 1250, 1200, 1080, 1000, 760; δ_H (80 MHz, $CDCl_3$) 1.82 (d, 3 H, CH_3 *J* 8 Hz), 2.26 (s, 3 H, $ArCH_3$), 4.55 (q, 1 H, CHCl, *J* 6 Hz), 6.93–7.33 (m, 3 H, ArH), 7.78 (dd, 1 H, ArH , *J* 2 Hz each), 8.22 (br, 1 H, NH); *m*/*z* 197 (M^+, 4%), 134 (72), 133 (56), 107 (53), 106 (100), 105 (54), 91 (27), 90 (26), 71 (13), 63 (2).

2-*Chloro*-N-(2-*fluorophenyl*)*propanamide* (**3a**).—Mp 74–76 °C; ν_{max}/cm^{-1} (Nujol) 3260, 1680, 1550, 1500, 1460, 1370, 1300, 1250, 1000, 810, 770; δ_H (80 MHz, $CDCl_3$) 1.8 (d, 3 H, CH_3, *J* 7.5 Hz), 4.5 (q, 1 H, CHCl, *J* 8 Hz), 6.9–7.32 (m, 3 H, ArH), 8.25 (m, 1 H, ArH), 8.51 (br, 1 H, NH); δ_C (200 MHz, $CDCl_3$) 22.7, 56.2 (CH),



Scheme 2

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

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Table 1 $AlCl_3$-catalysed *trans* N-acylation of anilides with α-chloropropionyl chloride

No.	Substrates (**1**) R	Product (**3**) yield[a](%)	Mp (lit.[c])[11] (°C)
a	H	57[c]	82–83 (82)
b	2-CH_3	67	101–102 (101–102)
c	2-F	32[d]	74–76 (74–76)
d	2-Cl	33[c,d]	60–62 (62)
e	2-Br	45	73–76 (73–76)
f	2-NO_2	60	68–70 (70)
g	4-OMe	44[c]	101–102 (101–102)
h	4-Cl	68	112–114 (112)
i	4-Br	35	122–125 (124)
j	Cyclohexylacetamide	10	104 (105)

[a]Isolated after column chromatographic purification; the rest is essentially unreacted anilide. [b]20% Yield obtained in the absence of catalyst. [c]Even with the use of 2 molar equivalent of α-chloropropionyl chloride, no significant improvement in yield was realised. [d]No reaction took place in the absence of catalyst.

115.0, 115.3, 121.8, 124.7, 124.8, 125.3, 150.4 (CF), 167.7 (CO); *m*/*z* 203 (M + 2, 51%), 202 (M + 1, 12), 201 (M^+, 100), 138 (38), 111 (30), 109 (21), 90 (12), 83 (42), 63 (10).

2-*Chloro*-N-(2-*chlorophenyl*)*propanamide* (**3d**).—Mp 60–62 °C; ν_{max}/cm^{-1} (Nujol) 3260, 1670, 1600, 1540, 1450, 1200, 1060, 1000, 770; δ_H (60 MHz, $CDCl_3$) 1.88 (d, 3 H, CH_3, *J* 8 Hz), 4.56 (q, 1 H, CHCl, *J* 8 Hz), 6.88–7.44 (m, 3 H, ArH), 8.31 (d, 1 H, ArH, *J* 6 Hz), 8.88 (br, 1 H, NH); *m*/*z* 219 (M + 2, 16%), 218 (M + 1, 1), 217 (M^+, 20); 184 (27), 182 (100), 154 (39), 146 (15), 129 (20), 127 (66), 126 (55), 99 (33), 90 (20), 63 (34).

2-*Chloro*-N-(2-*bromophenyl*)*propanamide* (**3e**).—mp 73–76 °C; ν_{max}/cm^{-1} (Nujol) 3260, 1675, 1600, 1550, 1450, 1050, 770; δ_H (80 MHz, $CDCl_3$) 1.88 (d, 3 H, CH_3, *J* 7.5 Hz), 4.5 (q, 1 H, CHCl, *J* 6 Hz), 6.82–7.56 (m, 3 H, ArH), 8.25 (dd, 1 H, ArH, *J* 2 Hz each), 8.87 (br, 1 H, NH); *m*/*z* 263 (M + 2, 7%), 261 (M^+, 5), 200 (16), 198 (19), 184 (30), 182 (100), 173 (23), 172 (17), 171 (23), 170 (10), 146 (29), 119 (9), 90 (8).

2-*Chloro*-N-(2-*nitrophenyl*)*propanamide* (**3f**).—Mp 68–70 °C ν_{max}/cm^{-1} (Nujol) 3360, 1700, 1610, 1600, 1510, 1350, 810, 760; δ_H (60 MHz, $CDCl_3$) 1.76 (d, 3 H, CH_3, *J* 8 Hz), 4.4 (q, 1 H, CHCl, *J* 7.5 Hz), 6.73–8.0 (m, 4 H, ArH), 10.45 (br, 1 H, NH); *m*/*z* 230 (M + 2, 15%), 229 (M + 1, 5), 228 (M^+, 46), 184 (31), 182 (100), 165 (47), 145 (23), 138 (76), 121 (41), 92 (29), 91 (36), 90 (29), 65 (25), 63 (50).

2-*Chloro*-N-(4-*methoxyphenyl*)*propanamide* (**3g**).—Mp 101–102 °C; ν_{max}/cm^{-1} (Nujol) 3280, 1670, 1560, 1520, 1400, 1260, 950, 850; δ_H (60 MHz, $CDCl_3$) 1.76 (d, 3 H, CH_3, *J* 8 Hz), 3.75 (s, 3 H, OCH_3), 4.43 (q, 1 H, CHCl, *J* 7 Hz), 6.75 (d, 2 H, ArH, *J* 10 Hz), 7.26 (d, 2 H, ArH, *J* 10 Hz); 8.0 (br, 1 H, NH); δ_C (200 MHz, $CDCl_3$) 22.6, 55.6, 56.1, 114.3, 122.2, 130.2, 157.2, 167.7; *m*/*z* 215 (M + 2, 15%), 214 (M + 1, 5), 213 (M^+, 52), 178 (8), 150 (20), 123 (52), 122 (100), 108 (47), 95 (13), 63 (8).

2-*Chloro*-N-(4-*chlorophenyl*)*propanamide* (**3h**).—Mp 112–114 °C; ν_{max}/cm^{-1} (Nujol) 3220, 1650, 1580, 1520, 1480, 1385, 1220, 1180, 1080, 1060, 800, 820; δ_H (80 MHz, $CDCl_3$) 1.82 (d, 3 H, CH_3, *J* 7.5 Hz), 4.5 (q, 1 H, CHCL, *J* 6 Hz), 7.25–7.5 (AB quartet, 4 H, ArH, *J* 10 Hz), 8.25 (br, 1 H, NH); *m*/*z* 219 (M + 2, 70%), 218 (M + 1, 10), 217 (M^+, 98), 182 (10), 156 (32), 154 (100), 129 (29), 127 (77), 126 (29), 99 (8).

2-*Chloro*-N-(4-*bromophenyl*)*propanamide* (**3i**).—Mp 122–125 °C; ν_{max}/cm^{-1} (Nujol) 3230, 1675, 1600, 1550, 1500, 1410, 1310, 1250, 1200, 1085, 1020, 820; δ_H (80 MHz, $CDCl_3$) 1.81 (d, 3 H, CH_3, *J* 7.5 Hz), 4.5 (q, 1 H, CHCl, *J* 6 Hz), 7.44 (s, 4 H, ArH), 8.25 (br, 1 H, NH); *m*/*z* 265 (M + 4, 26%), 263 (M + 2, 100), 261 (M^+, 90), 200 (75), 198 (80), 173 (94), 172 (50), 171 (96), 170 (41), 147 (5).

2-*Chloro*-N-*cyclohexylpropanamide* (**3j**).—Mp 104 °C; ν_{max}/cm^{-1} (Nujol) 3250, 1640, 1550, 1450, 1370; δ_H (80 MHz, $CDCl_3$) 1.25–2.15 (m, 10 H, cyclohexyl CH_2), 1.88 (d, 3 H, CH_3, *J* 8 Hz), 3.81 (br, 1 H, CHNH), 4.5 (q, 1 H, CHCl, *J* 7 Hz), 6.56 (br, 1 H, NH).

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References

1 *Friedel–Crafts and Related Reactions*, ed. G. A. Olah, Wiley–Interscience, New York, 1963, p. 65; H. Heaney in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, New York, 1991, vol. 2, p. 733.
2 H. R. Sonawane, D. G. Kulkarni and N. R. Ayyangar, *Tetrahedron Lett*., 1990, **31**, 7495.
3 C. Giordano, G. Castaldi, F. Casagrande and L. Abis, *Tetrahedron Lett*., 1982, **23**, 1385; G. Giordano, G. Castaldi, F. Uggeri and F. Gurzoni, *Synthesis*, 1985, 436.
4 H. R. Sonawane, B. S. Nanjundiah, J. R. Ahuja and D. G. Kulkarni, *Tetrahedron: Asymmetry*, 1992, **3**, 163; J. P. Rieu, A. Boucharle, H. Cousse and G. Mouzin, *Tetrahedron*, 1986, **42**, 4095.
5 C. Erbing, K. Granath, L. Kenne and B. Lindberg, *Carbohydr. Res*., 1976, **47**, C5.
6 A. G. M. Barrett, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1629.
7 B. Nilsson and S. Svensson, *Carbohydr. Res*., 1978, **62**, 377.
8 M. Michman, S. Patai and I. Shenfield, *J. Chem. Soc. C*, 1967, 1337; M. Michman and D. Meider, *J. Chem. Soc. Perkin Trans. 2*, 1972, 300.
9 H. R. Sonawane, A. V. Pol, P. P. Moghe, A. Sudalai and S. S. Biswas, *Tetrahedron Lett*., 1994, **35**, 8877.
10 K. Kobayashi and S. Yamagiwa, *Jpn. Kokai Tokkyo Koho*, 1990, JP 02,225,648 (*Chem. Abstr*., 1991; **114**, 142 892p); T. Yoshimoto, K. Igarashi and Y. Takasawa, *CHEMTECH*, 1989, **19**, 431; H. Yang, X. Li, Z. Zhang and M. Chang, *Chem. Abstr*., 1993, **119**, 8873h.
11 G. Snatzke and M. M. El-Abadelah, *Chem. Ber*., 1973, 106, 2072.