Tetrahedron Vol. 48, No. 42, pp. 9233-9236, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00
Pergamon Press Ltd

Magnesium Chloride Catalysed Acylation Reaction

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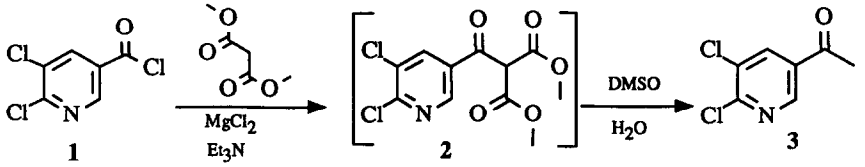
(*Received in Germany* 12 *May* 1992)

Abstract: An efficient and practical preparation of methyl ketones, *via* a magnesium chloride catalysed acylation reaction of dimethyl malonate with acid chlorides in the presence of tertiary base and followed by a decarbmethoxylation reaction, is described.

In 1985, Rathke and co-workers[1] reported a convenient single-step acylation procedure of diethyl malonate or ethyl-acetoacetate with acid chlorides, in which one equivalent of magnesium chloride was employed to complex the carbonyl functionality of these carbon acids in order to enhance their acidity to the point that triethylamine or pyridine could be used as a mild and non-destructive base. Unlike others, this procedure gives a high yield of tricarbonyl-product with significant advantages in cost and simplicity of operation, and has received much attention in the chemical industry.

In connection with our interest in the preparation of 1-(5,6-dichloropyridin-3-yl)ethanone[2] **3** from 5,6-dichloronicotinic acid chloride **1**,[3] a key intermediate for the synthesis of a number of potentially active animal growth promotors,[4] we considered extending this attractive acylation procedure to synthesise **3** via a decarbmethoxylation of the acyl malonate **2** (Table 1).

Table 1 The influence of the amount of magnesium chloride on the yield of 3



Entry	1	2	3	4	5	6	7	8	9	10
$MgCl_2$ [a] (equivalents)	1.18	1.0	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0.0
Yield (%) [b] **3**	79.6	91.9	91.6	92.8	86.6	83.7	70.4	54.0	45.0	0.0

a) Purchased from Aldrich Chemical Company and was used directly without further purification

b) The overall yield (on a 0.5 mole scale) after both acylation and decarbmethoxylation

Thus, 5,6-dichloronicotinic acid chloride **1** was treated with triethylamine (2 equivalents), $MgCl_2$ (1.18 equivalents)[2] and dimethyl malonate (1 equivalent) in CH_2Cl_2/CH_3CN and afforded crude **2**, which was subjected to the decarbmethoxylation in wet dimethyl sulfoxide at 150-160°C to provide **3** in ca. 80% yield (Table 1, Entry 1). During our optimization of the acylation step, we were however confronted by the environmental problem associated with the salt waste produced from the acylation reaction. In order to reduce the large amount of salt waste, we considered a possible catalytic role of $MgCl_2$ in the acylation reaction using the preferable toluene as the solvent (Table 1, Entries 2-10), and initiated a study directed towards this goal. First of all, we examined the effect of the amount of $MgCl_2$ (0.1-1.0 equivalent) on the overall yield of **3** from **1**, the result of which is summarised in Table 1. An excellent overall yield (ca. 84-93%) was obtained when 0.4-0.7 equivalents of $MgCl_2$ were used (Entries 3-6), but the yield of **3** dropped slightly to ca. 70% with 0.3 equivalents of $MgCl_2$ (Entry 7). Interestingly enough, in the presence of as little as 0.1-0.2 equivalents of $MgCl_2$ (Entries 8-9), a modest overall yield (ca. 45-54%) of **3** was also achieved. In the absence of $MgCl_2$, however, no product **2** was isolated (Entry 10).

The catalytic role of $MgCl_2$ can be rationalised as depicted in Figure 1, by proposing a cycle in which chelation with the carbonyl functionality of dimethyl malonate, complex **4**, occurs. This then reacts with the acid chloride via its enolate **5** to provide **6**. It is reasonable to suggest that the $MgCl_2$ also formed then reenters the catalytic cycle. A ^{1}H-NMR study was conducted to provide evidence for the formation of the magnesium enolate of dimethyl malonate[5] **5** under the reaction conditions. Thus, addition of $MgCl_2$ (0.1-1.0 equivalent) to the triethylamine (1 equivalent)-dimethyl malonate (1 equivalent) solution resulted in a heterogeneous mixture which was filtered and gave a solid identified as a mixture of triethylamine hydrochloride (^{1}H-NMR) and $MgCl_2 \cdot 6\ H_2O$ (X-ray diffraction). The ^{1}H-NMR spectra (in C_7D_8) of the filtrate showed triethylamine hydrochloride. In addition, the complexation of $MgCl_2$ with dimethyl malonate was identified by the downshifting of the methylene protons of the dimethyl malonate, for example from 3.05 to 3.33 ppm with 0.3 equivalents of $MgCl_2$.

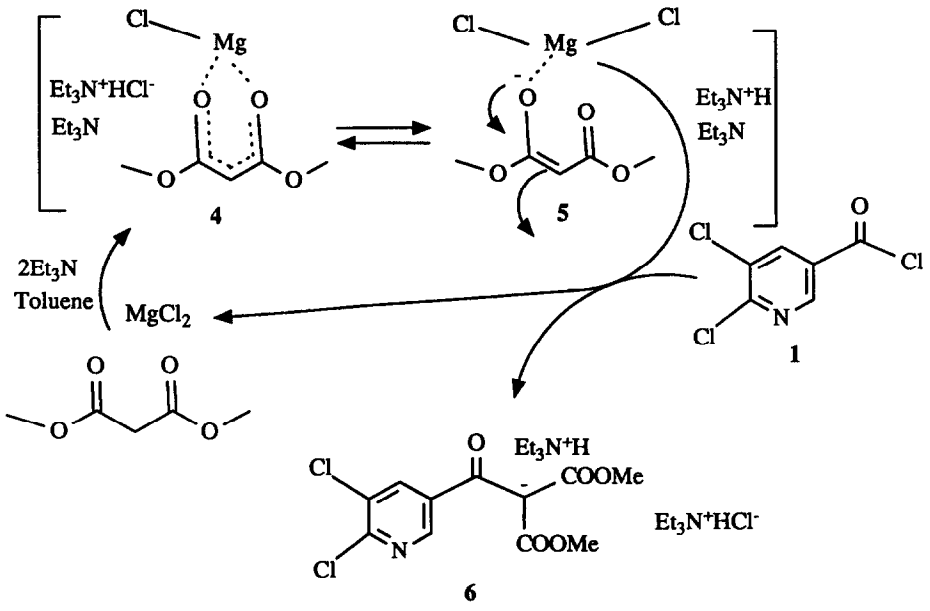
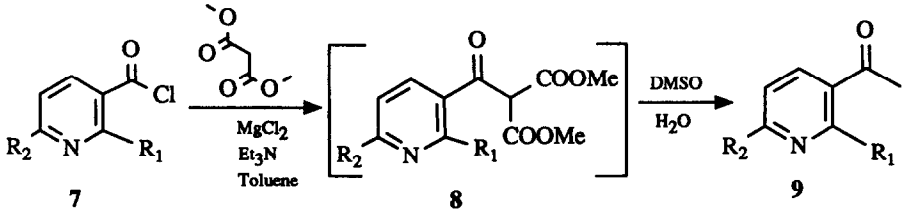


Figure 1. The proposed catalytic cycle of Magnesium chloride in the acylation reaction

As part of further development of this concept, we have extended our refined procedure as a general acylation reaction and have tested it with other acid chlorides[6] such as nicotinic acid chloride **7a**, 6-chloronicotinic acid chloride **7b**, and 2-chloronicotinic acid chloride **7c** (Table 2), and obtained the corresponding ketones **9a**, **9b**, and **9c** in very good overall yield (not optimized).

Table 2 Some applications of the refined acylation reaction [a)]



7	a	b	c
R_1	H	H	Cl
R_2	H	Cl	H
Yield (%) [b)] **9**	65-70	91.7	85.6

a) 0.7 equivalent of $MgCl_2$, and 2.0 equivalents of triethylamine in toluene.

b) The overall yield after both acylation and decarbmethoxylation reactions

In addition to the advantages mentioned earlier, this novel application of $MgCl_2$-catalysed acylation reaction also facilitates a smoother stirring in such a concentrated heterogeneous reaction mixture, provides a high overall yield of the desired ketones after the decarbmethoxylation reaction, and moreover, it allows a substantial reduction of salt waste produced from the reaction. The scope and limitation of this concept will be further explored in our laboratory.

Experimental

General. Melting points were determined on a Büchi apparatus, and are reported uncorrected. ^{1}H-NMR spectra were obtained on a Nicolet NT 300 (300 MHz) or Varian Unity 400 (400 MHz) instrument using deuterchloroform solvent and tetramethylsilane internal standard. Mass spectra were recorded on a Finnegen 4021 instrument.

Typical procedure for the preparation of 1-(5,6-dichloropyridin-3-yl)ethanone 3

Triethylamine (Fluka Chemical Company, 122.1 g, 1.20 mol), followed by dimethyl malonate (Lonza Ltd., 79.30 g, 0.60 mol) were added to a 1.5 liter round-bottom flask containing magnesium chloride (Aldrich Chemical Company, 34.04 g, 0.35 mol) in dry toluene (401 mL). The resulting gray and heterogeneous mixture was stirred at 25°C for 1 hour before a solution of 5,6-dichloronicotinicacid chloride **1** (Lonza Ltd., 108.1 g, 0.50 mol) in toluene (64 mL) was slowly introduced over a period of 30 minutes. The reaction mixture immediately turned pink-red. Stirring was continued for 20 minutes before conc. HCl (174.0 g, 1.54 mol) was carefully added to quench the reaction. After work-up, it gave crude dimethyl(5,6-dichloronicotinoyl)malonate **2** (160.1 g) which was directly treated with dimethyl sulfoxide (Fluka Chemical Company, 500 mL), and water

(18.01 mL). The mixture was heated at 155° C for ca. 2 hours and cooled. It was then worked up to provide the desired **3** (87.03 g) in 91.6% overall yield from **1**. Mp 84-85°C; (lit.[2] mp 80°C); ^{1}H-NMR (300 MHz, $CDCl_3$): 2.65 (s, 3H), 8.30 (d, 1H, J = 2.5 Hz), 8.81 (d, 1H, J = 2.5 Hz); Mass spectrum (relative intensity): 190 (M^+, 36), 148 (18), 112 (22), 43 (100).

Other methyl ketones were prepared also similar to the typical procedure:

9a: Yield 65-70%. Bp 92.5-93°C (15.0 mmHg); (lit.[7] bp 219-221°C, 760 mmHg); ^{1}H-NMR (300 MHz, $CDCl_3$): 2.66 (s, 3H), 7.43 (dd, 1H, J = 5, 7.5 Hz), 8.25 (dt, 1H, J= 2.5, 7.5 Hz), 8.80 (dd, 1H, J = 1.25, 2.5 Hz), 9.19 (d, 1H, J = 1.25 Hz). Mass spectrum (relative intensity): 121 (M^+, 52), 106 (90), 78 (100), 51 (47), 43 (35).

9b: Yield 91.7%. Mp 102-103°C; lit.[8] mp 104°C; ^{1}H-NMR (400 MHz, $CDCl_3$): 2.61 (s, 3H), 7.44 (d, 1H, J = 10 Hz), 8.20 (dd, 1H, J = 5, 10 Hz), 8.95 (s, 1H); Mass spectrum (relative intensity): 155 (M^+, 19), 140 (68), 112 (45), 76 (33), 50 (65), 43 (100).

9c: Yield 85.6%. Bp 112-113.5°C (15.0 mmHg); (lit.[9] bp 83°C, 1.0 mmHg); ^{1}H-NMR (400 MHz, $CDCl_3$): 2.64 (s, 1H), 7.38 (dd, 1H, J = 4.7, 4.7 Hz), 7.93 (dd, 1H, J = 1.9, 7.7 Hz), 8.49 (dd, 1H, J = 1.9, 4.7 Hz); Mass spectrum (relative intensity): 155 (M^+, 25), 140 (100), 114 (16), 112 (50).

Acknowledgements: Mr. Edwin Vogel and Miss Susan Aufdenblattens' assistance in the laboratory, and Dr. M. Hauck and Dr. M. Bokels' analytical services are gratefully acknowledged, and I thank Lonza Ltd. for the permission to publish this work.

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