SHORT REPORTS

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ACYLATION OF 2-ARYL-2-DIMETHYLAMINOACETONITRILES. SIMPLE SYNTHESES OF UNSYMMETRICAL α -DICARBONYL COMPOUNDS AND α KETOESTERS

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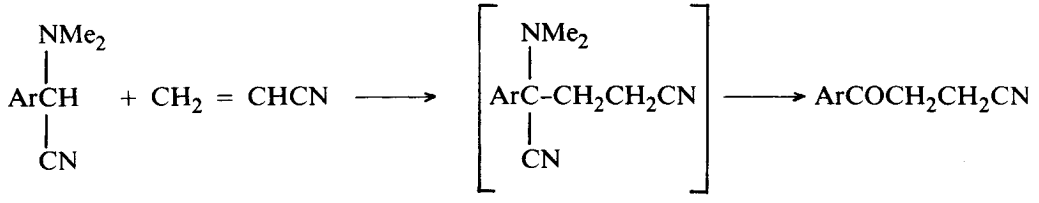
Abstract

Reactions of 2-lithio anions derived from 2-aryl-2-dimethylaminoacetonitriles with acyl halides or ethyl chloroformate followed by hydrolysis with copper (II) sulfate in 95% ethanol provide convenient syntheses of various unsymmetrical α -diketones and α -ketoesters, respectively.

It has been demonstrated that carbanions derived from α -aminonitriles are valuable intermediates in a range of organic syntheses[1-6]. In particular, we reported[2] that addition of 2-aryl-2-dimethylaminoacetonitriles (1) to acrylonitrile followed by hydrolysis of the product (2) with copper (II) sulfate in 95% ethanol gave good yields of the corresponding 3-aroylpropio-nitriles (3) (Scheme I).

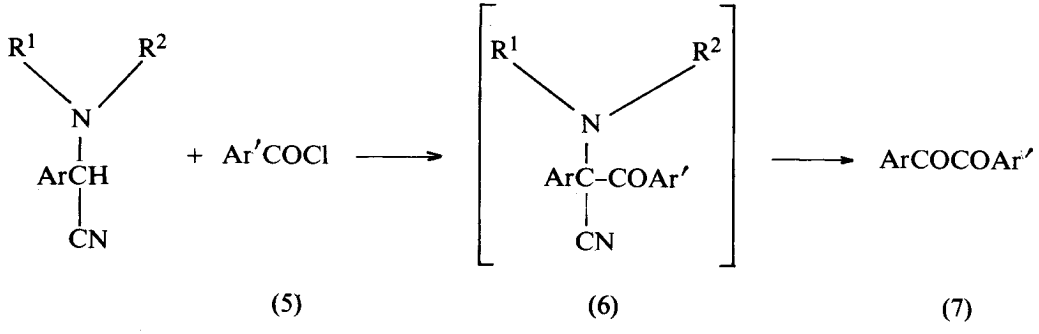
Scheme I



(1) (2) (3)

Similar results were obtained subsequently by McEvoy and Albright[3] who employed the corresponding 2-aryl-2-(N-morpholino)-acetonitriles (4). These authors[3] also investigated the acylation of the anion derived from (4) with aroyl halides (5) (Scheme II) and showed that in two cases hydrolysis of the adducts (6) with acetic acid gave moderate yields (31-50%) of the substituted benzils (7).

Scheme II



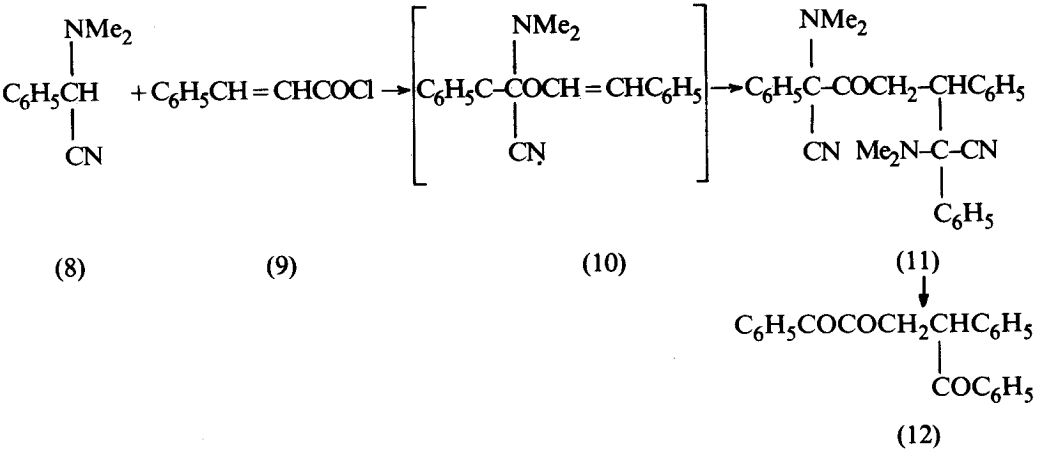
(5) (6) (7)

(4) $R^1, R^2 = -CH_2CH_2OCH_2CH_2-$
(1) $R^1 = R^2 = Me$

We had also been working along similar lines and now report that acylation of the 2-lithio anion derived from 2-aryl-2-dimethylaminoacetonitriles (1) with benzoyl chloride [(5), $Ar' = C_6H_5$] followed by hydrolysis of the condensation product (6) with copper (II) sulfate in 95% ethanol usually gave moderate to good yields (43-75%) of the unsymmetrical benzils (7). Several 2-aryl-2-dimethylaminoacetonitriles (Table 1) were examined and the reaction failed only in one case; no 4-nitrobenzil could be obtained by this method. The results are collected in Table 2.

It was also found that treatment of the 2-lithio anion derived from 2-phenyl--2-dimethylamino-acetonitrile (8) with cinnamoyl chloride (9) followed by hydrolysis yielded 1,4,5-triphenylpentane-1,2,5-trione (12). Presumably formation of (12) involves Michael addition of (8) to the α, β,unsaturated carbonyl system of the adduct (10) to yield (11), prior to hydrolysis as set out in Scheme III.

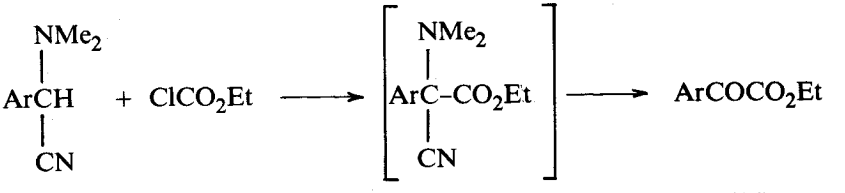
Scheme III



(8) (9) (10) (11) (12)

McEvoy and Albright[3] also showed that 2-(4′-chlorophenyl)-2-(*N*-morpholino)-acetonitrile [(4) Ar = 4-ClC_6H_4-] reacted with ethyl chloroformate to yield ethyl 2-(4′-chlorophenyl)-2-cyano-2-(N-morpholino)-acetate in high yield (94% crude) but they did not investigate the hydrolysis of this substance. We have studied the acylation of several 2-lithio anions derived from 2-aryl-2-dimethylaminoacetonitriles (1) with ethyl chloroformate and have found that hydrolysis of the condensation products (13) with copper (II) sulfate in 95% ethanol gives the corresponding α-ketoesters (14) in moderate to good yields (30-83%) (Scheme IV). The results are collected in Table 3.

Scheme IV



(4) (13) (14)

It has also been found during this work that acylation of the 2-lithio anion derived from 2-phenyl-2-dimethylamino-acetonitrile (8) with methyl chloroglyoxylate, followed by the hydrolysis of the condensation product with copper (II) sulfate in 95% ethanol provides a convenient method for the preparation of the sensitive methyl 3-phenyl-2,3-dioxopropanoate (15).

$C_6H_5COCOCO_2CH_3$

(15)

TABLE 1

PREPARATION OF 2 - ARYL - 2 - DIMETHYLAMINOACETONITRILES (1)

(1), Ar =	Yield %	Bp°C/mm Hg	NMR ($CDCl_3$, δ)	Ref.
Phenyl	78	98-99/2.0	2.29,s,6H; 4.85,s,1H; 7.40, m,5H.	7
4-Methoxyphenyl	76	130-131/2.0	2.29,s,6H; 3.82,s,3H; 4.80, s,1H; 6.90,d,J 9Hz,2H; 7.42,d,J 9Hz,2H. Found: C,69.6; H,7.6 Calc. for $C_{11}H_{14}N_2O$: C,69.5; H,7.7.	8
3-Methoxyphenyl	73	98-99/0.2	2.29,s,6H; 3.82,s,3H; 4.83, s,1H; 6.65-7.39,m,4H.	-
3,4-Methylenedioxyphenyl	93[a]	Mp.67-68°C	2.30,s,6H; 4.80,s,1H; 6.00, s,2H; 7.15-7.75,m,3H. Found: C,64.7; H,5.9 $C_{11}H_{12}N_2O_2$ requires: C, 64.7; H,5.9.	
4-Chlorophenyl	86	92-93/0.6	2.30,s,6H; 4.80,s,1H; 7.42, m,4H; Found: C,61.8; H, 5.5 Calc. for $C_{10}H_{11}N_2Cl$: C,61.7; H,5.7.	8
2-Chlorophenyl	79	82-83/0.3	2.30,s,6H; 5.05,s,1H; 7.35, m,4H.	-
4-Nitrophenyl	72	124-125/0.03	3.25,s,6H; 5.40,s,1H; 7.60, d,J 8Hz,2H; 8.18,d,J 8Hz, 2H.	
2-Furyl	69	40-50/0.05	2.32,s,6H; 4.90,s,1H; 6.40-7.00,m,3H.	-

[a] Product was recrystallized from benzene: hexane 1:1.

TABLE 2

PREPARATION OF UNSYMMETRICALLY SUBSTITUTED BENZILS

AR - C(=O) - C(=O) - AR′ (7) ACCORDING TO SCHEME II

(7) Ar′ = Ph; Ar =	Yield %	Mp.°C	NMR ($CDCl_3$, σ)	Ref.
Phenyl	62[a]	94–95	7.47–7.75,m,6H; 8.00,dd, J 2,8Hz,4H.	9
4-Methoxyphenyl	69[a]	61–62	3.80,s,3H; 6.96,d,J 8Hz, 2H; 7.20–7.71,m,3H; 7.94, J 2,8Hz,4H.	10
3-Methoxyphenyl	74[a]	59–60	3.80,s,3H; 7.20–7.71,m,6H; 7.94,dd,J 2,8Hz,2H.	11
3,4-Methylenedioxyphenyl	75[a]	178–180	6.10,s,2H; 6.88,d,J 8Hz, 1H; 7.39–7.72,m,4H; 8.00, dd,J 2,8Hz,3H.	-
4-Chlorophenyl	63[a]	78–79	7.42–7.75,m,5H; 7.87–8.15, m,4H.	11
2-Chlorophenyl	72[b]	Bp.133/ 0.05 mm	7.31–7.75,m,6H; 7.75–8.19, m,3H.	
4-Nitrophenyl	-	-	-	-
2-Furyl	42[b]	Bp.145/ 0.05 mm	6.60,dd,J 4,4Hz,1H; 7.30–7.57,m,4H; 7.67,dd,J 2, 8Hz,1H; 8.04,dd,J 2,8Hz, 2H.	-

[a] Products were recrystallized from aqueous ethanol.

[b] Products were puribied by preparative layer chromatography (Merck silica gel PF_{254}) using chloroform as eluting solvent.

TABLE 3

PREPARATION OF α - KETOESTERS $ArC(=O)-C(=O)OCH_2CH_3$ ACCORDING TO SCHEME IV

(14), Ar =	Yield %	Bp°C/mm	NMR ($CDCl_3$, σ)	Ref.
Phenyl	60[a]	122/0.01	1.42,t,J 7Hz,3H; 4.48,q, J 7Hz,2H; 7.60-8.10,m,5H.	12
4-Methoxyphenyl	73[a]	124-126/ 0.01	1.32,t,J 7Hz,3H; 3.80,s, J 7Hz,2H; 4.38,q,J 7Hz, 2H; 7.03,d,J 8Hz,2H; 8.07, d,J 8Hz,2H.	13
3-Methoxyphenyl	60[a]	108-110/0.01	1.43,t,J 7Hz,3H; 3.77,s,3H; 4.38,q,J 7Hz,2H; 7.07-7.67, m,4H; Found: C,63.5; H,5.8 $C_{11}H_{12}O_4$ requires: C 63.5; H,5.8.	-
3,4-Methylenedioxyphenyl	30[a]	163-164/0.01	1.45,t,J 7Hz,3H; 4.47,q, J 7Hz,2H; 6.10,s,2H, 6.90, d,J 8Hz,1H; 7.50,d,J 2Hz, 1H; 7.60,dd,J 2,8Hz,1H.	-
4-Chlorophenyl	83[a]	Mp. 145-147	1.40,t,J 7Hz,3H; 4.47,q, J 7Hz,2H; 7.50,dd,J 2,8Hz, 2H; 8.00,d,J 8Hz,2H.	14
2-Chlorophenyl	59[a]	Mp.124-125	1.49,t,J 7Hz; 4.42,q,J 7Hz, 2H; 7.34-8.07,m,4H.	15
4-Nitrophenyl	36[a]	172-173/0.05	1.36,t,J 7Hz,3H; 4.35,q, J 7Hz,2H; 7.67,d,J 8Hz, 2H; 7.95,d,J 8Hz,2H.	16
2-Furyl	29[a]	78-79/0.03	1.41,t,J 7Hz,3H; 4.42,q, J 7Hz,2H; 6.66,m,1H; 7.74, m,2H.	17

[a] Products were purified by preparative layer chromatography using chloroform as eluent.

Analyses were carried out by the Australian Microanalytical Service, Melbourne. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Nuclear magnetic resonance (n.m.r.) spectra were recorded on either a Varian EM360L or A60D instrument at 60MHz. The mass spectra were measured with a Dupont 490F GC–MS instrument by direct inlet.

Preparation of 2 - aryl - 2 - dimethylaminoacetonitrile (1) [Table 1].

The arylaldehyde (0.1 mole) in a minimum volume of methanol was added over 1 hour to a solution of dimethylamine hydrochloride (0.12 mole) and potassium cyanide (0.12 mole) in water (50 ml). After the addition was completed, the mixture was stirred at room temperature for 4 hours, quenched with water (400 ml) and extracted with ether (3 × 100 ml). The combined ether extracts were washed with saturated sodium metabisulphite solution (3 × 50 ml) and water (3 × 100 ml). After drying over magnesium sulphate, the ether solution was filtered and the filtrate was evaporated to afford the crude 2-aryl-2-dimethylaminoacetonitrile which was further purified by either vacuum distillation or recrystallization.

Preparation of benzil [Table 2].

The 2-lithio-2-aryl-2-dimethylaminoacetonitrile was generated by slowly adding a solution of 2-aryl-2-dimethylaminoacetonitrile (5.0 mmole) in anhydrous tetrahydrofuran (5.0 ml) to a stirred solution of lithium diisopropylamide (7.5 mmole, generated by the reaction of equimolar of *n*-butyllithium and diisopropylamine in anhydrous tetrahydrofuran) in anhydrous tetrahydrofuran (50 ml) under nitrogen at -78°C. The solution was stirred for 30 minutes before the dropwise addition of the aroyl chloride (1.05 g; 7.5 mmole). The reaction mixture was stirred for 3 hours at -78°C and then 30 minutes at room temperature, quenched with saturated aqueous ammonium chloride (10 ml) and extracted into chloroform (3 × 100 ml). The combined chloroform extracts were washed with 2N hydrochloric acid (3 × 50 ml) and water (3 × 100 ml). After drying with anhydrous sodium sulphate, the chloroform was evaporated and the residue was hydrolyzed with $CuSO_4.5H_2O$ (12.5 mmole, 2.5 equiv.) in absolute ethanol (30 ml) and water (5 ml) under reflux for 4 hours. The cooled solution was extracted with chloroform (3 × 100 ml) and the combined chloroform extracts were washed with saturated sodium metabisulphite solution (3 × 75 ml), water (3 × 100 ml) and then dried over sodium sulphate. The solvent was removed on a rotary evaporator and the residue was purified by either recrystallization (for solids) or preparative layer chromatography (for liquid).

Preparation of α- ketoester [Table 3].

Ethyl chloroformate (2.16 g; 20.0 mmole) was slowly added to a stirred solution of 2-lithio-2-aryl-2-dimethylaminoacetonitrile (15.0 mmole; in 50 ml anhydrous tetrahydrofuran), generated as described previously, at -78°C under nitrogen. The

reaction mixture was stirred for 3 hours at this temperature and then quenched with saturated aqueous ammonium chloride. The aqueous solution was extracted with chloroform (3 × 100 ml), the combined chloroform extracts were washed with 2N hydrochloric acid (3 × 50 ml) and water (3 × 100 ml). The organic layer was dried with sodium sulfate and evaporated under reduced pressure. The residue was hydrolyzed with $CuSO_4.5H_2O$ (25.0 mmole; 2.5 equiv.) in absolute ethanol (30 ml), water (5 ml) under reflux for 4 hours. The cooled solution was worked up as described previously. The crude product was purified by preparative layer chromatography.

Preparation of 1, 4, 5 - triphenylpetane - 1, 2, 5 - trione (12).

Cinnamoyl chloride (1.0 g; 6.0 mmole) in anhydrous tetrahydrofuran (2 ml) was slowly added to a stirred solution of 2-lithio-2-phenyl-2-dimethyl-aminoacetonitrile (0.8 g; 5.0 mmole) in anhydrous tetrahydrofuran (30 ml), prepared by the method as described previously, at -78°C under nitrogen. The reaction mixture was stirred at this temperature for 3 hours and then at room temperature for 30 minutes before being quenched with saturated aqueous ammonium chloride. The aqueous solution was worked up as before and the product was hydrolyzed with $CuSO_4.5H_2O$ in the usual manner. The crude product was purified by preparative layer chromatography using chloroform as an eluent to give a yellow wax in 31% yield. ν_{max} (nujol) 2920, 1710, 1650, 1200 cm^{-1}. N.m.r. ($CDCl_3$): δ 3.25(dd, 1H, J 5, 18 Hz, -CO-C*H*$_2$-CHCO); 3.90 (dd, 1H, J 10, 18 Hz, -COC*H*$_2$CH-CO); 5.21, dd, 1H, J 5, 10 Hz); 7.40-8.17 (m, 15H, Ar*H*). Mass spectrum m/e 342 (1%), 237(65), 219(15), 131(18), 105(100), 77(96).

Preparation of methyl 3 - phenyl - 2, 3 - diketo - propanoate (15).

Methyl chloroglyoxylate (0.92 g; 7.5 mmole) in anhydrous tetrahydrofuran was slowly added to a stirred solution of 2-lithio-2-phenyl-2-dimethylaminoacetonitrile in anhydrous tetrahydrofuran, generate by the method described previously, at -78°C under nitrogen. The reaction mixture was stirred at this temperature for 3 hours before being quenched with saturated aqueous ammonium chloride. The aqueous solution was worked up with chloroform and the product was hydrolyzed with $CuSO_4.5H_2O$ in the usual way. The crude product was purified by preparative layer chromatography using chloroform as an eluent to give a yellow liquid (26% yield). ν_{max} (neat), 2980, 1740, 1690, 1220 cm^{-1}. N.m.r. ($CDCl_3$) 3.90 (s, 3H, C*H*$_3$O-); 7.35-8.18 (m, 5H, Ar*H*); Mass spectrum m/e 210 (2%), 139 (8), 105 (100), 77 (40).

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บทคัดย่อ

ได้สังเคราะห์ unsymmetrical α- dicarbonyl compounds และ α - ketoesters จาก ปฏิกิริยา acylation ของ 2 - lithio - 2 - aryl - 2 - dimethylamino - acetonitriles.