[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES, MONSANTO CHEMICAL COMPANY]

The Knoevenagel Condensation of Aryl Alkyl Ketones with Malononitrile

BY DAVID T. MOWRY

The ammonium acetate–acetic acid catalyzed condensation of acetophenone with malononitrile[1] in refluxing benzene solution was observed to proceed at a convenient and reproducible rate, the theoretical amount of water being removed in twelve hours. Furthermore, the rate of reaction was not markedly affected by small changes in catalyst concentration. Since a number of related compounds were desired for work in progress in these laboratories, the relative rates of reaction of various aryl alkyl ketones with malononitrile were measured in an attempt to qualitatively correlate structure with reactivity.

Substitution of the para hydrogen by groups such as phenyl, nitro or alkoxy group has a pronounced activating effect. Such negative or unsaturated substituents would be expected to promote the dehydration of intermediate hydroxy compound[2] from addition of malononitrile to the carbonyl group.

A considerable increase in the rate of reaction of the *p*-alkylacetophenones was noted as the chain was branched increasingly in the α-position. Thus *p*-isopropylacetophenone and *p*-*t*-butylacetophenone reacted two to three times as rapidly as the *p*-methyl and *p*-ethyl compounds. Substitution of the α-thienyl nucleus for the phenyl radical promoted the speed of condensation.

Lengthening the alkyl chain in the aryl alkyl ketone slightly lowered the rate of reaction progressively with increasing chain length. However, when the alkyl chain was bound in a restricted position, as in α-tetralone, the reactivity was enhanced. The influence of coplanarity of alkyl aryl ketones in the Grignard reaction and in oxime formation has been recently emphasized by Kadesch.[3] As was expected, little or no condensation was observed by the hindered ketone, acetomesitylene, even after two days of refluxing.

Phenacyl bromide would not react under these conditions, probably because of destruction of the catalyst through a secondary metathetical reaction. Phenacyl acetate, however, reacted extremely rapidly, the theoretical amount of water being removed in one hour although no well-defined product could be isolated from the tarry residue either by crystallization or distillation. No product was obtained when phenylglyoxal was used.

In Table I are given the physical constants, yields, analytical data and reaction times for the series of reactions.

Experimental

Reagents.—Malononitrile was prepared according to the procedure of Carson, Scott and Vose.[4] *p*-Fluoroacetophenone,[5] *p*-ethylacetophenone,[6] α-acetothienone,[7] *p*-isopropylacetophenone[8] and *p*-*t*-butylacetophenone[8] were prepared by the Friedel–Crafts method.

α-Tetralone[9] was prepared by air oxidation of tetralin. In a similar fashion, following a procedure similar to that used by Binapfl and Krey,[10] *m*-diethylbenzene was oxidized by bubbling air through a suspension of 1% chromia and 4% calcium carbonate in the liquid reagent at 130° for forty hours, removing the water as it was formed in a trap beneath the reflux condenser. The yield of *m*-ethylacetophenone, b. p. 113–116° (14 mm.), $n^{25}D$ 1.5232 was 45–50% with conversions of 30–35%. The structure of this ketone has been established[11] by alkaline permanganate oxidation to isophthalic acid and by analysis. The use of commercial diethylbenzene (Dow Chemical Co.) containing approximately 70% of the meta isomer instead of carefully purified[12] *m*-diethylbenzene does not adversely affect the yield or quality of product.

Similar oxidation of technical grade triethylbenzene at 135° for twenty-eight hours gave 20–25% conversions and 32% yields of 3,5-diethylacetophenone b. p. 136° (13 mm.), $n^{25}D$ 1.5188.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.76; H, 9.15. Found: C, 81.45; H, 9.20.

The semicarbazone from this ketone melted at 124–125°.

Anal. Calcd. for $C_{13}H_{19}ON_3$: C, 66.63; H, 8.18; N, 17.93. Found: C, 66.91; H, 8.14; N, 17.98.

The structure of this compound was confirmed by sodium hypochlorite oxidation to 3,5-diethylbenzoic acid, m. p. 128–129°. Preparation of the acid by this method represents a considerable improvement over the elaborate six-step synthesis of Snyder, Adams and McIntosh.[13]

Condensation Reactions.—The method of Cope,[14] *et al.*, who studied condensations of ketones with cyanoacetic acid esters was adapted for the present series of reactions. Half-mole portions of malononitrile and the ketone were dissolved in 200 cc. of benzene containing 4.0 g. of ammonium acetate and 12.0 cc. of glacial acetic acid in a 500-cc. flask. By refluxing vigorously the water formed in the reaction was removed by a Dean and Stark trap placed under the reflux condenser. The length of time required to collect 11 cc. of aqueous layer was taken as the reaction time, recorded in Table I, although the refluxing was continued an additional three hours to insure completion of reaction. (In a control experiment, 11 cc. of aqueous layer formed in the trap in fifteen min., when half a mole of water, solvent and catalyst were refluxed without the reagents.) Evaporation of the benzene left a residue which was recrystallized from dilute alcohol or distilled under vacuum. The yield figures given are based on crude prod-

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[1] Mowry, THIS JOURNAL, **65**, 991 (1943).

[2] The mechanism involving formation of an intermediate hydroxy compound in Knoevenagel condensations has been proposed by Hann and Lapworth, *J. Chem. Soc.*, **85**, 46 (1904), and confirmed by Kohler and Carson, THIS JOURNAL, **45**, 1975 (1923), and by Cope, *ibid.*, **59**, 2327 (1937).

[3] Kadesch, *ibid.*, **66**, 1207 (1944).

[4] Carson, Scott and Vose, "Organic Syntheses," Coll. Vol. II, 1943, p. 379.

[5] Evans, Morgan and Watson, *J. Chem. Soc.*, 1167 (1935).

[6] Klages, *Ber.*, **32**, 1588 (1899); **35**, 2250 (1902).

[7] Johnson and May, "Organic Syntheses," Coll. Vol. II, 1943, p. 8.

[8] Allen, *ibid.*, p. 3.

[9] Martin and Fieser, *ibid.*, **20**, 94 (1940).

[10] Binapfl and Krey, U. S. Patent 1,813,606 (1931); Senseman and Stubbs, *Ind. Eng. Chem.*, **25**, 1286 (1933).

[11] Milton Kosmin, unpublished data.

[12] Copenhaver and Reid, THIS JOURNAL, **49**, 3157 (1927).

[13] Snyder, Adams and McIntosh, *ibid.*, **63**, 3280 (1941).

[14] Cope, Hofmann, Wyckoff and Hardenbergh, *ibid.*, **63**, 3452 (1941).

TABLE I

ARYLALKYLIDENEMALONONITRILES

Ethylidenemalononitriles	Formula	Reaction time, hr.	Yield,[a] %	M. p.,[b] °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen[c] Calcd.	Nitrogen Found
1-Phenyl-	$C_{11}H_8N_2$	12	70	94	...[d]	...	..	..	...	...
1-(*p*-Chlorophenyl)-	$C_{11}H_7N_2Cl$	10	75	96	65.19	65.49	3.46	3.50	13.83	14.06
1-(*p*-Fluorophenyl)[e]	$C_{11}H_7N_2F$	5	79	122	70.94	71.14	3.79	3.89	15.05	15.51
1-Xenyl-	$C_{17}H_{12}N_2$	2	74	159	83.56	83.34	4.96	4.93	11.47	11.73
1-(*p*-Nitrophenyl)-	$C_{11}H_7O_2N_3$	4	80	154	61.90	61.58	3.31	4.38	19.71	19.20
1-(*p*-Ethoxyphenyl)-	$C_{13}H_{12}ON_2$	2	78	88	73.56	73.58	5.70	5.79	13.18	13.47
1-(*p*-Tolyl)-	$C_{12}H_{10}N_2$	11	85	97	79.09	79.30	5.53	5.54	15.38	15.72
1-(2′,5′-Dimethylphenyl)-	$C_{13}H_{12}N_2$	5	60	87	79.56	79.44	6.17	6.22	14.28	14.37
1-(*p*-Ethylphenyl)-	$C_{13}H_{12}N_2$	10	60	67	79.56	79.84	6.17	5.99	14.28	13.74
1-(*p*-Isopropylphenyl)[f]	$C_{14}H_{14}N_2$	4	63	..[g]	79.95	79.82	6.72	6.62	13.33	13.88
1-(*p*-*t*-Butylphenyl)-[f]	$C_{15}H_{16}N_2$	3	67	..[h]	80.31	80.29	7.19	7.10	12.48	12.83
1-(*m*-Ethylphenyl)-	$C_{13}H_{12}N_2$	7	61	67[i]	79.56	79.74	6.17	6.17	14.28	14.34
1-(3′,5′-Diethylphenyl)-	$C_{15}H_{16}N_2$	6	60	83–84	80.31	80.43	7.19	7.54	12.48	12.38
1-(α-Thienyl)-	$C_9H_6N_2S$	8	71	86	61.71	62.14	4.03	3.56	15.99	15.90
Other Malononitriles										
1-Phenylbutylidene-	$C_{13}H_{12}N_2$	14	70	57	79.56	79.61	6.17	6.31	14.28	14.41
1-Phenylhexylidene-	$C_{15}H_{16}N_2$	16	61	..[j]	80.31	80.25	7.19	7.12	12.48	12.60
1,2,3,4-Tetrahydro-1-naphthylidene-	$C_{13}H_{10}N_2$	4	79	109	80.27	80.21	5.20	5.29	14.43	14.60

[a] Actually conversion. The yields were all in excess of 90% based on unrecovered ketone. [b] Taken with calibrated thermometers uncorrected for stem exposure. [c] By the micro Dumas method. Kjeldahl values were often somewhat low. [d] Mowry, *loc. cit.*, b. p. 122–124° (2 mm.). [e] *p*-Fluoroacetophenone obtained through the courtesy of Miss Mary Renoll. The condensation product had 10.38% F (calcd. 10.21%). [f] *p*-Isopropylacetophenone and *p*-*t*-butylacetophenone obtained through the courtesy of Dr. W. Frederick Huber. [g] B. p. 152–154° (2 mm.), $n^{25}D$ 1.5740. [h] B. p. 158–159° (2 mm.), $n^{25}D$ 1.5700. [i] Mixed m. p. with 1-(*p*-ethylphenyl)-ethylidenemalononitrile, 53–60°. [j] B. p. 154–156° (3 mm.), $n^{25}D$ 1.5484.

uct after the first recrystallization or first distillation. The solid products were then recrystallized, usually three or four times, to constant melting point. The crystalline malononitrile derivatives were all colorless or pale yellow needles with the exception of the α-tetralone condensation product which formed well-defined plates.

Summary

The effect of variation in structure and position of substituents of aryl alkyl ketones on their reaction rate in the Knoevenagel condensation with malononitrile has been studied. Sixteen new malononitrile derivatives are reported.

3,5-Diethylacetophenone has been prepared and an improved synthesis of 3,5-diethylbenzoic acid is described.

DAYTON, OHIO RECEIVED JANUARY 2, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Polymethylene-bis-(*p*-aminophenyl Sulfones)

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A series of polymethylene-bis-(*p*-aminophenyl sulfones) has been prepared with a view to their possible therapeutic use. However, since their preparation and properties have not previously been reported, it appears desirable to give a brief description of the work.

With the exception of the methylene derivative, the polymethylene-bis-(*p*-aminophenyl sulfones) are readily obtained by the action of the sodium salt of *p*-acetamidobenzenesulfinic acid on the corresponding alkyl dihalide in aqueous ethanol solution, followed by hydrolysis of the resulting acetamido compound to the free amine.

$$2\ CH_3CONHC_6H_4SO_2Na + Br(CH_2)_nBr \longrightarrow CH_3CONHC_6H_4SO_2(CH_2)_nSO_2C_6H_4NHCOCH_3 + 2NaBr$$

$$CH_3CONHC_6H_4SO_2(CH_2)_nSO_2C_6H_4NHCOCH_3 + H_2O(HCl) \longrightarrow H_2NC_6H_4SO_2(CH_2)_nSO_2C_6H_4NH_2{\cdot}2HCl + 2CH_3COOH$$

The methylene compound could not be prepared by the condensation of sodium *p*-acetamidobenzenesulfinate with methylene bromide or iodide. One molecule of the salt reacted readily forming *p*-acetamidophenyl iodomethyl sulfone, but a second molecule of the salt could not be made to react. This is probably owing to the well-known effect of the sulfone group in deactivating alpha halogens toward double decomposition reactions.[1] The compound was

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[1] Ziegler and Connor, THIS JOURNAL, 62, 2596 (1940); Michael and Palmer, *Am. Chem. J.*, 6, 254 (1884).