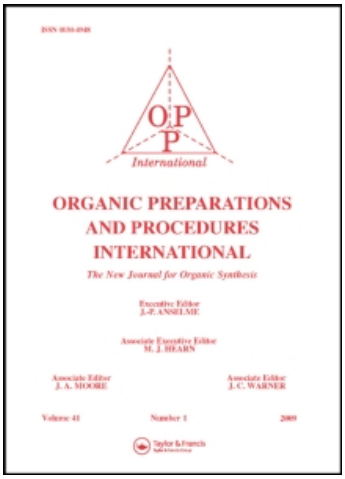

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A NOVEL SYNTHESIS OF 2-AMINO DIARYLKETONE DERIVATIVES AND OF POLYFUNCTIONALLY SUBSTITUTED QUINOLINES

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OPPI BRIEFS

A NOVEL SYNTHESIS OF 2-AMINO DIARYLKETONE DERIVATIVES AND OF POLYFUNCTIONALLY SUBSTITUTED QUINOLINES

Submitted by (04/18/97)

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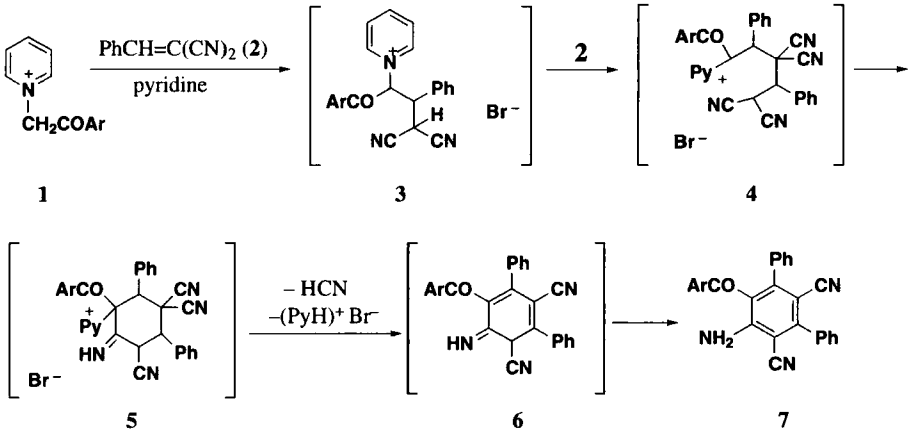
Polyfunctionally substituted benzophenone derivatives are interesting as blood vessel β-adrenegeric receptor blockers and as an anti-inflammatory agents.[1,2] Synthesis of these compounds *via* functionalisation of benzophenones or *via* aroylation of benzene derivatives has its limitations, to our knowledge synthesis *via* the formation of at least one of the two benzene rings adjacent to the ketone groups has not yet been reported. While Krohnke and co-workers described the synthesis of pyridines by reaction of pyridinium salts **1** with chalcones,[3-5] the reaction with α,β-unsaturated nitriles has not yet been reported. The present article reports an efficient synthesis of benzophenones by reaction of pyridinium salts **1** with benzylidenemalononitrile and their utility for synthesis of polyfunctionally substituted quinolines.



1 **3** **4**

5 **6** **7**

a) Ar = Ph b) Ar = *p*-chlorophenyl b) Ar = 2-naphthyl

Scheme 1

Thus, treatment of **1a** with benzylidenemalononitrile (**2**) in pyridine at reflux, afforded product of molecular formula $C_{27}H_{17}N_3O$ ($M^+ = 399$). Its IR as well as its ^{13}C NMR indicated the presence of one carbonyl group and two cyano groups. The product was assigned structure **7a** and is presumed to be formed *via* the intermediate adduct **3a** which further reacts with one additional equivalent of **2** to yield **4a**. The latter then cyclizes into **5a** which aromatizes *via* loss of hydrogen cyanide and pyridinium salt to yield the final product **7a** (**Scheme 1**). Similarly benzylidenemalononitrile (**2**) reacted with **1b,c** in pyridine to afford compound **7b,c** in good yields (Tables 1 and 2). Treatment of **7a** with hydrazine hydrate afforded hydrazone **8**.

On the other hand, the reaction of benzylidenemalononitrile with ethyl chloroacetate in pyridine gave 2-ethoxycarbonyl-3,5-diphenyl-4,6-dicyanoaniline **9**, formed *via* a route analogous to that suggested to account for the formation of reaction products of **1a-c** with **2**. The structure of **9** was established on the basis of spectral data (IR, ^1H NMR and ^{13}C NMR). Its ^1H NMR spectrum exhibited a triplet at δ 0.96 for CH_3 (J = 8Hz) and revealed -CH_2O- as a quartet at δ 3.93 (J = 8Hz). The ^{13}C NMR spectrum showed two signals for the ethyl group at δ 13.69, 66.76 and signal at δ 165.74 for the ester CO group.

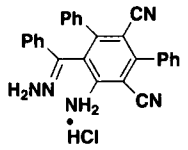
Table 1. Yields, mps, Color and Elemental Analyses for Compounds **7a-c**, **8**, **9**, **10a,b** and **11**

Compd No.	Yield (%)	mp. (°C)	Color	Elemental Analyses (Found) C	H	N
7a[a]	82	240-242	red	81.18 (81.23)	4.28 (4.36)	10.60 (10.60)
7b	83	320-322	brown red	68.94 (68.64)	3.64 (3.93)	8.93 (9.03)
7c[b]	79	270-272	deep-violet	82.83 (82.53)	4.26 (4.31)	9.34 (9.51)
8	73	230-232	yellow	72.07 (72.07)	4.48 (4.68)	15.56 (15.34)
9[c]	79	154-156	green	75.18 (74.89)	4.66 (4.53)	11.43 (11.72)
10a	68	220-222	brown	74.45 (74.53)	3.74 (3.52)	14.47 (14.23)
10b	70	310-312	deep-brown	69.50 (69.26)	3.30 (3.52)	13.50 13.52)
11	69	234-236	brown	69.37 (69.26)	3.10 (3.23)	10.78 (10.63)

a) MS (EI), m/z =399 (M^+). b) MS (EI), m/z = 449 (M^+). c) MS (EI), m/z = 367 (M^+).

Table 2. Spectral Data for Compounds **7a-c, 8,9,10a-b** and **11** (IR, ^{1}H NMR and ^{13}C NMR).

Compd No.	IR (cm^{-1})	^{1}H NMR (δ_H)	^{13}C NMR (δ_C)
7a	3445-3230 (NH_2) 2210 (CN) 1663 (CO)	6.75-7.73 (15H, m, arom-H) 9.00 (2H,brm, NH_2)	194.52(CO), 152.29 (C-3), 151.49 (C-1), 148.36 (C-5), 136.96, 135.6, 135.36, 134.82, 131.23, 129.73, 129.37, 129.20, 128.65, 128.16, 127.59 (arom. carbons), 127.45 (C-4), 115.62, 114.96 (CN), 99.15 (C-6), 92.95 (C-2)
7b	3430-3195 (NH_2) 2205 (CN) 1651 (CO)	6.46-8.33 (14H, m, arom-H) 8.65 (2H, NH_2)	194.26 (CO), 151.11(C-3), 148.98 (C-1), 146.98 (C-5), 140.73, 140.02, 137.25, 135.91, 134.98, 134.40, 132.04, 131.74, 131.04, 130.06, 129.40, 128.84, 127.45 (arom. carbons), 125.32 (C-4), 116.14, 115.46 (CN), 99.84 (C-6), 93.33 (C-2).
7c	3445-3230 (NH_2) 2210 (CN) 1663 (CO)	6.60-8.40 (17H, m, arom-H) 8.80 (2H, NH_2)	194.40 (CO), 152.36 (C-3), 148.46 (C-1), 137.07 (C-5), 135.83, 133.32, 132.74, 131.14, 130.26, 129.70, 128.65, 128.16, 127.56 (arom. carbons), 123.7 (C-4), 115.68, 115.07 (CN), 99.25 (C-6) and 93.19 (C-2).
8	3335 (NH_2) 2200 (CN)	6.86-7.80 (15H, m, arom-H) 8.60 and 9.20 (4H, $2NH_2$)	152.40 (C-1), 150.53 (benzoyl carbon), 144.21 (C-5), 142.44-125.87 (14 line arom. carbons; and C-2 and C-3), 115.62 and 114.96 (2CN), 99.32 (C-4), 92.81 (C-6).
9	3425 (NH_2) 2210 (CN) 1718 (CO ester)	0.96 (3H, t, J = 8Hz, CH_3) 3.98 (2H, q, J = 8Hz, CH_2) 6.86-7.37 (12H, m, arom-H, NH_2)	165.74 (CO), 152.18 (C-3), 136.89, 136.15 (C-1 and C-5) 130.51, 129.57, 128.73, 127.95 (arom. carbons), 127.74 (C-4), 99.45 and 96.00 (2CN), 66.76 (OCH_2), 13.69 (CH_3)
10a	3430 (NH_2) 2160 (CN)	6.50-8.33 (15H, m, arom-H) 9.05 (2H, brs, NH_2)	149.92 (C-2), 146.71 (C-8a), 144.78, 144.52, 144.01 (C-4, C-5 and C-7), 139.34-120.51 (13 line arom. carbons and C-4a), 115.73, 115.60, 113.10 (3CN), 99.53 (C-6), 93.11 and 92.91 (C-8 and C-3).
10b	3360 (NH_2) 2185 (CN)	6.88-8.03 (14H, m, arom-H) 9.00 (2H, brs, NH_2)	152.34 (C-2), 151.34 (C-8a), 140.65, 140.10 (C-4 and C-7), 139.11 (C-4), 138.34-121.14 (13 line arom. carbons and C-4a), 115.64, 114.98, 113.03 (3CN), 99.44 (C-6), 92.99, 92.81 (C-8 and C-3).
11	3130 (NH) 2180 (CN)	6.43-8.43 (14H, m, arom-H) 10.35 (1H, brs, OH).	153.53 (C-2), 151.53 (C-8a), 140.53, 140.12 (C-5 and C-7), 139.89 (C-4), 135.51-125.83 (13 line arom. carbons and C-4a), 115.54, 114.89, 113.79 (3CN), 99.34 (C-6), 92.91 and 92.55 (C-8 and C-3)



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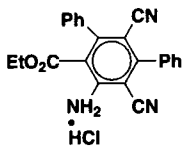

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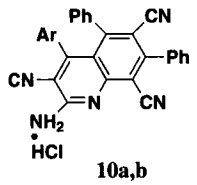
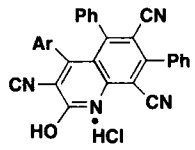


10a,b

a) Ar = phenyl
b) Ar = *p*-chlorophenyl



11

Ar = *p*-chlorophenyl

Condensation of compounds **7a,b** with malononitrile in the presence of ammonium acetate afforded products whose analytical and spectral data were in full agreement with the proposed structures **10a,b**. Similar condensation of **7b** with ethyl cyanoacetate afforded 4-(*p*-chlorophenyl)-5,7-diphenyl-2-hydroxy-1H-quinoline-3,6,8-tricarbonitrile hydrochloride **11** in good yield (Tables 1 and 2).

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Shimadzu IR- 740 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker-Ac-80 spectrometer with DMSO-d_6 as a solvent and TMS as an internal standard; chemical shifts δ are reported in ppm, coupling constants are given in Hz. Mass spectra wre measured on GS/MS INCOS LXL Finnigan MAT. Microanalyses were performed on Leco CHNS-932.

General Procedure. 2-Aroyl-3,5-diphenyl-4,6-dicyanoanilines (7a-c).- A suspension of **1a-c** (0.01 mol) in pyridine (30 mL) was treated with benzylidenemalononitrile (0.02 mol, 3.08 g). The reaction mixture was refluxed for 4 h, then poured into ice-cold water, neutralized with 10% HCl. The solid was collected and crystallized from a mixture of ethanol and dimethylformamide (3:1).

2-Benzoyl-3,5-diphenyl-4,6-dicyanoaniline Hydrazone Hydrochlorides (8).- A suspension of **7a** (0.01 mol, 3.99 g) in ethanol (50 mL) was treated with hydrazine hydrate (0.01 mol, 0.5mL). The reaction mixture was refluxed for 3 h, then cooled to room temperature. The solid was collected and crystallized from a mixture of dimethylformamide and methanol (1:1).

2-Ethoxycarbonyl-3,5-diphenyl-4,6-dicyanoaniline (9).- A suspension of **2** (0.01 mol, 1.54 g) in pyridine (20 mL) was treated with ethyl chloroacetate (0.02 mol, 2.45 g). The reaction mixture was refluxed for 5-7 h, allowed to cool to room temperature, then poured into ice-cold water and neutralized with HCl (10%). The solid was collected and recrystallized from dioxane.

2-Amino-4-aryl-3,6,8-tricyano-5,7-diphenylquinoline Hydrochlorides (10a,b).- To a solution of **7a,b** (0.01mol) in benzene (30 mL), ammonium acetate (0.01 mol) in acetic acid (2 mL) was added, followed by addition of malononitrile (0.01 mol, 0.66 g). The reaction mixture was refluxed for 4-5 h with stirring, then 2-3 drops of HCl were added. The solid was collected and recrystallized from a mixture of chloroform and ethanol (3:1) to give **10a**, while compound **10b** was recrystallized from a mixture of ethanol and dimethylformamide (1:1).

4-(*p*-Chlorophenyl)-3,6-8-tricyano-2-hydroxy-5,7-diphenyl-1H-quinoline Hydrochloride (11).- A mixture of **7b** (0.01 mol, 4.49 g) and ammonium acetate (0.01 mol) in acetic acid (2 mL) was treated with ethyl cyanoacetate (0.01 mol, 1.13 g). The reaction mixture was refluxed for 3 h and allowed to cool at room temperature, then poured into ice-cold water, and 2-3 drops of conc. HCl was added. The solid was collected and recrystallized from a mixture of ethanol and dimethylformamide (1:1).

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PREPARATION OF ALUMINA-SUPPORTED DIMETHYLAMMONIUM CHLOROCHROMATE (DMCC) AND ITS USE IN THE OXIDATION OF ALCOHOLS AND BENZOINS

Submitted by (07/26/97)

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Chromium compounds have played an important role in the formulation of reagents adsorbed on inert inorganic supports as oxidants in organic synthesis.[1-7] These reagents oxidize a wide variety of alcohols to carbonyl compounds under mild reaction conditions and afford the products in high yields. However, they have the disadvantage of being photosensitive and unstable and can be stored for only several weeks under vacuum in the dark. We now report that dimethylammonium chlorochromate ($Me_2NH_2CrO_3Cl$, DMCC) adsorbed on alumina (DMCC/alumina) is a new reagent