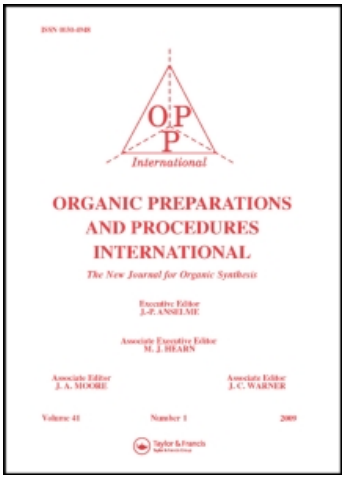

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A NEW AND CONVENIENT SYNTHESIS OF 4-AMINO-3-NITROBENZOPHENONE AND 2-AMINO-5-NITROBENZOPHENONE AND THEIR N-ALKYL DERIVATIVES†

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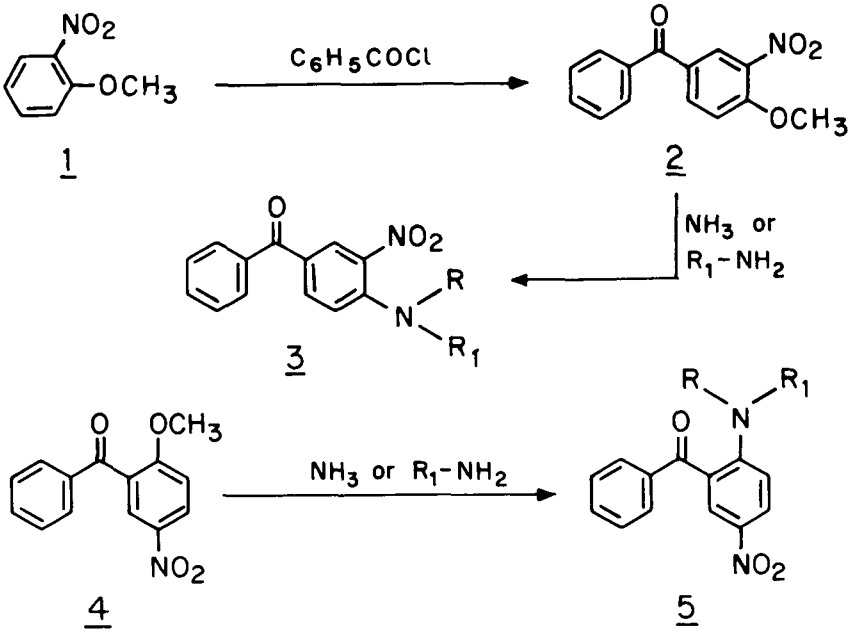
Mebendazole, a valuable anthelmintic drug, is obtained from 3,4-diaminobenzophenone.[1,2] The general method of preparation of 3,4-diaminobenzophenone, however, involves the reduction of 4-amino-3-nitrobenzophenone (**3a**), which is obtained either from fluorobenzene[3] or from p-chlorobenzoic acid;[4] these known processes involve expensive starting materials such as fluorobenzene and p-chlorobenzoic acid. A Japanese patent[5] reports the formation of **3a** from aniline, which involves benzoylation and subsequent nitration of the resulting 4-aminobenzophenone. However, this process has the inherent disadvantage of simultaneous benzoylation occurring at the amino function which introduces an additional unit process of selective alkaline hydrolysis of 4-benzamidobenzophenone. The conventional route for nitrazepam, a well known tranquiliser, employs 2-amino-5-nitrobenzophenone (**5**) as a starting material.[6] The reported route for the synthesis of **5** involves the benzoylation of p-nitroaniline, mostly reported in the form of patents.[7] Moreover, the benzoylation may not be selective due to the presence of the free amino group. This communication describes a new and convenient synthesis of 4-amino-3-nitrobenzophenone, 2-amino-5-nitrobenzophenone, and their N-alkyl derivatives in high yields and purity by treating 4-methoxy-3-nitrobenzophenone (**2**) and 2-methoxy-5-nitrobenzophenone (**4**) with aqueous ammonia or with aqueous or non-aqueous alkylamines in a closed pressure vessel at 120° for 5 hrs.



The methoxy group undergoes a nucleophilic displacement by an amino, alkylamino or cycloalkylamino substituent (see Table 1) with the liberation of methanol. The high lability of the methoxy group is due to the presence of the electron withdrawing nitro and benzoyl groups at the ortho and para positions respectively. The formation of methanol could be detected by glc of an aliquot of the reaction mixture. The reported method for the synthesis of the starting material 2 is from anisole which involves benzoylation and a subsequent nitration of the resulting benzophenone requiring rigidly anhydrous conditions.[8] We synthesised 4-methoxy-3-nitrobenzophenone (2) by benzoylation of the easily available o-nitroanisole (1) in the presence of anhydrous ferric chloride as catalyst at 135-140° for 5 hrs. This method has not been reported in the literature. All the compounds synthesised have been characterised by spectral and elemental analyses. The yield data and mps have been recorded in Table 1. The analytical data for the new compounds are described in the Experimental Section.

Table 1: Aminonitrobenzophenones[a]

Compd.	R	R_1	Cryst. Solvent	Yield (%)	mp (°C)	lit. mp (° C)
3a	H	H	Ethanol	98	140	140[9]
3b	H	Me	Ethanol	96	205	205[10]
3c	H	Et	Hexane	96	99[b]	-
3d	H	Me_2CH	Methanol	88	88[b]	-
3e	H	n-$C_{11}H_9$	Methanol	98	65[b]	-
3f	H	c-C_6H_{11}	Acetone	98	170[b]	-
3g	Me	Me	Pet. ether	70	116[b]	-
5a	H	H	Acetic acid	96	161	161.5[11]
5b	H	c-C_6H_{11}	Acetone	90	95[b]	-

a) The ^1H NMR, IR and mass spectra of the products and their elemental analyses were in accordance with their structures.

b) The analytical data are recorded in detail in the Experimental Section.

An alternative route to 4-amino-3-nitro-benzophenone from 4-chloro-3-nitrobenzophenone could also be visualised. Attempted benzoylation of o-nitrochlorobenzene in the presence of various Lewis-acid catalysts such as ferric chloride, zinc chloride, and aluminium chloride was unsuccessful.

EXPERIMENTAL SECTION

Melting points were recorded in capillary tubes. IR spectra were recorded using a Perkin-Elmer 221 spectrophotometer and values are expressed in cm^{-1}. ^1H NMR spectra were obtained using a Varian FT-80 spectrometer and chemical shifts are reported in δ ppm with TMS as the internal reference. Mass spectra were recorded on a CEC-21-110B mass spectrometer.

4-Methoxy-3-nitrobenzophenone (2).- Benzoyl chloride (34.8 g, 0.24 mole) was added dropwise over a period of 1 hr to a stirred mixture of o-nitro-anisole (1) (30.6 g, 0.2 mole) and anhydrous ferric chloride (2 g) at 30°. The temperature of the reaction mixture was slowly raised over 0.5 hr to 135-140° and maintained at this temperature for 5 hrs. The reaction mixture was cooled to 30° and poured into a mixture of 10N hydrochloric acid (5 ml) with crushed ice (300 g). The product was extracted with chloroform (200 ml). The organic layer was dried over anhydrous potassium carbonate.

After removal of the drying agent, the organic filtrate was evaporated under vacuum to give a residue which was recrystallised from methanol to yield 30.8 g (60%) of yellow needle of **2**, mp. 105°, lit.[8] 105°.

4-Amino-3-nitrobenzophenone and its N-Alkyl Derivatives (3).

General Procedure.- A mixture of 4-methoxy-3-nitrobenzophenone (**2**) (25.7g, 0.1 mole) and excess of either aqueous ammonia (25%) or alkylamine (0.6 mole) was heated in a closed pressure vessel at 120° for 5 hrs. The reaction mixture was cooled to 30° and diluted with water (500 ml). The product which separated out was filtered and recrystallised to give yellow needles. **2-Amino-5-nitrobenzophenones and its N-Alkyl Derivatives (5)** were prepared by the general procedure described for **3**. The yield and other data are recorded in Table 1. The analytical data for the new benzophenones are as follows.

4-Ethylamino-3-nitrobenzophenone (3c): IR (nujol): 3360, 1660, 1640, 1580, 1240; ^{1}H NMR ($CDCl_3$): 1.4 (t, 3H, CH_3), 3.36 (m, 2H, CH_2). 6.7 (d, 1H), H ortho to NHEt, J = 9 Hz), 7.2-7.9 (m, 6H, Ar-H), 8.4 (d, 1H, H ortho to C=O and NO_2, J = 1.5 Hz), 8.1 (t, 1H, NH, exchangeable with D_2O); MS m/z): 270 (M^+), 254, 240, 235, 223, 210, 193.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.18; N, 10.37

Found: C, 67.01; H, 5.32; N, 10.41

4-Isopropylamino-3-nitrobenzophenone (3d): IR (Nujol): 3370, 1655, 1625, 1532, 1257; ^{1}H NMR ($CDCl_3$): 1.4 (d, 6H, CH_3), 3.9 (m, 1H, CH), 6.7 (d, 2H, H ortho to isopropylamino, J = 8 Hz), 7.2-7.9 (m, 6H, Ar-H), 8.4 (d, 1H, H ortho to C=O and NO_2, J = 1.5 Hz), 8.1 (d, 1H, NH, exchangeable with D_2O); MS (m/z): 284 (M^+), 269, 239, 186.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.60; H, 5.63; N, 9.85

Found: C, 68.10; H, 5.61; N,10.11

4-n-Butylamino-3-nitrobenzophenone (3e): IR (Nujol): 3360, 1640, 1610, 1450,

1270; ^{1}H NMR ($CDCl_3$): 1.1 (t, 3H, CH_3), 1.3-2.1 (m, 4H, $-CH_2$), 3.3-3.7 (m, 2H, $-NCH_2$), 7.2 (d, 5H, H ortho to butylamino, J = 9 Hz), 7.7-8.4 (m, 6H, Ar-H), 8.7 (t, 1H, NH, exchangeable with D_2O), 8.9 (d, 1H, H ortho to C=O and NO_2, J = 1.5 Hz); MS (m/z): 298 (M^+), 269, 255, 225.

Anal. Cald. for $C_{17}H_{18}N_2O_3$: C, 68.45; H, 6.04; N, 9.39

Found: C 68.81; H, 6.42; N, 9.35

4-Cyclohexylamino-3-nitrobenzophenone (3f): IR (Nujol): 3350, 1650, 1620, 1570, 1450, 1270; ^{1}H NMR ($CDCl_3$): 1.2-2.3 (m, 10H, cyclohexyl), 3.7 (m, 1H, CH), 7.1 (d, 1H, H, ortho to cyclohexylamino, J = 8 Hz), 7.5-8.3 (m, 6H, Ar-H), 8.8 (d, 1H, H ortho to C = O and NO_2, J = 1.5 Hz); MS (m/z): 324 (M^+), 294, 281, 242.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70 37; H, 6.17; N, 8.64

Found : C, 70.00; H, 6.41; N, 8.72

4-Dimethylamino-3-nitrobenzophenone (3g): IR (Nujol): 1645, 1610, 1550, 1470, 1270; ^{1}H NMR ($CDCl_3$): 3.1 (s, 6H, CH_3), 7.07 (d, 1H, H ortho to dimethylamino, J = 9 Hz), 7.5-7.9 (m, 6H, Ar-H), 8.3 (d, 1H, H ortho to C = O and NO_2, J = 1.5 Hz); MS (m/z): 270 (M^+), 253, 244, 226, 167, 105.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.18; N, 10.37

Found: C, 66.62; H, 5.33; N, 10.05

2-Cyclohexylamino-5-nitrobenzophenone (5b): IR (Nujol): 3270, 1630, 1610, 1580, 1460, 1260; ^{1}H NMR ($CDCl_3$): 1.1-2.1 (m, 10H, CH_2 of cyclohexyl), 3.2-3.7 (m, 1H, CH of cyclohexyl), 6.4 (d, 1H, H ortho to cyclohexylamino, J = 9 Hz), 7.1-7.3 (m, 5H, Ar-H), 8.0 (d, 1H, H ortho to cyclohexylamino, J = 9 Hz), 7.1-7.3 (m, 5H, Ar-H), 8.0 (d, 1H, H ortho to C=O and NO_2, J = 1.5 Hz), 8.9 (d, 1H, NH, exchangeable with D_2O); MS (m/z): 324 (M^+), 305, 294, 281.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.37; H, 6.17; N, 8.64

Found : C, 70.40; H, 6.32; N, 8.82

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