Specific Phase-Transfer Catalyzed *N*-Monoalkylation of 2-Aminobenzophenones

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The 2-alkylaminobenzophenones, especially 5-chloro-2-methylaminobenzophenone, are synthetic intermediates used in the manufacture of anxiolytics such as diazepam* and in the synthesis of a new generation of non-diazepam-like anxiolytics[1,2,3], the glycanilides[4,5,6].

The presently used methods of alkylating 2-aminobenzophenone are as follows:

(a) tosylation of 2-aminobenzophenones, alkylation of the sulfonamide intermediate, and hydrolysis with concentrated sulfuric acid[7];

(b) amidation of 2-aminobenzophenones with benzoyl chloride, alkylation of the secondary amide thus formed, and hydrolysis[7];

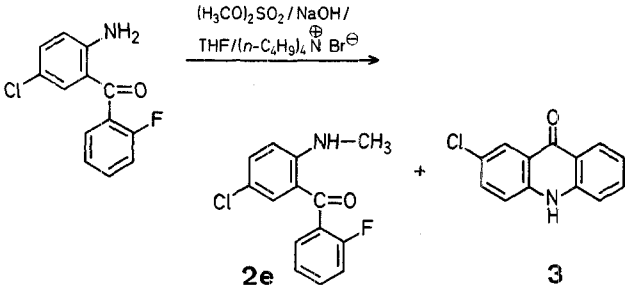
(c) direct alkylation of 2-aminobenzophenones, in solution in acetic acid, with an alkyl sulfate[8];

(d) formylation of 2-aminobenzophenones[9];

(e) alkylation of 2-aminobenzophenones with polyphosphate esters[10].

Methods (a) and (b) are selective, but relatively slow (three steps), whereas with the direct methods (c), (d), and (e) the alkylation is not selective, and obtaining pure monoalkyl derivatives proves difficult. To reduce these disadvantages, we have developed a new method of alkylation using a phase-transfer catalytic technique.

2-Aminobenzophenones (**1**) are alkylated in solution in tetrahydrofuran in the presence of powdered sodium hydroxide and tetrabutylammonium bromide.



Compound **3** *was identified by comparison with an authentic sample* (m.p. 394–396 °C) prepared by the method of Ref.[12].

5-Chloro-2-methylaminobenzophenone (2a); Typical Procedure:
Finely powdered sodium hydroxide (160 g, 4 mol) is added to a stirred solution of 5-chloro-2-aminobenzophenone (231 g, 1 mol) and tetrabutylammonium bromide (3.22 g, 0.01 mol) in tetrahydrofuran (2000 ml) and stirring is continued for 5 min at room temperature. Then, dimethyl sulfate (378 g, 3 mol) is added and the stirred mixture is heated at 60 °C for 1 h. The tetrahydrofuran is evaporated under reduced pressure and the residue taken up in ethyl acetate. This organic solution is washed with water until it is neutral, dried with sodium sulfate, filtered, and evaporated to dryness; yield of **2a**: 245 g (100%); m.p. 95 °C (Ref.[7], m.p. 94–95 °C); purity: >99% [G.L.C. analysis (10% SE 30)].

The 2-alkylaminobenzophenones **2b–g** are prepared following the same procedure except that in the preparation of **2f** diethyl sulfate is used as alkylating agent and in the preparation of **2g** allyl bromide is used.

The I.R. and ^{1}H-N.M.R. spectra of all products **2** (except **2d**) thus obtained were identical with those of authentic samples prepared by method (a)[7].

5,4′-Dichloro-2-methylaminobenzophenone (**2d**); yield: 90%; m.p. 123 °C, golden-yellow crystals.

$C_{14}H_{11}Cl_2NO$	calc.	C 60.02	H 3.95	Cl 25.31	N 4.99
(280.2)	found	59.97	3.87	25.33	5.02

I.R. (KBr): ν = 3340 (NH); 1625 (C=O); 1560 (C=C_{arom}) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 7.5–7.1 (m, 7 H_{arom}); 6.6 (d, 1H); 2.9 ppm (s, 3H).

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* Trade names of commercial (diazepam preparation): Valium, Ansiolin, Apaurin, Apozepam, Atensine, Atilen, Bialzepam, Calmpose, Ceregulart, Dipum, Eridan, Faustan, Lembrol, Levium, Morosan, Noan, Puritram, Tranimul, Vival, and Vivol.

Table. 2-Alkylaminobenzophenones (**2**)

Product 2	X^1	X^2	R	Reaction time at 60 °C	Yield [%]	m.p. [°C] found	m.p. [°C] reported[7]
a	Cl	H	CH_3	1 h	100	95°	94–95°
b	Br	H	CH_3	2 h	94	97°	97–98°
c	Cl	2-Cl	CH_3	1 h	98	89°	88–90°
d	Cl	4-Cl	CH_3	2 h	90	123°	$C_{14}H_{11}Cl_2NO$ (280.2)
e	Cl	2-F	CH_3	2 h	68	121°	118–119°
f	Cl	H	$-C_2H_5$	2 h	95	58°	56–57°
g	Cl	H	$-CH_2-CH=CH_2$	30 min	100	76°	76–77°

By this method[11], the 2-alkylaminobenzophenones (**2**) listed in the Table may be obtained in a single step and in high yields. Product **2d** is a new compound.

The relatively low yield (68%) of product **2e** is caused by the formation of 7-chloroacridanone (**3**; 20%) as a side product by intramolecular cyclization of compound **1**.

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