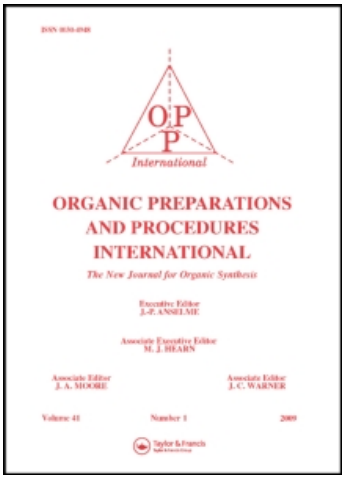

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BENZIMIDAZOLE ANTIVIRALS. REGIOSPECIFIC SYNTHESIS OF ARYL BENZIMIDAZOYL KETONES BY SULFONAMIDE ANION DISPLACEMENT OF AROMATIC FLUORIDE

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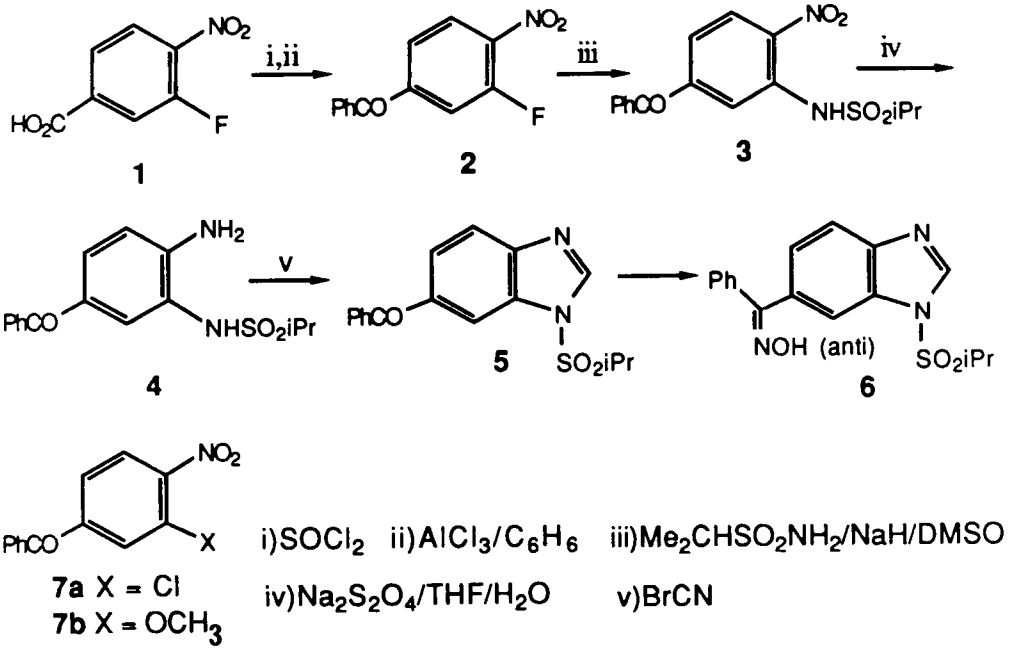
An earlier publication from these laboratories[1] described the synthesis of ketone 5 by sulfonylation of 2-amino-5-benzoylbenzimidazole and its conversion to the antiviral agent Enviroxime 6. The recent report of the selective acylation of 2-amino-5-benzoylbenzimidazole and subsequent conversion to 5[2] prompts this account of an alternate, regiospecific synthesis of 5 not requiring selective acylation. Some years ago, Davis et al. reported the preparation of 3-chloro-4-nitrobenzophenone 7a by methanolic KOH induced reaction of phenylacetonitrile with o-chloronitrobenzene, followed by alkaline hydrogen peroxide oxidation.[3] Nucleophilic displacement of chloride from 7a by isopropylsulfonamide would lead regiospecifically to 3, an intermediate clearly suited for conversion to 5. However, all attempts to induce the conversion of 7a to 3 failed. As it is well known that displacements of activated fluoride proceed much more



readily than displacements of other aromatic halides,[4] the synthesis of 2 was examined. Attempts to apply the Davis procedure to o-fluoronitrobenzene to prepare 2 failed; the only product isolated was the known methoxy compound 7b.[3] Compound 2 was prepared by a Friedel-Crafts reaction of the known acid 1[5] via its acid chloride with benzene. Reaction of

isopropylsulfonamide with 2 then provided 3 in 95% yield. Reduction of 3, followed by cyclization with cyanogen bromide produced 5, identical to authentic material, in 50% overall yield.

Although the improved[7] original selective acylation is preferred for the large scale synthesis of 5, for the preparation of putative metabolites of 6 or of radiolabelled material, the regiospecific synthesis herein described is the method of choice. The conversion of 2 to 3 appears to be the first reported example of displacement of activated fluoride using a sulfonamide anion as the nucleophile.

EXPERIMENTAL SECTION

Mps were determined in a Mel-Temp apparatus and are uncorrected. Spectral data (NMR, IR, MS) for all new compounds were in accord with the assigned structures. Reactions were worked up by dilution as specified and extraction with the indicated solvent. The pooled extracts were washed with water, brine, dried over the specified agent and concentrated in vacuo.

3-Fluoro-4-nitrobenzophenone (2).- A solution of 14.6 g (0.079 mol) of 3-fluoro-4-nitrobenzoic acid,[5] 200 mL of benzene, 10 mL of thionyl chloride and 1 mL of DMF was stirred overnight at room temperature ($CaCl_2$ drying tube). The resulting clear solution was heated under reflux 1 hr and then distilled to reduce the initial volume by ca. 25%. The solution was cooled in an ice bath and 20 g of $AlCl_3$ was added in portions over 45 min with continuous stirring. The resulting dark solution was allowed to warm to room temperature and kept overnight. The reaction flask was again cooled in ice and 300 mL of 1N HCl was added dropwise. Work up (3 x 50 mL EtOAc, $MgSO_4$) afforded 16.9 g (87%) of an oil which solidified on scratching. Recrystallization from 95% EtOH produced 15.1 g (78%) of 2 as yellow needles, mp. 77-79°.

Anal. Calcd. for $C_{13}H_8FNO_3$: C, 63.68; H, 3.29; N, 5.71; F, 7.75
Found : C, 63.75; H, 3.02; N, 5.66; F, 7.70

3-(Isopropylsulfonyl)amino-4-nitrobenzophenone (3).- To 50 mL of dimethyl sulfoxide was added 1.019 g of 50% sodium hydride/oil dispersion (0.021 mol NaH). After the initial gas evolution had ceased, isopropylsulfonamide[6] (2.53 g, 0.0206 mol) was added and the resulting mixture was stirred for 10 min ($CaCl_2$ tube). Then compound 2 (4.90 g, 0.020 mol) was added, followed by an additional 20 mL of DMSO to break up the resulting foam. The mixture was stirred for 5 hrs at room temperature, warmed to 90° for 1 hr, cooled and then poured into 300 mL of cold 1 N HCl. Work up (4 x 50 mL EtOAc, $MgSO_4$) afforded a yellow oil which on tituration with cold i-PrOH provided 6.65 g (95%) of 3 as a yellow powder which crystallized from i-PrOH as pale yellow needles (5.82 g, 83%), mp. 115-116°.

Anal. Calcd. for $C_{16}H_{16}N_2O_5S$: C, 55.16; H, 4.63; N, 8.04; S, 9.20
Found : C, 55.06; H, 4.65; N, 7.93; S, 9.16

2-Amino-6-benzoyl-1-isopropylsufonylbenzimidazole (5).- A solution of 3 (3.91 g, 0.0112 mol) in 60 mL of THF was added dropwise over 30 min to a stirred solution of sodium dithionite (23.7 g) in 200 mL of H_2O. After an additional hr, the mixture was saturated with solid NaCl and the resulting layers separated. The aqueous phase was extracted with THF (3 x

25 mL) and the combined THF layers were washed with brine. Evaporation of the THF gave crude 3-(isopropylsulfonyl)amino-4-aminobenzophenone (4) which tended to discolor rapidly and consequently was used directly.[8] Dissolution in 50 mL of i-PrOH was followed by addition of 1.29 g (0.11 mol) of BrCN and 5 mL of 2N NaOH. After 2 hrs at room temperature, an additional 1.6 g of BrCN was added. The mixture was stirred overnight and then treated with 300mL of saturated NH_4Cl. Work up (2 x 50 mL EtOAc, Na_2SO_4) afforded a dark residue which on trituration with small volumes of EtOAc produced a brown powder. Recrystallization from THF/EtOAc (decolorizing carbon) provided 1.71 g (50%) of pure 5 as off-white granules, mp. 191-193°, identical in spectral properties to authentic material.[1]

Anal. Calcd. for $C_{17}H_{17}N_3O_3S$: C, 59.46; H, 4.99; N, 12.24; S, 9.34
Found : C, 59.20; H, 4.72; N, 12.14; S, 9.39

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8. Several recrystallizations of crude 4 from i-PrOH afforded stable material as colorless blocks, mp. 143-145° (Anal. Calcd. for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80; S, 10.70. Found: C, 60.46; H, 5.75; N, 8.59; S, 10.30) but substantial loss of compound was encountered.

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