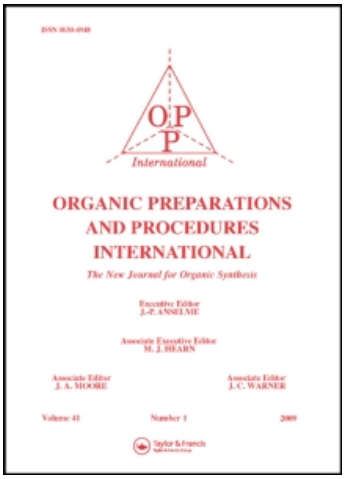

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AN IMPROVED SYNTHESIS OF METHYL [5-BENZOYL- AND 5-p-FLUOROBENZOYLBENZIMIDAZOL-2-YL]CARBAMATES

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AN IMPROVED SYNTHESIS OF METHYL [5-BENZOYL- AND 5-p-FLUOROBENZOYLBENZIMIDAZOL-2-YL]CARBAMATES

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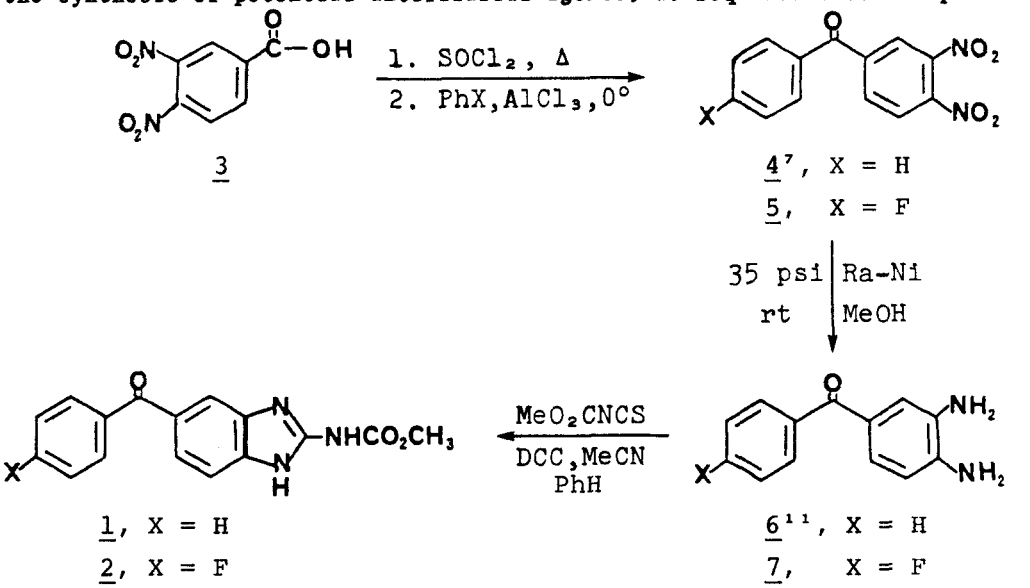
Methyl [5-benzoylbenzimidazol-2-yl]carbamate (1, **mebendazole**) and the 5-p-fluorobenzoyl congener of mebendazole, **flubendazole** (2), are two of the most important benzimidazole carbamates currently in use as broad spectrum human and veterinary anthelmintic drugs.[1,2] As part of our recent work on the synthesis of potential antifilarial agents, we required these compounds



3

4[7], X = H
5, X = F

1, X = H
2, X = F

6[11], X = H
7, X = F

in large quantities since both 1 and 2 have demonstrated significant antifilarial activity.[2] A perusal of the literature revealed that although the synthesis of 1 and 2 had been accomplished,[3,4] in our hands, these procedures were less than satisfactory for large scale syntheses. We now describe a new high yield synthesis of 7, and a subsequent new high yield annelation procedure using the reagent methoxycarbonyl isothiocyanate in the presence of N,N'-dicyclohexylcarbodiimide.

The Friedel-Crafts reaction of 3,4-dinitrobenzoyl chloride, obtained from 3,4-dinitrobenzoic acid and thionyl chloride at reflux,[5] with fluorobenzene at 0° afforded 3,4-dinitro-4'-fluorobenzophenone (5) in 70% yield. Catalytic reduction of 5 in the presence of T-1 Raney nickel[6] in methanol gave a nearly quantitative yield of the desired 3,4-diamino-4'-fluorobenzophenone (7). The diamines 6[7] and 7 on cyclization with methoxycarbonyl isothiocyanate[8,9] in the presence of N,N'-dicyclohexylcarbodiimide (DCC) in acetonitrile or benzene afforded 77% and 55% overall yields of compounds 1 and 2 respectively. The physicochemical data, with the exception of the melting point and spectroscopic data of the known compounds were identical to literature values.[3-5]

EXPERIMENTAL SECTION

Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 281 spectrophotometer and values are expressed in cm^{-1}. ^1H NMR spectra were obtained using a Varian EM-360 60 MHz spectrophotometer and chemical shifts are reported in parts per million on the δ scale with tetramethylsilane as the internal reference.

3,4-Dinitro-4'-fluorobenzophenone (5).- A mixture of 3,4-dinitrobenzoic acid[7] (50 g, 0.236 mole) and thionyl chloride (80 ml) was stirred at reflux for 12 hrs and then cooled to room temperature. The excess thionyl chloride was removed under vacuum and the resulting acid chloride was dissolved in fluorobenzene (60 ml) and added dropwise to an ice-cold stirred suspension of aluminum chloride (51.0 g, 0.383 mole) in fluorobenzene (140 ml). After the addition, the reaction mixture was stirred a 0° for 2 hrs and then poured into ice-water (1 L) with stirring. The product was extracted with CH_2Cl_2 (600 ml x 3) and the combined organic layer was washed with aqueous 10% sodium hydroxide solution (300 ml x 3), then with water (500 ml) and dried over anhydrous potassium carbonate. The drying agent was removed by filtration and the organic filtrate was evaporated under vacuum to give a residue which was crystallized from

isopropanol to yield 48 g (70%) of 5, mp. 113°; IR (KBr): 1665, 1600, 1545-1525, 1360-1355, 770 740, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ 7.2-8.75 (m, 7 H, Ar-H).

Anal. Calcd. for $C_{13}H_7FN_2O_5$: C, 53.80; H, 2.43; N, 9.65

Found: C, 53.95; H, 2.62; N, 9.42

3,4-Diamino-4'-fluorobenzophenone (7).- A suspension of compound 5 (15 g) in methanol (80 ml) was hydrogenated in a Parr apparatus in the presence of T-1 Raney nickel[6] (8.0 g, wet) at 35 psi for 2 hrs. The catalyst was removed by filtration through Celite, and the Celite pad washed thoroughly with methanol. The filtrate on evaporation under vacuum gave 11.56 g (97%) of a yellow solid. A small sample was purified by crystallization from either methanol or ethanol after treatment with charcoal, mp. 113-114°, mp. (as HCl salt) 228-231°, lit.[3] mp. 226-230.5°; IR (KBr): 3440, 3360, 1660, 1615, 755 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 60 MHz): δ 3.97 [bs, 2 H, NH_2, exchangeable with D_2O], 4.62 [bs, 2 H, NH_2, exchangeable with D_2O)], 6.50-8.08 (m, 7 H, Ar-H).

Methyl [5-p-Fluorobenzoylbenzimidazol-2-yl]carbamate (2).- Methoxycarbonyl isothiocyanate[8,9] (7 g, 0.060 mole) was added to a stirred solution of the diamine 7 (12.0 g, 0.052 mole) in a 1:4 (v/v) acetonitrile:benzene mixture. The reaction mixture was stirred for 15 min. at room temperature and then N,N'-dicyclohexylcarbodiimide (15.2 g, 0.0737 mole) was added. The resulting mixture was stirred at reflux temperature for 5 hrs and then cooled to room temperature. The solid which separated was collected by filtration. This solid was suspended in toluene (150 ml) and heated at reflux on a steam bath for 1 hr and filtered hot. The solid was dried in an oven at 50° to yield 9.0 g (55%), mp. >300°, lit.,[5] mp. 260°. MS, (m/z): 313(M^+), 281, 218, 186, 123; IR(KBr): 3400, 1730, 1645, 1600, 760 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 60 MHz): δ 3.81 [s, 3 H, CH_3], 7.05-8.1 (m, 7 H, Ar-H), 11.6 [bs, 2 H, NH, exchangeable with D_2O].

Methyl [5-Benzoylbenzimidazol-2-yl]carbamate (1).- Compound 1 was prepared in 77% as described for 2, mp. >300°, lit.[3] mp 288.5°. MS (m/z): 295 (M^+), 218, 186, 105; IR(KBR): 3400, 1735, 1650, 755 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 60 MHz): δ 3.82 [s, 3 H, CH_3], 7.4-8.0 (m, 8 H, Ar-H), 12.0 [bs, 2 H, NH, exchangeable with D_2O].

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REFERENCES

1. H. Van den Bossche, F. Rochette and C. Horig, Adv. Pharmacol and Chemother., 19, 67 (1982); J. S. Keystone, J. K. Murdoch, Ann. Intern. Med., 91, 582 (1979); J. P. Nazais, Med. Afr. Noire, 25, 473 (1976).

2. WHO Scientific Working Group on Filariasis, Report No. TDR/filariasis, 3, 79.3 (1979).

3. A. H. M. Raeymaehers, J. L. H. Van Gelder, L. F. C. Roevens and P. A. J. Janssen, Arzneim-Forsch., 28, 586 (1978).

4. F. Jozsef, A. Frusza, H. Jeno, G. Istvan, P. Istvan, P. Magdolna, and F. Jano, Ger. Offen. 2,547,325; Chem. Abstr., 85, P94069j (1976).

5. T. Kametani and M. Shio, J. Heterocyclic Chem., 8, 545 (1971).

6. X. A. Dominguez, I. C. Lopez, R. Franco, J. Org. Chem., 26, 1625 (1961).

7. Purchased from Aldrich Chemical Co.

8. A. E. Dixon and J. Taylor, J. Chem. Soc., 93, 648 (1908).

9. R. W. Lamon, J. Heterocyclic Chem., 5, 837 (1968).