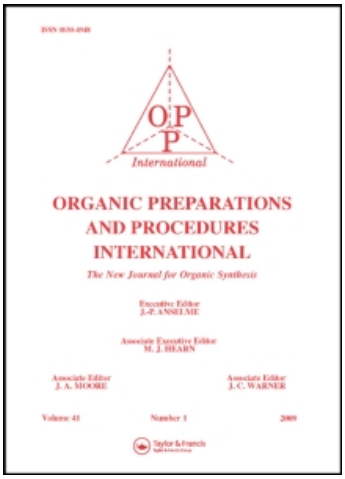


**Organic Preparations and Procedures International**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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**To cite this Article** Ravindranathan, T. , Wakharkar, R. D. and Landge, A. B.(1987) 'SYNTHESIS OF MEBENDAZOLE AND ENVIROXIME. ACYLATION OF 2-AMINO-5-BENZOYLBENZIMIDAZOLE', Organic Preparations and Procedures International, 19: 1, 9 — 16
**To link to this Article: DOI:** 10.1080/00304948709354865
**URL:** http://dx.doi.org/10.1080/00304948709354865

ORGANIC PREPARATIONS AND PROCEDURES INT. 19(1), 9-16 (1987)

# SYNTHESIS OF MEBENDAZOLE AND ENVIROXIME. ACYLATION OF 2-AMINO-5-BENZOYLBENZIMIDAZOLE

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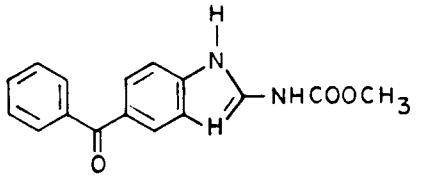
Recently we reported[1] a method for the preparation of 2-amino-5-benzoylbenzimidazole (1). Ready conversion of this intermediate 1 into the title compound, viz. anthelmintic mebendazole (2) (also reported[2] to possess antifilarial activity) and the viricide enviroxime (3) was studied.

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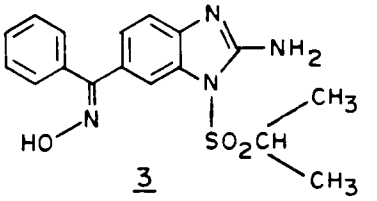
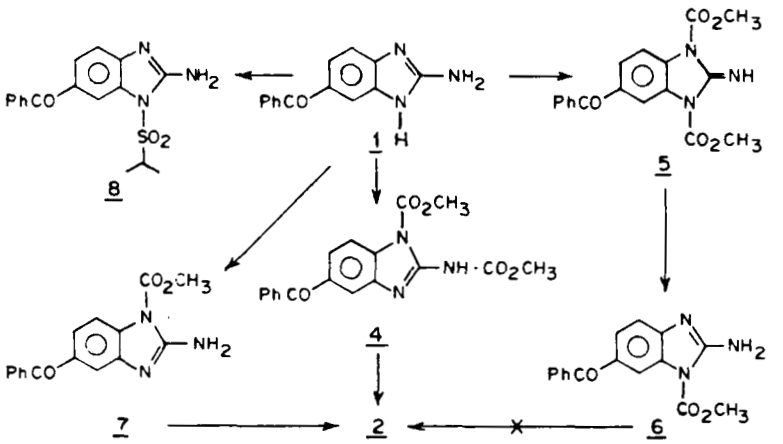



3

Compound 1 can be converted to mebendazole and enviroxime by selective acylation techniques at the proper nitrogen with methyl chloroformate or isopropylsulfonyl chloride respectively. Since the imidazole ring in 2-aminobenzimidazole exhibits guanidine-type reactivity, alkylation and acylation reactions would be expected to lead to the mono-, di- and tri-substituted products. A literature[3-7] survey conveyed that 1-acyl and 1,3-diacyl 2-aminobenzimidazole could be converted to methyl N-(2-benzimidazolyl)carbamate with considerable ease. Under similar conditions, acylation of 1 gave variable products and the reaction was solvent and pH dependent.[8] The regioselecti-

vity of the reaction and the stability of the acylation products can only be attributed to the benzoyl group at the 5-position. Mebendazole could be synthesized in two ways from 1, viz. (i) by diacylation to 4 and methanolysis, and (ii) by monoacylation to 7 and rearrangement (Scheme 1). The latter method in particular was found to be very efficient and gave mebendazole in nearly quantitative yields.

Scheme 1





Diacylation of 1 using two equivalents of methylchloroformate and excess of sodium bicarbonate (3 eq. to maintain pH = 7.8 throughout the reaction) in aqueous acetone medium resulted in clean conversion to 4. Changing the solvent from aqueous acetone to chloroform with 1 to 2 equivalents of base gave almost exclusively 1,3-diacyl derivative 5. Subsequent methanolysis of 4 and 5 at room temperature gave the corresponding monoacyl derivatives 2 and 6 respectively. The substitution pattern in 4 and 5 as 1,2- and 1,3-diacyl respectively was ascertained by several means: a) PMR spectrum

where the C-4 aromatic hydrogen in 5 was deshielded and appeared at $\delta$ 8.3 in comparison with 4; b) the ease of the methanolysis of the acyl groups at N-1 position of both 4 and 5 and c) the identity of the methanolysis product 2 derived from 4 with authentic mebendazole.

Monoacylation of 1 with methyl chloroformate in acetone using excess sodium bicarbonate cleanly gave 1-acyl derivative 7 (as shown by TLC) which at the reflux temperature of acetone in the presence of a few drops of triethylamine rearranged to mebendazole (2). The acyl derivative 7 was isolated in one experiment and characterized; it was converted to 2 under the above conditions to establish its intermediacy. By contrast 6 was resistant to rearrangement under the conditions described above as well as in other solvents such as chloroform, dichloromethane, tetrachloroethane and cumene upto a temperature of 155-160°. The PMR spectrum of 7 showed a deshielded aromatic hydrogen at $\delta$ 8.16 for C-4 compared to $\delta$ 8.55 for the C-7 proton in 6, thus showing the comparatively higher deshielding effect of the 6-benzoyl substituent as well as of the N-1 methoxy carbonyl group.

The known[9] method of preparation of the enviroxime intermediate 8 suffers mainly in yield. Isopropylsulfonylation of 1 in our experiments gave better yields using milder bases like sodium bicarbonate, triethylamine or pyridine in acetone. The best results were obtained with triethylamine in acetone at reflux temperature. The product obtained was identical with 8 (Scheme 1) (an authentic sample was made by using the reported[9] procedure) as shown by PMR, superimposable IR spectra

and mixed melting points. This intermediate can be converted to enviroxime (3) by oximation and separation of the syn and anti isomers as shown earlier.[9] In the above sulfonylation with isopropylsulfonyl chloride, selective N-3 substitution of 1 was observed in contrast to the N-1 acylation with methyl chloroformate.

## EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer. NMR spectra were obtained with a Varian T-60 spectrometer, using Me4Si as an internal standard. Mass spectral analyses were conducted using an AEI MS 30 double beam spectrometer on CEC 21-11013 spectrometer.

Diacylation of 1 to 4. - A suspension of 1 (5 g, 0.02 mole) and sodium carbonate (5 g, 0.047 mole) in aqueous acetone (35 ml; 1:1 ratio) was placed in a test tube with a joint, equipped with an efficient mechanical stirrer (screw type). The reaction mixture was stirred vigorously and methyl chloroformate (5 ml, 0.052 mole) was added slowly with a syringe at room temperature. After addition, stirring was continued for 4-5 hrs (reaction was monitored by TLC, silica gel; $CHCl_3$:MeOH, (9.5:0.5). The precipitated diacylated product was collected and washed with water to remove inorganic salts. The product 4 was crystallized from a mixture of chloroform and pet. ether to give 7 g (94%) of colourless crystals, mp. 233-235° (lit.[8] mp. 157-159°).

IR(Nujol): 3300, 1765, 1725, 1650 $cm^{-1}$. NMR ($CDCl_3$): $\delta$ 3.8 (s, 3H, $-OCH_3$), 4.1 (s, 3H, $-OCH_3$), 7.2-8 (m, 9H, 8 aromatic + 1 NH). $M^+$ 353:

Anal. Calcd for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89

Found: C, 61.46; H, 4.55; N, 11.68

Diacylation of 1 to 5.- This was carried out as described in the above experiment, except that chloroform was used as solvent instead, along with sodium carbonate (2.5 g, 0.023 mole). Since the product 5 was soluble in chloroform, the reaction mixture was filtered and the filtrate was concentrated. The residue crystallized from chloroform, pet. ether to afford 6.7 g (90%) of 5, mp. 170-172°.

IR(Nujol): 1800, 1740, 1650 $cm^{-1}$. NMR($CDCl_3$): δ 4.1 (2s, 6H, 2-$OCH_3$), 7.3-8 (m, 8H, aromatic + 1H), 8.3 (bs), 1H, C-4). $M^+$ 353.

Anal. Calcd. for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89

Found: C, 60.92, H, 4.3; N, 11.70

Deacylation to 2 and 6.- An equal amount of methanol was added in the same reaction mixture of 4 and 5 (before work up) and the mixture was stirred for another 1 hr. The diacylated products 4 and 5 were thus converted to the monoacyl derivatives 2 and 6 respectively in 75 to 80% yield.

Compound 2 was crystallized from acetic acid + methanol, mp. 288-289°. Lit.[10] (for Mebendazole) mp. 288.5°

IR (Nujol): 3360, 1730, 1650, 1600 $cm^{-1}$. NMR (TFAA): δ 4.1 (s, 3H, -$OCH_3$), 7.4-8.2 (m, 9H, 8 aromatic + 1 NH). $M^+$ 295.

Compound 6 was crystallized from methanol, mp. 305-307°, (Lit.[8] 310-313°)

IR(Nujol): 3300, 1750, 1650 $cm^{-1}$. NMR ($CDCl_3$): δ 4.33 (s, 3H, -$OCH_3$), 7.3-8 (m, 9H, aromatic + 2-NH), 8.55 (d, (J = 3 cps), 1H, C-4). $M^+$ 295.

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.40; N, 14.23

Found: C, 65.20; H, 4.38; N, 14.02

Direct Monoacylation of 1 and Rearrangement to Mebendazole(2). Compound 1 (5 g, 0.02 mole) and sodium bicarbonate (5 g, 0.06 mole) were placed in a test tube with joint, equipped with a mechanical screw stirrer. Acetone (35 ml) was used as a solvent. To this vigorously stirred suspension methyl chloroformate (2.5 ml, 0.026 mole) was added using a syringe pump at room temperature. The complete conversion of 1 to 7 took 4 hr. which was monitored by TLC. A catalytic amount (2-3 drops) of triethylamine was added and the mixture was refluxed for 5 hrs. The reaction mixture was cooled to room temperature, filtered and washed with chloroform, water and methanol successively to remove organic and inorganic impurities. The residue was dried (6 g) and crystallized from acetic acid and methanol mixture providing a quantitative yield of Mebendazole, mp. 288.9°, lit.[10] mp. 288.5°. Spectral data identical with compound 2.

Isolation of Compound 7.- The above monoacylation experiment was repeated. After vigorous stirring for 4 hrs the hetereogeneous mixture was filtered and washed with acetone and chloforom. The washings were mixed and concentrated to dryness. The solid residue was crystallized from chloroform providing 7 which melted at 176-177°. The rf on a thin layer chromatogram was the same as 6. However, the spot turned green, on exposure to iodine (compared to yellow colour for 6). IR(Nujol): 3450, 1750, 1650, 1610 $cm^{-1}$. NMR ($CDCl_3$):δ 4.08 (s, 3H, $-OCH_3$), 7.32-7.8 (m, 9H, aromatic + 2-NH), 8.16 (d, J = 3 cps, 1H, C-4).

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.40; N, 14.23

Found: C, 65.32; H, 4.67 ; N. 14.10

Compound 7 (200 mg) and sodium bicarbonate (200 mg) were taken in acetone (2 ml) and refluxed with a catalytic amount of triethylamine for 4-5 hrs. The reaction was monitored by TLC and formation of 2 and traces of 1 were observed.

1-Isopropylsulfonyl-2-amino-5-benzoylbenzimidazole (8)

Method A.- Isopropylsulfonyl chloride[11] was used instead of methyl chloroformate in the general procedure (acetone/$NaHCO_3$ - 2 eq.). It was found that the reaction did not go to completion under these conditions (5 hrs). However, the product was worked up and purified by column chromatography. It was identical in all respects with the authentic sample prepared by the reported[9] method, mp. 186-188° (yield 50%).

IR (Nujol): 3430, 1670, 1640, 1600, 1460 $cm^{-1}$. NMR($CDCl_3$): δ 1.6 [d(7 = 3 cps), 6H, 2-$CH_3$]. 3.8 [q (7 = 3 cps), 1H, -CH $(CH_3)_2$], 6.6 (bs, 2H, exchangeable with $D_2O$, $NH_2$), 7.4-8 (m, 7H, aromatic), 8.1 (s, 1H, C-7). $M^+$ 343.

Anal. Calcd. for $C_{17}H_{17}N_3O_3S$: C, 59.47; H, 4.95; N, 12.24; S, 9.33

Found: C, 59.80; H, 5.25; N, 12.04; S, 9.13

Method B.- Compound 1 (1 g, 0.004 mole) was taken in acetone (7 ml) and triethylamine (0.7 ml, 0.006 mole), and isopropylsulfonyl chloride (0.7 g, 0.0049 mole) was added slowly with stirring at room temperature. After the complete addition the mixture of reactants was refluxed for 6 hrs when only traces of starting material was left and the reaction did not proceed further (as monitored by TLC, silica gel; $CHCl_3$:MeOH, 9:1). The solvent was evaporated; the residue was diluted

with water (10 ml) and extracted with ethyl acetate. The crude product after removal of solvent was crystallized from ethyl acetate (0.9 g, 65% yield).

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(Received November 12, 1985; in revised form June 16, 1986)