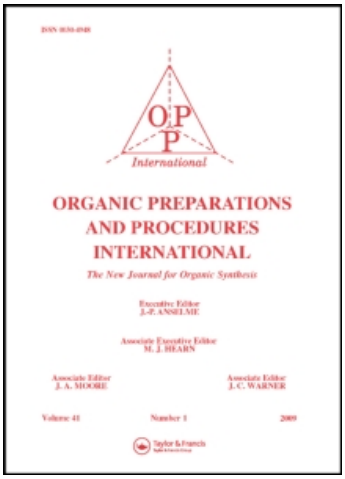


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN ALTERNATE SYNTHESIS OF 3,4-DIAMINOBEZOPHENONE AND OF MEBENDAZOLE

N. R. Ayyangar[a]; R. J. Lahoti[a]; Thomas Daniel[a]
[a] National Chemical Laboratory, Pune, INDIA

To cite this Article Ayyangar, N. R. , Lahoti, R. J. and Daniel, Thomas(1991) 'AN ALTERNATE SYNTHESIS OF 3,4-DIAMINOBEZOPHENONE AND OF MEBENDAZOLE', Organic Preparations and Procedures International, 23: 5, 627 — 631
To link to this Article: DOI: 10.1080/00304949109457915
URL: http://dx.doi.org/10.1080/00304949109457915

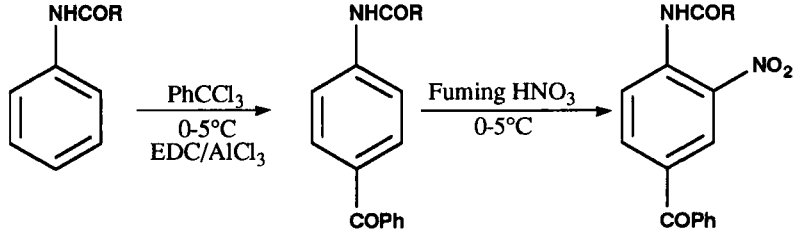
ORGANIC PREPARATIONS AND PROCEDURES INT., 23 (5), 627-631 (1991)

AN ALTERNATE SYNTHESIS OF 3,4-DIAMINOBENZOPHENONE AND OF MEBENDAZOLE†

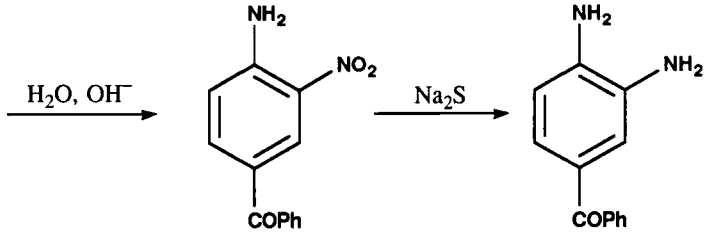
N. R. Ayyangar*, R. J. Lahoti and Thomas Daniel

National Chemical Laboratory
Pune 411 008, INDIA

Methyl [5-(benzoyl)-benzimidazol-2-yl]carbamate or mebendazole (**9**)[1] is one of the important benzimidazole carbamates currently in use as a broad spectrum human and veterinary anthelmintic drug. The main intermediate for mebendazole is 3,4-diaminobenzophenone (**5**). It is easily obtained by the reduction of 3-nitro-4-aminobenzophenone. Earlier we reported the preparation of 3-nitro-4-amino-benzophenone from *o*-nitroanisole and benzoyl chloride by a Friedel-Crafts reaction followed by ammonolysis.[2] This communication describes a new and convenient synthesis of 5 in high yield and purity from methyl N-phenylcarbamate (**1a**) and from acetanilide (**1b**). An important aspect in this one-pot synthesis from readily available starting material is the involvement of an exceptionally stable phenyl dichlorocarbenium tetrachloroaluminate complex as a reactive species.[3]



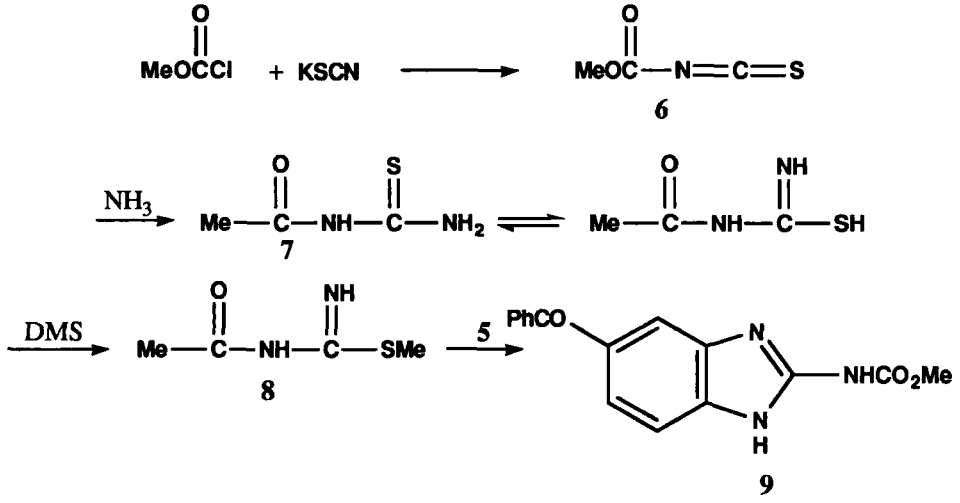
1a: R = OCH_3 **2a**: R = OCH_3 **3a**: R = OCH_3
1b: R = CH_3 **2b**: R = CH_3 **3b**: R = CH_3



4 **5**

Our first approach for the synthesis of **5** from **1a** involved benzoylation, nitration, hydrolysis and reduction. Methyl N-phenylcarbamate (**1a**)[4] was benzoylated under mild conditions using benzotrichloride in quantitative yield; under the same conditions, benzoyl chloride failed to react and benzoic acid was recovered along with **1a**. Compound **2a** was nitrated with fuming nitric acid at low temperature to give methyl (4-benzoyl-2-nitrophenyl)carbamate (**3a**) in quantitative yield. Alkaline hydrolysis of **3a** and subsequent reduction with sodium sulfide gave **5**. All the intermediates were characterized by spectral and elemental analyses. The synthesis of **5** from acetanilide (**1b**) was also carried out[5] under the same conditions in nearly quantitative yield. These routes are comparable and provide alternate approaches to **5**.

The reported methods for the synthesis of mebendazole (**9**) are mostly covered by patents with sketchy descriptions of reaction conditions.[6] A few methods have also been reported which involve either inaccessible reagents or high pressure.[7,8] We have standardized the preparation of **9**, which can be carried out in a one-pot operation, from easily accessible starting materials. The



required reagent (**8**)[9] is obtained from methyl chloroformate by stepwise reactions with potassium thiocyanate, ammonia and dimethyl sulfate. The reaction of **8** with 3,4-diaminobenzophenone 5 gave mebendazole 9 in 95% yield. The structure of **9** was in conformity with its spectral data.[7]

EXPERIMENTAL SECTION

Melting points were obtained in capillary tubes. IR spectra were recorded using a Perkin-Elmer 221 spectrophotometer and ^{1}H NMR spectra were obtained using a Varian FT-80 spectrometer using TMS as the internal reference. Mass spectra were recorded on a Finnigan Mat 1020 automated GC/MS spectrometer.

From Methyl N-Phenylcarbamate

Methyl N-(4-Benzoylphenyl)carbamate (2a).- To a cooled solution (0-5°) of anhydrous aluminium

chloride (40 g, 0.3 mol) in ethylene dichloride (250 ml), benzotrichloride (21.5 g, 0.11 mol) was added over 15 min. This was followed by the addition of **1a** (15.1 g, 0.1 mol) over 0.5 hr. The reaction mixture was stirred for 5 hrs. Completion of the reaction was checked by TLC on silica gel using petroleum ether and ethyl acetate (4:1) as the eluent. The reaction mixture was poured into crushed ice (500 g) and conc. hydrochloric acid (10 ml). The resulting mixture was stirred at 70° for 0.5 hr. After cooling, the organic layer was separated, washed with water (3x250 ml) and dried. The solvent was removed by distillation and the resulting product (**2a**) was crystallized from a mixture of acetone and petroleum ether (v/v, 1:1) as cream white crystals (24.9 g, 98%), mp. 160°. IR (Nujol): 3310, 1730, 1640, 1590, 1460, 1420, 1380, 1330, 1290, 1230, 1080, 930, 850 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.73 (s, 3H, CH_3), 6.7-7.8 (m, 10H, Ar-H and NH); MS: m/e (rel. int. %) 255 (M^+, 100), 239 (20), 222 (71), 178 (100), 168 (20), 141 (21), 118 (40), 105 (89), 77 (86), 63 (44), 44(60).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.09; N, 5.49
Found: C, 70.34; H, 5.20; N, 5.32

Methyl N-(4-Benzoyl-2-nitrophenyl)carbamate (3a).- To an ice cooled (0-5°) solution of methyl N-(4-benzoylphenyl)carbamate (25.5 g, 0.1 mol) was added dropwise fuming nitric acid (9.45 g, 0.15 mol) over 0.5 hr. The temperature was allowed to reach 25° in 15 min. The reaction mixture was maintained at 25° for 0.5 hr, poured into ice and the product collected. Crystallization from methanol gave 28.8 g (96%) of **3a** as brownish yellow needles, mp. 300°. IR (Nujol): 3340, 1740, 1660, 1620, 1580, 1450, 1340, 1280, 1240, 1200, 1170, 1080, 1060, 970, 850, 810, 730 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.88 (s, 3H, OCH_3), 7.4-7.8 (m, 6H, Ar-H); 8.12 (dd, IN, 5.H), 8.72 (d, 1H, 3-H, J = 3Hz), 10.12 (bs, 1H, NH, partially exchangeable with D_2O); MS: m/e (rel. int. %) 300 (M+, 68), 254 (75), 223 (54), 196 (8), 191 (11), 178 (100), 168 (9), 146 (28), 105 (41), 77 (33), 59 (8).

Anal. Calcd. for $C_{15}N_{12}N_2O_5$: C, 60.00; H, 4.00; N, 9.33
Found: C, 59.81; H, 4.15; N, 9.10

4-Amino-3-nitrobenzophenone (4).- Methyl carbamate (**3a**, 30 g, 0.1 mol) was slowly added as a solid with stirring to 100 ml of 6% methanolic sodium hydroxide solution containing 5 ml of water. The reaction mixture was heated at reflux (3 hrs) and excess methanol was distilled off. The residue was poured into water and the product **4** separated. It was collected and crystallized from methanol to yield 22.7 g (94%) of yellow needles, mp. 140°, lit.[10] mp. 140°. ^1H ($CDCl_3$): 3260, 3200, 1660, 1630, 1570, 1530, 1490, 1450, 1420 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.3 (s, 2H, HN_2), 6.66 (d, 1H, 5-H, J = 8Hz), 7.2-7.8 (m, 6H, Ar-H), 8.26 (d, 1H, 2-H, J = 1.5Hz); MS m/e (rel. int. %) 242 (M^+, 18), 195 (6), 165 (100), 139 (5), 119 (44), 105 (62), 91 (14), 77 (32).

3,4-Diaminobenzophenone (5).- Sodium sulfide hexahydrate (60.1 g, 0.25 mol) was dissolved in 250 ml of hot water and was filtered to give a clear solution. 4- Amino-3-nitrobenzophenone (**4**) (24.2 g, 0.1 mol) in 50 ml water was warmed to 85° and sodium sulfide was added in a dropwise manner (4 hrs). The mixture was heated at reflux with stirring for 5 additional hrs, cooled, diluted with water and

the product that separated was collected. Crystallization from a mixture of benzene and petroleum ether (v/v, 1:1) afforded **5** in 19.1 g (90%), mp. 115°, lit.[11] mp. 115-117°. UV λ_{max} MeOH: 253 nm (ε = 13165), 365 nm (ε = 9680); IR (Nujol): 3460, 3380, 3210, 1660, 1610, 1590, 1560, 1450, 1320, 1290, 1160, 1140, 1080, 920, 850, 820, 800, 750, 720, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.40 (bs, 4H, HN_2 exchangeable with D_2O), 6.32 (d, 1H, 5-H, J = 8Hz), 6.76-7.38 (m, 6H, Ar-H), 7.43 (d, 1H, 2-H, J = 3Hz); MS: m/e (rel. int. %)135 (M^+, 100), 107 (27), 91 (18), 80 (14), 77 (21).

Anal. Calcd. for $C_{13}N_{12}N_2O$: C, 73.58; H, 5.66; N, 13.12
Found: C, 73.90; H, 5.60; N, 13.25

Preparation of 3,4-Diaminobenzophenone (5) from Acetanilide.- The reaction procedures for the benzoylation of acetanilide, the subsequent nitration, hydrolysis and reduction are similar to those from methyl N-phenylcarbamate (**1a**) described above.

4-Acetamidobenzophenone (2b).- White needles from aqueous ethanol, yield 23.4 g 12 (98%), mp. 156°, lit.[12] mp. 156°; IR (Nujol): 3340, 1700, 1620, 1575, 1450, 1375,1310, 1250, 1160, 1020, 860, 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, CH_3), 7.2-7.9 (m, 9H, Ar-H), 8.12 (bs, 1H, HN, exchangeable with D_2O); MS: m/e (rel. int. %) 239 (M^+, 68), 197 (62), 180 (3), 162 (10), 141 (14), 120 (100), 150 (5), 92 (8), 77 (3).

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.31; H, 5.43; N, 5.85
Found: C, 75.12; H, 5.35; N, 5.60

4-Acetamido-3-nitrobenzophenone (3b).- Brownish yellow needles from methanol, yield 26.9 g (95%), mp. 144-145°; IR (Nujol): 1700, 1640, 1605, 1570, 1510, 1440, 1360, 1330, 1280, 1220, 1160, 980, 840, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.33 (s, 3H, OCH_3), 7.2-7.8 (m, 5H, Ar-H), 7.93-8.11 (dd, 1H, 6-H); 8.62 (d, 1H, 2H, J = 3Hz), 8.86 (d, 1H, 5H, J = 9Hz), 10.4 (bs, IH, NH, exchangeable with D_2O); MS: m/e (rel. int. %): 284 (M^+, 10), 242 (59), 165 (100), 138 (19), 119 (16), 105 (32), 91 (9), 77 (42).

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.36; H, 4.22; N, 9.40
Found: C, 63.24; H, 4.14; N, 9.26

Preparation of Mebendazole (9).- To a solution of potassium thiocyanate (10.2 g, 0.11 mol) in ethyl acetate (70 ml) was added methyl chloroformate (8.9 g, 0.09 mol) over about 10 min. After stirring at 60° for 1 hr, the reaction niixture was cooled to 0-5° and aqueous ammonia (25%, 7.3 g) was added slowly and stirring was continued for 15 min. The residue obtained on removal of ethyl acetate was warmed with dimethyl sulfate (15.1 g, 0.12 mol) and 50 ml of water for 30 min. The pH of the solution was brought to 6.0 by the addition of aqueous sodium hydroxide. To this solution was added 3,4-diaminobenzophenone (13 g, 0.06 mol) and the mixture was heated between 85-90° for 3 hrs. The product that separated out on cooling was collected and pressed dry. Crystallization from acetic acid gave 16.91 g (95%) of **9** as a colorless product, mp. 303°, lit.[7] mp. 300°.

REFERENCES

† NCL Communication No. 5078

1. H. V. D. Bossche, F. Rochette and C. Horig, "Advances in Pharmacology & Chemotherapy", Vol. **19**, 67, Academic Press, NY (1982).

2. N. R. Ayyangar, R. J. Lahoti, K.V. Srinivasan and T. Daniel, Org. Prep. Proc. Int., **19**, 167 (1987).

3. (a) U. S. Racherla, T. Daniel, P. R. Rajmohanan and N. R. Ayyangar, J. Am. Chem. Soc., **111**, 7659 (1989); (b) N. R. Ayyangar, R. J. Lahoti, K. V. Srinivasan and T. Daniel, Synthesis, 322 (**1991**).

4. T. Boehm and D. Mehta, Ber., **71B**, 1797 (1938); CA, **32**, 9043 (1938).

5. S. D. Rai, T.B. Shivaprasa, S. C. Prasad, R. G. Subbaraghava and N. V. Lakshmi, India IN 157725 (1986); CA, **105**, 226074a (1986).

6. B. A. Charles and R. G. Foster (Imperial Chemical Industries Ltd.), Ger. Offen. 22,246,605 (1973); CA, **81**, 3936t (1974); N. Kalman, T. Geza, S. Antal, G. Csaba, T. Kalman and A. Ilona, Hung Teljes 5800 (1973); CA, **79**, 78801n (1973); H. Kalman, T. Geza, S. Antal, G. Csaba, T. Kalman and A. Ilona K, B. P. 1348460 (1974); CA, **81**, 3936t (1974); B. A. Charles and R. Gregory, B. P. 1350277 (1974); CA, **81**, 256691c (1974); C. R. Taelc, Japan Kokai 77, 19665 (1977); CA, **87**, 117855v (1977); A. H. M. Raeymaker, J. L. H. Van Gelder, L. F. C. Roevens and P. A. J. Janssen; Arzmein. Forsch., **28**, 586 (1978) CA, **89**, 43241j (1978).

7. S. Ram, D. S. Wise and B. Townsend, Org. Prep. Proced. Int., **17**, 215 (1986).

8. T. Ravindranathan, R. D. Wakharkar and A. B. Landge, ibid., **19**, 9 (1987); C. C. Jose, Span E. S. 549233 (1986); CA, **107**, P 7192a (1987).

9. R. W. Lenon, J. Heterocyclic Chem., **5**, 837 (1068).

10. A. Maron and C. Fox, Ber., **47**, 2774 (1914).

11. Catalogue Handbook of Fine Chemicals, Aldrich (USA), 395 (**1990-91**).

12. M. Yasue, M. ltaya and Y. Takai, Yakugaku Zasshi, **81**, 458 (1961); CA, **55**, 18651i (1961).

(Received January 14, 1991; in revised form August 13, 1991)