Synthesis of 6-Chloro-1,5-dimethylbenzimidazole

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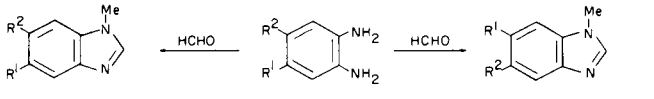
The title compound 6-chloro-1,5-dimethylbenzimidazole (VI) has been synthesized from 5-chloro-4,*N*-dimethyl-2-nitroaniline (X) which was prepared by two independent methods.

J. Heterocyclic Chem., 18, 1635 (1981).

The reaction between 1,2-phenylenediamine and a two-fold molar proportion of formaldehyde in an acidic medium gives 1-methylbenzimidazole (1). When this reaction is applied to unsymmetrically substituted 1,2-phenylenediamines II, two products I and III are possible (2). Only one other example of this reaction was found in the literature; Morgan and Challenor (3) condensed 4-chloro-5-methyl-1,2-phenylenediamine (V) with formaldehyde and described the only product isolated (no yield was given) as 5-chloro-1,6-dimethylbenzimidazole (IV). No mention was made of the possibility of 6-chloro-1,5-dimethylbenzimidazole (VI) being produced. We wish to report the synthesis of this benzimidazole.

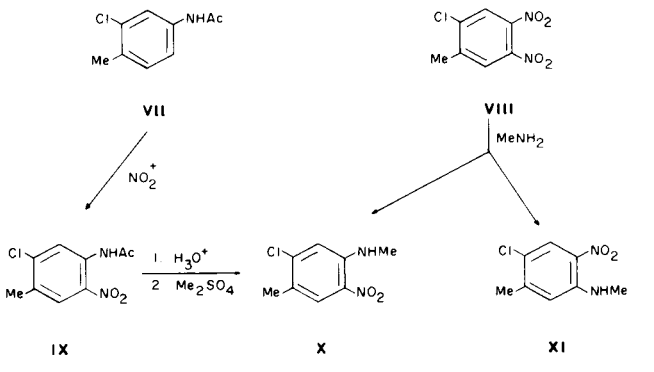


I $R^1 \neq R^2$ II $R^1 \neq R^2$ III $R^1 \neq R^2$

IV R^1 = Cl, R^2 = Me V R^1 = Cl, R^2 = Me VI R^1 = Cl, R^2 = Me

Treatment of 2-chloro-4,5-dinitrotoluene (VIII) (4) with gaseous methylamine gave a mixture of two isomers X and XI in the ratio of 1:0.47. These could not be separated by crystallization or column chromatography but glc gave good separation. Isomer X was also synthesized from 3-chloro-4-methylacetanilide (VII) by nitration (5), hydrolysis of the acyl group and monomethylation (Scheme I). The methylaniline X was cyclized to 6-chloro-1,5-dimethylbenzimidazole (VI) with formic acid;

Scheme I



IX X XI

VI was lower melting than its isomer IV obtained by us from the methylaniline XI and by Morgan and Challenor (3) by the formaldehyde condensation of diamine V.

EXPERIMENTAL

Melting points were determined on a Reichert hot-stage apparatus. Nmr specta were obtained with a Perkin-Elmer R32 (90 MHz) instrument using deuteriochloroform as the solvent. Preparative glc was effected using a Perkin-Elmer F21 Preparative Gas Chromatograph fitted with a 200 cm × 2.5 cm column (10% Carbowax 20M on 60-80 mesh Celite). An ethanol solution of the mixture was injected automatically and the following instrument settings were necessary: column temperature 190°; carrier gas, nitrogen; inlet pressure 18 kNm^{-1}; autoinjection time 15 seconds; injection port, manifold and connecting line temperatures, 250°; detector, flame ionization. The Leeds and Northrup Type W recorder was fitted with a retransmitting potentiometer for trap control. Samples were collected using air-cooled Vigreux-type glass traps with additional filtration with glass beads and glass wool.

Reaction of 2-Chloro-4,5-dinitrotoluene with Methylamine.

Gaseous methylamine was passed into a solution of VIII (10 g) in absolute ethanol (20 ml) at 15°. The mixture (2.5 g) of isomers, mp 120°, was separated by preparative glc (see above) to give two isomers: 5-chloro-4,*N*-dimethyl-2-nitroaniline (X), mp 133-135°; δ 8.00 (1H, s, 3-H) 7.85 (1H, broad, NH), 6.81 (1H, s, 6-H), 2.98 (3H, d, J = 5.0 Hz, N-Me), 2.28 (3H, s, ArMe).

Anal. Calcd. for $C_9H_9ClN_2O_2$: C, 47.9; H, 4.5; Cl, 17.7; N, 14.0. Found: C, 48.2; H, 4.5; Cl, 17.7; N, 14.0.

4-Chloro-5,*N*-dimethyl-2-nitroaniline (XI).

This compound had mp 124-125° (literature (3) 126°).

Anal. Found: C, 47.6; H, 4.5; Cl, 17.7; N, 14.0.

5-Chloro-4,*N*-dimethyl-2-nitroaniline (X).

Acetanilide (IX) was hydrolysed (3) in 88% yield by sulphuric acid at 125-130° to 5-chloro-4-methyl-2-nitroaniline, mp 163-164° (literature (3) 165°). This (4 g) was heated on a steambath for 4 hours with dimethyl sulphate (5 ml) in toluene (30 ml). Removal of the solvent gave the dimethylnitroaniline X (1.9 g, 44%) mp 133-135°, identical with the sample prepared above from 2-chloro-4,5-dinitrotoluene.

6-Chloro-1,5-dimethylbenzimidazole (VI).

A mixture of the nitroaniline (X) (1.5 g) and Adams catalyst (1 g) in ethanol (150 ml) was shaken under hydrogen at 5 atmospheres pressure at room temperature until hydrogen absorption ceased. Ethanol was distilled off and the residue was refluxed for 2 hours with an excess of formic acid. After cooling and basifying with ammonia solution (d, 0.88), the oil was extracted with ether and yielded the benzimidazole VI (0.7 g, 53%), mp 128-129° (light petroleum, bp 40-60°); δ 7.74 (1H, s, 2-H), 7.60 (1H, s, 4-H), 7.34 (1H, s, 7-H), 3.75 (3H, s, N-Me), 2.48 (3H, s, ArMe).

Anal. Calcd. for $C_9H_9ClN_2$: C, 59.8; H, 5.0; Cl, 19.6; N, 15.5. Found: C,

59.4; H, 5.0; Cl, 19.4; N, 15.4.

5-Chloro-1,6-dimethylbenzimidazole (IV).

When the nitromethylaniline XI was similarly treated, it gave a 46% yield of the benzimidazole IV, mp 156-157° (literature (3) 154°); δ 7.72 (2H, s, 2-H and 4-H), 7.14 (1H, s, 7-H), 3.72 (3H, s, N-Me), 2.48 (3H, s, ArMe).

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