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SOLID-PHASE SYNTHESIS OF 1,2-BENZOPHENAZINE AND SOME FUSED IMIDAZOLE DERIVATIVES

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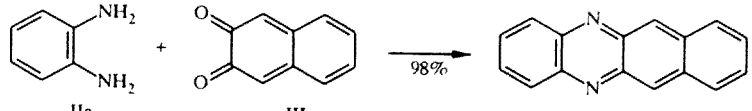
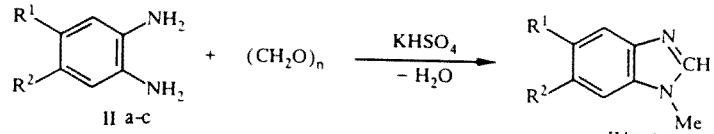
The solid-phase synthesis of 1,2-benzophenazine and various N-methylbenzimidazoles using o-*diaminoarenes is very promising and permits the synthesis of 1-methyl-4,5-[b]naphtho-1H-imidazole, which could not be obtained by the condensation of* o-*diaminoarenes with paraformaldehyde using the standard liquid-phase method.*

Solid-phase synthesis has been extensively studied in recent years as a promising method in organic synthesis and industrial chemistry [1, 2]. Without regard to the mechanism of the interaction of pulverizable materials examined in detail by Enikolopyan [2], the additional energetic (mechanical) effect on the reaction mixture in solid-phase synthesis sometimes eliminates the need for heating, permitting increased reaction selectivity and suppression of the formation of side-products. Thus, we have found that the synthesis of benzo[*b*]phenazine (I) occurs in 98% yield upon treating a mixture of 1,2-phenylenediamine (IIa) and 2,3-naphthoquinone (III) in a vibrational ball mill.



IIa III I

The solid-phase method was also used for the oxidation—reduction condensation of paraformaldehyde with some aromatic 1,2-diamines IIa-IIc, leading to N-methylbenzimidazoles (IVa-IVc). Using the standard procedure [3], N-methylbenzimidazoles IVa and IVb are obtained by heating formaldehyde with the corresponding diamine IIa or IIb in a mixture of ethanol and hydrochloric acid [3].



II a-c IV a-c

In the case of N-methylbenzimidazole IVa and N-methyl-5-chlorobenzimidazole IVb, the solid-phase synthesis leads to the same products as in the reaction in solution but the corresponding procedure is more convenient and suitable for industrial use since it permits the use of available paraformaldehyde and eliminates the need for heating and the use of readily inflammable ethanol and aggressive hydrochloric acid.

Naphtho derivative IVc could not be obtained in solution according to the procedure of Ellis and Jones [3] since the active site 1 in the naphthalene fragment, which is additionally activated by two amino groups, probably is readily hydroxymethylated by paraformaldehyde, which leads to the formation of a polymeric product similar to phenol—formaldehyde resin. However, the use of the solid-phase method led to the first-reported synthesis of N-methylnaphthimidazole IVc.

Thus, the use of the solid-phase method for the synthesis of heterocyclic compounds may significantly simplify the preparation of such compounds and provide for the synthesis of derivatives, which cannot be obtained in solution.

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TABLE 1. Comparison of the Synthesis of Benzimidazoles IV by Different Methods (%, yield)

Compound	Substituents	Standard method	Solid-phase synthesis		
			vibrational mill, steel balls	vibrational mill, silica gel particles	mortar
IVa	$R^1 = H$, $R^2 = H$	35	36	45	30
IVb	$R^1 = Cl$, $R^2 = H$	43 [3]	36	40*	52
IVc	$R^1, R^2 = CH{=}CH{-}CH{=}CH$	0	18	15†	10‡

*The mixture was maintained for 96 h after the solid-phase synthesis.

†After treatment with silica gel particles, the mixture was treated with steel balls and maintained for two months.

‡The solid phase synthesis led to a compound yielding IVa upon sublimation in vacuum.

EXPERIMENTAL

The starting reagents were subjected in the solid state to different types of mechanical treatment: 1) grinding in a mortar, 2) synthesis in an SVM-0.4 vibrational ball mill (120 cm^3 chamber volume, 24 Hz rotation frequency, 1-5 mm vibration amplitude), or 3) synthesis in a 20-cm^3 plastic chamber containing steel beads and activated by a VP mixer. The PMR spectra were taken on a T-60 spectrometer at 60 MHz using HMDS as the internal standard.

Benzo[*b*]phenazine. A mixture of 3.16 g (0.02 mole) 2,3-naphthoquinone III and 2.16 g (0.02 mole) *o*-phenylenediamine IIa was treated in an SVM-0.4 vibrational mill for 10 min at 25-30°C to give 4.5 g (98%) benzo[*b*]phenazine as a yellow powder, mp 142-143°C (142.5°C [4]).

1-Methylbenzimidazole (IVa). A. A mixture of 0.1 g (0.93 mmole) *o*-phenylenediamine IIa, 0.1 g (3.3 mmoles) paraformaldehyde, and 0.45 g (3.3 mmoles) potassium hydrosulfate was stirred in a VP mixer with 1 g sodium sulfate using steel beads as the working element for 4 h and then treated with 5 ml 5% aq. sodium hydroxide. The mixture was extracted with three 3-ml portions of methylene chloride and dried over sodium sulfate. The solvent was evaporated. The residue was dissolved in 1 ml methylene chloride and subjected to chromatography on an alumina column with an upper layer of silica gel using 10:1 methylene chloride—2-propanol as the eluent to obtain 0.047 (36%) 1-methylbenzimidazole IVa as an oil. PMR spectrum in $CDCl_3$: 3.7 (3H, s, CH_3), 7.0-8.0 (5H, m, arom). Lit. mp 33°C [5].

B. The synthesis was carried out analogously to procedure A but solid silica gel particles were used as the working element in the vibration treatment to give 0.06 g (45%) 1-methylbenzimidazole identical to the sample obtained in procedure A.

C. A mixture of *o*-phenylenediamine IIa, paraformaldehyde, potassium hydrosulfate, and sodium sulfate in the amounts indicated in procedure A was maintained in a porcelain mortar for 48 h with intermittent grinding with a pestle. The mixture was treated as in procedure A to give 0.04 g (30%) 1-methylbenzimidazole IVa identical to the sample obtained in procedure A.

1-Methyl-5-chlorobenzimidazole (IVb). A mixture of 0.14 g (1 mmole) 4-chloro-1,2-diaminobenzene, 0.1 g (3.3 mmoles) paraformaldehyde, 0.34 g (2.5 mmoles) potassium hydrosulfate, and 1 g sodium sulfate was stirred in a VP mixer using steel balls as the working element for 4 h and treated as in the above procedures to give 0.06 g (36%) 1-methyl-5-chlorobenzimidazole IVb as an oil. PMR spectrum in CCl_4: 3.8 (3H, s, CH_3), 7.0-8.0 (5H, m, arom). Lit. mp 23-24°C [3].

B. The synthesis was carried out analogously to procedure A but using solid silica gel particles as the working element and then maintaining the mixture for 96 h to give 0.066 g (40%) 1-methyl-5-chlorobenzimidazole IVb identical to the sample obtained in procedure A.

C. A mixture of 4-chloro-1,2-diaminobenzene IIb, paraformaldehyde, potassium hydrosulfate, and sodium sulfate in amounts indicated in procedure A was maintained in a porcelain mortar for 24 h with intermittent grinding using a pestle and treated analogously to procedure A to give 0.085 g (52%) 1-methyl-5-chlorobenzimidazole IVb identical to the sample obtained in procedure A.

1-Methylnaphth[2,3-*d*]imidazole (IVc). A. A mixture of 0.195 g (1.23 mmole) 2,3-diaminonaphthalene, 0.11 g (3.75 mmoles) paraformaldehyde, 0.51 g (3.75 mmoles) potassium hydrosulfate, and 1 g sodium sulfate was treated in a VP

mixture with steel balls as the working element for 3 h and separated as described above to give 0.04 g (18%) 1-methylnaphth[2,3-*d*]imidazole IVc, mp 146-148°C [after sublimation at 160-180°C (15 mm Hg)], mp 154°C (from petroleum ether). Lit. mp 158°C (from octane) [6]. PMR spectrum in $CDCl_3$: 3.86 (3H, s, CH_3), 7.1-8.3 (7H, m, arom).

B. The synthesis was carried out analogously to procedure A but using silica gel particles as the working element, maintained for 24 h, treated in VP mixer with steel balls for 2 h, maintained for two months, and then treated as in procedure A to give 0.033 g (15%) 1-methylnaphth[2,3-*d*]imidazole IVc identical to the sample obtained in procedure A.

C. A mixture of 2,3-diaminonaphthalene IIc, paraformaldehyde, potassium hydrosulfate, and sodium sulfate in the amounts indicated in procedure A was maintained in a porcelain mortar for 24 h with intermittent grinding using a pestle, and then treated analogously to procedure A to give 0.05 g crude product, which upon sublimation at 160°C (15 mm Hg) gave 0.022 g (10%) 1-methylnaphth[2,3-*d*]imidazole (IVc) identical to the sample obtained in procedure A.

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