

A simple route to the preparation of benzimidazoles and benzoxazoles[†]

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The synthesis of benzimidazoles and benzoxazoles by the condensation reaction of *o*-phenylenediamines and *o*-aminophenols with *S*-methylisothioamide hydroiodides on silica gel under microwave irradiation, and also in solvent under reflux, is reported.

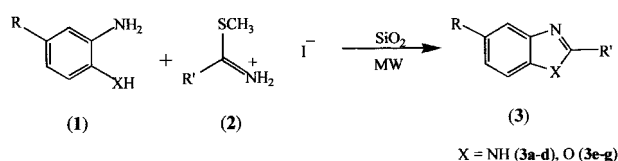
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Reaction under dry condition, *i.e.* in the absence of solvent, on solid support with or without catalyst, are of great interest and is increasingly widespread due to the improved efficiency of many surface bound reagents.^{1,2} Further, with the advent of the microwave dielectric heating technique, the synthesis of organic compounds under microwave irradiation has been developed.^{3–5} Since benzimidazoles are useful heterocycles which have various pharmaceutical⁶ and industrial applications and are used as precursors for the preparation of biologically active compounds,⁷ their synthesis has received considerable attention.

Benzimidazoles were first prepared from the reduction of 2-nitroacetoanilide derivatives.⁸ In 1928, Phillip prepared them by heating carboxylic acids with *o*-phenylenediamines in aqueous hydrochloric acid.⁹ Certain 2-aryl substituted benzimidazoles have been obtained in fair to poor yield by this method.¹⁰ In 1956 Leavitt¹¹ and co-workers reported that polyphosphoric acid is a highly effective, convenient and very generally catalyst for promoting condensation of this type and also for promoting similar condensation leading to benzoxazoles.

Benzoxazoles were first prepared from the reaction of *o*-aminophenols with acetic anhydride.¹² Since then numerous synthetic routes to these compounds have been reported.^{13–15}

In the present work, benzimidazole and benzoxazole derivatives (**3a–g**) have been prepared from the reaction of *o*-phenylenediamines (**1**, X = NH) and *o*-aminophenols (**1**, X = OH) with *S*-methylisothioamide hydroiodides (**2**) on silica gel under microwave irradiation (Scheme 1). These compounds were also prepared in ethanol under reflux; the results are summarized in Table 1. High yields, short reaction times and easy work-up are advantages of the microwave method in comparison to other methods and the conventional reflux conditions.



	R	R'	X
3a	H	Ph	NH
3b	Me	Ph	NH
3c	H	Me	NH
3d	Me	Me	NH
3e	H	Ph	O
3f	Me	Ph	O
3g	Cl	Ph	O

Scheme 1

Experimental

All products are known compounds and were characterised by comparison of their spectral and physical data with those of authentic samples.

Melting points were taken on an Electrothermal 9100 melting point apparatus. IR spectra were recorded with a Shimadzu IR-408 spectrometer (KBr). The ¹H NMR spectra were determined in chloroform-*d* and DMSO-*d*₆ solutions on a FT-NMR Bruker AC-80 (80 MHz). Microwave irradiation was carried out using the commercial microwave oven Moulinex 2735A. Merck silica gel 60GF254 was used for analytical and preparative TLC, and for the solid-phase microwave irradiations.

S-methylisothioamide hydroiodides were prepared according to a literature method.¹⁶

Synthesis of benzimidazole and benzoxazole derivatives under MW irradiation: A mixture of *o*-phenylenediamine (**1a–d**) or *o*-aminophenol (**1e–g**) (2 mmole), *S*-methylisothioamide hydroiodide (2 mmol) and silica gel (2g) was well-ground with a pestle and introduced to the microwave irradiation at full power (850 W) in an open Pyrex

Table 1 Products of the reaction of *o*-phenylenediamines and *o*-aminophenols with *S*-methylisothioamide hydroiodides

Product	Time/min		Yield/%		m.p./°C	lit.m.p.
	Solvent ^a	MW ^b	Solvent ^a	MW ^b		
3a	60	5	77.32	87.63	292–4	294 ⁷
3b	60	4	84.13	93.75	239	239 ⁷
3c	70	5	72.1	83.33	175	176 ⁷
3d	65	5	75	89.2	202	203 ⁷
3e	60	2	79.49	92.3	101–2	101 ¹⁷
3f	60	2	81	95	104	104 ¹⁸
3g	65	2.5	80.2	87.15	103	101 ¹⁸

^aReflux in solvent; ^bwith microwave heating on silica.

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beaker for the appropriate time (Table 1). After complete conversion as indicated by TLC, the mixture was extracted with methylene chloride. The solvent was then evaporated *in vacuo* and the product was purified either by chromatography on a short silica gel column eluting with a suitable solvent, or recrystallised directly from an appropriate solvent. The results are summarized in Table 1.

Synthesis of benzimidazole and benzoxazole derivatives under reflux conditions: A mixture of *o*-phenylenediamine (**1a-d**) or *o*-aminophenol (**1e-g**) (2mmol), and *S*-methylisothioamide hydroiodide (2 mmol) in ethanol (20 ml) was refluxed for appropriate time under a well ventilated hood (due to formation of highly toxic methanethiol). After complete conversion as indicated by TLC, methylene chloride (50 ml) was added to the mixture and the whole was washed with 1N NaOH (50 ml) and saturated aqueous NaCl (50 ml). The dichloromethane layer was dried over MgSO₄ and evaporated *in vacuo* and the product was purified by chromatography on a short silica gel column or recrystallised directly from an appropriate solvent. The results are shown in Table 1.

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