

A Single-step Synthesis of 2-Substituted Benzo-azoles

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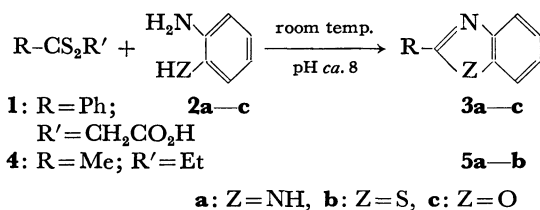
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Synopsis. 2-Substituted benzimidazoles (**3a** and **5a**), benzothiazoles (**3b** and **5b**), and benzoxazole (**3c**) are readily synthesized in good yields by treating (thiobenzoylthio)acetic acid (**1**) or ethyl dithioacetate (**4**) with the corresponding *o*-substituted anilines (**2a**, **2b**, and **2c**) in slightly alkaline media at room temperature.

Numerous methods have been reported for the preparation of 2-substituted benzo-azoles.¹⁾ However, most of them require a procedure with several steps and/or severe reaction conditions.

In our attempt to prepare a series of 2-substituted thiazolines, (thiobenzoylthio)acetic acid²⁾ (**1**) or ethyl dithioacetate³⁾ (**4**) was treated with *o*-substituted anilines having a protic group, such as $-\text{NH}_2$, $-\text{SH}$, or $-\text{OH}$ (**2a**, **2b**, and **2c**), in a similar manner to that reported in a previous paper⁴⁾ to give the corresponding 2-substituted benzo-azoles (**3a**, **3b**, **3c**, **5a**, and **5b**) in good yields. However, **4** with **2c** gave only an acetanilide (**6c**) instead of 2-methylbenzoxazole (**5c**), in a moderate yield.



In a typical experiment, (thiobenzoylthio)acetic acid²⁾ (**1**: 2.0 mmol) and *o*-aminothiophenol (**2b**: 2.2 mmol) were dissolved in aqueous MeOH (3: 1) (40 ml), its pH being adjusted to ca. 8 with 1M NaOH. The solution was stirred at room temperature⁵⁾ under a slightly reduced pressure (aspirator) to remove H₂S

generated until the red coloration of **1** disappeared. The progress of reaction was also monitored by tlc [silica gel, PF₂₅₄-gipshaltig (Merck), hexane-acetone (3: 1)]. The pH of the solution was checked occasionally and adjusted to ca. 8 with alkali. After being acidified with 1M HCl (to pH ca. 3), the resulting 2-phenylbenzothiazole (**3b**) was isolated from the reaction mixture by extraction with CH₂Cl₂ and CHCl₃. Evaporation of solvents followed by crystallization of the residue from aqueous EtOH afforded crystals of **3b**.

Similarly, except for the use of an aqueous EtOH (2: 1) as a solvent, **3a**, **3c**, **5a**, and **5b** were obtained in good yields from the corresponding starting materials (**1** and **4**, with **2a**, **2b**, and **2c**). In the case of **3c**, additional steam distillation of the extracts was necessary to obtain crystals. The reaction conditions and results are summarized in Table 1. The products (**3a**, **3b**, and **3c**) were identified by mp, IR, NMR and mass spectra. Structures of **5a** and **5b** were confirmed by comparison of their mp or bp, IR,⁶⁾ and mass spectra with those of the corresponding authentic samples.

An attempted synthesis of 2-methylbenzoxazole (**5c**) (treatment of **4** with **2c**) gave a colorless crystal, mp 204.5—206 °C (lit, bp of **5c**: 200—201 °C) in a moderate yield, which was identified as *N*-acetyl-*o*-aminophenol (**6c**) by its mp, IR,⁶⁾ and mass spectra. This seems to be a hydrolysis product of *N*-thioacetyl-*o*-aminophenol (**7**).

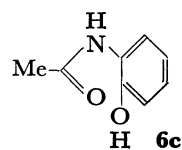


TABLE 1. SYNTHESIS AND PROPERTIES OF 2-SUBSTITUTED BENZO-AZOLES (**3a**, **3b**, **3c**, **5a**, AND **5b**) AND ACETYL-*o*-AMINOPHENOL (**6c**)

Product	Reactn. time (hr)	Solv. ^{a)}	Isolatn. ^{b)}	Yield ^{c)} (%)	mp (bp) [lit.]	<i>m/e</i> (M ⁺)
3a	74	E	A	89	288.5—291 °C [282 °C ^{1e)} , 294.5—295.5 °C ^{1d)}]	194
3b	22	M	B	98	112—113 °C [112.7—113.9 °C ^{1d)}]	211
3c	25	E	C	85	101.5—103 °C [102.5—103.9 °C ^{1d)}]	195
5a	49	E	A	88	178.5—179.5 °C [178.5—179 °C ⁷⁾]	132
5b	66	E	A	85	(121.—123.5 °C/20 mmHg) [(235—239 °C ⁸⁾)]	149
6c	49	E	A	57	204.5—206 °C [201—203 °C, 209 °C ⁹⁾]	151

a) M: aqueous MeOH (1: 1); E: aqueous EtOH (1: 1). b) A: Extd. with EtOAc and CHCl₃; B: Extd. with CH₂Cl₂ and CHCl₃; C: Extd. with CHCl₃, followed by steam distillation. c) Based on **1** or **4** used.

Experimental

The mp and bp are uncorrected. The following instruments were used for the spectral measurements: IR: JASCO IR-G; NMR: JEOL JNM-MH-100 (100 MHz) and MS: JEOL D-100.

The authentic 2-methyl-benzimidazole⁷⁾ (**5a**) and -benzothiazole⁸⁾ (**5b**) were prepared by the methods described in the lit. **5a**: Colorless fine-needles, mp 179–180 °C (64%). **5b**: Colorless liq. bp 121–122.5 °C/20 mmHg (44%). (Thio-benzoylthio)acetic acid⁹⁾ (**1**) and ethyl dithioacetate³⁾ (**4**) were prepared according to the methods described in the lit. **1**: Red fine needles, mp 125 °C (lit.²⁾ 121–124 °C). **4**: Orange-yellow liq., bp 47–50 °C/12 mmHg (lit.³⁾ 52 °C/12 mmHg). $\nu_{\max}$ (neat) 1450, 1190, 1100 cm^{-1} , δ (ppm) (CCl_4) 1.31 (3H, t, $J=7.6$ Hz), 2.79 (3H, s), and 3.17 (2H, q, 7.6).

General Procedure of the synthesis of the azoles (**3a**, **3b**, **3c**, **5a**, and **5b**) is given in the text and their reaction conditions and results are shown in Table 1.

Attempted Synthesis of **5c** (formation of **6c**). Synthetic procedures were similar to the general procedure shown above. The conditions and results are also given in Table 1. **6c**: Colorless leaflets: $\nu_{\max}$ (KBr) 3400, 1655, 1545 cm^{-1} .

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