BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 49(1), 353—354 (1976)

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

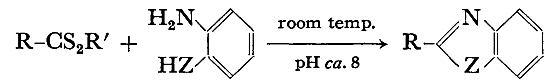
Nobutaka SUZUKI, Toshiyuki YAMABAYASHI, and Yasuji IZAWA*
Department of Industrial Chemistry, Faculty of Engineering, Mie University, Tsu 514

(Received July 28, 1975)

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 acid[2] (**1**) or ethyl dithioacetate[3] (**4**) was treated with *o*-substituted anilines having a protic group, such as $-NH_2$, $-SH$, or $-OH$ (**2a**, **2b**, and **2c**), in a similar manner to that reported in a previous paper[4] 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.



1: R=Ph; **2a**—**c** **3a**—**c**
$R'=CH_2CO_2H$
4: R=Me; R'=Et **5a**—**b**
a: Z=NH, **b**: Z=S, **c**: Z=O

In a typical experiment, (thiobenzoylthio)acetic acid[2] (**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 temperature[5] under a slightly reduced pressure (aspirator) to remove H_2S generated until the red coloration of **1** disappeared. The progress of reaction was also monitored by tlc [silica gel, PF_{254}-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 CH_2Cl_2 and $CHCl_3$. 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**).

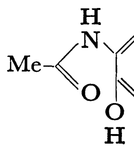

6c

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.]	*m/e* (M+)
3a	74	E	A	89	288.5—291 °C [282 °C[1c], 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 $CHCl_3$; B: Extd. with CH_2Cl_2 and $CHCl_3$; C: Extd. with $CHCl_3$, 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-benzimidazole[7] (**5a**) and -benzothiazole[8] (**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%). (Thiobenzoylthio)acetic acid[2] (**1**) and ethyl dithioacetate[3] (**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). ν_{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: ν_{max} (KBr) 3400, 1655, 1545 cm^{-1}.

References

1) For the reviews: (a) E. Haruki, *Yuki Gosei Kagaku Kyokai Shi*, **26**, 770 (1968); (b) P. N. Preston, *Chem. Revs.*, **74**, 279 (1974). For examples: (c) B. L. Bastic, R. P. Saper, and V. B. Glubovic, *Glasnik Khem. Drushtva Beograd*, **21**, 151 (1956); *Chem. Abstr.*, **54**, 4545a (1960); (d) D. W. Hein, R. J. Alheim, and J. J. Leavitt, *J. Amer. Chem. Soc.*, **79**, 427 (1957); (e) G. L. Jenkins, A. M. Knevel, and C. S. Davis, *J. Org. Chem.*, **26**, 274 (1961); (f) S. Seto, K. Ogura, and Y. Nishiyama, This Bulletin, **36**, 331 (1963); (g) B. L. Bastic and M. V. Piletic, *Glasnik Khem. Drushtva Beograd*, **29**, 139 (1965); *Chem. Abstr.*, **64**, 15863 (1965); (h) H. Fujita, T. Endo, J. Murayama, and T. Ichii, This Bulletin, **45**, 1581 (1972); (i) H. Igeta, T. Nakai, and T. Tsuchiya, *Chem. Commun.*, **1973**, 622; (j) C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, *J. Org. Chem.*, **38**, 613 (1973); (k) F. Hervans and H.-G. Viehe, *Angew. Chem.*, **85**, 446 (1973); (l) G. P. Ellis and R. T. Jones, *J. Chem. Soc. Perkin I*, **1974**, 903; (m) J. Takahashi, T. Suzuki, Y. Suzuki, H. Takeda, T. Zaima, and K. Mitsuhashi, *Nippon Kagaku Kaishi*, **1974**, 1595; (n) J. Chodowska-Palicka and M. Milsson, *Synthesis*, **1974**, 128; (o) B. Stanovnik and M. Tisler, *ibid.*, **1974**, 120, and references cited therein.

2) F. Kurzer and A. Lawson, "Org. Syntheses, Coll. Vol. V," p. 1046 (1973); F. Kurzer, *Chem. Ind.* (London), **1961**, 1333.

3) J. Meijer, P. Vermeer, and L. Vrandsma, *Rec. Trav. Chem. Pays-Bas*, **92**, 601 (1973).

4) N. Suzuki and Y. Izawa, *Tetrahedron Lett.*, **1974**, 1863, and references cited therein.

5) When the reaction mixtures were refluxed in aqueous EtOH or aqueous MeOH until the red coloration of **1** (red) or **4** (reddish orange) disappeared (*ca.* 3 hr), no corresponding benzo-azoles could be obtained.

6) C. J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Co., Inc., Milwaukee, Wisconsin (1970).

7) M. A. Phillips, *J. Chem. Soc.*, **1928**, 2395.

8) A. Hofmann, *Ber.*, **13**, 21, 1236, 1238 (1880).

9) E. Bamberger, *ibid.*, **36**, 2050 (1903).