A Facile Synthesis of 2-(2-Benzothiazolylamino)-1,3-heterazoles

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A simple and versatile method for the synthesis of molecules where an —NH— group links two different heterocyclic moieties is reported. Yields range from moderate to excellent.

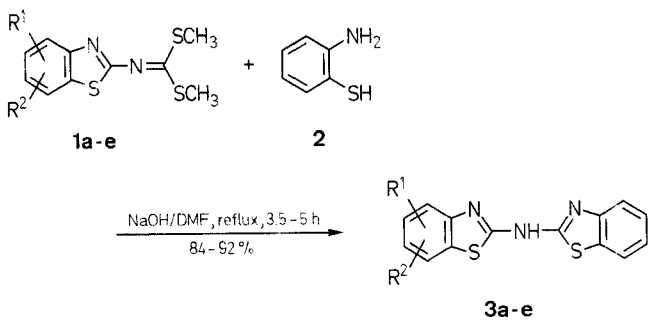
One of the most useful routes to benzo- and heterofused 1,3-heterazoles (e.g., oxazoles, thiazoles) bearing a 2-alkylamino or 2-arylamino group involves the formation of 1,2 and 2,3 bonds from the appropriate *o*-disubstituted aromatic compound and an electrophile supplying the C-2 atom of the new ring. In this context, isothiocyanates, have been widely employed to prepare benzothiazoles,[1] benzoxazoles,[1,2] benzimidazoles[3] and deazapurines,[4] among others.

Nevertheless, these methods are severely limited when 2-(heteroarylamino)-1,3-heterazoles are to be synthesized, mainly due to the instability of the required isothiocyanates (especially those derived from α-aminoheterocycles). A similar situation is found with heteroarylisocyanates and carbodiimides. Furthermore other approaches, such as nucleophilic substitutions on 2-halo- or 2-methylthioazoles using weakly nucleophilic heteroarylamines are only of restricted applicability.

Because of these difficulties, the chemistry of 2-heteroarylamino-1,3-heterazoles remains largely unexplored, and only a few examples are known, despite the interest that these compounds could give rise to in tautomerism studies. In fact, some symmetrically substituted compounds of this type have been prepared,[5–8] but with a few exceptions,[6,9] a simple method for the synthesis of non-symmetrical compounds is still lacking.

In the present paper, and as a continuation of our interest in the field of dithiocarbonimidic acid derivatives,[10,11] we report a facile synthesis of 2-(2-benzothiazolylamino)derivatives of benzothiazole, benzoxazole and oxazolo[4,5-*b*]pyridine. All of them are easily obtained from the corresponding dinucleophilic *o*-disubstituted aromatic compound and substituted dimethyl *N*-(2-benzothiazolyl)dithiocarbonimidates **1**, which, in turn, can be prepared[12] in one step from the corresponding commercially available substituted 2-aminobenzothiazoles, in 60–80% yield. Compounds **3**, **5** and **7** are obtained in moderate to excellent yields (Table).

Thus, reaction of **1** with 2-aminothiophenol in refluxing dimethylformamide, in the presence of one equivalent of sodium hydroxide, yields compounds **3** in very good yield (Scheme **A**). The high nucleophilicity of the thiolate anion thus generated allows compounds **3** to be obtained in good yield and in short reaction times.



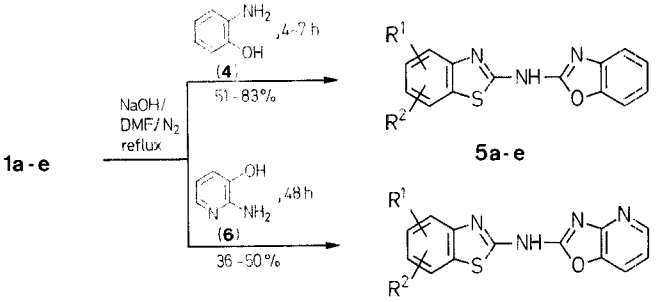
1, 3	R^1	R^2
a	H	H
b	4-Cl	H
c	6-NO_2	H
d	6-OCH_3	H
e	5-CH_3	6-CH_3

Scheme A

In a similar way, the 2-heteroarylamino derivatives of benzoxazole, compounds **5**, and of oxazolo[4,5-*b*]pyridine, compounds **7**, can be prepared from the appropriate *o*-aminohydroxy derivative (Scheme **B**).

In both cases the reactions are carried out in the presence of one equivalent of base and under nitrogen atmosphere to avoid darkening and tar formation due to air oxidation of the corresponding dinucleophile.

When using 2-amino-3-hydroxypyridine (**6**), despite longer reaction times, yields are only moderate and could not be improved by addition of a second equivalent of base.



Scheme **B**

In an attempt to widen the scope of the reaction, dimethyl *N*-(2-thiazolyl)dithiocarbonimidate[13] was reacted with **2**, **4** and **6**, respectively, but extensive decomposition occurred.

The present method of preparing 2-(substituted heteroarylamino)-1,3-heterazoles offers several advantages over previously described procedures: i) it allows greater flexibility, since non-symmetrical compounds can be prepared; ii) starting compounds **1** are readily available[12] and iii) no desulfurizing agent is needed, as is the case when isothiocyanates are used (dicyclohexylcarbodiimide,[1,2] mercury(II)[3] or copper(II)[4] derivatives, etc.).

Melting points were determined using a Büchi 510 apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on a Bruker WP 80 CW spectrometer. Mass spectra were recorded using a Hewlett-Packard 5995-C spectrometer.

2-(2-Benzothiazolylamino)benzothiazoles 3, 2-(2-benzothiazolylamino) benzoxazoles 5 and 2-(2-benzothiazolylamino)oxazolo[4,5-*b*]pyridines 7; General Procedure:

A solution of 2-aminothiophenol, 2-aminophenol or 2-amino-3-hydroxy-pyridine (**2**, **4**, or **6**, respectively; 2.0 mmol) in dimethyl-

Table. Compounds **3**, **5** and **7** Prepared

Product	Reaction Time (hours)	Yield (%)	m.p. (°C) (solvent)	Molecular Formula[a] or Lit. m.p. (°C)	^{1}H-NMR (DMSO-d_6/TMS) δ (ppm)	MS (70 eV) *m/e* (%)
3a	4.5	85	256–257 (butanol)	257–258[5]	7.1–8.1 (m)	283 (M^+, 100)
3b	4.5	90	275–276 (butanol)	$C_{14}H_8ClN_3S_2$ (317.8)	7.1–8.3 (m)	317 (M^+, 100)
3c	3.5	92	294–296 (CH_3CN)	$C_{14}H_8N_4O_2S_2$ (328.4)	7.1–8.3 (m, 6H); 8.85 (d, 1H, J = 2 Hz, H-7)	–[b]
3d	5	84	223–225 (butanol)	$C_{15}H_{11}N_3OS_2$ (313.4)	3.9 (s, 3H, OCH_3); 6.9–8.0 (m, 7H)	313 (M^+, 100)
3e	4.5	87	270–271 (butanol)	$C_{16}H_{13}N_3S_2$ (311.4)	2.3 (s, 6H, $2CH_3$); 7.1–8.0 (m, 6H)	311 (M^+, 100)
5a	6	52	265–266 (butanol)	–[c]	7.0–8.0 (m)	267 (M^+, 100)
5b	6	78	242–244 (butanol)	$C_{14}H_8ClN_3OS$ (301.7)	7.1–8.0 (m)	301 (M^+, 100)
5c	4	83	> 300 (DMF)	$C_{14}H_8N_4O_3S$ (312.3)	7.5–8.0 (m, 5H); 8.55 (dd, 1H, J = 8 Hz, 2 Hz, H-5); 8.85 (d, 1H, J = 2 Hz, H-7)[d]	–[b]
5d	7	51	278–280 (butanol)	$C_{15}H_{11}N_3O_2S$ (297.3)	3.8 (s, 3H, OCH_3); 6.8–7.6 (m, 7H)	297 (M^+, 100)
5e	6	60	> 300 (DMF)	$C_{16}H_{13}N_3OS$ (295.4)	2.4 (s, 6H, $2CH_3$); 7.4–7.8 (m, 6H)[d]	–[b]
7a	48	37	260–262 (butanol)	$C_{13}H_8N_4OS$ (268.3)	7.4–8.8 (m)[d]	268 (M^+, 100)
7b	48	50	266–267 (butanol)	$C_{13}H_7ClN_4OS$ (302.7)	7.4–8.8 (m)[d]	302 (M^+, 100)
7d	48	36	293–295 (DMF)	$C_{14}H_{10}N_4O_2S$ (298.3)	4.05 (s, 3H, OCH_3); 7.3–8.0 (m, 4H); 8.4–8.6 (m, 2H)[d]	298 (M^+, 100)
7e	48	39	> 300 (DMF)	$C_{15}H_{12}N_4OS$ (296.4)	2.5 (s, 6H, $2CH_3$); 7.6–8.0 (m, 3H); 8.4–8.6 (m, 2H)[d]	–[b]

[a] Satisfactory microanalyses obtained: C ±0.25, H ±0.18, N ±0.20.
[b] No volatilization.
[c] Ref. 9, m.p. not stated.
[d] In trifluoroacetic acid/TMS.

formamide (10 ml) is treated with aqueous 5 molar sodium hydroxide (0.4 ml, 2.0 mmol), and the mixture is stirred at room temperature for 30 minutes. Then, a solution of the appropriate dimethyl *N*-(2-benzothiazolyl)dithiocarbonimidate (**1**; 2.0 mmol) in dimethylformamide (15 ml; for **1c** 30 ml are needed) is added dropwise and the reaction mixture is heated under reflux until no more methylmercaptan is evolved. (When reagents **4** or **6** are used, a nitrogen atmosphere is maintained throughout). After cooling, the mixture is poured into water (300 ml) and neutralized to litmus with concentrated hydrochloric acid. The precipitate thus obtained is filtered, washed with water, dried *in vacuo* and recrystallized from the solvent specified in the Table.

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