A Simple, One-Pot Synthesis of Novel 1*H*,3*H*-Thiazolo-[3,4-*a*]benzimidazoles

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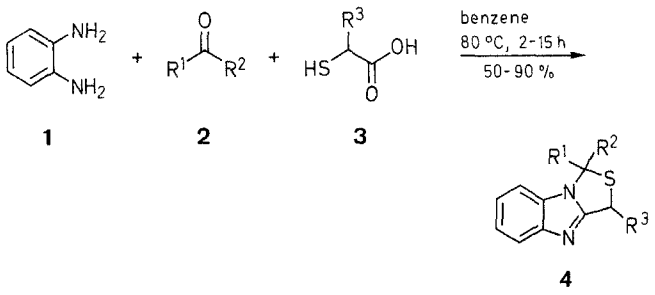
A novel one-pot synthesis of 1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles has been developed by the reaction between *o*-phenylenediamine, 2-mercaptocarboxylic acid and a variety of carbonyl compounds in refluxing benzene.

Thiazolo[3,4-*a*]benzimidazole derivatives have been found to possess interesting biological activity[1] and have therefore attracted interest concerning their synthesis[2,3] and their chemical behavior.[4] In the great majority of the reported cases, syntheses of a variety thiazolo[3,4-*a*]benzimidazoles have been exploited from suitably substituted benzimidazoles as starting material, by promoting cyclization with sulfur containing compounds.[2,3]

In connection with our studies on heteropolycyclic compounds with potential biological activity,[5] we have devised a new approach to the 1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole system and report here a novel one-step synthesis of compounds **4**. To our knowledge, compounds of this class have not been previously reported.

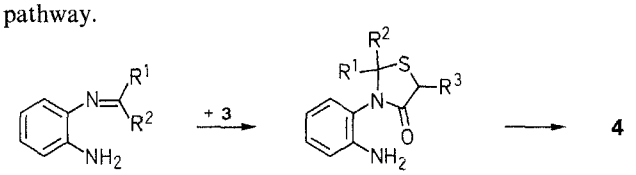


1 2 3 4

o-Phenylenediamine **1** was made to react with a variety of carbonyl compounds **2**, in the presence an excess of 2-mercaptocarboxylic acids **3**, by refluxing in anhydrous benzene. The reaction time has been found to depend on the nature of carbonyl compounds, with ketones being far less reactive than aldehydes. After removal of solvent, 1*H*,3*H*-thiazolo[3,4-*a*]-benzimidazoles **4** were obtained by conventional work-up in satisfactory yields ranging from 50 to 90%.

When aldehydes were used as substrates, bis-azomethine derivatives were obtained as by-products. Their formation, which lowers the yields of 1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles **4**, has been limited by a careful choice of the reaction time and ratio of reactants (see experimental and Table).

The overall reaction can be rationalized as follows: the attack of the 2-mercaptocarboxylic acid at the C=N bond of imino derivative **5**, originating in the first step, affords a thiazolidinone **6** which cyclizes readily to give **4** with elimination of water. The detection,[6] by GC/MS analysis of compounds **5** and **6** in the crude reaction mixture, supports the proposed reaction pathway.



5 6 4

The advantages of the present approach to the novel 1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole system are that the reaction proceeds in one pot, starting from very simple and easily available or commercial precursors, when compared to those approaches

Table. 1*H*,3*H*-Thiazolo[3,4-*a*]benzimidazoles **4a–i** Prepared

Product	R^1	R^2	R^3	Reflux Time (h)	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]	MS (70 eV)[d] *m/z* (%)	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, *J*(Hz)
4a	H	H	H	2	55	137–138	$C_9H_8N_2S$ (176.2)	176 (M^+, 100); 175 (32); 131 (40); 130 (14); 103 (29)	4.25 (s, 2H, 3-CH_2); 5.1 (s, 2H, 1-CH_2); 6.98–7.38 (m, 3H_{arom}); 7.68 (m, 1H_{arom}, H-5)
4b	CH_3	H	H	2	58	73–75	$C_{10}H_{10}N_2S$ (190.2)	190 (M^+, 92); 175 (100); 157 (27); 132 (20); 131 (47)	1.92 (d, 3H, *J* = 6, CH_3); 4.28, 4.38 (dd, 2H, *J* = 15.5, 15.5, CH_2); 5.68 (q, 1H, *J* = 6, CH); 7.07–7.47 (m, 3H_{arom}); 7.73 (m, H_{arom}, 5-H)
4c	*i*-C_3H_7	H	H	2	50	oil	$C_{12}H_{14}N_2S$ (218.3)	218 (M^+, 23); 175 (100); 131 (12)	0.7 (d, 3H, *J* = 7, CH_3); 0.9 (d, 3H, *J* = 7, CH_3); 2.77 [m, 1H, C$\underline{H}$(CH_3)$_2$]; 4.07, 4.17 (dd, 2H, *J* = 15, 15, CH_2); 5.5 (d, 1H, *J* = 3, 1-CH); 6.96–7.33 (m, 3H_{arom}); 7.61 (m, 1H_{arom}, H-5)
4d	*c*-C_6H_{11}	H	H	2	50	121–123	$C_{15}H_{18}N_2S$ (258.4)	258 (M^+, 13); 175; 100; 131 (10)	0.43–2.43 (m, 11H, *c*-C_6H_{11}); 3.95, 4.04 (dd, 2H, *J* = 15.5, 15.5, CH_2); 5.34 (d, 1H, *J* = 3, CH); 6.85–7.25 (m, 3H_{arom}); 7.51 (m, 1H_{arom}, H-5)
4e	C_6H_5	H	H	2	55	134–135	$C_{15}H_{12}N_2S$ (252.3)	252 (M^+, 68); 219 (14); 175 (22); 121 (100)	4.45, 4.54 (dd, 2H, *J* = 15.5, CH_2); 6.56 (br s, 1H, CH); 6.7–7.56 (m, 8H_{arom}); 7.81 (m, 1H_{arom}, H-5)
4f	CH_3	CH_3	H	15	90	108–110	$C_{10}H_{10}N_2S$ (204.3)	204 (M^+, 65); 189 (56); 171 (78); 131 (100)	2.05 (s, 6H, CH_3); 4.27 (s, 2H, CH_2); 7.10–7.42 (m, 3H_{arom}); 7.66 (m, 1H_{arom}, H-5)
4g	C_2H_5	C_2H_5	H	15	60	oil	$C_{11}H_{12}N_2S$ (232.3)	232 (M^+, 19); 203 (100); 131 (20)	0.9 (t, 6H, *J* = 7, CH_3); 2.28 (q, 4H, *J* = 7, C$\underline{H}_2$$CH_3$); 4.33 (s, 2H, CH_2S); 7.01–7.46 (m, 3H_{arom}); 7.68 (m, 1H_{arom}, H-5)
4h	C_6H_5	CH_3	H	20	50	oil	$C_{16}H_{14}N_2S$ (266.3)	266 (M^+, 56); 233 (100); 219 (14); 131 (56); 121 (38); 77 (25)	2.38 (s, 3H, CH_3); 4.4 (s, 2H, CH_2); 6.71–7.81 (m, 9H_{arom})
4i	CH_3	CH_3	CH_3	15	65	oil	$C_{12}H_{14}N_2S$ (218.3)	218 (M^+, 57); 203 (81); 185 (34); 145 (100); 118 (13)	1.85 (d, 3H, *J* = 7, C$\underline{H}_3$CH); 2.05 (s, 3H, C$\underline{H}_3$C); 2.11 (s, 3H, C$\underline{H}_3$C); 4.93 (q, 1H, *J* = 7, C$\underline{H}$$CH_3$); 7.18–7.58 (m, 3$H_{arom}$); 7.88 (m, 1$H_{arom}$, H-5)

[a] Yield of isolated product.
[b] Uncorrected, measured on a Kofler hot-stage apparatus.
[c] Satisfactory microanalysis obtained: C ±0.24, H ±0.16, N ±0.23.
[d] Recorded on a Hewlett-Packard 5995-A GC/MS.
[e] Obtained on a Bruker WP 80 SY spectrometer.

reported earlier. Furthermore, the synthesis allows to introduce a variety of substituents at positions 1 and 3. The method has been tested successfully with more sterically hindered aldehydes and ketones (see Table); only aromatic ketones such as benzophenone, failed to give the expected 1*H*,3*H*-thiazolo[3,4-*a*]-benzimidazoles.

1*H*,3*H*-Thiazolo[3,4-*a*]benzimidazoles 4; General Procedure:
To a stirred solution of *o*-phenylenediamine (**1**; 1.08 g, 10.0 mmol) and the appropriate carbonyl compound **2** (10.0 mmol) in anhydrous benzene (80 mL), an excess of 2-mercaptocarboxylic acid **3** (12.0 mmol) is added. The mixture is then heated under reflux for 2–20 h, the optimum reaction time being determined by TLC monitoring (silica gel; ether/light petroleum, 8:2).

The solvent is evaporated *in vacuo* and the crude product is chromatographed on a silica gel (200 g) column using ether/light petroleum (1:1, 500 mL) as eluent. Crystallization from ether gives product **4** as colorless oil or crystals.

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(6) GC/MS analysis of the crude mixture performed at the earlier steps of the reaction gave correct molecular weights for all the suggested intermediates.