

SYNTHESIS OF PYRAZOLO[1,5-*b*][1,2]BENZISOTHIAZOLES

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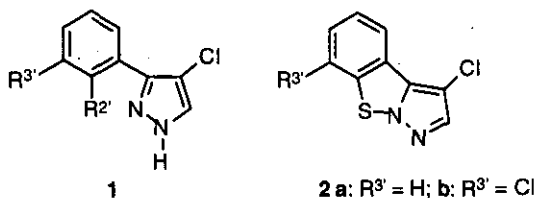
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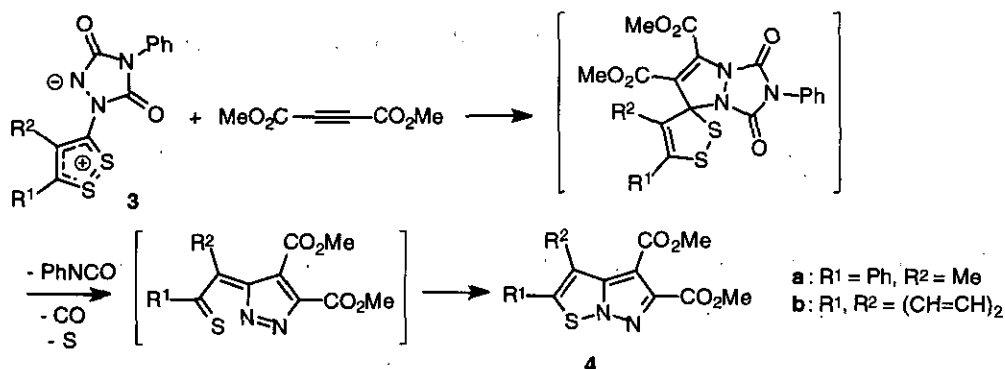
Abstract — The synthesis of some pyrazolo[1,5-*b*][1,2]benzisothiazoles is described. The route is based on the reaction between 3(5)-[2'-methylthiophenyl]pyrazoles and its derivatives with *N*-chlorosuccinimide.

As part of our ongoing effort to screen for new fungicides, we have been examining routes to new heterocycles derived from 3(5*H*)-aryl-4-chloropyrazoles (**1**).¹ We have previously shown that the substituent in position 2' of the phenyl ring appears to be crucial for antifungal activity. Therefore, we designed pyrazolo[1,5-*b*][1,2]benzisothiazoles (**2**) as compounds closely related to **1** with potent biological activity.



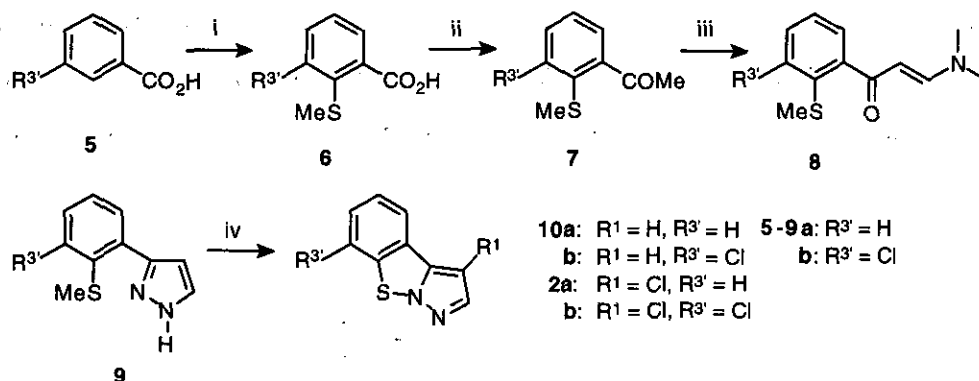
In the literature, there appears to be only one reference to the preparation of pyrazolo[1,5-*b*][1,2]benzisothiazoles.² These investigators reported that heterocyclic azomethine imines with a strongly delocalized positive charge, 1-[3-(1,2-dithio)]urazolides (**3a,b**) formed by the action of 4-phenyl-1,2,4-triazoline-3,5-dione on 3*H*-1,2-dithiol-3-thiones, react as a 1,3-dipole with dimethyl acetylene dicarboxylate, giving pyrazolo[1,5-*b*]isothiazoles (**4a,b**) according to Scheme 1.³ Structure proof was

offered by X-ray crystallographic analysis of **4a**.⁴



Scheme 1

It is apparent from examining Scheme 1 that there is no general method for preparing pyrazolo[1,5-*b*]-[1,2]benzothiazoles and we report in this paper our results related to the preparation of this ring system. In earlier studies we developed efficient synthetic methodologies, involving *ortho*-directed lithiation, for the preparation of *ortho*-substituted benzoic acids.^{1,5} Thus, metalation of unprotected benzoic acids (**5a,b**) under standard conditions (*s*-BuLi/TMEDA/THF/-90 °C) followed by quenching with dimethyl disulfide gave 2-methylthiobenzoic acid (**6a**) and 3-chloro-2-methylthiobenzoic acid (**6b**) in moderate yields (Scheme 2).



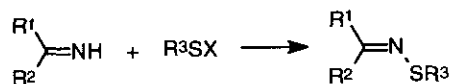
Scheme 2

(i) 2.2 equiv *s*-BuLi/TMEDA, THF, -90 °C; MeSSMe, -78 °C; 4N HCl (**6a**, 52%, **6b**, 65%); (ii) SOCl₂, (CH₂Cl)₂, Δ; EtOMgCH(CO₂Et)₂, Et₂O, Δ; H₂SO₄, AcOH; NaOH, H₂O, pH 7 (**7a**, 78%, **7b**, 57%); (iii) Me₂NCH(OMe)₂, Δ (**8a**, 95%, **8b**, 98%); (iv) NH₂NH₂·H₂O, EtOH, Δ (**9a**, **9b**, 100%); NCS, CH₂Cl₂, room temperature (**2a** 58%; **10b,2b** 69%, 71:19).

The one-pot reaction of the chloride of **6a** or **6b** with diethylmalonate magnesium ethoxide in ether

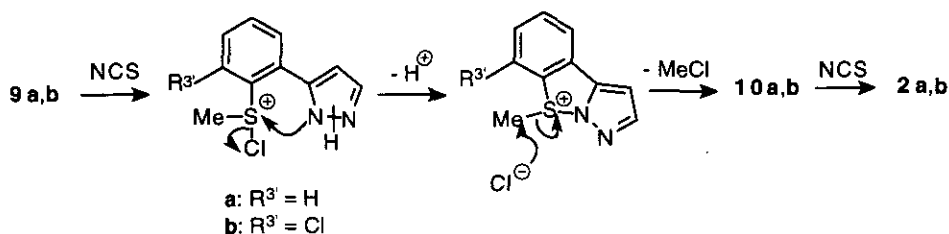
followed by acid hydrolysis afforded the respective acetophenones (**7a**) and (**7b**) in 78 and 57% yields.^{5,6} Subsequent reaction with an excess of *N,N*-dimethylformamide dimethyl acetal⁷ gave 3-dimethylamino-1-[3'(*H*/chloro)-2'-methylthiophenyl]propenones (**8a**) and (**8b**) in almost quantitative yields. The thermal cyclization of the latter compounds with hydrazine hydrate afforded the corresponding 3(5)-3-[3'(*H*/chloro)-2'-methylthiophenyl]pyrazoles (**9a**) and (**9b**) in quantitative yields.^{8,9} The structures of the pyrazole derivatives were secured by their spectral and analytical data (see Experimental).

Examination of the literature reveals that the usual route of synthesis of sulfenylimines involves reaction of an imine with a disulfide or sulfenyl chloride ($X = \text{Cl}, \text{SR}^3$).^{10,11} It thus seemed reasonable to expect that 3-chloropyrazolo[1,5-*b*]isothiazoles could be formed by reaction of **9a** or **9b** with 2 equimolecular amounts of *N*-chlorosuccinimide.¹²



Consequently these two reagents were reacted together in dichloromethane at ambient temperature. After 24 hours the solvent was evaporated and the residue was purified on silica gel column. While derivative (**9b**) containing a chlorine substituent in position 3' of the phenyl ring readily reacted with NCS and yielded **10b** and **2b** as a mixture (71:19) in moderate yield, the derivative unsubstituted in position 3' in phenyl moiety, **9a**, underwent **2a** exclusively. Attempts at the improvement of the yield of the reaction met only a limited success: the use of **9a** in a 3-fold excess of NCS enhanced the yield only to 60%.

The ring closure itself was convincingly revealed—beside the routine infrared data—by significant downfield shifts of the pyrazole protons in ¹H-nmr in accordance with the extension of the heteroaromatic ring current (see Experimental).



Scheme 3

The ring closure reaction may be envisioned to go through the sequential nucleophilic heteroaromatic nitrogen displacement of a chlorine atom followed by dealkylation of the resulting sulfonium salt to form

the sulfenylimine moiety (Scheme 3). Such a reaction path may possibly be initiated by the reaction of the lone pair electrons on the sulfur atom with NCS. Furthermore, it is possible to state that chlorination of the pyrazole ring takes place after the sulfenylimine formation as evidenced by the isolation of **10b**.

In conclusion, the above results provide a fairly simple route to the differently functionalized pyrazolo[1,5-*b*][1,2]benzisothiazoles.

ACKNOWLEDGMENT

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EXPERIMENTAL

Melting points are uncorrected. ¹H-Nmr spectra were recorded on a Bruker AC-250 spectrometer. ¹³C-Nmr spectra were obtained with broad band proton decoupling. For spectra recorded in CDCl₃, chemical shifts are recorded relative to the internal TMS reference signal. For DMSO-*d*₆ and CD₃COCD₃ used as solvents, chemical shifts are given relative to the solvent signals. Infrared spectra were collected with a Bruker IFS-45 spectrometer. Mass spectra were obtained with a VG 70 E mass spectrometer.

Reactions were performed in oven-dried glassware under an argon atmosphere for acid preparation. THF was distilled from deep blue solutions of sodium/benzophenone ketyl prior to use. *s*-BuLi, 1.3 M in cyclohexane, purchased from Janssen Chimica and Aldrich Chemical Company, Inc., was titrated periodically against 2,5-dimethoxybenzyl alcohol. *N,N,N',N'*-Tetramethyl-1,2-ethylenediamine (TMEDA) was distilled from CaH₂ before use.

General procedure for preparation of acids 6a and 6b. To a stirred solution of *s*-BuLi (325 ml of a 1.3 M solution, 0.422 mol) and TMEDA (64 ml, 0.422 mol) in anhydrous THF (300 ml) at -90 °C was added dropwise under argon the recrystallized benzoic acid (**5a**) or (**5b**) (0.192 mol) dissolved in dry THF (100 ml). After 30 min at -90 °C, the mixture was allowed to warm to -78 °C and treated with a solution of dimethyl disulfide (69.1 ml, 0.768 mol) in THF (60 ml). The resulting solution was allowed to warm to ambient temperature, after which water was added. The aqueous layer was washed with ether, and shaken, and then acidified with 4N HCl. The mixture was diluted with ether and the organic layer was separated, dried (MgSO₄) and evaporated. The residue was subjected to recrystallization.

2-Methylthiobenzoic acid (6a). Recrystallization in water afforded 4.37 g (52%) of **6a**.^{13,14}

3-Chloro-2-methylthiobenzoic acid (6b). Recrystallization in heptane/Et₂O afforded 25.2 g (65%) of **6b** as a colorless solid: mp 126-128 °C. ¹H-Nmr (250 MHz, CD₃COCD₃) δ: 9.60 (br, 1H), 7.64 (dd, *J* = 1.2, 7.9 Hz; 1H), 7.52 (dd, *J* = 1.2, 7.9 Hz; 1H), 7.48 (t, *J* = 7.9 Hz; 1H), 2.46 (s, 3H). ¹³C-Nmr (62.9 MHz, CDCl₃) δ: 168.6, 141.9, 138.9, 131.5, 131.1, 129.9, 126.2, 18.7. Eims: *m/z* (relative intensity) 202 (100), 187 (34), 155 (44), 45 (47). Anal. Calcd for C₈H₇O₂ClS: C, 47.41; H, 3.48; Cl, 17.49. Found: C, 47.61; H, 3.44; Cl, 17.42.

General procedure for preparation of acetophenones (7a) and (7b). Benzoic acid (**6a**) or (**6b**) (0.05 mol) was converted into the chloride by heating with thionyl chloride (4.37 ml, 0.06 mol) and a catalytic amount of DMF in 1,2-dichloroethane (50 ml). Solvent and excess of thionyl chloride were removed, and the last traces of the latter were entrained in toluene. The chloride, dissolved in ether (20 ml) was added to a solution of diethyl malonate magnesium ethoxide—prepared from 7.44 g magnesium ethoxide (0.0326 mol) and 10.4 g diethyl malonate (0.0649 mol) in 50 ml refluxing ether. The mixture was warmed for 20 min, cooled, and treated with water and 2N sulfuric acid. The ether solution was separated, dried with MgSO₄, and evaporated. The residue was then refluxed for 2 h with a mixture of concentrated sulfuric acid (2 ml), glacial acetic acid (15 ml), and water (10 ml). The mixture was cooled, poured into cold water, and neutralized with 20% NaOH. The aqueous solution was treated with ethyl acetate. The organic layer was separated, dried with MgSO₄, filtered and concentrated *in vacuo*.

2-Methylthioacetophenone (7a). Chromatography on silica gel (heptane/EtOAc) afforded 6.48 g (78%) of **7a**^{13,15} as a colorless solid: mp 42-44 °C.

3-Chloro-2-methylthioacetophenone (7b). Chromatography on silica gel (heptane/EtOAc) afforded 5.72 g (57%) of **7b** as a colorless oil. ¹H-Nmr (250 MHz, CDCl₃) δ: 7.52 (dd, *J* = 1.0, 7.6 Hz; 1H), 7.30 (t, *J* = 7.6 Hz; 1H), 7.18 (dd, *J* = 1.0, 7.6 Hz; 1H), 2.52 (s, 3H), 2.41 (s, 3H). ¹³C-Nmr (62.9 MHz, CDCl₃) δ: 202.8, 149.3, 140.1, 131.1, 130.6, 129.7, 124.4, 31.3, 19.4. Eims: *m/z* (relative intensity) 200 (30), 185 (100), 170 (6), 150 (24). Ir (KBr): 1703, 1404, 1271, 789 cm⁻¹. Anal. Calcd for C₉H₉OClS: C, 53.87; H, 4.52; Cl, 17.66. Found: C, 53.79; H, 4.71; Cl, 17.48.

General procedure for preparation of propenones (8a) and (8b). Acetophenone (**7a**) or (**7b**) (8.4 mmol) was heated to 40 °C in *N,N*-dimethylformamide dimethyl acetal (5 ml) for 5 h with Dean Stark separator. The solution was cooled and the excess of *N,N*-dimethylformamide dimethyl acetal was removed *in vacuo*.

3-Dimethylamino-1-[2'-methylthiophenyl]propenone (8a). Chromatography on silica gel (dichloromethane/methanol 95:5) gave **8a** (1.76 g, 95%) as a yellow oil. $^1\text{H-Nmr}$ (250 MHz, CDCl_3) δ : 7.58 (d, $J = 12.8$ Hz; 1H), 7.48 (d, $J = 7.6$ Hz; 1H), 7.35-7.25 (m, 2H), 7.12 (t, $J = 7.6$ Hz; 1H), 5.45 (d, $J = 12.8$ Hz; 1H), 3.10 (s, 3H), 2.88 (s, 3H), 2.45 (s, 3H). $^{13}\text{C-Nmr}$ (62.9 MHz, CDCl_3) δ : 191.5, 154.9, 137.7, 129.6, 127.7, 125.8, 124.1, 96.2, 45.0, 37.3, 16.4.

3-Dimethylamino-1-[3'-chloro-2'-methylthiophenyl]propenone (8b). Chromatography on silica gel (ethyl acetate) gave 2.10 g (98%) of **8b** as a yellow solid: mp 105-107 °C. $^1\text{H-Nmr}$ (250 MHz, CDCl_3) δ : 7.45 (dd, $J = 1.8, 7.6$ Hz; 1H), 7.30-7.10 (m, 3H), 5.30 (d, $J = 12.8$ Hz; 1H), 3.09 (s, 3H), 2.88 (s, 3H), 2.40 (s, 3H). $^{13}\text{C-Nmr}$ (62.9 MHz, CDCl_3) δ : 193.0, 155.0, 139.8, 131.4, 129.8, 129.5, 129.1, 125.6, 96.0, 45.0, 37.1, 19.6. Eims: m/z (relative intensity) 255 (15), 240 (40), 237 (22), 98 (100). Ir (KBr): 1632, 1582, 1570, 1348, 1271 cm^{-1} .

General procedure for preparation of pyrazoles (9a) and (9b). A solution of **8a** or **8b** (8.0 mmol) and hydrazine hydrate (0.49 ml, 10.0 mmol) in ethanol (50 ml) was refluxed under a nitrogen stream for 2 h. The solution was then cooled and evaporated. The residue was dissolved in ethyl acetate (100 ml), and the organic layer was washed with water, dried with MgSO_4 , filtered and evaporated to give almost pure **9a** and **9b** in nearly quantitative yield. This was subjected to the following reaction without further purification.

3(5)-[2'-Methylthiophenyl]pyrazole (9a). This compound was obtained as a colorless solid: mp 90-92 °C. $^1\text{H-Nmr}$ (250 MHz, CDCl_3) δ : 7.62 (d, $J = 1.8$ Hz; 1H), 7.51 (d, $J = 7.3$ Hz; 1H), 7.40-7.10 (m, 3H), 6.60 (d, $J = 1.8$ Hz; 1H), 2.40 (s, 3H). Ir (KBr): 3169 cm^{-1} .

3(5)-[3'-Chloro-2'-methylthiophenyl]pyrazole (9b). This compound was obtained as an oil. $^1\text{H-Nmr}$ (250 MHz, CDCl_3) δ : 7.60 (d, $J = 1.8$ Hz; 1H), 7.46 (m, 2H), 7.23 (t, $J = 7.6$ Hz; 1H), 6.65 (d, $J = 1.8$ Hz; 1H), 2.25 (s, 3H).

General procedure for preparation of pyrazolo[1,5-*b*][1,2]benzothiazoles. A mixture of **9a** or **9b** (6.5 mmol) and *N*-chlorosuccinimide (1.73 g, 13.0 mmol) in dichloromethane (50 ml) was stirred under nitrogen for 24 h. After removal of the solvent, the residue was purified.

3-Chloropyrazolo[1,5-*b*][1,2]benzothiazole (2a). Chromatography on silica gel (heptane/ethyl acetate) gave 0.79 g (58%) of **2a** as a colorless solid: mp 146-149 °C. $^1\text{H-Nmr}$ (250 MHz, CDCl_3) δ : 8.13 (m, 1H), 7.72 (s, 1H), 7.60-7.40 (m, 3H). $^{13}\text{C-Nmr}$ (62.9 MHz, CDCl_3) δ : 143.3, 140.7, 139.9, 127.8, 126.0,

122.5, 122.0, 120.0, 102.4. Eims: m/z (relative intensity) 208 (90), 173 (12), 146 (100). Ir (KBr): 1628, 1435, 1346, 1198, 754 cm^{-1} . Anal. Calcd for $\text{C}_9\text{H}_5\text{N}_2\text{ClS}$: C, 51.80; H, 2.42; Cl, 16.99; N, 13.42. Found: C, 51.62; H, 2.41; Cl, 17.05; N, 13.24.

7-Chloropyrazolo[1,5-*b*][1,2]benzisothiazole (10b) and 3,7-dichloropyrazolo[1,5-*b*][1,2]benzisothiazole (2b). Chromatography on silica gel (heptane/ethyl acetate) gave **10b** (0.66 g, 49%) and **2b** (0.32 g, 20%) as colorless solids.

10b: mp 103-105 °C. $^1\text{H-Nmr}$ (250 MHz, CDCl_3) δ : 7.9 (d, $J = 2.4$ Hz; 1H), 7.78 (dd, $J = 2.8, 5.8$ Hz; 1H), 7.50-7.35 (m, 2H), 6.78 (d, $J = 2.4$ Hz; 1H). $^{13}\text{C-Nmr}$ (62.9 MHz, CDCl_3) δ : 145.8, 145.3, 140.0, 127.3, 126.9, 125.7, 125.1, 120.2, 98.3. Eims: m/z (relative intensity) 208 (100), 173 (75), 154 (25), 119 (18). Anal. Calcd for $\text{C}_9\text{H}_5\text{N}_2\text{ClS}$: C, 51.80; H, 2.42; Cl, 16.99; N, 13.42. Found: C, 51.62; H, 2.40; Cl, 17.20; N, 13.62.

2b: mp 135-138 °C. $^1\text{H Nmr}$ (250 MHz, CDCl_3) δ : 8.02 (dd, $J = 2.8, 5.8$ Hz; 1H), 7.78 (s, 1H), 7.50-7.40 (m, 2H). $^{13}\text{C-Nmr}$ (62.9 MHz, CDCl_3) δ : 143.5, 141.2, 139.7, 127.7, 127.4, 125.5, 124.2, 120.2, 103.1. Eims: m/z (relative intensity) 242 (82), 207 (38), 180 (100), 145 (15). Anal. Calcd for $\text{C}_9\text{H}_4\text{N}_2\text{Cl}_2\text{S}$: C, 44.47; H, 1.66; Cl, 29.16; N, 11.52. Found: C, 44.25; H, 1.55; Cl, 29.38; N, 11.50.

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