SYNTHESIS OF 5,7-DIMETHYLPYRAZOLO[3',4':4,5]THIAZOLO-[2,3-*c*]-1,2,4-TRIAZOLE, AN ANALOGUE OF TRICYCLAZOLE

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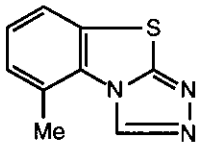
Abstract - An efficient synthesis of 5,7-dimethylpyrazolo[3',4':4,5]thiazolo-[2,3-*c*]-1,2,4-triazole (**2**), an analogue of tricyclazole, was achieved by treatment of 4-(4'-amino-1',3'-dimethylpyrazol-5'-yl)-1,2,4-triazole-3-thione (**7**) with sodium nitrite in acidic medium followed by irradiation with UV light.

New approaches are developing in the search of new fungicides.[1] Melanin biosynthesis inhibition is a new biochemical target aiming at the discovery of selective fungicides. Of the few commercial compounds resulted from this approach, the most important is tricyclazole (**1**) patented by Eli Lilly, which controls *Pyricularia oryzae* by preventing penetration of plant epidermis by fungal hyphae. Tricyclazole caused a weakening of fungal walls by inhibiting melanin synthesis in appressorial cells of fungal pathogens, which lost the ability to penetrate host epidermis and to infect the plant tissues.[2]

Continuing a previous program aimed at the synthesis and biological evaluation of pyrazole derivatives as fungicides, our interest was focused on the synthesis of 5,7-dimethylpyrazolo[3',4':4,5]thiazolo[2,3-*c*]-1,2,4-triazole (**2**), based on the isosterism of the benzene and the pyrazole ring.



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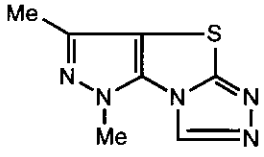
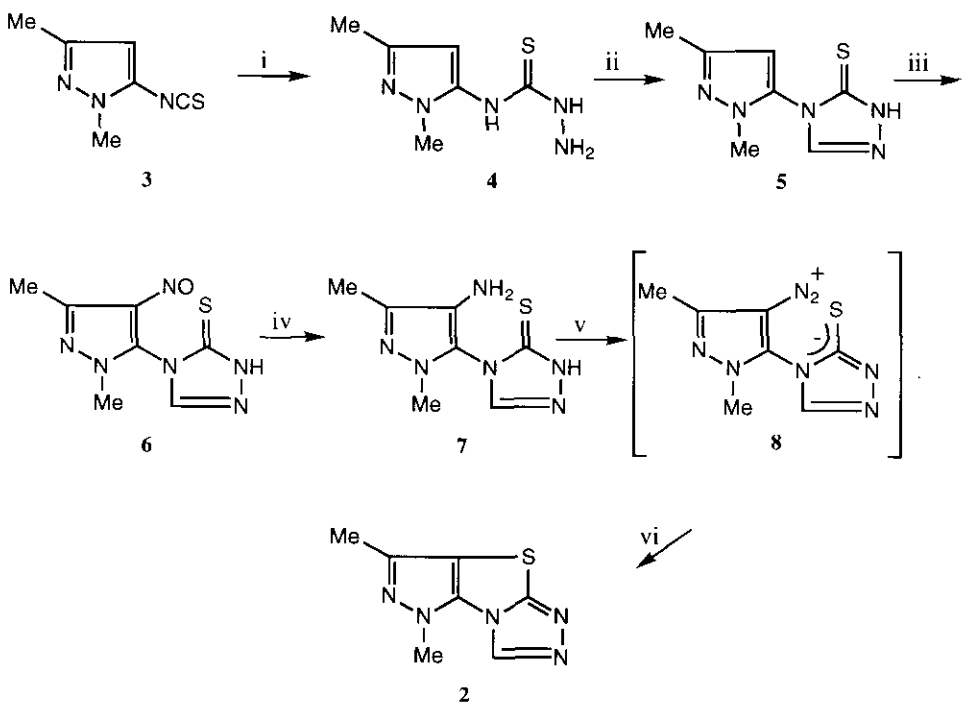


2

Because of the importance of tricyclazole (**1**) and its derivatives, the preparative route to 1,2,4-triazolo-[3,4-*b*]benzothiazoles has been extensively studied. The construction of the benzothiazole-triazole condensed ring was generally achieved by reaction of 2-hydrazinobenzothiazole derivatives with triethyl orthoformate[3] or formic acid.[4] Wikel and Paget also reported the synthesis of analogues of **1** *via* the reaction of 4-(2-halophenyl)-1-acyl-3-thiosemicarbazides with sodium hydride.[5]

Earlier work in our laboratory have shown that diazotization of *N*-(4-aminopyrazol-5-yl)thiocarboxamides afforded the corresponding *N*-alkyl/aryl-*N'*-(4-diazopyrazol-5-yl)ureas which on irradiation with UV light furnished high yields of pyrazolo[3,4-*d*]thiazoles.[6]

Starting from these informations, we decided to investigate a synthetic entry to 5,7-dimethylpyrazolo[3',4':4,5]thiazolo[2,3-*c*]-1,2,4-triazole (**2**), an analogue of tricyclazole (**1**), based on the diazotization of 4-(pyrazol-5'-yl)-1,2,4-triazole-3-thione (**5**).



Reagents: i, N_2H_4; ii, HCOOH, Ac_2O; iii, ethyl nitrite; iv, N_2H_4, 5% Pd/C; v, $NaNO_2$/AcOH; vi, UV irradiation

Scheme

The synthetic plan involves the use of 4-(1',3'-dimethylpyrazol-5'-yl)thiosemicabazide (**4**) obtained from the isothiocyanate (**3**)[7] by condensation with hydrazine hydrate. Cyclization of **4** with formic acid-acetic anhydride provided the key intemediate 4-(1',3'-dimethylpyrazol-5'-yl)-1,2,4-triazole-3-thione (**5**). Nitrosation of **5** and reduction with hydrazine hydrate in the presence of palladized charcoal afforded 4-(4'-aminopyrazol-5'-yl)-1,2,4-triazole-3-thione (**7**). Since **7** was unstable during the usual workup for isolation, it was directly reacted with an equivalent of sodium nitrite in acidic medium. Diazotization of **7** under UV (λ>300 nm) irradiation provided directly the required 5,7-dimethylpyrazolo[3',4':4,5]-thiazolo[2,3-*c*]-1,2,4-triazole (**2**) without isolation of the diazo intermediate (**8**).

The structures of all compounds were confirmed by analytical and spectral data. In particular ^{1}H-NMR spectra of all compounds agree with the proposed structures. The spectrum of compound (**5**) shows two

resonances at 6.00 and 8.44 attributable to the C-H of pyrazole and triazole rings respectively. The spectrum of compound (**2**) shows instead only one resonance attributable to CH of triazole at 8.43 ppm. The ^{13}C-NMR spectrum of compound (**5**) shows resonances at *ca.* 95 (doublet), 141 and 147 ppm attributable to the C-4, C-5 and C-3 of pyrazole ring and at *ca.* 142 (doublet) and 168 ppm attributable to C-5 and C-3 of triazole ring respectively. The ^{13}C-NMR spectrum of compound (**2**) differs from the spectrum of the compound (**5**) mainly in the absorptions of C-5 and C-4a which occur at *ca.* 126 and 115 ppm respectively. These resonances which agree with the values found for similar condensed heterocycles described by us[6,8,9] together with the disappearance of the doublet at *ca.* 95 ppm attributable to CH of pyrazole ring confirm the cyclisation to compound (**2**).

EXPERIMENTAL

Melting point were determined with a Büchi capillary apparatus. The IR spectra were recorded on a Perkin-Elmer Paragon 500 FT-IR spectrophotomether. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC 200 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as internal standard. Column chromatography was performed using Merck silica gel (70-230 mesh); for the flash chromatography tecnique, silica gel (230-400 mesh) was employed. The irradiation of the sample was performed with Pyrex-filtered light from a Helios Italquartz 125W medium-pressure (λ>300 nm) mercury lamp.

4-(1',3'-Dimethylpyrazol-5'-yl)thiosemicarbazide (4)

Hydrazine hydrate (99%, 0.49 mL, 10 mmol) was added to a solution of 1.53 g (10 mmol) of 1,3-dimethyl-5-isothiocyanatopyrazole[7] (**3**) dissolved in 5 mL of ethanol. After the addition was completed, the reaction mixture was stirred at rt for 1 h and filtered. The product was washed with 1 mL of ice-cold ethanol. This compound was obtained as colorless crystals (1.34 g, 72%), mp 169-171°C (ethanol); IR (KBr): 3297, 3178, 1636, 1571 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.09 (s, 3H, Me), 3.51 (s, 3H, NMe), 5.85 (s, 1H, CH), 6.53 (br, 3H, NH_2 + NH), 9.42 (br, 1H, NH). *Anal.* Calcd for $C_6H_{11}N_5S$: C, 38.90; H, 5.99; N, 37.81; S, 17.31. Found: C, 38.78; H, 5.92; N, 37.75; S, 17.22.

2,4-Dihydro-4-(1',3'-dimethylpyrazol-5'-yl)-3*H*-1,2,4-triazole-3-thione (5)

A solution of 0.37 g (2 mmol) of 4-(1',3'-dimethylpyrazol-5'-yl)thiosemicarbazide (**4**) in a mixture of 10 mL of formic acid and 2 mL of acetic anhydride was stirred at rt for 2 h; the solvent was evaporated to yield a residue which was purified by column chromatography, eluent dichloromethane:methanol:toluene 17:2:1,v/v). This compound was obtained as colorless crystals (200 mg, 51%), mp 164-167°C (ethyl acetate/petroleum ether); IR (KBr): 3401, 1602, 1559, 1452 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.26 (s, 3H, Me), 3.86 (s, 3H, NMe), 6.00 (s, 1H, CH), 7.40 (br, 1H, NH), 8.44 (s, 1H, CH); ^{13}C-NMR ($CDCl_3$): δ 14.03 (q, J=126.5 Hz, Me), 35.23 (q, J=139.3 Hz, N-Me), 95.71 (d, J=174.5 Hz, C-4'), 140.98 (s, C-5'), 142.07 (d, J=213.2 Hz, C-5), 147.64 (s, C-3'), 168.69 (s, C-3). *Anal.* Calcd for $C_7H_9N_5S$: C, 43.06; H, 4.65; N, 35.87; S, 16.42. Found: C, 43.15; H, 4.58; N, 35.93; S, 16.31.

2,4-Dihydro-4-(1',3'-dimethyl-4'-nitrosopyrazol-5'-yl)-3*H*-1,2,4-triazole-3-thione (6)

Gaseous ethyl nitrite was bubbled through a solution of 0.58 g (3 mmol) of 2,4-dihydro-4-(1',3'-dimethylpyrazol-5'-yl)-3*H*-1,2,4-triazole-3-thione (**5**) in 18 mL of ethanol for 10 min, then a few drops of concentrated hydrochloric acid were added and the ethyl nitrite bubbling was continued for 30 min. The

ethanol was evaporated and the red solid was collected and washed with petroleum ether to yield 0.42 mg (62%) of **6**, mp 158-160°C (ethyl acetate); IR (KBr): 3400, 1609 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.49 (s, 3H, Me), 3.55 (s, 3H, NMe), 6.13 (br, 1H, NH), 8.75 (s, 1H, CH). *Anal.* Calcd for $C_7H_8N_6SO$: C, 37.49; H, 3.60; N, 37.48; S, 14.30. Found: C, 37.61; H, 3.55; N, 37.60; S, 14.29.

5,7-Dimethylpyrazolo[3',4':4,5]thiazolo[2,3-*c*]-1,2,4-triazole (2)

Hydrazine hydrate (99%, 0.49 mL, 10 mmol) and 5% palladized charcoal (0.15 g) were added to a solution of 0.45 g (2 mmol) of 2,4-dihydro-4-(1',3'-dimethyl-4'-nitrosopyrazol-5'-yl)-3*H*-1,2,4-triazole-3-thione (**6**) in methanol (20 mL). After heating under reflux for 5 min, the catalyst was removed and the filtrate was evaporated to dryness *in vacuo* to give 2,4-dihydro-4-(4'-amino-1',3'-dimethylpyrazol-5'-yl)-3*H*-1,2,4-triazole-3-thione (**7**). The colorless solid was collected, washed with ether (quantitative yield) and directly reacted as follows.

To a stirred and cooled (0°C) solution of 2,4-dihydro-4-(4'-amino-1',3'-dimethylpyrazol-5'-yl)-3*H*-1,2,4-triazole-3-thione (**7**) in 140 mL of methanol and 6 mL of 1 *M* hydrochloric acid, a solution of 0.15 g (2.2 mmol) of sodium nitrite in 5 mL of water was added dropwise and the reaction mixture was allowed to stand at that temperature for 30 min. After being warmed to rt gradually, the mixture was irradiated for 4 h with UV light (λ >300 nm). After evaporation of the solvent, the crude residue was purified by flash column chromatography (eluent dichloromethane:methanol:toluene, 17:2:1, v/v). Compound (**2**) was obtained as colorless crystals (260 mg, 68%), mp 166-168°C (ethyl acetate/petroleum ether); IR (KBr): 1595, 1551, 1472, 1429, 1419 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.58 (s, 3H, Me), 3.94 (s, 3H, NMe), 8.43 (s, 1H, CH); ^{1}H-NMR (DMSO-d_6): δ 2.40 (s, 3H, Me), 3.78 (s, 3H, NMe), 9.07 (s, 1H, CH); ^{13}C-NMR (DMSO-d_6): δ 12.26 (q, J=127.1 Hz, Me), 34.43 (q, J=138.9 Hz, N-Me), 115.11 (s, C-4a), 126.20 (s, C-5), 146.06 (d, J=223.3 Hz, C-1), 151.98 (s, C-7a), 154.36 (s, C-3a). *Anal.* Calcd for $C_7H_7N_5S$: C, 43.51; H, 3.65; N, 36.24; S, 16.59. Found: C, 43.34; H, 3.70; N, 36.37; S, 16.41.

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