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A Novel Route to Fully Substituted 1*H*-Pyrazoles

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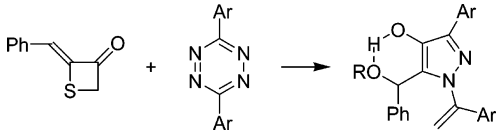


A novel one-step synthesis route to fully substituted pyrazol-4-ols is reported. This simple yet nonobvious method for the construction of pyrazol-4-ols by the condensation−fragmentation−cyclization−extrusion reactions of thietanones with 1,2,4,5-tetrazines is reported. All of the elements of the thietanone except its sulfur are incorporated in these novel products.

Introduction

Synthetic heterocyclic compounds afford solutions to a wide variety of important pharmaceutical[1] and agrochemical[2] problems. As a consequence, extensive research efforts are continually directed at the discovery of novel, small molecule heterocycles with appropriate biological effects. Of special relevance to this work are three substituted pyrazoles (Figure 1):[3] HIV-1 reverse transcriptase inhibitors (e.g., PNU-32945),[4] sodium ion exchanger NHE-1 inhibitors (e.g., zoniporide),[5] and cyclooxygenase-2 COX-2 inhibitors (e.g., celecoxib).[6] In that context, we report here an intriguing new route to 1*H*-pyrazoles which derives from the base-mediated reaction between thietanones and 1,2,4,5-tetrazines.

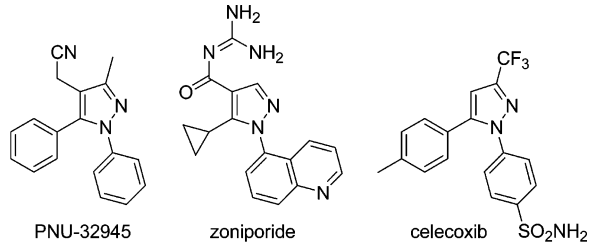
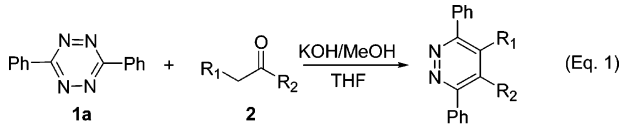
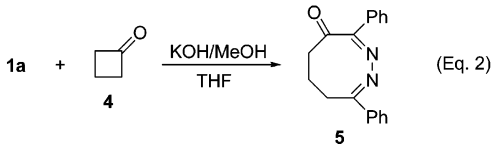


FIGURE 1. Pyrazoles with reverse transcriptase HIV-1, NHE-1, and COX-2 inhibitor properties.

The reactions of electrophilic tetrazines are well documented.[7] For example, in previous work we reported the reactions of 3,6-diphenyl-1,2,4,5-tetrazine (**1a**) with enolate anions as an effective method for pyridazine synthesis (**3**; eq 1).[8] However, we found that when employing the enolate of cyclobutanone, the reaction led not to a pyridazine but to a [1,2]diazocin-4-one (**5**; eq 2).[9]



(Eq. 1)



(Eq. 2)

Results and Discussion

Based on these observations, we were intrigued by the possibility of introducing an additional heteroatom using

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(1) See, for example: (a) Vullo, D.; Voipio, J.; Innocenti, A.; Rivera, C.; Ranki, H.; Scozzafava, A.; Kaila, K.; Supuran, C. T. *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 971−976. (b) Pillai, A. D.; Rani, S.; Rathod, P. D.; Xavier, F. P.; Vasu, K. K.; Padh, H.; Sudarsanam, V. *Bioorg. Med. Chem.* **2005**, *13*, 1275−1283. (c) Broughton, Howard B.; Watson, Ian A. *J. Mol. Graphics Modell.* **2004**, *23*, 51−58.

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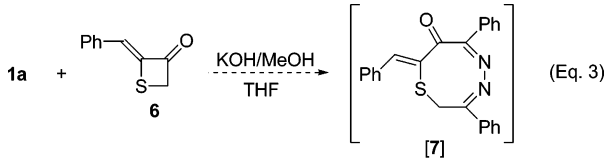
a functionalized cyclobutanone as the starting substrate. Since a reliable route to thietanone **6** was available,[10] we set out to explore its base-mediated reaction with 1,2,4,5-tetrazines. As with observations from **1a** + **4** → **5**, the reaction of thietanone **6** with tetrazine **1a** in 5% methanolic KOH resulted in the immediate evolution of nitrogen gas as well as the discharge of the tetrazine-derived red color of the reaction mixture. However, to our surprise, 2*H*-[1,4,5]thiadiazocin-7-one (**7**) was not isolated from the reaction (eq 3). Rather, the major product from



(Eq. 3)

this reaction displayed a downfield methyl group (~3.5 ppm), suggesting the incorporation of a methoxy from methanolic solvent. ^{1}H NMR also revealed three individual protons at 5.1, 5.2, and 5.6 ppm, and the APT spectrum established that the two protons at 5.2 and 5.6 ppm were attached to the same carbon with a coupling constant of 0.8 Hz. The ^{13}C NMR showed only one C=N and clearly ruled out the possibility of a C=O moiety. IR also confirmed the absence of a carbonyl functional group, but it did display a broad signal consistent with an OH moiety. Low-resolution MS established a mass of 382 *m/z* (interestingly, a molecular weight consistent with 2*H*-[1,4,5]thiadiazocin-7-one (**7**)).

In light of these data, it was our conjecture that the sulfur atom in thietanone **6** was eliminated during the reaction. However, because of the addition of methanol, the product had the same mass as the anticipated thiadiazocinone (**7**). Sulfur extrusion in analogous heterocycle chemistry has been observed previously. For example, the [4 + 2] reactions of tetrazines with R_2C=S heterodienophiles delivers 6*H*-[1,3,4]thiadiazines which can extrude sulfur (Scheme 1).[11]

On the basis of this information, we hypothesized that the product of this thietanone reaction may be a 4*H*-[1,2]-diazepine formed by a ring contraction-based sulfur extrusion with subsequent Michael addition of methanol and enolization to form (**9a**) (R = Me; eq 4). Indeed, reacting **1a** + **6** in ethanolic KOH delivered the analogous ethoxy-containing heterocycle, consistent with our hypothesis (**9b**, R = Et; eq 4). However, this diazepine structure is inconsistent with both the observed ^{1}H NMR coupling constant for the geminal protons (0.8 Hz) as well as the ^{13}C NMR requirement that there be only one C,N-double bond.

SCHEME 1

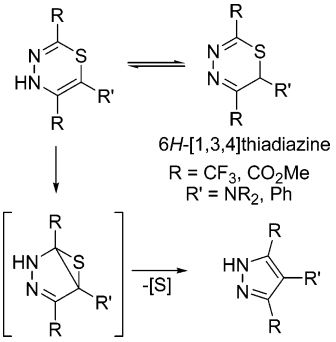
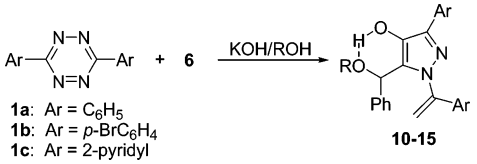
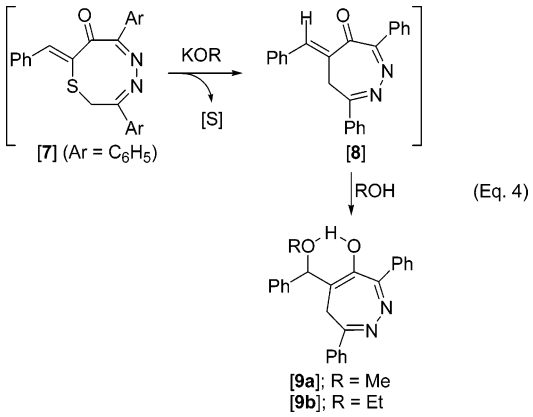


TABLE 1. Synthesis of Fully Substituted 1*H*-Pyrazoles



1,2,4,5-tetrazine	solvent	1*H*-pyrazole
1a	MeOH	**10** (R = Me, 56%)
1a	EtOH	**11** (R = Et, 45%)
1b	MeOH	**12** (R = Me, 48%)
1b	$HOCH_2CH_2OH$	**13** (R = CH_2CH_2OH, 35%)
1c	MeOH	**14** (R = Me, 15%)
1c	$HOCH_2CH_2OH$	**15** (R = CH_2CH_2OH, 9%)



(Eq. 4)

The lack of proton coupling information required us to pursue an X-ray crystallography structure determination. As outlined in Table 1, the reactions of **6** with aryl-substituted tetrazines **1a**–**c** in methanol, ethanol, or ethylene glycol delivered the sulfur-extruded product. The yields were lower with pyridyl-substituted tetrazine **1c** (<20%) both because this highly electrophilic tetrazine decomposes in alcoholic KOH and the electron-withdrawing 2-pyridyl group hampers the nucleophilicity of the enamine nitrogen to effect ring cyclization to a pyrazole moiety (see Scheme 2). While a number of these condensation products were solids, we were consistently unable to obtain crystals suitable for X-ray crystallography. Eventually, repeated recrystallization attempts with a variety of solvents on the product of **1c** + **6** in ethylene glycol produced a collection of feather-like crystals. Under crossed polarizers, one of these appeared to be predomi-

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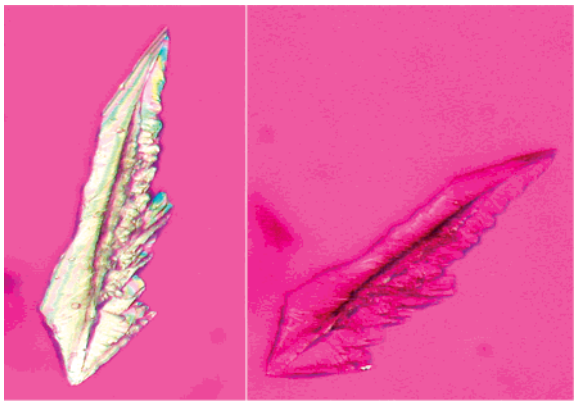


FIGURE 2. Crystal of **15**, viewed under crossed polarizers with a λ plate. The left panel shows the crystal in a general orientation. The right panel shows the crystal aligned to the polarization plane, suggesting that the sample is essentially one single crystal.

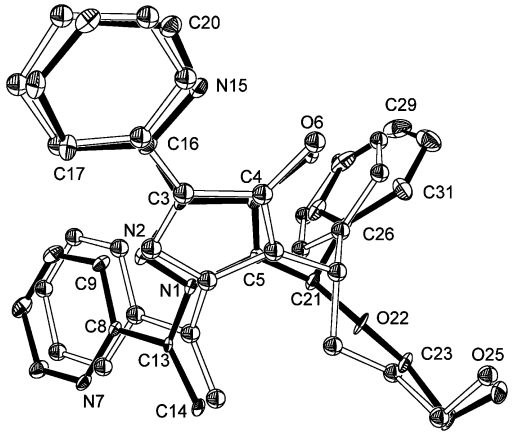
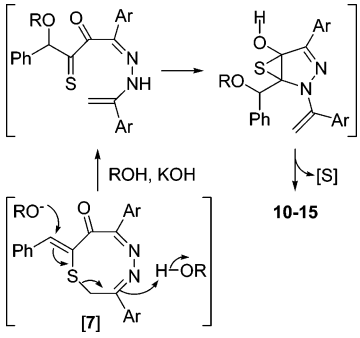


FIGURE 3. X-ray crystal structure of **15**. The fully outlined part represents the main component, with 91% occupancy. The two components are enantiomers. Displacement ellipsoids are drawn at the 50% level (T = 17 K).

SCHEME 2



nantly a single crystal (Figure 2). At the time, the diffractometer was set up for near-liquid He temperature cooling (17 K). Reflections from the unusual-looking crystal were readily indexed, and a data set was obtained. The data yielded the structure shown in Figure 3. While the sample as a whole is a racemic mixture, two enantiomeric molecules are present in a 10:1 ratio in the analyzed crystal. We believe that the very low temperature contributed to a relatively simple resolution of the disorder.[12] Thus, while it was difficult to arrive at a unique interpretation of the NMR spectrum, our X-ray determination afforded a rational answer to this structural problem despite the unusual appearance of the crystal.

The structure solution shows the remarkable outcome that these condensation reactions deliver fully substituted pyrazol-4-ols. This unprecedented pyrazole synthesis poses interesting mechanistic questions—one which we surmise proceeds through the process depicted in Scheme 2. Briefly, we speculate that a Michael addition to **7** initiates a cascade event leading to a ring-opened thioketo/enamine structure. The nitrogen of this enamine attacks the thioketo group which, perhaps via a three-membered thiirane ring intermediate, ultimately extrudes sulfur and delivers the pyrazol-4-ol product. In any case, the spectroscopic data for products **10**–**15** are consistent with the pyrazol-4-ol structural assignment (see Figure 3) as conclusively determined by X-ray crystallography.

In conclusion, we have discovered a simple yet nonobvious method for the construction of pyrazol-4-ols by a consecutive series of condensation–fragmentation–cyclization–extrusion reactions of thietanones with 1,2,4,5-tetrazines. While all of the elements of the thietanone except its sulfur are incorporated in these novel products, the structure of the thietanone is wildly disassembled.

Experimental Section

Preparation of Thietanone 6.[10] Thionyl chloride (20 g, 168 mmol) was added to a flask charged with benzyl acetone (5 g, 33.8 mmol) and 0.2 mL of pyridine at 0 °C, and the resulting mixture was stirred for 14 h at which time the mixture was concentrated in vacuo. Ice–water was added to quench the residual $SOCl_2$, and the mixture was extracted with DCM three times. The combined organic layer was washed with water twice and then with brine. Flash chromatography (SiO_2, 5% EtOAc in hexanes → 15% EtOAc in hexanes) gave **6** (3.60 g, 61%) as a pale yellow solid: ^{1}H NMR δ 7.40 (5H, m), 7.26 (1H, s), 4.44 (2H, s); ^{13}C NMR 188.5, 146.4, 134.2, 129.8, 129.7, 129.3, 122.5, 55.4. These NMR data matched with the reported data.

General Procedure for Preparing Tetrazines.[13] To a solution of 4-bromobenzonitrile (1.5 g, 8.2 mmol) in 10 mL of absolute ethanol containing S_8 (0.18 g, 5.7 mmol) was added hydrazine (0.52 g, 16.4 mmol). The mixture was refluxed for 3 h. The deep orange dihydro-3,6-bis(4-bromophenyl)[1,2,4,5]-tetrazine was isolated by filtration and washed carefully with cold ethanol. Acetic acid (10 mL) and 3 equiv of $NaNO_2$ (1.76 g) were added to the resulting dihydrotetrazine mixture and the mixture stirred for 20 min at which time the orange color turned purple. The solid was washed with a copious amount of water and then methanol. Upon drying, product **1b** (0.88 g, 54%) was used in further reactions without additional purification. All spectral data matched the reported values.[13] For the 3,6-di-2-pyridyl[1,2,4,5]tetrazine (**1c**), a similar procedure was followed (90% yield).

General Procedure for Preparing Pyrazol-4-ol. To a mixture of thietanone **6** (32 mg, 0.18 mmol) and tetrazine **1b** (140 mg, 0.36 mmol) in 6 mL of THF was added 2 mL of 5%

(12) Crystallographic data: colorless, monoclinic, space group $P21/c$; a = 8.5483(11) Å, b = 11.9018(15) Å, c = 20.470(3) Å, β = 100.168(2)°, V = 2050.0(5) Å^3, T = 17(2) K, Z = 4; 6941 reflections, 5435 > 2$\sigma(I)$, R = 0.094; whole molecule disorder, 10:1. Data collection: Bruker SMART APEX II. Structure solution and refinement: SHELXS97 and SHELXL97, Sheldrick, G. M. University of Göttingen, Germany, 1997.

KOH/MeOH. The mixture was stirred for 10 min until TLC showed that all of the thietanone had disappeared. Another three portions of thietanone (3 × 0.18 mmol) were added over a 5 min interval. (In the case of tetrazine **1a**, the reaction rate was much faster.) The mixture was then diluted with water, made slightly acidic with 3 M HCl (in the case of **1c**, the workup was done under basic conditions), and extracted with DCM (3×). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness. Flash chromatography (SiO_2, 15−20% EtOAc/hexanes) delivered **12** as a brown oil (93.5 mg, 48.5%).

Spectral Data. Compound **10** (55.5%): ^{1}H NMR δ 8.01 (2H, d, J = 8.0 Hz), 7.34 (2H, t, J = 7.6 Hz), 7.21(7H, m), 7.11 (2H, m), 7.05 (2H, m), 6.49 (1H, s), 5.47 (1H, d, J = 0.8 Hz), 5.12 (1H, d, J = 0.8 Hz), 5.02 (1H, s), 3.22 (3H, s); ^{13}C NMR 145.5, 139.1, 139.0, 138.3, 136.2, 132.6, 129.5, 129.1, 128.9, 128.7, 128.6, 128.2, 127.6, 126.7, 126.6, 126.4, 112.6, 81.1, 57.3; IR (neat) 3407, 3061, 3028, 2933, 2890, 2828, 1629, 1605, 1585, 1492, 1448, 1364, 1310, 1238, 1074, 1026, 952, 911, 777, 697 cm^{-1}; HPLC purity = 96.3%; LRMS (ESI) calcd for $C_{25}H_{23}N_2O_2$ $(M + H)^+$ 383.18, found 383.24.

Compound **11** (45%): ^{1}H NMR δ 8.02 (2H, d, J = 8.4 Hz), 7.34 (2H, t, J = 7.6 Hz), 7.21 (7H, m), 7.10 (2H, m), 7.05 (2H, m), 6.70 (1H, s), 5.46 (1H, s), 5.12 (1H, s), 5.12 (1H, d, J = 0.8 Hz), 3.36 (2H, m) 1.13 (3H, t, J = 7.2 Hz); ^{13}C NMR 145.5, 139.1, 139.0, 138.8, 136.2, 132.6, 129.4, 128.9, 128.9, 128.7, 128.6, 128.2, 127.6, 126.7, 126.58, 126.5, 112.6, 79.3, 65.3, 15.3; IR (neat) 3417, 3052, 3038, 2976, 2924, 2871, 1633, 1604, 1586, 1493, 1446, 1361, 1239, 1067, 1020, 1002, 903, 773, 691 cm^{-1}; HPLC purity = 100%; LRMS (ESI) calcd for $C_{26}H_{25}N_2O_2$ $(M + H)^+$ 397.19, found 397.12.

Compound **12** (48%): ^{1}H NMR δ 7.94 (2H, d, J = 8.8 Hz), 7.52 (2H, J = 8.8 Hz), 7.34 (2H, J = 8.8 Hz), 7.26 (3H, m), 7.14 (2H, m), 6.90 (2H, J = 8.8 Hz), 6.70 (1H, s), 5.55 (1H, d, J = 0.8 Hz), 5.20 (1H, d, J = 0.8 Hz), 5.12 (1H, s), 3.30 (3H, s); ^{13}C NMR 144.5, 139.0, 138.3, 137.9, 134.9, 131.8, 131.7, 131.4, 129.2, 129.0, 128.3, 128.1, 128.1, 126.6, 123.7, 121.6, 113.2, 81.2, 57.2; IR (neat) 3360, 2971, 2947, 2834, 1630, 1584, 1485, 1440, 1400, 1356, 1236, 1072, 1007, 834, 692, 622 cm^{-1}; HPLC purity = 100%; LRMS (ESI) calcd for $C_{25}H_{21}Br_2N_2O_2$ $(M + H)^+$ 539.00, found 538.90.

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Compound **13** (35%): ^{1}H NMR δ 7.96 (2H, d, J = 8.4 Hz), 7.51 (2H, d, J = 8.4 Hz), 7.35 (2H, d, J = 8.0 Hz), 7.28 (3H, m), 7.18 (2H, m), 6.92 (2H, d, J = 8.0 Hz), 5.51 (1H, d, J = 0.8 Hz), 5.23 (1H, s), 5.18 (1H, d, J = 0.8 Hz), 3.78 (2H, m), 3.60 (1H, m), 3.50 (2H, m); ^{13}C NMR 144.5, 138.9, 138.8, 138.2, 135.0, 131.9, 131.7, 131.4, 129.2, 129.1, 128.2, 128.1, 128.1, 127.0, 123.8, 121.7, 113.3, 79.4, 70.3, 61.8; IR (neat) 3379, 2986, 2933, 2881, 2834, 1630, 1589, 1555, 1486, 1443, 1404, 1355, 1301, 1241, 1090, 1071, 1008, 912, 834, 735, 708 cm^{-1}; HPLC purity = 93.6%; LRMS (ESI) calcd for $C_{26}H_{23}Br_2N_2O_3$ $(M + H)^+$ 569.01, found 569.00.

Compound **14** (15%): ^{1}H NMR δ 8.60 (1H, d, J = 4.8 Hz), 8.50 (1H, d, J = 5.2 Hz), 7.96 (1H, d, J = 8.0 Hz), 7.74 (1H, td, J = 7.6, 1.6 Hz), 7.44 (1H, td, J = 7.6, 2.0 Hz), 7.35 (2H, m), 7.18 (5H, m), 6.61 (1H, d, J = 8.0), 6.58 (1H, s), 5.60 (1H, s), 5.37 (1H, s), 3.31 (3H, s); ^{13}C NMR 154.1, 153.4, 149.5, 147.5, 144.6, 142.6, 139.3, 137.5, 136.8, 135.8, 128.3, 127.8, 127.7, 127.2, 123.6, 122.3, 121.0, 119.1, 118.0, 76.7, 57.2; IR (neat) 3061, 2995, 2971, 2933, 2895, 1598, 1582, 1566, 1517, 1489, 1449, 1423, 1370, 1312, 1272, 1218, 1147, 1115, 1089, 962, 914, 791, 735, 701 cm^{-1}; HPLC purity = 100%; LRMS (ESI) calcd for $C_{23}H_{21}N_4O_2 - HOCH_3$ $(M + H - HOCH_3)^+$ 353.14, found 353.17.

Compound **15** (9%): ^{1}H NMR δ 8.54 (1H, d, J = 5.2), 8.43 (1H, d, J = 5.2), 7.89 (1H, d, J = 8.4), 7.70 (1H, td, J = 8.0, 1.6 Hz), 7.39 (1H, td, J = 8.0, 2.0), 7.27 (2H, m), 7.15 (5H, m), 6.61 (1H, d, J = 8.0), 6.44 (1H, s), 5.50 (1H, s), 5.41 (1H, s), 3.67 (1H, m), 3.52 (3H, m); ^{13}C NMR 153.9, 153.5, 149.6, 147.5, 144.8, 142.1, 139.3, 137.6, 136.9, 135.9, 128.5, 128.1, 127.7, 127.3, 123.7, 122.4, 121.0, 119.1, 118.0, 76.0, 70.9, 62.1; IR (neat) 3360, 3047, 2924, 1601, 1584, 1569, 1448, 1428, 1375, 1320, 1272, 1247, 1124, 1099, 1063, 792, 751, 701 cm^{-1}; HPLC purity = 97.8%; LRMS (ESI) calcd for $C_{24}H_{23}N_4O_3 - HOCH_2CH_2OH$ $(M + H - HOCH_2CH_2OH)^+$ 353.14, found 353.11.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and HPLC data for compounds **10**−**15** as well as X-ray crystallographic data for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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