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Expedient synthesis of pyrazoles substituted with amino, hydroxyl and thioamide groups

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Abstract

The reaction of α,β-acetylenic γ-hydroxy nitriles with thiosemicarbazide, under mild conditions (rt, no catalyst, in 1:1 aqueous ethanol, 4–14 h), proceeds chemo-, regio- and stereoselectively to give atypically so far inaccessible tri-functionalized (amino, hydroxyl and thioamide groups) pyrazoles in 53–91% yields. The hydroxyl function is easily protected by using the corresponding acetals of the starting acetylenic hydroxy nitriles.

Keywords: α,β-Acetylenic γ-hydroxy nitriles; Thiosemicarbazide; Pyrazoles; Nucleophilic addition/cyclization; X-ray crystal structure

Pyrazoles are important compounds in the pharmaceutical industry as the pyrazole motif forms the core structure of numerous biologically active compounds.[1] Pyrazole derivatives have been used as analgesic,[2] antiinflammatory,[3] antipyretic,[4] antidepressant,[5] antibacterial,[6] antimicrobial,[7] anticonvulsant and antifilarial agents,[8] and for the treatment of rheumatoid arthritis.[9] They are also applied as herbicides,[10] fungicides,[11] insecticides[12] and dyestuffs[13] in sunscreen materials,[14] and as analytical reagents.[15]

Hence, numerous methods for the preparation of pyrazoles have been developed. However, the regioselective synthesis of densely functionalized pyrazoles still remains a significant challenge for organic chemists. Thus, a new expedient method for the regioselective synthesis of the functionalized pyrazole derivatives would be an important contribution to pyrazole chemistry.[1b,16] Hydrazines, as starting materials, are employed for the synthesis of pyrazoles. For example, in the usual route to pyrazoles, the reaction of hydrazines with 1,3-dicarbonyl compounds results, as a rule, in a mixture of regioisomers.[1b,17] Also, the syntheses of substituted pyrazoles by the reaction of hydrazones with electron-deficient alkynes are non-regioselective.[18]

In this Letter, we report on the regioselective synthesis of 5-amino-3-hydroxyalkyl-1-aminothiocarbonyl-pyrazoles **2** (in 53–91% yields) by the cyclization of α,β-acetylenic γ-hydroxy nitriles **1a–d** with thiosemicarbazide.[19]

The structural assignment proved to be a difficult task. Indeed, a number of alternative structures with the same composition and mass as well as similar spectra (IR, NMR and UV) could be expected to be formed (Table 1).

For an unambiguous structure assignment, we performed an X-ray analysis of a single crystal of product **2d**, which proved to be 5-amino-3-(1-hydroxycyclohexyl)-1*H*-pyrazole-1-carbothioamide[20] (Fig. 1).

The pyrazole ring is planar, with the maximum deviation of the C(4) and C(5) atoms out of the plane being 0.006 Å. The dihedral angle between the pyrazole ring

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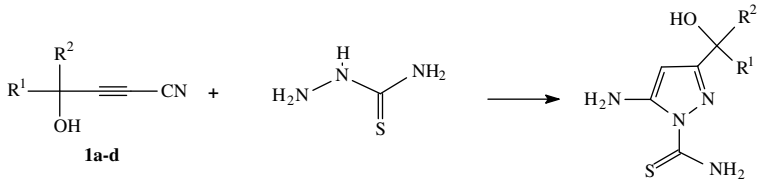
Table 1
The synthesis of 5-amino-3-(1-hydroxyalkyl)-1*H*-pyrazole-1-carbothioamides[a]



R^1	R^2	Product	Time (h)	Yield (%)
Me	Me	**2a**	4	91
Me	Et	**2b**	5	73
Cyclopentyl		**2c**	14	53
Cyclohexyl		**2d**	14	68

[a] The reaction proceeds in aqueous ethanol (1:1 vol) at room temperature.

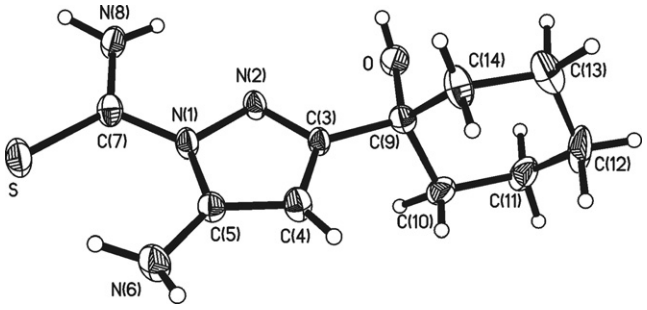


Fig. 1. The X-ray structure of 5-amino-3-(1-hydroxycyclohexyl)-1*H*-pyrazole-1-carbothioamide **2d**.

plane and the SC(7)N(8) plane is 168.2°. In the crystal, all the molecules are directed by thioamide functions to each other and are linked by hydrogen bonds [S···H(8B)—2.61(3) Å, O···H(8A)—2.23(3) Å, N(2)···H(6A)—2.54(3) Å, N(6)···H(O)—2.50(3) Å; Van der Waals radii are S···H—3.15 Å, O···H—2.7 Å, N···H—2.8 Å].[21] Thus, a supramolecular structure exists in the solid state (Figs. 2 and 3).

In the IR spectra of pyrazoles **2a**–**d** (dilute CCl_4 solutions, $c = 1 \times 10^{-1}$ M, $d = 0.5$–200 mm) four absorption bands were present at ca. 3510, 3478, 3356 and 3271 cm^{-1}, which are assigned to the OH (non-associated) and NH_2 (non-associated and associated) groups, respectively.[22]

In the ^1H NMR spectra of compounds **2**, the proton of the pyrazole ring occurred as a singlet at δ 5.43–5.49 ppm. The NH_2 group at the pyrazole C-5 appeared as a broad singlet at δ 7.07–7.11 ppm, while the NH_2 group of the thioamide function appeared as two broad singlets at 8.88–9.00 ppm and 8.37–8.45 ppm. The ^{13}C NMR spectra corresponded with the structures of pyrazoles **2**.[22]

The present cyclization reaction is unexpected. Indeed, it is known that thiosemicarbazide attacks electron-deficient acetylenes (dimethyl acetylenedicarboxylate) initially through the sulfur (as shown for substituted thiosemicarbazides: 4-methyl- and 4-allylthiosemicarbazide).[23] Also

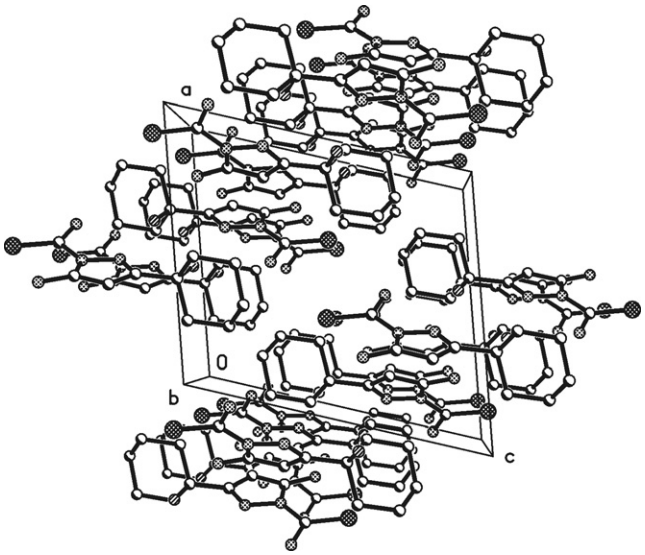


Fig. 2. The supramolecular crystal structure of 5-amino-3-(1-hydroxycyclohexyl)-1*H*-pyrazole-1-carbothioamide **2d** (hydrogen atoms are not shown).

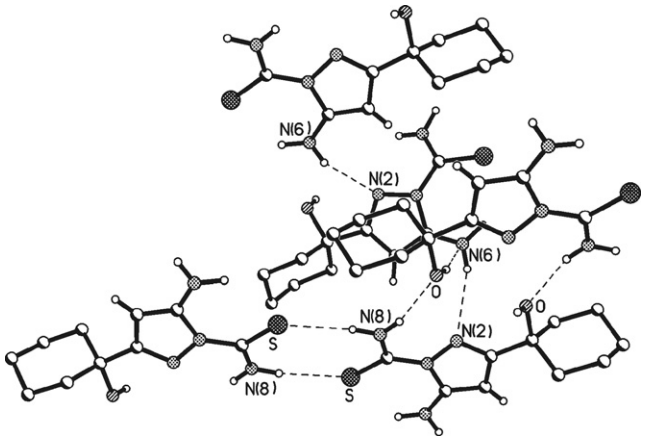
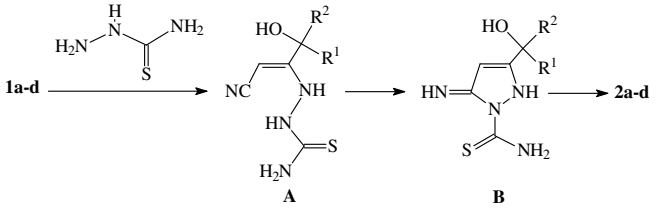


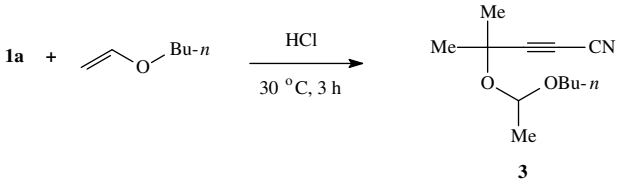
Fig. 3. Fragments of the supramolecular network of 5-amino-3-(1-hydroxycyclohexyl)-1*H*-pyrazole-1-carbothioamide **2d** (hydrogen atoms of cyclohexane are not shown).

reported are examples of thiosemicarbazide addition to triple bonds through the amino group.[24,25] In a short note,[24] it was reported, that the reaction of 1,3-diphenyl-2-propyn-1-one with 1-phenylthiosemicarbazide gave 1,3,5-triphenylpyrazole (characterized by mp and IR spectroscopy). Meanwhile, the addition of thiosemicarbazide to cyanoacetylene stopped after the first step to afford the open-chain adduct.[25]

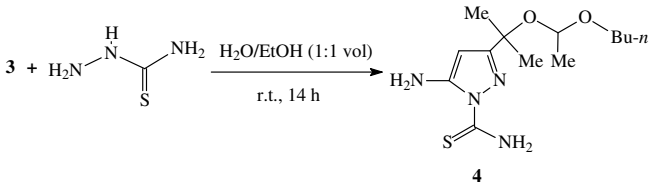
The formation of pyrazoles **2a–d** is likely to start with the addition of the hydrazide amino group to the triple bond of **1** to form intermediate **A**, which cyclizes through the cyano group to furnish iminodihydropyrazole **B**. Finally, a prototropic shift yields pyrazoles **2**.



The synthetic value of this cyclization can be enlarged by the protection of the hydroxyl function in the pyrazoles formed. This was realized by employing the corresponding acetals of type **3** instead of alcohols **1a–d**. Such acetals are readily prepared by the electrophilic addition of the hydroxy derivatives **1a–d** to vinyl ethers.[26]



Acetal **3** reacted with thiosemicarbazide to give pyrazole **4**, with a protected hydroxyl function, in 40% isolated yield (not optimized).



Thus, chemo-, regio- and stereoselective addition of thiosemicarbazide to α,β-acetylenic γ-hydroxy nitriles and their acetal derivatives yields an expedient route to previously inaccessible densely functionalized (amino, hydroxyl, acetal and thioamide groups) pyrazoles, which are the promising substrates for drug design.

Acknowledgements

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19. The reaction was monitored by TLC on Al_2O_3 with chloroform–benzene–ethanol (20:4:1) used as an eluent. Thiosemicarbazide recrystallized from water was employed, mp 183–184 °C. The starting α,β-acetylenic γ-hydroxy nitriles **1a–d** were synthesized from bromo

derivatives of acetylenic alcohols and CuCN in DMF.[27] Nitriles **1a–d** are stable compounds and can be stored at −5 to −8 °C for longer than one year without visible decomposition.

20. Crystal and experimental data: $C_{10}H_{16}N_4OS$, M = 240.33, monoclinic, $P2_1/n$, $a = 10.487(2)$ Å, $b = 10.164(2)$ Å, $c = 11.765(2)$ Å, $\beta = 107.14(3)°$, $V = 1198.3(4)$ Å^3, $Z = 4$, $D_{calcd} = 1.33$ g cm^{-3}, $\mu = 0.256$ mm^{-1}, reflections observed/independent 2475/1906, 194 parameters refined, $R = 0.067$ for 860 reflections with $[F_0 > 4\sigma(F_0)]$. X-ray diffraction was carried out on an Enraf Nonius diffractometer at room temperature ($\omega/2\theta$-scanning, Mo-K_α radiation, graphite monochromator). The crystal structure was solved by direct methods followed by Fourier synthesis using SHELXS-97.[28] All the non-hydrogen atoms were refined using full-matrix anisotropic approximation using SHELXL-97.[28] The coordinates of the hydrogen atoms were defined experimentally and refined isotropically. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 675539. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; (fax: +44 (0)1223 336033; or e-mail: deposit@ccdc.cam.ac.uk).
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22. *General procedure for the synthesis of pyrazoles*: A solution of thiosemicarbazide (0.23 g, 2.5 mmol) in water (4 mL) and ethanol (2 mL) was heated to 43–45 °C, then a solution of hydroxylalkynenitrile (2.5 mmol) **1** in ethanol (2 mL) was slowly added (15 min). The mixture was stirred for 4–14 h at 20–25 °C, after which the majority of the solvent was removed in vacuum. The residue was passed through an Al_2O_3 column (4–5 cm, chloroform–benzene–ethanol as an eluent, 20:4:1). After the removal of the solvents, the crude product was washed consecutively with diethyl ether and hexane, then dried in vacuum to give compounds **2a–d**.

    5-Amino-3-(1-hydroxy-1-methylethyl)-1*H*-pyrazole-1-carbothioamide (**2a**): mp 132–134 °C. ^{1}H NMR [$(CD_3)_2CO$, 400.13 MHz]: δ 8.95 (s, 1H, NH), 8.42 (s, 1H, NH), 7.11 (s, 2H, NH_2), 5.48 (s, 1H, =CH), 4.03 (br s, 1H, OH), 1.43 (s, 6H, CH_3). ^{13}C NMR [$(CD_3)_2CO$, 101.61 MHz]: δ 179.95 (S=C–NH_2), 162.55 (H_2N–*C*=CH), 153.33 (–N=*C*–CH=), 86.64 (=CH), 69.53 [*C*(CH_3)$_2$], 30.38 [(*C*H_3)$_2$C]. IR (KBr): 3381, 3276, 3242, 3140, 2980, 1620, 1600, 1560, 1490, 1460, 1370, 1330, 1220, 1170, 1130, 1090, 1040, 980, 940, 880, 840, 760, 720, 680, 620, 550 cm^{-1}. UV (ethanol): 242 (lgε = 4.08), 275 (lgε = 4.26), 317 (lgε = 3.41) nm. Anal. Calcd for $C_7H_{12}N_4OS$: C, 41.98; H, 6.04; N, 27.98; S, 16.01. Found: C, 42.24; H, 6.20; N, 27.65; S, 15.98.

    5-Amino-3-(1-hydroxy-1-methylpropyl)-1*H*-pyrazole-1-carbothioamide (**2b**): mp 120–122 °C. ^{1}H NMR [$(CD_3)_2CO$, 400.13 MHz]: δ 9.00 (s, 1H, NH), 8.45 (s, 1H, NH), 7.13 (s, 2H, NH_2), 5.43 (s, 1H, =CH), 3.93 (br s, 1H, OH), 1.70, 1.69 (dq, 2H, CH_2, J = 7.26 Hz), 1.37 (s, 3H, CH_3), 0.80 (t, 3H, CH_3, J = 7.53 Hz). ^{13}C NMR [$(CD_3)_2CO$, 101.61 MHz]: δ 178.54 (S=C–NH_2), 160.07 (H_2N–*C*=CH), 151.89 (–N=*C*–CH=), 86.70 (=CH), 72.18 (C_2H_5–*C*–CH_3), 35.06 (*C*H_2–CH_3), 27.84 (CH_3), 7.91 (CH_2–*C*H_3). IR (KBr): 3395, 3276, 3161, 2971, 2932, 2878, 1615, 1557, 1494, 1461, 1416, 1368, 1335, 1201, 1168, 1106, 1037, 999, 976, 917, 899, 846,758, 723, 627, 595, 552 cm^{-1}. Anal. Calcd for $C_8H_{14}N_4OS$: C, 44.84; H, 6.59; N, 26.15; S, 14.66. Found: C, 45.13; H, 6.44; N, 26.35; S, 14.96.

    5-Amino-3-(1-hydroxycyclopentyl)-1*H*-pyrazole-1-carbothioamide (**2c**): mp 122–124 °C. ^{1}H NMR [$(CD_3)_2CO$, 400.13 MHz]: δ 8.95 (s, 1H, NH), 8.40 (s, 1H, NH), 7.11 (s, 2H, NH_2), 5.49 (s, 1H, =CH), 3.90 (s, 1H, OH), 1.98–1.63 (m, 8H, CH_2). ^{13}C NMR [$(CD_3)_2CO$, 101.61 MHz]: δ 179.71 (S=C–NH_2), 161.25 (H_2N–*C*=CH), 153.18 (–N=*C*–CH=), 87.15 (=CH), 80.02, 41.36, 24.50 (*C*-cyclopentyl). IR (KBr): 3522, 3398, 3337, 3287, 3250, 3168, 2964, 2934, 2871, 1615, 1556, 1491, 1451, 1423, 1363, 1328, 1292, 1215, 1179, 1096, 1073, 1039, 1006, 905, 886, 870, 756, 707, 652, 625, 554, 463 cm^{-1}. Anal. Calcd for $C_9H_{14}N_4OS$: C, 47.77; H, 6.24; N, 24.76; S, 14.17. Found: C, 47.69; H, 6.43; N, 24.88; S, 14.55.

    5-Amino-3-(1-hydroxycyclohexyl)-1*H*-pyrazole-1-carbothioamide (**2d**): mp 142–144 °C. ^{1}H NMR [$(CD_3)_2CO$, 400.13 MHz]: δ 8.93 (s, 1H, NH), 8.37 (s, 1H, NH), 7.07 (s, 2H, NH_2), 5.47 (s, 1H, =CH), 3.69 (s, 1H, OH), 1.76–1.49 (m, 10H, CH_2). ^{13}C NMR [$(CD_3)_2CO$, 101.61 MHz]: δ 179.95 (S=C–NH_2), 162.63 (H_2N–*C*=CH), 153.28 (–N=*C*–CH=), 86.69 (=CH), 70.44, 38.29, 26.30, 22.48 (*C*-cyclohexyl). IR (KBr): 3512, 3387, 3343, 3267, 3249, 3171, 3152, 2940, 2912, 2850, 1612, 1555, 1487, 1449, 1422, 1362, 1342, 1259, 1250, 1191, 1178, 1137, 1127, 1079, 1035, 970, 905, 872, 840, 755, 719, 664, 638, 596, 495, 462, 449 cm^{-1}. UV (ethanol): 243 (lgε = 3.98), 275 (lgε = 4.23), 317 (lgε = 3.24) nm. Anal. Calcd for $C_{10}H_{16}N_4OS$: C, 49.98; H, 6.71; N, 23.31; S, 13.34. Found: C, 50.19; H, 6.90; N, 23.61; S, 13.53.
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26. The acetal, 4-(1-butoxyethoxy)-4-methyl-2-pentynenitrile, **3** was synthesized as follows: to a solution of butyl vinyl ether (10 mL) and nitrile **1a** (3.27 g, 30 mmol), a saturated solution of HCl in dry dioxane (0.06 g) was added. The reaction mixture was heated to 30 °C and the mixture was stirred for 3 h. After neutralization with K_2CO_3, the reaction mixture was distilled under vacuum to give 3.76 g (60%) of acetal **3**, bp 88–92 °C (1 mmHg), $[n]_D^{25}$ 1.4415. ^{1}H NMR [$(CD_3)_2CO$, 400.13 MHz]: δ 5.04 (q, 1H, OCHO, ^3J = 5.44 Hz), 3.47 (m, 2H, OCH_2), 1.56 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.49 (m, 2H, CH_2), 1.36 (m, 2H, CH_2), 1.25 (d, 3H, OCHC*H*$_3$O, ^3J = 5.12 Hz), 0.89 (t, 3H, CH_3, ^3J = 7.29 Hz). ^{13}C NMR [$(CD_3)_2CO$, 101.61 MHz]: δ 105.46 (CN), 97.62 [OC*H*(CH$_3$)O], 89.07 (≡*C*C), 70.55 (≡C*C*), 64.85 (OCH_2), 58.08 (≡*C*CN), 32.62 (CH_2), 28.70 [(*C*H_3)$_2$C], 21.67 (OC*C*H_3), 20.09 (*C*H_2CH$_3$), 14.03 (CH_3). IR (KBr): 2975, 2950, 2930, 2863, 2292, 2265, 1460, 1450, 1373, 1360, 1333, 1227, 1155, 1115, 1065, 1020, 1010, 970, 905, 890, 825, 735, 600, 487 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.80; H, 8.94; N, 6.72.

    5-Amino-3-[1-(1-butoxyethoxy)-1-methylethyl]-1*H*-pyrazole-1-carbothioamide (**4**): ^{1}H NMR [$(CD_3)_2CO$, 400.13 MHz]: δ 8.88 (s, 1H, NH), 8.45 (s, 1H, NH), 7.11 (s, 2H, NH_2), 5.45 (s, 1H, =CH), 4.73 [q, 1H, OC*H*(CH$_3$)O, ^3J = 5.37 Hz], 3.32 (m, 2H, OCH_2), 1.52 (s, 6H, CH_3), 1.42–1.31 (m, 4H, CH_2), 1.13 [d, 3H, OCH(C*H*$_3$)O, ^3J = 5.37 Hz], 0.86 (t, 3H, CH_3, ^3J = 7.30 Hz). ^{13}C NMR [$(CD_3)_2CO$, 101.61 MHz]: δ 179.85 (S=C–NH_2), 159.22 (H_2N–*C*=CH), 153.26 (–N=*C*CH=), 95.74 [O*C*H(CH$_3$)O], 87.50 (=CH), 74.54 [*C*(CH$_3$)$_2$], 67.47 (OCH_2), 32.71 (CH_2), 26.35 [(*C*H_3)$_2$C], 21.71 (OC*C*H_3), 19.97 (*C*H_2CH$_3$), 14.14 (CH_3). IR (KBr): 3401, 3279, 3161, 2958, 2932, 2871, 1617, 1561, 1492, 1467, 1381, 1348, 1232, 1150, 1121, 1084, 976, 916, 888, 759, 729, 629, 567 cm^{-1}. Anal. Calcd for $C_{13}H_{24}N_4O_2S$: C, 51.98; H, 8.05; N, 18.30; S, 10.67. Found: C, 52.24; H, 8.23; N, 18.47; S, 10.98.
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