ISSN 1070-4280, Russian Journal of Organic Chemistry, 2012, Vol. 48, No. 10, pp. 1388–1389. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © D.O. Samultsev, E.V. Rudyakova, G.G. Levkovskaya, 2012, published in Zhurnal Organicheskoi Khimii, 2012, Vol. 48, No. 10, pp. 1391–1392.

SHORT COMMUNICATIONS

Selective Synthesis of 3-[1-(Organylsulfanyl)ethyl]- and 3-[2-(Organylsulfanyl)ethyl]-5-chloro-1*H*-pyrazoles

D. O. Samultsev, E. V. Rudyakova, and G. G. Levkovskaya

Favorskii Irkutsk Institute of Chemistry, Siberian Division, Russian Academy of Sciences, ul. Favorskogo 1, Irkutsk, 664033 Russia
e-mail: ggl@irioch.irk.ru

Received May 13, 2012

DOI: 10.1134/S1070428012100259

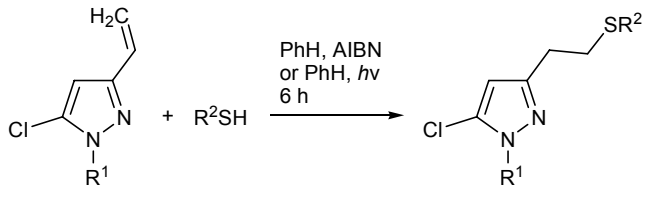
Pyrazole ring constitutes a structural fragment of many up-do-date pharmacologically active compounds possessing analgesic, anti-inflammatory, antibacterial, and other properties. Pyrazole derivatives have found application as insectoacaricides, dyes, luminophores, ligands, etc. [1–4]. At present, search for new synthons for the preparation of pyrazole derivatives is an extensively developing field of study [1–3].

We recently synthesized 3-haloalkyl-5-chloropyrazoles which were used as starting compounds for the preparation of previously unknown 3-alkenyl-5-chloropyrazoles [5] as versatile building blocks for purposeful synthesis of materials for advanced technologies.

The present communication describes a chemoselective synthesis of new regioisomeric 3-{1-[butyl(benzyl)sulfanyl]ethyl}- and 3-{2-[butyl(benzyl)sulfanyl]ethyl}-5-chloropyrazoles by reaction of 3-(1-chloroethyl)- and 3-vinyl-5-chloropyrazoles with butane-1-thiol and phenylmethanethiol, respectively.

Radical addition of thiols to 5-chloro-3-vinyl-1*H*-pyrazoles **Ia** and **Ib** gave the corresponding anti-Markovnikov adducts, 3-{2-[butyl(benzyl)sulfanyl]-ethyl}-5-chloro-1*H*-pyrazoles **IIa** and **IIb** in 77–80% yield. The reactions were carried out by heating equimolar amounts of the reactants in benzene at 60°C in the presence of azobis(isobutyronitrile) (AIBN) or under UV irradiation over a period of 6 h (Scheme 1).

Scheme 1.

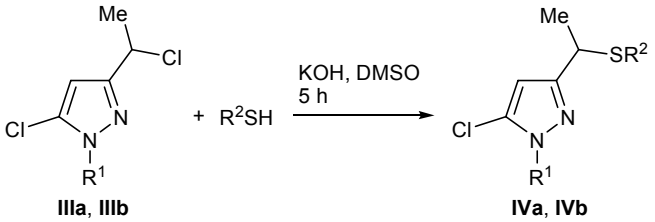


Ia, **Ib** **IIa**, **IIb**

R^1 = Me, R^2 = $PhCH_2$ (**a**); R^1 = $PhCH_2$, R^2 = Bu (**b**).

3-{1-[Butyl(benzyl)sulfanyl]ethyl}-5-chloro-1*H*-pyrazoles **IVa** and **IVb** were synthesized in 80–82% yield by reaction of 5-chloro-3-(1-chloroethyl)-1*H*-pyrazoles **IIIa** and **IIIb** with an equimolar amount of the corresponding thiol in DMSO in the presence of KOH at room temperature (Scheme 2). It should be noted that the use of 3-(1-bromoethyl)pyrazole derivatives [5] was not efficient; in this case, mixtures of compounds **IV** and vinylpyrazoles **I** at a ratio of ~1:10 were obtained.

Scheme 2.



IIIa, **IIIb** **IVa**, **IVb**

R^1 = Me, R^2 = $PhCH_2$ (**a**); R^1 = $PhCH_2$, R^2 = Bu (**b**).

Compounds **IIa**, **IIb**, **IVa**, and **IVb** were isolated as oily liquids which were readily soluble in organic solvents.

3-[2-(Benzylsulfanyl)ethyl]-5-chloro-1-methyl-1*H*-pyrazole (IIa). A mixture of 0.14 g (0.001 mol) of vinylpyrazole **Ia** and 0.12 g (0.001 mol) of phenylmethanethiol in 5 ml of benzene was irradiated with UV light over a period of 6 h at 60°C. The solvent was removed under reduced pressure, and the oily product was washed with cold hexane and dried under reduced

pressure. Yield 0.21 g (80%). IR spectrum, ν, cm^{-1}: 3130 (=C–H_{Pyr}), 3084, 3061, 3027, 3003 (=C–H_{Ph}), 2941, 2919, 2850 (CH_{Alk}), 1601, 1513 (C=C, C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.64 t (2H, $CH_2C\mathbf{H}_2S$, ^3J = 6.9 Hz), 2.76 t (2H, 3-CH_2, ^3J = 6.9 Hz), 3.57 s (2H, $SC\mathbf{H}_2C_6H_5$), 3.76 s (3H, NCH_3), 5.96 s (1H, 4-H), 7.20 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 28.43 ($CH_2\mathbf{C}H_2S$), 30.38 (3-CH_2), 35.43 ($S\mathbf{C}H_2C_6H_5$), 35.94 (NCH_3), 103.05 (C^4), 126.44 (C^5), 126.58 (C^p), 128.08 (C^m), 128.56 (C^o), 138.02 (C^i), 150.27 (C^3). Found, %: C 58.50; H 5.62; Cl 13.21; N 10.54; S 12.08. $C_{13}H_{15}ClN_2S$. Calculated, %: C 58.53; H 5.67; Cl 13.29; N 10.50; S 12.01.

1-Benzyl-3-[2-(butylsulfanyl)ethyl]-5-chloro-1*H*-pyrazole (IIb) was synthesized in a similar way from 0.22 g (0.001 mol) of 1-benzyl-5-chloro-3-vinyl-1*H*-pyrazole (**Ib**) and 0.09 g (0.001 mol) of butane-1-thiol [yield 0.24 g (80%)], as well as by heating the same amounts of the reactants and 0.0001 mol of AIBN in benzene for 6 h at 60°C [yield 0.23 g (77%)]. IR spectrum, ν, cm^{-1}: 3131 (=C–H_{Pyr}), 3082, 3060, 3027, 3004 (=C–H_{Ph}), 2940, 2933, 2920, 2850 (C–H_{Alk}), 1600, 1515 (C=C, C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.91 t (3H, CH_3, J = 7.3 Hz), 1.43 m (2H, CH_2, J = 7.3 Hz), 1.57 m (2H, CH_2, J = 7.3 Hz), 2.54 t (2H, CH_2, J = 7.3 Hz), 2.79 t (2H, $CH_2C\mathbf{H}_2S$, J = 6.9 Hz), 2.81 t (2H, 3-CH_2, J = 6.9 Hz), 5.28 s (2H, NCH_2), 6.12 s (1H, 4-H), 7.25 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 13.82 (CH_3), 22.09 (CH_2), 22.17 (CH_2), 29.57 ($CH_2\mathbf{C}H_2S$), 31.80 ($S\mathbf{C}H_2C_3H_7$), 32.08 (3-CH_2), 52.76 (NCH_2), 104.18 (C^4), 127.39 (C^5), 127.97 (C^p), 128.07 (C^i), 128.84 (C^o), 136.42 (C^i), 151.79 (C^3). Found, %: C 62.38; H 6.84; Cl 11.45; N 9.11; S 10.40. $C_{16}H_{21}ClN_2S$. Calculated, %: C 62.22; H 6.85; Cl 11.48; N 9.07; S 10.38.

3-[1-(Benzylsulfanyl)ethyl]-5-chloro-1-methyl-1*H*-pyrazole (IVa). Potassium hydroxide, 0.17 g (0.003 mol), was added to a solution of 0.18 g (0.001 mol) of 5-chloro-3-(1-chloroethyl)-1-methyl-1*H*-pyrazole (**IIIa**) in 3 ml of DMSO, the mixture was stirred for 20 min, 0.12 g (0.001 mol) of phenylmethanethiol was added, and the mixture was stirred for 5 h at 20°C. Yield 0.21 g (82%). IR spectrum, ν, cm^{-1}: 3131 (=C–H_{Pyr}), 3085, 3063, 3027, 3008 (=C–H_{Ph}), 2950, 2919, 2855 (C–H_{Alk}), 1601, 1515 (C=C, C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.50 d (3H, CH_3, J = 7.1 Hz), 3.63 s (2H, SCH_2), 3.77 s (3H, NCH_3), 3.87 q (1H, CHS, J = 7.1 Hz), 6.14 s (1H, 4-H), 7.26 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 21.07 (CH_3), 35.93 (SCH_2), 36.21 (SCH), 37.53 (NCH_3), 102.36 (C^4), 127.00 (C^5), 127.01 (C^p), 128.55 (C^m), 129.13 (C^o), 138.62 (C^i), 154.94 (C^3). Found, %: C 58.51; H 5.65; Cl 13.33; N 10.51; S 11.99. $C_{13}H_{15}ClN_2S$. Calculated, %: C 58.53; H 5.67; Cl 13.29; N 10.50; S 12.02.

1-Benzyl-3-[1-(butylsulfanyl)ethyl]-5-chloro-1*H*-pyrazole (IVb) was synthesized in a similar way from 0.25 g (0.001 mol) of 1-benzyl-5-chloro-3-(1-chloroethyl)-1*H*-pyrazole and 0.09 g (0.001 mol) of butane-1-thiol. Yield 0.24 g (80%). IR spectrum, ν, cm^{-1}: 3130 (=C–H_{Pyr}), 3083, 3063, 3010 (=C–H_{Ph}), 2952, 2940, 2930, 2919, 2850 (C–H_{Alk}), 1601, 1513 (C=C, C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.83 t (3H, CH_3, J = 7.3 Hz), 1.30 m (2H, CH_2, J = 7.3 Hz), 1.46 m (2H, CH_2, J = 7.3 Hz), 1.54 d (3H, CH_3, J = 7.2 Hz), 2.39 m (2H, CH_2, J = 7.3 Hz), 3.99 q (1H, CHS, J = 7.2 Hz), 5.25 s (2H, CH_2), 6.21 s (1H, 4-H), 7.26 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 13.76 (CH_3), 21.12 (CH_3), 22.18 (CH_2), 30.96 (CH_2), 31.58 (CH_2), 37.64 (SCH), 52.69 (NCH_2), 102.51 (C^4), 127.29 (C^5), 127.30 (C^p), 127.91 (C^m), 128.74 (C^o), 136.29 (C^i), 155.80 (C^3). Found, %: C 62.31; H 6.83; Cl 11.44; N 9.06; S 10.40. $C_{16}H_{21}ClN_2S$. Calculated, %: C 62.22; H 6.85; Cl 11.48; N 9.07; S 10.38.

The IR spectra were recorded on a Varian-3100 spectrometer with Fourier transform. The ^1H and ^{13}C NMR spectra were measured on a Bruker DPX-400 spectrometer at 400.13 and 101.61 MHz, respectively, using hexamethyldisiloxane as internal reference. UV irradiation was generated by a DRT-240 lamp (λ 240–320 nm; 240 W). Compounds **Ia**, **Ib**, **IIIa**, and **IIIb** were synthesized according to the procedures described in [5].

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 11-03-00461_a).

REFERENCES

1. Fustero, S., Sanchez-Rosello, M., Barrio, P., and Simon-Fuentes, A., *Chem. Rev*., 2011, vol. 111, p. 6984.
2. Elguero, J., Goya, P., Jagerovic, N., and Silva, A.M.S., *Targets in Heterocyclic Systems. Chemistry and Properties*, Attanasi, O.A. and Spinelli, D., Eds., Rome: Italian Soc. Chem., 2002, vol. 6, p. 53.
3. Janin, Y.L., *Chem. Rev*., 2012, vol. 112, p. 3924.
4. Grapov, A.F., *Usp. Khim*., 1999, vol. 68, p. 773.
5. Levkovskaya, G.G., Kobelevskaya, V.A., Rudyakova, E.V., Ha, Q.Kh., Samultsev, D.O., and Rozentsveig, I.B., *Tetrahedron*, 2011, vol. 67, p. 1844.