Synthesis of 2,3-Dihydropyrazolo[5,1-*b*]thiazoles *via* a Tandem Condensation Sulfur-Extrusion Reaction

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2,3-Dihydropyrazolo[5,1-*b*]thiazoles **3** are the first representatives of a heterocyclic system, which are conveniently prepared by heating 3-aminorhodanines **1** with ethyl 2-bromo-3,3-diethoxypropionate (**2**), *via* a tandem condensation-sulfur extrusion reaction.

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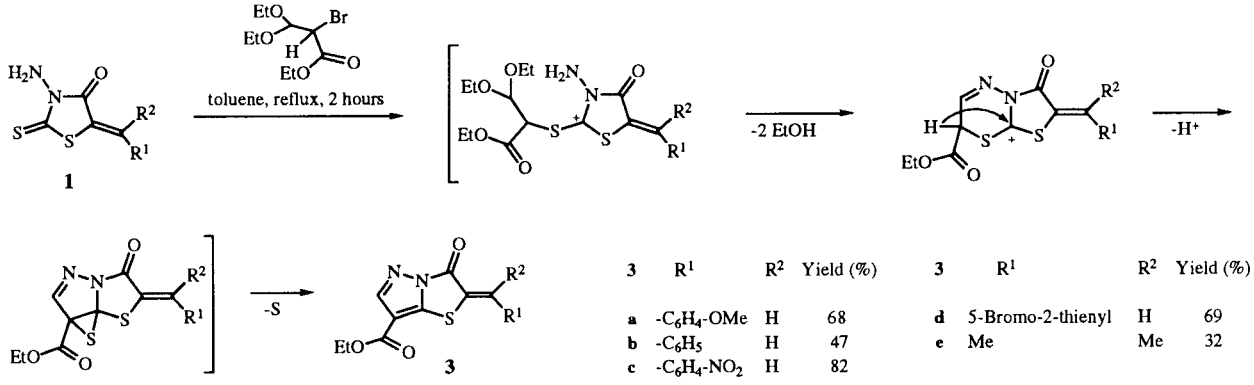
Substituted rhodanine derivatives and their corresponding 2-oxo analoges have received considerable interest because of their various biological activities *e. g.* antimicrobial [1,2], antiinflammatory [3-5] or antihyperglycaemic [6,7]. As a part of our general interest in condensation reactions of 3-aminorhodanine derivatives [8,9], we reacted 5-substituted rhodanines **1** with ethyl 2-bromo-3,3-diethoxpropionate (**2**) [10]. Rather unexpectedly, the products of this reaction turned out to be the 2,3-dihydropyrazolo[5,1-*b*]thiazoles **3**. A literature survey revealed that there are only a few examples of structurally related heterocycles [11-13] known, which differ from **3** in saturation and substitution pattern. Therefore, our dihydropyrazolothiazoles **3** represent a new type of a thiazolidine based bicyclic heterocyclic system, which can be prepared in a convenient way by simply heating **1** and **2** in toluene. The starting compounds are easily obtained in one step reactions from commercially available material [9,10]. The *Z*-Conformation of the semicyclic double bond of **3a-d** was established by the $^3J_{CH}$-coupling constant of 5.5-6 Hz of the exocyclic proton to the carbonyl carbon.

Table 1

Physical and Spectroscopic Data of 2,3-Dihydropyrazolo[5,1-*b*]thiazoles **3**

Product	Mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H NMR ($CDCl_3$) δ	^{13}C NMR ($CDCl_3$)	MS m/z (%)
3a	175	1725, 1705, 1580, 1560, 1420, 1285	8.21 (s, 1H), 8.11 (s, 1H), 7.63-7.60 (m, 2H), 7.06-7.03 (m, 2H), 4.39 (q, 2H), 3. 91 (s, 3H), 1.41 (t, 3H)	162.4 (s), 161.3 (s), 158.4 (s), 149.1 (d), 145.8 (s), 139.9 (d), 133.1 (d), 125.3 (s), 120.1 (s), 115.0 (d), 110.5 (s), 61.1 (t), 55.5 (q), 14.4 (q)	330 (M$^+$, 100), 285 (22)
3b	126	1735, 1690, 1590, 1420, 1285	8.21 (s, 1H), 8.14 (s, 1H), 7.65-7.63 (m, 2H), 7.56-7.49 (m, 3H), 4.38 (q, 2H), 1.41 (t, 3 H)	161.5, 158.4, 149.8, 146.3, 140.3, 132.9, 132.0, 131.2, 129.8, 123.7, 111.2, 61.5, 14.7	300 (M$^+$, 100), 255 (62)
3c	216	1730, 1705, 1515, 1340, 1250	8.40-8.37 (m, 2H), 8.24 (s, 1H), 8.16 (s, 1H), 7.81-7.79 (m, 2H), 4.40 (q, 2H), 1.41 (t, 3H)	160.3, 157.0, 149.0, 148.0, 145.5, 138.3, 135.8, 131.3, 127.8, 124.1, 110.1, 60.6, 13.9	345 (M$^+$, 16), 179 (100)
3d	234	1725, 1585, 1410 1265	8.20 (s, 1H), 8.14 (s, 1H), 7.27 (m, 1H), 7.21 (m, 1H), 4.39 (q, 2H), 1.42 (t, 3H)	161.2, 157.9, 149.5, 145.0, 138.5, 135.3, 132.1, 131.0, 122.1, 121.7, 111.1, 61.3, 14.5	386 (100), 384 (M$^+$, 90)
3e	158	1710, 1605, 1540 1380, 1345, 1275	8.15 (s, 1H), 4.34 (q, 2H), 2.58 (s, 3H), 2.19 (s, 3H), 1.38 (t, 3H)	161.5, 158.5, 156.8, 148.6, 144.7, 121.4, 109.7, 60.9, 26.7, 21.7, 14.4	252 (M$^+$, 100), 207 (22)



1

3

3	R^1	R^2	Yield (%)	3	R^1	R^2	Yield (%)
a	-C_6H_4-OMe	H	68	**d**	5-Bromo-2-thienyl	H	69
b	-C_6H_5	H	47	**e**	Me	Me	32
c	-C_6H_4-NO_2	H	82				

Table 2

Elemental Analysis of 2,3-Dihydropyrazolo[5,1-b]thiazoles **3**

Product	Molecular Formular	Elemental Analysis Calcd./ Found			
3a	$C_{16}H_{14}N_2O_4S$	C, 58.17	H, 4.27	N, 8.48	S, 9.71
	(330.3)	C, 58.00	H, 4.30	N, 8.45	S, 9.78
3b	$C_{15}H_{12}N_2O_3S$	C, 59.99	H, 4.03	N, 9.33	S, 10.68
	(300.3)	C, 59.77	H, 4.05	N, 9.31	S, 10.95
3d	$C_{13}H_9BrN_2O_3S_2$	C, 40.53	H, 2.35	N, 7.27	S, 16.64
	(385.3)	C, 40.22	H, 2.54	N, 7.15	S, 16.28
3e	$C_{11}H_{12}N_2O_3S$	C, 52.37	H, 4.79	N, 11.10	S, 12.71
	(252.3)	C, 52.68	H, 4.78	N, 10.77	S, 12.58

3c: HRMS Calcd. for $C_{15}H_{11}N_3O_5S$ (345.3): 345.0419. Found: 345.0409.

The emergence of **3** can be understood as nucleophilic substitution of the bromine atom by the thione sulfur, followed by a condensation of the acetal function of **2** with the amino group of **1**, which in turn is followed by sulfur extrusion. Comparable sulfur extrusions are well known in literature [14-18]. In contrast to most of them, which require either very high temperatures (up to 250°) or the aid of a catalyst, our sulfur extrusion is observed under comparatively mild conditions.This is probably due to the stability gained by the aromatic character of one part of the heterocycle formed.

EXPERIMENTAL

Melting points were determined on a Leitz HM Lux apparatus. They are uncorrected. Microanalyses were obtained on a Hewlett Packard CHN-Autoanalyser (N only) and a Labormatic CH-Analyser. Mass spectra were recorded on a Vacuum Generators Spectrometer 7070H with El (70 eV). The infrared spectra were run using a Perkin Elmer PE 398 instrument. The ^1H and ^{13}C nmr spectra were recorded on a Jeol JNM-GX 400 instrument.

General Procedure for Preparation of 2,3-Dihydropyrazolo[5,1-*b*]-thiazoles **3**.

To a solution of 5-substituted 3-aminorhodanines (**1**) (5-10 mmoles) in hot toluene was added a solution of ethyl 2-bromo-3,3-diethoxypropionate (**2**) (2 equivalents) in toluene (10-20 ml). The resulting mixture was refluxed for 2 hours. After cooling the solution was concentrated in vacuum to 20-30 ml. The precipitated solid was collected and purified by column chromatography over silica gel (**3c**: ethyl acetate/*n*-hexane 1:1; **3d**: ethyl acetate/*n*-hexane 3:1) and/or recrystallization from toluene.

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REFERENCES AND NOTES

[1] F. C. Brown and C. K Bradsher, *Nature,* **168**, 171 (1951).

[2] E. H. C. Menezes, A. J. S. Goes, M. B. S. Diu, S. L. Galdino, I. R. Pitta and C. Luu-Duc, *Pharmazie,* **47**, 457 (1992).

[3] T. Takebayashi, T. Onodera, K. Hasegawa, T. Fujita and T. Yoshioka, European Patent Appl. EP 454,501 (1991); *Chem. Abstr.,* **116**, 59.361k (1992).

[4] R. R. Mohan, *Indian Drugs,* **29**, 120 (1991); *Chem. Abstr.,* **116**, 106155h (1992).

[5] D. H. Boschelli and D. T. Connor, (Warner-Lambert Co.) US Patent 5,143,927 (1992); *Chem. Abstr.,* **118**, 22244q (1993).

[6] I. Iijima, M. Ozeki, K. Okumura and M. Inamasu, (Tanabe Seiyaku Co., Ltd.)
European Patent Appl. EP 283,035 (1988); *Chem. Abstr.,* **110**, 57657p (1989).

[7] A. D. Clark, St. W. Goldstein and B. Hulin, (Pfizer Inc.) European Patent Appl. EP 389,699 (1990); *Chem. Abstr.,* **114,** 122359s (1991).

[8] W. Hanefeld, V. Helfrich, M. A. Jalili and M. Schlitzer, *Arch. Pharm. (Weinheim),* **326**, 359 (1993).

[9] W. Hanefeld and M. Schlitzer, *Arch. Pharm. (Weinheim),* **326**, 887 (1993).

[10] W. Oroshnik and P. E. Spoerri, *J. Am. Chem. Soc.,* **67**, 721 (1945).

[11] K. Peseke, R. Rodriguez Palacio, E. Muro Bernal and C. Vogel, *Wiss. Z. Wilhelm-Pieck-Univ. Rostock, Naturwiss. Reihe,* **31**, 49 (1982); *Chem. Abstr.,* **99**, 158318p (1983).

[12] K. Peseke, R. Rodriguez Palacio and E. Muro Bernal, East German DD 207,721 (1984); *Chem. Abstr.,* **101**, 191896h (1984).

[13] K. Peseke, C. Vogel, J. Blaesche and K.-H. Kollhof, *J. Prakt. Chem.,* **324**, 639 (1982).

[14] E. B. Knott, *J. Chem. Soc.,* 916 (1955).

[15] E. B. Knott and R. A. Jeffreys, J. *Chem. Soc.,* 927 (1955).

[16] J. D. Loudon in Organic Sulfur Compounds N. Kharasch, Ed. Pergamon Press, London, 1961, pp 299-305.

[17] M. Takaku, S. Mitamura and H. Nozaki, *Tetrahedron Letters,* 3651 (1969).

[18] M. Roth, P. Dubs, E. Götschi and A. Eschenmoser, *Helv. Chim. Acta,* **54**, 710 (1971).