Synthesis of 3-thienyl substituted 2-pyrazolines by 1,3-dipolar cycloaddition

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1,3,5-Trisubstituted 3-thienylpyrazolines have been prepared in high yields by the reaction of substituted *N*-(*p*-nitrophenyl)-3-thiophenecarbohydrazonoyl chlorides with Et_3N in CH_2Cl_2 in the presence of an excess of a monosubstituted olefin. The reaction probably occurs as 1,3-dipolar cycloaddition of the corresponding 3-thiophenecarbonitrile imines formed *in situ* at the double bond of the olefin.

Key words: 1,3-dipolar cycloaddition, hydrazonoyl chlorides, 3-thienylpyrazolines, 3-thienylpyrazoles.

Previously[1,2] it has been shown that nitrilium betaines may be advantageously used in the preparation of thienyl substituted five-membered heterocycles incorporating C=N—X (X = O, S) fragments by their 1,3-dipolar cycloaddition to various dipolarophiles. By these reactions, a series of stable thiophene-3-carbonitrile oxides containing the electron-withdrawing alkylsulfonyl group in position 2 were prepared for the first time.[1,3] It has been of interest to study the possibility of synthesizing the similarly built nitrile imines **1c** and of using them for the preparation of the corresponding thienylpyrazolines. Stable aromatic nitrile imines have not been isolated so far. Recently, the preparation of stable type **2** nitrile imines was reported. The stability of these compounds is probably due to steric factors.[4,5]

$RC{\equiv}N^+{-}X^-$ **1a—c**

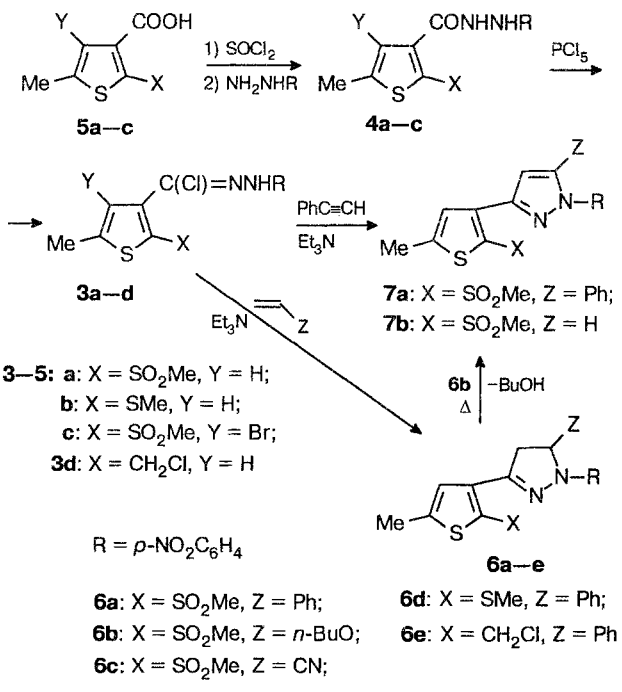
R is substituted thienyl;
a: X = O; **b**: X = S;
c: X = *p*-$NO_2C_6H_4N$

$A{-}C{\equiv}N^+{-}N^-{-}B$ **2**

A = Pr^i_3Si, $Pr^i_2P{=}S$
B = Pr^i_3Si, Pr^i_2P

We used hydrazonoyl halides (**3a—c**) prepared by the standard route from the *p*-nitrophenyl hydrazides (**4a—c**) of substituted 3-thiophenecarboxylic acids (**5a—c**) (Scheme 1) as the starting compounds for the generation of nitrile imines. Conversion of hydrazides **4a,b** into chlorides **3**, according to the previously described method,[6] occurs under more drastic conditions than that of the analogous aromatic derivatives. The highest yield of hydrazonyl halides **3a,c** is achieved with a 1.5-fold excess of PCl_5 at 80 °C (boiling in CCl_4) (or at 30—40 °C for aromatic compounds). Under the same conditions, the methylthio derivative **4b**, along with monochloride **3b**, affords the product of its halogenation at the methylthio group, **3d**; the **3b** : **3d** ratio is ~3:4 (see Ref. 7). When 2 equiv of PCl_5 are taken for the reaction, dichloride **3d** is the only product; in the case of 1 equiv of PCl_5 only monochloride **3b** has been isolated. We could not prepare the corresponding hydrazonoyl bromides by bromination of *p*-nitrophenylhydrazones of 3-thiophenecarbaldehydes, as has been described for many compounds of the aromatic series.

Scheme 1



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The treatment of hydrazonoyl halides **3a,b,d** with Et_3N in CH_2Cl_2 in the presence of an excess of a monosubstituted olefin affords 1,3,5-trisubstituted thienylpyrazolines in high yields. The reaction is complete after 3—6 h, irrespective of the nature of the substituents in the thiophene ring and at the double bond of the dipolarophile (styrene, *n*-butyl vinyl ether, or acrylonitrile); however, the reaction is considerably decelerated in dioxane or THF (100—200 h). This may be due to hydrogen bonding between the NH proton of halide **3** and the oxygen atom of the solvent which slows down the formation of nitrile imine. One piece of evidence for this idea is that the frequency of the N—H vibration in the IR-spectrum of **3a** is shifted from 3328 cm^{-1} in CH_2Cl_2 to 3232 cm^{-1} in dioxane and THF. The reaction of chloride **3a** with phenylacetylene and Et_3N gives the trisubstituted phenylpyrazole **7a**, however, it proceeds more slowly and with a lower yield than the reactions with olefins. The 1,3-disubstituted thienylpyrazole **7b** was obtained in quantitative yield by

Table 1. Characteristics of compounds **3—7** synthesized

Compound	M.p., °C (solvent)	Mass spectrum, *m/z* (I_{rel} (%))	Molecular Formula (mol. weight)	Found / Calculated (%) C	H	N	S	Cl(Br)	Yield (%)
3a	216—217 (THF)	375/373(50)[a], 296/294(45), 269/267(100), 259/258(75)	$C_{13}H_{12}ClN_3O_4S_2$ (373.83)	41.85 / 41.76	3.28 / 3.24	11.25 / 11.24	17.27 / 17.15	9.57 / 9.48	76
3b	172—173 (C_6H_6)	343/341(100)[a], 328/326(78), 304(95), 290(38), 258(74)	$C_{13}H_{12}ClN_3O_2S_2$ (341.83)	45.53 / 45.68	3.45 / 3.54	12.27 / 12.29	18.53 / 18.76	10.28 / 10.37	64
3c	232—233 (acetone)	455/453/451(28)[a], 375/373(95), 337(65), 293(97), 266(100), 249(20)	$C_{13}H_{11}BrClN_3O_4S_2$[b] (452.72)	34.29 / 34.49	2.81 / 2.45	9.28 / 9.49	13.91 / 14.16	7.56 / 7.83	87
3d	195—196 (C_6H_6)	377/375(100)[a], 330/328(10), 306(32), 280(20), 258(16)	$C_{13}H_{11}Cl_2N_3O_2S_2$ (376.27)	42.11 / 41.48	3.08 / 2.97	16.82 / 16.85	10.62 / 11.17	18.94 / 18.70	62
4a	215—216 (EtOH)	355(37), 284(2), 202(100), 148(26), 139(16)	$C_{13}H_{13}N_3O_5S_2$ (355.39)	43.51 / 43.95	3.92 / 3.68	11.69 / 11.82	17.57 / 18.04		71
4b	242—243 (EtOH)	323(12), 202(9), 200(7), 171(100), 156(9), 143(8)	$C_{13}H_{13}N_3O_3S_2$ (323.39)	48.34 / 48.28	4.28 / 4.05	12.79 / 13.00	19.85 / 19.83		65
4c	212—214 (THF, CH_3CN)	435/433(20)[a], 321/319(12), 282(100), 256(10), 188(15)	$C_{13}H_{12}BrN_3O_5S_2$ (434.27)	36.41 / 35.95	3.15 / 2.79	10.34 / 9.68	13.77 / 14.16	17.85 / 18.40	61
5c	185—186 (water)	300/298(100)[a] [M−H_2O], 285/283(20), 241/239(40), 236(40), 192(40), 177(10)	$C_7H_9BrO_5S_2$ (317.17)	26.30 / 26.51	3.22 / 3.06	19.98 / 20.22	24.94 / 25.19		100
6a	191—192 (MePh)	441(48), 364(100), 318(10), 316(10), 285(38), 142(25)	$C_{21}H_{19}N_3O_4S_2$ (441.51)	57.05 / 57.12	4.38 / 4.34	9.47 / 9.52	14.32 / 14.53		95
6b	116—118 (C_6H_6)	437(60), 411(10), 364(100), 318(8), 316(10), 285(35)	$C_{19}H_{23}N_3O_5S_2$ (437.53)	51.86 / 52.15	5.27 / 5.30	9.51 / 9.60	14.57 / 14.66		100
6c	267—268 (CH_3CN)	390(75), 364(65), 363(100), 311(36), 299(35), 285(25)	$C_{16}H_{14}N_4O_4S_2$ (390.43)	49.31 / 49.22	3.42 / 3.61	13.72 / 14.35	15.76 / 16.43		90
6d	232—233 (MePh)	409(100), 393(65), 362(31), 332(80), 284(20), 169(55)	$C_{21}H_{19}N_3O_2S_2$ (409.52)	61.71 / 61.59	4.43 / 4.68	10.18 / 10.26	15.31 / 15.66		71
6e	167—168 (MePh)	444(60), 442(100), 408(12), 406(10), 393(60), 329(45)	$C_{21}H_{18}ClN_3O_2S_2$ (443.96)	56.76 / 56.82	4.12 / 4.09	9.95 / 9.68	14.18 / 14.44	7.84 / 7.99	85
7a	250—251	439(100), 362(65), 354(20), 322(40), 320(35)	$C_{21}H_{17}N_3O_4S_2$ (439.50)	57.21 / 57.39	3.98 / 3.90	9.44 / 9.56	14.81 / 14.59		40
7b	213—215 (MePh)	363(100), 344(5), 298(25), 284(7), 238(12)	$C_{15}H_{13}N_3O_4S_2$ (363.41)	49.43 / 49.57	3.77 / 3.61	11.24 / 11.56	17.33 / 17.65		97

[a] The intensities of peaks presented correspond to ^{35}Cl. [b] Br (%): found 17.37; calculated 17.65.

the thermally-induced abstraction of *n*-butanol from 1,3,5-trisubstituted pyrazoline **6b**.

We did not manage to isolate stable nitrile imines or their dimerization products upon dehydrohalogenation of hydrazonoyl halides **3a—d** in the absence of dipolarophiles owing to substantial resinification of the reaction mixture. However, as has been shown above, the dipoles **1b** formed can be used *in situ* for the synthesis of various substituted 3-thienyl-Δ^2-pyrazolines which are of interest as possible biologically active compounds. Notice that some 2-thienylpyrazolines were prepared previously from 2-thienyl substituted α,β-unsaturated ketones and hydrazine.[8,9]

Table 2. IR- and ^{1}H NMR spectra of compounds synthesized

Compound	IR (ν/cm^{-1}) (pressed with KBr)				^{1}H NMR CD_2Cl_2, δ (*J*/Hz)				
	NH	SO_2	NO_2	CO	5-Me (3 H)	SO_2Me(SMe) (s, 3 H)	4-H (1 H)	$C_6H_4NO_2$ (d, 2×2 H)	Other signals
3a	3320	1500 1330	1310 1140		2.54 c	3.35	7.20	7.31; 8.20 (9.5)	8.58 (br. s, 1 H, NH)
3b	3340	1330			2.45 d (1)	2.62	7.07 d (1)	7.28; 8.19 (9.0)	8.43 (br. s, 1 H, NH)
3c[a]	3330		1310 1140		2.54 c	3.38		7.15; 8.22 (9.25)	8.60 (br. s, 1 H, NH)
3d[a]	3340	1336			2.50 d (1)	5.00 (2 H, CH_2)	7.08	7.21; 8.21 (9.0)	8.37 (br. s, 1 H, NH)
4a[b]	3290	1490 1325	1310 1136	1640	2.61 d (1)	3.44	7.35 d (1)	7.11; 8.13 (9.5)	9.85 (br. s, 1 H, NH)
4b[b]	3260	1500 1325		1620	2.45 d (1)	2.52	7.25 d (1)	7.05; 8.10 (9.5)	8.60; 8.85 (br. s, 2×1 H, NH)
4c[b]	3280	1480 1336	1310 1140	1680	2.68 c	3.39		6.45; 8.20 (9.25)	10.25 (br. s, 1 H, NH)
5c[b]			1315 1140	1695	2.52 c	3.40			
6a		1510	1320 1110		2.51 d (1.25)	3.49	6.96	7.05; 8.06 (9.5)	The protons of the pyrazoline ring: 3.25 (dd, *J* = 5.5 and 18, 1 H, H-4); 4.00 (dd, *J* = 12.5 and 18, 1 H, H-4) and 5.47 (dd, *J* = 5.5 and 12.5, 1 H, H-5); 7.33 (m, 5 H, Ph)
6b		1510	1320 1110		2.56 c	3.44	7.03	7.29; 8.19 (9.5)	0.83 (т, *J* = 7.25, 3 H, CH_3); 1.30 and 1.52 (m, 4 H, CH_2CH_2); 3.30 (m, 3 H, OCH_2 + H-4 of the pyrazoline ring); 3.51 (dd, *J* = 8.5 and 18.5, 1 H, H-4); 5.88 (dd, *J* = 2.5 and 8.5, 1 H, H-5)
6c[b]		1500	1376 1100		2.58 c	3.52	7.35	7.46; 8.28 (9.5)	The protons of the pyrazoline ring: 4.01 (dd, *J* = 5.5 and 18.5, 1 H, H-4); 4.11 (dd, *J* = 11.5 and 18.5, 1 H, H-4); 5.80 (dd, *J* = 5.5 and 11.5, 1 H, H-5)
6d		1510 1330			2.45 c	2.57	6.93	7.00; 8.06 (9.5)	The protons of the pyrazoline ring: 3.33 (dd, *J* = 5.25 and 17.25, 1 H, H-4); 4.02 (dd, *J* = 12.0 and 17.25, 1 H, H-4) and 5.36 (dd, *J* = 5.25 and 12.0, 1 H, H-5); 7.30 (m, 5 H, Ph)
6e		1510 1325			2.56	4.84 (2 H, CH_2)	7.3	7.00; 8.06 (9.5)	The protons of the pyrazoline ring: 3.58 (dd, *J* = 5.5 and 17.25, 1 H, H-4); 4.11 (dd, *J* = 12.0 and 17.25, 1 H, H-4) and 5.39 (dd, *J*= 5.5 and 12.0, 1 H, H-5); 7.3 (m, 6 H, H-4 + Ph)
7a		1510	1320 1110		2.57	3.42	7.03	7.52; 8.20 (9.5)	7.28 (c, 1 H, H of the pyrazole ring); 7.38 (m, 5 H, Ph)
7b		1520	1316 1110		2.56 d (1.25)	3.37	7.27 d (1.25)	7.93; 8.35 (9.5)	The protons of the pyrazole ring: 7.05 (d, *J* = 2.5, 1 H, H-4); 8.12 (d, *J* = 2.5, 1 H, H-5)

[a] The ^{1}H NMR spectrum was recorded in $CDCl_3$. [b] The ^{1}H NMR spectrum was recorded in in $(CD_3)_2CO$.

Experimental

IR spectra were recorded on a Specord IR 275 instrument and ^1H NMR spectra were run on Bruker WM-250 (250 MHz) and Jeol FX-90Q (90 MHz) spectrometers. Molecular weights were determined on a Varian MAT CH-6 spectrometer at an ionizing voltage of 70 eV with direct sample injection into the ion source. The data of elemental analysis, yields, and spectroscopic characteristics of the compounds synthesized are given in Tables 1 and 2.

4-Bromo-5-methyl-2-methylsulfonyl-3-thiophenecarboxylic acid hydrate (5c). 30 % H_2O_2 (3 mL) was added to 4-bromo-2-methylthio-3-thiophenecarbaldehyde[3] (0.75 g, 3.72 mmol) in 15 mL of glacial AcOH, the mixture was allowed to stand for 24 h at 20 °C and concentrated to dryness, and the residue was recrystallized.

***N*-(*p*-Nitrophenyl)-5-methyl-2-methylsulfonyl-, *N*-(*p*-nitrophenyl)-5-methyl-2-methylthio-, and *N*-(*p*-nitrophenyl)-4-bromo-5-methyl-2-methylsulfonyl-3-thiophenecarbohydrazides (4a-c)** were prepared from the corresponding substituted 3-thiophenecarboxylic acids **5a,b**[11] and **5c** according to the known method.[10]

N-(*p*-nitrophenyl)-5-methyl-2-methylsulfonyl-, N-(*p*-nitrophenyl)-4-bromo-2-methylsulfonyl-, and N-(*p*-nitrophenyl)-2-chloromethyl-5-methyl-3-thiophenecarbohydrazonoyl chlorides (3a,c,d). A mixture of 1 mmol of hydrazide **4a—c** and 1.5 mmol of PCl_5 (for **4b**, 2 mmol of PCl_5) in 35 mL of CCl_4 was boiled for 4—5 h; 1 g of PhOH in 10 mL of CCl_4 and 5 mL of MeOH was added to the mixture. The precipitate was filtered off, washed with CCl_4, and recrystallized.

N-(*p*-nitrophenyl)-5-methyl-2-methylthio-3-thiophenecarbohydrazonoyl chloride (3b). A mixture of 0.3 g of hydrazide **4b** and 0.2 g (1 mmol) of PCl_5 in 20 mL of CCl_4 was boiled for 2 h; 1 g of PhOH in 10 mL of CCl_4 and 5 mL of MeOH was added, the solvents were evaporated, and the precipitate was filtered off, washed with hexane, and recrystallized.

Synthesis of 1,3,5-trisubstituted pyrazolines 6a—e. At 20 °C 1—1.2 mmol of Et_3N was added to a solution of 1 mmol of hydrazonoyl chloride **3a,b,d** in 50 mL of CH_2Cl_2 containing a 5-fold excess of an olefin (styrene, *n*-butyl vinyl ether, or acrylonitrile). The mixture was held for 3—6 h until the starting hydrazonoyl chloride disappeared (TLC, Silufol UV-254, elution with EtOC—hexane (1:2)), washed with water, and dried with $CaCl_2$; CH_2Cl_2 was evaporated and the residue was recrystallized.

3-(5-Methyl-2-methylsulfonyl-3-thienyl)-1-*p*-nitrophenyl-5-phenylpyrazole (7a) was prepared as described above, from hydrazonoyl chloride **3a** and PhC≡CH over a period of 100 h; it was purified by chromatography on a column packed with silica gel L (100—200 mesh) using a 1:2 ethyl acetate—hexane mixture as the eluent.

3-(5-Methyl-2-methylsulfonyl-3-thienyl)-1-*p*-nitrophenylpyrazole (7b). A solution of 1 mmol of *n*-butoxypyrazoline **6b** in toluene was heated at reflux for 3 h, the solvent was evaporated, and the residue was recrystallized.

References

1. M. M. Krayushkin, M. A. Kalik, V. K. Zav'yalova, and V. S. Bogdanov, *Khim. Geterotsikl. Soed.*, 1988, 403 [*Chem. Heterocycl. Comp.*, 1988 (Engl. Transl.)].
2. M. M. Krayushkin, M. A. Kalik, and A. Ya. Kudryavtseva, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 1892 [*Bull. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 1477 (Engl. Transl.)].
3. M. M. Krayushkin, M. A. Kalik, V. K. Zav'yalova, A. A. Loktionov, and V. S. Bogdanov, *Khim. Geterotsikl. Soed.*, 1989, 1620 [*Chem. Heterocycl. Comp.*, 1989 (Engl. Transl.)].
4. F. Castan, A. Bacciredo, and G. Bertrand, *Angew. Chem. Int. Ed.*, 1989, **28**, 1250.
5. G. Sicard, A. Bacciredo, and G. Bertrand, *J. Am. Chem. Soc.*, 1988, **110**, 2663.
6. J. K. Stille, F. W. Harris, and M. A. Bedford, *J. Heterocyclic Chem.*, 1966, **3**, 155.
7. G. E. Nilson, *Tetrahedron*, 1982, **38**, 2597.
8. S. V. Tsukerman, V. M. Nikitchenko, and V. F. Lavrushin, *Khim. Geterotsikl. Soed.*, 1968, 1093; 1965, 693 [*Chem. Heterocycl. Comp.*, 1968; 1965 (Engl. Transl.)].
9. W. Ried, G. Dankert, *Chem. Ber.*, 1957, **90**, 2707.
10. T. Sasaki, T. Joshioka, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 1254.
11. Ya. L. Gol'dfarb, M. A. Kalik, and M. L. Kirmalova, *Zh. Org. Khim.*, 1960, **30**, 1012 [*J. Ogr. Chem.*, 1960, **30** (Engl. Transl.)].

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