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4-Functionally Substituted 3-heterylpyrazoles: XII.* 4-Chlorothieno[2,3-c]pyrazole-5-carbonyl Chlorides

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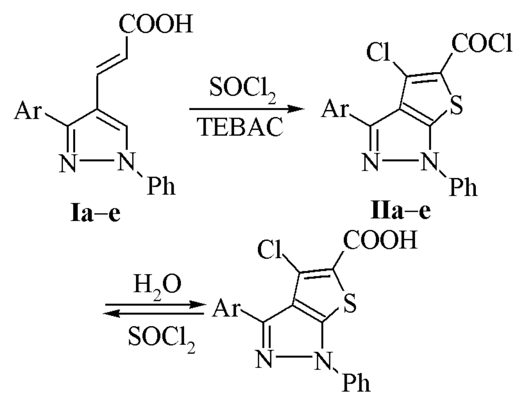
Abstract—3-(4-Pyrazolyl)acrylic acids reacted with excess thionyl chloride in the presence of benzyltriethylammonium chloride affording 4-chlorothieno[2,3-c]pyrazole-5-carbonyl chlorides which were converted into the corresponding acids, esters, and amides.

Reactions of substituted cinnamic acids and their derivatives with excess thionyl chloride in the presence of pyridine acquired preparative importance in the synthesis of 3-chloro[*b*]thiophene-2-carbonyl chlorides [2–7]. Among heterocyclic analogs of cinnamic acids this reaction was investigated only for benzo[*b*]thiophen-3-acrylic [8] and (*E*,*E*)-2,5-thiophenedi(2-ethenyl)carboxylic [7] acids.

We report here on results of investigation of the reaction between thionyl chloride and 3-(4-pyrazolyl)-acrylic acids **Ia**–**e** we have recently synthesized [1]. The reaction is carried out in the presence of pyridine or benzyltriethylammonium chloride (BTEAC). Our previous attempts to substitute the position *5* of 4-functionalized pyrazoles by treatment with common electrophilic reagents were unsuccessful. However taking into consideration the assumption [4] that the conversion of cinnamic acids into derivatives of benzo[*b*]thiophene probably occurred involving highly electrophilic sulfenyl chlorides we got hope to carry out similar reaction with the 3-(3-pyrazolyl)-acrylic acids.

It was shown by an example of acid Ia that after heating for 10 h at 140°C with 5-fold excess of thionyl chloride in the presence of pyridine (10% from equimolar amount) 1,3-dipheny-4-chloro-141*H*-thieno[2,3-*c*]pyrazole-5-carbonyl chloride (**IIa**) actually formed but its yield was only 18%. We succeeded in raising the yield in the reaction of acids Ia–e with 4-fold excess of thionyl chloride at 160°C using BTEAC in 50% to equimolar amount instead of pyridine [9]. As a result acyl chloride **IIa** was isolated in the analytically pure state in 43% yield. The content of acyl chlorides **IIb**–**d** in the reaction products according to ^{1}H NMR spectra was 80–86%. Their hydrolysis made possible isolation of analytically pure acids **IIIa**–**e** that further by treating with thionyl chloride almost quantitatively were converted into pure acyl chlorides **IIa**–**e**.



I–**III**, Ar = Ph (**a**), 4-F-C_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-BrC_6H_4 (**d**), 4-MeC_6H_4 (**e**).

Taking into account that 3-phenylpropanoic acid treated with thionyl chloride is able to undergo cyclization into 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride [10, 11] we tried to perform similar reaction with 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)propanoic acid **IV**. It was found that under above described conditions acid **IV** in 40% yield afforded acyl chloride **IIa**.

3-Aryl-1-phenyl-4-chloro-1*H*-thieno[2,3-*c*]pyrazole-5-carbonyl chlorides (IIa–e) and corresponding acids IIIa–e (Table 1, 2) are colorless or light-yellow high-melting crystalline compounds whose assumed composition is in agreement with elemental analysis, and the structure is consistent with the measured IR and ^{1}H NMR spectra. In particular in

* For communication XI see [1].

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Table 1. Yields, melting points, and elemental analyses of 4-chlorothieno[2,3-*c*]pyrazole-5-carbonyl chlorides (**IIa**–**e**) and 4-chlorothieno[2,3-*c*]pyrazole-5-carboxylic acids (**IIIa**–**e**)

Compd. no.	Yield, %[a]	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIa	43(40)[b]	209–210	58.25	2.54	7.73	$C_{18}H_{10}Cl_2N_2OS$	57.92	2.70	7.50
IIb	49	240–242	55.61	2.39	7.01	$C_{18}H_9Cl_2FN_2OS$	55.26	2.32	7.19
IIc	65	231–232	52.72	2.04	7.05	$C_{18}H_9Cl_3N_2OS$	53.03	2.23	6.87
IId	54	243-244	48.10	1.93	6.47	$C_{18}H_9BrCl_2N_2OS$	47.82	2.01	6.20
IIe	61	215–216	58.51	3.35	7.45	$C_{19}H_{12}Cl_2N_2OS$	58.93	3.12	7.23
IIIa	47	272–273	61.17	3.24	8.09	$C_{18}H_{11}ClN_2O_2S$	60.93	3.12	7.90
IIIb	52	284–285	58.24	2.81	7.29	$C_{18}H_{10}ClFN_2O_2S$	57.99	2.70	7.51
IIIc	67	324–325	5.57	2.43	7.41	$C_{18}H_{10}ClN_2O_2S$	55.54	2.59	7.20
IIId	59	294–295	50.10	2.09	6.83	$C_{18}H_{10}ClBrN_2O_2S$	48.85	2.32	6.46
IIIe	65	267–268	61.59	3.54	7.70	$C_{19}H_{13}ClN_2O_2S$	61.87	3.55	7.59

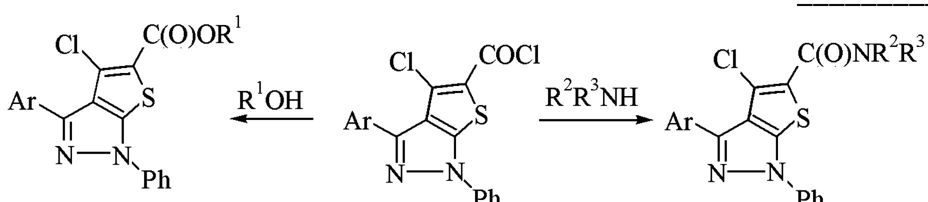
[a] For compounds **IIa**–**e** with respect to the corresponding 3-(4-pyrazolyl)acrylic acid.
[b] From acid (**IV**).

Table 2. IR and ^{1}H NMR of 4-chlorothieno[2,3-*c*]pyrazole-5-carbonyl chlorides (**IIa**–**e**) and 4-chlorothieno[2,3-*c*]-pyrazole-5-carboxylic acids (**IIIa**–**e**)

Compd. no.	IR spectrum, cm^{-1}		^{1}H NMR spectrum, δ, ppm
	ν(C=O)	ν(OH)	
IIa	1760		7.35 t (1H arom), 7.47–7.82 m (9H arom)
IIb	1765		7.33–7.47 m (3H arom), 7.61–7.82 m (6H arom)
IIc	1770		7.33–7.60 m (5H arom), 7.81 d, 7.93 d (4H arom)
IId	1760		7.44 t (1H arom), 7.60–7.99 m (8H arom)
IIe	1765		2.42 s (3H, CH_3), 7.33 t (1H arom), 7.50–7.79 m (8H arom)
IIIa	1700	2600–3000	7.37 t (1H arom), 7.49–7.79 m (9H arom), 10.82 br.s (1H, COOH)
IIIb	1705	2650–3050	7.29–7.40 m (3H arom), 7.62–7.78 m (4H arom), 7.90–7.94 m (2H arom), 11.08 br.s (1H, COOH)
IIIc	1710	2650–3100	7.38 t (1H arom), 7.53–7.62 m (4H arom), 7.79 d, 7.90 d (4H arom) 11.20 br.s (1H, COOH)
IIId	1710	2600–2950	7.39 t (1H arom), 7.52–7.94 m (8H arom) 10.91 br.s (1H, COOH)
IIIe	1700	2650–3050	2.42 s (3H, CH_3), 7.38 d (2H arom), 7.42 s (1H arom) 7.59–7.62 m (2H arom), 7.75–7.82 m (4H arom), 11.03 br.s (1H, COOH)

the downfield part of the latter (8.4–9.3 ppm) lacked the singlet from C^5–H proton of the original acids **Ia**–**e** indicating that the pyrazole ring fused at this position.

The approach we developed to the synthesis of 5-functionalized thieno[2,3-*c*]pyrazole systems significantly extends the existing methods of their preparation [12, 14].



Va, b **IIa–e** **VIa–f**

V, Ar = Ph, R^1 = Me (**a**); Ar = 4-ClC_6H_4, R^1 = 2-(MeO)-4-(CH=O)C_6H_3 (**b**); **VI**, Ar = 4-FC_6H_4, R^2 = H, R^3 = 2-phurmethyl (**a**); Ar = 4-ClC_6H_4, R^2 = H, R^3 = 3-piridylmethyl (**b**); Ar = 4-BrC_6H_4; R^2 = H, R^3 = Ph (**c**), R^2R^3 = $(CH_2)_5$ (**d**); Ar = 4-MeC_6H_4; R^2 = H, R^3 = 4-$MeOC_6H_4$ (**e**); R^2R^3 = $(CH_2)_2CH(CH_3)(CH_2)_2$ (**f**).

Table 3. Yields, melting points, ^{1}H NMR spectra, and elemental analyses of 4-chlorothieno[2,3-*c*]pyrazole-5-carboxylic acids esters and amides

Compd. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %			^{1}H NMR spectrum, δ, ppm
			C	H	N		C	H	N	
Va	71	160–161	62.05	3.52	7.69	$C_{19}H_{13}ClN_2O_2S$	61.87	3.55	7.59	3.88 s (3H, OM”), 7.46–7.87 m (10H arom)
Vb	68	209–210	59.39	3.18	5.52	$C_{26}H_{16}Cl_2N_2O_4S$	59.67	3.08	5.35	3.82 s (3H, OM”), 7.38–7.99 m (12H arom), 10.02 s (1H, CH=O)
VIa	73	146–147	61.47	3.27	9.54	$C_{23}H_{15}ClFN_3O_2S$	61.13	3.35	9.30	4.50 d (2H, CH_2), 6.31 d (1H, CH=), 6.42 d (1H, CH=), 7.30–7.87 m (10H arom), 8.57 t (1H, NH)
VIb	64	186–188	59.85	3.25	11.90	$C_{24}H_{16}Cl_2N_4OS$	60.13	3.36	11.69	5.47 d (2H, CH_2), 7.35–7.98 m (13H arom), 8.72 t (1H, NH)
VIc	78	194–195	56.72	3.11	8.48	$C_{24}H_{15}BrClN_3OS$	56.65	2.97	8.26	7.36–7.88 m (14H arom), 9.15 s (1H, NH)
VId	81	171–172	55.43	3.99	8.18	$C_{23}H_{19}BrClN_3OS$	55.16	3.82	8.39	1.56–1.65 m (6H, CH_2), 3.54–3.58 m (4H, CH_2), 7.41–7.86 m (9H arom)
VIe	83	174–175	65.80	4.37	8.71	$C_{26}H_{20}ClN_3O_2S$	65.89	4.25	8.87	2.42 s (3H, M”), 3.76 s (3H, M”O), 6.88 d (2H arom), 7.35–7.82 m (11H arom), 9.94 s (1H, NH)
VIf	69	175–176	66.81	5.40	9.22	$C_{25}H_{24}ClN_3OS$	66.73	5.38	9.34	0.96 d (3H, M”), 1.11–1.16 m (2H, CH_2), 1.65–1.72 m (2H, CH_2), 2.40s (3H, M”), 2.95–3.01 m (4H, CH_2), 4.12–4.16 m (1H, CH), 7.33–7.78 m (9H arom)

The acyl chlorides proper can be successfully used in preparation of various derivatives, e.g., esters **Va, b**, amides **VIa–f** (Table 3).

EXPERIMENTAL

IR spectra were recorded on spectrophotometer UR-20 from samples pelletized with KBr. ^{1}H NMR spectra were registered on spectrometer Varian-Gemini (300 MHz) from solutions in DMSO-d_6, internal reference TMS.

3-Aryl-1-phenyl-4-chloro-1*H*-thieno[2,3-*c*]pyrazole-5-carbonyl chlorides (IIa–e). A mixture of 0.02 mol of acid **Ia–e** or **IV**, 9.52 g (0.08 mol) of thionyl chloride, and 2.28 g (0.01 mol) of BTEAC was heated at 160°C on an oil bath for 4 h. Then the bath temperature was reduced to 100–110°C, and the excessive thionyl chloride was distilled off. To the residue was added 25 ml of chloroform, and the mixture was boiled for 0.5 h (for dissolving resinous products and BTEAC). The precipitate formed on cooling was filtered, washed with chloroform (2 × 15 ml), then heated in toluene till dissolution (compounds **IIa**) or in a mixture toluene–dioxane, 1 : 2 (compounds **IIb–e**), and the solution was cooled. The content of acyl chloride in the formed solid precipitate amounted to 80–86%. To 0.005 mol (recalculated to the content of the main substance) of compound **IIa–e** in 25 ml of dioxane was added 20 ml of 2 N water solution of NaOH, and the mixture was heated at reflux for 2 h. On cooling the reaction mixture was diluted with water (100 ml), acidified with 2 N HCl to pH 5–6, the precipitate was filtered off, dried, and crystallized from acetic acid (compounds **IIIa, e**) or from a mixture acetic acid–dioxane (compounds **IIIb–d**). To a suspension of 0.005 mol of acid **IIIb–e** in 5 ml of thionyl chloride was added 2 drops of DMF and the mixture was heated at reflux for 2 h. On cooling 10 ml of benzene was added, the precipitate was filtered off, washed with benzene (2 × 10 ml), and dried. Thus were obtained analytically pure samples of acyl chlorides **IIb–e**.

3-Aryl-1-phenyl-4-chloro-1*H*-thieno[2,3-*s*]pyrazole-5-carboxylic acids esters (Va, b) and amides (**VIa–f).** To a solution of 0.003 mol of acyl chloride **IIa–e** in 5 ml of pyridine was added 0.003 mol of an appropriate alcohol, phenol, or amine, and the mixture was heated at reflux for 2 h. The reaction mixture was then cooled, diluted with 50 ml of water, the separated precipitate was filtered off and recrystallized from acetic acid.

REFERENCES

1. Bratenko, M.K., Chornous, V.A., and Vovk, M.V., *Zh. Org. Khim.*, 2002, vol. 38, p. 1223.
2. Nakagawa, S., Okumura, J., Sakai, F., Hoshi, H., and Naito, T., *Tetrahedron Lett.*, 1970, no. 42, p. 3719.
3. Wright, W.B. and Brabander, H., *J. Heterocyclic Chem.*, 1971, vol. 8, p. 711.
4. Higa, T. and Krubsack, A.J., *J. Org. Chem.*, 1975, vol. 40, no. 21, p. 3037.
5. Ried, W., Oremek, C., and Ocarcioglu, B., *Lieb. Ann.*, 1980, no. 9, p. 1424.
6. Garhar, H.K., Kaur, R., and Gupta, S.P., *Monatsh. Chem.*, 1995, vol. 126, p. 1235.
7. Dogan, J., Karminski-Zamola, G.M., and Boykin, O.W., *Heterocycles*, 1995, vol. 41, p. 1659.
8. Luo, J.K., Kudo, H., Federspiel, R.F., and Castle, R.N., *J. Heterocyclic Chem.*, 1995, vol. 32, p. 317.
9. *Sintez sul'fidov tiofenov i tiolov* (Synthesis of Sulfides, Thiophenes, and Thyols), Karaulova N., Ed., Moscow: Nauka, 1988, p. 178.
10. Krubsack, A.J. and Higa, T., *Tetrahedron Lett.*, 1968, no. 49, p. 5149.
11. Krubsack, A.J. and Higa, T., *Tetrahedron Lett.*, 1973, p. 125.
12. Brown, K.J. and Meth-Cohn, O., *Tetrahedron Lett.*, 1974, no. 46, p. 4069.
13. Menozzi, G., Mosti, L., Scenone, P., D'Amico M., Filippeli, A., and Rossi, F., *Farmaco.*, 1992, vol. 47, p. 1495.
14. Alluwalia, V.K., Dahiya, A., and Bola, M., *Indian J. Chem. Sect. B*, 1996, vol. 35, p. 715.