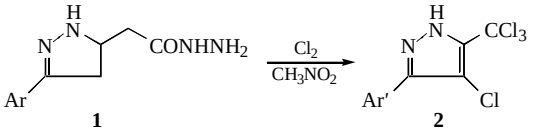
An unexpected reaction of 3-aryl-2-pyrazolin-5-ylacetohydrazides with chlorine: formation of 3-aryl-4-chloro-5-trichloromethylpyrazoles

Sergei A. Voznesenskii, Leonid I. Belen'kii,* Arkady A. Dudinov, Marina I. Struchkova and Mikhail M. Krayushkin

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation. Fax: +7 095 135 5328

In attempting to synthesize 3-aryl-2-pyrazolin-5-ylacetyl chlorides by chlorination of the respective hydrazides, 3-aryl-4-chloro-5-trichloromethylpyrazoles have been obtained; a probable mechanism for the transformation is discussed.

Previously we described the preparation of 3-aryl-2-pyrazolin-5-ylacetohydrazides **1** from 1-aryl-5,5-dichloropenta-2,4-dien-1-ones through 6-aryl-2-pyrones.[1] It seemed interesting to study the possibility of using hydrazides **1** in the synthesis of other derivatives of 3-aryl-2-pyrazolin-5-ylacetic acids, in particular, of their halides, which can be used for the preparation of modified β-lactam antibiotics. A direct transformation of hydrazides to acid chlorides upon chlorination in nitromethane,[2,3] as well as the preparation of acid bromides when employing bromination under similar conditions,[3] are described. We have carried out the chlorination of hydrazides **1**† under the conditions described in ref. 2 (suspension of hydrazide hydrochloride in nitromethane, room temperature, stirring). However, instead of the anticipated acid chlorides, 3-aryl-4-chloro-5-trichloromethylpyrazoles **2**‡ were isolated (Scheme 1).



1

a Ar = Ar′ = Ph
b Ar = Ar′ = 4-ClC_6H_4
c Ar = Ar′ = 4-BrC_6H_4
d Ar = Ar′ = 3-$NO_2C_6H_4$
e Ar = 4-$MeOC_6H_4$
Ar′ = 3-Cl-4-$MeOC_6H_3$

2

Scheme 1

When considering a possible mechanism for the transformation observed one should take into account some properties of pyrazolines and pyrazoles. It is known that pyrazolines can be readily oxidized to pyrazoles by bromine.[4,5] Chlorination of methylpyrazoles in the ring and side chain is also described, the methyl groups being transformed to trichloromethyl groups.[6] Based on these data one may suppose that in our case the oxidation and halogenation of the pyrazoline ring take place in an initial step of the reaction to give 3-aryl-4-chloro-5-pyrazolylacetohydrazides **3**. Under the reaction conditions employed an aryl substituent can undergo chlorination. The latter, however, requires the presence of a group such as OMe, which strongly activates the benzene ring towards electrophilic substitution. Simultaneously or after ring chlorination cleavage of the hydrazide fragment takes place, and the chloropyrazolylacetyl chloride **4** formed undergoes chlorination of the methylene group. Finally, chlorinolysis of the CCl_2–COCl bond in the intermediate 3-aryl-4-chloro-5-pyrazoledichloroacetyl chloride **5** proceeds to form trichloromethylpyrazole **2** (Scheme 2). However, the proposed sequence of aromatization, chlorination and chlorinolysis steps requires additional investigation.

It should be noted that phenylacetohydrazide readily transforms to the respective acid chloride.[2] Since in ref. 2 the reaction of this hydrazide with chlorine was carried out under considerably milder conditions than for the majority of other subjects we performed an experiment with phenylacetohydrazide under the standard conditions used for hydrazides **1**, phenylacetyl chloride also being obtained. Thus, the transformation found is specific for pyrazolinylacetohydrazides.

† 3-Aryl-2-pyrazolin-5-ylacetohydrazides **1a**, **1c**, **1d** were described by us previously (ref. 1), and compounds **1b**, **1e** were prepared analogously.

3-(4-*Chlorophenyl*)-2-*pyrazolin-5-ylacetohydrazide* **1b**: mp 155–156 °C (ethanol), yield 77%. ^{1}H NMR, δ: 2.25 (m, 2H, CH_2CO), 2.70 and 3.05 (dd, 1H, $CH_{2\ pyrazoline}$), 4.10 (m, 1H, $CH_{pyrazoline}$), 7.40 and 7.60 (d, 2H, H_{Ar}), 9.00 (s, 1H, NH). ^{13}C NMR: 36.9 (CH_2), 38.5 ($C_{(4)}$), 57.2 ($C_{(5)}$), 126.9 ($C_{Ar\text{-}ipso}$), 128.4 ($C_{Ar\text{-}meta}$), 132.2 ($C_{Ar\text{-}para}$), 132.4 ($C_{Ar\text{-}ortho}$), 148.0 ($C_{(3)}$), 169.0 (CO). Found (%): C 52.45, 52.33; H 5.28, 5.11; Cl 14.33, 13.90. Calc. for $C_{11}H_{11}ClN_4O$ (%): C 52.28; H 5.19; Cl 14.03.

3-(4-*Methoxyphenyl*)-2-*pyrazolin-5-ylacetohydrazide* **1e**: mp 173–174 °C (ethanol), yield 68%. ^{1}H NMR, δ: 2.22 (m, 2H, CH_2CO), 2.65 and 3.04 (dd, 1H, $CH_{2\ pyrazoline}$), 3.75 (s, 3H, OCH_3), 3.95 (m, 1H, $CH_{pyrazoline}$), 6.93 and 7.52 (d, 2H, H_{Ar}), 9.00 (s, 1H, NH). ^{13}C NMR: 37.4 (CH_2), 55.1 ($C_{(4)}$), 56.8 (CH_3), 113.8 ($C_{Ar\text{-}ipso}$), 126.0 ($C_{Ar\text{-}meta}$), 126.8 ($C_{Ar\text{-}para}$), 159.3 ($C_{Ar\text{-}ortho}$), 149.4 ($C_{(3)}$), 169.5 (CO). Found (%): C 58.09, 58.22; H 6.29, 6.36. Calc. for $C_{12}H_{14}N_4O$ (%): C 58.05; H 6.49.

‡ *Typical procedure for the preparation of* 3-*aryl*-4-*chloro*-5-*trichloromethylpyrazoles* **2**. Hydrazide **1** (1 g) was dissolved with heating (50–70 °C) in 30–35 ml of nitromethane and HCl was bubbled through until precipitation of sediment ceased. After cooling to room temperature a slow stream of chlorine was bubbled with stirring through the suspension formed until complete dissolution of the precipitate (1.5–2.5 h) and then the mixture was left to stand overnight at room temperature. The solvent was removed on a rotary evaporator, and the residue was recrystallized from nitromethane or heptane.

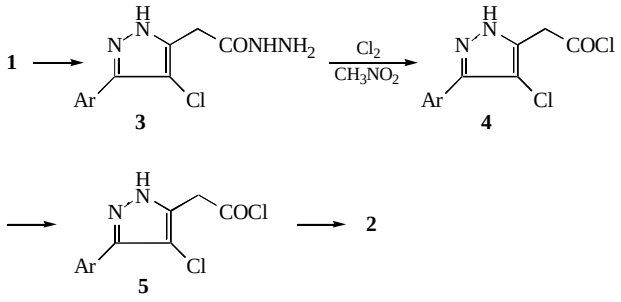
4-*Chloro*-3-*phenyl*-5-*trichloromethylpyrazole* **2a**: mp 201–202 °C, yield 67%. ^{1}H NMR, δ: 7.5–7.8 (m, 5H, Ph), 14.1 (br., 1H, NH). ^{13}C NMR, δ: 103.4 ($C_{(4)}$), 126.8 ($C_{Ar\text{-}ipso}$), 127.1 and 127.3 ($C_{Ar\text{-}meta}$), 128.8 and 129.0 ($C_{Ar\text{-}para}$), 129.1 and 129.6 ($C_{Ar\text{-}ortho}$), 141.7 ($C_{(3)}$), 148.0 ($C_{(5)}$). Found (%): C 40.46, 40.41; H 2.10, 2.15; Cl 47.69, 47.54; N 9.56, 9,48. Calc. for $C_{10}H_6Cl_4N_2$ (%): C 36.35; H 1.53; Cl 53.65; N 8.48.

4-*Chloro*-3-(4-*chlorophenyl*)-5-*trichloromethylpyrazole* **2b**, mp 188–189 °C, yield 73%. ^{1}H NMR, δ: 7.60 (d, 2H, *m*-H), 7.77 (d, 2H, *o*-H), 14.1 (br., 1H, NH). ^{13}C NMR, δ: 89.5 (CCl_3), 103.6 ($C_{(4)}$), 125.6 ($C_{Ar\text{-}ipso}$), 128.7 ($C_{Ar\text{-}meta}$), 129.0 and 129.1 ($C_{Ar\text{-}ortho}$), 133.3 and 134.3 ($C_{Ar\text{-}para}$), 140.6 ($C_{(3)}$), 148.0 ($C_{(5)}$). Found (%): C 36.75, 36.45; H 1.60, 1.64; Cl 53.61, 53.21; N 8.60, 8.61. Calc. for $C_{10}H_5Cl_5N_2$ (%): C 36.35; H 1.53; Cl 53.65; N 8.48.

3-(4-*Bromophenyl*)-4-*chloro*-5-(*trichloromethyl*)*pyrazole* **2c**, mp 199.5–201.5 °C, yield 58%. ^{1}H NMR, δ: 7.62 (d, 2H, *m*-H), 7.8 (d, 2H, *o*-H), 14.1 (br., NH). ^{13}C NMR, δ: 89.9 (CCl_3), 103.8 ($C_{(4)}$), 123.1 ($C_{Ar\text{-}para}$), 126.0 ($C_{Ar\text{-}ipso}$), 129.0 and 129.2 ($C_{Ar\text{-}meta}$), 131.7 and 132.1 ($C_{Ar\text{-}ortho}$), 140.6 ($C_{(3)}$), 148.1 ($C_{(5)}$). Found (high resolution MS, Varian MAT-311A): M = 371.84096. Calc. for $C_{10}H_5BrCl_4N_2$: M = 371.83903.

4-*Chloro*-3-(3-*nitrophenyl*)-5-*trichloromethylpyrazole* **2d**: mp 164 °C, yield 63%. ^{1}H NMR, δ: 7.87 (t, 1H, 5′-H), 8.23 (d, 1H, 4′-H), 8.35 (d, 1H, 6′-H), 8.62 (s, 1H, 2′-H). ^{13}C NMR, δ: 89.6 (CCl_3), 104.4 ($C_{(4)}$), 121.2 and 121.8 ($C_{(4')}$), 123.2 and 124.1 ($C_{(6')}$), 128.2 ($C_{(1')}$), 130.5 and 130.8 ($C_{(5')}$), 133.1 and 133.3 ($C_{(2')}$), 133.5 ($C_{(3')}$), 139.7 ($C_{(3)}$), 148.0 ($C_{(5)}$). Found (%): C 35.89, 35.53; H 1.58, 1.49; Cl 40.91, 40.60; N 12.60, 12.51. Calc. for $C_{10}H_5Cl_4N_3O_2$ (%): C 35.22; H 1.48; Cl 41.59; N 12.32.

4-*Chloro*-3-(3-*chloro*-4-*methoxyphenyl*)-5-*trichloromethylpyrazole* **2e**, mp 191–192 °C, yield 68%. ^{1}H NMR, δ: 7.33 (d, 1H, 5′-H), 7.75 (d, 1H, 6′-H), 7.85 (s, 1H, 2′-H). ^{13}C NMR, δ: 56.3 and 56.4 (OCH_3), 86.4 (CCl_3), 103.1 ($C_{(4)}$), 113.0 and 113.2 ($C_{(5')}$), 119.9 ($C_{(1')}$), 121.3 and 121.6 ($C_{(3')}$), 127.5 and 127.9 ($C_{(6')}$), 128.2 and 128.5 ($C_{(2')}$), 154.8 and 155.4 ($C_{(4')}$), 140.3 ($C_{(3)}$), 147.9 ($C_{(5)}$). Found (%): C 36.83, 36.85; H 2.06, 1.89; Cl 49.02, 48.90. Calc. for $C_{11}H_7Cl_5N_2O$ (%): C 36.65; H 1.96; Cl 49.18.



Scheme 2

The structures of compounds **2** obtained were supported by ^{1}H and ^{13}C NMR spectra.[§] ^{1}H NMR spectra contain only signals due to the protons of aryl substituents and broad NH signals (for compounds **2d**,**e** the broadening is so strong that the signals were impossible to identify). In the ^{13}C NMR spectra signals due to the CCl_3 group at 86.5–90 ppm are present (for compound **2a** this signal could not be identified). Obtaining and interpretating the ^{13}C NMR spectra are difficult since most carbon atoms in the molecules of the compounds **2** are quaternary and give signals of low intensity. In addition, carbon atoms bearing hydrogen atoms, and in some cases selected quaternary atoms, are also represented by double sets of signals of unequal intensity. Similar peculiarities are characteristic of the ^{13}C NMR spectrum of methyl 4-chloro-3-(4-chlorophenyl)-pyrazole-5-carboxylate[¶] that was obtained from trichloride **2b**. In this ester the NH proton manifests itself as two broadened signals when the ^{1}H NMR spectrum is obtained at a temperature close to the freezing point of [$^2H_6$]DMSO. The phenomena mentioned can be explained by either hindered rotation around the C–C bond of the bound aryl group and pyrazole ring or by the presence of two tautomeric forms with an H atom at different nitrogen atoms of the heterocycle. The true origin of the 'duplication' of the signals requires additional investigation.

The authors are very grateful to B. V. Lichitskii for helpful discussions and to A. V. Ignatenko for recording some of the NMR spectra.

Partial financial support by the Russian Foundation for Basic Research (grant no. 95-03-09748) is gratefully acknowledged.

References

1 A. A. Dudinov, S. A. Voznesenskii, I. S. Poddubnyi, B. I. Ugrak, L. I. Belen'kii and M. M. Krayushkin, *Khim. Geterotsikl. Soedin*., 1995, 1511 [*Chem. Heterocycl. Compd*. (*Engl. Transl*.), 1995, 1311].
2 L. A. Carpino, *J. Am. Chem. Soc.*, 1957, **79**, 96.
3 L. A. Carpino, *Chem. Ind*., 1956, 123.
4 T. Jacobs, in *Geterotsiklicheskie Soedineniya* (*Heterocyclic Compounds*), ed. R. Elderfield, Inostrannaya Literatura, Moscow, 1961, vol. 5, p. 84 (in Russian).
5 J. Elguero, in *Comprehensive Heterocyclic Chemistry*, eds. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 5, p. 254.
6 R. Hüttel, O. Schäfer and G. Welzel, *Lieb. Ann*., 1956, **598**, 186.
7 E. Pretsch, T. Clerc, J. Seibl and W. Simon, *Tables of Spectral Data for Structure Determination of Organic Compounds*, Springer–Verlag, Berlin, 1983.

Received: Moscow, 31st October 1997
Cambridge, 9th December 1997; Com. 7/07983D

[§] NMR spectra (in [$^2H_6$]DMSO) were recorded on Bruker AM-300 and Bruker AC-200 instruments. Assignments of the spectra were made taking into account the values of the chemical shifts and increments summarized in ref. 7.

[¶] *Methyl* 4-*chloro*-3-(4-*chlorophenyl*)*pyrazole*-5-*carboxylate*. A solution of trichloride **2b** (0.2 g, 0.6 mmol) in 8 ml of absolute methanol was refluxed for 5 h and left for 2 days. Excess methanol was removed and the residue recrystallized from methanol. Mp 193–195 °C, yield 0.16 g (nearly quantitative). ^{1}H NMR, δ: 3.90 (s, 3H, Me), 7.59 (d, 2H, *o*-H), 7.83 (d, 2H, *m*-H), 14.3 (br., 1H, NH); ^{13}C NMR, δ: 52.1 (OCH_3), 109.5 ($C_{(4)}$), 125.5 ($C_{(1')}$), 127.3 ($C_{(4')}$), 130.4 and 130.5 ($C_{(2')}$ and $C_{(6')}$), 135.0 ($C_{(4')}$), 138.7 ($C_{(3)}$), 146.3 ($C_{(5)}$), 158.3 and 160.9 ($C_{(CO)}$). Found (%): C 48.64, 48.46; H 3.10, 3.21; Cl 26.48, 26.18; N 10.31. Calc. for $C_{11}H_8Cl_2N_2O_2$ (%): C 48.73; H 2.97; Cl 26.16; N 10.33.