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Synthesis of 3-Aryl-5-dichloromethyl-1*H*-pyrazole-1-carboxamides from 1-Aryl-3,4,4-trichlorobut-3-en-1-ones

S. K. Petkevich, V. I. Potkin, and R. V. Kaberdin

Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus, ul. Surganova 13, Minsk, 220072 Belarus
e-mail: potkin@ifoch.bas-net.by

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Abstract—The reaction of 1-aryl-3,4,4-trichlorobut-3-en-1-ones with semicarbazide hydrochloride in the presence of sodium acetate is accompanied by prototropic allylic rearrangement, leading to the formation of two isomeric products, semicarbazones of the initial ketones and 1-aryl-3,4,4-trichlorobut-2-en-1-one semicarbazones. The latter undergo heterocyclization in the presence of triethylamine to give the corresponding 3-aryl-5-dichloromethyl-1*H*-pyrazole-1-carboxamides.

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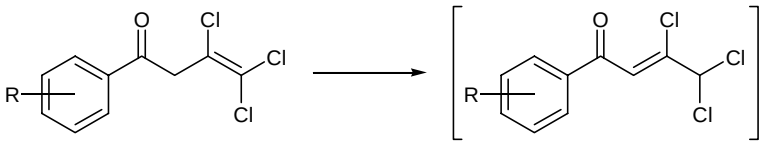
We previously described a convenient procedure for the synthesis of 1-aryl-3,4,4-trichlorobut-3-en-1-ones **Ia**–**IVa** by acylation of substituted benzenes with 3,4,4-trichlorobut-3-enoyl chloride which is prepared in turn from accessible trichloroethylene dimer [1, 2]. Ketones **Ia**–**IVa** are capable of undergoing prototropic allylic rearrangement into isomeric 1-aryl-3,4,4-trichlorobut-2-en-1-ones **Ib**–**IVb** (Scheme 1). The chlorine atom in position *3* of the latter is activated due to conjugation between the double bond and the carbonyl group; thus their molecules possess several potential reaction centers, which makes them promising synthons for building up heterocyclic systems [3, 4].

The present study was aimed at synthesizing *N*-substituted 3-aryl-5-dichloromethylpyrazoles via heterocyclization of semicarbazones derived from ketones **Ia**–**IVa**. Pyrazole derivatives are widely used in the preparation of effective medical agents, chemical means for plant protection, and dyes [3, 5–7]; therefore, search for reactive synthons for functionally substituted pyrazoles and synthesis of new pyrazole derivatives attract interest from both theoretical and practical viewpoints.

Ketones **Ia**–**IVa** were converted into the corresponding semicarbazones according to a standard procedure by treatment with semicarbazide hydrochloride in methanol in the presence of sodium acetate [8]. We found that the reaction was accompanied by prototropic rearrangement in the allyl fragment. As a result, we obtained mixtures of two isomeric products, expected semicarbazones **Va**–**VIIIa** and those derived from the rearrangement products, 1-aryl-3.4,4-trichlorobut-2-en-1-one semicarbazones **Vb**–**VIIIb** in an overall yield of 52–95% (Scheme 2). The yield and isomer ratio depended on the reaction conditions and initial ketone (see table). When the reaction was carried out at 20°C, the overall yield of semicarbazones **V**–**VIII** was 87–95%, and the major products were unrearranged semicarbazones **Va**–**VIIIa** (67–86%), whereas the yield of isomeric compounds **Vb**–**VIIIb** did not exceed 9–20%. In the reactions performed in boiling methanol, the overall yield decreased

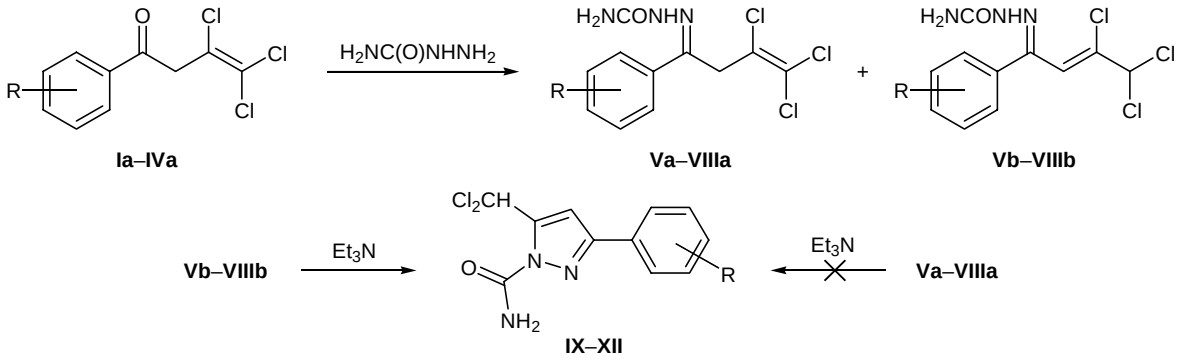
Scheme 1.



Ia–**IVa** **Ib**–**IVb**

I, R = H; **II**, R = 4-Me; **III**, R = 2,5-Me_2; **IV**, R = 4-Br.

Scheme 2.



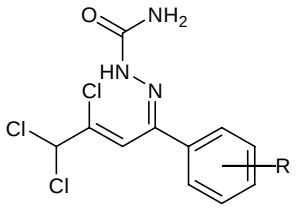
I, **V**, **IX**, R = H; **II**, **VI**, **X**, R = 4-Me; **III**, **VII**, **XI**, R = 2,5-Me_2; **IV**, **VIII**, **XII**, R = 4-Br.

to 52–62%, appreciable tarring occurred, and the fraction of the rearranged products increased (yield 22–45%), while the yield of unrearranged semicarbazones fell down to 8–32%. The largest yields of the rearranged products were obtained in the reactions of semicarbazide with 2,5-dimethylphenyl and 4-bromophenyl derivatives **IIIa** and **IVa** both at 20°C and under reflux. Compounds **Va**–**VIIIa** and their isomers **Vb**–**VIIIb** are characterized by different solubilities, so that they can be separated by fractional crystallization.

The structure of semicarbazones **V**–**VIII** was determined on the basis of their IR, ^{1}H NMR, and mass spectra and elemental analyses. The ^{1}H NMR spectra of semicarbazones **Vb**–**VIIIb** contained one-proton singlets in the regions δ 5.82–7.08 and 7.0–7.8 ppm due to the =CH– and $CHCl_2$ protons, respectively, while no CH_2 signal at δ 4.05–4.57 ppm, typical of initial ketones **Ia**–**IVa** and semicarbazones **Va**–**VIIIa**, was present. The mass spectra of all semicarbazones **V**–**VIII** lacked the molecular ion peaks; the observed fragment ion peaks resulted from elimination of aryl groups, chlorine atoms, amide groups, and vinyl fragments.

Treatment of semicarbazones **Vb**–**VIIIb** with triethylamine promoted their heterocyclization with elimination of hydrogen chloride to give 63–76% of the corresponding 3-aryl-5-dichloromethyl-1*H*-pyrazole-1-carboxamides **IX**–**XII**. Semicarbazones **Va**–**VIIIa** could also be expected to undergo prototropic alllylic rearrangement, followed by heterocyclization of isomers **Vb**–**VIIIb** thus formed. However, semicarbazones **Va**–**VIIIa** failed to react with triethylamine or pyridine even on prolonged heating of the reactants, whereas complete tarring of the reaction mixture occurred in the presence of potassium hydroxide (no individual products were isolated).

Obviously, the *s-cis-syn* configuration of semicarbazones **Vb**–**VIIIb** (*Z* configuration of the chlorovinyl group) is favorable for heterocyclization. Therefore, we presumed just that structure of compounds **Vb**–**VIIIb**. An additional proof for the *s-cis-syn* configuration of semicarbazones **Vb**–**VIIIb** is a considerable downfield shift of the NH proton signal in their ^{1}H NMR spectra (to δ 13.1–13.3 ppm) relative to the corresponding signal in the spectra of unrearranged semicarbazones **Va**–**VIIIa** (δ 9.1–10.4 ppm). The chemical shifts of the NH_2 protons are similar for both isomeric structures (δ 5.7–6.6 ppm). The downfield position of the NH signals in the ^{1}H NMR spectra of semicarbazones **Vb**–**VIIIb** may be rationalized by formation of the hydrogen bond =N–N–H···Cl–C=C–, which is possible for the *Z-s-cis-syn* configuration.



In the IR spectra of pyrazoles **IX**–**XII**, stretching vibrations of the amide carbonyl group give rise to absorption in the region 1687–1716 cm^{-1}, and strong absorption bands at 1575–1587 cm^{-1} belong to vibrations of the C=N bond. Broad absorption bands in the region 3195–3242 cm^{-1} correspond to stretching vibrations of the amide N–H bonds. The ^{1}H NMR spectra of **IX**–**XII** contain broadened singlets at δ 6.1–6.3 ppm from the NH_2 protons, multiplet signals from aromatic protons, and two singlets at δ 6.85–7.0 and 8.0–8.06 ppm. The singlet at δ 6.85–7.0 ppm was assigned to the 4-H proton in the pyrazole ring, and that at δ 6.85–7.0 ppm, to the exocyclic $CHCl_2$ proton. The

Yields of isomeric semicarbazones **V**–**VIII** in the reactions of ketones **Ia**–**IVa** with semicarbazide hydrochloride in the presence of sodium acetate

Reaction conditions	Yield, %							
	Va	**Vb**	**VIa**	**VIb**	**VIIa**	**VIIb**	**VIIIa**	**VIIIb**
20°C, 3 h	84	9	86	9	67	20	72	15
Reflux, 3 h	30	22	32	30	8	45	10	45

latter signal is located in a weak field due to intramolecular hydrogen bonding between the $CHCl_2$ proton and carbonyl oxygen atom; the formation of such hydrogen bond is typical of structurally related compounds, as was shown previously by ^{1}H NMR spectroscopy for molecular fragments of amino derivatives of dichlorocrotonic acid [9, 10].

Pyrazoles **IX**–**XII** showed in the electron-impact mass spectra molecular ion clusters and fragment ions resulting from elimination of chlorine atoms, aryl residue, and amide group. The $^{35}Cl/^{37}Cl$ isotope peak ratio for the molecular ion (100:65) corresponds to the presence of two chlorine atoms in the molecules of compounds **IX**–**XII** [11, 12].

EXPERIMENTAL

The IR spectra were recorded in KBr on a Protege-460 Fourier-transform spectrometer. The ^{1}H NMR spectra were measured on a Tesla-587A spectrometer (80 MHz) from solutions in DMSO-d_6 (semicarbazones **V**–**VIII**) and acetone-d_6 (pyrazoles **IX**–**XII**); tetramethylsilane was used as reference. The mass spectra (electron impact, 50 eV) were obtained on an MKh-1320 instrument.

Reaction of 1-aryl-3,4,4-trichlorobut-3-en-1-ones Ia–IVa with semicarbazide hydrochloride (*general procedure*). *a*. A mixture of 7.5 mmol of ketone **Ia**–**IVa**, 15 mmol of semicarbazide hydrochloride, and 15 mmol of sodium acetate in 30 ml of methanol was stirred for 3 h at 20°C 3 h. The mixture was then poured into water, and the precipitate was filtered off, washed with water, and dried over P_2O_5. The product was treated with methylene chloride, and the undissolved material was filtered off, washed with methylene chloride, and dried under reduced pressure. The filtrate was evaporated by half, and the product was precipitated with hexane, filtered off, and dried under reduced pressure.

b. A mixture of 7.5 mmol of ketone **Ia**–**IVa**, 15 mmol of semicarbazide hydrochloride, and 15 mmol of sodium acetate in 30 ml of methanol was heated for 3 h under reflux. The products were isolated and purified as described above in *a*.

3,4,4-Trichloro-1-phenylbut-3-en-1-one semicarbazone (Va). mp 130–132°C. IR spectrum, ν, cm^{-1}: 1530, 1620 (C=C); 1586 (C=N); 1694 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.05 s (2H, CH_2), 5.7 br.s (2H, NH_2), 7.45 m (3H, H_{arom}), 7.65 m (2H, H_{arom}), 9.1 br.s (1H, NH). Found, %: C 42.80; H 3.40; Cl 34.55; N 13.56. *m*/*z* 270 $[M - Cl]^+$. $C_{11}H_{10}Cl_3N_3O$. Calculated, %: C 43.09; H 3.29; Cl 34.69; N 13.71. *M* 306.59.

3,4,4-Trichloro-1-(4-methylphenyl)but-3-en-1-one semicarbazone (VIa). mp 135–137°C. IR spectrum, ν, cm^{-1}: 1510, 1589, 1615 (C=C); 1557 (C=N); 1710 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.31 s (3H, CH_3), 4.18 s (2H, CH_2), 6.5 br.s (2H, NH_2), 7.18 d (2H, H_{arom}, ^3J = 7.8 Hz), 7.62 d (2H, H_{arom}, ^3J = 7.8 Hz), 9.8 br.s (1H, NH). Found, %: C 44.82; H 3.87; Cl 33.02; N 13.15. *m*/*z* 284 $[M - Cl]^+$. $C_{12}H_{12}Cl_3N_3O$. Calculated, %: C 44.95; H 3.78; Cl 33.17; N 13.11. *M* 320.62.

3,4,4-Trichloro-1-(2,5-dimethylphenyl)but-3-en-1-one semicarbazone (VIIa). mp 140–142°C. IR spectrum, ν, cm^{-1}: 1544, 1586, 1610 (C=C); 1678 (C=N); 1735 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 2.38 s (3H, CH_3), 4.44 s (2H, CH_2), 6.5 br.s (2H, NH_2), 7.12 d and 7.27 d (1H each, H_{arom}, ^3J = 8 Hz), 7.69 br.s (1H, H_{arom}), 10.4 br.s (1H, NH). Found, %: C 46.49; H 4.32; Cl 31.58; N 12.67. *m*/*z* 298 $[M - Cl]^+$. $C_{13}H_{14}Cl_3N_3O$. Calculated, %: C 46.65; H 4.23; Cl 31.78; N 12.56. *M* 334.65.

1-(4-Bromophenyl)-3,4,4-trichlorobut-3-en-1-one semicarbazone (VIIIa). mp 158–160°C. IR spectrum, ν, cm^{-1}: 1567, 1584, 1610 (C=C); 1682 (C=N); 1743 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.57 s (2H, CH_2), 6.6 br.s (2H, NH_2), 7.45 d (2H, H_{arom}, ^3J = 8 Hz), 7.88 d (2H, H_{arom}, ^3J = 8 Hz), 10.4 br.s (1H, NH). Found, %: C 34.50; H 2.49; Hlg 48.53; N 10.79. *m*/*z* 348 $[M - Cl]^+$. $C_{11}H_9BrCl_3N_3O$. Calculated, %: C 34.27; H 2.36; Hlg 48.32; N 10.90. *M* 385.48.

3,4,4-Trichloro-1-phenylbut-2-en-1-one semicarbazone (Vb). mp 252–254°C. IR spectrum, ν, cm^{-1}: 1512, 1601, 1620 (C=C); 1660 (C=N); 1702 (C=O). ^1H NMR spectrum, δ, ppm: 5.82 s (1H, =CH), 6.6 br.s (2H, NH_2), 7.0 s (1H, $CHCl_2$), 7.4 m (2H, H_{arom}), 7.7 m (2H, H_{arom}), 13.3 br.s (1H, NH). Found, %: C 42.92; H 3.44; Cl 34.45; N 13.92. *m*/*z* 270 $[M - Cl]^+$. $C_{11}H_{10}Cl_3N_3O$. Calculated, %: C 43.09; H 3.29; Cl 34.69; N 13.71. *M* 306.59.

3,4,4-Trichloro-1-(4-methylphenyl)but-2-en-1-one semicarbazone (VIb). mp 266–268°C. IR spectrum, ν, cm^{-1}: 1512, 1600, 1620 (C=C); 1660 (C=N); 1732 (C=O). ^1H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3), 5.9 br.s (2H, NH_2), 6.5 s (1H, =CH), 7.20 d (2H, H_{arom}, ^3J = 7.9 Hz), 7.65 m (3H, $CHCl_2$, H_{arom}), 13.1 br.s (1H, NH). Found, %: C 45.15; H 3.92; Cl 33.01; N 13.00. *m*/*z* 284 $[M - Cl]^+$. $C_{12}H_{12}Cl_3N_3O$. Calculated, %: C 44.95; H 3.78; Cl 33.17; N 13.11. *M* 320.62.

3,4,4-Trichloro-1-(2,5-dimethylphenyl)but-2-en-1-one semicarbazone (VIIb). mp 242–244°C. IR spectrum, ν, cm^{-1}: 1506, 1588, 1621 (C=C); 1677 (C=N); 1702 (C=O). ^1H NMR spectrum, δ, ppm: 2.27 s (3H, CH_3), 2.36 s (3H, CH_3), 6.5 br.s (2H, NH_2), 6.75 s (1H, =CH), 7.05 d and 7.12 d (1H each, H_{arom}, ^3J = 8 Hz), 7.25 s (1H, $CHCl_2$), 7.89 br.s (1H, H_{arom}), 13.1 br.s (1H, NH). Found, %: C 46.70; H 4.03; Cl 31.55; N 12.65. *m*/*z* 298 $[M - Cl]^+$. $C_{13}H_{14}Cl_3N_3O$. Calculated, %: C 46.65; H 4.23; Cl 31.78; N 12.56. *M* 334.65.

1-(4-Bromophenyl)-3,4,4-trichlorobut-2-en-1-one semicarbazone (VIIIb). mp 251–253°C. IR spectrum, ν, cm^{-1}: 1530, 1584, 1630 (C=C); 1681 (C=N); 1740 (C=O). ^1H NMR spectrum, δ, ppm: 6.6 br.s (2H, NH_2), 7.08 s (1H, =CH), 7.40 d (2H, H_{arom}, ^3J = 8 Hz), 7.65 m (3H, $CHCl_2$), 7.85 d (2H, H_{arom}, ^3J = 8 Hz), 13.3 br.s (1H, NH). Found, %: C 34.07; H 2.65; Hlg 48.40; N 10.93. *m*/*z* 348 $[M - Cl]^+$. $C_{11}H_9BrCl_3N_3O$. Calculated, %: C 34.27; H 2.36; Hlg 48.32; N 10.90. *M* 385.48.

3-Aryl-5-dichloromethyl-1*H*-pyrazole-1-carboxamides IX–XII (*general procedure*). A mixture of 5 mmol of semicarbazone **Vb**–**VIIIb** and 10 mmol of triethylamine in 50 ml of ethanol was heated for 30 h under reflux. The mixture was then poured into water and acidified to pH 3 with hydrochloric acid, and the precipitate was filtered off, washed with water, and dried under reduced pressure. The product was purified by recrystallization from hexane.

5-Dichloromethyl-3-phenyl-1*H*-pyrazole-1-carboxamide (IX). Yield 68%, mp 201–202°C. IR spectrum, ν, cm^{-1}: 1532, 1625 (C=C); 1587 (C=N); 1703 (C=O). ^1H NMR spectrum, δ, ppm: 6.3 br.s (2H, NH_2), 7.0 s (1H, =CH), 7.4 m (3H, H_{arom}), 7.85 m (2H, H_{arom}), 8.0 s (1H, $CHCl_2$). Found, %: C 48.72; H 3.54; Cl 26.05; N 15.43. *m*/*z* 269 $[M]^+$. $C_{11}H_9Cl_2N_3O$. Calculated, %: C 48.91; H 3.37; Cl 26.25; N 15.56. *M* 270.13.

5-Dichloromethyl-3-(4-methylphenyl)-1*H*-pyrazole-1-carboxamide (X). Yield 63%, mp 214–215°C. IR spectrum, ν, cm^{-1}: 1593, 1655 (C=C); 1581 (C=N); 1687 (C=O). ^1H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 6.1 br.s (2H, NH_2), 6.9 s (1H, =CH), 7.4 d (2H, H_{arom}, ^3J = 7.9 Hz), 7.75 d (2H, H_{arom}, ^3J = 7.9 Hz), 8.0 s (1H, $CHCl_2$). Found, %: C 50.55; H 4.09; Cl 24.66; N 14.70. *m*/*z* 283 $[M]^+$. $C_{12}H_{11}Cl_2N_3O$. Calculated, %: C 50.72; H 3.91; Cl 24.95; N 14.79. *M* 284.16.

5-Dichloromethyl-3-(2,5-dimethylphenyl)-1*H*-pyrazole-1-carboxamide (XI). Yield 76%, mp 211–212°C. IR spectrum, ν, cm^{-1}: 1507, 1618 (C=C); 1585 (C=N); 1700 (C=O). ^1H NMR spectrum, δ, ppm: 2.36 s (3H, CH_3), 2.48 s (3H, CH_3), 6.2 br.s (2H, NH_2), 6.85 s (1H, =CH), 7.15 m (2H, H_{arom}), 7.42 br.s (1H, H_{arom}), 8.06 s (1H, $CHCl_2$). Found, %: C 52.60; H 4.12; Cl 23.99; N 13.89. *m*/*z* 297 $[M]^+$. $C_{13}H_{13}Cl_2N_3O$. Calculated, %: C 52.36; H 4.40; Cl 23.78. N 14.10. *M* 298.19.

3-(4-Bromophenyl)-5-dichloromethyl-1*H*-pyrazole-1-carboxamide (XII). Yield 72%, mp 229–231°C. IR spectrum, ν, cm^{-1}: 1550, 1623 (C=C); 1575 (C=N); 1716 (C=O). ^1H NMR spectrum, δ, ppm: 6.2 br.s (2H, NH_2), 7.0 s (1H, =CH), 7.63 d (2H, H_{arom}, ^3J = 8 Hz), 7.87 d (2H, H_{arom}, ^3J = 8 Hz), 8.0 s (3H, $CHCl_2$). Found, %: C 37.58; H 2.50; Hlg 42.98; N 11.88. *m*/*z* 347 $[M]^+$. $C_{11}H_8BrCl_2N_3O$. Calculated, %: C 37.85; H 2.32; Hlg 43.20; N 12.04. *M* 349.02.

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