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1,1-Bis(3,5-dimethyl-1-pyrazolyl)- and 1-Amino-1-(3,5-dimethyl-1-pyrazolyl)-4,4-dichloro-1-buten-3-ones

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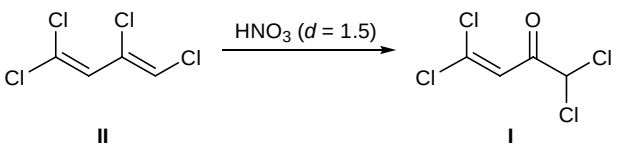
Abstract—Reaction of 1,1,4,4-tetrachloro-3-buten-2-one with 3,5-dimethylpyrazole gave 1,1-dichloro-4,4-bis-(3,5-dimethyl-1-pyrazolyl)-3-buten-2-one. Treatment of the latter with amines resulted in replacement of one pyrazole ring by the amine residue with formation of the corresponding 4-amino-1,1-dichloro-4-(3,5-dimethyl-1-pyrazolyl)-3-buten-2-ones.

Functionalized pyrazole derivatives are widely used in industry, agriculture, and medicine, specifically in the synthesis of dyes, chemical bleaching agents, luminescent and fluorescent components for various materials, fuel antioxidants [1], chemical means for plant protection [2], and effective drugs with versatile activity [3]. Synthesis of pyrazoles containing a chlorinated ketone moiety attracts interest, for chlorinated aliphatic ketones of the C_4 series have been successfully used for the preparation of various biologically active compounds [4]. In addition, it is known that introduction of chlorine atoms usually enhances biological effect of a chemical compounds [5]. An accessible and reactive chlorinated ketone is 1,1,4,4-tetrachloro-3-buten-2-one (**I**) which is obtained by oxidation of 1,1,3,4-tetrachloro-1,3-butadiene (**II**) with concentrated nitric acid (Scheme 1); compound **II** is readily available via dechlorination of trichloroethylene dimer [6].

As shown in [6], ketone **I** readily reacts with primary and secondary amines to give the corresponding amino ketones as a result of replacement of the terminal chlorine atoms in the vinyl group. The high reactivity of ketone **I** in nucleophilic substitution processes originates from activating effect of the conjugated carbonyl group, which induces electron density redistribution in the molecule thus creating a strongly electrophilic center on C^4. In the present work we examined alkylation with ketone **I** of a weakly reactive N-nucleophile, 3,5-dimethylpyrazole, with a view to obtain functionally substituted pyrazole derivatives. Ketone **I** failed to react with 3,5-dimethylpyrazole at room temperature, but heating of the reactants in boiling benzene over a period of 30 h gave 1,1-dichloro-4,4-bis(3,5-dimethyl-1-pyrazolyl)-1-buten-3-one (**III**) as a result of alkylation of two 3,5-dimethylpyrazole molecules. By the action of primary and secondary amines on compound **III**, one pyrazole fragment in the latter was replaced by the amine residue to afford the corresponding 4-amino-1,1-dichloro-4-(3,5-dimethyl-1-pyrazolyl)-1-buten-3-ones **IV**–**XII**. The following amines were used: 4-bromoaniline, 4-toluidine, anisidine, 2-methoxyaniline, phenetidine, ethyl 4-aminobenzoate, 1-naphthylamine, diethylamine, and morpholine. The carbonyl group in molecule **III** remained intact in these reactions.

Scheme 1.



II **I**

The structure of products **III**–**XII** was confirmed by their elemental compositions and IR, ^{1}H NMR, and mass spectra. The IR spectra contain absorption bands at 1629–1694 cm^{-1} due to stretching vibrations of the carbonyl group. The carbonyl vibration frequency in the spectra of compounds **IV**–**X** having a secondary amino group is considerably lower (1629–1649 cm^{-1}) than the corresponding frequency for compounds **XI** and **XII** with a tertiary amino group (1655–1694 cm^{-1}). This difference indicates formation in molecules **IV**–**X** of intramolecular hydrogen bond –N–H···O=C– which closes a six-membered H-chelate ring typical of

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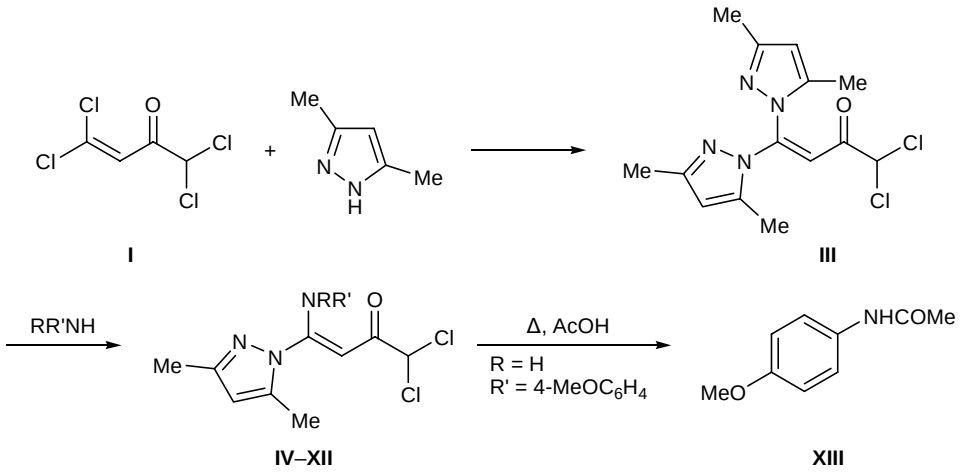
Scheme 2.



IV, R = H, R' = 4-BrC_6H_4; **V**, R = H, R' = 4-MeC_6H_4; **VI**, R = H, R' = 4-$MeOC_6H_4$; **VII**, R = H, R' = 2-$MeOC_6H_4$; **VIII**, R = H, R' = 4-$EtOC_6H_4$; **IX**, R = H, R' = 4-$EtOC(O)C_6H_4$; **X**, R = H, R' = 1-naphthyl; **XI**, R = R' = Et; **XII**, RR'N = morpholino.

conjugated β-enaminovinyl ketones [7]. In the ^{1}H NMR spectra of **III**–**XII** we observed a singlet at δ 5.63–6.06 ppm due to proton of the dichloromethyl group. This finding confirms that the $CHCl_2$ group is not involved in the nucleophilic substitution process. The ^{1}H NMR spectra also contained signals from the =CH– proton in the ketone fragment and protons in the pyrazole ring and amine residue. The NH signals appear in the spectra of **IV**–**X** as broadened singlets at δ 8.4–12.3 ppm. Compounds **III**–**XII** showed in the mass spectra the molecular ion peaks with an isotope ratio of 100:65:1.1 which corresponds to the presence of two chlorine atoms [8, 9]. The fragment ions arise from elimination of chlorine atoms, methyl groups, and amine residues from the molecular ion.

We previously revealed an unusual transformation of 3,4,4-trichloro-1-azolyl-1-arylamino-2-nitro-1,3-butadienes on heating in proton-donor solvents (such as methanol or acetic acid). This transformation includes elimination of the azole fragment and subsequent intramolecular cyclization to give benzazetine structures with trichloronitropropenyl group in position *2* [10]. This reaction opens a new synthetic route to difficultly accessible and poorly studied benzazetines. We tried to effect an analogous transformation of 1,1-dichloro-4-(3,5-dimethyl-1-pyrazolyl)-4-(4-methoxyphenylamino)-1-buten-3-one (**VI**) which can be regarded as somewhat related to 3,4,4-trichloro-1-azolyl-1-arylamino-2-nitro-1,3-butadienes; like the latter, compound **VI** contains a chlorinated C_4-aliphatic chain with a conjugated vinyl group which is activated by electron-acceptor effect of the carbonyl group.

Compound **VI** remained unchanged on heating in boiling methanol, while heating of **VI** in glacial acetic acid resulted in its decomposition to form a complex mixture of tarry products. Among the products, we succeeded in isolating and identifying by gas chromatography–mass spectrometry *N*-(4-methoxyphenyl)-acetamide (**XIII**). Obviously, amide **XIII** is formed via cleavage of the HN–C_{ketone} bond, and its yield does not exceed 20%.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Protégé-460 Fourier spectrometer. The ^{1}H NMR spectra were measured on a Tesla-567A instrument (100 MHz) from solutions in $CDCl_3$ using tetramethylsilane as reference. The mass spectra (electron impact, 50 eV) were run on an MKh-1320 mass spectrometer. GC–MS analysis was performed on a Hewlett–Packard HP 5972 mass-selective detector coupled with an HP 5890 gas chromatograph.

1,1-Dichloro-4,4-bis(3,5-dimethyl-1-pyrazolyl)-3-buten-2-one (III). Ketone **I**, 2.16 g (10.4 mmol), was added under stirring to a solution of 4 g (41.6 mmol) of 3,5-dimethylpyrazole in 20 ml of benzene. The mixture was heated for 30 h under reflux, the solvent was distilled off, the residue was diluted with 20 ml of diethyl ether, the precipitate of 3,5-dimethylpyrazole hydrochloride was filtered off, the filtrate was evaporated under reduced pressure, and the residue was recrystallized from hexane. Yield 2.44 g (72%), mp 71°C. IR spectrum, ν, cm^{-1}: 776 (C–Cl); 1566,

1601, 1663 (C=C, C=N); 1694 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.70 s (3H, CH_3), 2.03 s (3H, CH_3), 2.26 s (6H, $2CH_3$), 5.76 s (1H, $CHCl_2$), 5.99 s and 6.06 s (2H, 4-H, pyrazole), 6.84 s (1H, =CHCO). Found, %: C 51.17; H 4.99; Cl 21.78; N 17.41. $[M]^+$ 326. $C_{14}H_{16}Cl_2N_4O$. Calculated, %: C 51.39; H 4.93; Cl 21.67; N 17.12. *M* 327.21.

Reactions of 1,1-dichloro-4,4-bis(3,5-dimethyl-1-pyrazolyl)-3-buten-2-one (III) with amines (*general procedure***).** Appropriate amine, 3.2 mmol, was added under stirring to a mixture of 1.05 g (3.2 mmol) of bispyrazole derivative **III** and 15 ml of diethyl ether, and the mixture was heated for 4 h under reflux. The sol-vent was distilled off under reduced pressure to 2/3 of the initial volume, 10 ml of hexane was added to the residue, and the precipitate was filtered off and recrystallized from hexane.

4-(4-Bromophenyl)-1,1-dichloro-4-(3,5-dimethyl-1-pyrazolyl)-3-buten-2-one (IV). Yield 71%, mp 113–115°C. IR spectrum, ν, cm^{-1}: 787 (C–Cl); 1509, 1567, 1605 (C=C, C=N); 1636 (C=O); 3265 (NH). ^{1}H NMR spectrum, δ, ppm: 2.04 s (3H, CH_3), 2.22 s (3H, CH_3), 5.85 s (1H, $CHCl_2$), 5.92 s (1H, 4-H, pyrazole), 5.96 s (1H, =CHCO), 6.42 d.d (2H, H_{arom}), 7.29 d.d (2H, H_{arom}), 11.50 br.s (1H, NH). Found, %: C 44.50; H 3.32; Hlg 37.53; N 10.48. $[M]^+$ 401. $C_{15}H_{14}BrCl_2N_3O$. Calculated, %: C 44.69; H 3.50; Hlg 37.41; N 10.42. *M* 403.10.

1,1-Dichloro-4-(3,5-dimethyl-1-pyrazolyl)-4-(4-methylphenyl)-3-buten-2-one (V). Yield 35%, mp 85–87°C. IR spectrum, ν, cm^{-1}: 784 (C–Cl); 1519, 1572, 1607 (C=C, C=N); 1638 (C=O); 3260 (NH). ^{1}H NMR spectrum, δ, ppm: 1.98 s (3H, CH_3), 2.24 s (6H, $2CH_3$), 5.82 s (1H, $CHCl_2$), 5.88 s (1H, 4-H, pyrazole), 5.97 s (1H, =CHCO), 6.48 d.d (2H, H_{arom}), 6.98 d.d (2H, H_{arom}), 11.70 br.s (1H, NH). Found, %: C 56.60; H 4.88; Cl 20.70; N 12.50. $[M]^+$ 337. $C_{16}H_{17}Cl_2N_3O$. Calculated, %: C 56.82; H 5.07; Cl 20.96; N 12.42. *M* 338.24.

1,1-Dichloro-4-(3,5-dimethyl-1-pyrazolyl)-4-(4-methoxyphenyl)-3-buten-2-one (VI). Yield 80%, mp 130–131°C. IR spectrum, ν, cm^{-1}: 776 (C–Cl); 1511, 1565, 1598, 1606 (C=C, C=N); 1630 (C=O); 3250 (NH). ^{1}H NMR spectrum, δ, ppm: 1.98 s (3H, CH_3), 2.22 s (3H, CH_3), 3.73 s (3H, CH_3O), 5.79 s (1H, $CHCl_2$), 5.86 s (1H, 4-H, pyrazole), 5.96 s (1H, =CHCO), 6.40–6.90 m (4H, H_{arom}), 11.70 br.s (1H, NH). Found, %: C 54.52; H 4.99; Cl 19.73; N 11.81. $[M]^+$ 353. $C_{16}H_{17}Cl_2N_3O_2$. Calculated, %: C 54.25; H 4.84; Cl 20.02; N 11.86. *M* 354.24.

1,1-Dichloro-4-(3,5-dimethyl-1-pyrazolyl)-4-(2-methoxyphenyl)-3-buten-2-one (VII). Yield 55%, mp 104–105°C. IR spectrum, ν, cm^{-1}: 785 (C–Cl); 1512, 1559, 1575, 1607 (C=C, C=N); 1643 (C=O); 3280 (NH). ^{1}H NMR spectrum, δ, ppm: 1.97 s (3H, CH_3), 2.24 s (3H, CH_3), 3.90 s (3H, CH_3O), 5.82 s (1H, $CHCl_2$), 5.87 s (1H, 4-H, pyrazole), 5.97 s (1H, =CHCO), 5.92 d (1H, H_{arom}), 6.54–7.10 m (3H, H_{arom}), 11.70 br.s (1H, NH). Found, %: C 54.31; H 4.92; Cl 19.97; N 11.98. $[M]^+$ 353. $C_{16}H_{17}Cl_2N_3O_2$. Calculated, %: C 54.25; H 4.84; Cl 20.02; N 11.86. *M* 354.24.

1,1-Dichloro-4-(3,5-dimethyl-1-pyrazolyl)-4-(4-ethoxyphenyl)-3-buten-2-one (VIII). Yield 58%, mp 62–64°C. IR spectrum, ν, cm^{-1}: 779 (C–Cl); 1509, 1563, 1596 (C=C, C=N); 1629 (C=O); 3255 (NH). ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, $CH_2C\mathbf{H}_3$), 1.98 s (3H, CH_3), 2.25 s (3H, CH_3), 3.94 q (2H, CH_2O), 5.77 s (1H, $CHCl_2$), 5.86 s (1H, 4-H, pyrazole), 5.97 s (1H, =CHCO), 6.45–6.85 m (4H, H_{arom}), 8.40 br.s (1H, NH). Found, %: C 55.76; H 5.12; Cl 19.50; N 11.71. $[M]^+$ 367. $C_{17}H_{19}Cl_2N_3O_2$. Calculated, %: C 55.45; H 5.20; Cl 19.25; N 11.41. *M* 368.26.

Ethyl 4-[4,4-dichloro-1-(3,5-dimethyl-1-pyrazolyl)-3-oxo-1-butenylamino]benzoate (IX). Yield 24%, mp 117–119°C. IR spectrum, ν, cm^{-1}: 767 (C–Cl); 1510, 1566, 1571, 1593 (C=C, C=N); 1649, 1698 (C=O); 3290 (NH). ^{1}H NMR spectrum, δ, ppm: 1.37 t (3H, $CH_2C\mathbf{H}_3$), 2.07 s (3H, CH_3), 2.26 s (3H, CH_3), 4.34 q (2H, CH_2O), 5.93 s (1H, $CHCl_2$), 5.97 s (1H, =CHCO), 6.00 s (1H, 4-H, pyrazole), 6.56 d.d (2H, H_{arom}), 7.91 d.d (2H, H_{arom}), 11.60 br.s (1H, NH). Found, %: C 54.72; H 4.71; Cl 17.49; N 10.82. $[M]^+$ 395. $C_{18}H_{19}Cl_2N_3O_3$. Calculated, %: C 54.56; H 4.83; Cl 17.89; N 10.60. *M* 396.27.

1,1-Dichloro-4-(3,5-dimethyl-1-pyrazolyl)-4-(1-naphthyl)-3-buten-2-one (X). Yield 59%, mp 144–145°C. IR spectrum, ν, cm^{-1}: 766 (C–Cl); 1513, 1564, 1572, 1609 (C=C, C=N); 1633 (C=O); 3255 (NH). ^{1}H NMR spectrum, δ, ppm: 1.80 s (3H, CH_3), 2.21 s (3H, CH_3), 5.84 s (1H, $CHCl_2$), 6.01 s (1H, 4-H, pyrazole), 6.04 s (1H, =CHCO), 6.43 d (1H, H_{arom}), 7.07–8.30 m (6H, H_{arom}), 12.30 br.s (1H, NH). Found, %: C 60.78; H 4.73; Cl 18.59; N 11.09. $[M]^+$ 373. $C_{19}H_{17}Cl_2N_3O$. Calculated, %: C 60.97; H 4.58; Cl 18.94; N 11.23. *M* 374.27.

1,1-Dichloro-4-diethylamino-4-(3,5-dimethyl-1-pyrazolyl)-3-buten-2-one (XI). Yield 61%, mp 88–90°C. IR spectrum, ν, cm^{-1}: 777 (C–Cl); 1550, 1570

(C=C, C=N); 1665 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.25 t (6H, $NCH_2C\mathbf{H}_3$), 2.26 s (6H, CH_3), 3.25 q (4H, CH_2N), 5.63 s (1H, $CHCl_2$), 5.83 s (1H, 4-H, pyrazole), 5.95 s (1H, =CHCO). Found, %: C 51.42; H 6.01; Cl 23.09; N 13.91. $[M]^+$ 303. $C_{13}H_{19}Cl_2N_3O$. Calculated, %: C 51.33; H 6.30; Cl 23.31; N 13.81. *M* 304.22.

4,4-Dichloro-4-(3,5-dimethyl-1-pyrazolyl)-4-morpholino-3-buten-2-one (XII). Yield 90%, mp 109–111°C. IR spectrum, ν, cm^{-1}: 774 (C–Cl); 1575, 1594 (C=C, C=N); 1668 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.24 s (6H, CH_3), 3.05–3.35 m (4H, CH_2N), 3.65–3.97 m (4H, CH_2O), 5.63 s (1H, $CHCl_2$), 5.81 s (1H, 4-H, pyrazole), 5.98 s (1H, =CHCO). Found, %: C 49.38; H 5.09; Cl 22.01; N 13.52. $[M]^+$ 317. $C_{13}H_{17}Cl_2N_3O_2$. Calculated, %: C 49.07; H 5.38; Cl 22.28; N 13.21. *M* 318.20.

Decomposition of 1,1-dichloro-4-(3,5-dimethyl-1-pyrazolyl)-4-(4-methoxyphenyl)-3-buten-2-one (VI) in acetic acid. A mixture of 0.4 g (1.1 mmol) of 1,1-dichloro-4,4-bis(3,5-dimethyl-1-pyrazolyl)-3-buten-2-one (**VI**) and 15 ml of glacial acetic acid was stirred for 15 h at 60°C. The mixture was poured into an ice–water mixture and treated with methylene chloride. The extract was dried over magnesium sulfate, and the solvent was distilled off. Analysis of the residue by gas chromatography–mass spectrometry showed the presence of *N*-(4-methoxyphenyl)acetamide (**XIII**).

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