Electrophilic 1,5-addition of acyl chlorides to the azocyclopropane system of spiro(1-pyrazoline-3,1′-cyclopropanes)

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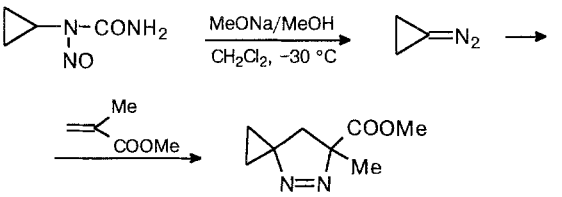
1-Pyrazolines **1–4**, which contain a spiro cyclopropane fragment at the adjacent azo group, react selectively with acetyl (benzoyl) chloride or acetic anhydride in the presence of $AlCl_3$ to give high yields of the corresponding 1-acyl-3-(2-chloroethyl)-2-pyrazolines **5–8**, adducts of electrophilic 1,5-addition of acyl chlorides to the conjugated azocyclopropane system.

Key words: spiro(1-pyrazoline-3,1′-cyclopropanes), 3-(2-chloroethyl)-2-pyrazolines, electrophilic addition, cyclopropane ring opening.

Cyclopropyl-substituted azo compounds can be regarded as analogs of vinylcyclopropanes, cyclopropylketones, and analogous compounds with heteroatoms forming a multiple bond in the vicinity of a three-membered carbon ring. Consideration of the model of vinylcyclopropane shows that the maximum overlapping of asymmetric orbitals of the cyclopropane moiety with the π- or π^*-orbitals of such a double bond, which provides the possibility of conjugation of these fragments, occurs most completely in the case of their *s-trans* conformation. Such a system often behaves like a united moiety in chemical reactions; radical or electrophilic addition of this moiety to a double bond results in opening of the cyclopropane ring and addition of a nucleophilic species to it.[1,2] In particular, such transformations are typical of cyclopropylketones.[3] A general property of vinylcyclopropanes and related systems containing a heteroatom in the alkene part of the molecule is that they undergo isomerization into cyclopentanes (heterocyclopentanes) rather readily.[4]

In the series of compounds of this type, cyclopropanes incorporating a neighboring azo group have been studied insufficiently. The known examples of chemical transformations of azocyclopropanes are generally restricted to their thermal and photochemical isomerization[5–7] and radical reduction,[8] which result in opening of the cyclopropane ring.

In the present work, we have studied for the first time reactions of acyl chlorides with 1-pyrazolines that contain the azo group neighboring with a spiro-coupled cyclopropane moiety, namely, spiro(1-pyrazoline-5,1′-cyclopropane) (**1**), spiro(3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-3-ene-5,1′-cyclopropane) (**2**), spiro(6,6-dimethyl-2,3-diazabicyclo[3.1.0]hex-2-ene-4,1′-cyclopropane) (**3**), and spiro(3-methoxycarbonyl-3-methyl-1-pyrazoline-5,1′-cyclopropane) (**4**). Pyrazolines **1**—**3** were obtained by procedures reported previously. Compound **1** was synthesized by adding diazomethane to methylcyclopropane followed by separation of the isomers;[9] compounds **2** and **3** were obtained by adding diazocyclopropane generated *in situ* to norbornene and 3,3-dimethylcyclopropene.[10] Compound **4** was synthesized in ~75 % yield similarly to compounds **2** and **3** by 1,3-dipolar addition of diazocyclopropane generated *in situ* to methyl methacrylate at −30 °C (molar ratio of *N*-nitrozo-*N*-cyclopropylurea : olefin ~ 1 : 1.2).



4: ~75%

We found that the reaction of pyrazolines **1** and **2** with an equimolar amount of acetyl chloride in haloalkanes (preferably CH_2Cl_2) occurs with a weak exothermic effect to give the corresponding 1-acetyl-3-(2-chloroethyl)-2-pyrazolines **5** and **6a** in high yields. According to data of elemental analysis and ^1H NMR spectroscopy, removal of the solvents *in vacuo* gave the adducts as sufficiently pure individual compounds.

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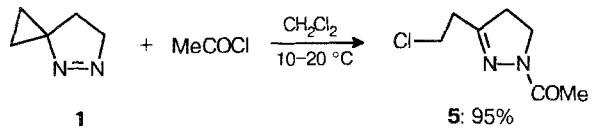
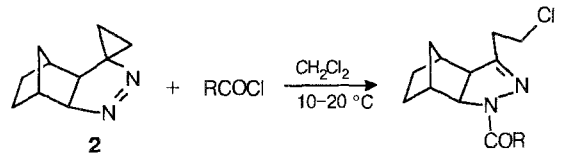


1 5: 95%



2

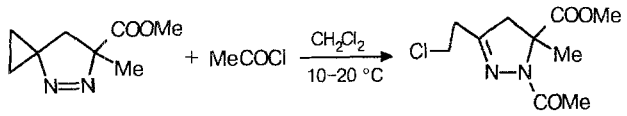
1 : 1

6a: R = Me (96%)

6b: R = Ph (95%)

Benzoyl chloride also reacts rather readily with pyrazoline **2** in CH_2Cl_2 at 20 °C to give, after removal of the solvent, a crystalline product of conjugated addition, **6b**.

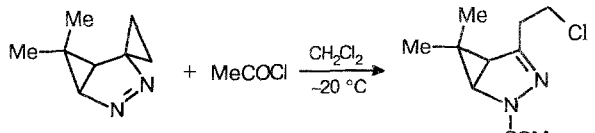
Addition of MeCOCl to pyrazoline **4**, which contains an ester group at the heterocycle, occurs in a similar way to give the corresponding 1-acetyl-3-(2-chloroethyl)-2-pyrazoline **7** in ~96 % yield.



4 7: 96%

The results obtained demonstrate that, regardless of the nature of the substituents in the starting 1-pyrazolines, the reaction proceeds highly regioselectively through electrophilic attack of the acyl group on the N atom that is remote from the cyclopropane ring. The appearance of a positive charge on the neighboring nitrogen atom causes opening of the cyclopropane ring and addition of a chloride ion to the latter.

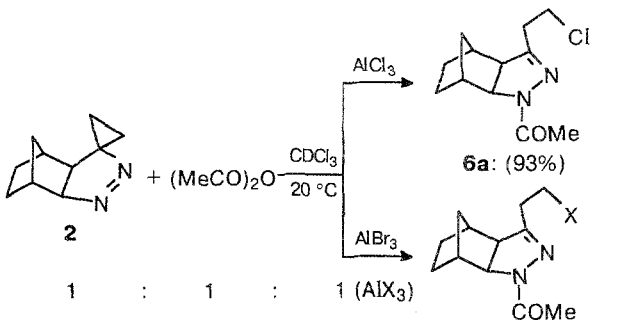
To establish the effect of the orientation of the cyclopropane moieties in 1-pyrazolines on their reaction with acyl halides, we studied the reaction of tricyclic pyrazoline **3**, which simultaneously incorporates a spiro-coupled cyclopropane moiety, whose plane is orthogonal to the π-orbitals of the N=N double bond, and an annelated cyclopropane moiety partially approximated to the plane of the pyrazoline ring. It turned out that adding an equimolar amount of MeCOCl to pyrazoline **3** at 20 °C results in selective opening of the spiro-coupled cyclopropane ring to give 2-acetyl-6,6-dimethyl-4-(2-chloroethyl)-2,3-diazabicyclo[3.1.0]hex-3-ene **8**. The annelated cyclopropane moiety remained unchanged even when a twofold excess of acetyl chloride was used and the reaction was carried out for 8 h at 20 °C, although its opening would yield the more stable tertiary carbonium ion.



3 1 : 1 8: ~96%

Thus, the readily occurring 1,5-addition of acyl halides to the azacyclopropane ring, whose plane is orthogonal to the π-orbitals of the N=N double bond, as is the case for spiro(1-pyrazoline-3,1′-cyclopropanes), indicates that conjugation can exist between the double bond and the cyclopropane ring. In addition, due to the high selectivity of the process it can be assumed that the electrophilic attack of the nitrogen atom and the attack of cyclopropane by the nucleophile occur almost simultaneously, since the intermediate formation of a primary carbocation without rearrangement or deprotonation of the latter seems rather unlikely. On the other hand, the existence of conjugation in the above azocyclopropanes probably decreases the energy of the system and renders it more stable. In particular, this is indicated by the high thermal stability of polycyclic spiro(1-pyrazoline-3,1′-cyclopropanes) that we reported previously.[11]

Replacement of acetyl chloride by acetic anhydride does not result in any noticeable transformations of pyrazoline **2** in $CDCl_3$ (according to ^1H NMR spectral data), and the reaction occurs only when $AlCl_3$ or $AlBr_3$ is added. In the case of $AlCl_3$, the chloride ion rather than AcO^- adds to the CH_2 group of the opened cyclopropane ring, which results in the chloride **6a** described above. According to ^1H NMR and chromatomass spectroscopy, the reaction in the presence of $AlBr_3$ gives rise to two compounds, namely, bromide **6c** and acetate **6d** in a ratio of ~2.8 : 1. Both products were isolated in the individual state using preparative TLC.



2 1 : 1 : 1 (AlX_3)

6a: (93%)

6c + **6d**

6c: X = Br (70%)

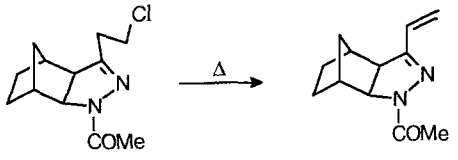
6d: X = OCOMe (25%)

The compounds obtained are sufficiently stable under ordinary conditions and can be chromatographed by

Table 1. Chemical shifts and coupling constants of protons of the $CH^aH^bCH^cH^dCl$ group in 2-pyrazoline **6b**, calculated by the CALM program[12] (the spectrum was recorded at 200 MHz)

Proton	δ	$\Delta\delta_{H(gem)}$/Hz	(H,H)	*J*/Hz
H(a)	2.682	16.00	a,b	17.04
H(b)	2.762		a,c	5.99
H(c)	3.692	4.49	b,c	6.33
H(d)	3.715		a,d	7.69
			b,d	7.99
			c,d	11.10

both TLC and GLC (provided that the evaporator temperature does not exceed 200 °C). At higher temperatures, as shown by thermolysis of 2-pyrazoline **2a** in the condensed phase at 150—160 °C and with passage of its vapors through a quartz tube at 270 °C, partial dehydrochlorination of **6a** occurs to give 3-acetyl-5-vinyl-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene **(9)** (yield ~20 %) along with strong resinification.



6a **9**: ~20%

The structures of the adducts obtained were unambiguously determined from spectral data. The ^{13}C NMR spectra contain weak-field signals in the range of 168—170 and 156—160 ppm that correspond to quaternary C atoms, which indicates the presence of acyl and substituted C=N groups in structures **5**—**8**. The signals at 3.7 and 2.8 ppm in the ^1H NMR spectrum indicate the presence of a 2-chloroethyl moiety. It should be noted that both signals for 2-pyrazolines **5** and **7** appear as triplets with equal coupling constants. The signal of the CH_2 group at the double bond in the more bulky pyrazolines **6a—d** appears as a complex multiplet due to magnetic nonequivalence of the geminal protons (^2J ~ 16 Hz). Furthermore, the ^1H NMR spectra of pyrazolines **6a,d** also displayed a significant splitting of the β-CH_2 unit. A calculation of the multiplicity of the signals for the four protons in the CH_2CH_2X group of compound **6b** by the CALM program[12] showed that they coincide completely with the experimental spectrum and provided an estimate of all coupling constants (see Table 1).

Experimental

^1H and ^{13}C NMR spectra were recorded on Bruker WM-250 (250 MHz) and Bruker AC-200 (200 MHz) spectrometers for solutions in $CDCl_3$ containing 0.1 % Me_4Si as the internal standard. IR spectra were obtained in thin films on a Bruker IFS-113v spectrometer. Mass spectra were obtained on a Finnigan MAT INCOS-50 instrument (70 eV, an RSL-200 capillary column 30 m in length).

Synthesis of 1-acyl-3-(2-chloroethyl)-2-pyrazolines (general procedure). A solution of acetyl chloride or benzoyl chloride (6 mmol) in CH_2Cl_2 (5 mL) was added dropwise with vigorous stirring to a solution of 1-pyrazoline **1—4** (6 mmol) in CH_2Cl_2 (5 mL) over 5—7 min at 10—20 °C. The reaction was accompanied by weak self-heating. The mixture was stirred for 30 min, the solvent was removed *in vacuo*, and the almost colorless residue was analyzed by spectroscopic methods. The individuality of the compounds obtained was confirmed by TLC data (Silufol; hexane—ether, 1 : 1).

1-Acetyl-3-(2-chloroethyl)-2-pyrazoline (5). Yield ~95 %. ^1H NMR, δ: 3.86 and 2.90 (two br.t, J = 9.2 Hz, NCH_2CH_2), 3.69 and 2.80 (two t, J = 6.5 Hz, $ClCH_2CH_2$), 2.30 (s, CH_3). ^{13}C NMR, δ: 170.0 (CO), 161.9 (C=N), 43.9 (NCH_2), 39.9, 34.9, and 33.2 (all CH_2).

3-Acetyl-5-(2-chloroethyl)-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene (6a). Yield ~96 %. IR, ν/cm^{-1}: 1658 (C=O), 1637 (C=N). ^1H NMR, δ: 4.10 (br.d, J = 8.0 Hz, H(2)), 3.72 (t, J = 6.8 Hz, CH_2Cl), 2.91 (br.d, J = 8.0 Hz, H(6)), 2.58—2.82 (m, 3 H, H(1) and $=CCH_2$), 2.33 (m, H(7)), 2.19 (s, CH_3), 1.40—1.68 (m, 2 H, *exo*-H(8,9)), 1.05—1.30 (m, 4 H, *endo*-H(8,9) and 2 H(10)). ^{13}C NMR, δ: 168.7 (CO), 157.2 (C=N), 63.8 (C(2)), 57.1 (C(6)), 40.8 (C(1)), 40.3 ($ClCH_2$), 39.2 (C(7)), 32.4 (C(10)), 32.2 ($=CCH_2$), 27.4 and 24.4 (C(8) and C(9)), 21.8 (CH_3). MS, *m/z* (*I* (%)): 242 (7.5) and 240 (21) M^+; 200 (30); 198 (90); 169 (29); 163 (57); 157 (39); 131 (100); 95 (91). Found (%): C, 59.76; H, 7.22; N, 11.77; Cl, 14.63. $C_{12}H_{17}ClN_2O$. Calculated (%): C, 59.87; H, 7.06; N, 11.64; Cl, 14.76.

3-Benzoyl-5-(2-chloroethyl)-3,4-diazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene (6b). Yield ~95 %, m.p. 85—86 °C (from EtOH). IR, ν/cm^{-1}: 1633 (C=O), 1605 (C=N), 1575 (C_6H_5). ^1H NMR, δ: 7.82 (2 H, m) and 7.38 (3 H, m, C_6H_5), 4.38 (br.d, J = 8.0 Hz, H(2)), 3.70 (m, J = 6.8 Hz, CH_2Cl), 2.96 (br.d, J = 8.0 Hz, H(6)), 2.92 (m, H(1)), 2.73 (m, $=CCH_2$), 2.40 (m, H(7)), 1.60 (m, 2 H, *exo*-H(8,9)), 1.13—1.40 (m, 4 H, *endo*-H(8,9) and 2H(10), ^2J = 10.1 Hz). ^{13}C NMR, δ: 166.3 (CO), 158.1 (C=N), 134.7, 130.6, 129.7 and 127.5 (C_6H_5), 65.0 (C(2)), 56.3 (C(6)), 40.7 (C(1)), 40.3 ($ClCH_2$), 39.2 (C(7)), 32.5 (C(10)), 32.2 ($=CCH_2$), 27.5 and 24.5 (C(8) and C(9)). MS, *m/z* (*I* (%)): 304 (0.7) and 302 (1.8) M^+; 213 (1.7); 185 (2.2); 133 (5); 131 (11); 105 (100); 77 (38). Found (%): C, 67.66; H, 6.55; N, 9.23; Cl, 10.89. $C_{17}H_{19}ClN_2O$. Calculated (%): C, 67.43; H, 6.28; N, 9.25; Cl, 11.73.

1-Acetyl-5-methyl-5-(methoxycarbonyl)-3-(2-chloroethyl)-2-pyrazoline (7). Yield 96 %. IR, ν/cm^{-1}: 1745 (COOMe), 1662 (C=O), 1640 (C=N). ^1H NMR, δ: 3.74 (m, J = 6.6 Hz, CH_2Cl), 3.70 (s, OCH_3), 3.15 and 2.75 (d, ^2J = 17.0 Hz, CH_2 in the ring), 2.78 (br.t, J = 6.6 Hz, CH_2), 2.21 (s, CH_3CO), 1.59 (s, CH_3). ^{13}C NMR, δ: 172.0 (CO), 168.0 (COO), 152.9 (C=N), 65.5 (C(5)), 52.4 (OCH_3), 48.7 (C(4)), 40.5 (CH_2Cl), 32.9 (CH_2), 21.9 and 21.7 (CH_3CO and CH_3). MS, *m/z* (*I* (%)): 248 (2) and 246 (5) M^+; 189 (6); 187 (17); 147 (36); 145 (100); 109 (42).

2-Acetyl-4-(2-chloroethyl)-6,6-dimethyl-2,3-diazabicyclo-[3.1.0]hex-3-ene (8). Yield 96 %. IR, ν/cm^{-1}: 1655 (CO), 1583 (C=N). ^1H NMR, δ: 4.28 (d, J = 5.8 Hz, H(1)), 3.71 (t, J = 6.6 Hz, CH_2Cl), 2.80 (m, CH_2), 2.35 (d, J = 5.8 Hz,

H(5)), 2.29 (s, $COCH_3$), 1.13 and 0.72 (two s, 2 CH_3). ^{13}C NMR, δ: 169.7 (CO), 155.5 (C=N), 50.5 (C(1)), 40.8 (CH_2Cl), 40.1 (C(5)), 34.0 (CH_2), 23.0 (CH_3), 21.2 (CH_3CO), 14.3 (C(6)), 13.6 (CH_3). Found (%): C, 55.86; H, 6.95; N, 13.19; Cl, 16.61. $C_{10}H_{15}ClN_2O$. Calculated (%): C, 55.94; H, 7.04; N, 13.05; Cl, 16.51.

Reaction of spiro{3,4-diazatricyclo[5.2.1.0^{2,4}]dec-3-ene-5,1′-cyclopropane} with acetic anhydride. A solution of Ac_2O (0.102 g, 1 mmol) in $CHCl_3$ (1 mL) was added at 20 °C with vigorous stirring to pyrazoline **2** (0.161 g, ~1 mmol), and then an aluminum halide (~1 mmol) was added. The mixture was stirred for 1 h at 20 °C, quenched with H_2O (0.5 mL), and extracted with $CHCl_3$. The extract was dried with $MgSO_4$, the solvent was removed *in vacuo*, and the product was purified by TLC. The reaction in the presence of $AlCl_3$ gave 0.223 g (93 %) of a compound identical to chloride **6a**. In the case of $AlBr_3$, separation by preparative TLC yielded 0.20 g (~70 %) of 3-acetyl-5-(2-bromoethyl)-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-ene **(6c)** and 0.066 g (~25 %) of 3-acetyl-5-(2-acetoxyethyl)-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-ene **(6d)**.

Compound **6c**. ^1H NMR, δ: 4.10 (br.d, J = 8.0 Hz, H(2)), 3.57 (t, J = 6.8 Hz, CH_2Br), 2.92 (br.d, J = 8.0 Hz, H(6)), 2.82 (m, $=CCH_2$), 2.77 (m, H(1)), 2.34 (m, H(7)), 2.20 (s, CH_3), 1.4–1.65 (m, 2 H, *exo*-H(8,9)), 1.1–1.35 (m, 4 H, *endo*-H(8,9) and 2H(10)). MS, *m/z* (*I* (%)): 286 (6) and 284 (6) M^+; 244 (32); 242 (30); 215 (9); 213 (9); 203 (12); 201 (12); 163 (58); 95 (100).

Compound **6d**. IR, ν/cm^{-1}: 1765 (COO), 1692 (C=O), 1630 (C=N). ^1H NMR, δ: 4.30 (m, 2H, OCH_2), 4.08 (br.d, J = 8.1 Hz, H(2)), 2.91 (br.d, J = 8.1 Hz, H(6)), 2.76 (m, H(1)), 2.58 (m, $=CCH_2$), 2.34 (m, H(7)), 2.19 (s, $COCH_3$), 2.03 (s, $OCOCH_3$), 1.4–1.65 (m, 2 H, *exo*-H(8,9)), 1.0–1.32 (m, 4 H, *endo*-H(8,9) and 2H(10)). MS, *m/z* (*I* (%)): 264 (3) M^+; 204 (28); 162 (100); 95 (52).

3-Acetyl-5-vinyl-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-ene (9). A solution of 2-pyrazoline **6a** (0.12 g) in a hexane—CH_2Cl_2 mixture (2 : 1, 1 mL) was passed through a quartz tube (15×0.5 cm) equipped with a trap over 15 min at 290 °C, and then an additional 0.6 mL of the hexane—CH_2Cl_2 mixture (2 : 1) was passed. The pyrolizate was filtered through a thin layer of silica gel, the latter was washed with CH_2Cl_2. Removal of the solvents gave 0.036 g of a residue containing ~35 % of the original chloride **6a** and ~65 % of vinylpyrazoline **9** (yield ~20 %), which were then separated by preparative TLC (silica gel; hexane—ether, 2 : 1).

Compound **9**: IR, ν/cm^{-1}: 3093 ($=CH_2$), 1665 (C=O), 1651, 1620 (C=S, C=N). ^1H NMR, δ: 6.41 (dd, J_{trans} = 17.0, J_{cis} = 10.5 Hz, =CH), 5.52 (m, 2 H, $=CH_2$), 4.09 (br.d, J = 8.1 Hz, H(2)), 3.07 (br.d, J = 8.1 Hz, H(6)), 2.72 (br.s, H(1)), 2.41 (br.s, H(7)), 2.17 (s, CH_3), 1.32–1.56 (m, 2 H, *exo*-H(8,9)), 1.0–1.30 (m, 4 H, *endo*-H(8,9) and 2H(10)). ^{13}C NMR, δ: 168.8 (CO), 157.0 (C=N), 129.1 (=CH), 121.8 ($=CH_2$), 64.6 (C(2)), 53.1 (C(6)), 40.8 (C(1)), 39.9 (C(7)), 32.3 (C(10)), 27.4 and 24.2 (C(8) and C(9)), 21.6 (CH_3). MS, *m/z* (*I* (%)): 204 (24) M^+, 162 (100), 133 (31), 121 (26), 95 (80).

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