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REARRANGEMENTS AND CYCLIZATIONS—XVI

RING-OPENING REACTIONS OF 1,1-DIACETYLCYCLOPROPANE WITH HYDRAZINE AND HYDROXYLAMINE DERIVATIVES AS THE NOVEL SYNTHESIS OF β-X-ETHYL SUBSTITUTED PYRAZOLES AND ISOXAZOLES

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Abstract—The reactions of 1,1-diacetylcyclopropane (**1**) with a number of hydrazine and hydroxylamine derivatives proceed *via* cyclopropane ring opening with incorporation of external nucleophile (solvent) to give the 4-β-X-ethyl derivatives of 3,5-dimethylpyrazoles and -isoxazoles, a novel route to these heterocycles. This ring cleavage occurs especially smoothly in water as a solvent. A rationale for this unusually mild nucleophilic cyclopropane ring opening is discussed.

The chemical characteristics of molecules containing cyclopropane rings continue to be fascinating topics.[1,2] Because of the double bond-like properties of the cyclopropane ring its reactivity towards electrophilic reagents is very well documented.[3-5] Electronic interaction of cyclopropane ring with unsaturated electron withdrawing groups, e.g. C=O (usually designated as "conjugation") may completely change the mode of reactivity leading to the possibility of achieving ring-opening by nucleophiles. Starting from the classical work of Bone and Perkin[6] cyclopropyl ring fission reactions by nucleophiles are the subject of current interest.[7] For example, pyridinium chloride is a mild reagent for cyclopropyl ring-opening of derivatives of cyclopropyl ketones.[8] However, monosubstituted cyclopropanes usually require a strong nucleophile and rather drastic conditions,[9] while two electron-withdrawing groups will make a cyclopropane derivatives especially susceptible to ring-opening by nucleophilic attack.[7]

Another possibility of achieving ring-opening of activated cyclopropanes is intramolecular attack by a properly situated nucleophile. The formalized presentation of two usually observed modes of intramolecular nucleophilic cyclization with designation introduced in Refs. [10, 11] is shown on Chart 1.

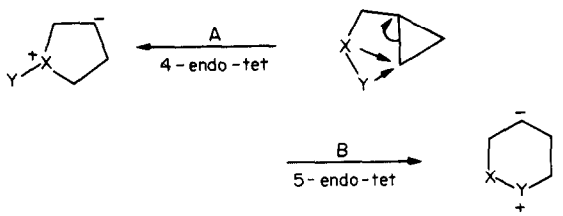


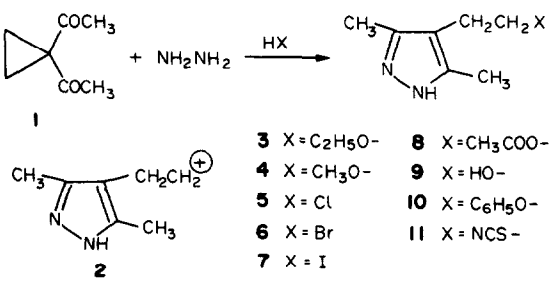
Chart 1.

The example of route **A**, Chart 1, is the well known acid-catalyzed rearrangement of cyclopropyl imines, discovered by Cloke in 1929,[12] which has been exploited as a general method of synthesis of pyrrolines.[13] The example of route **B**, Chart 1, is the reaction of the diethyl ester of cyclopropane-1,1-dicarboxylic action with $NH_2NH_2 \cdot H_2O$ which proceeds to give the hydrazide of 3 - oxo - 1,2,5,6 - tetrahydropyridazine - 4 - carboxylic acid.[14] Another example is the cyclization of oxime of a cyclopropyl ketone into a 3 - substituted-5,6-dihydro-4H-1,2 - oxazine.[15]

Recently we have found surprisingly that the reaction of 1,1 - diacetylcyclopropane (**1**) with hydrazine hydrate in EtOH proceeded *via* cyclopropane ring-opening, incorporation of external nucleophile (solvent) and pyrazole ring closure to give 3,5 - dimethyl - 4 - (β - ethoxyethyl)pyrazole.[16] Analogous reaction of **1** with hydroxylamine hydrochloride gave the corresponding β-chloroethyl derivative of isoxazole. Thus instead of expected 5 - *endo-tet* mode of ring-opening we observed the extremely facile nucleophilic cleavage with simultaneous formation of the five-membered heterocyclic systems. The idea behind that was to present the rationalization of the origins of this extremely facile nucleophilic ring-opening of cyclopropane ring.

RESULTS

Reactions of diketone **1** *with hydrazine.* The first ring-opening reaction to be investigated was the interaction of diketone **1** with hydrazine hydrate. We found that stirring of their mixture (1:1) in ethanol at room temperature gives 3,5 - dimethyl - 4 - (β - ethoxyethyl)pyrazole **3**, in 63% yield. The remarkable aspect of this reaction is the incorporation of the solvent into the product; the data clearly show that the system $1 + NH_2NH_2$ may be formally regarded to as a synthetical equivalent of carbocation **2** (Scheme 1). Analogously the reaction of diketone **1** with $NH_2NH_2 \cdot H_2O$ in methanol gives the corresponding β-methoxyethyl derivative **4**. However the use of water or t-BuOH as a



3 X = C_2H_5O- **8** X = CH_3COO-
4 X = CH_3O- **9** X = HO-
5 X = Cl **10** X = C_6H_5O-
6 X = Br **11** X = NCS-
7 X = I

Scheme 1.

solvent gives only unidentified polymeric products. Analogous negative results had been achieved using the aprotic solvents (DMSO, THF, ether).

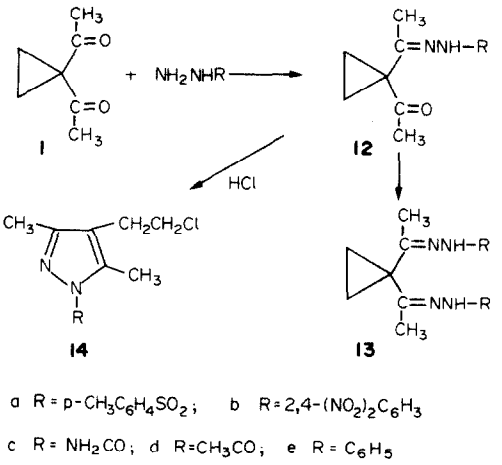
We further examined the reaction of system **1** and NH_2NH_2 with a variety of nucleophiles in different media. It was found that the reaction of **1** with $NH_2NH_2 \cdot HCl$ in ethanol gives the hydrochloride of **5**; the free base **5** has been obtained by treatment with KOH. However, the reaction of **1** with $NH_2NH_2 \cdot HBr$ gives the mixture of expected bromide **6** together with compound **3**.

Careful study of reaction conditions reveals that water appears to be the best solvent. For example, the reaction of **1** with $NH_2NH_2 \cdot H_2O$ in 10% aqueous AcOH gives easily the corresponding β-acetoxyethyl compound **8**, the methanolysis of which in the presence of H_2SO_4 gives, in turn, β-hydroxypyrazole **9**. Analogously the reaction of **1** and $NH_2NH_2 \cdot H_2O$ in water in presence of sodium phenoxide proceeds smoothly to give the phenoxyethyl derivative **10**. The use of aqueous solutions of such salts as LiCl, NaCl, NaI, KBr and KI gave in all cases the small yields (5–10%) of expected halides **5–7**. Fortunately, the application of the corresponding salts of ammonia (10% solution in water) leads to sharp increase of yields of corresponding pyrazoles **5–7** up to 55–60%. These reactions were carried out during several minutes at room temperature. Moreover, the reaction in the presence of ammonium thiocyanate gives the corresponding thiocyanopyrazole **11**.

Another way to increase the yields of pyrazoles is to perform the reaction of **1** with hydrazine salts, $NH_2NH_2 \cdot HX$ (where X=Cl, Br and I) in water. This process is also very mild and gives high yields of **5–7**.

Reactions of diketone **1** *with mono-substituted hydrazines.* The reactions described above include the cyclization step due to nucleophilic attack at the carbonyl group by the hydrazine nitrogen atom. However, we previously described the synthesis of bis-tosylhydrazone (**13a**) of diketone **1**, which has been further used as the precursor of 1,1-divinylcyclopropane and then of 1,1-diethynylcyclopropane.[17,18] The remarkable difference between these two results seems to indicate that introduction of electron-withdrawing substituents adjacent to the hydrazine group disfavours the pyrazole ring-closure process. Here we wish to report our results on the reactions of diketone **1** with a series of substituted hydrazines that demonstrates a dependence of reaction pathway on their structure and experimental conditions.

We have found that tosylhydrazine, 2,4-dinitrophenylhydrazine, semicarbazide and acetylhydrazine react with diketone **1** in ethanol to give the normal



a R = p-$CH_3C_6H_4SO_2$; b R = 2,4-$(NO_2)_2C_6H_3$

c R = NH_2CO; d R = CH_3CO; e R = C_6H_5

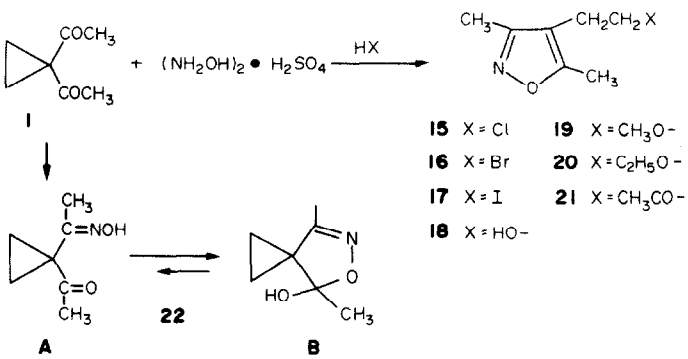
Scheme 2.

derivates of types **12** and **13** (Scheme 2). However, the treatment of mono-hydrazones **12a** and **12c** with 5–10% hydrochloric acid leads smoothly to pyrazole ring closure and cyclopropane ring opening with formation of pyrazoles **14a** and **14c**. In the case of hydrazone **12d** analogous cyclization gave the pyrazole **5** instead of **14d** due to hydrolysis of amide group. These data are of special interest because they provide *conclusive evidence of a two stage mechanism* for the processes under investigation *via* mono-derivatives of type **12** with their subsequent cyclization into pyrazole compounds.

In addition we have studied in detail the reaction of **1** with semicarbazide hydrochloride as a function of solvent. This reaction is absolute ethanol proceeds exclusively with formation of semicarbazones **12c** and **13c**. However, the use of 95% ethanol gives the mixture of semicarbazone **12c** and chloride **14c**. The reaction in water gave nicely pure chloride **14c**. Thus, the solvent is crucial for these processes.

In conclusion of this section we wish to describe the results of the reaction of diketone **1** with phenylhydrazine. The reaction of free phenylhydrazine in EtOH proceeds to give 1-phenyl - 3,5 - dimethyl - 4 - (2 - ethoxyethyl)pyrazole which is too unstable to be isolated but can be clearly identified by ^1H NMR. Analogously for the reaction of phenylhydrazine hydrochloride in EtOH, ^1H NMR-spectroscopy shows formation of chloropyrazole **14e**.

Reactions of diketone **1** *with hydroxylamine.* First we have shown that the reaction of diketone **1** with $NH_2OH \cdot HCl$ in ethanol proceeds to give 3,5 - dimethyl - 4 - (β - chloroethyl)isoxazole, **15** (Scheme 3). As in the



15 X = Cl **19** X = CH_3O-

16 X = Br **20** X = C_2H_5O-

17 X = I **21** X = CH_3CO-

18 X = HO-

Scheme 3.

case of hydrazine, this reaction includes the participation of the solvent as a nucleophile in the ring-opening step of the process. From a synthetic point of view hydroxylamine sulphate was the most convenient for use. Application of this salt in 1% aqueous solutions of HX (X=Cl, Br, I) leads to the corresponding halogenoethyl isoxazoles **15–17**, with yields of 35–55%. The reaction of hydroxylamine sulphate with **1** in aqueous alcohol gives the β-hydroxyethyl derivative **18**; the reaction in anhydrous alcohols (methanol and ethanol) leads to the corresponding alkoxyethyl isoxazoles, **19** and **20**, and the one in acetic acid gives acetoxyethyl derivative **21**.

It is of special interest that similar cyclization was not observed in the reaction of diketone **1** with free NH_2OH in absolute ethanol. The reaction proceeds with the formation of monooxime **22** (see data for the reaction with semicarbazide). Moreover, this compound exists in cyclic tautomeric form **22B**, as established by IR and ^1H NMR. Treatment of **22B** with dilute hydrochloric acid leads to quantitiative formation of chloride **15**. This also serves as conclusive evidence of the two stage mechanism of azole formation *via* mono-derivatives of type **22B**.

DISCUSSION

Two following main conclusions can be drawn from the experiments just discussed: these reactions are (i) an example of surprisingly gentle conditions for cyclopropane ring opening by an external nucleophile and (ii) a novel and convenient method of synthesis of pyrazoles and isoxazoles containing β-X-ethyl substituent.

We have presented a short review of nucleophilic ring-opening of cyclopropanes as the start of this paper. It is worth repeating that the most nucleophilic openings have involved two geminally placed activated groups.[19] However, severe conditions are usually required for intermolecular processes even with two activating groups.[20] Moreover, a special strategy, so-called "spiro-activation", has been elaborated and successfully introduced to improve the cyclopropane ring activation and, therefore, to increase the attraction of these nucleophilic processes as a synthetic method.[7]

In contrast, the nucleophilic ring opening studied in the present work proceeds in aqueous solution even at room temperature, i.e. under extraordinarily mild conditions for such processes. Evidently, this must indicate the operation of several factors favouring the cyclopropane ring-opening pathway. A reasonable mechanism for the reactions studied on the basis of general literature data is shown on Chart 2. In accordance with that mechanism

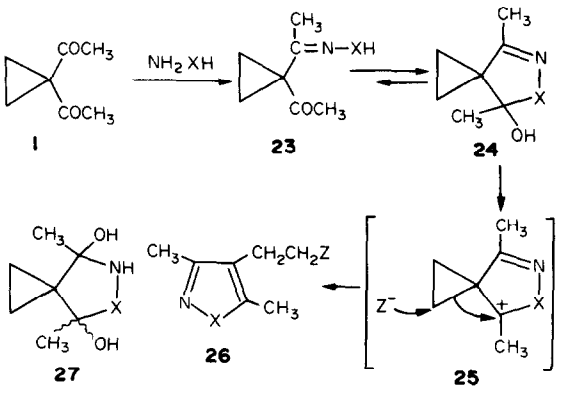


Chart 2.

the successful ring-opening is the result of contribution from (1) intermediacy of cyclic product of type **24** where the plane of cyclopropane is orthogonal to the C–N plane, (2) easy departure of hydroxyl group in **24** due to the stabilization of cationic center by both cyclopropane ring and neighbour heteroatom, (3) conditions for spiro-activation in the species of type **24**, and (4) the aromaticity of azole ring, which may give additional driving force for the ring-opening process.

Indeed the interaction of the reagents must give the corresponding mono-derivatives containing the C=N bond, in the first step of the reaction. Both the starting diketone **1** and its mono-derivatives, such as monohydrazone or mono-oxime in their open form (for example, **22A**) have nothing special to react with nucleophiles more rapidly as compared with other double activated cyclopropanes. However, these mono-derivatives have the possibility to form the cyclic compounds of type **24** (the observation of the existence of the monooxime in the cyclic form **22B**), which completely changes the situation.

We believe that the cyclization of type **23**→**24** is the key step. This type of ring closure immobilizes the conformer with two mutually perpendicular rings due to connection of the second heteroatom of the mono-derivative with the second carbonyl group. It is well known that in conformationally mobile systems the conjugation between cyclopropane ring and substituent depends on the rotameric conformation.[1] In bicyclic system the fixed geometry may force the most favourable overlap of conjugating orbitals which in turn may lead to particularly facile nucleophilic cleavage of cyclopropane ring (see phenomenon of "spiro-activation");[7] in analogy with this literature term we may label the phenomenon, observed in our case, as "dynamic or transient spiro-activation".

Moreover, the cyclic intermediate **24** has several good reasons to lose the OH-group with concerted or stepwise cyclopropane ring-opening. First, cationic cyclopropylmethyl systems in general are known to rearrange to homoallyl systems *via* ring opening[1] and dynamic spiro-activation favours that process. Secondly, the additional stabilization of transient carbocationic species came from neighbour heteroatom, which should be especially powerful in the case of X=N.[21]

A third noteworthy factor is assumed to be related to product stability. Indeed the departure of OH group and ring-opening leads to formation of stable structures of aromatic character. The extra stability due to the aromaticity of the forming azoles may appear in transition state of the final step of this process. It is worth mentioning that water is an especially favourable solvent for these reactions due to both the facilitation of the dissociation pathway (**24**→**25**) and the possible acid catalysis for this step, followed by nucleophilic ring-opening (stepwise or concerted).

We should like to emphasize that the mechanism of Chart 2 is a compilation of literature data and the problem of stepwise vs concerted character of some steps as well as the involvement of some other intermediates still remains open. For example, the intermediacy of the dihydroxy derivatives of type **27** seems also to the probable taking into account the NMR stopped-flow study of the reaction of acetylacetone with NH_2NH_2.[22] Hence, the mechanism of Chart 2 should be taken as the general outline of the processes observed.

Anyhow, the operation of several factors leads to the

observed extremely facile cyclopropane ring-opening and dynamic spiro-activation, which is absent in the starting compound and is generated in the intermediates, seems to be of the decisive importance. Moreover, idea of the transient appearance of spiro-activational relationships in intermediates looks very promising in designing of cyclopropane systems sensitive to nucleophilic attack.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer. ^{1}H NMR spectra were measured at 60 MHz on Varian T-60 and at 100 MHz on Tesla BS-497 spectrometers. ^{13}C NMR-spectra were measured at 25.16 MHz on Varian CFT-20 spectrometrometer with proton decoupling. All reactions were followed by TLC on Silufol UV-254 plates (Kavalier, Czechoslovakia). Solutions in organic solvents were dried over magnesium sulphate. The synthesis of diketone **1** has been previously described;[23] its purification from the impurity of acetyldihydrofuran[24] can be achieved by preparative glc.

General methods

(1) A mixture of diketone **1** and hydrazine hydrate was stirred in alcohol for 12 hr at room temp, the solvent was removed and the residue was distilled *in vacuo*.

(2) A suspension of hydroxylamins sulphate in alcoholic solution of diketone **1** was refluxed until the precipitate dissolved. The mixture was diluted with water and extracted with chloroform, the chloroform was dried and evaporated, the residue was distilled *in vacuo*.

(3) A mixture of diketone **1** and $NH_2NH_2 \cdot H_2O$ was stirred with 10% aqueous NH_4X (X = Cl, Br, I) at room temp. The precipitate was filtered off, washed with H_2O, dried and recrystallized from hexane.

(4) A mixture of diketone **1**, $NH_2NH_2 \cdot H_2O$, ammonium salt and H_2SO_4 was stirred in water at room temp. The precipitate obtained was purified as described above.

(5) A mixture of diketone **1** and hydrazine hydrohalogenide was stirred in H_2O at room temp. The precipitate was purified as described above.

(6) A mixture of diketone **1**, $(NH_2OH)_2 \cdot H_2SO_4$, ammonium halogenide and H_2SO_4 was stirred in H_2O at room temp for 12 h. The solution was made slightly basic (pH 8–9) by treatment with 10% aqueous soln of KOH, the product was isolated as in the Method 2.

Azole synthesis

3,5 - *Dimethyl* - 4 - (2 - *ethoxyethyl*)*pyrazole* (**3**). Method 1; from 5 g (40 mmole) of **1** and 2 g (40 mmole) of $NH_2NH_2 \cdot H_2O$ in 100 ml EtOH 5.3 g (63%) **3** was obtained; b.p. 120–2° (2 mm), n_D^{20} 1.4875; IR 1605 (C=N); 1630 (C=C); 3200 (NH) cm^{-1}; NMR ($CDCl_3$) δ 1.01 (3 H, t, J 7 Hz); 2.16 (6 H, s); 2.50 (2 H, t, J 8 Hz); 3.41 (4 H, m from overlapped q, J 7 Hz and t, J 8 Hz); 12.36 (1 H, s). ^{13}C NMR (CCl_4) 10.5 ($2\,CH_3$); 15.2 ($\underline{CH_3}CH_2$); 24.05 (CH_2); 65.8 and 71.0 (CH_2OCH_2); 111.7 and 141.4 (C arom.). (Found: C, 64.02; H, 9.93; N, 16.62. Calc. for $C_9H_{16}N_2O$: C, 64.28; H, 9.52; N, 16.67%).

3,5 - *Dimethyl* - 4 - (2 - *methoxyethyl*)*pyrazole* (**4**). Method 1; the same quantities of reagents in 100 ml of MeOH gave 4.5 g (58%) of **4**, b.p. 128–30°, m.p. 36–7° (from hexane); NMR (CCl_4) δ 2.25 (6 H, s); 2.63 (2 H, t, J 7 Hz); 3.35 (3 H, s); 3.41 (2 H, t, J 7 Hz); 12.23 (1 H, s). (Found: C, 62.91; H, 9.32; N, 17.84. Calc. for $C_8H_{14}N_2O$: C, 62.34; H, 9.08; N, 18.18%).

3,5 - *Dimethyl* - 4 - (2 - *acetoxyethyl*)*pyrazole* (**8**) was obtained by method 1 using 10% aq AcOH as solvent followed by extraction with ether. The same quantities of reagents gave 2.63 g (32%) of **8**: b.p. 150–2° (2 mm), n_D^{20} 1.4920. NMR (CCl_4) δ 2.0 (3 H, s); 2.20 (6 H, s); 2.63 (2 H, t, J 8 Hz); 3.96 (2 H, t, J 8 Hz); 12.56 (1 H, s). (Found: C, 59.28; H, 7.88; Calc. for $C_9H_{14}N_2O_2$: C, 59.34; H, 7.69%).

3,5 - *Dimethyl* - 4 - (2 - *phenoxyethyl*)*pyrazole* (**10**) was obtained as described above in 100 ml of 10% aq PhONa giving 9.85 g (93%) of **10**, b.p. 196–7° (1 mm), m.p. 56–7° (from pentane–CCl_4, 10:1). NMR ($CDCl_3$) δ 2.28 (6 H, s); 2.83 (2 H, t, J 7 Hz); 3.97 (2 H, t, J 7 Hz); 7.08 (5 H, m); 12.82 (1 H, s). (Found: C, 72.07; H, 7.49; N, 13.57. Calc. for $C_{13}H_{16}N_2O$: C, 72.22; H, 7.41; N, 12.96%).

3,5 - *Dimethyl* - 4 - (2 - *chloroethyl*)*pyrazole* (**5**). (a) Method 1, from 5 g (40 mmole) of **1** and 3.5 g (50 mmole) of $NH_2NH_2 \cdot HCl$ in 150 ml EtOH gave 3.2 g (46%) of hydrochloride of **5** m.p. 216–17° from EtOH. (Found: C, 43.70; H, 6.20; N, 14.36. Calc. for $C_7H_{12}Cl_2N_2$: C, 43.08; H, 6.15; N, 14.36%). This substance was treated with 10% aq KOH and extracted with ether. The residue after evaporation of the ether was recrystallized from hexane giving **5**, m.p. 127°, NMR ($CDCl_3$) δ 2.27 (6 H, s); 2.83 (2 H, t, J 7 Hz); 3.57 (2 H, t, J 7 Hz); 11.75 (1 H, s). (Found: C, 52.56; H, 7.11; N, 17.56. Calc. for $C_7H_{11}ClN_2$: C, 53.0; H, 6.94; N, 17.67%).

(b) Method 3; from 0.63 g (5 mmole) of **1** and 0.3 g (6 mmole) of $NH_2NH_2 \cdot H_2O$ in 20 ml of 10% aq NH_4Cl 0.8 g (60%) of **5** was obtained.

(c) Method 5; from 5 g (40 mmole) of **1** and 3.5 g of $NH_2NH_2 \cdot HCl$ in 100 ml H_2O, 5 g (80%) of **5** was obtained.

3,5 - *Dimethyl* - 4 - (2 - *bromoethyl*)*pyrazole* (**6**). (a) Method 3; the yield 55%. (b) Method 5; from 5 g (40 mmole) of **1** and 8.7 g (90 mmole) of $NH_2NH_2 \cdot HBr$ 6.7 g (83%) of **6** was obtained, m.p. 127–8°, NMR ($CDCl_3$) δ 2.18 (6 H, s); 2.85 (2 H, t, J 7 Hz); 3.30 (2 H, t, J 7 Hz); 11.63 (1 H, s). (Found: C, 41.99; H, 5.53. Calc. for $C_7H_{11}BrN_2$: C, 41.34: H, 5.42%).

3,5 - *Dimethyl* - 4 - (2 - *iodoethyl*)*pyrazole* (**7**). Method 5; yield 99%: m.p. 132–3°; NMR ($CDCl_3$) δ 2.21 (6 H, s); 2.92 (2 H, t, J 7 Hz); 3.14 (2 H, t, J 7 Hz); 11.05 (1 H, s). (Found: I, 50.72; Calc. for $C_7H_{11}IN_2$: I, 50.80%).

3,5 - *Dimethyl* - 4 - (2 - *thiocyanoethyl*)*pyrazole* (**11**). Method 4; from 5 g (40 mmole) of **1**, 3 g (40 mmole) of NH_4SCN, 2 g (40 mmole) of $NH_2NH_2 \cdot H_2O$ and 1 ml of H_2SO_4 conc. 2.3 g (34%) of **11** was obtained: m.p. 83°; NMR ($CDCl_3$) δ 2.25 (6 H, s); 2.95 (4 H, m A_2B_2, δ_A 2.88, δ_B 3.01, J 7.5 Hz); 10.78 (1 H, s). (Found: C, 53.90; H, 4.98. Calc. for $C_8H_{12}N_3S$: C, 53.03; H, 6.08%).

3,5 - *Dimethyl* - 4 - (2 - *hydroxyethyl*)*pyrazole* (**9**). 1 g (5.5 mmole) of **8** was stirred in 10 ml of MeOH with 0.1 ml of 30% oleum for 3 h. The precipitate was filtered, washed with cold MeOH and recrystallized from acetone giving 0.62 g (80%) of **9**, m.p. 120–1°, NMR (CD_3OD) δ 2.20 (6 H, s); 2.60 (2 H, t, J 7 Hz); 3.58 (2 H, t, J 7 Hz). (Found: C, 60.65; H, 8.27; N, 19.99. Calc for $C_7H_{12}N_2O$: C, 60.00; H, 8.57; N, 20.00%).

3,5 - *Dimethyl* - 4 - (2 - *methoxyethyl*)*isoxazole* (**19**). Method 2, from 5 g (40 mmole) of **1** and 3.35 g (20 mmole) of $(NH_2OH)_2 \cdot H_2SO_4$ in 200 ml of MeOH 3.04 g (63%) of **19** was obtained, b.p. 61° (0.5 mm), n_D^{20} 1.4658. NMR (CCl_4) δ 2.07 (3 H, s); 2.23 (3 H, s); 2.48 (2 H, t, J 7 Hz); 3.20 (3 H, s); 3.39 (2 H, t, J 7.5 Hz). (Found: C, 62.17; H, 8.40: N, 9.03. Calc. for $C_8H_{13}NO_2$: C, 61.94; H, 8.39; N, 9.03%).

3,5 - *Dimethyl* - 4 - (2 - *ethoxyethyl*)*isoxazole* (**20**). Method 2; yield 48%, b.p. 75–7° (1 mm), n_D^{20} 1.4613. NMR (CCl_4) δ 1.08 (3 H, t, J 6.5 Hz); 2.07 (3 H, s); 2.18 (3 H, s); 2.43 (2 H, t, J 6.3 Hz); 3.33 (4 H, m from overlapped q, J 6.5 Hz and t, J 6.3 Hz).

3,5 - *Dimethyl* - 4 - (2 - *hydroxyethyl*)*isoxazole* (**18**) was obtained by Method 2 in 53% yield using an MeOH–H_2O (2:1) as solvent; b.p. 126–7° (1.5 mm) n_D^{20} 1.4858, NMR (CCl_4) δ 2.13 (3 H, s); 2.27 (3 H, s); 2.48 (2 H, t, J 6 Hz); 3.63 (2 H, t, J 6 Hz); 4.58 (1 H, s). (Found: C, 59.63; H, 8.02; N, 10.38. Calc. for $C_7H_{11}NO_2$: C, 59.57; H, 7.80; N, 9.93%).

3,5 - *Dimethyl* - 4 - (2 - *chloroethyl*)*isoxazole* (**15**). Method 5; procedure of isolation of **15** as described in Method 2; from 6.3 g (50 mmole) of **1** and 4 g (60 mmole) of $NH_2OH \cdot HCl$ 4.6 g (58%) of **15** was obtained: b.p. 93° (2 mm), n_D^{20} 1.4870. NMR (CCl_4) δ 2.13 (3 H, s); 2.30 (3 H, s); 2.70 (2 H, t, J 7 Hz); 3.56 (2 H, t, J 7 Hz).(Found: C, 52.60; H, 6.54; N, 8.26. Calc. for $C_7H_{10}ClNO$: C, 52.66; H, 6.27; N, 8.78%).

3,5 - *Dimethyl* - 4 - (2 - *bromoethyl*)*isoxazole* (**16**). Method 6; yield 34%, b.p. 96–8° (1 mm), n_D^{20} 1.5123; NMR (CCl_4) δ 2.17 (3 H, s); 2.28 (3 H, s); 2.85 (2 H, t, J 6 Hz); 3.40 (2 H, t, J 6 Hz). (Found: C, 41.55; H, 5.28; N, 6.20. Calc. for $C_7H_{10}BrNO$: C, 41.20; H, 4.90; N, 6.78%).

3,5 - *Dimethyl* - 4 - (2 - *iodoethyl*)*isoxazole* (**17**). Method 6; yield 55%, b.p. 120–1° (1 mm), n_D^{20} 1.5529. NMR ($CDCl_3$) δ 2.17 (3 H, s); 2.30 (3 H, s); 2.85 (2 H, t, J 6 Hz); 3.20 (2 H, t, J 6 Hz). (Found: C, 33.54; H, 4.03; N, 5.44. Calc. for $C_7H_{10}INO$: C, 33.48; H, 3.99: N, 5.58%).

3,5 - *Dimethyl* - 4 - (2 - *acetoxyethyl)isoxazole* (**21**) was obtained by Method 2 using AcOH as a solvent. For 5 g (40 mmole) of **1** and 3.4 g (20 mmole) of $(NH_2OH)_2 \cdot H_2SO_4$ was obtained 3.2 g (44%) of isoxazole **21**: b.p. 94° (1 mm), n_D^{20} 1.4654. NMR (CCl_4) δ 1.95 (3 H, s); 2.15 (3 H, s); 2.30 (3 H, s); 2.58 (2 H, t, J 6.5 Hz); 4.0 (2 H, t, J 6.5 Hz). (Found: C, 58.88; H, 7.32. Calc. for $C_9H_{13}NO_3$: C, 59.02; H, 7.11%).

1 - *Phenyl* - 3,5 - *dimethyl* - 4 - (2 - *ethoxyethyl)pyrazole.* A mixture of 0.54 g (5 mmole) phenylhydrazine and 0.63 g (5 mmole) of **1** in 50 ml of EtOH was stirred for 3 h at room temp; the solvent was removed. Chromatography over silica gel (eluting with acetone–chloroform) gave 0.4 g (40%) of the titled compounds: NMR (CCl_4) δ 1.13 (3 H, t, J 7 Hz); 2.10 (3 H, s); 2.17 (2 H, t, J 7 Hz); 3.30 (4 H, m); 7.30 (5 H, m). The product is unstable because of rapid oxidation on the air.

1 - *Phenyl* - 3,5 - *dimethyl* - 4 - (2 - *chloroethyl)pyrazole* (**14e**) was obtained in the same way from **1** and $PhNHNH_2 \cdot HCl$ (CCl_4 δ 2.06 (3 H, s); 2.16 (3 H, s); 2.66 (2 H, t, J 7 Hz); 3.80 (2 H, t, J 7 Hz); 7.20 (5 H, m). The compound is unstable because of rapid oxydation during contact with air.

Substituted hydrazones of diketone **1**

Mono-semicarbazone of **1** (**12c**). A mixture of 4 g (36 mmole) semicarbazide hydrochloride and 4 g (49 mmole) of dried sodium acetate was refluxed in 50 ml of absolute EtOH for 15 min; then the mixture was filtered and a soln of 4.5 g (36 mmole) of **1** was added to the filtrate. The mixture was stirred for 12 hr, the solvent was removed and the residue was recrystallized from absolute EtOH. 3 g (45%) of **12c** was obtained, m.p. 169–70°, IR 3430, 3300 (NH, NH_2); 1700 (C=O); 1585 (C=N) cm^{-1}. NMR (DMSO-d_6) δ 1.28 (4 H, s); 1.85 (3 H, s); 1.97 (3 H, s); 3.50 (1 H, s); 6.37 (2 H, s). (Found: C, 52.05; H, 7.18; N, 22.99. Calc. for $C_8H_{13}N_3O_2$: C, 52.46; H, 7.10; N, 22.95%).

Bis-semicarbazone of **1** (**13c**) was obtained as described above in a reaction of **1** with 2 equiv semicarbazide, m.p. 230°, insoluble in organic solvents: IR 3235 (NH); 1700 (C=O); 1600 (C=N) cm^{-1}.

Mono- and bis-tosylhydrazones of **1** (**12a** and **13a**) were obtained in a reaction of **1** with 1 or 2 equiv tosylhydrazine in EtOH with the yield of 75% and 83% respectively. Compound **12a**: m.p. 169–70° (from EtOH); IR 3210 (NH); 1630 (C=N); 1683 (C=O) cm^{-1}. NMR (DMSO-d_6) δ 1.08 (4 H, m); 1.80 (6 H, s); 2.32 (3 H, s); 7.50 (4 H, m). (Found: C, 56.87; H, 6.11; N, 9.63. Calc. for $C_{14}H_{18}N_2O_3$; C, 57.14; H, 6.12, N, 9.52%). Compound **13a**: m.p. 199–200° (from EtOH); IR: 3200, 3223 (NH): 1600 (C=H); 1580 (arom) cm^{-1}. NMR (DMSO-d_6) δ 1.17 (4 H, s); 1.80 (6 H, s); 2.32 (6 H, s); 2.62 (2 H, s); 7.50 (8 H, m).

Mono- and bis - 2,4 - dinitrophenylhydrazones of **1** (**12b** and **13b**) were obtained by reaction of **1** with 1 or 2 equiv 2,4 - dinitrophenylhydrazine in H_2O in the presence of H_2SO_4 in yields 76% (**12b**) and 79% (**13b**). Compound **12b**: m.p. 160–2° (from EtOH); IR: 3320 (NH); 1700 (C=O); 1626 (C=O); 1500 (arom) cm^{-1}. Compound **13b**: m.p. 175–7° (from EtOH); IR: 3320 (NH); 1600, 1630 (C=N); 1527 (arom) cm^{-1}.

1 - *Carbamoyl* - 3,5 - *dimethyl* - 4 - (2 - *chloroethyl)pyrazole* (**14c**). (a) Method 5; from 6.3 g (50 mmole) of **1** and 5.6 g (50 mmole) of semicarbazide hydrochloride in 75 ml of H_2O 7 g (70%) of **14c** was obtained, m.p. 136–7°, NMR ($CDCl_3$) δ 1.23 (3 H, s); 1.50 (3 H, s); 1.83 (2 H, t, J 7 Hz); 2.70 (2 H, t, J 7 Hz); 6.45 (2 H, s). (Found: C, 47.59; H, 5.97. Calc. for $C_8H_{12}ClN_3O$: C, 47.64; H, 5.96%).

(b) To a solution of 1 g (5 mmole) of **12c** in 200 ml of H_2O 0.5 ml of conc HCl was added. The precipitate was recrystallized from hexane. Compound **14c** was obtained in quantitative yield.

1 - *Tosyl* - 3,5 - *dimethyl* - 4 - (2 - *chloroethyl)pyrazole* (**14a**) was obtained as described above in quantitative yield, m.p. 94–5°, NMR ($CDCl_3$) δ 2.30 (6 H, s); 2.80 (2 H, t, J 6.5 Hz); 3.70 (2 H, t, J 6.5 Hz); 7.30 (4 H, m). (Found: C, 54.05; H, 5.41. Calc. for $C_{14}H_{17}N_2ClO_2S$: C, 53.76; H, 5.44%).

Mono-oxime of **1** (**22**). To the cooled saturated soln of 2.76 g (40 mmole) of $NH_2OH \cdot HCl$ in EtOH was added rapidly a soln of 2.5 g (45 mmole) of KOH in 30 ml EtOH. The mixture was filtered from KCl precipitate into a flask, which contained a soln of 5 g (40 mmole) of **1** in 50 ml EtOH. After 1 h stirring, the solvent was removed and the residue was recrystallized from acetone, giving 2.1 g (38%) of **22**, m.p. 113–15°, IR: 3420 (OH); 1610 (C=N) cm^{-1}. NMR ($CDCl_3$) δ 1.03 (4 H, s); 1.33 (3 H, s); 1.66 (3 H, s); 3.90 (1 H, s). (Found: C, 59.81; H, 7.75. Calc. for $C_7H_{11}NO_2$: C, 59.57; H, 7.80%).

A drop of conc HCl was added to the chloroform soln of **22** in an NMR tube and the mixture was shaken several times. The NMR-spectrum showed the complete absence of signals of **22** and quantitative formation of **15**.

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REFERENCES

[1]A. Meijere, *Angew. Chem., Int. Ed.* **18**, 809 (1979).
[2]L. N. Ferguson, *Highlights of Alicyclic Chemistry.* Part 1, Chap. 3. Franklin, New York (1973).
[3]S. Sarel, J. Yovell and M. Sarel-Imber, *Angew. Chem.* **80**, 592 (1968).
[4]Houben-Weyl, Methoden der organischen Chemie, Band IV/3, 509 (1971).
[5]D. Caine, A. Boucugnani and Ch. Chu. *Tetrahedron Letters* 2667 (1978).
[6]W. A. Bone and W. H. Perkin, *J. Chem. Soc.* **67**, 108 (1895).
[7]S. Danishefsky, *Acc. Chem. Research* **12**, 66 (1979).
[8]M. Loreto, L. Pellacani and P. Fardella, *J. Heterocyclic Chem.* **16**, 1233 (1979).
[9]A. Smith and R. Scarborough, *Tetrahedron Letters* 1649 (1978).
[10]L. Tenud, S. Farood, J. Seibe and A. Eschenmoser, *Helv. Chim. Acta* **53**, 2059 (1970).
[11]J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* 734 (1976).
[12]J. Cloke, *J. Am. Chem. Soc.* **51**, 1174 (1929); J. Cloke, *Ibid.* **67**, 2155 (1945).
[13]R. Stevens, M. Ellis and M. Wentland, *Ibid.* **90**, 5576 (1968).
[14]A. S. Kozmin, S. A. Gladir, R. Ya. Levina and I. G. Bolesov, *Zh. Org. Khim.* **7**, 2224 (1971).
[15]C. N. Rentzea, *Angew. Chem.* **92**, 195 (1980).
[16]N. S. Zefirov, T. S. Kuznetsova, S. I. Kozhushkov, Sh. T. Akhmedov, N. S. Sadykov and A. M. Magerramov, *Khim. Het. Soed.* 847 (1981).
[17]N. S. Zefirov, M. I. Budika, T. S. Kuznetsova and A. S. Kozmin, *Zh. Org. Khim.* **14**, 2007 (1978).
[18]N. S. Zefirov, T. S. Kuznetsova, M. I. Budika, A. S. Kozmin, N. V. Averina and S. S. Yarovoi, *Ibid.* **15**, 1779 (1979).
[19]S. Danishefsky and R. K. Singh, *J. Am. Chem. Soc.* **97**, 3239 (1975); S. Danishefsky and G. Rovnyak, *J. Org. Chem.* **40**, 114 (1975); R. K. Singh and S. Danishefsky, *Ibid.* **41**, 1668 (1976).
[20]J. Stewart and H. Westberg, *Ibid.* **30**, 1951 (1965).
[21]H. Krabbenhoft, J. Wiseman and C. Quinn, *J. Am. Chem. Soc.* **96**, 258 (1974).
[22]S. I. Selivanov, R. A. Bogatkin and B. A. Ershov, *Zh. Org. Khim.* **17**, 886 (1981).
[23]aI. Katsniko, I. Osaniu, K. Takahisa, F. Mutsuso and U. Tamotsu, *J. Org. Chem.* **31**, 447 (1966); bWe have also prepared diketone **1** by alkylation of acetylacetone by 1,2-dibromoethane in DMSO in presence of excess of K_2CO_3 at room temperature. This procedure will be published separately.
[24]N. S. Zefirov, S. I. Kozhushkov and T. S. Kuznetsova, *Khim. Het. Soed.* in press (1981).