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REARRANGEMENTS AND CYCLIZATION—XVII

MECHANISM OF THE FORMATION OF 1,2-AZOLES IN REACTIONS OF 1,1-DIACYCLOPROPANES WITH HYDRAZINE AND HYDROXYLAMINE DERIVATIVES

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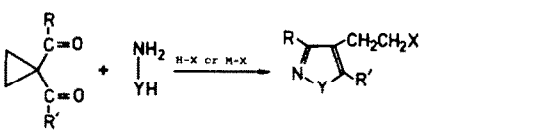
Abstract—The mechanism of recently discovered ring-opening reactions of 1,1-diacyclopropanes with hydrazine and hydroxylamine derivatives is investigated using the ^{1}H-NMR flow (and stopped-flow) method and transient formation of spiro-activated intermediates of type **4** and **19** is proved. The mechanistic and synthetic sequences of these findings are discussed.

Nucleophilic ring cleavage of cyclopropanes activated by electron-withdrawing substituents has been known since 1895,[1] but only recently has received intensive development.[2–6] For instance, these reactions have found many applications in the total synthesis of natural products.[7] Detailed mechanistic studies of these ring-cleavage reactions[8] permit one to classify them into three types, namely (i) "strictly nucleophilic reactions" (a term introduced by Danishefsky)[2] which proceed in the absence of forced electrophilic catalysis, (ii) electrophile assisted reactions with elimination of the activating group (e.g. reactions of cyclopropylcarbinoles[4]) and (iii) electrophile assisted reactions without elimination of the activating group (e.g. nucleophilic ring opening for cyclopropylketones).[3] The reactions of type (i) and, to a lesser extent, of the other types usually require the presence of several activating groups,[2] powerful nucleophiles and rather drastic conditions.[9,10] The main exception is the so-called "spiro-activated"[2] structures where closure of the activating groups into a cyclic framework forces a more favorable overlap of the conjugating orbitals, which in turn leads to a particularly facile nucleophilic cleavage of the cyclopropane ring.

Recently we have found that the reactions of 1,1-diacetylcyclopropane with hydrazine derivatives and hydroxylamine proceed via cyclopropane ring opening with incorporation of external nucleophiles (including nucleophilic solvents) into the product structure. These processes are summarized in Scheme 1.[11,12]



Scheme 1.

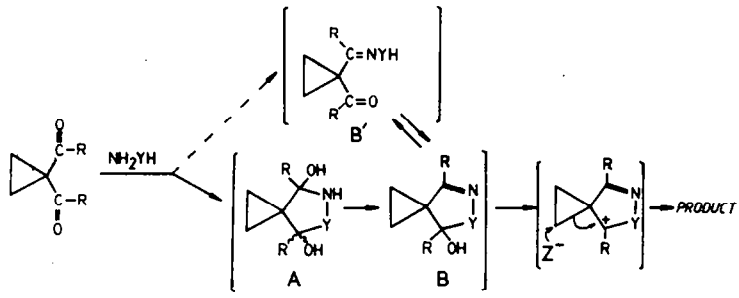
The observed reactions have two remarkable aspects: (i) they represent a novel and convenient method of synthesis of 1,2-azoles, containing a β-X-ethyl substituent and (ii) they are an example of surprisingly gentle conditions for cyclopropane ring opening by nucleophiles. We have suggested also a plausible mechanism (see related literature data)[13–16] which is shown in Scheme 2.

The key step of the mechanism is the intermediacy of cyclic products such as **A** or **B** (Scheme 2), where the ring closure immobilizes the conformer with two mutually perpendicular rings. This fixed geometry is characteristic of the spiro-activated cyclopropanes (cf. Ref. 2). Taking into account the transient formation of cyclic intermediates (e.g. **B**) in Scheme 2 we have labelled the observed phenomenon as "dynamic spiro-activation".[11,12]

However, the proof of intermediate structures, the possible involvement of some other intermediates as well as the detailed sequence of different steps for these reactions are still unknown, and the purpose of the present paper is to fill this gap. We have approached this mechanistic problem using the ^{1}H-NMR flow (and stopped-flow) method.[15,16] This method has been enthusiastically and successfully applied to several mechanistic problems[17,18] because it permits one to interpret the chemical nature of the intermediates for liquid phase reactions more easily and with less ambiguity than other spectroscopic methods.

RESULTS

(a) *Reactions with hydrazine.* Interaction of 1,1-diacetylcyclopropane (**1**) with hydrazine in CD_3OD at room temperature proceeds quite rapidly to give the final product, pyrazole **5**,[11] after 30–40 s (Chart 1). However, the performance of this reaction at $-40°$ permits one to observe the signals of the first intermediate, **A** (**2**) (Fig. 1). Its formation is the most rapid stage: it has been observed after 10 s even at $-70°$. Then the signals of intermediate **B** (**3**) then of **C** (**4**) and finally of pyrazole **5** begin to appear. The



Scheme 2.

intensity of the signals for intermediate **B** is low and approximately constant (quasi-stationary state). Thus, the data suggest a complex combination of consecutive reactions with at least three distinguishable intermediates, **A**–**C** (Fig. 1).

The reaction of **1** in $CDCl_3$ exhibited analogous regularities but proceeded to give a solution of the intermediate **C** (**4**) which can be kept at ~70 h with subsequent transformation into an unidentified polymeric material. However, the addition of an external nucleophile (e.g. CD_3OD) leads to the rapid formation of a pyrazole system (e.g. **5**). Moreover, a solution of the intermediate **C** (**4**) can be easily obtained by refluxing a benzene solution of equimolar amounts of diketone **1** and NH_2NH_2 in a Dean–Stark apparatus. However, all attempts to isolate **4** in a pure form failed.

The reaction of 1-acetyl-1-benzoylcyclopropane (**6**) with hydrazine[12] in CD_3OD at −40° gives 98% of the first intermediate **A** (**7**) after 50 s and proceeds further very slowly. At 0° it gives **A**, then a mixture of two isomeric intermediates **B** (**8**) (~2 min), then intermediate **C** (**9**) (~ 20 min) and finally pyrazole **10**.

The structural assignments for the intermediates of types **A**–**C** have been made on the basis of ^{1}H-NMR data (Table 1). Evidently, the intermediates of type **A** are the dihydroxypyrazolidine derivatives (**2** and **7**, Chart 1) which is in good agreement with analogous literature data.[15] The intermediates of type **B** having unsymmetrical structures are the cyclic tautomeric forms of the monohydrazone of the starting ketones (Chart 1; cf. structures **B** and **B'** in Scheme 2). At last, we assign the isopyrazole structures **4** and **9** (Chart 1) for the intermediates of type **C**. The values of chemical shifts are in good accordance with literature data for compounds of type **A**,[15,16] **B**,[11,19–21] and **C**.[2,22–24] The analogous reaction of diketone **11**, containing a cyclopentane ring proceeds via the same intermediates **12** and **13** (Table 1 and Chart 1) to give the corresponding isopyrazole **14** (corresponding to intermediate **C**) as a final product (Refs 25 and 26).

Thus, the above data suggest the formation of three types of intermediates, which can be identified as the dihydroxy compounds (type **A**), cyclic form of the monohydrazones (type **B**) and, last but not least, the isopyrazoles (type **C**). In the absence of external nucleophiles the isopyrazoles of type **C** (e.g. **4** and **9**) are the final products. It is known that 2,2-gem-disubstituted 1,3-diketones normally give the corresponding isopyrazoles on treatment with hydrazine.[25–27] While the isopyrazole ⇄ pyrazole rearrangements are also known[20,25,26,28] they occur only under rather drastic conditions. For example, we have found that isopyrazole **14** can be recovered unchanged after 48 hr refluxing in ethanol containing HCl. On the other hand, the isopyrazoles, containing the spiro-cyclopropane framework (e.g. **4** and **9**) being spiro-activated structures are extremely sensitive towards nucleophiles and undergo three-membered ring opening with formation of the aromatic structure of the substituted pyrazole.

(b) [4 + 2] *Cycloaddition of isopyrazoles.* It is known that isopyrazoles exhibit relatively poor dienic character, but can react with powerful dienophiles, such as cyclopropene,[29] cyclobutadiene[30] and 4-phenyl-1,2,3-triazoline-3,5-dione (PTAD).[29,31,32] Indeed, we have found that isopyrazole **14** rapidly reacts with PTAD to give the stable adduct **16** (Scheme 3).

We have found that PTAD rapidly reacts with a solution of the pyrazole **4** to give the extremely unstable white crystals of the adduct which in turn loses nitrogen even with a work-up at −20° to give a tarry material. While PTAD has poor solubility in common solvents, we have been able to detect the formation of the adduct **15** by the ^{1}H-NMR flow method in D_8-THF solution: δ

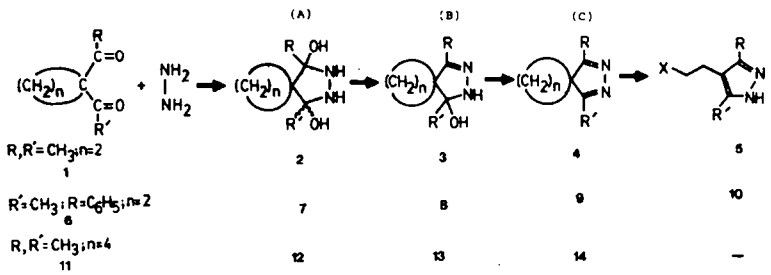


Chart 1.

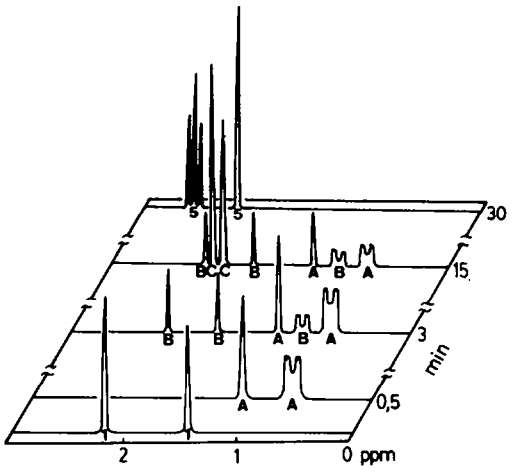


Fig. 1. ^{1}H-NMR detected dynamic of the reaction of diketone 1 with NH_2NH_2 in CD_3OD.

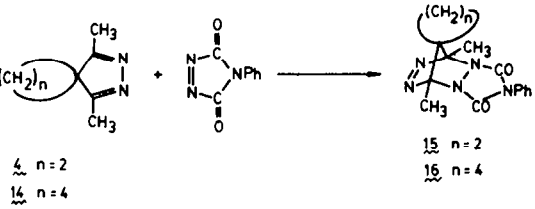
0.16 (2H, s), 0.42 (2H, s), 1.23 (6H, s), 7.44 (5H, m). In the ^{1}H-NMR spectra of both of the adducts, **15** and **16**, a pronounced deshielding effect for the methylene protons of the spiro-cycle, positioned in the *syn*-configuration with respect to the azo group, has been observed.

(c) *Reaction of diketone* **1** *with* $NH_2OH \cdot HCl$. The reaction of diketone **1** with hydroxyl amine and its salts proceeds to give the corresponding β-X-ethyl substituted isoxazoles[11,12] (Scheme 1). We were able to extract the ^{1}H-NMR data for the reaction of **1** with $NH_2OH \cdot HCl$ in CD_3OD at 30° which suggests the transient subsequent formation of three intermediates **A** → **B** → **C** and then the final isoxazole **20** (Chart 2).

The intermediate **A** is the dihydroxy compound **17**. The intermediate of type **B** is definitely the cyclic tautomeric form of the monooxime (**18**) of the diketone **1**[11] (cf. Ref. 12). The main problem is the structure of the intermediate **C**. It is known that the 2,2-disubstituted 1,3-diketones react with hydroxylamine to give the methyleneisoxazolines due to hydrogen abstraction from the methyl group.[19,20,26] The same was observed for the reactions of these diketones with alkylhydrazines.[19,20] We suggest that the intermediate **C** is the methylene spiro-activated derivative **19**. However, this conclusion should be accepted with some reservation because the most informative part of the ^{1}H-NMR spectra is masked by the signals of the solvent.

DISCUSSION

Three main conclusions which can be drawn from the experiments just discussed are the following: these reactions (i) proceed in a stepwise manner via discrete intermediates of recognized structure, (ii) include the formation of the dihydroxy compounds of type **A** at the first *observable* step and these intermediates are the precursors of the monoderivatives of the diketones, such as **3**, **8**, **13** and **18**, (iii) include the isopyrazoles (or related methylene derivative **19**, Chart 2) as *real* spiro-activated structures which undergo a subsequent three-membered ring opening. In turn, these facts support, firstly, the idea of the transient formation of spiro-activated structure(s) (i.e. the idea of "dynamic spiro-activation")[11] and, secondly, lead to several important conclusions that are developed below.



4 n = 2
14 n = 4

15 n = 2
16 n = 4

Scheme 3.

First of all, the formation of observable dihydroxy compounds of type **A** (Charts 1 and 2) is in accordance with the latest literature data on the subject.[15,16] Indeed, the interaction of 1,3-diketones of type **1** should be initiated by the NH_2X attack on the carbonyl group to give the first *plausible* intermediate **21** (Scheme 4). In our case, this invisible intermediate **21** rapidly transforms into dihydroxy compounds of type **A** via intramolecular attack on the second carbonyl group by its own nucleophilic group X but neither *directly* into the monohydrazone (or alternatively into monooxime) of type **B'** (Scheme 2) or its cyclic tautomer **B** (Charts 1 and 2) nor into the ring-opened structures.

Secondly, the data presented above prove the crucial role of electrophilic catalysis in this ring-opening reaction. The net result of the observed process shows that the combination of the diketone **1** + NH_2NH_2 may be formally regarded as synthetically equivalent to the carbocation **23**. Indeed, the principal pathway may be regarded as the carbocationic transformation **22** → **23**, which is an example of the well-known carbocationic interrelation of type **24** → **25**[4–7] (Scheme 4). Both observed spiro-activated intermediates, **4** and **8**, must be capable of creating carbocationic-like species of type **22**. This transformation in the case of isopyrazole **4** should proceed especially easily because it needs only protonation (or even coordination of the lone pair on the nitrogen atom) without any abstraction of a leaving group.

However, the real mechanism may or may not involve the formation of carbocationic species. In other words, the stepwise (carbocationic) vs concerted (analogous to the "push–pull" mechanism with synchronous attack by both electrophile and nucleophile) character of the ring-opening step still remains open. Some indirect arguments such as (i) the attack by sulfur but not by nitrogen atom in the case of the reaction with SCN^- anion[11] and (ii) the regioselectivity of the ring opening in the case of 1,1-diacetyl-2-methylcyclopropane[12] seems to support the view that the reaction proceeds without the transient formation of carbocationic species of type **22**.

Thus, we should conclude that the observed reaction is a particular type of cyclopropane ring opening which necessitates the transient formation of a spiro-activated intermediate, in which the nucleophilic ring opening is *enormously facilitated* by electrophilic catalysis. It is worthwhile to emphasize that the strategy of spiro-activation of cyclopropane ring opening in its *dynamic version* is very attractive as a basis for designing key molecular structures that are useful in the synthesis of seemingly unrelated target compounds and is worthy of further development and refinement (see also Refs. 11 and 12).

Table 1. Chemical shift values for ^{1}H-NMR spectra of intermediates A–C (Chart 1) in the reactions of the diketones with hydrazine

		Starting diketone				Intermediates (δ, ppm)									
						A			B			C			
		R	R^1	CH_2	n	R	R^1	CH_2	R	R^1	CH_2	R	R^1	CH_2	Product of reaction
1	CD_3OD	CH_3	CH_3		2										**5**
		2.12	2.12	1.42		1.12	1.12	0.65	2.10	1.64	0.94	1.98	1.98	2.06	2.10 (s, 6H), 2.45 (t, 2H,
		(s)	(s)	(s)		(s)	(s)	(m)	(s)	(s)	(d of m)	(s)	(s)	(s)	J = 7.5), 3.39 (t, 2H, J = 7.5)
1	$CDCl_3$	CH_3	CH_3		2										**5** (after addition of
		2.06	2.06	1.3		1.17	1.17	0.88	1.94	1.42	1.13	1.97	1.97	1.73	CD_3OD) 2.25 (s, 6H),
		(s)	(s)	(s)		(s)	(s)	(s)	(s)	(s)	(d of m)	(s)	(s)	(s)	2.63 (t, 2H, J = 7.5), 3.4
															(t, 2H, J = 7.5)
1	C_6H_6	CH_3	CH_3		2										
		1.75	1.75	0.93		—	—	—	—	—	—	1.98	1.98	1.2	
		(s)	(s)	(s)								(s)	(s)	(s)	
6	CD_3OD	C_6H_5	CH_3		2										**10**
		8.68	1.94	1.48		7.42	1.10	0.65	7.37	1.52	1.19	7.24	2.71	2.23	2.16 (s, 3H), 2.68 (t, 2H,
		(m)	(s)	(m)		(m)	(s)	(d of m)	(m)	(s)	(d of m)	(m)	(s)	(s)	J = 8.5), 3.45 (t, 2H, J = 8.5),
															7.5 (m, 5H)
		CH_3	C_6H_5						1.68	7.7	0.98				
									(s)	(m)	(d of m)				
11	CD_3OD	CH_3	CH_3		4										
		2.11	2.11	1.82		1.27	1.27	1.71	1.84	1.27	1.69	2.12	2.12	1.85	
		(s)	(s)	(m)		(s)	(s)	(m)	(s)	(s)	(m)	(s)	(s)	(m)	

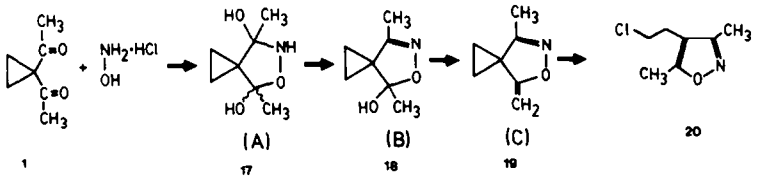
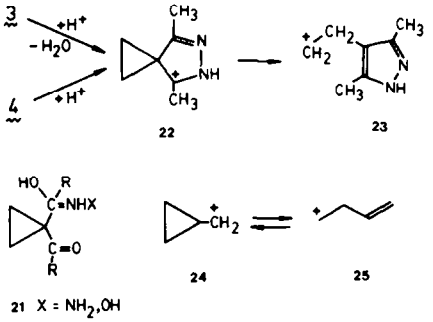


Chart 2.



Scheme 4.

EXPERIMENTAL

^{1}H-NMR spectra were recorded at 60 MHz on a Varian S-60T spectrometer and at 100 MHz on a Tesla BS-497 spectrometer in $CDCl_3$ with TMS as the internal standard. Stopped-flow NMR investigations were carried out with 0.5 M solns of the reagents on a Varian H-100D-15 spectrometer equipped with an apparatus for flow and stopped-flow experiments.[15,18,33]

Compounds **1**, **6**, **11**, **14** and 4-phenyl-1,2,4-triazolin-2,4-dione (PTAD) were prepared according to methods described in the literature.[12,34,35] Hydrazine was prepared from its hydrate by distillation over BaO.

Reaction of **14** *with PTAD.* To a stirred soln of **14** (205 mg, 1.37 mmol) in dry benzene (10 ml) was added a soln of PTAD (239 mg, 1.37 mmol) in benzene (15 ml) at 10°. Within 5 min the red colour of the azo compound disappeared and the solvent was evaporated *in vacuo* at room temp. Recrystallization of the residue from pentane–CH_2Cl_2 (10 : 1) afforded 385 mg (80%) of **16** as yellow crystals, m.p. 127–128° dec. NMR : 1.1 (m, 2H); 1.63 (m, 4H), 1.71 (m, 2H), (CH_2 cycl); 2.11 (s, 6H, CH_3); 7.35 (m, 5H, Ph). (Found : C, 63.29; H, 5.61; N, 21.55%. Calc for $C_{17}H_{19}N_5O_2$: C, 62.76; H, 5.89; N, 21.52%.)

Reaction of diketone **1** *with hydrazine hydrate in acetonitrile.* 2 g (15.9 mmol) of **1**, 0.77 ml (15.9 mmol) of $NH_2NH_2 \cdot H_2O$ and 0.3 ml (17 mmol) of H_2O were stirred in 30 ml of CH_3CN for 72 hr at 60°. The polymer-like ppt obtained was dissolved in $CHCl_3$ (10 ml) and precipitated with ether, filtered, and dried *in vacuo* (1 mm Hg). 1.66 g of polymer (85%) was obtained, m.p. 35–80°. NMR : 1.96 and 2.10 (narrow m, 6H, 2 × CH_3); 2.56 and 3.88 (overlapping broad m, 4H, CH_2, CH_2).

The same result was obtained when DMSO, $CHCl_3$, ether, pyridine, and THF were used as solvents.

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