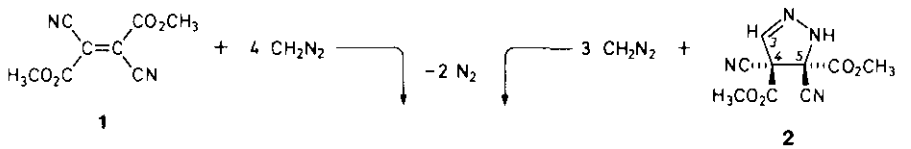
THE ASTOUNDING REACTION OF DIAZOMETHANE WITH DIMETHYL 2,3-DICYANOFUMARATE

Rolf Huisgen,* Abhijit Mitra, and Joaquin Rodriguez Moran
Institut für Organische Chemie der Universität München
Karlstr. 23, D-8000 München 2, FRG

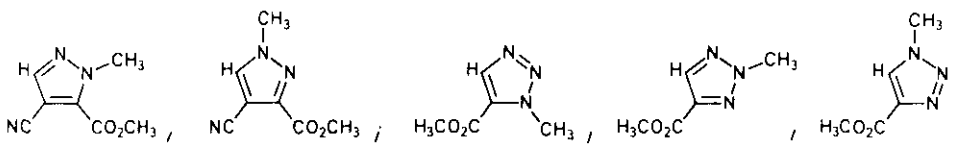
Dedicated to Professor Bruno Werdelmann on the occasion of his 65th birthday

Abstract — The title reaction afforded the pyrazole derivatives 3 and 4 as well as the *N*-methyl-1,2,3-triazolecarboxylic esters 5 - 7. The poly-step sequence was clarified; the key intermediates are the 1-pyrazoline 18, the 2-pyrazoline 2, the *4H*-pyrazole 12, the pyrazole 22, and methyl cyanoformate.

The additions of diazoalkanes to α,β-unsaturated carboxylic esters, discovered by Buchner [1] in 1888, constitute not only the oldest 1,3-dipolar cycloadditions, but still one of their best studied types.[2] Nevertheless, the treatment of dimethyl 2,3-dicyanofumarate (1) with an excess of diazomethane (10 equiv) in THF (4 d, 20°C) took an astounding course. The yields of 3 - 7 were monitored by ^{1}H NMR and are based on all the C-atoms of 1. Closer investigation revealed a drama in many acts.



1 2



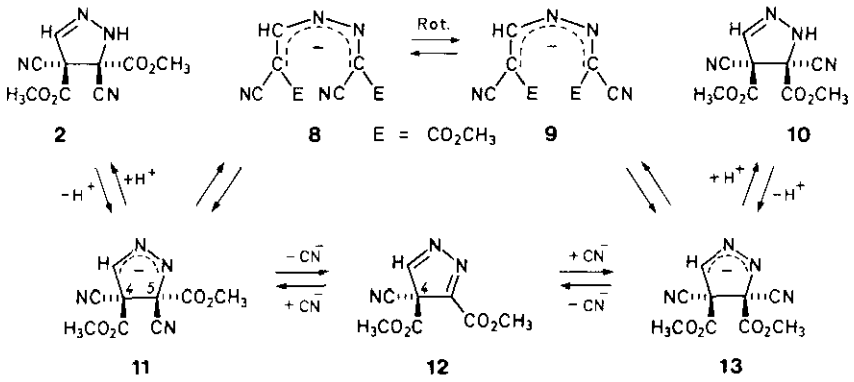
	3	4	5	6	7
1 →	68 %	7 %	47 %	18 %	6 %
2 →	78	14	45	28	5

Dimethyl trans- and cis-4,5-Dicyano-2-pyrazoline-4,5-dicarboxylate (2 *and* 10)

The stirred suspension of 1 in THF at -78°C instantaneously combined with 0.96 equiv

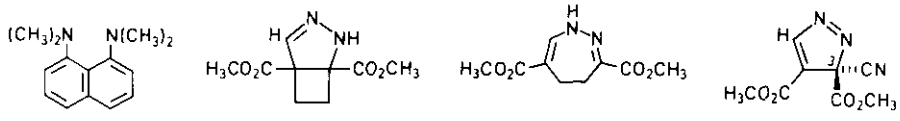
of diazomethane. The colorless 2-pyrazoline 2,[3] mp 120-121°C, crystallized from chloroform in 85% yield. The conversion of 2 to 3 - 7 by diazomethane (8 equiv, THF, 26 h 20°C) left no doubt that 2 is a common precursor. The infrared NH bands and δ(3-H) = 6.73 fit the 2-pyrazoline structure 2.

The colorless solution of 2 in $CDCl_3$ or [D_6]acetone turned yellow when a small crystal of "proton sponge" 14 [4] was added; the ^1H NMR spectrum recorded an equilibration with the more soluble *cis* isomer 10, until 2/10 = 38:62 was reached after several hours. The same isomerization took place spontaneously in [D_6]DMSO within several weeks; it was accelerated by a trace of base and inhibited by addition of acetic acid. An equilibrium of 2/10 = 43:57 in [D_6]DMSO was established from both sides; before it was reached, irreversible changes started which are described below. The isolated *cis* compound 10, mp 84-86°C, shows IR vibrations for free and associated N-H, and δ(3-H) amounts to 6.75.



2 8 9 10 11 12 13

The two stereocenters of 2 and 10 being quaternary, the capability of *cis,trans* isomerization is not obvious. After deprotonation, an *electrocyclic ring opening* of 11 may lead to a heteropentadienyl type anion 8 which undergoes rotation and recyclizes to give 13. This route is attractive, because four substituents and the middle *N*-atom stabilize the open-chain species 8 and 9. 1,5-Electrocyclic reactions are widespread in heterocyclic chemistry.[5] The related conversion 15 → 16 has been described;[6] it is promoted by the release of ring strain.



14 15 16 17

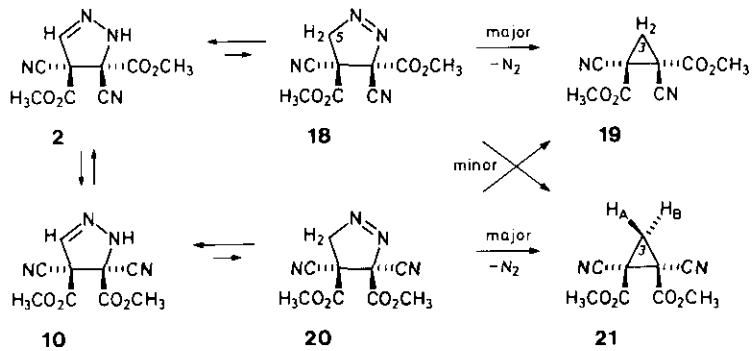
Not less enticing is an equilibration of the anions 11 and 13 by an *elimination and addition of the cyanide anion.* The *4H*-pyrazole 12 or the *3H*-pyrazole 17 may act as an intermediate. One calculates from bond energy increments that 12 is energetically favored over 17 by 46 kcal mol^{-1}.

Also *diazomethane* belongs to the basic catalysts which equilibrate the 2-pyrazolines 2 and 10. One must assume that the intermediate methyldiazonium ion transfers methyl to another substrate in the solution. Then a catalytic amount of the anions 11 and 13 can bring about the equilibration 2 ⇌ 10. The ^{1}H and ^{13}C NMR spectra as well as the mass spectra of 2 and 10 are indicative of 2-pyrazolines, yet what is the basis of the *trans,cis* assignment ?

The 1-Pyrazoline 18 as Primary Cycloadduct

The mother liquor of 2 contained 4% dimethyl *trans*-1,2-dicyanocyclopropane-1,2-dicarboxylate (19). When 1 was reacted with diazomethane in THF *at room temperature*, the yield of 19 rose to 20%, accompanied by 1.5% of the *cis* isomer 21.

1-Pyrazolinecarboxylic esters undergo base-catalyzed tautomerizations to 2-pyrazolines. In one experiment - reaction of 1 and diazomethane *in ether at 25°C* for 5 min - the AB spectrum of 5-H_2 at δ 5.20 and 5.76 with J = 17.9 Hz ($CDCl_3$) indicated the presence of the 1-pyrazoline 18; 10 min later the signal had disappeared. The tautomerization 18 → 2 competes with the N_2 extrusion; the share of the latter as a unimolecular reaction grows with increasing temperature. Without touching the mechanistic problem of N_2 elimination from 1-pyrazolines and its steric course,[7] it may be stated that pyrazolines substituted by ester groups prefer a retentive mode of cyclopropane formation.[8] The occurrence of 20% 19 (*trans*) + 1.5% 21 (*cis*) along with 2 accords with cases described previously.



2 18 19

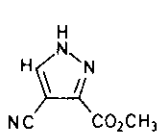
10 20 21

When samples of the 2-pyrazolines 2 and 10 were heated to 140°C for 4 h, N_2 extrusion competed with the equilibration, 2 ⇌ 10, and made the steric course less clear-cut. 2 (*trans*) afforded *trans*- and *cis*-cyclopropane, 19 and 21, in a ratio of 75:25 (37% yield), whereas 19/21 = 55:45 resulted from 10, and 19/21 = 60:40 from an equilibrium mixture of 2 and 10 (38:62).

The *trans*-cyclopropane 19, mp 124-127°C, showed singlets at δ 2.56 for 3-H_2 and at 3.92 for 2 OCH_3 ($CDCl_3$). The ^{13}C NMR spectrum supports the symmetry: δ 25.6 (t, C-3), 28.3 (s, C-1 + C-2), 55.1 (q, 2 OCH_3), 112.1 (s, 2 CN), 161.9 (s, 2 C=O). The *cis*-cyclopropane 21 was enriched to 92% by tlc and recrystallization, mp 70-80°C. The AB spectrum at δ 2.36 and 2.57 with J = 6.3 Hz for 3-H_2 together with s 3.84 for 2 OCH_3 reveals C_s for 21 in contrast to C_2 for 19. The unequivocal assignment of 19 and 21 establishes the configurations of 2 and 10 as well as - indirectly - that of dimethyl 2,3-dicyanofumarate (1).[9]

Methyl 4-Cyanopyrazole-3-carboxylate (22) *and its N-Methylation*

When the stirred suspension of 1 in THF was reacted with 2.2 equiv of diazomethane at 0°C for 3 h, fractional crystallization of the product afforded 31% of pyrazole 22, mp 225-228°C, 37% of methyl 4-cyano-1-methylpyrazole-5-carboxylate (3), mp 84-86°C, and 6% of the isomeric 3-carboxylate 4, mp 164°C; 22 turned out to be the precursor of 3 and 4. On the basis of the known ^{13}C NMR spectra of pyrazole [10] and 1-methyl-pyrazole [11] as well as substituent increments of the benzene series,[12] the δ values of the ring C-atoms and their multiplicity allowed an elegant and unambiguous assignment of structures 22, 3 and 4; especially, the isomer 23 and its *N*-methyl derivatives were excluded. The occurrence of *N*-unsubstituted pyrazoles as cyclic NH-bonded dimers makes the distinction of NH tautomers unnecessary. Nevertheless, the δ_C calculated for 22 are much closer to the experimental values than those calculated for the second NH tautomer.



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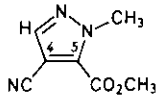

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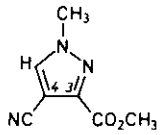

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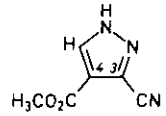

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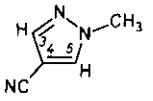

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Supporting chemical evidence came from saponification of the ester group of 3 and distillative decarboxylation at 230°C/11 Torr. The 4-cyano-1-methylpyrazole (24, 74% yield), mp 60°C, was identified by two low-field *singlets* for the ring protons,

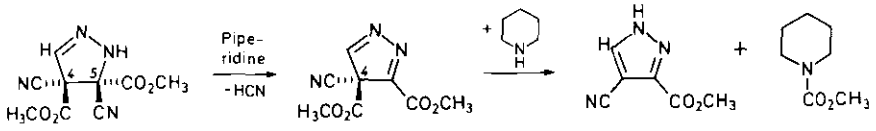
δ 7.94 and 8.41 in [D_6]DMSO. The *N*-methyl derivatives of 23 should have produced 3- or 5-cyano-1-methylpyrazole.

Unexpectedly, the ratio 3/4 in the methylation of the pyrazole 22 depends on the *stationary concentration* of diazomethane. Dropwise addition of diazomethane in THF to the stirred suspension of 22 in THF over 1 h furnished 3/4 = 58:42. When the reaction was carried out in 0.7 M diazomethane in THF, ^{1}H NMR analysis indicated 3/4 = 73:27. In the reaction of 2 with 8 equiv of diazomethane described above, 3/4 amounted to 85:15. It is conceivable that the dimer of pyrazole 22 and the two monomeric tautomers differ in their interaction with diazomethane.

The *basicity* of diazomethane appears to be responsible for the conversion of 2-pyrazoline 2 to pyrazole 22. The conversion is likewise effected by proton sponge 14 and in the slow spontaneous reaction of 2 in DMSO; the equilibration 2 ⇌ 10 is faster than the irreversible reaction 2 → 22. How does the latter come about ?

Dimethyl 4-Cyano-4H-pyrazole-3,4-dicarboxylate (12) *as a Key Intermediate*

The 2-pyrazoline 2 exothermally reacted in DMSO with 2.1 equiv of piperidine to give quantitative yields of pyrazole 22 and methyl piperidine-*N*-carboxylate (25); piperidinium cyanide was a further product identified by ^{1}H NMR spectroscopy. Piperidine induces the HCN elimination from 2, followed by a transfer of the 4-ester group of 12. The highly reactive *4H*-pyrazole 12 was not detected by ^{1}H NMR; yet this elusive species is the logical intermediate, because the isomeric *3H*-pyrazole 17 cannot furnish the structurally secured pyrazole 22. Also sodium methoxide in methanol smoothly converts 2 into the pyrazole 22 + dimethyl carbonate + NaCN.



2 12 22 25

Proton sponge (14) is a base *without nucleophilicity*.[4] How can it convert 12 into 22 ? A three-step cycle explains the catalysis by the base B:

$$2 + B \rightarrow 12 + BH^+ + CN^-$$

$$12 + CN^- \rightarrow \text{anion of } 22 + N{\equiv}C\text{-}CO_2CH_3$$

$$\text{anion of } 22 + BH^+ \rightarrow 22 + B$$

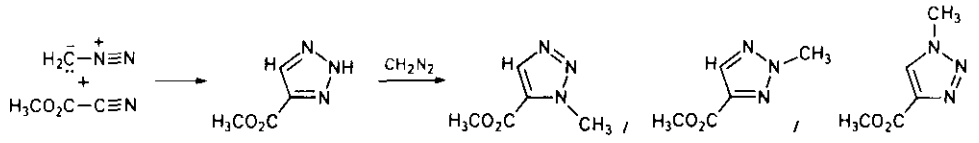
Indeed *methyl cyanoformate* (26) was identified amongst the products by ^{13}C NMR sig-

nals ([D_6]DMSO): δ 145.1 (s, C=O), 109.4 (s, CN), 55.2 (q, OCH_3).

Diazomethane is both a base *and a nucleophile*. The transfer of the ester group to diazomethane was conceivable in the conversion 12 → 22. However, neither methyl diazoacetate nor acetonitrile (methyldiazonium ion + CN^-) was observed in the ^1H NMR spectrum, when 2 reacted with diazomethane in [D_6]DMSO. Thus, diazomethane must act as a base B in the three-step cycle above to explain the formation of 22. However, diazomethane is available in stoichiometric amount; the methylpyrazoles 3 and 4 could emerge from the combination of 22-anion and the methyldiazonium ion.

The Role of Methyl Cyanoformate (26)

In a formal stoichiometry the 2-pyrazoline 2 fragments into pyrazole 22 + NC-CO_2CH_3; the mechanistic pathways were discussed above. The next step would be the 1,3-dipolar cycloaddition of diazomethane to methyl cyanoformate (26) furnishing methyl 1,2,3-triazole-4-carboxylate (27), which is *N*-methylated by diazomethane in the concluding step.



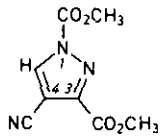
26 **27** **5** 48% **6** 24% **7** 5%

Methyl cyanoformate reacted with 2.5 equiv of diazomethane in THF at room temperature with 1.0 equiv of N_2 evolving in 4 h. ^1H NMR analysis indicated 77% of the three *N*-methyl-1,2,3-triazolecarboxylic esters 5 - 7 in the ratio 62:31:7. They were separated by tlc and isolated pure; mp (δ ring-H, $CDCl_3$): 5, 55.5-56.5°C (8.04); 6, 63-64°C (7.95); 7, 157-158°C (8.00). The δ_C of ring and methyl C-atoms allowed a clear assignment on the basis of the ^{13}C NMR spectra of 1-methyl- and 2-methyl-1,2,3-triazole [10] modified by increments of CO_2CH_3.[12]

The correspondence of the isomer ratios of 5 - 7 with those obtained from 1 or 2 with diazomethane (first formula scheme) leaves no doubt that 26 occurs in the reaction and is intercepted by cycloaddition. No evidence was gained for an accumulation of methyl 1,2,3-triazole-4-carboxylate (27); it should be more acidic than 1,2,3-triazole (pK_a 9.3) and is subject to fast *N*-methylation by diazomethane.

In 1910, Oliveri-Mandalà [13] merely described the formation of 6 from 26 and diazomethane; the Italian author hydrolyzed the ester group and recognized the identity with the known osotriazole derivative. In the reactions of cyanogen bromide [14] and

tosyl cyanide [15] with diazomethane three *N*-methyl-1,2,3-triazoles were observed; the case reported here is the first where assignments and isomer ratios are known.



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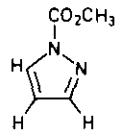

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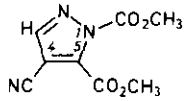

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The yields of the triazoles 5 - 7 starting from 1 (71%) or 2 (78%) signifies that most of the methyl cyanoformate occurring is captured by diazomethane. In the reaction of the 2-pyrazoline 2 catalyzed by proton sponge 14 in DMSO, 26 appears in the ^{1}H NMR spectrum as reported above, but part of it combines with pyrazole 22 to give dimethyl 4-cyanopyrazole-1,3-dicarboxylate (28). We are dealing with an equilibrium reaction: when 22 and a trace of 14 were dissolved in an excess of methyl cyanoformate (26) with HCN being pumped off, the reaction went to completion and 98% 28, mp 106-106.5°C, resulted. Compound 26 appears to be an active reagent for *N*-methoxycarbonylation, as the conversion of pyrazole into 29 (99%, mp 33-35°C) by the same procedure testifies. ^{13}C NMR comparison of 28 and 29 suggests - albeit not unequivocally - that we are dealing with 28 and not its isomer 30.

In the treatment mentioned of 2 with a trace of 14 in DMSO at 20°C, the yield of dicarboxylic ester 28 reached 23% after 30 min and decreased to 15% after 2 d; now the signals of the *N*-methylparazoles 3 and 4 disclosed a double role of methyl cyanoformate: *reversible* introduction of CO_2CH_3 into pyrazole 22 and slow, but *irreversible* methylation. Addition of some crystals of NaCN increased the formation rate of 3 and 4. When pure 28 and some NaCN were dissolved in [D_6]DMSO, the ^{1}H NMR spectrum indicated 58% 22, 19% 3, and 23% 4 after 24 h.

At elevated temperatures, pyrazole-*N*-carboxylic esters themselves act as alkylating agents, with CO_2 evolution.[16] After heating 28 at 145°C for 15 min, ^{1}H NMR analysis signaled 21% of pyrazole 22 and 66% of the methyl derivatives 3 and 4 in the ratio 40:60; this ratio is distinctly different from that observed for the methylation of 22 by diazomethane.

The detective story has found its solution. Most of the steps of the long reaction sequence were elucidated and insight was gained into the chemistry of the little known *4H*-pyrazoles.

ACKNOWLEDGMENT

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