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ON THE REACTIVITY OF 3,4-DIMETHOXYCARBONYL-2-PYRAZOLINES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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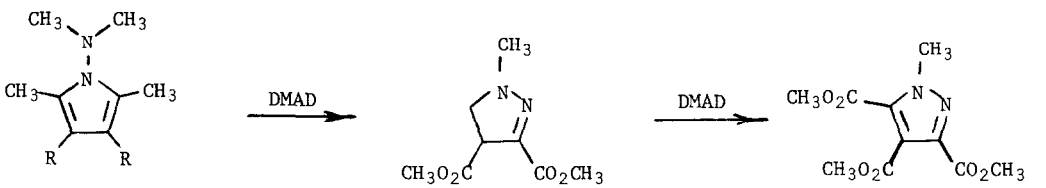
The title pyrazolines react with dimethyl acetylenedicarboxylate to give 1-alkyl-3,4,5-trimethoxycarbonylpyrazoles.

In the preceeding communication we report that reaction of 1-(N,N-dimethylamino)2,3,4,5-tetramethylpyrrole (1a) with excess dimethyl acetylenedicarboxylate (DMAD) results in formation of 1-methyl-3,4-dimethoxycarbonyl-2-pyrazoline (2). Furthermore, other 1-(N,N-dialkylamino) derivatives of 1a produce corresponding 3,4-dimethoxycarbonyl-2-pyrazolines under similar mild reaction conditions ($CHCl_3$, 25°C). We were, therefore, surprised to find that with the less reactive pyrrole 1b and DMAD (3 equiv, toluene, reflux, 24 h), 1-methyl-3,4,5-trimethoxycarbonylpyrazole (3, mp 98-99°C)[1] is isolated (72% yield) in place of 2.



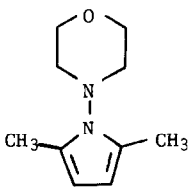
1a, R = CH_3
b, R = H

2

3

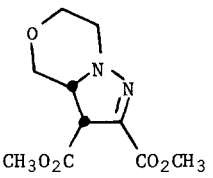
That pyrazoline 2 is an intermediate in the formation of 3 is demonstrated by the near quantitative conversion of 2 to 3 on treatment with DMAD in refluxing toluene solution. Furthermore, control studies indicate that dehydrogenated 2 (i.e., 1-methyl-3,4-dimethoxycarbonylpyrazole) is not an intermediate in the conversion 2 → 3[2] and that 2 is completely stable in refluxing toluene solution in the absence of DMAD.[3]

Similar reactivity is noted for pyrrole 4, from which pyrazole 6 is obtained (57%, oil). Z-stereochemistry for the side chain in 6 is clearly evident from comparison of ^{1}H NMR coupling constants for H_a, H_b and H_c with those reported for Z-methyl 4-methoxy-2-butenoate (7); see formulae for relevant coupling constants.[4]



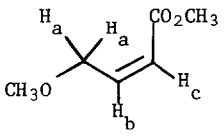
4

DMAD



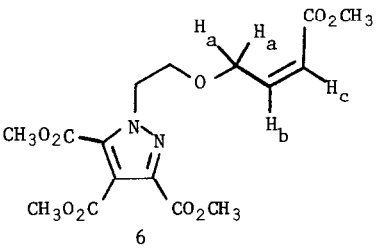
5

DMAD



7

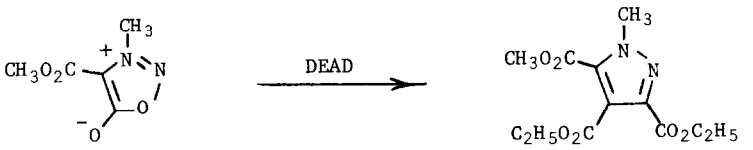
J_{bc} = 11.7 Hz
J_{ab} = 4.9 Hz
J_{ac} = 3.2 Hz



6

J_{bc} = 11.0 Hz
J_{ab} = 4.5 Hz
J_{ac} = 2.0 Hz

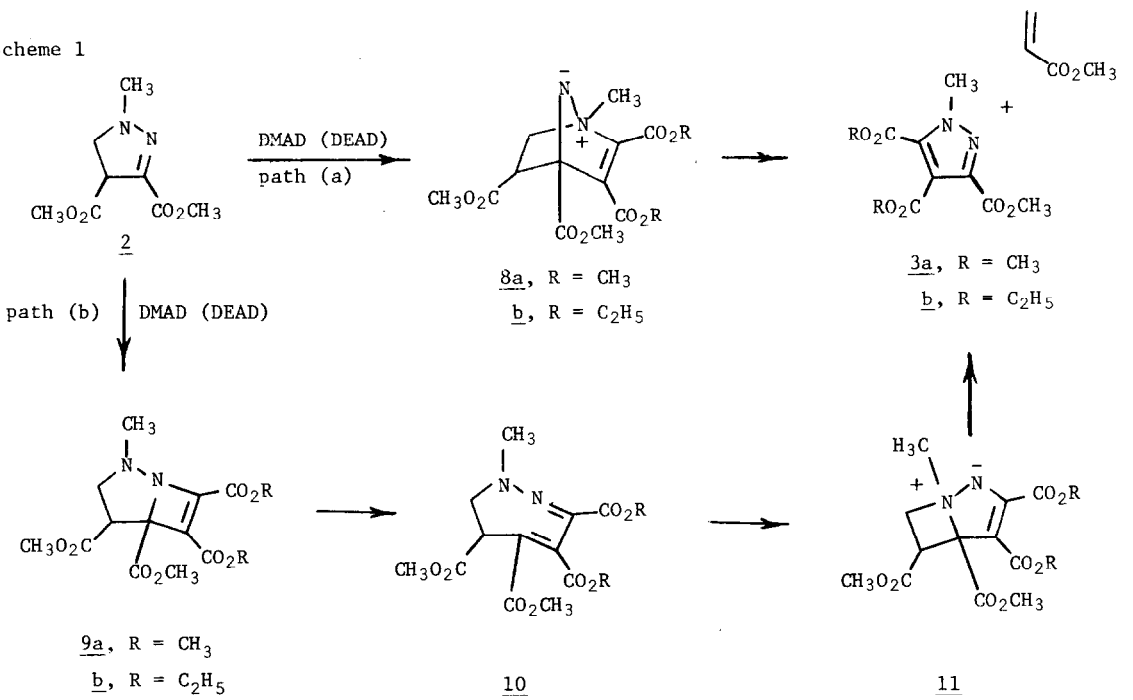
A. Priori, there are at least two reasonable mechanisms which account for conversion of pyrazolines to pyrazoles. On inspection of both mechanisms presented in Scheme 1, it may be appreciated that methyl group migration in both 8a and 11a might occur without detection. To explore this possibility, pryazoline 2 was treated with diethyl acetylenedicarboxylate (DEAD); the resulting pyrazole 3b was found to be different from the pyrazole 13 prepared by DEAD addition to 3-methyl-4-methoxycarbonyl sydnone (12).[5,6] Thus, N-methyl group migration can not occur during formation of pyrazole 3 if path (a) is correct, but must occur if path (b) is correct. Additional labeling studies would be required to differentiate between paths (a) and (b).



12 13

It is noteworthy that the conversion of 5 to Z-6 occurs with retention of stereochemistry. This observation is consistent with the suggestion of a reaction mechanism for 5 → 6 analogous to that shown in Scheme 1, and excludes any that involve non-concerted formation of the C(b)-C(c) double bond.

Scheme 1



2

8a, R = CH_3
b, R = C_2H_5

3a, R = CH_3
b, R = C_2H_5

9a, R = CH_3
b, R = C_2H_5

10

11

We intend to further explore the synthetic utility of N-aminopyrrole Diels-Alder chemistry. The possibility of intramolecular variants of the reactions described in this and the preceeding communication seem especially attractive. Application of studies completed thus far to natural products synthesis is described in the following note.

Acknowledgment

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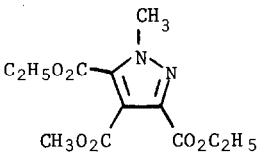
References

1. Lit. mp 76-78°C: A. N. Kost, G. A. Golubeva, L. A. Sviridova, I. I. Grandberg, N. B. Chernyshova, Dokl. Akad. Nauk. SSSR, 179, 337 (1968); C. A. 69, 59149h (1968) and 96-98°C; R. Husigen, K. V. Fraunberg and H. J. Sturm, Tetrahedron Lett., 30, 2589 (1969).
2. M. K. Saxena, M. N. Gudi and M. V. George, Tetrahedron, 29, 101 (1973).
3. The stability of 2 in the absence of DMAD excludes the involvement of nitrileimine i in formation of 3. Nitrileimine i might have been formed by cycloreversion of 2 and would have been expected to undergo cycloaddition to DMAD to give 3; see H. Ogura, K. Kubo, Y. Watanabe, and T. Itoh, Chem. Pharm. Bull., 21, 2026 (1973) and C. S. Angadiyavar and M. V. George, J. Org. Chem., 36, 1589 (1971).

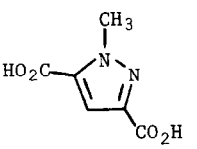
$$CH_3\text{-}\overset{-}{N}\text{-}\overset{+}{N}\equiv C\text{-}CO_2CH_3$$

i

4. S. J. Rhoads, J. K. Chattopadhyay, and E. E. Waali, J. Org. Chem., 35, 3352 (1970); for E-7, J_{bc} = 15.6 Hz.
5. As expected, reaction of 12 with DMAD gives 3a. Sydnone 12 (mp 97-98°C, 97%) is prepared by reaction of 3-methyl-4-carboxy sydnone [C. V. Greco and B. P. O'Reilly, J. Het. Chem., 9, 123 (1972)] with diazomethane.
6. One other structural assignment for 3b cannot at this time be rigorously excluded, namely 1-methyl-3,5-diethoxycarbonyl-4-methoxycarbonylpyrazole (ii). We have attempted to prepare (ii), but have not been able to metallate or halogenate diesters derived from previously reported 1-Methyl-3,5-dicarboxypyrazole (iii); R. Hüttel and M. E. Schön, Ann 625, 55 (1959). On the other hand, a mechanism by which 2 might be converted to ii is not readily apparent.



ii



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