Tetrahedron Letters,Vol.26,No.50,pp 6151-6154,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

AN UNEXPECTED CYCLIZATION PATH TO SOME PYRAZOLES

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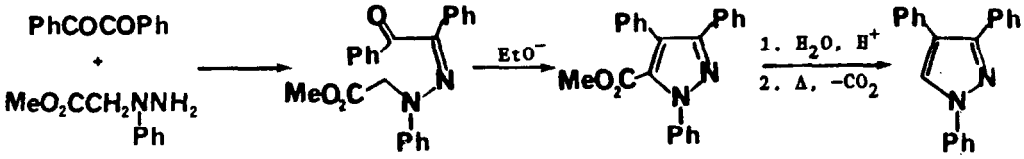
Abstract: The treatment of ketal hydrazones of arylglyoxals (2) with 75% sulfuric acid leads to 3-aroyl-4-phenyl-1-methylpyrazoles (6) as well as 4-phenyl-1-methylpyrazole (7) and the corresponding benzoic acids. Possible mechanisms are discussed.

In the context of another investigation,[1] we were interested in the synthesis of 5-benzoyl-4-phenyl-1-methylpyrazole (4). Although electrophilic substitution allows the introduction of certain groups at the 4-position of the pyrazole ring,[2] the synthesis of moderately complex pyrazoles is not a routine matter and usually requires several steps. These difficulties make any potentially general route to pyrazoles a premium commodity.

Several years ago, a Russian group[3a] reported the formation of a compound claimed to be 3,4-diphenyl-1-methylpyrazole from the cyclization of the monodimethylhydrazone of



(1)

benzil; this report was followed by the description of related cyclizations (e.g. Eq. 1)[4,5] which appeared particularly well-suited to our needs. Indeed, the formation of

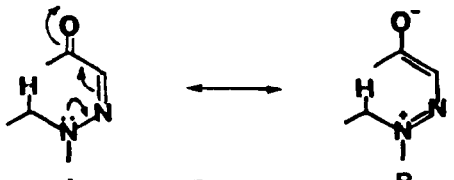
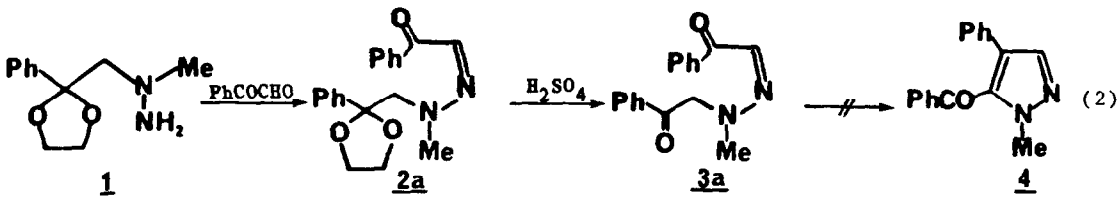


Fig. 1

pyrazoles from the work of both the Italian and Russian groups seemed predicated on an "aldol-like" condensation of the "δ-hydrogens" (of the N-alkyl group) presumably activated by the apparent extensive conjugation suggested by resonance structure B.[6] A somewhat different but related cyclization had been described much earlier by von Auwers and Mauss[7] who reported the formation of 4-benzoyl-1,5-diphenylpyrazole from treatment of the 1-benzoyl-1-phenylhydrazone of benzoylacetaldehyde with ethanolic alkali.

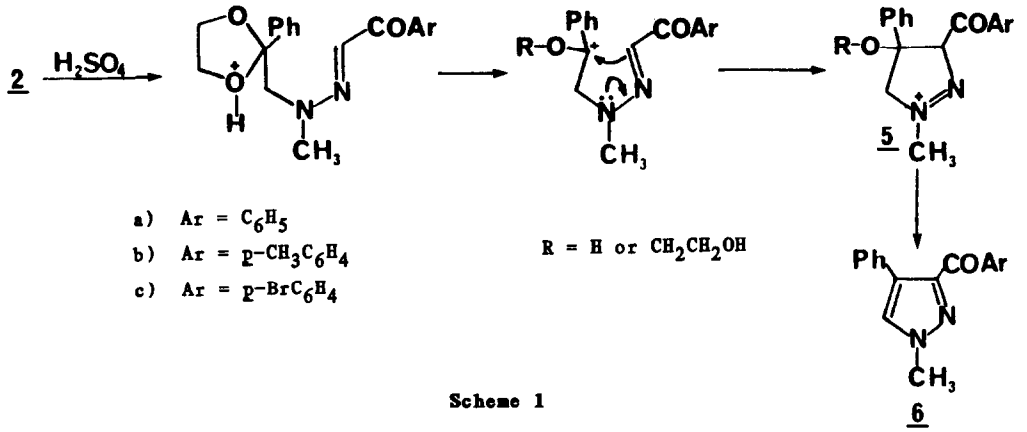
The well-known instability of α-hydrazino ketones (presumably the basis for the osazone reaction of sugars[8]) coupled with the necessity to have the N-methyl substituent of 4 already in place, led us to design our synthesis of 4 as outlined in Eq. 2. The ketal hydrazine 1, obtained by alkylation of methylhydrazine with phenacyl bromide ethylene ketal, was condensed with phenylglyoxal to lead to the required hydrazone 2a. The deketalization step was apparently followed by concurrent cyclization to a product which initially appeared to be the desired 5-benzoyl-4-phenyl-1-methylpyrazole (4).



(2)

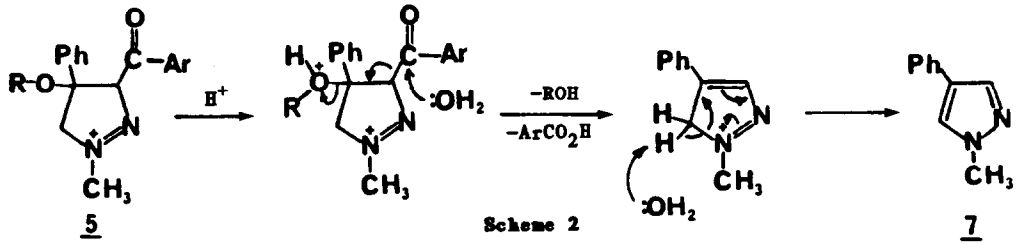
However, this product turned out to be identical to 3-benzoyl-4-phenyl-1-methylpyrazole (6a, Ar = Ph), obtained by three different routes; unequivocal confirmation was provided by an X-ray crystal structure determination.[1] The fact that 5a and not 4 was the product of reaction 2 suggests that the benzoyl group attached to the imino carbon becomes the substituent benzoyl group of the pyrazole and that the cyclization of 2 (or 3) is proceeding not via an "aldol" type condensation of the methylene group but rather by an acid-promoted attack of the "aldehydic" carbon on the ketal carbon (or carbonyl) as shown in Scheme 1. Support for this path was adduced from the cyclization of the ketalized hydrazones of p-methyl phenylglyoxal and of p-bromophenylglyoxal (2b and 2c). Had the anticipated "aldol-like" condensation path been operative, the glyoxal carbonyl would have been incorporated into the pyrazole ring. However, in both cases, the characteristic

pattern of p-substituted aroyl groups was readily apparent in the nmr spectra, thus indicating 6b and 6c to be the products;[9] authentic 6c was obtained by the addition of diazomethane to the corresponding chalcone,[10] followed by the N-methylation and



Scheme 1

aromatization with sulfur.[1] In addition, 4-phenyl-1-methylpyrazole (7) was obtained as a second major product of this cyclization [11] and evidently was formed by loss of the aroyl groups; the corresponding benzoic acids were isolated and characterized in each case. Since none of the expected "aldol" products 5-aroyl-4-phenyl-1-methylpyrazoles was detected,[11] it is presumed that 7 arose from intermediate 5 and, given the stability of 3-benzoyl-4-phenyl-1-methylpyrazole to the reaction conditions, that the cleavage of the aroyl groups must be occurring during the cyclization. A possible rationalization may be depicted as shown in Scheme 2.[12]



Scheme 2

Further work to investigate the scope and utility on this unusual cyclization is currently being carried out in our laboratories.

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†† Taken in part from the B. Sc. thesis of D. Scarpetti, University of Massachusetts at Boston, June 1986.

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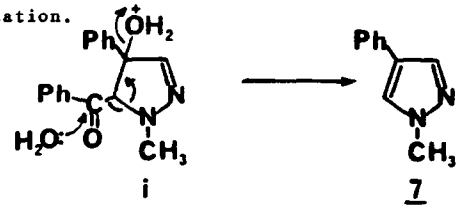
5. A. Alemagna, T. Bacchetti and S. Rossi, Gazz. Chim. Ital., 93, 748 (1963).
6. The "acidity" of the "δ-hydrogens" would evidently be enhanced greatly by being further activated by a carbonyl group in the examples described by both Italian groups.
7. K. von Auwers and H. Mauss, J. prakt. Chem., [2], 117, 311 (1927).
8. a) M. Busch and W. Foerst, ibid., 119, 287 (1928).
   b) M. Koga and J.-P. Anselme, Chem. Comm., 53 (1973).
9. It is interesting to note that while the product of the Russian workers (ref. 3a) has been shown to be an imidazole (ref. 3b), the work of Alemagna et al. (ref. 5) seems to indeed have proceeded through an "aldol-like" condensation to give the pyrazoles.
10. L. I. Smith and W. B. Pings, J. Org. Chem., 2, 23 (1937).
11. The yields of 6 and 7 combined are nearly quantitative.
12. Similar mechanism could be written from the putative pyrazoline (i) derived from the "aldol-type" cyclization.



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(Received in USA 2 August 1985)