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ALDOL-TYPE REACTIONS OF DIAZOKETONES

T. L. Burkoth[1]

Department of Chemistry, Columbia University, New York, N. Y. 10027

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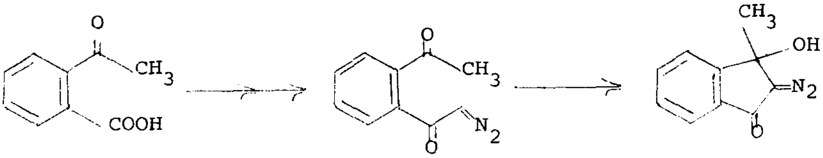
Despite diverse reaction types and synthetic applications of diazoketones,[2] chemical involvement of this moiety in an aldol sense has not been reported. The facility with which intramolecular reactions of this type can occur is described herein:

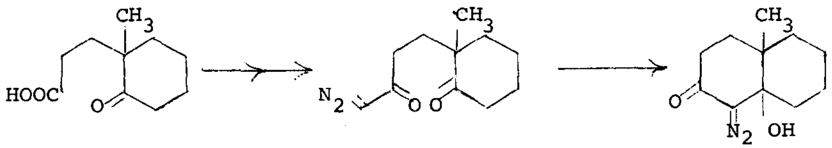
The diazoketone II was prepared by the method of Tarbell and Price[3] from the keto acid I.[4] A 0.1M methanolic solution of the crude diazoketone, when treated with 3 eq. of 10% aq. KOH (45 min.), afforded, as the sole neutral product the crystalline diazoketol III in 60% overall from I. Spectroscopic evidence[5]



I II III

indicated the transformation as written. The methyl ketone function was converted to a tertiary hydroxyl and substitution occurred at the carbon bearing the still-intact diazo function. This reaction sequence was unsuccessful on levulinic acid, the simplest acyclic case.

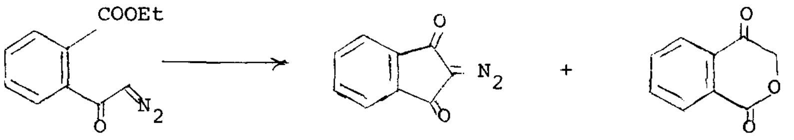
Application of the reaction to the formation of six-membered rings was successfully made on the keto acid IV[6]. Identical reaction sequence and conditions led to formation of VI in 65% yield (overall from the acid IV).



IV V VI

Crystalline material of m.p. 95-6° exhibited satisfactory spectral characteristics[7] to permit assignment of gross structure as in VI. The observation of a single isomer prompts tentative assignment of ring juncture stereochemistry as *cis* by analogy to related ring closures[8].

Extension of the reaction to a Dieckmann type process led to a new synthesis of the interesting 2-diazoinadane-1,3-dione (VIII)[9,10]. The known diazoketo ester VII[11], when treated under the basic conditions above afforded VIII[12] in 30% yield from VII (as the sole neutral before acidification.) Competing base catalyzed ester hydrolysis, leads to isochroman-1,4-dione (IX)[13] *after acidification*. This ketolactone m.p. 144-6° accounts for the balance of material and is the *sole* neutral product of various other reaction media studied.[10]



VII VIII IX

Application of cyclization conditions to the simple acyclic system derived from succinic acid was without success.

Recent description by Schöllkopf and Rieber[14] of the preparation and facile alkylation of silver salts of diazoketones attests to the nucleophilicity of the diazoketone anion and points to a likely mechanism for the cyclizations described here. Indication that proton removal is very rapid under conditions approximating those of cyclization is provided by a simple nmr experiment (Fig. 1). Dissolving a non-cyclizable diazoketone in CH_3OD

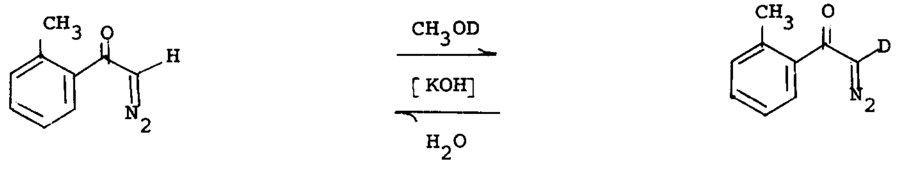


Fig. 1

and adding catalytic $KOH-D_2O$ completely and instantly removes the sharp azomethine singlet. Addition of H_2O has the immediate reverse effect. Proton exchange under cyclization conditions is compatible with a mechanism involving nucleophilic cyclization of an anionic species after the fashion of a typical aldol process. However, no data is in hand which rules out the more complex mechanism for interaction of base with diazoketones apparently favored by other workers.[15] It is noteworthy that exchange is equally fast and reversible in the two-phase system CCl_4 $-D_2O$[KOH], a convenient system for exposing this proton type.

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References

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5. Found for III : C, 64.14; H, 4.35; N, 14.85. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. The following data were also obtained: Strong M^+ at m/e 188; λ max. (CH_3OH) 336, 262, 238 nm. (ϵ 4500, 5300, 7300) ; ir max. ($CHCl_3$) 3500, 2100, 1680 cm^{-1} (ν OH, ν N=N, ν C=O); nmr ($CDCl_3$) in addition to 1H (exchangeable), a 3H sing. 1.8 δ, and 4H

mult. centered at 7. 5 δ.

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7. Found for VI : M^+ *m/e* 208; λmax. (CH_3OH) 291, 262(s) nm. (ε 6000, 3900); ir max. ($CHCl_3$) 3500, 2080, 1600 cm^{-1} (νOH, νN=N, ν C=O); nmr ($CDCl_3$) in addition to 1H (exchangeable) 4.8δ, a sing. methyl 1.15δ, a 2H quart., 2.45 δ, and a 10 H envelope 1.4-2.2δ.

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12. The m.p., mass, ir, and nmr spectra of this material were consistent with the literature and expectations.

12. This simple compound has not been adequately described in the literature[11]. The nmr spectrum ($CDCl_3$) contained a 2H sing. at 5.3δ, and a 4 H complex mult. at 8.2δ. The ketolactone IX exhibited ir max. ($CHCl_3$) 1700, 1740 cm^{-1}. (ν C=O) and 1600 cm^{-1} (νC=C). The mass spectrum had *m/e* 162 M^+ and *m/e* 104 base peak.

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