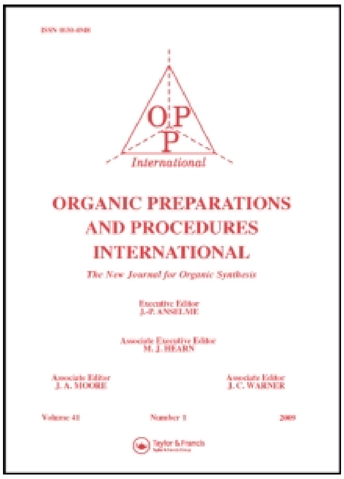

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SUBSTITUTED PYRAZINES
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THE CATALYTIC REDUCTION OF α-AZIDOKETONES

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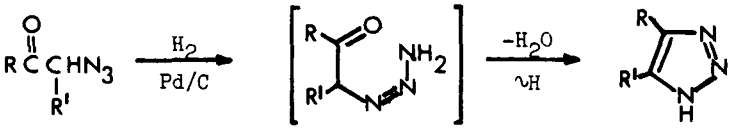
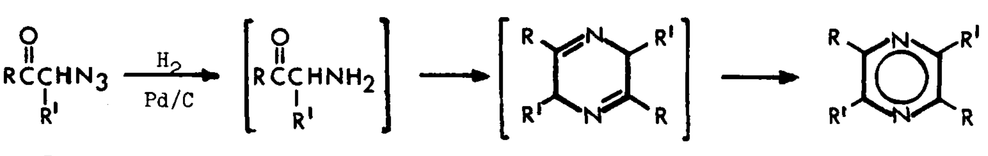
Dedicated to Professor C.G. Overberger on the Occasion of his 60th Birthday

As a part of another investigation, the reduction of α-azidoketones was carried out with the hope that the putative triazenes would cyclize to the 1,2,3-triazoles (V).[1] However, the catalytic reduction of phenacyl azide (Ia) over 5% Pd/C failed to give the desired triazole; instead 2,5-diphenylpyrazine (IVa) was obtained in nearly quantitative yield. In view of the fact that pyrazines exhibit biological activity and have been found to be important flavor constituents,[2] the conversion of α-azidoketones (I) to the corresponding pyrazines (IV) was investigated as a method for the synthesis of pyrazines and we now report our results.



I V



I II III IV

a) $R = C_6H_5$, $R' = H$ b) $R = \underline{p}\text{-}CH_3OC_6H_4$, $R' = H$

c) $R = (CH_3)_2CH$, $R' = H$ d) $R = (CH_3)_3C$, $R' = H$ e) $R = CH_3$, $R' = CH_3CH_2$

The reduction of p-methoxyphenacyl azide (Ib) gave the corresponding pyrazine IVb in better than 85% yield. The reaction presumably proceeds via initial reduction of I to the phenacylamines (II),[3] which then undergo rapid self-condensation to the dihydropyrazines (III).[4] Recently Sbiral and Stroh[5] reported the formation of 2,5-disubstituted pyrazines in 44-75% yields, from the reaction of α-azidoketones with triphenylphosphine. Earlier Birkofer[6] had described the catalytic reduction of benzoyl diazomethane to 2,5-diphenylpyrazine (IVa). Just as in our case, these reactions probably afford the dihydropyrazines III which undergo air oxidation to the pyrazines. The reduction of p-bromophenacyl azide apparently resulted in cleavage of the carbon-bromine bond and the hydrogen bromide thus generated may have caused reduction to proceed to the amino alcohol.

Reduction of α-azidopinacolone (Id) over 10% Pd/C gave nearly colorless crystals of a compound whose nmr spectrum indicated it to be the intermediate dihydropyrazine IIId [δ 3.90, s, 4H and 1.10, s, 18H].[7] Its slow air oxidation to 2,5-di-t-butylpyrazine [δ 8.40, s, 2H and 1.35, s, 18H], mp. 109-110°, lit.[7]mp. 110-110.5°, in 83% yield, could be monitored by nmr and was complete within a few days. Considerable and unexpected difficulties were encountered with the reduction of α-azidoacetone which under the same conditions was incomplete, even after several days as indicated by the presence of the azide band in the infrared spectrum; only trace amounts of the expected 2,5-dimethylpyrazine were formed. Perhaps poisoning of the catalyst by further condensation products[4] of intermediate dihydropyrazine may account for this failure. Reduction of 1-azido-3-methyl-2-butanone (Ic) gave 2,5-diisopropylpyrazine in 82% yield.

Attempts to extend this synthesis to the preparation of tetrasubstituted pyrazines met with varying success. While 2-azido-3-pentanone (Ie) gave a 61% yield of 2,5-dimethyl-3,6-diethylpyrazine (IVe), the reduction of desyl azide (I, R = R' = Ph) gave only the corresponding amino alcohol in nearly quantitative yield. It is possible that the self-condensation of the initially generated α-amino ketone is sufficiently slow (steric hindrance) under these conditions to allow the carbonyl group to be reduced. Birkofer[6] also obtained the same product from the reduction of azibenzil. The isolation of α-amino-α-phenyldesoxybenzoin from the reduction of α-azido-α-phenyldesoxybenzoin would seem to provide support for the steric argument.

EXPERIMENTAL

All mps are uncorrected. Infrared spectra were determined on a Perkin-Elmer Infracord and the nmr spectra were obtained using a Hitachi-Perkin-Elmer R24 spectrometer.

General Procedure for the Reduction of Phenacyl Azides.- A solution of the azide (1-2 g.) in ethanol (250 ml) was reduced over 5% Pd/C (0.30 g.) in a Parr apparatus in the presence of a few drops of acetic acid at ∿ 50 psi for 24 hrs. Removal of the catalyst followed by evaporation of the filtrate gave the pyrazine.[8]

2,5-Diphenyl- and 2,5-bis(*p*-anisyl)pyrazines (Ia and Ib) were obtained in 85-95% yields. Ia and Ib are known compounds.[5]

General Procedure for the Reduction of Aliphatic α-Azidoketones.- A solution of the α-azidoketone (1-3 g.) in ethanol (200 ml) was reduced over 10% Pd/C (0.050 g.) in a Parr apparatus in the presence of a few drops of acetic acid at ∿ 50 psi for 24 hrs. The catalyst was filtered and air was bubbled through the filtrate overnight. Removal of the solvent gave the pyrazine.

2,5-Di-*t*-butylpyrazine (IVd) was obtained as crystals while 2,5-diisopropylpyrazine (IVc)[9] and 2,5-dimethyl-3,6-diethylpyrazine (IVe)[10] were liquids, readily purified by passage through a short column (2-3 inches) of silica gel (chloroform). The nmr spectrum of IVc displayed the aromatic hydrogens at δ 8.30 (2H) while the methine hydrogens and the methyl groups of the isopropyl groups appeared at δ 3.03 (q, 2H) and 1.33 (d, 12H) respectively.

A picrate of IVc was obtained by standard procedure, mp. 99-99.5°.

Anal. Calcd. for $C_{16}H_{19}N_5O_7$: C, 48.85; H, 4.87; N, 17.81
Found: C, 48.73; H, 4.70; N, 17.87

The spectrum of IVe showed a methyl singlet at δ 2.40 (6H) and typical triplet-quartet pattern of the ethyl group at δ 1.20 (6H) and 2.66 (4H) respectively.

Anal. Calcd.for $C_{10}H_{16}N_2 \cdot 1/2\ H_2O$: C, 69.32; H, 9.89; N, 16.17
Found: C, 69.43; H, 9.92; N, 16.07

1,2-Diphenyl-2-aminoethanol.- A solution of 1.13 g. (4.76 mmoles) of α-azidodesoxybenzoin in 200 ml. of ethanol was hydrogenated over 5% Pd/C for three days at room temperature. After removal of the catalyst and evaporation of the filtrate, 1.13 g. (100%) of crude product was obtained. Two crystallizations from aqueous ethanol gave a pure sample, mp. 163.5-164.5°, lit.[6] mp. 165°.

A similar reduction of α-azido-α-phenyldesoxybenzoin in the presence of a few drops of acetic acid gave after removal of unreduced starting material, a 70% conversion to α-amino-α-phenyldesoxybenzoin, mp. 132.5-133.5°, lit.[11] mp. 132°.

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