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AN EFFICIENT SYNTHESIS OF 5-MEMBERED CYCLIC NITRONES FROM γ-NITRO KETONES

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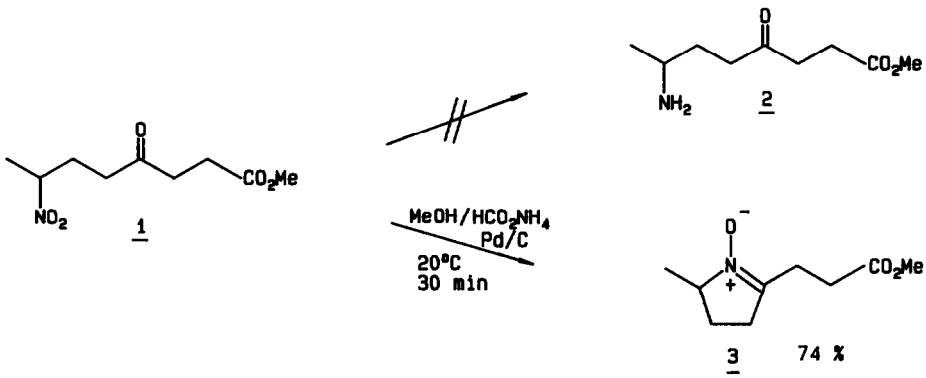
Summary: Substituted and functionalized pyrroline-1-oxides are obtained in high yield from γ-nitro ketones employing ammonium formiate / Pd on carbon as reducing system.

Recently we tried to prepare methyl 7-amino-4-oxooctanoate 2 by reduction of the nitro compound 1. However, employing the conditions described by Ram and Ehrenkaufer [1] with ammonium formiate as hydrogen transfer agent and palladium on carbon as catalyst we exclusively isolated the cyclic nitrone 3 in good yield.[2]



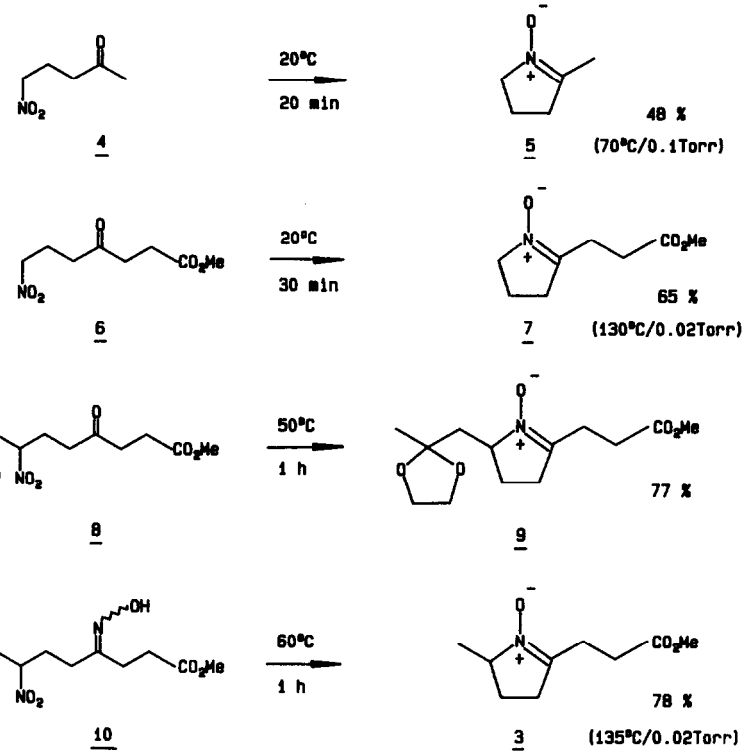
Apparently the nitro group of 1 is reduced to the hydroxylamine which undergoes fast intramolecular condensation to provide the nitrone.[3] This conversion is conventionially performed with zinc/NH_4Cl, but due to the presence of water the work up can be rather tedious and yields are often moderate.[4] A synthesis of pyrroline-1-oxides from γ-nitro ketones has also been reported employing H_2/Pd/C.[5] Under these conditions, however, overreduction to the corresponding cyclic hydroxylamine seems to be unavoidable.

The examples confined in Scheme I demonstrate that our method is highly efficient, regioselective, and compatible with several other functional groups.[6] The procedure is operationally very simple and employs filtrations in the work up process.[7] Yields are generally good with the exception of 5 which is very hygroscopic and not easily purified.

Whereas a dioxolane unit is not touched under the reaction conditions (see 8 → 9), the oxime 10 also gives nitrone 3. If C=C-bonds are present the method is not applicable: a substrate with an alkenyl group is transformed to a mixture of nitro compound and nitrone, both with completely saturated substituent. Since γ-nitro ketones are easily available from nitroalkanes and enones [8] in great variety, this method for synthesis of nitrones should simplify the access to many members of this important class of 1,3-dipoles.

Scheme I:
Reaction conditions:
HCO_2NH_4/Pd/C in CH_3OH

in brackets:
temperature of the
kugelrohroven
during distillation



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References and Notes: 1)a) S. Ram, R.E. Ehrenkaufer, Tetrahedron Lett. 25(1984) 3415; b) S. Ram, R.E. Ehrenkaufer, Synthesis 1986, 133; S. Ram, R.E. Ehrenkaufer, Synthesis 1988, 91. - 2) If the keto function in 1 is protected as dioxolane the anticipated transformation $-NO_2 \rightarrow -NH_2$ could be accomplished in high yield (R. Zschiesche, to be published). - 3) The intermolecular mode of this reaction, e.g. reduction of $Ph-NO_2$ in the presence of Ph-CHO, does not afford nitrones. - 4) W. Rundel in Methoden der Organischen Chemie (Houben-Weyl-Müller) vol. 10/4 p. 345, G. Thieme Verlag, Stuttgart 1968. - 5) M.J. Turner, L.A. Luckenbach, E.L. Turner, Synthetic Commun. 16(1986) 1377. - 6) All new compounds provide correct elemental analysis and appropriate spectra; all nitrones show the characteristic IR absorption for the C=N-bond at 1595-1620 cm^{-1}. - 7) General Procedure: A mixture of the γ-nitro ketone in dry methanol (2 ml/1 mmol), HCO_2NH_4 (4.6 equiv.) and Pd/C (0.01 equiv. Pd) are gently heated under an atmosphere of nitrogen until gas bubbles can be observed. The mixture is stirred at room temperature or at 50-60°C for 20-60 min as indicated in Scheme I. Removal of the catalyst by filtration through a pad of celite and evaporation give a solid which is in part soluble in CH_2Cl_2. Insoluble material (HCO_2NH_4) is discarded. Traces of formic acid are removed by subsequent filtration through Al_2O_3 (neutral, activity III, eluation with CH_2Cl_2/CH_3OH). Kugelrohrdistillation provides analytically pure nitrones. - 8) For synthesis of γ-nitro ketones 1 and 6 see: E.L. Grimm, R. Zschiesche, H.-U. Reissig, J. Org. Chem. 50(1985) 5543.

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