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SYNTHESIS OF α-AMIDOKETONES. AN APPLICATION OF THE MULTI-HETERO COPE REARRANGEMENT.

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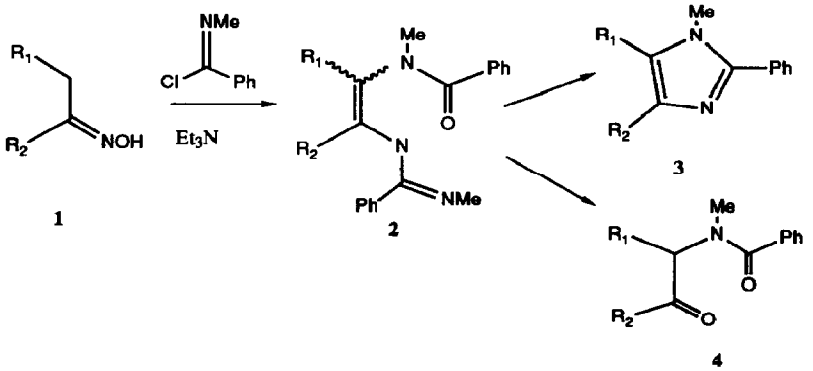
Abstract: Condensation of ketone derived nitrones with N-methylcarboximidoyl chloride affords after hydrolytic workup α-amidoketones. The results are interpreted in terms of the formation of an intermediate capable of undergoing a facile [3,3] sigmatropic rearrangement. Aldehyde derived nitrones form imides via a [3+2] cycloaddition reaction.

Our interest in the synthesis of α-amidoketones and the related β-amino alcohols, with potential application *inter alia* as enzyme inhibitors[1] or adrenergic agents[2] led us to examine the possibility of obtaining these compounds via a multi-hetero Cope process involving oxime derived imidates. Previously, we have shown[3] that these short lived intermediates, under specific conditions, undergo [3,3] sigmatropic rearrangements to afford amidino-amides **2** that could be smoothly converted to imidazoles **3** (Scheme I).

Scheme I

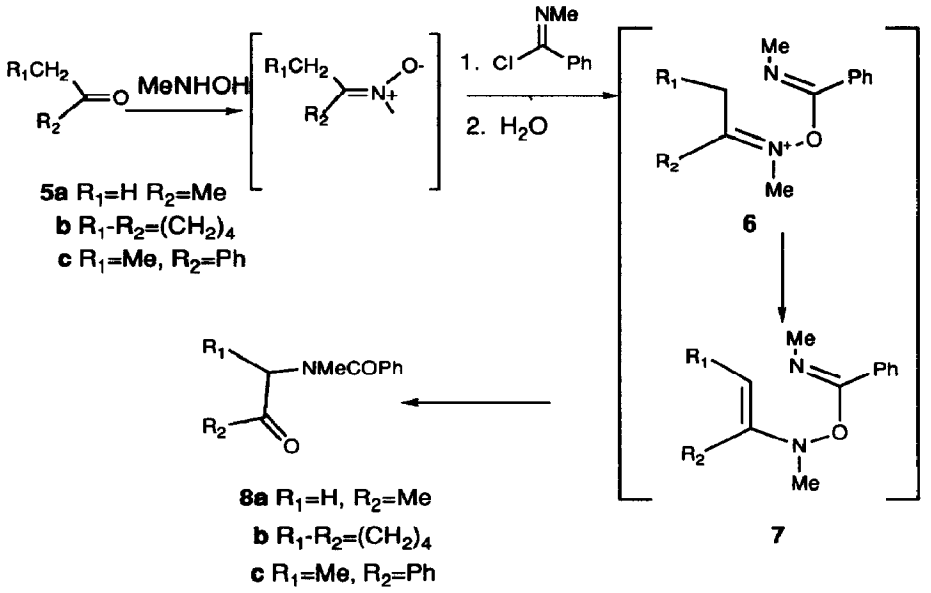


Unfortunately, hydrolytic interception of the amidines **2** to obtain alpha-amidoketones **4** was only possible in one example, in the cyclohexyl case (where R_1=R_2=$(CH_2)_4$). It occurred to us the multi-hetero [3,3] rearrangement could also be applied to an intermediate obtained from the reaction of the halo-imidate with ketone derived nitrones. The rearranged products in this instance however, would be α-amido imines instead of the amidines which would under the workup conditions transform to α-amidoketones.

Nitrones as building blocks have played a major role in the construction of complex molecules.[4] There is a large body of literature based on the cycloaddition of nitrones to various dipolarophiles[5] and their role in the synthesis of hydroxylamines[1a,b,d] and/or amines[1c] by condensation with various organometallic reagents has also been demonstrated. However, application of nitrones in [3.3] multi-hetero Cope rearrangement processes has been much less frequent. Cummins and Coates[6] showed that rearrangement of N-vinyl-O-acylhydroxylamines affords α-acyloxy ketones or aldehydes via a [3.3] process and Abramovitch[7] applied the reaction to the synthesis of α-benzamido acids. The process is also some what analogous to the preparation of α-hydroxy-ketones by House[8], except in that case the acyl-hydroxylamines undergoing the rearrangement were readily formed from oxime precursors.

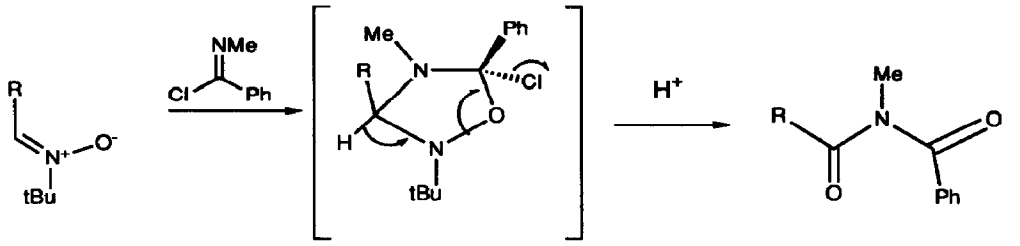
In our investigation several ketones were converted to their respective nitrones, according to the procedure of Exner[9] or Coates[6] (ketone,MeNHOH,solvent,) which were then treated with N-methylbenzene-carboximidoyl chloride (Scheme II). After hydrolytic workup the derived N-methylbenzamidoketones **8a,b,c** were obtained in reasonable yields (**8a**, 60% ,**8b** 56% **8c**, 71%).

Scheme II



Surprisingly, and in contrast to the results found by Coates[6], application of the transformation to aldehyde derived nitrones took a completely different course (Scheme III). Treatment of nitrones **9a** or **b** with the chloroimidate under identical conditions resulted in the formation of imides **11 a,b**. We interpret this result via the formation of intermediate **10**, a product of [3+2] dipolar cycloaddition of the reactants. Fragmentation as shown, a process not available to the secondary nitrones, affords an intermediate imine which then falls apart under the acidic conditions.

Scheme III



9 a, R=Et
b, =Cyclohexyl

10

11a,b

In summary, we have presented a novel method for the preparation of α-amidoketones in racemic form. The method makes use of the facile [3,3] sigmatropic rearrangement of imidate adducts of ketone derived nitrones. Extension of the method to chiral substrates is in progress and will be reported in the future. It is also noted that nitrones of carboxaldehydes undergo a different reaction, via a 3+2 cycloaddition affording imides.

General Procedure for the Preparation of N-methyl benzamide ketones and imides: The procedure for the preparation of N-methylbenzamide acetone (**8a**) is representative. A solution of the N-2-propylidenemethanamine N-oxide[9] (1.24 g, 10 mmol) in 30 ml anhydrous THF was cooled to 0° C and stirred under nitrogen as 3.03 g, (30 mmol) triethylamine was introduced via syringe. A solution of the N-methylbenzene carboximidoyl chloride[3] (2.02 g, 13 mmol) in 5ml THF was added dropwise. The resulting suspension of precipitate was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched into a solution of acetate buffer and stirred for 30 min at 25° C. The product was extracted into dichloromethane (30 ml x 3), the organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with 5:1 hexane-ethyl acetate as solvent and afforded colorless oil 1.15 g of **8a**.

All new compounds were fully characterized by spectroscopic means and elemental analysis. Spectral data for **8a** (59.8 %): FT-IR (KBr) 3060, 2924, 1730, 1636, 1602, 1578, 1397, 722, 702 cm-1; ^{1}H NMR ($CDCL_3$) δ 7.25-7.46, (m, 5H), 4.30 (s, 2H), 2.96 (s, 3H), 2.20 (s, 3H). ; ^{13}C NMR δ ($CDCL_3$) 202.8, 171.9, 135.4, 129.8, 128.3, 127.1, 57.3, 38.8, 27.3.; mass spectra 191 (m/z); Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09, H, 6.85, N, 7.32. Found: C, 69.25, H, 6.90, N, 7.34. **8b** (55.8%): FT-IR (KBr) 3423, 2949, 2871, 1719, 1620, 1600, 1577, 1369, 1071, 793, 727, 702.cm-1; ^{1}H NMR ($CDCL_3$) δ7.17-7.43 (m, 5H), 5.2 (dd, 1H, J=7.5 Hz), 2.7 (s, 3H), 1.4-2.5 (m, 8H).; ^{13}C NMR ($CDCL_3$) δ206.2, 172.3, 136.2, 129.5, 128.3, 127.0, 61.8, 41.5, 34.2, 30.7, 26.6, 24.6.; mass spectra 231(m/z).; Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70, H, 7.41, N, 6.06. Found: C, 72.41, H, 7.33, H, 6.02. **8c** (71%): FT-IR 3060, 2983, 2936, 1690, 1628, 1598, 1577, 1235, 1219, 1074, 789, 699.cm-1; ^{1}H NMR ($CDCL_3$) δ 7.22-8.09 (m, 10H), 6.22 (q, 1H, J=7.5 Hz), 2.71 (s, 3H), 1.48 (d, 3H, J=7.5 Hz).; ^{13}C NMR ($CDCL_3$) δ 199.2, 171.1, 135.8, 135.3, 133.5, 128.7, 128.4, 128.3, 126.6, 53.5, 32.8, 12.8.; mass spectra 267 (m/z); Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38, H, 6.41, N, 5.24, Found: C, 75.86, H, 6.27, N.5.18. **11a** (71.1 %): FT-IR: 3062.5, 2964.4, 2933.9, 2875.4, 1687.1, 1661.8, 1600.5, 1580.9, 1320.7, 1053.9, 799.4, 722.9, 699.1.cm-1; ^{1}H NMR ($CDCL_3$) δ 7.36-7.56 (m, 5H), 3.13 (s, 3H), 2.83 (t, 2H, J=7.5 Hz), 2.53 (m, 2H), 0.84 (t, 3H, J=7.5 Hz).; ^{13}C NMR ($CDCL_3$) δ 176.4, 174.0, 135.4, 132.1, 128.6,

128.3, 39.5, 34.1, 18.7, 13.6.; mass spectra 205 (m/z); Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22, H, 7.37, N, 6.82. Found: C, 69.87, H, 7.20, N, 6.85. **11b** (70.7 %): FT-IR: 2934.6, 2923.7, 2851.9, 1698.6, 1677.6, 1324.4, 1063.9, 796.4, 723.0, 693.4 cm^{-1}; ^1H NMR ($CDCL_3$) δ 7.25-7.61 (m, 5H), 3.19 (s, 3H), 2.76 (m, 1H), 1.07-1.85 (m, 10H).; ^{13}C NMR ($CDCL_3$) δ 180.5, 174.3, 135.5, 132.3, 128.7, 128.6, 45.1, 34.4, 29.7, 25.7, 25.6.; mass spectra 245 (m/z);. Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44, H, 7.81, N, 5.71. Found: C, 73.81, H, 7.71, N, 5.80.

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