Tetrahedron Letters,Vol.24,No.6,pp 593-596,1983 0040-4039/83/060593-04$03.00/0
Printed in Great Britain

A NOVEL SYNTHESIS OF N-SUBSTITUTED α-AMINO KETONES

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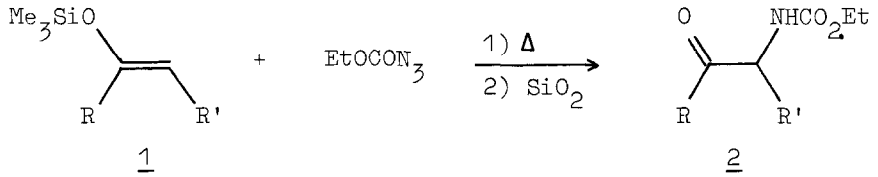
SUMMARY. The thermolysis of ethyl azidoformate in enol trimethylsilyl ethers, followed by silica gel treatment, offers a new route to N-ethoxycarbonyl α-amino ketones.

Insertion and addition reactions of ethoxycarbonylnitrene (EtOCON) are usually not very selective. In particular, ketones[1] and ketone ethylene acetals[2] are known to give reaction mixtures containing variable amounts of 2-functionalized products, according to the reaction conditions. α-Amino ketones are important intermediates in preparative organic chemistry[3] and they are biologically significant substances.[4] Recently we found N-ethoxycarbonyl α-amino ketones (together with similar amounts of substituted hydrazines) in the reaction between enamines and 4-nitrobenzenesulphonyloxyurethane without Et_3N.[5]

We report here that N-protected α-amino ketones are obtained in a single step and in good yields upon thermolysis of ethyl azidoformate ($EtOCON_3$) in enol trimethylsilyl ethers. We tested enol ethers derived from alkyl, cycloalkyl, and alkyl aryl ketones, namely (1-tert-butyl)ethenyl trimethylsilyl ether (1a),[6] (1-propyl)-1-butenyl trimethylsilyl ether (1b),[7] 1-cyclohexenyl trimethylsilyl ether (1c),[8] (4-tert-butyl)-1-cyclohexenyl trimethylsilyl ether (1d),[9] 1-cyclopentenyl trimethylsilyl ether (1f),[8] and 1-phenylethenyl trimethylsilyl ether (1e).[8]

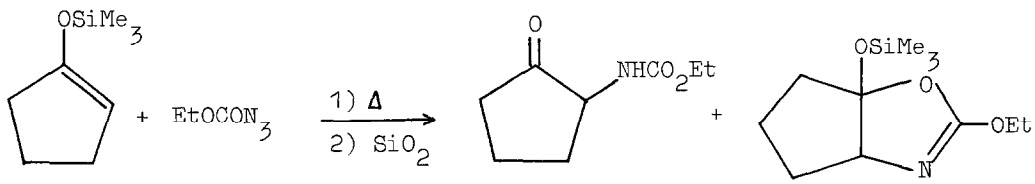
The thermolyses were carried out at 110 °C for 15 h in sealed tubes containing a mixture of $EtOCON_3$ and substrate (volume ratio 1:10). After distillation of the excess of substrate, the crude reaction mixtures were chromatographed on silica gel[10] and N-ethoxycarbonyl α-amino ketones were collected as pure products (2a: 65%, 2b: 56%, 2c: 49%, 2d: 36%, 2e: 35%, 2f: 40% not optimized isolated yields). Only in the case of 1f, an additional product, 3-ethoxy-1-trimethylsiloxy-2-oxa-4-azabicyclo[3.3.0]oct-3-ene (3) was isolated in 18% yield; it probably arises from 1,3-dipolar addition of EtOCON to the good dipolarophilic double bond.[11]



1 2

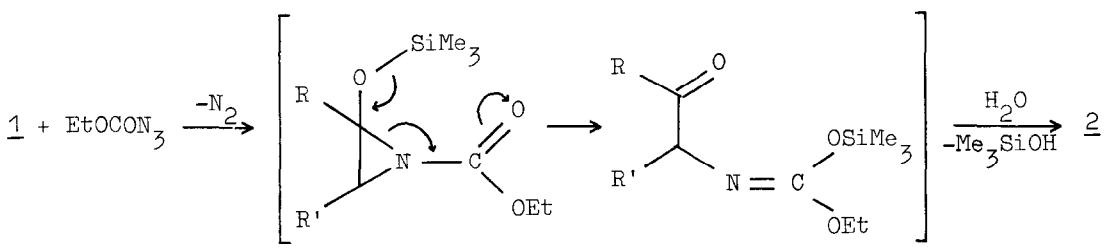
a) R=tBu R'=H c) R....R'=-$(CH_2)_4$- e) R=Ph R'=H

b) R=Pr R'=Et d) R....R'=-$(CH_2)_2$-CHtBu-CH_2-



1f 2f 3

We assume EtOCON to be the reactive intermediate in the formation of N-substituted α-amino ketones, as $EtOCON_3$ and enol trimethylsilyl ethers do not react either at room temperature for several days or at 60 °C for several hours; a complex reaction mixture was found after several hours at 69 °C, but α-amino ketones were minor components. In one case we have been able to detect (by GC-MS) the product of nitrene addition to the enol ether 1b, but it was never possible to isolate it. We tentatively propose the mechanism depicted below:



A similar reaction sequence has been postulated for ring cleavage of a cyclopropane 1,2-disubstituted with an acetyl group and a trimethylsiloxy group (silatropic retro-aldol reaction).[12]

As further support to our assumption, recently we found another example of clean EtOCON addition to electron-rich olefins such as vinyl chlorides[13] and other scattered examples have been reported in the literature.[14]

On the other hand enol trimethylsilyl ethers are known to react with arenesulphonyl azide[15] and with carbenes;[16] in both cases the primary reaction products undergo synthetic useful rearrangements.

Compounds 2c[1] and 2f[5] have been previously described. Physical (boiling points are uncorrected and determined by microtube distillation) and spectral data (IR: CCl_4, cm^{-1}; ^1H NMR: 90 MHz, $CDCl_3$, δ vs. int. TMS; ^{13}C NMR: 20 MHz, $CDCl_3$, δ vs. int. TMS; MS: 70 eV, m/z) for the other products are given below:

2a: bp 120-122 °C(6 mm); IR:3425(NH), 1725(COO), 1705(CO); ^1H NMR: 1.2(s, 9H), 1.25(t, 3H), 4.15(q, 2H), 4.25(d, J=5 Hz, 2H), 5.65(br, 1H); ^{13}C NMR: 14.6 (q), 26.4(q), 42.7(s), 46.2(t), 61.2(t), 151.6(s), 210.5(s); MS: 187(M^+, 1%), 142, 130, 103, 102(base), 85, 74, 57.

2b: bp 98-99°C(1mm); IR($CHCl_3$) 3425(NH), 1720(COO), 1705(CO); ^1H NMR 0.9(t, 6H), 1.25(t, 3H), 1.6(m, 4H), 2.5(t, 2H), 4.05(q, 2H), 4.3(m, 1H), 6.0(d br, 1H); ^{13}C NMR: 8.9(q), 13.5(q), 14.4(q), 16.9(t), 24.6(t), 41.6(t), 60.6(d), 60.9(t), 156.3(s), 209.1(s); MS: 201(M^+, < 1%), 130(base), 102, 86, 71, 58.

2d: bp 146-148°C(4.5 mm); IR: 3420(NH), 1710(COO+CO); ^1H NMR: 0.9(s, 9H), 1.25 (t, 3H), 1.0-2.8(m, 7H), 3.8-4.5(m, 1H); 4.1(q, 2H), 5.7(br, 1H); ^{13}C NMR: 14.5(q), 27.6(q), 28.8(t), 32.4(s), 37.1(t), 40.0(t), 45.9(d), 58.8(d), 60.9 (t), 156.1(s), 207.7(s); MS: 241(M^+, 8%), 185, 184, 183, 156, 138, 137, 128, 111, 110, 109, 95, 90, 84, 83, 82, 81, 80, 69, 67, 62, 57(base), 56, 55, 43.

2e: mp 120-122°C; IR: 3425(NH), 1725(COO), 1690(CO); ^1H NMR: 1.25(t, 3H), 4.15 (q, 2H), 4.7(d, J=5 Hz, 2H), 5.8(br, 1H), 7.4(m, 3H), 8.0(m, 2H); ^{13}C NMR: 14.6(q), 47.9(t), 61.3(t), 127.9(d), 128.9(d), 134.1(d), 137.6(s), 156.6(s), 194.3(s); MS: 207(M^+, 5%), 179, 162, 150, 118, 106, 105(base), 102, 77, 51.

3: bp 100-103°C(4.5 mm); IR: 1655(C=N); ^1H NMR: 0.2(s, 9H), 1.4(t, 3H), 1.6-2.2 (m, 6H), 4.3(q, 2H), 4.6(m, 1H); ^{13}C NMR: 1.8(q), 14.4(q), 23.3(t), 34.6(t), 41.8(t), 66.7(t), 90.8(d), 107.6(s), 162.8(s): only one isomer, most probably the cis one; MS: 243(M^+, 59%), 228, 215, 214(base), 186, 170, 157, 100, 75, 74, 73, 71, 59, 55, 45.

Acknowledgment. This work has been financially supported by National Research Council (CNR), Rome - Progetto Finalizzato "Chimica Fine e Secondaria".

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7. Synthesized according to the House method (see ref. 8): bp 70-72°C(20 mm); IR (CCl_4) 1670 cm^{-1}; ^1H NMR (CCl_4) δ 0.15(s, 9H), 0.7-2.3(m, 12H), 4.35(t, 0.5H, (Z)-isomer), 4.5(t, 0.5H, (E)-isomer); MS m/z 186 (M^+), 171, 75, 73.
8. House, H. O.; Czuba, L. J.; Gall, M.; Olmsted, H. D. J. Org. Chem. 1969, 34, 2324.
9. Prepared by the House method (see ref. 8): bp 133-134°C(20 mm); IR (CCl_4) 1670 cm^{-1}; ^1H NMR (CCl_4) δ 0.15(s, 9H), 0.9(s, 9H), 0.9-2.5(m, 7H), 4.7(m, 1H); MS m/z 226(M^+, 22%), 211, 128(base), 75, 73, 57.
10. The reaction mixtures coming from 1a and 1e dissolved in $CHCl_3$ have been treated at room temperature with silica gel (containing 10% of water) for 20 hrs, in order to have 2a and 2e as the main components. However, in the latter case also phenacyl alcohol ($C_6H_5COCH_2OH$) was produced.
11. Attempts to transform 3 into 2f were unsuccessful under the different conditions already used for cleavage of: a) acetals, i) SiO_2, 10% oxalic acid, CH_2Cl_2, ii) SiO_2, 15% H_2SO_4 (Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. Synthesis 1978, 63); b) silyl ethers, KF on Celite (1:1), 2M in CH_3CN (Manis, P. A.; Rathke, M. W. J. Org. Chem. 1981, 46, 5348); c) oxazolines, i) 4.5N HCl, 40-50°C, ii) 4.5N HCl, reflux (Meyers, A. I.; Knaus, G.; Kamata, K. J. Am. Chem. Soc. 1974, 96, 268).
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(Received in UK 2 December 1982)