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Note

Silylated N,O-ketals from the reaction of ketones with N-trimethylsilylimidazole

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Enol silyl ethers have found important roles in the derivatization of ketone functional groups for analysis by gas chromatography (GC) and in organic synthesis [1–8]. N-Trimethylsilylimidazole is one of the many silylating reagents available for the silylation of preformed enolate anions or enol derivatives [2,7,8]. In the course of the gas chromatographic–mass spectrometric (GC–MS) analysis of amino sugars derivatized with N-trimethylsilylimidazole [9], samples contaminated with acetone produced an earlier eluting substance in addition to the per-O-silylated imine anomers. Identification of this substance led to the elucidation of a novel side-reaction encountered during routine silylations of ketones with N-trimethylsilylimidazole. In addition to the expected enol silyl ether products, silylated N,O-ketals were identified (Fig. 1). The work suggests that silylating reagents with nucleophilic leaving groups may yield unwanted side-reactions during the protection of ketones as enol silyl ethers.

EXPERIMENTAL

Materials and instrumentation

N-Trimethylsilylimidazole was obtained from Pierce (Rockford, IL, U.S.A.). Acetone, methyl ethyl ketone, phenyl-2-propanone, propiohenone, and [$^2H_6$]-

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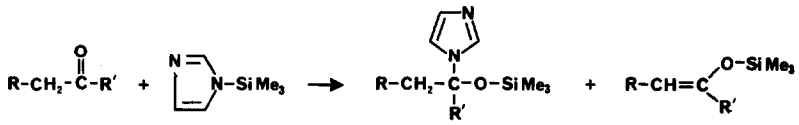

R	R′
H	CH_3
CH_3	CH_3
$-CH_2CH_2CH_2CH_2-$	
C_6H_5	CH_3
$C_6H_5CH_2$	CH_3

Fig. 1. Side-reaction encountered during routine silylations of ketones with N-trimethylsilylimidazole producing silylated N,O-ketals.

acetone were obtained in the highest purity available from Aldrich (Milwaukee, WI, U.S.A.).

GC–MS was carried out on an Extrel Simulscan mass spectrometer interfaced with a Carlo Erba Model 4130 capillary gas chromatograph equipped with a 15 m × 0.25 mm I.D. Durabond 1701 column with helium as carrier gas. The column was heated at a rate of 15 °C/min from a starting temperature of 50 °C to a final temperature of 250 °C. Electron-ionization (EI) mass spectra were recorded at 70 eV and positive-ion chemical-ionization (CI) mass spectra were obtained with methane as reagent gas at approximately 1 Torr source pressure and an ionizing voltage of 300 eV. Product ratios were determined by integration of peak areas of reconstructed total ion chromatograms generated by an Extrel 1000 data system during GC–EI-MS runs.

^1H and ^{13}C NMR spectra were recorded on a General Electric QE-300 magnetic resonance spectrometer with tetramethylsilane as internal standard.

General silylation procedure

A mixture of N-trimethylsilylimidazole (6.0 g, 43 mmol) and ketone (43 mmol) was heated to reflux. Disappearance of N-trimethylsilylimidazole was monitored by GC and was complete at 70 h. Pure silylated N,O-ketal was obtained by vacuum distillation.

N-(2-Trimethylsilyloxy-2-propyl)imidazole, the N,O-ketal of acetone, was purified in 81% yield: b.p. 61 °C at 0.4 Torr; ^1H NMR (C^2HCl_3), 0.03 ppm (9 H, s, $SiCH_3$), 1.68 (6 H, s, CCH_3), 6.94, 6.99 (2 H, m, C-4 and C-5 CH imidazole), 7.79 (1 H, s, C-2 CH imidazole); ^{13}C NMR, off-resonance decoupled, 0.1 ppm (q, $SiCH_3$), 32 (q, CCH_3), 86 (s, CCH_3), 117 (d, C-5 imidazole), 130 (d, C-4 imidazole), 135 (d, C-2 imidazole); EI mass spectrum, *m/z* (relative intensity), 198 (0.5%), 183 ($M-CH_3$, 4.8%), 140 ($M-C_3H_6O$, 13.1%), 131 (M–imidazolyl, 63.0%); CI mass spectrum (CH_4), *m/z* 199 (MH^+).

TABLE I

RELATIVE PROPORTIONS OF N,O-KETAL AND ENOL SILYL ETHER PRODUCTS FORMED FROM THE REACTION OF N-TRIMETHYLSILYLIMIDAZOLE WITH VARIOUS KETONES

Product ratios were determined by GC–MS from integrated total iron current chromatograms.

Ketone	N,O-Ketal/enol ether ratio
Acetone	> 100
Methylethylketone	> 100
Cyclohexanone	2.7
Propiophenone	0.02
Phenyl-2-propanone	< 0.01

RESULTS

The expected product from the reaction of acetone and trimethylsilylating agents such as N-trimethylsilylimidazole is the enol ether, 2-trimethylsilyloxypropene. However, based on NMR and MS evidence, the structure of the major product formed from the reaction of acetone with N-trimethylsilylimidazole was deduced to be N-(2-trimethylsilyloxy-2-propyl)imidazole. A small degree of decomposition, indicated by observation of a singlet for acetone (2.1 ppm) in the ^{1}H NMR spectrum, was detected after storage at room temperature for two years. Additional evidence for the N,O-ketal structure was gained by reaction of hexadeutero acetone with N-trimethylsilylimidazole to yield the product containing six deuterium atoms.

Since the expected enol silyl ether was not detected, the reactivity of N-trimethylsilylimidazole with some simple ketones was evaluated (Table I). Condensation of methyl ethyl ketone with N-trimethylsilylimidazole produced the corresponding silylated N,O-ketal, N-(2-trimethylsilyloxy-2-butyl)imidazole. Cyclohexanone, on the other hand, reacted to form a mixture of its enol silyl ether, 1-(trimethylsilyloxy)cyclohexane, and N-(1-trimethylsilyloxy-1-cyclohexyl)imidazole with the N,O-ketal as the predominant product (Fig. 2). Phenyl-2-propanone, a ketone which exists in an enol tautomer stabilized by conjugation, yielded its enol silyl ether along with a small amount of N,O-ketal when reacted with N-trimethylsilylimidazole.

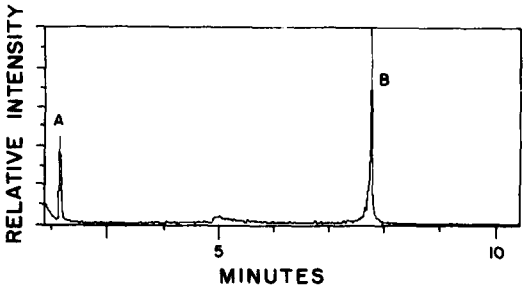

Fig. 2. Total ion current mass chromatogram of the products of the reaction of N-trimethylsilylimidazole with cyclohexanone. Peaks: A corresponds to the enol silyl ether and B to the N,O-ketal derivative.

DISCUSSION

An established method for the protection of ketones for chromatography or synthesis purposes is conversion to enol silyl ethers [10]. In a study of enol silyl ether formation of steroids containing hindered ketone moieties, Sakauchi and Horning [4] found that N-trimethylsilylimidazole as silylating reagent produced multiple products some of which were not identified. In the present study, products other than enol silyl ethers were identified from the reaction of N-trimethylsilylimidazole with ketones. The identified N,O-ketals are a result of the addition of both the silyl portion of the reagent and the nucleophilic leaving group, imidazole.

While apparent 1,2-addition reactions have not been described previously for N-trimethylsilylimidazole reacting at an electrophilic carbonyl group, such reactions are known to occur with cyanotrimethylsilane. Silylated cyanohydrins are formed in the reaction of cyanotrimethylsilane with selected carbonyl compounds through the action of cyanide as a nucleophile [11,12].

In the series of ketones studied, with the exception of propiophenone, the greater the proportion of keto tautomer in the pure state [13], the greater was the tendency to form an N,O-ketal derivative. Propiophenone, which exists only to a small extent as an enol [13], reacts to form an enol silyl ether almost exclusively. Steric interactions arising from the phenyl group hindering 1,2-addition of imidazole may provide an explanation of the anomalous behavior of propiophenone.

The results of the work suggest that the choice of N-trimethylsilylimidazole as a reagent for enol ether formation may lead to undesired products, especially in biochemical or biomedical applications. On the other hand, the relative ease with which the silylated N,O-ketals were formed from certain ketones and the stability under distillation conditions and long-term storage suggest that the reaction may be developed as a new derivatization method for ketone moieties which exist primarily in the keto tautomeric form.

REFERENCES

1 E.W. Colvin, Silicon in Organic Synthesis, Butterworths, London, 1981.
2 J. Hooz and J. Oudenes, Tetrahedron Lett., 24 (1983) 5695–5698.
3 G. Stork and P.F. Hudrlik, J. Am. Chem. Soc., 90 (1968) 4462–4464.
4 N. Sakauchi and E.C. Horning, Anal. Lett., 4 (1971) 41–52.
5 H.O. House, L.J. Czuba, M. Gall and H.D. Olmstead, J. Org. Chem., 34 (1969) 2324–2336.
6 E. Nakamura, T. Murofushi, M. Shimizu and I. Kuwajima, J. Am. Chem. Soc., 98 (1976) 2346–2348.
7 E.M. Chambaz, G. Maume, B. Maume and E.C. Horning, Anal. Lett., 1 (1968) 749–761.
8 E.M. Chambaz, G. Defaye and C. Madani, Anal. Chem., 45 (1973) 1090–1098.
9 P.A. Andrews, P.S. Callery, F.E. Chou, M.E. May and N.R. Bachur, Anal. Biochem., 126 (1982) 258–267.
10 C.F. Poole, in K. Blau and G.S. King (Editors), Handbook of Derivatives for Chromatography, Heyden, London, 1978, pp. 160–163.
11 D.A. Evans, J.M. Hoffman and L.K. Truesdale, J. Am. Chem. Soc., 95 (1973) 5822–5823.
12 K. Utimoto, Y. Wakabayashi, T. Horiie, M. Inoue, Y. Shishiyama, M. Obayashi and H. Nozaki, Tetrahedron, 39 (1983) 967–973.
13 A. Gero, J. Org. Chem., 19 (1954) 1960–1970.