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THE MANNICH REACTION OF CARBONYL COMPOUNDS VIA SILYL ENOL ETHERS BY A COMBINATION OF CHLOROIODOMETHANE AND N,N,N',N'-TETRAMETHYLDIAMINOMETHANE

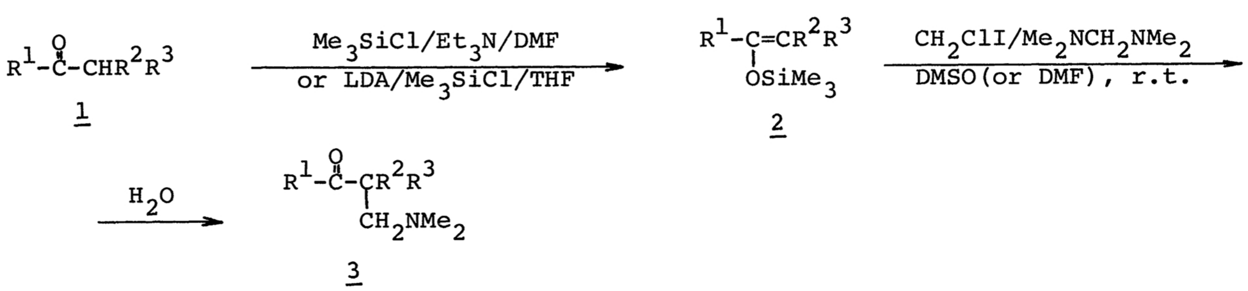
Sotaro MIYANO, Hiroshi HOKARI, Akira MORI, and Harukichi HASHIMOTO
Department of Applied Chemistry, Faculty of Engineering,
Tohoku University, Aramaki-Aoba, Sendai 980

The Mannich dimethylaminomethylation of carbonyl compounds is conveniently carried out via trimethylsilyl enol ethers by a combination of chloroiodomethane and N,N,N',N'-tetramethyldiaminomethane in DMSO or DMF as the solvent at ambient temperature.

In recent years considerable effort has been devoted to the syntheses$^{1)}$ of α-methylene carbonyl compounds via the "modern" Mannich reaction which utilizes preformed N,N-dimethylmethyleneiminium salts, $(Me_2\overset{+}{N}=CH_2)\overset{-}{X}$,$^{2)}$ particularly, the Eschenmoser's salt where X is iodine.$^{3)}$ From the preparative point of view, however, the time-consuming preparation and the handling of these moisture-sensitive iminium salts are somewhat troublesome.

We report here a convenient method for the Mannich dimethylaminomethylation of carbonyl compounds (1) via trimethylsilyl enol ethers (2) by a combination of chloroiodomethane$^{4)}$ and N,N,N',N'-tetramethyldiaminomethane (TMDM) (Scheme 1).

The reaction was simply carried out by adding TMDM to a DMSO (or DMF) solution of chloroiodomethane and 2, followed by stirring the mixture under nitrogen at ambient temperature (Table). After the usual work-up, distillation gave the corresponding Mannich base (3) in fair to good yields, where R^1 and $R^2 \neq$ H. For example, the reaction of 3-pentanone silyl enol ether gave the corresponding amino ketone, $CH_3-CH_2-CO-CH(CH_3)-CH_2N(CH_3)_2$ (3a), in as high as 93% yield as determined by GLC. The amino ketone was isolated in a 68% yield by distillation; considering thermal instability of the product, only middle cut boiling at 42 - 43 °C/3 mmHg was collected without so much effort to improve the isolation yield.$^{5)}$ DMF was also useful as the solvent affording similar results, while the GLC yield of 3a was reduced to 46% when CH_2I_2 was used as the methylene source.$^{6)}$



$$R^1-\overset{O}{\overset{\|}{C}}-CHR^2R^3 \xrightarrow[\text{or LDA/Me}_3\text{SiCl/THF}]{\text{Me}_3\text{SiCl/Et}_3\text{N/DMF}} R^1-\underset{OSiMe_3}{\underset{|}{C}}=CR^2R^3 \xrightarrow[\text{DMSO(or DMF), r.t.}]{\text{CH}_2\text{ClI/Me}_2\text{NCH}_2\text{NMe}_2} \xrightarrow{H_2O} R^1-\overset{O}{\overset{\|}{C}}-\underset{CH_2NMe_2}{\underset{|}{C}}R^2R^3$$

Scheme 1.

Table. Reaction of Some Trimethylsilyl Enol Ethers with CH_2ClI/TMDM[a)]

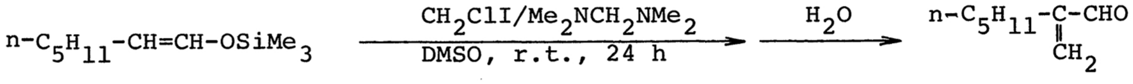
2				$[CH_2ClI]$	[TMDM]	Time	3
R^1	R^2	R^3	/mmol	/mmol	/mmol	/h	Yield(%)[b)]
Et	Me	H	15	30	32	3	68(93)
$-(CH_2)_4-$		H	18	31	31	3	67
Ph	Me	H	17	29	31	24	71
Me	Ph	H	20	31	33	3	54
H	$-(CH_2)_4-$		19	30	32	24	71
Ph	H	H	16	24	27	3	(22)[c)]
H	$n-C_5H_{11}$	H	18	28	29	3	18
EtO	$n-C_4H_9$	H	20	32	33	3	46(66)

a) Conditions: DMSO (20 ml); ambient temperature; under nitrogen.

b) Yields are referred to the isolated products of analytical purity, and based on 2. In parentheses are given the yields determined by GLC or NMR.

c) $Ph-CO-CH(CH_2NMe_2)_2$ was isolated in 58% yield, mp 57 - 58 °C.

The reaction of acetophenone silyl enol ether was accompanied by the formation of significant amount of the diamino ketone (Table, footnote c) even under the reaction conditions where substantial part of the substrate silyl ether was remained unchanged. Heptanal silyl enol ether gave a poor result leaving a resinous material after distillation, but it is noteworthy that after hydrolytic work-up of the reaction mixture (24 h reaction), α-methyleneheptanal was detected in a 42% yield: this may be of some utility for the synthesis of α-methylenealdehydes (Scheme 2).



$$n-C_5H_{11}-CH=CH-OSiMe_3 \xrightarrow[DMSO,\ r.t.,\ 24\ h]{CH_2ClI/Me_2NCH_2NMe_2} \xrightarrow{H_2O} n-C_5H_{11}-\underset{\underset{CH_2}{\|}}{C}-CHO$$

Scheme 2.

References and Notes

1. For example, J. A. Marshall and G. A. Flynn, J. Org. Chem., 44, 1391 (1979).
2. a) S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, J. Am. Chem. Soc., 98, 6715 (1976); b) J. L. Roberts, P. S. Borromeo, and C. D. Poulter, Tetrahedron Lett., 1977, 1621; c) N. Holy, R. Fowler, E. Burnett, and R. Lorenz, Tetrahedron, 15, 613 (1979).
3. a) J. Schreiber, H. Maag, N. Hashimoto, and A. Eschenmoser, Angew. Chem., 83, 355 (1971); b) T. A. Bryson, G. H. Bonitz, C. J. Reichel, and R. E. Dardis, J. Org. Chem., 45, 524 (1980), and references cited therein.
4. S. Miyano and H. Hashimoto, Bull. Chem. Soc. Jpn., 44, 2864 (1971).
5. 3a: Calcd(Found); C, 67.29(67.08); H, 11.89(11.97); N, 9.88(9.78)%. IR(neat); 2780 (νNCH_3), 1710 (νCO), 1460 cm^{-1} (νCH_3).
6. It has been known that TMDM slowly reacts with CH_2Br_2 to afford $(Me_2\overset{+}{N}=CH_2)\overset{-}{Br}$; H. Böhme, M. Hilp, L. Koch, and E. Ritter, Chem. Ber., 104, 2018 (1971).

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