Carbon-Carbon Bond Formation by the Use of Chloroiodomethane as a C_1 Unit. III.[1] A Convenient Synthesis of the Mannich Base from Enol Silyl Ether by a Combination of Chloroiodomethane and *N,N,N′,N′*-Tetramethylmethanediamine[2]

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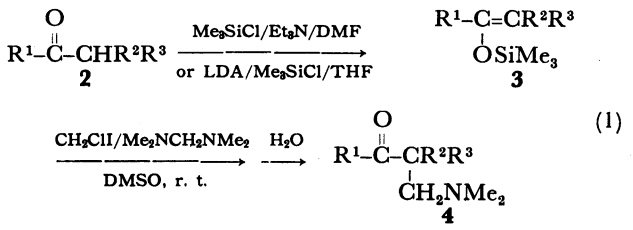
The Mannich dimethylaminomethylation of carbonyl compounds is conveniently carried out *via* enol trimethylsilyl ethers by a combination of chloroiodomethane (CH_2ClI) and *N,N,N′,N′*-tetramethylmethanediamine (TMMD) in DMSO as the solvent at ambient temperature. The mechanism of the transformation is discussed on the basis of product analysis and ^1H NMR spectral studies. The reagent system CH_2ClI/TMMD also provides a convenient route to the Eschenmoser's salt ($Me_2\overset{+}{N}=CH_2,\bar{I}$).

One of the most general entrances into the α-methylene carbonyl system[3] is by deamination of α-aminomethyl carbonyl compounds, *i.e.* the Mannich base.[4] In this context, much attention has been centered in the last few years on the Mannich reaction of carbonyl substrates *via* enolates by means of preformed *N,N*-dimethylmethyleneiminium reagents, ($Me_2\overset{+}{N}=CH_2$, $\bar{X}$) (**1**),[5] among which the Eschenmoser's salt (X=I)[6] has conventionally been utilized because of its relative easiness of handling and compatibility with a variety of reaction conditions.[7]

From a practical point of view, however, operationally simple Mannich reaction which does not require separate preparation and handling of these highly reactive iminium salts may be desirable.[8]

We recently communicated briefly that the reagent system chloroiodomethane (CH_2ClI)/*N,N,N′,N′*-tetramethylmethanediamine (TMMD) can serve as the *in situ* Mannich dimethylaminomethylation reagent of enol trimethylsilyl ethers under mild conditions (Eq. 1),[9] and herein we wish to report the results we have obtained in the course of this investigation and the relative experimental details.



(1)

Results and Discussion

Synthesis of the Mannich Base. 3-Pentanone enol silyl ether (**3a**) was treated with 1.5 molar amounts of CH_2ClI and TMMD in DMSO; after 3-h stirring at ambient temperature, almost all of the substrate was consumed with the formation of 2-(dimethylaminomethyl)-3-pentanone (**4a**) in a 93% yield. After the usual work-up, a pure sample of the amino ketone was isolated in a 68% yield by distillation; the product was fully characterized by IR and ^1H NMR spectral studies and elemental analysis.

As the transformation seemed to be of synthetic utility because of its mildness, operational simplicity, and reasonable yield of the Mannich base, further investigations with respect to both reagent system and substrate were carried out. Among the several solvents examined, DMSO gave the best result in the reaction of cyclohexanone enol silyl ether (**3c**) with CH_2ClI/TMMD (Table 1). Both DMF and CH_2Cl_2 may also be utilized as the reaction medium, while THF and diethyl ether gave poor results. It is reported that preformed iminium salts **1** (X=Cl, I) did not work in diethyl ether for the aminomethylation of propiophenone enol silyl ether (**3b**), presumably because of the insolubility of the halide salts.[7]

As for the dihalide component, CH_2ClI seemed to be the one of choice under a given reaction conditions (3-h reaction in DMSO), while even CH_2Br_2 gave a good result when the reaction was allowed to continue for 50 h (Table 2). It is interesting that the reactivity of the dihalides was in the order of $CH_2ClI > CH_2I_2 > CH_2Br_2 > CH_2Cl_2$ as judged by the unchanged halide.

Table 1. Effect of solvent on the reaction of cyclohexanone enol silyl ether (**3c**)[a]

Solvent	Mannich base (**4c**) yield/%[b]
DMSO	83
DMF	76
CH_2Cl_2	68
THF	6.2
Et_2O	0

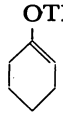
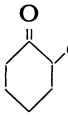
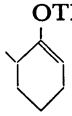
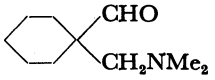
a) **3c**, 10 mmol; TMMD, 15 mmol; CH_2ClI, 15 mmol; solvent, 10 ml; r. t., 3 h. b) Determined by GLC using dodecane as the internal standard (Silicone GE SE-52 column).

Table 2. The Mannich reaction of cyclohexanone enol silyl ether (**3c**) with CH_2X_2/TMMD[a]

CH_2X_2	Mannich base (**4c**) yield/%
CH_2ClI	83
CH_2I_2	55
CH_2Br_2	23 (88)[b]
CH_2Cl_2	0

a) Reaction conditions like those described in Table 1. b) Reaction time, 50 h.

TABLE 3. THE MANNICH REACTION OF ENOL SILYL ETHERS WITH CH_2ClI/TMMD[a]

	Enol silyl ether (3)	Reaction time/h	Product(s) (4, 4′, 5)	Yield/%[b]	Bp θ_p/°C (mmHg)
a	C_2H_5–C(OTMS)=CH–CH_3	3	C_2H_5–CO–CH(CH_2NMe_2)–CH_3	68 (93)[c]	42—43(3)
b	Ph–C(OTMS)=CH–CH_3	3	Ph–CO–CH(CH_2NMe_2)–CH_3	51	39—40(0.4)
		24		71	
c		3		67 (83)[c]	42—47(0.3—0.4)
d		3		65	34—35.5(0.3)
e		3		22	52—55(0.2)
		24		71	
f	n-C_5H_{11}–CH=C(OTMS)–H	3	n-C_5H_{11}–CH(CH_2NMe_2)–CHO	18	38—40(0.8)
			n-C_5H_{11}–C(=CH_2)–CHO	(12)[c]	
		24	n-C_5H_{11}–C(=CH_2)–CHO	(42)[c]	
g	Ph–CH=C(OTMS)–CH_3	3	Ph–CH(CH_2NMe_2)–CO–CH_3	54	65—68(0.4)
			Ph–C(=CH_2)–CO–CH_3	(22)[c]	
h	Ph–CH=C(OTMS)–Ph	80	Ph–CH(CH_2NMe_2)–CO–Ph	67	Mp 78.2 °C
			Ph–C(=CH_2)–CO–Ph	(22)[d]	
i	n-C_4H_9–CH=C(OTMS)–OC_2H_5	3	n-C_4H_9–CH(CH_2NMe_2)–$COOC_2H_5$	46 (66)[c]	35—36/0.3
			n-C_4H_9–C(=CH_2)–$COOC_2H_5$	(13)[c]	
j	$(CH_3)_3$C–C(OTMS)=CH_2	5	$(CH_3)_3$C–CO–CH(CH_2NMe_2)$_2$	36	Mp 58.5 °C
		0.5[e]	$(CH_3)_3$C–CO–$CH_2CH_2NMe_2$	36	32(2)
			$(CH_3)_3$C–CO–CH(CH_2NMe_2)$_2$	12	
k	Ph–C(OTMS)=CH_2	3	Ph–CO–$CH_2CH_2NMe_2$	(22)[d]	
			Ph–CO–CH(CH_2NMe_2)$_2$	58 (78)[d]	Mp 57—58 °C

a) **3**, 15—20 mmol; **3**/CH_2ClI/TMMD≈1/1.5/1.5 (molar ratio); solvent, DMSO, 20 ml; room temp. b) Isolated yields unless otherwise noted. c) Determined by GLC. d) Determined by ^1H NMR. e) After CH_2ClI and TMMD had been stirred for 3 h, the enol silyl ether was added.

Table 3 lists the results of the Mannich reaction of various carbonyl compounds *via* enol silyl ethers with CH_2ClI/TMMD in DMSO as the solvent. It can be seen that the substrates in the Table can be divided into three categories: The first group enol silyl ethers (**3a** to **3e**) gave the corresponding mono(aminomethylation) products in fair to good yields, though **3e** required a longer reaction period in order to obtain appreciable yield. It should be noted that regioselective aminomethylation of 1-methylcyclohexanone was accomplished *via* enol silyl ether **3d**.

In the case of the second group enol silyl ethers (**3f** to **3i**), the Mannich reaction was accompanied by the formation of considerable amounts of α-methylenation products. GLC analysis showed that the reaction mixture of heptanal enol silyl ether (**3f**) (3-h reaction) contained 2-methyleneheptanal in a 12% yield based on the starting substrate. Distillation caused serious resinification of the reaction mixture, allowing the isolation of the desired Mannich base in a poor yield (18%). The exact mechanism by which the α-methylene carbonyl derivatives were formed remains to be determined, while it seems that the initially formed Mannich base released dimethylamine under

the reaction conditions.[10] Thus, upon treatment of **3f** with CH_2ClI/TMMD in DMSO for 24 h, the amount of the α-methylene aldehyde reached a 42% yield; this may be of some utility for the synthesis of α-methylene aldehydes (Eq. 2).

$$n\text{-}C_5H_{11}\text{-}CH{=}CH\text{-}OSiMe_3 \quad \textbf{3f}$$

$$\xrightarrow[\text{DMSO, r.t., 24h}]{CH_2ClI/Me_2NCH_2NMe_2} \xrightarrow{H_2O} n\text{-}C_5H_{11}\text{-}\underset{\underset{CH_2}{\|}}{C}\text{-}CHO \quad \textbf{5f} \qquad (2)$$

As was stated earlier the Mannich base itself is frequently utilized as the precursor for the α-methylene carbonyl compound, so the concurrent deamination in these transformations may not always be deteriorative to the Mannich aminomethylation.

The third group enol silyl ethers (**3j** and **3k**) which are characterized by bearing terminal methylene function gave bis(aminomethylation) products (**4'**) preferentially (Eq. 3). Even under the reaction conditions

$$\underset{Me_3SiO}{\overset{R}{\diagdown}}C{=}CH_2 \xrightarrow[\text{DMSO, r. t., 3h}]{CH_2ClI/Me_2NCH_2NMe_2} \xrightarrow{H_2O}$$

3j or **3k**

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2CH_2NMe_2 \quad \textbf{4}$$

$$+\,R\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH(CH_2NMe_2)_2 \quad \textbf{4'} \qquad (3)$$

where 40% of the substrate **3k** was remained unchanged, a 57 : 43 mixture of mono- to diamino ketone was resulted (Table 4). This is a sharp contrast to the report that the preformed Mannich reagent (**1**) did not afford disubstitution products from these type of enol silyl ethers.[7] At present, we have no idea to explain these discrepancies.

A Convenient Synthesis of the Eschenmoser's Salt (1, X=I) from CH_2ClI and TMMD. In 1971, Böhme *et al.* reported that CH_2Br_2 slowly reacts with TMMD to afford **1** (X=Br)[11] (Eq. 4).

$$Me_2NCH_2NMe_2 + CH_2Br_2 \longrightarrow 2Me_2\overset{+}{N}{=}CH_2,\ Br^- \qquad (4)$$

From the results in Table 2, it seems reasonable to anticipate that CH_2ClI would react more promptly with TMMD than CH_2Br_2 to give similar iminium salt of mixed halides (**1**, X=Cl and I). Thus, upon mixing TMMD with CH_2ClI, a mild exothermic reaction set in with the formation of white precipitate. To our surprise, however, the solid was shown to be the Eschenmoser's salt (**1**, X=I), as was evidenced by elemental analysis (*vide infra*). NMR and GLC study showed the presence of CH_2Cl_2 as a reaction product in the liquid part of the reaction mixture. Then, the overall transformation may be represented as follows:

$$Me_2NCH_2NMe_2 + 2CH_2ClI \longrightarrow 2Me_2\overset{+}{N}{=}CH_2,\ \bar{I} + CH_2Cl_2. \qquad (5)$$

On the basis of the stoichiometry according to Eq. 5, an 82% yield of the iminium iodide was attained after the mixture was allowed to stand for 3 d at ambient temperature in the dark. Under the similar reaction conditions, CH_2Br_2 and CH_2I_2 did not give appreciable amounts of the corresponding precipitate.

The conventional method for the preparation of the Eschenmoser's salt requires time-consuming, two-step procedure which must be carried out under strictly anhydrous conditions.[6] Recently Bryson *et al.* reported a convenient preparation of the iodide *via* cleavage of TMMD with stoichiometric amount of trimethylsilyl iodide.[12] In our Mannich reaction, separate preparation of the iminium reagent is not required for the aminomethylation of groups 1 and 2 enol silyl ethers in Table 3, but if desired, the transformation depicted in Eq. 5 will provide another convenient route to the Eschenmoser's salt.

Mechanistic Aspects of the Mannich Reaction of Enol Silyl Ether with CH_2ClI/TMMD. The time-course of the reaction of CH_2ClI with TMMD in DMSO was followed quantitatively by GLC (Fig. 1). On the basis of the material balance on chlorine and CH_2ClI, the amount of iminium iodide and chloride species are obtainable (see Experimental part). In this regard, NMR study of the reaction in DMSO-d_6 is suggestive

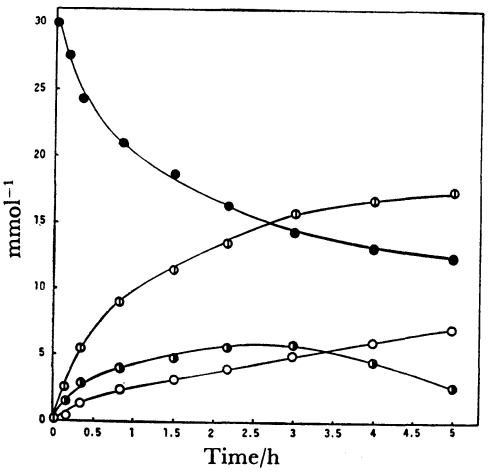


Fig. 1. Reaction of CH_2ClI with TMMD in DMSO. Reaction conditions: CH_2ClI, 30 mmol; TMMD, 30 mmol; DMSO, 20 ml; room temp. ●: CH_2ClI, ◑: $Me_2\overset{+}{N}{=}CH_2,\bar{I}$, ◑: $Me_2\overset{+}{N}{=}CH_2,\bar{Cl}$, ○: CH_2Cl_2.

Table 4. Reaction of acetophenone enol silyl ether (**3k**)[a]

3k (mmol)	CH_2ClI (mmol)	TMMD (mmol)	Solvent (ml)	Reacted **3k**(%)	Reacted CH_2ClI (mmol)	**4k/4'k** Ratio	Me_2NCH_2- Required (mmol equiv.)
16.1	24.0	27.4	DMSO 20	100	16.3	22/78	28.7
10.5	17.4	17.6	DMF 15	98	10.1	35/65	17.0
10.5	5.72	11.4	DMSO 15	61	4.64	57/43	9.2

a) Room temp, 3 h.

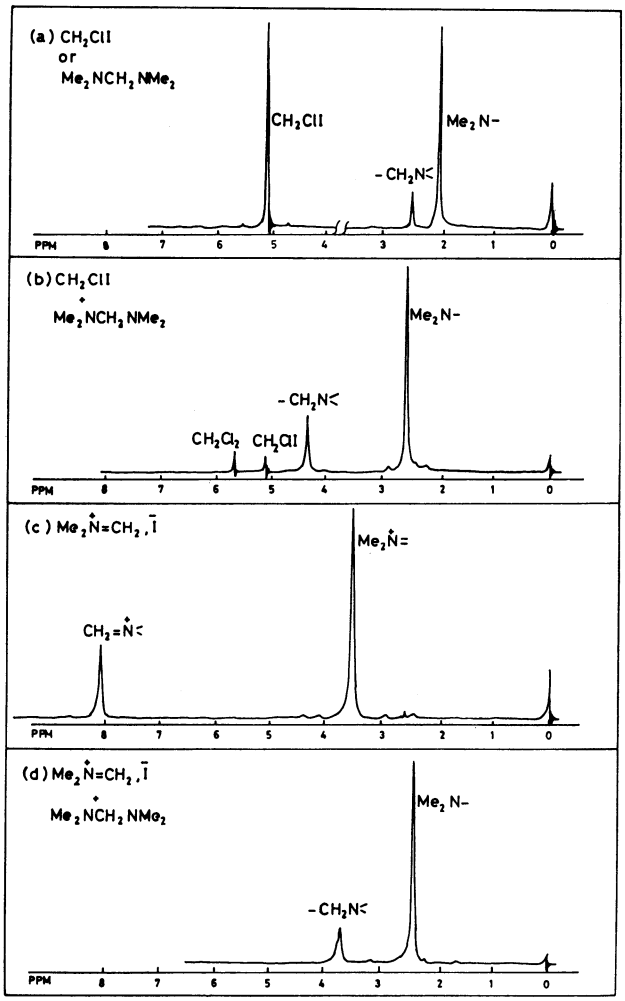
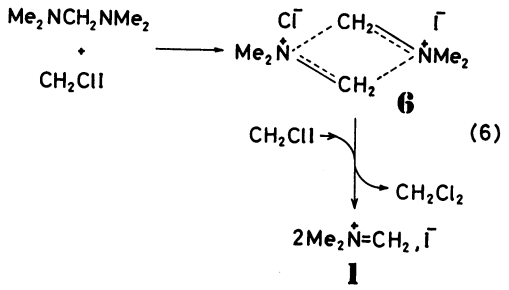


Fig. 2. NMR study of the reaction of CH_2ClI with TMMD in DMSO-d_6.
Internal standard, hexamethyldisiloxane; 35 °C.
(a) Spectrum of CH_2ClI and TMMD before mixing.
(b) A mixture of CH_2ClI (3.46 mmol) and TMMD (4.88 mmol) was stirred in DMSO-d_6 for 2 h at 35 °C.
(c) Eschenmoser's salt ($Me_2\overset{+}{N}=CH_2,\bar{I}$). (d) A mixture of $Me_2\overset{+}{N}=CH_2$, $\bar{I}$(0.146 mmol) and TMMD (0.166 mmol).

(Fig. 2). Mixing of the two components (Fig. 2-a) caused gradual decrease of CH_2ClI proton with concomitant downfield shift of the $-CH_2N<$ proton, accompanied by the formation of CH_2Cl_2 (Fig. 2-b). In some cases, depending on the relative amounts of the reagents and the solvent, a white precipitate separated from the reaction mixture. The precipitate, upon dissolution in another portion of DMSO-d_6, showed identical NMR spectrum with that of the authentic sample of the Eschenmoser's salt (Fig. 2-c). On the other hand, a mixture of the Eschenmoser's salt and TMMD showed only two signals of ^1H NMR absorption at 35 °C, which were assigned to CH_3–N and $-CH_2$–N protons, suggesting rapid exchange between iminium species and TMMD (Fig. 2-d).

These observations indicate that the reagent system CH_2ClI/TMMD contains complex iminium species, while most simply, the reaction of CH_2ClI and TMMD is depicted as follows (Eq. 6) (TMMD complexed with **6** or **1** is omitted), where plausibe intermediate species such as **6** can also serve as the Mannich reagent for the enol silyl ether present in the system.



In fact, detailed inspection of the results in Table 4 indicates that up to 2 molar amounts of Me_2NCH_2- moiety could be trapped into acetophenone enol silyl ether from 1 mol of CH_2ClI and TMMD. It is well demonstrated that iminium salt (**1**) readily reacts with not only enol silyl ethers but also various enolates,[5b,13] where highly electrophilic iminium methylene attacks enolate carbon in a regiospecific manner.[7,14]

Experimental

IR spectra were obtained on a Shimadzu IR 430 spectrophotometer. NMR spectra were determined on a Hitachi R-24A instrument using hexamethyldisiloxane as an internal standard in CCl_4 unless otherwise stated. Mass spectra were recorded on a JEOL JMS-D 300 double focusing spectrometer. Analytical GLC was recorded on a Shimadzu GC 3AF with FID detector or Shimadzu 3BT with TCD detector, on a Silicone GE SE-52 on Chromosorb W(AW), Apiezon Grease L on Diasolid M, or Silicone DC 550 on Uniport C column. Preparative GLC was carried out on a Shimadzu GC 6AM using appropriate column mentioned above. Microanalyses were performed at the Microanalysis Center, Chemical Research Institute of Nonaqueous Solutions, Tohoku University.

Materials. CH_2ClI (bp 108 °C) and CH_2I_2 (bp 70 °C/12 mmHg)† were obtained *via* halogen exchange of CH_2Cl_2 with NaI, and stored over a few tin pellets in the dark.[15] CH_2Br_2 was dried over $CaCl_2$, and distilled before use (bp 94—95 °C). Commercial carbonyl compounds were dried over $MgSO_4$ and distilled before use, while 1,2-diphenylethanone (**2h**) (mp 55—56 °C) was used as purchased. TMMD (bp 83—84 °C)[16] and Et_3N (bp 90 °C) were distilled from CaH_2 after having been refluxed for several hours. Solvents were purified as usual. Purified materials were stored under positive nitrogen pressure.

Phenylacetone (2g): The method of Hass *et al.*[17] was slightly modified. A mixture of benzaldehyde (106 g, 1 mol) and nitroethane (≈85 g, ≈1.1 mol) in 50 ml of benzene was refluxed for 15 h with continuous removal of water as benzene azeotrope. Volatiles were removed *in vacuo*, and the residue was recrystallized from ethanol to give 135 g of 1-phenyl-2-nitropropene (83%), mp 64—65 °C (lit,[17] mp 65 °C). A 75 g sample of the phenylacetone, bp 74—74.2 °C/3 mmHg, was prepared from 100 g of the 1-phenyl-2-nitropropene by treatment with 250 g of Fe powder as was described in the literature.[17]

† 1 mmHg≈133.322 Pa.

Enol Silyl Ethers (3): These were prepared from the corresponding carbonyl compounds and trimethylsilyl chloride[18] by means of lithium diisopropylamide in THF (**3d**, bp 33—35 °C/1.5—1.7 mmHg; **3i**, bp 72—76 °C/6—7 mmHg), or by refluxing in Et_3N-DMF (**3a**, bp 65—70 °C/50 mmHg, $E/Z=35/65$; **3b**, bp 54—57 °C/3—4 mmHg; **3c**, bp 65—66 °C/17—18 mmHg; **3e**, bp 68—71 °C/9—10 mmHg; **3f**, bp 60—62 °C/16 mmHg, $E/Z=59/41$; **3g**, bp 87—89 °C/3 mmHg; **3h**, bp 135 °C/1.3 mmHg; **3j**, bp 58—59 °C/45—46 mmHg; **3k**, 97—99 °C/16—17 mmHg).

General Procedure for the Synthesis of the Mannich Base from Enol Silyl Ether (3) with CH_2ClI/TMMD. The reactions were conveniently carried out in a two-necked, 50 ml Schlenk tube under a nitrogen atmosphere. To a water-cooled, stirred solution of the enol silyl ether (**3**) (≈20 mmol) and CH_2ClI (≈30 mmol) was added ≈30 mmol of TMMD. After a slight exothermic reaction subsided, the mixture was stirred at room temperature. Net reaction times are specified in Table 3. At the end of the reaction, 30 ml of 2 M HCl was added, and the mixture was stirred for *ca.* 1 h. Non-basic components, which included unchanged CH_2ClI, starting carbonyl substrate or enol silyl ether, and α-methylenation product, were extracted with portions of cyclohexane. The aqueous phase was made alkaline with 10% NaOH, and extracted with CH_2Cl_2 (4×30 ml). The combined extracts were washed successively with 10% NaOH, brine, and water. After the solution had been dried over $MgSO_4$, CH_2Cl_2 was evaporated *in vacuo*, and the residue was trap-to-trap distilled under reduced pressure; after a small forerun was discarded, middle distillate was collected as the product Mannich base. Results are summarized in Tables 3 and 5.

Upon termination of the reaction of **3h**, addition of aq HCl caused separation of hydrogen halide salt of the Mannich base; the solid was separated by filtration. The Mannich base (**4h**) was liberated by treatment with aq NaOH, and taken into ether.

The cyclohexane extracts were treated as usual, concentrated to an appropriate volume, which was subjected to preparative GLC to recover the α-methylene products (**5**).

5f: NMR: δ ≈0.9 (3H, Me–), 1.1—1.6 (6H, $-(\underline{CH_2})_3-$Me), 2.0—2.5 (2H, $-CH_2-\dot{C}=C\langle$), 5.8 (1H, br) and 6.1 (1H, br) (2H for $H_2C=C\langle$), 9.4 (1H, s, –CHO). MS (70 eV), *m/e* (%): 126 (M^+, 0.53), 97 (M−CHO, 28.3), 95 (10.2), 79 (6.1), 71 (10.4), 70 (11.7). IR (liq. film): 2700, 1690, 1460, 940 cm^{-1}.

5g: NMR: δ 2.35 (3H, s, –Me), 5.7 (1H, br) and 5.9

Table 5. Spectral and analytical data for the Mannich base

Mannich base	IR (liq. film) ν_{max}/cm^{-1}	NMR (CCl_4) δ	Found(%) (Calcd (%)) or MS (70 eV), *m/e* (%)
4a	2820, 2780, 1710, 1460, 1380, 1045	0.91 (3H, d, J=6.4 Hz, Me–CH⟨), 0.93 (3H, t, J=7.0 Hz, Me–CH_2–), 2.05 (6H, s, Me_2N–), 2.31 (2H, d, J=7.3 Hz, $-CH_2-N\langle$), 2.0—2.8 (3H, $-CH_2-CO-CH\langle$)	C 67.29(67.08) H 11.89(11.97) N 9.88(9.78)
4b	2830, 2770, 1680, 1460, 1235, 980	1.1 (3H, d, J=6.8 Hz, Me–CH⟨), 2.1 (6H, s, Me_2N–), 2.1—2.7 (2H, $-CH_2N\langle$), 3.5—4.0 (1H, –CH⟨), 7.2—8.1 (5H, –Ph)	C 75.55(75.35) H 8.68(8.96) N 7.06(7.32)
4c	2800, 2750, 1710, 1450, 1125, 1030	1.1—3.0 (11H), 2.04 (6H, s, Me_2N–)	MS: 110 (M−Me_2NH, 14.3), 82 (17.1), 67 (36.8), 54 (8.9)
4d	2850, 2780, 1710, 1460, 1375, 1130, 1050	0.90 (d, J=6.8 Hz) and 0.94 (d, J=6.4 Hz) (3H, Me–CH⟨), 1.5—2.1 (6H, $-(CH_2)_3-$), 2.1 (s, 6H, Me_2N–), 2.1—3.0 (4H, Me–$\dot{C}H$–CO–$\dot{C}H$–CH_2–N⟨)	C 70.73(70.96) H 10.95(11.31) N 8.08(8.27)
4e	2750, 2700, 1720, 1450, 1265, 1045	1.0—2.0 (10H, $-(CH_2)_5-$), 2.1 (6H, s, Me_2N–), 2.27 (2H, s, $-CH_2N\langle$), 9.33 (1H, s, –CHO)	C 70.81(70.96) H 11.02(11.31) N 7.91(8.27)
4f	2800, 2770, 2720, 1715, 1460, 1375, 1265, 1160, 1040	0.9 (3H, Me–CH_2–), 1.0—1.8 (8H, $-(CH_2)_4-$), 2.1 (6H, s, Me_2N–), 2.2—2.5 (2H, $-CH_2N\langle$), 2.5—2.8 (1H, –CH⟨), 9.4 (1H, br, –CHO)	C 70.32(70.12) H 12.21(12.36) N 8.07(8.18)
4g	2840, 2780, 1710, 1465, 1360, 1160, 1030	2.0 (3H, s, Me–CO–), 2.1 (6H, s, Me_2N–), 2.2—3.2 (2H, $-CH_2N\langle$), 3.5—3.9 (1H, –CH⟨), 6.8—7.5 (5H, –Ph)	MS: 191 (M^+, 0.70), 146 (M−Me_2NH, 10.5), 103 (44.2)
4h	a) 2810, 2770, 1665, 1450, 1250, 1210	2.2 (6H, s, Me_2N–), 2.4—2.8 (2H, $-CH_2N\langle$), 4.6—5.0 (1H, –CH⟨), 6.9—8.1 (10H, 2Ph–)	C 80.78(80.60) H 7.79(7.56) N 5.39(5.53)
4i	2820, 2770, 1730, 1460, 1380, 1035, 850	0.8 (3H, Me–$(CH_2)_3-$), 1.0—1.6 (9H, Me–CH_2–O–+Me–$(\underline{CH_2})_3-$), 2.1 (6H, s, Me_2N–), 1.9—2.7 (3H, $-\dot{C}H-CH_2-N\langle$), 4.0 (2H, q, J=7.2 Hz, $-CH_2O-$)	C 65.76(65.63) H 11.61(11.52) N 6.53(6.96)
4j	2810, 2750, 1700, 1460, 1385, 1080	1.05 (9H, s, Me_3C–), 2.1 (6H, s, Me_2N–), 2.4 (4H, s, $-(CH_2)_2-$)	MS: 157 (M^+, 3.8), 72 (4.9), 59 (3.1), 58 (80.5)
4'j	a) 2820, 2750, 1690, 1460, 1365, 1275, 1195, 1035, 985	1.05 (9H, s, Me_3C–), 2.1 (12H, s, $2Me_2N$–), 2.2—2.4 (4H, 2-$CH_2N\langle$), 3.0—3.4 (1H, –CH⟨)	MS: 169 (M−Me_2NH, 8.4), 156 (M−*t*-BuH, 45.7), 154 (4.3), 138(7.2), 137 (16.0)
4k	2830, 2790, 1680, *1450, 1240*	2.12 (6H, s, Me_2N–), 2.3—3.1 (4H, $-(CH_2)_2-$), 7.1—8.0 (5H, –Ph)	
4'k	a) 2770, 1670, 1450, 1280, 1235	2.06 (6H, s, Me_2N–), 2.2—2.8 (4H, 2-$CH_2N\langle$), 3.4—3.9 (1H, –CH⟨), 7.1—8.0 (5H, –Ph)	C 71.52(71.76) H 9.74(9.46) N 11.83(11.95)

a) KBr disk.

(1H, br) (2H for H_2C=C<), 7.1 (5H, -Ph). MS (70 eV), *m/e* (%): 146 (M^+, 24.4), 131 (16.3), 104 (6.6), 103 (36.7), 77 (3.3).

5h: NMR: δ 5.4 (1H, s) and 5.8 (1H, s) (2H for H_2C=C<), 6.9—8.0 (10H, 2Ph-). IR (liq. film): 1670, 1440, 1215, 990 cm^{-1}.

5i: NMR: δ ≈0.9 (3H, Me-$(CH_2)_3$-), 1.2 (3H, t, J=6.8 Hz, Me-CH_2O-), 1.1—1.8 (4H, Me-$(CH_2)_2$-), 2.2 (2H, t, J=6.0 Hz, -CH_2-C=C<), 4.1 (2H, q, J=6.8 Hz, Me-CH_2O-), 5.35 (1H, br) and 5.95 (1H, br) (2H for H_2C=C<).

*Reaction of Acetophenone Enol Silyl Ether (**3k**)*: The following example is illustrative. A mixture of **3k** (3.10 g, 16.1 mmol), CH_2ClI (4.24 g, 24.0 mmol), and TMMD (2.80 g, 27.4 mmol) was stirred in 20 ml of DMSO at room temperature for 3 h, and was worked up as above. The cyclohexane extract was analyzed by GLC to determine the amount of CH_2ClI and acetophenone (Table 4). Evaporation of the CH_2Cl_2 layer *in vacuo* left a 3.5 g of syrupy residue which was comprised of the monoamino (**4k**) and diamino ketone (**4'k**) as was evidenced by NMR. The relative amount of the two was estimated to be 22/78 by integration of the Me_2N-resonance (δ 2.12 for **4k** and δ 2.06 for **4'k**). The residue was dissolved in 15 ml of hot pentane, and was kept at −20 °C overnight to give 2.19 g of **4'k** as white crystals (Table 5). Distillation of the filtrate caused serious deamination of the amino ketones, while following distillates were recovered:

Phenyl Vinyl Ketone: Trace, bp 55 °C/0.7 mmHg. NMR: δ 5.7 (1H, dd, J_{cis}=10.2 Hz, J_{gem}=2.4 Hz, for HC=C< *trans* to -CO-Ph), 6.25 (1H, dd, J_{trans}=16.8 Hz, for HC=C< *cis* to -CO-Ph), 7.0 (1H, dd, -CH=CH_2), 7.1—8.0 (5H, -Ph). IR (liq. film): 1670, 1660, 1610, 1450, 1400, 1230, ≈1000—960 cm^{-1}.

4k: Trace, see Table 5.

2-Methylene-3-(dimethylamino)propiophenone: 0.74 g, bp 115—120 °C/3 mmHg. NMR: δ 2.1 (6H, s, Me_2N-), 3.1 (2H, br, -CH_2N<), 5.5 (1H, br) and 5.75 (1H, br) (2H for H_2C=C<), 7.1—8.0 (5H, -Ph). IR (liq. film): 2820, 2780, 1660, 1450, 1325, 1280, 1040, ≈1000—970, 860 cm^{-1}.

Formation of the Eschenmoser's Salt from CH_2ClI and TMMD. Under a nitrogen atmosphere, 1.18 g (11.5 mmol) of TMMD was added to a 6.0 g (34 mmol) of CH_2ClI which was chilled in an ice-water bath. The bath was removed after 3 h, and the mixture was allowed to stand at room temperature for 3 d in the dark. Precipitated white crystal was filtered under nitrogen, and was washed with CCl_4, yield, 3.50 g (18.9 mmol calculated as **1** (X=I), 82% based on TMMD). Found: C, 19.60; H, 4.58; N, 7.60; I, 69.0%. Calcd for C_3H_8IN: C, 19.48; H, 4.36; N, 7.57; I, 68.59%. NMR (DMSO-d_6): δ 8.05 (2H, br, $CH_2\overset{+}{N}$=), 3.52 (6H, br, $Me_2\overset{+}{N}$=). On heating, the precipitate colored from white to yellow (≈100 °C) and to dark-brown (≈220 °C), and melted with decomposition at *ca.* 235 °C. By the use of 1 ml of DMSO as the solvent, the yield of the precipitate was improved to 90%. Control of the temperature at the early stage of the reaction and exclusion of moisture seemed essential in order to obtain pure product.

Time-course of the Reaction of CH_2ClI with TMMD. A mixture of CH_2ClI (5.30 g, 30 mmol), TMMD (3.07 g, 30 mmol), and 1.20 g of ethylbenzene (internal standard) in 20 ml of DMSO was stirred at room temperature. Samples (*ca.* 1 ml) were withdrawn at various times through a septum cap by means of a hypodermic syringe, and quenched with aq HCl. After three extractions with cyclohexane, the combined organic phase was analyzed by GLC (Apiezon Grease L column); only CH_2Cl_2 was detected as the reaction product. Material balance on chlorine and CH_2ClI requires following equations:

$$[CH_2ClI\ \text{reacted}] = [Me_2\overset{+}{N}=CH_2, \bar{I}],$$

$$[Me_2\overset{+}{N}=CH_2, \bar{Cl}] = [CH_2ClI\ \text{reacted}] - 2[CH_2Cl_2],$$

where it is supposed that species which lose halide ion on hydrolysis can be represented as **1** (X=Cl or I).

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References

1) Part II: S. Miyano, H. Hokari, Y. Umeda, and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **53**, 770 (1980).

2) Part of this work was presented at the 42nd National Meeting of the Chemical Society of Japan, Sendai, 1980, Abstr. No. 1L13.

3) Recent review: T. Shono and Y. Matsumura, *Yuki Gosei Kagaku Kyokai Shi*, **39**, 358 (1981).

4) a) M. Tramontini, *Synthesis*, **1973**, 703; b) J. Mathieu and J. Weill-Raynal, "Formation of C-C Bonds," Georg Thieme Publ., Stuttgart (1973), Vol. 1, pp. 78—91; c) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Inc., California (1972), pp. 654—660.

5) a) "Iminium Salts in Organic Chemistry," ed by H. Böhme and H. G. Viehe, Wiley-Interscienc, New York (1976), Part 1; b) S. Murahashi, *Kagaku (Chemistry)*, **34**, 922 (1979).

6) J. Schreiber, H. Maag, N. Hashimoto, and A. Eschenmoser, *Angew. Chem.*, **83**, 355 (1971).

7) N. Holy, R. Fowler, E. Burnett, and R. Lorenz, *Tetrahedron*, **35**, 613 (1979).

8) The Mannich reaction of enol silyl ether by a combination of aminomethyl ethers and trimethylsilyl iodide catalyst has recently been reported: S. Iijima, A. Hosomi, and H. Sakurai, The 43rd National Meeting of the Chemical Society of Japan, Tokyo, 1981, Abstr. No. 1D08.

9) S. Miyano, H. Hokari, A. Mori, and H. Hashimoto, *Chem. Lett.*, **1980**, 1213.

10) *Cf.* J.-L. Gras, *Tetrahedron Lett.*, **1978**, 2111.

11) H. Böhme, M. Hilp, L. Koch, and E. Ritter, *Chem. Ber.*, **104**, 2018 (1971).

12) T. A. Bryson, G. H. Bonitz, C. J. Reichel, and R. E. Dardis, *J. Org. Chem.*, **45**, 524 (1980); See also Ref. 8.

13) a) J. L. Roberts, P. S. Borromeo, and C. D. Paulter, *Tetrahedron Lett.*, **1977**, 1621; b) S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Am. Chem. Soc.*, **98**, 6715 (1976); c) J. Hooz and J. N. Bridson, *ibid.*, **95**, 602 (1973).

14) S. Danishefsky, M. Prisbylla, and B. Lipisko, *Tetrahedron Lett.*, **1980**, 805.

15) S. Miyano and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **44**, 2864 (1971).

16) Though commercially available, it can easily be prepared in large quantities: D. Lednicer and C. R. Hauser, *Org. Synth.*, Coll. Vol. 5, p. 434 (1973).

17) H. B. Hass, A. G. Susie, and R. L. Herder, *J. Org. Chem.*, **15**, 8 (1950).

18) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).