Synthesis of Mannich bases from electrochemically generated iminium salts in the presence of silyl enol ethers[1]

ROGER N. RENAUD,[2] DENIS BÉRUBÉ, AND CAMPBELL J. STEPHENS
Division of Chemistry, National Research Council of Canada, Ottawa, Ont., Canada K1A 0R6

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The formation of Mannich bases from the reaction of silyl enol ethers with *N*-methyl-*N*-mesitylmethyleniminium salt, generated by the electrochemical oxidation of *N*,*N*-dimethylmesidine, was studied. Important factors influencing the reaction are: (a) the silyl enol ether must be nucleophilic enough to react with the iminium salt and, at the same time, must be more difficult to oxidize than the tertiary amine, (b) the product of the reaction must not be oxidized at the operating potential. Examples are presented in this paper illustrating the successes and limitations of this reaction.

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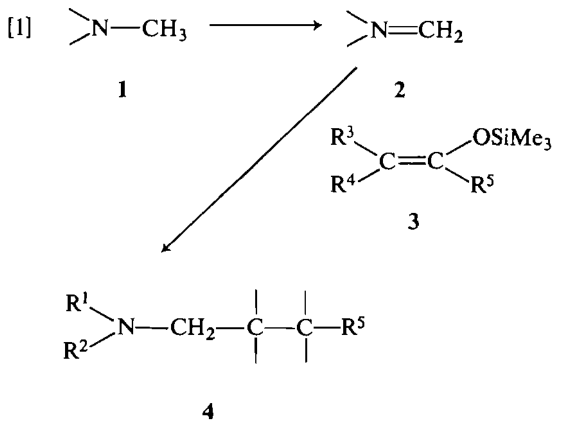
La formation de bases de Mannich a été étudiée en faisant réagir des éthers silyl énoliques sur le sel *N*-méthyl-*N*-mésitylméthyleniminium préparé par oxydation électrochimique de la *N*,*N*-diméthylmésidine. Les facteurs pouvant influencer la réaction sont: (a) l'éther silyl énolique doit étre assez nucléophilique pour réagir avec le sel iminium et, en même temps, doit être plus difficile à oxyder que l'amine tertiaire, (b) le produit de la réaction ne doit être oxydé au potentiel employé. Des exemples montrant le succès et la limitation de cette réaction sont présentés dans cette étude.

Many methods describing the aminomethylation of ketones are reported in the literature. The classical Mannich reaction is a typical example (1). Recently, aminomethylation was achieved successfully by the nucleophilic attack of silyl enol ethers on *N*,*N*-dimethylmethyleniminium salts (2, 3), chloromethyl methylurethan (4), and aminomethyl ethers (5).

The electrochemical formation of iminium cations from tertiary amines has been extensively studied (6–9). Recently, it was shown that the iminium cation, obtained from the electrochemical oxidation of *N*,*N*-dimethylanilines, gave good yields of addition products with nucleophiles such as diethyl phosphate and dialkylmalonates (7, 8). It seemed to be interesting for us to study the preparation of Mannich bases **4** by the nucleophilic attack of silyl enol ethers **3** on electrochemically prepared iminium cations **2**, according to Scheme 1. Only a selection of silyl enol ethers in the presence of the iminium salt of *N*,*N*-dimethylmesidine **1** are reported in this paper in order to present the scope of the potential of this preparative method.

[1]



SCHEME 1

Results and discussion

Controlled potential electrolyses were performed at a platinum electrode in acetonitrile containing 0.1 M lithium perchlorate. By using a one-compartment cell, a dark solution and an electrode passivation were obtained. The current was reversed for 2 s every minute in order to regenerate the surface of the electrode. A two-compartment cell eliminated these problems and simplified the purification of the products. Nevertheless, the yield of products increased only slightly by using a divided cell. Good yields (Table 1) of **4***a*–**4***d* were obtained[3] for the electrolysis of *N*,*N*-dimethylmesidine in the presence of the silyl enol ethers **3***a*–**3***d*, respectively. However, the Mannich base **4***e* was obtained in low yield from **3***e* while **4***f* was not detected from **3***f*.

Examination of the oxidation potentials of the reactants and the products gave some light on the electrolysis results. The current–potential curve of *N*,*N*-dimethylmesidine in $CH_3CN-LiClO_4$ (0.1 M) at a platinum rotating disc electrode showed a half-wave potential ($E_{1/2}$) of 0.55 V. As a result of this experimental condition, the $E_{1/2}$ of the silyl enol ethers and the products have to be considered. Figure 1 illustrates the current–potential curves of the electrochemical oxidation of *N*,*N*-dimethylmesidine, the silyl enol ether **3***a*, and the Mannich base product **4***a*. At 0.45 V, only a small quantity of the product **4***a* is oxidized while the current for the oxidation of *N*,*N*-dimethylmesidine is still reasonable (100–150 mA). Acceptable yields of **4***a*–**4***d* ($E_{1/2} \approx 0.6$ V) were obtained from the silyl enol ethers **3***a*–**3***d* respectively ($E_{1/2} > 1.2$ V) (Table 1). For O-methyl-O-trimethyl silyl isobutylketene acetal (**3***f*) ($E_{1/2} = 0.4$ V), the electrolysis has to be conducted at a potential higher than its own oxidation potential. On the other hand, even if ethyl 3-trimethylsiloxy-2-butenoate (**3***e*) has an oxidation potential ($E_{1/2} = 1.95$ V) high enough, a large quantity of the silyl enol ether **3***e* was recovered and the product **4***e* was obtained in only a very low yield. Further studies are in progress with other silyl enol ethers in order to obtain an explanation for this observation.

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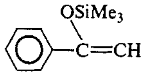
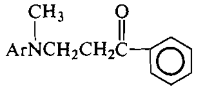
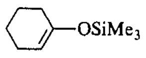
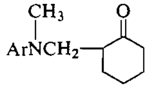
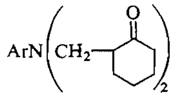
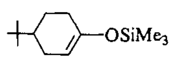
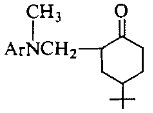
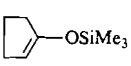
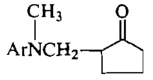
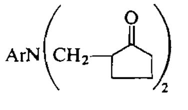
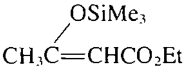
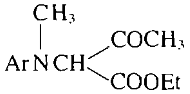
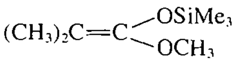
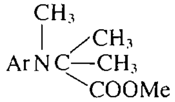
[1] NRCC No. 20111.

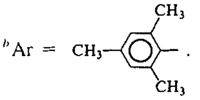
[2] Author to whom correspondence should be addressed.

[3] No aminomethylated product **4***a* was observed when the electrolysis was conducted in the presence of acetophenone. The formation of the Mannich base ω-[*N*-*tert*-butyl-*N*-methylamino]-propiophenone has been obtained, however, from *N*-methyl-*N*-*tert* methyleniminium perchlorate in the presence of acetophenone in methylene chloride (10).

TABLE 1. Controlled potential electrolysis of *N,N*-dimethylmesidine at 0.45 V^a in the presence of silyl enol ethers

Silyl ether 3		$E_{1/2}$ (V)	Product^b 4		Yield^c (%)	$E_{1/2}$ (V)	Product^b 5		Yield^c (%)
3*a*		1.30	4*a*		42.7	0.62	—		—
3*b*		1.25	4*b*		57.9	0.61	5*b*		11.5
3*c*		1.35	4*c*		39.4^d	0.57(ax) 0.68(eq)	—		
3*d*		1.22	4*d*		51.1	0.65	5*d*		7.3
3*e*	 $CH_3C(OSiMe_3)=CHCO_2Et$	1.95	4*e*	 $ArN(CH_3)CH(COCH_3)COOEt$	1.3	0.60	—		—
3*f*	 $(CH_3)_2C=C(OSiMe_3)OCH_3$	0.4	4*f*	 $ArN(CH_3)C(CH_3)_2COOMe$	0	—	—		—

^{a}The potentials are reported vs. Ag/AgNO$_3$ 10^{-2} *M*.

^{b}Ar =  .

^{c}Isolated yields and current yields.

^{d}A mixture of axial and equatorial stereoisomers in a ratio 1:3 respectively.

Besides the major products 4*b* and 4*d*, some compounds 5*b* and 5*d* were also isolated.[4] These compounds were determined to be the result of the oxidation of 4*b* and 4*d* to give a new iminium cation which reacted with another molecule of silyl enol ether to give 5 (Scheme 2). The same observation was noticed by Shono *et al.* (11) for the oxidation of dimethyl aniline in the presence of methanol as the nucleophile. For 4*a* and 4*c*, the compounds 5*a* and 5*c* are probably formed but could not be obtained pure enough for identification.

The product 4*c* is actually a mixture of two stereoisomers, the axial and the equatorial 2-substituted-4-butyl cyclohexanone in a ratio of 1:3. This ratio was determined by a current–potential curve on the mixture. The axial substituted product has a $E_{1/2}$ of 0.57 V while the equatorial equivalent is at 0.68 V. The stereochemistry was assigned by comparing the wideband proton decoupled, the proton undecoupled, and the spin echo spectra. The methylene carbon at C-2 is adjacent to a nitrogen and most likely appears at 58.05 ppm for the equatorial isomer and at 55.38 ppm for the axial isomer. Also, C-6 for the axial 2-substitution (33.84 ppm) has an upfield shift compared with the equatorial 2-substitution (38.30 ppm). This δ-effect of 4.9 ppm is comparable with the δ-effect of 5 ppm observed for 2-methyl cyclohexane (12). The carbonyl carbon appears at 214.68 ppm and 212.97 ppm for the axial and the equatorial isomers, respectively. Therefore, this downfield shift (208.8 ppm for cyclohexanone and 210.3 ppm for 2-methyl cyclohexanone) is due to the aromatic amino group attached to the methylene group at C-2.

Experimental

Reagents

N,N-dimethylmesidine was prepared by the Eschweider–Clarke reaction (13). The silyl enol ethers and the O-methyl-O-trimethylsilyl-isobutylketene acetal were obtained by reported methods (14). The acetonitrile was purified as reported in the literature (15).

Analytical methods

Infrared spectra were recorded on a Perkin–Elmer Model 267 spectrophotometer. Proton magnetic resonance spectra were taken in deuteriochloroform on a Varian Associates spectrometer model E.M. 360 and are reported in the δ scale. The ^{13}C magnetic resonance spectra were taken on a Bruker WP-80 apparatus. The mass spectra were obtained from a Finnigan 400 gc–ms spectrometer. The moleculear weight determinations were done on a Mechrolab vapor pressure osmometer model 301A.

Electrochemical instrumentation

All potentials were referred to Ag/0.01 *M* AgNO$_3$ in acetonitrile–LiClO$_4$ (0.1 *M*). Current–potential measurements were obtained using a conventional three-electrode cell equipped with a programmer PAR 175, a potentiostat PAR 173, a coulometer PAR 379, a rotating disc electrode from Tacussel, and a Hewlett–Packard 7045B X–Y recorder. The controlled potential electrolyses for the preparative scale synthesis were carried out in a H-type cell. This cell has a glass frit diaphragm separating the two compartments. The

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[4] A complete study on the electrochemical oxidation of *N,N*-dimethylmesidine in the presence of nucleophiles has been published (7, 8).

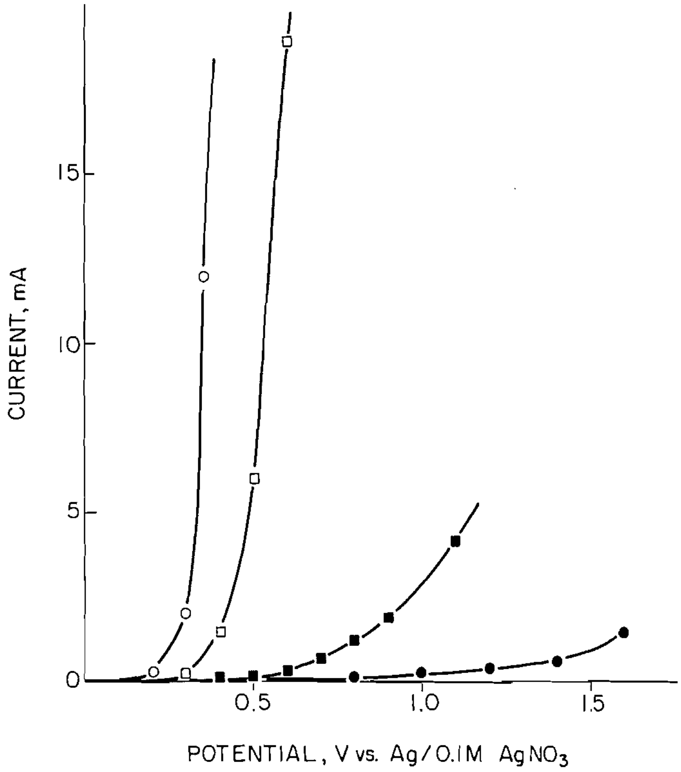


FIG. 1. Current–potential curves. Curve ●: acetonitrile–LiClO$_4$ (0.1 *M*). Curve ■: 1-phenyl-1-trimethylsilyloxyethylene (3*a*) (0.1 *M*). Curve ○: *N*,*N*-dimethylmesidine (0.1 *M*). Curve □: *N*-methyl-*N*-3-phenylpropanone-3 mesidine 4*a* (0.1 *M*).

anodic compartment (150 mL) contained a semi-circular platinum screen (4 cm × 9 cm). A platinum screen (1 cm × 1 cm) was used as the cathode. The source of energy was obtained from a 300 V Lambda power supply model LB-706-FM, and the potential was controlled manually by means of a high resistance voltmeter.

General procedure

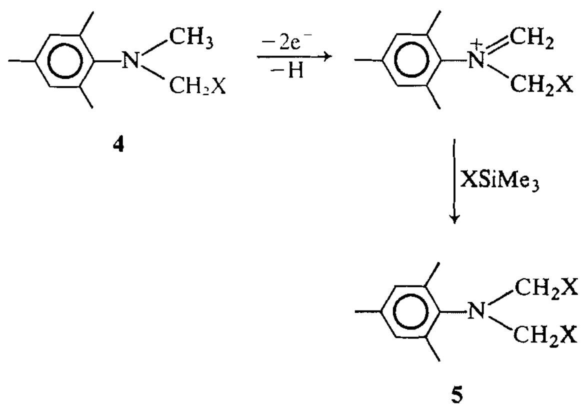
A mixture of LiClO$_4$ (1.34 g), Na$_2$CO$_3$ (2.12 g), silyl compound (≈5 mol excess), and *N*,*N*-dimethylmesidine (1.63 g; 0.01 mol) in acetonitrile (125 mL) was placed in the anodic compartment. The cathodic solution was LiClO$_4$ (0.1 *M*) in acetonitrile. The potential of the anodic solution was controlled at ≈0.45 V until 2.0 F/mol has been passed. The anodic solution was filtered and concentrated on a rotary vacuum evaporator. The oily residue was extracted with three 50-mL portions of n-pentane. The pentane was removed on a rotary evaporator. The residue was pumped under a pressure of 10^{-2} Torr for 24 h at room temperature. The volatiles, which were collected in a trap cooled in liquid nitrogen, consisted of unreacted starting materials. The remaining low vapor pressure oil was fractionated by flash chromatography (16) using a column of 2 cm diameter by 40 cm long and the main fraction was further purified by fractional distillation in a bulb-to-bulb apparatus under reduced pressure.

Physical properties of the products

(A) *From 1-phenyl-1-trimethylsilyloxy-ethylene* 3a

The crude product showed only one important spot on the tlc plate. Purification by flash chromatography using hexane – ethyl acetate (6:1) and by a bulb-to-bulb distillation at 100°C (10^{-2} Torr) gave 1.2 g (42.7%) of a yellow oild (4*a*) which crystallized on standing (mp 59–60°C); ir (CHCl$_3$): 1680 cm^{-1}; ^{1}H nmr: 2.18 (s, 9H), 2.61 (s, 3H), 3.22 (q, AB, 4H), 6.72 (s, 2H), 7.42 (m, 3H) 7.78 (m, 2H); ms *m*/*e*: 281 (M$^+$, 14), 162 (M$^+$ − C$_8$H$_7$O, 100). *Anal.* calcd. for C$_{19}$H$_{23}$NO: C 81.14, H 8.19, N 4.98; found: C 81.18, H 8.26, N 4.84.

(B) *From 1-trimethylsilyloxy-1-cyclohexene* 3b



X = the ketonic substituent

SCHEME 2

The residue obtained after removal of the high vapor pressure fraction at 10^{-2} Torr showed two important spots on the tlc plate. The crude product was fractionated by flash chromatography using hexane – ethyl acetate (6:1) as the eluent. Two fractions were obtained. The first one was purified further by bulf-to-bulb distillation at 85°C (10^{-2} Torr) to give 1.5 g (57.9%) of a yellow oil (4*b*); ir (film): 1710 cm^{-1}; ^{1}H nmr: 1.9 (broad m, 9H), 2.09 (s, 9H), 2.64 (s, 3H), 3.28 (m, 2H), 6.71 (s, 2H); ms *m*/*e*: 259 (M$^+$, 7), 162 (M$^+$ − C$_6$H$_9$O, 100). *Anal.* calcd. for C$_{17}$H$_{25}$NO: C 78.76, H 9.65, N 5.41; found: C 78.35, H 9.76, N 5.34. The second fraction amounted to 0.41 g (11.5%) of slightly impure 5*b*; ir (film): 1700 cm^{-1}; ^{1}H nmr: 1.4–2.6 (broad m including the aromatic CH$_3$ groups, 29H), 3.2 (m, 4H), 6.80 (s, 2H). Mol. Wt. calcd.: 355; found: 348.

(C) *From 1-trimethylsilyloxy-4-*tert*-butyl-1-cyclohexen* 3c

The oily product obtained was shown by tlc to contain one major compound and 5 minor ones. The main product 4*c* (1.24 g; 39.4%) was separated by flash chromatography using hexane – ethyl acetate 8:1 as the eluent. A sample of the purified product was distilled in a Späth bulb under a pressure of 10^{-2} Torr at 120°C. A very slight decomposition was noticed at that temperature. Infrared (film): 1703 cm^{-1}; ^{1}H nmr: 0.89 (s, 9H), 1.68 (m, 8H), 2.28 (broad s, 9H), 2.70 (s, 3H), 3.28 (m, 2H), 6.80 (s, 2H); ms *m*/*e*: 315 (M$^+$, 6), 162 (M$^+$ − C$_{10}$H$_{17}$O, 100). *Anal.* calcd. for C$_{21}$H$_{33}$NO: C 80.00, H 10.48, N 4.44; found: C 80.06, H 10.37, N 4.40.

(D) *From 1-trimethylsilyloxy-1-cyclopentene* 3d

The crude mixture contained two important spots on the tlc plate. It was purified by flash chromatography (hexane – ethyl acetate 6:1). The first fraction (4*d*) was purified further by bulb-to-bulb distillation under a pressure of 10^{-2} Torr at 70°C to give a nearly colorless oil (1.40 g; 57.1%); ir (film): 1725 cm^{-1}; ^{1}H nmr: 1.92 (m, 7H), 2.24 (s, 9H), 2.72 (s, 3H), 2.90–3.82 (m, 2H), 6.80 (s, 2H); ms *m*/*e*: 245 (M$^+$, 37), 162 (M$^+$ − C$_5$H$_7$O, 100). *Anal.* calcd. for C$_{16}$H$_{23}$NO: C 78.37, H 9.38, N 5.71; found: C 78.15, H 9.43, N 5.63. The second fraction which corresponded to 5*d* (0.24 g; 7.3%) always contained a slight impurity; ir (film): 1720 cm^{-1}; ^{1}H nmr: 1.60–2.60 (broad m including the aromatic methyl groups at 2.30, 16H), 2.70–3.70 (m, 4H), 6.80 (s, 2H). Mol. Wt. calcd.: 327; found: 332.

(E) *From ethyl 3-trimethylsilyloxy-2-butenoate* 3e

A dark brown product was obtained from the electrolytic reaction. The gummy residue, obtained after the removal of the volatile fraction at room temperature under reduced pressure (10^{-2} Torr), was a mixture of at least ten compounds by tlc. After separation by flash chromatography, one of the compounds seemed to correspond to 4*e* (0.02 g; 1.4%) but it was still slightly impure. Infrared (film): 1740 and 1715 cm^{-1}; ^{1}H nmr: 1.20 (t, 3H), 2.22 (broad s, 12 H), 2.71 (s, 3H) 2.80–3.82 (m, 3H), 4.20 (q, 2H), 6.86 (s, 2H). *Anal.* calcd. for C$_{17}$H$_{25}$NO$_3$: C 70.10, H 8.59, N 4.81; found: C 68.64, H 7.82, N 5.07.

(F) *From O-methyl-O-trimethylsilyl-isobutylketene acetal* (**3f**)

The crude product after removal of the volatile fraction at room temperautre (10^{-2} Torr) amounted to only 0.1 g from which no Mannich base could be obtained.

Acknowledgements

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