Synthesis and Application of Imidazole Derivatives. Synthesis of (1-Methyl-1H-imidazol-2-yl)methanol Derivatives and Conversion into Carbonyl Compounds

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(1-Methyl-1H-imidazol-2-yl)methanol derivatives (4 and 7) were prepared by treating carbonyl compounds with 2-lithio-1-methyl-1H-imidazole (2) or by treating 2-acyl-1H-imidazoles (3) with organometallic reagents or sodium borohydride. The alcohols (4 and 7) were convertible into the carbonyl compounds via the corresponding quaternary salts (8 and 10). The stable (1-methyl-1H-imidazol-2-yl)methanol system, R-C(OH)-C=N-CH=CH-NCH3, can be regarded as a masked form of the carbonyl group as well as a synthon of the group.

Keywords—(1-methyl-1H-imidazol-2-yl)methanol; 2-acyl-1-methyl-1H-imidazole; carbonyl compound synthesis; 1-κetoester; protecting group; latent functionality; symmetric ketone; dihydrojasmon

1-Acyl-1H-imidazoles have been widely applied in organic synthesis as an important active acyl species.1,2 On the other hand, 2-acyl-1-methyl-1H-imidazoles (3) have been little studied in regard to synthesis or their synthetic applications. In the previous paper, we reported syntheses of 2-acyl-1-methyl-1H-imidazoles (3) by treatment of various pyrrolidine amides (1) with 1-methyl-2-lithio-1H-imidazole, as well as the use of 3 as an active acyl source,3 and conversion of the imidazole ring in 3 into the imidazolium form having a superior leaving ability. This paper mainly deals with synthesis of (1-methyl-1H-imidazol-2-yl)methanol derivatives (4 and 7) starting from the 2-acylimidazole (3) and further conversions of these products into carbonyl compounds by making use of the imidazolium group as a leaving group.

In the literature, (1-methyl-1H-imidazol-2-yl)methanol derivatives (4 and 7) have been prepared by treatment of aldehydes or ketones with 2-lithio-1-methyl-1H-imidazole (2),4 and in one example by a Grignard reaction of 2-formyl-1-methyl-1H-imidazole (3a) with 4-phenoxymagnesium bromide.5 We attempted to use a similar Grignard reaction to prepare 4 and 7 from various 2-acylimidazoles (3).3 For example, the 2-cyclohexylcarbonylimidazole (3d) was added to an excess (more than two equivalents) of an ethereal benzylmagnesium bromide solution to give 7d in 79.0% yield. Lithium reagents such as phenyllithium and lithium enolate were also usable instead of the Grignard reagent without difficulty. The secondary alcohols (4) were also obtained by reduction of the 2-acylimidazoles (3) with sodium borohydride as well as by Grignard reactions of the 2-formylimidazole (3a). Table I gives the yields and various data for the (1-methyl-1H-imidazol-2-yl)methanol derivatives (4 and 7).

In view of the superior leaving ability of the 2-imidazolium moiety, we considered that the structures of 4 and 7 can be regarded as a protected form of carbonyl group, such as gem-cyanohydrin. It was reported by Breslow that benzaldehyde was produced upon treatment of
3,4-dimethyl-2-(hydroxyphenylmethyl)thiazolium salt with an organic base, but the reaction was reported as a qualitative, not a preparative, one.\(^6\) Quaternization of the alcohols 4a and 7a proceeded easily on refluxing them in ethyl acetate solution in the presence of an excess of
methyl iodide to give the corresponding crystalline imidazolium salt (8a and 10a, respectively) in almost quantitative yields. First, the reactivity of the imidazolium salt 8a were examined. When 8a was treated with 10% potassium carbonate at 60 °C for 2 h, benzophenone was quantitatively produced, as expected (method A). In the cases of other imidazolylmethanols (4 and 7), the corresponding imidazolium salts (10) were used without purification in the treatment with 10% potassium carbonate. As shown in Table II, the ketones were satisfactorily reduced. A possible reaction mechanism is illustrated in Chart 3, where removal of the proton from hydroxy group by the alkali occurs in an initial stage of the conversion of 8 to ketone and the equilibrium (a) seems to incline to the right. Although the method A was applicable to producing aromatic aldehydes from the corresponding imidazolium salts such as 10a, the method was not effective for producing aliphatic aldehydes, such as citronerall, from the imidazolium salt 10d, probably because the initial equilibrium (a) incline to the left owing to lower steric repulsion in 10 than 8 (Chart 3). When stronger alkali, 0.1 N sodium hydroxide, was used instead of 10% potassium carbonate, a considerable amount of citronellal was formed. However, in that case, thin-layer chromatography (TLC) of the crude product demonstrated that the desired aldehyde was contaminated by by-products which were presumably formed by aldol condensation reaction and possible subsequent reactions. Thus, an excess of sodium 6-aminocaproate was added to the reaction mixture in order to trap the aldehyde in the aqueous phase as the corresponding Schiff base (method B). As shown in Table II, formation of aldehydes proceeded satisfactorily. In method B, it is presumed that the equilibrium (a) may incline to the right owing to removal of the produced aldehyde by trapping with 6-aminocaproate through formation of the corresponding Schiff base, as well as owing to decomposition of the imidazolium counterpart via a pseudo-base (C) induced by the strong alkali (Chart 3).

When the imidazolium salt (7a) was treated with sodium hypochlorite in 20% acetic acid, benzophenone was obtained in high yield (method C). Since this procedure does not include a quaternization step, we expected that it might be generally applicable. However, in the case of
the imidazolymethanol (7b), acetophenone produced was contaminated by a small amount (15%) of chlorinated acetophenone, so that the usefulness of the procedure seems to be restricted. The oxidation of 7c with m-chloroperbenzoic acid followed by treatment with 10% potassium carbonate also afforded the corresponding ketone in almost quantitative yield, but the reaction did not proceed satisfactorily in other cases (method D) (Table II).

When the carbinol (7c) was refluxed in ethyl acetate in the presence of methyl iodide, we observed a gradual formation of valerophenone, the yield of which reached 86% after prolonged reflux (3 d). 1,3-Dimethyl-1H-imidazolium iodide (9) could also be isolated in 63% yield, indicating that the C–C bond fission occurs in a hydrolytic manner but not through any
TABLE II. Formation of the Carbonyl Compounds (5 and 6) by Methods A—D

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Method</th>
<th>Product</th>
<th>Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a</td>
<td>A</td>
<td>Benzophenone (6a)</td>
<td>96.6 (quant.)</td>
</tr>
<tr>
<td>2</td>
<td>7a</td>
<td>C</td>
<td>Benzophenone (6a)</td>
<td>(quant.)</td>
</tr>
<tr>
<td>3</td>
<td>7a</td>
<td>D</td>
<td>Benzophenone (6a)</td>
<td>80.0</td>
</tr>
<tr>
<td>4</td>
<td>7b</td>
<td>A</td>
<td>Acetophenone (6c)</td>
<td>(quant.)</td>
</tr>
<tr>
<td>5</td>
<td>7b</td>
<td>C</td>
<td>Acetophenone (6c)</td>
<td>(80.0)</td>
</tr>
<tr>
<td>6</td>
<td>7c</td>
<td>A</td>
<td>Valerophenone (6d)</td>
<td>(quant.)</td>
</tr>
<tr>
<td>7</td>
<td>7c</td>
<td>D</td>
<td>Valerophenone (6d)</td>
<td>(quant.)</td>
</tr>
<tr>
<td>8</td>
<td>7d</td>
<td>A</td>
<td>$R^1$=cyclo-$C_6H_{11}$; $R^2$=benzyl (6g)</td>
<td>90.0</td>
</tr>
<tr>
<td>9</td>
<td>7e</td>
<td>A</td>
<td>1-Tetralone (6e)</td>
<td>(quant.)</td>
</tr>
<tr>
<td>10</td>
<td>7f</td>
<td>A</td>
<td>COCH$_2$COO-tert-Bu (6h)</td>
<td>70.3</td>
</tr>
<tr>
<td>11</td>
<td>7g</td>
<td>A</td>
<td>COCH$_2$COO-tert-Bu</td>
<td>85.7</td>
</tr>
<tr>
<td>12</td>
<td>7h</td>
<td>A</td>
<td>CH$_3$(CH$_2$)$_3$COCH$_2$COO-tert-Bu (6j)</td>
<td>87.7</td>
</tr>
<tr>
<td>13</td>
<td>7i</td>
<td>A</td>
<td>2-Octanone (6b)</td>
<td>(quant.)</td>
</tr>
<tr>
<td>14</td>
<td>7j</td>
<td>A</td>
<td>COCH$_3$</td>
<td>(quant.)</td>
</tr>
<tr>
<td>15</td>
<td>4a</td>
<td>A</td>
<td>Piperonal (5a)</td>
<td>(quant.)</td>
</tr>
<tr>
<td>16</td>
<td>4a</td>
<td>B</td>
<td>Piperonal (5a)</td>
<td>(47.1)</td>
</tr>
<tr>
<td>17</td>
<td>4c</td>
<td>B</td>
<td>$R^1$=cyclo-$C_6H_{11}$ (5d)</td>
<td>(84.4)</td>
</tr>
<tr>
<td>18</td>
<td>4d</td>
<td>B</td>
<td>n-Heptanol (5c)</td>
<td>(83.9)</td>
</tr>
<tr>
<td>19</td>
<td>4e</td>
<td>A</td>
<td>Citronellal (5b)</td>
<td>(nil)</td>
</tr>
<tr>
<td>20</td>
<td>4e</td>
<td>B</td>
<td>Citronellal (5b)</td>
<td>74.5 (79.0)</td>
</tr>
</tbody>
</table>

*a) Yields in parentheses were obtained by GLC and those without parentheses are isolated yields.  b) $\alpha$-Chloroacetophenone was also produced in 5—15% yield.

![Chart 3](chart.png)
other process such as autoxidation.

Stability of the imidazolyl methanol derivatives (4a) under various severe conditions was examined as follows in order to evaluate the characteristics of the molecular system as protecting group for the carbonyl group: 1 N KOH/CH$_3$OH/70 °C/7 h; 20% H$_2$SO$_4$/70 °C/7 h; NaBH$_4$/CH$_3$OH/room temperature (r.t.)/20 h; LiAlH$_4$/THF/r.t./N$_2$/20 h; CF$_3$COOH/r.t./24 h; H$_2$/5% Pd–C/CH$_3$OH/1 atmosphere (atm)/r.t./18 h. Fortunately, it was found on the bases of gas-liquid layer chromatography (GLC) that the substrate (4a) survived almost intact under all of these conditions. It is noteworthy that the imidazolymethanols (4c and 7c), which might be expected to undergo relatively easy dehydration, were almost intact after treatment with 20% sulfuric acid at 70 °C for 7 h probably because the first protonation on the imidazole nitrogen prevented the second protonation on hydroxy group owing to repulsion between the two positive charges. Thus, we can use the imidazolemethanols (4 and 7) as a characteristic protecting group for the carbonyl group.

If the secondary imidazolymethanols (4) can be oxidized to the 2-acylimidazoles (3), various aldehydes may be convertible into ketones and active acyls by applying the present methodology, including the procedure in the previous report. Although pyridinium chlorochromate oxidation of 4a proceeded in 84.3% yield, the other imidazolymethanols (4) gave the 2-acyl derivatives in very low yield probably because of losses during extraction of the product. We are now investigating more convenient oxidation procedures.

Next, preparations of dihydrojasmine (16), a constituent of bergamot oil, was examined as an application of the present methodology. 1-(4,4-Ethlenedioxypentanoyl)-pyrrolidine (11) was treated with 2-lithio-1-methyl-1H-imidazole (2) to give the corresponding 2-acylimidazole (12) in 79.1% yield. A Grignard reaction of the acylimidazole (12) with an excess of n-hexylmagnesium bromide proceeded satisfactorily to afford the crystalline carbinol (13) in 92.6% yield, and 13 was treated with 10% hydrochloric acid for several minutes to give a ketocarbinol (14). Treatment of the ketocarbinol (14) according to method A, described above, furnished the diketone (15) in 97.4% yield; this product was firstly reported as an intermediate for the synthesis of dihydrojasmine (16) by Stork and Borche. In our experiment, a direct Grignard reaction of the ketal amide 11 with n-hexylmagnesium bromide resulted in formation of a complex mixture consisting of 11 (about 60%), the corresponding ketone (2-ethenenedioxyundecan-5-one; about 20%) and several
unidentified products. This result may be explained in terms of interference by the ketal function with the approach of the Grignard reagent and several known side reactions in the Bouveault ketone synthesis.\(^{11)}\)

Finally, syntheses of symmetric ketones were attempted. For example, 2-ethoxycarbonyl-1-methyl-1\(H\)-imidazole (3f)\(^5\) was treated with an excess of an ethereal solution of cyclohexylmagnesium bromide to give the corresponding symmetrically disubstituted imidazolylmethanol (7i: \(R^1 = R^2 = \text{cyclohexyl}\)) in 81.9\% yield. The imidazolylmethanol (7i) was treated according to method A to produce dicyclohexylketone (6i) in 78.9\% yield. Other examples listed in Table III also proceeded satisfactorily except for 7n. The reaction of ethyl formate with Grignard reagent has been well known as a convenient preparation method for symmetrically substituted secondary alcohols,\(^{12)}\) and the present reaction may provide a new and general procedure for linking two molecules of the same Grignard reagent with one carbonyl group.

In conclusion, the present methodology should be useful in organic synthesis not only as a protecting group for the carbonyl group but also as a synthon of various carbonyl compounds. Characteristic features of the present methodology can be summarized as follows. i) An excess of Grignard reagent and reducing agent (\(\text{NaBH}_4\)) can be used in their reaction with the 2-acyl-1\(H\)-imidazole (3). ii) The resulting imidazolylmethanols (4 and 7) can

![Chart 5](image)

### Table III. Conversion of 2-Ethoxycarbonyl-1-methyl-1\(H\)-imidazole (3f) into Symmetrically Substituted Ketones via Symmetrically Disubstituted Carbonoln (7)

| Entry | \(R^1\text{MgBr or } R^1\text{Li} \quad \text{mp (C)} \quad \text{Appearance (Recryst. solv.)} \quad \text{Yield (\%)} \quad \text{Method} \quad \text{mp or bp (C)} \quad \text{(Lit. value) (Reference)} \quad \text{Yield (\%)} |
|-------|-------------------------------------------------|-----------------|-----------------|----------------|----------------|----------------|----------------|
| 1     | \(\text{C} = \text{C-Li} \quad \text{MgBr} \quad \text{180.5—182 (dec.)} \quad \text{Needles (CCl}_4) \quad 92.6 \quad \text{A} \quad \text{mp 87—88.5 (Ref. 11)} | Quant. |
| 2     | \(\text{C}_6\text{H}_5 \quad \text{MgBr} \quad \text{153.5—155} \quad \text{Needles (EtOAc—n-hexane)} \quad 81.9 \quad \text{A} \quad \text{bp 130—135 (5 mmHg) (Ref. 15)} | 78.9 |
| 3     | \(\text{C} = \text{C-Li} \quad \text{MgBr} \quad \text{152—153} \quad \text{Needles (AcOEt)} \quad 85.0 \quad \text{D} \quad \text{bp 140—145 (3 mmHg) (Ref. 16)} | 70.5 |
| 4     | \(\text{C} = \text{C-Li} \quad \text{Prisms (CH}_3\text{OH)} \quad 88.8 \quad \text{A} \quad \text{—} | a) |

\(a\) A resinous material was produced.
be regarded as protected forms of carbonyl compounds, which are stable under various severe conditions and can be deprotected under relatively selective reaction conditions. Thus, the present carbonyl group protection system [-C(OH)-C=N-CH=CH-N(CH3)] is a new type, different from the known carbonyl protecting systems such as ketal, acetal, thioketal and gem-cyanohydrin. iii) The 2-acylimidazoles (3) can be regarded as synthons of various carbonyl compounds. iv) Imidazole compounds are extractable with aqueous acid, so they can be easily separated from neutral and acidic compounds. We are now investigating syntheses of several natural products as further applications of the present methodology.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were taken with a Shimadzu IR-410 spectrometer. Proton nuclear magnetic resonance (1H-NMR) spectra were recorded on a Varian CFT-20 spectrometer using tetramethylsilane as an internal standard and the chemical shifts are given in δ-values (ppm). Abbreviations of 1H-NMR signal patterns are as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). High-resolution mass spectra (HRMS) and low-resolution mass spectra (MS) were both taken with a Hitachi RMU-2 spectrometer. Ultraviolet (UV) spectra in ethanolic solutions were recorded on a Shimadzu-2005 spectrometer. Oily products and low-melting-point products were purified by vacuum distillation with a Kugel–Rohr distillation apparatus.

General Procedure for Synthesis of (1-Methyl-1H-imidazol-2-yl)-methanol Derivatives—a) 2-(1-Hydroxyheptyl)-1-methyl-1H-imidazole (4d): n-Butyllithium (1.6 M in hexane; 10 mmol) was added to a solution of 1-methyl-1H-imidazole (0.82 g, 10 mmol) in tetrahydrofuran (THF) at −78 °C under an N2 atmosphere and the mixture was stirred for 5 min. n-Heptanal (1.14 g, 10 mmol) was added dropwise to the solution and the mixture was stirred for 30 min while warming to ambient temperature (the cooling bath was removed). Ether (30 ml) and 10% HCl (10 ml) were added, and the aqueous layer was washed with ether (5 ml) and basified with solid K2CO3. The separated oil was extracted with ethyl acetate. The organic layer was evaporated after drying with Na2SO4 to give an oily residue, which was purified by vacuum distillation. bp, 132 °C. Yield, 1.38 g (70.3%). IR (CHCl3): 3160 cm−1 (OH). 1H-NMR (CDCl3): δ: 0.86 (t, 3H, CH3CH2-; J = 8 Hz), 1.05–1.65 (m, 8H, CH3(CH2)4-), 1.83 (t, 2H, -CH2CH(OH)-, J = 8 Hz), 3.68 (s, 3H, NCH3), 4.00 (br, 1H, OH), 4.67 (t, 1H, -CH(OH)-, J = 8 Hz), 6.76 and 6.86 (d each, 1H each, imidazole H, J = 1 Hz each). Elemental analysis was performed with the corresponding methiodide (10c) as described below.

b) 2-(1-Cyclohexyl-1-hydroxy-2-phenylethyl)-1-methyl-1H-imidazole (7d): 2-Cyclohexylcarbonyl-1-methyl-1H-imidazole (3d; 0.96 g, 5 mmol) was added under ice-cooling to a stirred ethereal solution of benzylmagnesium bromide, which was prepared from benzyl bromide (1.71 g, 10 mmol), magnesium metal (468 mg, 20 mg atorn) and ether (10 ml). The mixture was stirred at room temperature for 2 h and filtered. The mixture was acidified with 10% HCl and the aqueous layer was washed with ether then basified with solid K2CO3. Separated material was extracted with ethyl acetate. Evaporation of the solution after drying with Na2SO4 gave a crystalline residue, which was recrystallized from CCl4 to give colorless needles. mp 185–186 °C. Yield, 1.18 g (83.0%). IR (CHCl3): 3520 (OH), 3350 cm−1 (OH). 1H-NMR (CDCl3): δ: 0.95–2.20 (m, 11H, cyclohexyl H), 3.12 (s, 1H, OH), 3.25 (d, 2H, -CH2CH2OH, J = 8 Hz), 3.43 (s, 3H, NCH3), 6.55–7.30 (m, 7H, imidazole H and C6H5-). Anal. Calcd for C25H28N2O: C, 76.02; H, 8.47; N, 9.85. Found: C, 76.18; H, 8.47; N, 9.07.

c) 2-(Diphenylhydroxymethyl)-1-methyl-1H-imidazole (7a): Phenyllithium solution (2.4 M in ether, 6 mmol) was added to a solution of 2-benzoyl-1-methyl-1H-imidazole (3b; 0.93 g, 5 mmol) in tetrahydrofuran (THF; 10 ml) at −78 °C and the solution was stirred for 10 min followed by stirring for 30 min while warming to ambient temperature (the cooling bath and removed). Ether (30 ml) and 10% HCl (10 ml) were added and the aqueous layer was washed with ether and basified with solid K2CO3. The precipitated solid was filtered off and recrystallized from CC2H5 to give colorless prisms. mp 125.5–127.5 °C. Yield, 755 mg (72.5%). IR (CHCl3): 3420 (OH), 1700 cm−1 (C = O). 1H-NMR (CDCl3): δ: 1.45 (s, 9H, -(C(CH3)3), 2.66 and 3.41 (d each, 1H each, -CH2COO-, -CH2OH).
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1.3-Dimethyl-2-(1-hydroxy-1-phenylethyl)-1-methyl-1H-imidazolium Iodide (8c) (Typical Procedure for Synthesis of the Quaternary Salt 8 and 10) — A suspension of 2-(1-hydroxy-1-phenylethyl)-1-methyl-1H-imidazole (7b; 1.01 g, 5 mmol) in ethyl acetate (25 ml) was refluxed under N₂ for 2 h in the presence of methyl iodide (5 ml). Removal of the solvent gave a crystalline residue, which was recrystallized from CH₂Cl₂-ether to give leaflets. mp 141—143 °C. Yield, quantitative. IR (CHCl₃): 3120 cm⁻¹ (OH). ¹H-NMR (CDCl₃) δ: 1.00-1.60 (m, 4H, -(CH₂)₂CH₂-), 2.30-3.10 (m, 3H, -CH₂COO-), 3.35 (br, 1H, OH), 3.78 (s, 3H, NCH₃), 6.77 and 6.84 (d each, 1H each, imidazole H, J = 1 Hz each). Anal. Calcd for C₁₅H₂₀N₂O: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.76; H, 6.95; N, 12.24.

2-(1-Hydroxybut-3-enyl)-1-methyl-1H-imidazole (4b): IR (CHCl₃): 3200 cm⁻¹ (OH). ¹H-NMR (CDCl₃) δ: 0.85 (t, 3H, CH₃CH₂-, J = 8 Hz), 1.00-1.60 (m, 4H, -(CH₂)₂CH₂-), 2.30-3.10 (m, 3H, -CH₂COO-), 3.35 (br, 1H, OH), 3.78 (s, 3H, NCH₃), 6.77 and 6.84 (d each, 1H each, imidazole H, J = 1 Hz each). Anal. Calcd for C₁₅H₂₀N₂O: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.76; H, 6.95; N, 12.24.

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1,3-Dimethyl-2-(1-hydroxy-1-phenylethyl)-1-methyl-1H-imidazolium Iodide (8c) (Typical Procedure for Synthesis of the Quaternary Salt 8 and 10) — A suspension of 2-(1-hydroxy-1-phenylethyl)-1-methyl-1H-imidazole (7b; 1.01 g, 5 mmol) in ethyl acetate (25 ml) was refluxed under N₂ for 2 h in the presence of methyl iodide (5 ml). Removal of the solvent gave a crystalline residue, which was recrystallized from CH₂Cl₂-ether to give leaflets. mp 141—143 °C. Yield, quantitative. IR (CHCl₃): 3120 cm⁻¹ (OH). ¹H-NMR (CDCl₃) δ: 1.00-1.60 (m, 4H, -(CH₂)₂CH₂-), 2.30-3.10 (m, 3H, -CH₂COO-), 3.35 (br, 1H, OH), 3.78 (s, 3H, NCH₃), 6.77 and 6.84 (d each, 1H each, imidazole H, J = 1 Hz each). Anal. Calcd for C₁₅H₂₀N₂O: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.76; H, 6.95; N, 12.24.
1,3-Dimethyl-2-(1-hydroxy-1,3,4,5-tetrahydropyridin-1-yl)-1H-imidazolium Iodide (8b): Colorless leaflets from ethyl acetate, mp 195–202.5 °C. IR (KBr): 3250 cm⁻¹ (OH). ¹H-NMR (DMSO-d₆): δ: 1.60–2.35 (m, 4H, -C(OH)CH₂CH₂-), 2.70–3.00 (m, 2H, -CH₂CH₃-), 3.59 (s, 6H, NCH₃×2), 6.80 (br, 1H, -OH), 6.90–7.72 (m, 6H, Ar-H). Anal. Calcd for C₁₂H₂₁IN₂O: C, 42.61; H, 5.17; N, 7.57. Found: C, 42.61; H, 5.44; N, 7.73.

1,3-Dimethyl-2-[hydroxy(3,4-methylenedioxyphenyl)-methyl]-1H-imidazolium Iodide (10a): Colorless needles from ethanol–ether, mp 167–169 °C. IR (KBr): 3200 cm⁻¹ (OH). ¹H-NMR (CDCl₃): δ: 0.88 (t, 3H, CH₃CH₂-, J = 8 Hz), 1.02–2.10 (m, 10H, CH₃(CH₃)₂), 4.01 (s, 6H, NCH₃×2), 5.04 (s, 1H, -OH), 7.42 (s, 2H, imidazole H). Anal. Calcd for C₁₃H₁₅IN₂O: C, 41.73; H, 4.04; N, 7.49. Found: C, 41.84; H, 4.03; N, 7.52.

1,3-Dimethyl-2-cyclohexyl-1H-imidazolium Iodide (10b): Colorless needles from acetone–ether, mp 123–124 °C. IR (CHCl₃): 3280 cm⁻¹ (OH). ¹H-NMR (DMSO-d₆): δ: 0.80–2.30 (m, 1H, cyclo-C₆H₁₁-), 4.02 (s, 6H, NCH₃×2), 4.93 (s, 1H, -OH). Anal. Calcd for C₁₅H₁₉IN₂O: C, 48.66; H, 5.17; N, 7.57. Found: C, 48.77; H, 5.44; N, 7.73.
with 4a in the same manner as in i). mp 126–129°C. Yield, 170 mg (85.0%).

c) NaBH₄ (30 mg) was added to a solution of 4a (50 mg) in methanol (1.5 ml) followed by stirring at room temperature overnight. The solvent was evaporated off, and then ethyl acetate (20 ml) and water (5 ml) were added to the residue. The organic layer was dried with Na₂SO₄. Removal of the solvent gave a crystalline residue, which was shown to be identical with 4a by IR and TLC comparisons. mp 122–126°C. Yield, 50 mg (quantitative).

d) The imidazolylmethanol (4a; 232 mg) was hydrogenated in ethanol (5 ml) in the presence of 5% Pd–C (500 mg) under usual pressure for 2 h. Hydrogen uptake was not observed. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give a crystalline residue, which was identified as 4a by IR and TLC comparisons. mp 123–128°C. Yield, 204 mg (88.0%).

e) The imidazolylmethanol (4a; 232 mg) was added to a suspension of LiAlH₄ (76 mg) in THF (2 ml) and the mixture was stirred for 20 h. Water (1 ml) and ethyl acetate (10 ml) were added to the resulting mixture and the organic layer was dried with Na₂SO₄. Removal of the solvent under reduced pressure gave a crystalline residue, which was identified as 4a by IR and TLC comparisons. mp 122–127°C. Yield, 206 mg (88.8%).

f) A solution of 4a (200 mg) in trifluoroacetic acid (2 ml) was stirred at room temperature for 24 h followed by evaporation of the solvent under reduced pressure. The residue was basified with 10% K₂CO₃ and extracted with ethyl acetate. Removal of the solvent after drying with Na₂SO₄ gave a crystalline residue, which was identical with 4a on the basis of IR and TLC comparisons. mp 124–128°C. Yield, 201 mg (quantitative).

Oxidation of 2-(3,4-Methylenedioxyphenyl)hydroxymethyl-1-methyl-1H-imidazole (4a) —— Powdered pyridinium chlorochromate (1.72 g, 8 mmol) was added to a solution of the alcohol (4a; 928 mg, 4 mmol) in CH₂Cl₂ (20 ml) and the mixture was stirred for 30 min. Ether (50 ml) was added and the supernatant was passed through a column packed with Florisil. Evaporation of the eluate gave a crystalline mass. The residual chromium deposit was treated with 10% NaOH (30 ml) followed by extraction with EtOAc (30 ml × 3). The solvent was evaporated off after drying with Na₂SO₄ to give a crystalline residue. The combined crude product was recrystallized from CCl₄. The product was identical with 3c, mp 104–108°C. (lit. mp 105–107°C). ¹¹ Yield, 775 mg (84.3%).

2-(2,5-Undecadione (15) Method A was used, starting from the ketonic imidazolylmethanol (14; 532 mg, 2 mmol), dimethyl sulphate (303 mg, 2.4 mmol) and ethyl acetate (4 ml). The oily product was purified by vacuum distillation. bp 95–100°C (1 mmHg) [lit. bp 70°C (0.2 mmHg)]. Yield, 358 mg (97.4%). This product was characterized as 15 on the basis of the following spectral data. IR (CHCl₃): 1715 cm⁻¹ (C=O) [lit. value: 1715 cm⁻¹ (neat)].¹¹ MS m/z: M⁺ = 184. ¹¹H-NMR (CDCl₃): δ = 0.87 (t, 3H, CH₃CH₂-, J = 8 Hz), 1.10–1.85 (m, 8H, CH₂(C₃H₇)₂), 2.44 (t, 2H, –COCH₂CH₂CO–), 2.68 (s, 4H, –COCH₂CH₂CO–).
ethyl acetate–n-hexane to give colorless needles. The product was identified as 4c by IR and TLC comparisons. mp 108—110 °C. Yield, 168 mg (84.0%).

b) 2-(Butylhydroxyphenylmethyl)-1-methyl-1H-imidazole (7c; 200 mg) was reacted as described for a), resulting in a recovery of 7c in 89.0% yield. mp 151—152 °C.

References and Notes

7) In the preliminary report, we tentatively proposed a reaction mechanism, in which initial attack of the hydroxide ion occurred at the 2-position of the imidazolium salt (8 and 10) to produce a pseudo-base as an intermediate. The present mechanism seems to account for the difference of reactivities between the imidazolium salts (8 and 10) more reasonably than the previous mechanism. [S. Ohta, S. Hayakawa, K. Nishimura, and M. Okamoto, Tetrahedron Lett., 25, 3251 (1984).]