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Received December 22, 1995

## Dedicated to the memory of Professor Nicholas Alexandrou

2-(2-Arylethyl)-1-methylimidazoles **3** could be prepared by different methods. The best method was the Wittig reaction of aryltriphenylphosphonium chloride **8** with 2-formyl-1-methylimidazole to give compound **6**. Reduction of compound **6** with Raney nickel gave compound **3**.

*J. Heterocyclic Chem.*, **33**, 671 (1996).

The considerable biological importance of imidazoles has stimulated much work on this heterocycle [1]. We would like to report the syntheses of the title compounds as possible effective drugs in fertility regulation [2].

The most common method for the preparation of 2-substituted imidazoles is alkylation of 1-(*N,N*-dimethylaminomethyl)-2-methylimidazole **1** in the presence of *n*-butyllithium to give 2-(2-arylethyl)imidazoles **2** [3]. Methylation of the latter did not give the desired compounds, namely 2-(2-arylethyl)-1-methylimidazoles **3** in good yield [4] (Scheme 1).

Direct alkylation of 1,2-dimethylimidazole with 4-substituted benzyl halide gave compound **3** in low yield.

Another method for the preparation of compound **3** was the reaction of 1,2-dimethylimidazole **4** with an aldehyde to give 1-aryl-2-(1-methyl-2-imidazolyl)ethanol **5** [5]. Dehydration of **5** with acetic anhydride/acetic acid gave 2-arylethenyl-1-methylimidazoles **6** in moderate yield [6] (method A). Compound **6** could be obtained from the reaction of compound **4** with an arylaldehyde in the presence of acetic anhydride in poor to moderate yield [7] (method B). Finally compound **6** could be obtained from the reaction of aryltriphenylphosphonium chloride **8** or diethyl arylphosphonate with 2-formyl-1-methylimidazole **7** and sodium ethoxide in ethanol [8,9] in high yield (method C). Reduction of compound **6** with Raney nickel afforded the desired compound **3** in excellent yield.

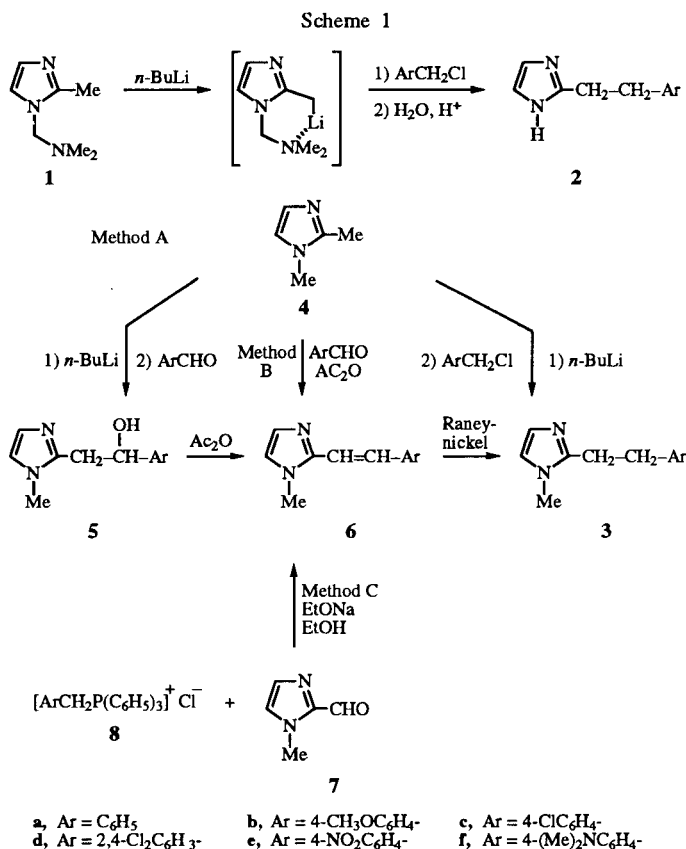


Table 1

Melting Points, Yields and Analytical Data for Compounds **6a-f**

Compound	Mp, °C	Yield method		Formula	Calcd./Found C%		Calc./Found H%		Calcd./Found N%	
		B	C							
<b>6a</b>	oil	71 [a]	75	C <sub>12</sub> H <sub>12</sub> N <sub>12</sub>	78.26	78.12	6.52	6.39	15.22	15.37
<b>6b</b>	oil	55	69	C <sub>13</sub> H <sub>14</sub> N <sub>2</sub> O	72.90	72.76	6.54	6.39	13.08	13.21
<b>6c</b>	107-109 [c]	- [b]	70	C <sub>12</sub> H <sub>11</sub> ClN <sub>2</sub>	65.90	65.72	5.03	5.21	12.81	12.94
<b>6d</b>	169-171 [c]	65	76	C <sub>12</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub>	56.92	57.02	3.95	4.12	11.07	11.21
<b>6e</b>	189-191 [c]	- [b]	50	C <sub>12</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub>	62.88	62.69	4.80	4.95	18.34	18.46
<b>6f</b>	183-185 [d]	15	- [e]	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub>	74.01	73.87	7.49	7.63	18.50	18.36

[a] This compound was prepared by method A. [b] The preparation of this compound by method B was not attempted. [c] This compound was crystallized as *trans* isomer from chloroform-ether. [d] This compound was crystallized as *trans* isomer from ether; [e] We could not prepare *p*-dimethylaminobenzyl bromide required for the reaction.

Table 2  
Melting Points, Yields and Analytical Data for Compounds **3a-3f**

Compound	Mp, °C	Yield	Formula	Calcd./Found		Calcd./Found		Calcd./Found	
				C%	H%	H%	N%		
<b>3a</b>	oil	60	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub>	77.42	77.59	7.53	7.41	15.05	15.23
<b>3b</b>	oil [a]	71	C <sub>13</sub> H <sub>17</sub> ClN <sub>2</sub> O	61.78	61.89	6.73	6.86	11.09	11.25
<b>3c</b>	oil	62	C <sub>12</sub> H <sub>13</sub> ClN <sub>2</sub>	65.31	65.46	5.90	6.01	12.70	12.84
<b>3d</b>	oil [b]	57	C <sub>12</sub> H <sub>13</sub> Cl <sub>3</sub> N <sub>2</sub>	49.40	49.54	4.46	4.29	9.61	9.47
<b>3f</b>	oil	45	C <sub>14</sub> H <sub>19</sub> N <sub>3</sub>	73.36	73.52	8.30	8.45	18.34	18.51

[a] As hydrochloride mp 166-168° (ethanol-ether). [b] As hydrochloride mp 188-190° (ethanol-ether).

The melting points, yields and analytical data of the compounds prepared are summarized in Tables 1 and 2.

## EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The uv spectra were recorded on a Perkin Elmer 550 SE spectrophotometer. The ir spectra were obtained on a Perkin Elmer 267 spectrophotometer (potassium bromide disks). The nmr spectra were recorded on a Bruker FT-80 or a Varian FT-400 unity plus spectrometers. Chemical shifts are reported in ppm from TMS as an internal standard and are given in  $\delta$  units. The mass spectra were run on Varian Model MAT-311 or Finigan TSQ-700 spectrometers at 70 eV.

### 1-Methyl-2-(2-Phenylethenyl)imidazole (**6a**).

#### Method A.

A stirring solution of 1-phenyl-2-(1-methyl-2-imidazolyl)-ethanol **5a** [5] (2.02 g, 0.01 mole), acetic anhydride (5 ml) and acetic acid (10 ml) was refluxed for 4 hours. The solvent was evaporated. To the residue water (10 ml) was added and stirred for 10 minutes. The solution was made alkaline with potassium carbonate and extracted with ethyl acetate (100 ml). The organic layer was dried (sodium sulfate) and filtered. The solvent was evaporated and the residue was distilled to give 1.3 g (71%) of **6a**, bp 132-134° (3 mm Hg); ms: m/z (%) 184 (M<sup>+</sup>, 84), 183 (100), 168 (34), 128 (16), 115 (24), 107 (10), 92 (10), 77 (10) and 42 (12).

### 2-[2-(2,4-Dichlorophenyl)ethenyl]-1-methylimidazole (**6d**).

#### Method B.

A stirring mixture of 2,4-dichloro-benzaldehyde (1.75 g, 0.01 mole), 1,2-dimethylimidazole (0.96 g, 0.01 mole) and acetic anhydride (0.51 g, 0.005 mole) was heated at 140° for 4 hours. After cooling, water (10 ml) was added and acidified with hydrochloric acid. The mixture was extracted with ether. The aqueous layer was made alkaline with sodium hydroxide and the precipitate was filtered and crystallized from chloroform-ether to give 1.64 g (65%) of **6d**, mp 169-171°; <sup>1</sup>H-nmr (deuteriochloroform): 7.82 (d, 1H, ethylene, J = 16 Hz), 7.57 (d, H<sub>6</sub> of phenyl, J<sub>5,6</sub> = 8.4 Hz), 7.42 (d, 1H, H<sub>3</sub> of phenyl, J<sub>3,5</sub> = 2.4 Hz), 7.24 (dd, 1H, H<sub>5</sub> of phenyl, J<sub>5,6</sub> = 8.4 Hz, J<sub>3,5</sub> = 2.4 Hz), 7.11 (s, 1H, imidazole), 6.91 (s, 1H, imidazole), 6.90 (d, 1H, ethylene, J = 16 Hz) and 3.74 ppm (s, 3H, NCH<sub>3</sub>); ms: m/z (%) 252 (M<sup>+</sup>, 81), 217 (100), 202 (45), 181 (16), 162 (12), 113 (12), 108 (28), 54 (11) and 42 (17).

Compounds **6b** and **6f** were prepared similarly (Table 1).

### 2-[2-(4-Chlorophenyl)ethenyl]-1-methylimidazole (**6c**).

#### Method C.

A mixture of *p*-chlorobenzyl chloride (1.61 g, 0.01 mole) and triphenylphosphine (2.62 g, 0.01 mole) was stirred. The temperature was raised slowly and a clear solution was obtained, which started to solidify at about 90°. The crude product was cooled, washed with ethyl ether to give *p*-chlorobenzyltriphenyl phosphonium chloride, mp 285-287°.

A solution of sodium (0.23 g, 0.01 mole) in 15 ml of absolute ethanol was added dropwise to stirred refluxing solution of *p*-chlorobenzyltriphenyl phosphonium chloride (4.23 g, 0.01 mole) and 2-formyl-1-methylimidazole (1.1 g, 0.01 mole) in 25 ml of absolute ethanol. After 3 hours the solution was cooled, filtered and evaporated. The residue was suspended in water, acidified with hydrochloric acid and extracted with ether. The aqueous layer was made alkaline with sodium hydroxide and extracted with ether. The organic layer was dried, filtered and evaporated to give a crude mixture of *trans* and *cis* of **6c**.

If triethyl phosphite instead of triphenylphosphine was used [9] only the *trans* isomer of **6c** was obtained in 70% yield, mp 107-109° (chloroform-ether); uv (methanol):  $\lambda_{\max}$  326 nm (log  $\epsilon$  = 4.68); ir (potassium bromide):  $\nu$  3020 (aromatic) and 1670 cm<sup>-1</sup> (*trans* C=C); <sup>1</sup>H-nmr (deuteriochloroform): 7.52 (d, 1H, ethylene, J = 16 Hz), 7.44 (d, 2H, phenyl, J = 8.4 Hz), 7.31 (d, 2H, phenyl, J = 8.4 Hz), 7.08 (s, 1H, imidazole), 6.88 (s, 1H, imidazole), 6.86 (d, 1H, ethylene, J = 16 Hz) and 3.71 ppm (s, 3H, CH<sub>3</sub>).

Compounds **6a** to **6e** were prepared similarly (Table 1).

### 2-[2-(2,4-Dichlorophenyl)ethyl]-1-methylimidazole (**3d**).

A stirring mixture of **6d** (2.53 g, 0.01 mole), dioxane (100 ml) and Raney nickel (11 g) was refluxed for 2 hours. After cooling, it was filtered. The solvent was evaporated and the residue was crystallized as hydrochloride from ethanol ether to give 1.66 g (57%) of **3d**, mp 188-190°; <sup>1</sup>H-nmr (deuteriochloroform, as a free base): 7.36 (s, 1H), 7.11 (s, 2H), 6.99 (s, 1H), 6.77 (s, 1H), 3.44 (s, 3H, NCH<sub>3</sub>) and 3.08 ppm (m, 4H, CH<sub>2</sub>); ms: m/z (%) 254 (M<sup>+</sup>, 39), 219 (100), 109 (19), 95 (91) and 54 (12).

Compounds **3a**, **3b**, **3c** and **3f** were prepared similarly (Table 2).

#### Acknowledgement.

This research was supported by a grant from the International Organization for Chemical Sciences in Development (IOCD).

## REFERENCES AND NOTES

- [1] A. Sharifian, K. Parang, H. Zorrieh-Amirian, M. Nazarinia and A. Shafiee, *J. Heterocyclic Chem.*, **31**, 1421 (1994) and references cited therein.
- [2] R. Maybury, *Chem. Eng. News*, August 12, p 28 (1991).
- [3] B. Tarnchompoo, C. Thebtaranonth and Y. Thebtaranonth, *Tetrahedron Letters*, **31**, 5779 (1990) and references cited therein.
- [4] A. Shafiee, A. Ghanbarpour and F. Ghasemian, *Synthesis*, **385** (1987).
- [5] D. S. Noyce, G. T. Stowe and W. Wong, *J. Org. Chem.*, **39**, 2301 (1974).
- [6] S. Ohta, M. Matsukawa, N. Ohashi and K. Nagayama, *Synthesis*, **78** (1990).
- [7] C. E. Kaslow and R. Dale Stayner, *J. Am. Chem. Soc.*, **67**, 1716 (1945).
- [8] G. Lindgren, K. E. Stensio and K. Wahlberg, *J. Heterocyclic Chem.*, **17**, 679 (1980).
- [9] E. J. Seus and C. V. Wilson, *J. Org. Chem.*, **26**, 5243 (1961).