A New and Simple Synthesis of Some 4-Substituted Imidazoles

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The syntheses of alkyl 4-imidazolecarboxylates and their derivatives have been reported[1,2] to involve tedious multistep reactions. We now report a simple method for such synthesis.

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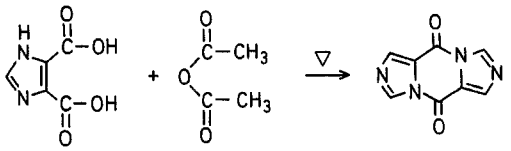
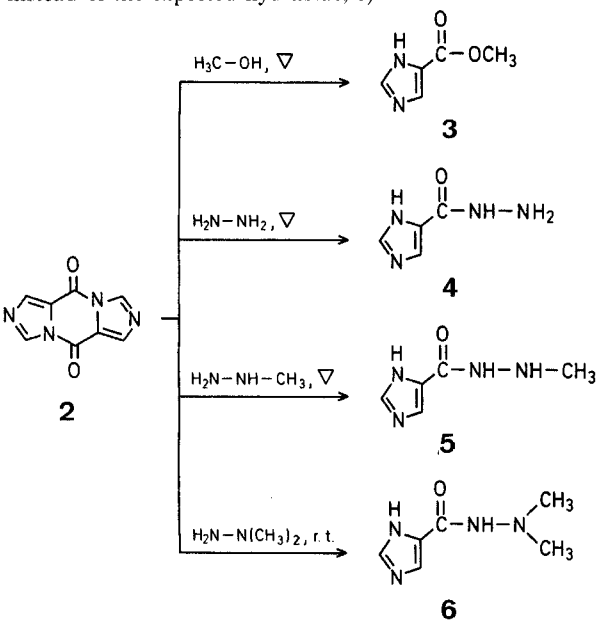
In an investigation on the reactivity of anhydrides with hydrazines[3], attempts were made to convert the easily available 4,5-imidazoledicarboxylic acid (**1**) to its anhydride via reaction with acetic anhydride. A product was isolated whose identity by using elemental analysis, I.R., N.M.R., and Mass spectrometry was proved to be diimidazo[3,4-*a*; 3′,4′-*d*] piperazin-2,5-dione (**2**).



1 **2**

Reactivity of **2** was explored by allowing it to react with a number of reagents: methanol, hydrazine, methylhydrazine, and 1,1-dimethylhydrazine. The yields were nearly quantitative. The latter reaction product, 4-(2,2-dimethyl)imidazolecarbohydrazide (**6**), was of particular interest, since such species cannot be prepared by the generally employed ester-hydrazine reaction[4] (a methyl ester and 1,1-dimethylhydrazine reaction affords trimethylhydrazonium carboxylate instead of the expected hydrazide, **6**).



2 **3** **4** **5** **6**

The proof for the structures of **3**, **4**, and **5** was carried out by comparing their m.p. and I.R. and N.M.R. spectra with those reported[2].

Diimidazo[3,4-*a*; 3′,4′-*d*′]piperazin-2,5-dione (2):
A mixture of an excess of acetic anhydride and 4,5-imidazoledicarboxylic acid (5.0 g, 0.032 mol) was stirred magnetically and heated under reflux for 36 h. The solution was evaporated in vacuo. After washing with tetrachloromethane, the residue was sublimed: yield: 3.1 g (51%). The compound for elemental analysis was crystallized from benzene; m.p. 254–255°.

$C_8H_4N_4O_2$	calc.	C 51.06	H 2.13	N 29.79
(188.1)	found	50.93	2.35	29.40

I.R. (KBr): $\nu_{max} = 1735$ (s) cm^{-1}.

^{1}H-N.M.R. (Trifluoroacetic acid): $\delta = 8.68$ and 9.55 ppm (s, 2 H_{arom}) down field from sodium 2,2,3,3-tetradeutero-(3-trimethylsilyl)-propanoate (TTP).

Mass Spectrum: $m/e = 188$ ($M^{\oplus}$).

4-(2,2-Dimethyl)imidazolecarbohydrazide (6):
1,1-Dimethylhydrazine (1.8 g, 0.03 mol) was added to **2** (0.5 g, 0.0027 mol) and left at room temperature for 24 h, at which time a semisolid product was formed. The mixture was washed with tetrachloromethane and dried under vacuum to give a crude crystalline **6**; yield: 0.39 g (94%). The compound for elemental analysis was crystallized from a mixture of benzene and methanol; m.p. 277–278°.

$C_6H_{10}N_4O$	calc.	C 46.75	H 6.49	N 36.36
(154.2)	found	47.02	6.55	36.12

I.R. (KBr): $\nu_{max} = 1630$ (s) cm^{-1}.

^{1}H-N.M.R. (Trifluoroacetic acid): $\delta = 3.53$ (s, 6 H), 8.40 and 8.95 ppm (s, 2 H_{arom}) down field from sodium 2,2,3,3-tetradeutero-(3-trimethylsilyl)-propanoate (TTP).

Mass Spectrum: $m/e = 154$ (M^+).

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[1] R. G. Jones, *J. Amer. Chem. Soc.* **71**, 644 (1949).
[2] J. R. Nulu, J. Nematollahi, *J. Med. Chem.* **12**, 804 (1969).
[3] J. Nematollahi, S. Kasina, S. Gautam. Presented in the Academy of Pharmaceutical Sciences meeting, November 12, 1974 (New Orleans).
[4] J. Nematollahi, S. Kasina, D. Maness, *J. Heterocycl. Chem.* **11**, 351 (1974).

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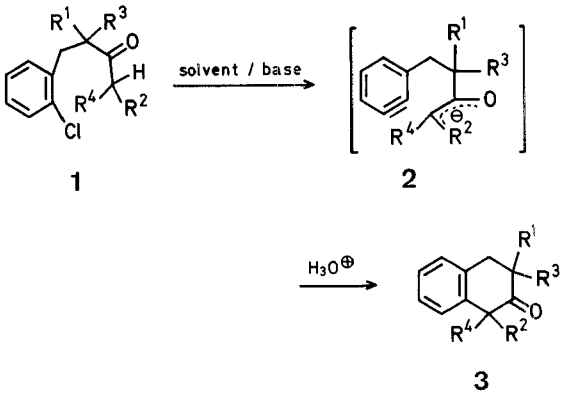
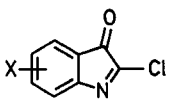
Errata

B. Loubinoux, P. Caubere, *Synthesis* **1974**, 201–203;
The formula scheme (p. 201) should be:



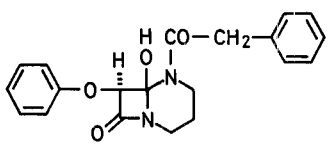
1 2 3

J. Grimshaw, W. J. Begley, *Synthesis* **1974**, 496–498;
The formula **2** in Table 1 (p. 497) should be:



2

A. K. Bose, J. C. Kapur, M. S. Manhas, *Synthesis* **1974**, 891–894;
The formula for compound **18** (p. 891) should be:

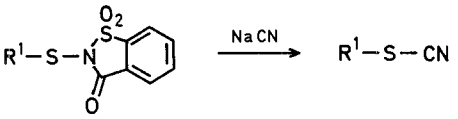


18

H. R. Kricheldorf, E. Leppert, *Synthesis* **1975**, 49–50;
The last entry in the first column of the Table (p. 50) should be:
N-phenyl-*N*-methylimido.

S. Kasina, J. Mematollahi, *Synthesis* **1975**, 162–163;
The name of compound **2** should be:
5,10-dioxo-5*H*,10*H*-diimidazo[3,4-*a*; 3′,4-*d*]pyrazine.

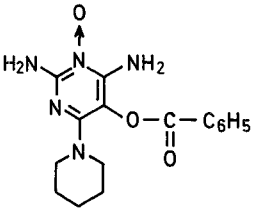
M. Furukawa, T. Suda, A. Tsukamoto, S. Hayashi, *Synthesis* **1975**, 165–167;
The reaction scheme **1**→**4** (p. 166) should be:



1 4

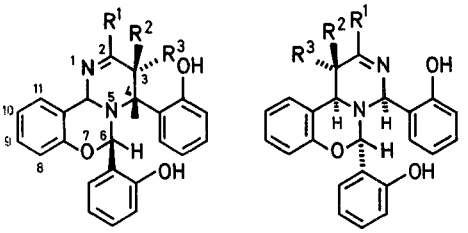
H. Singh, S. Sharma, R. N. Fyer, *Synthesis* **1975**, 325–326;
The name of the title compounds **2** should be:
5-oxobenzimidazo[2,1-*b*][1,3]benzoxazines.

J. M. McCall, R. E. TenBrink, *Synthesis* **1975**, 443–444;
The formula for compound **4** should be:



4

S. Kambe, T. Takajo, K. Saito, T. Hayashi, A. Sakurai, H. Midorikawa, *Synthesis* **1975**, 802–804;



6 7

The names for compounds **6** should be:
6a: 4,6-Bis[2-hydroxyphenyl]-3,3-dimethyl-3,4-dihydro-11b*H*-pyrimido[1,2-*c*][1,3]benzoxazine
6b: 4,6-Bis[2-hydroxyphenyl]-2,3,3-trimethyl-3,4-dihydro-11b*H*-pyrimido[1,2-*c*][1.3]benzoxazine
6c: 4,6-Bis[2-hydroxyphenyl]-2-methyl-3-phenyl-3,4-dihydro-11b*H*-pyrimido[1,2-*c*][1,3]benzoxazine

The names for compounds **7** should be:
7b: 4,6-Bis[2-hydroxyphenyl]-1,1,2-trimethyl-1,4-dihydro-11b*H*-pyrimido[3,4-*c*][1,3]benzoxazine
7c: 4,6-Bis[2-hydroxyphenyl]-1-methyl-2-phenyl-1,4-dihydro-11b*H*-pyrimido[3,4-*c*][1,3]benzoxazine

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