Synthesis of 4,5-Substituted Imidazoles by a Fast Condensation of 1,2-Diketones and Urotropine in Heterogeneous Medium

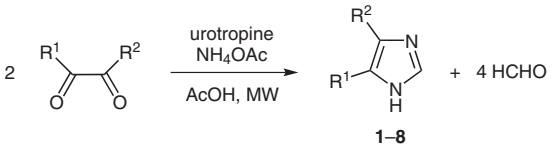
George Bratulescu*

University of Craiova, Faculty of Chemistry, 13 A.I. Cuza, 200396 Craiova, Romania
Fax +40(251)597048; E-mail: georgebratulescu@yahoo.com

Received 24 February 2009; revised 20 March 2009

Abstract: Starting from 1,2-diketones and urotropine in the presence of ammonium acetate, a simple and efficient solventless microwave-assisted synthesis of 4,5-disubstituted imidazoles was accomplished.

Key words: heterocycles, 4,5-disubstituted imidazoles, ketones, urotropine, microwave



1–8

Scheme 1

The imidazole ring has many important biological functions. For example, the imidazole ring is present in intermediates of purine biosynthesis, histamine is an important mediator of the immune response, and the amino acid histidine has many critical functions in protein and peptide structure.[1–3] Imidazole derivatives have also several important applications as antinociceptive and anti-inflammatory drugs,[4] selective antagonists of the glucagon receptor,[5] antifungal pest controls,[6] hypoxic cell therapy and imaging agents,[7] anti-hypertensive agents,[8] and ionic liquids.[9,10]

The syntheses of imidazoles reported in the literature generally require several steps.[1,6,11] The compounds are often synthesized in a solvent, and the presence of catalysts is frequently required.[2,12–17] The significant amount of waste products, difficult accessibility of starting materials, and lower yields remain disadvantages of these methods.[1,2]

Recently, a synthesis of 2,4,5-trisubstituted imidazoles in solvent medium with the aid of microwave irradiation was described. Unfortunately, the synthesis of 4,5-disubsituted imidazoles would have required the use of formaldehyde as reagent, and was thus not accomplished.[18]

To achieve the synthesis of 4,5-disubsituted imidazoles, we used urotropine (1,3,5,7-tetraazaadamantane, hexamethylenetetramine) as an 'in vitro' source of formaldehyde. We have previously carried out the synthesis of some organic compounds in a paste-like chemical medium.[19–21] The paste medium was obtained by adding a small amount of a polar solvent. In this medium, during microwave irradiation, hot spots similar to catalytic centers are generated.[21] Following this approach, we synthesized 4,5-disubstituted imidazoles from 1,2-diketones, urotropine, and ammonium acetate (Scheme 1). To generate the hot spots, a few drops of acetic acid were used. By this method, the reactions proceed rapidly, giving the products in high yields and purity, making this a very attractive procedure. The products synthesized by this protocol are summarized in Table 1.

The 1,2-diketone starting materials, urotropine, and NH_4OAc are commercially available. The synthesized products were identified by TLC (alumina, precoated plates, $CHCl_3$), elemental analysis, and ^1H NMR and IR spectra. ^1H NMR (300 MHz) spectra of samples in $CDCl_3$ (TMS as internal standard) were obtained on a Bruker ARX 300-MHz spectrometer. Elemental analyses were carried out on a Carlo Erba model 1106 Elemental Analyzer. IR spectra of samples prepared as KBr pellets were obtained on a Perkin-Elmer 1600 spectrometer. Melting points were determined on a Böetius melting point apparatus. An Optiquick Y71 microwave device operating at 650 W was employed for the reactions. The temperature during the microwave irradiation was determined with the aid of a Novo Quick digital thermometer.

4,5-Disubstituted Imidazoles 1–8; General Procedure

The appropriate 1,2-diketone (5 mmol), urotropine (1 mmol), and NH_4OAc (3.31 g, 43 mmol) were mixed in a 25-mL beaker. A few drops of AcOH were added. The obtained paste was irradiated in a microwave oven (λ = 12.2 cm) for the indicated time (see Table 1). The mixture was poured in H_2O (75 mL) and aq NH_3 was added until the pH reached 8. Products **6–8** were purified by filtration of the precipitate and subsequent recrystallization from py–H_2O. Products **1–5** were purified by recrystallization of the resulting reaction mixture from benzene–EtOH. The reaction conditions and the spectroscopic, analytical, and physical data of products **1–8** are summarized in Table 1.

References

(1) Yet, L. *Prog. Heterocycl. Chem.* **2004**, *16*, 198.
(2) Bajpai, D.; Tyagi, V. K. *J. Oleo Sci.* **2006**, *55*, 319.
(3) Bhaumik, J.; Yao, Z.; Borbas, K. E. *J. Org. Chem.* **2006**, *71*, 8807.
(4) Puratchikody, A.; Doble, M. *Bioorg. Med. Chem.* **2007**, *15*, 1083.
(5) Kumar, P. M.; Karthikeyan, C.; Moorthy, N. S. H. N.; Trivedi, P. *Chem. Pharm. Bull.* **2006**, *54*, 1586.
(6) Di Santo, R.; Costi, R.; Artico, M.; Massa, S.; Musiu, C.; Scintu, F.; Putzolu, M.; La Colla, P. *Eur. J. Med. Chem.* **1997**, *32*, 143.

SYNTHESIS 2009, No. 14, pp 2319–2320
Advanced online publication: 25.05.2009
DOI: 10.1055/s-0029-1216841; Art ID: Z02909SS

Table 1 4,5-Disubstituted 1*H*-Imidazole Derivatives

Prod.	R^1	R^2	Time (min)	Temp (°C)	Yield (%)	Anal. Calcd/Found C (%)	H (%)	N (%)	IR (cm^{-1})	^1H NMR (δ)	Mp (°C)
1	H	H	3.5	106	78	52.94/ 52.93	5.88/ 5.85	41.17/ 41.16	3124 (s, NH), 2916 (s), 1451 (s), 1066 (vs), 660 (vs)	7.12 (s, 2 H, H3,4), 7.72 (s, 1 H, H2), 10.52 (br s, 1 H, NH)	90.5 (Lit.[22] 88–91)
2	H	Me	4	103	76	58.53/ 58.51	7.31/ 7.67	34.14/ 34.13	3117 (s, NH), 2920 (vs), 1449 (s), 1126 (s), 663 (m)	2.24 (s, 3 H, 4-CH_3), 6.73 (s, 1 H, H5), 7.50 (s, 1 H, H2), 10.92 (br s, 1 H, NH)	56
3	Me	Me	3	101	72	62.50/ 62.48	8.33/ 8.30	29.16/ 29.15	3110 (s, NH), 2931 (vs), 1438 (s), 1132 (m), 677 (m)	2.25 (s, 3 H, 4-CH_3), 2.33 (s, 3 H, 5-CH_3), 7.43 (s, 1 H, H2), 10.67 (br s, 1 H, NH)	63
4	H	Et	4	105	75	62.50/ 62.47	8.33/ 8.32	29.16/ 29.13	3121 (s, NH), 2924 (vs), 1428 (s), 1129 (s), 657 (m)	1.29 (t, 3 H, CH_3), 2.65 (q, 2 H, CH_2), 6.97 (s, 1 H, H5), 7.48 (s, 1 H, H2), 10.79 (br s, 1 H, NH)	76
5	Et	Et	3.5	102	71	67.74/ 67.71	9.67/ 9.63	22.58/ 22.55	3105 (s, NH), 2915 (vs), 1435 (s), 1113 (s), 649 (m)	1.28 (t, 3 H, CH_3), 1.24 (t, 3 H, CH_3), 2.61 (q, 2 H, CH_2), 2.54 (q, 2 H, CH_2), 7.09 (s, 1 H, H2), 11.12 (br s, 1 H, NH)	97
6	H	Ph	4	108	79	75.00/ 74.98	5.55/ 5.52	19.44/ 19.43	3025 (s, NH), 2850 (m), 1490 (m), 1076 (m), 758 (vs)	7.24 (m, 1 H, H*p*-Ph), 7.34 (s, 1 H, H5), 7.38 (m, 2 H, H*m*,*m*′-Ph), 7.71 (s, 1 H, H2), 7.72 (m, 2 H, H*o*,*o*′-Ph), 11.06 (br s, 1 H, NH)	130
7	Ph	Ph	3.5	112	81	81.81/ 81.80	5.45/ 5.43	12.72/ 12.71	3061 (s, NH), 2990 (s), 1502s, 958 (vs), 768 (vs)	7.26–7.34 (m, 6 H, H*m*,*p*-2Ph), 7.48 (m, 4 H, H*o*-2Ph), 7.81 (s, 1 H, H2), 12.58 (br s, 1 H, NH)	230
8	4-ClC_6H_4	4-ClC_6H_4	4	117	83	62.28/ 62.25	3.46/ 3.45	9.68/ 9.67	3078 (s, NH), 2995 (s), 1511 (s), 964 (s), 759 (m)	7.27 (m, 4 H, H*m*-2Ph), 7.41 (m, 4 H, H*o*-2Ph), 7.68 (s, 1 H, H2), 12.75 (br s, 1 H, NH)	254

(7) Wiebe, L.; Mcewan, A. J. B.; Kumar, P. (The Governors of the University of Alberta, Canada) WO 102759, **2006**; *Chem. Abstr.* **2006**, *145*, 377533.
(8) Kumar, J. R.; Jat, J. L.; Pathak, D. P. *E-J. Chem.* **2006**, *3*, 278.
(9) Ou, W.-H.; Huang, Z.-Z. *Green Chem.* **2006**, *8*, 731.
(10) Mehdi, H.; Bodor, A.; Lantos, D.; Horvath, I. T.; De Vos, D. E. *J. Org. Chem.* **2007**, *72*, 517.
(11) Radziszewski, B. *Chem. Ber.* **1882**, *15*, 1493.
(12) Glister, J. F.; Vaughan, K. *J. Heterocycl. Chem.* **2006**, *43*, 217.
(13) Heim-Riether, A.; Healy, J. *J. Org. Chem.* **2005**, *70*, 7331.
(14) Kawakami, J. I.; Kimura, K.; Yamaoka, M. *Synthesis* **2003**, 677.
(15) Heras, M.; Ventura, M.; Linden, A.; Villalgordo, J. M. *Synthesis* **1999**, *9*, 1613.
(16) Zimmer, H.; Benson, H. D. *Chimia* **1972**, *26*, 131.
(17) Ellinger, L. P.; Goldberg, A. A. *J. Chem. Soc.* **1949**, 263.
(18) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453.
(19) Bratulescu, G.; Le Bigot, Y.; Delmas, M. *Synth. Commun.* **2000**, *30*, 171.
(20) Bratulescu, G. *Rev. Roum. Chim.* **2000**, *45*, 883.
(21) Bratulescu, G. *Synthesis* **2005**, 2833.
(22) Hiraoka, R.; Watanabe, H.; Senna, M. *Tetrahedron Lett.* **2006**, *47*, 3111.