Article

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

A Simple, Mild and Efficient One-Pot Synthesis of 2-Substituted Benzimidazoles in the Presence of H_2O_2/HCl under Microwave Irradiation

Hossein Naeimi* and Nasrin Alishahi

Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan, 87317, I.R. Iran

(Received: Oct. 5, 2011; Accepted: Mar. 9, 2012; Published Online: ??; DOI: 10.1002/jccs.201100591)

A simple, fast and efficient method for the preparation of several 2-substituted benzimidazole derivatives is reported. Compounds were synthesized through a rapid one-pot synthesis via microwave irradiation, starting from aldehydes and *o*-phenylenediamine, in the presence of H_2O_2/HCl system in acetonitrile. The significant features of this method are short reaction times, high yields, easy and quick isolation of the products.

Keywords: *O*-Phenylenediamine; Synthesis; Benzimidazoles; Aryl aldehydes; Microwave.

INTRODUCTION

Benzimidazole and its derivatives are important class of bioactive molecules in the field of drugs and pharmaceuticals.[1] The spectrum of the pharmacological activity of benzimidazole has been reviewed by several authors.[2-5] These heterocycles show various pharmaceutical properties such as, antiviral,[6] antibacterial,[7] antitumor[8] antifungal,[9] anticancer,[10] antibiotic,[11] and anti-inflammatory.[12] They have been also used as ligands in asymmetric synthesis.[13]

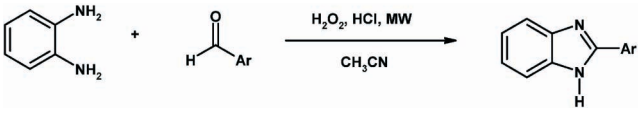
Due to their wide range of pharmacological activity, industrial and synthetic applications, a number of methods have been reported for the synthesis of benzimidazoles, which include the reaction between *N*-ethoxycarbonylthiomides with 1,2-diamines,[14] the coupling of phenylenediamines and carboxylic acids[15,16] or their derivatives (nitriles, imidates, or orthoesters).[17,18] However, most of these procedures have some drawbacks such as low yields of products, long reaction times and tedious work-up procedures.

Microwave as heating source has been used for the rapid synthesis of a variety of heterocyclic compounds both in solution phase as well as under solvent-free conditions.[19] Using microwave irradiation, the rates of reactions involving polar components are usually very fast. Reactions that require hours or even days by conventional heating may often be accomplished in seconds by microwave heating,[20] and that is the reason why this technology is widely applied to drug discovery.

RESULTS AND DISCUSSION

In this research, we herein, report a facile, rapid and efficient methodology for the synthesis of 2-substituted benzimidazoles by coupling of *o*-phenylenediamine with aryl aldehydes using aqueous HCl and H_2O_2 as oxidant system in acetonitrile solvent under microwave irradiation. The route for the synthesis of 2-substituted benzimidazoles by this procedure is shown in Scheme I.

Scheme I



The optimized microwave irradiation power level was used 100 W and the corresponding benzimidazoles were obtained in excellent yields and short reaction times.

Firstly, in order to find the effect of solvent on this reaction, several solvents including acetone, acetonitrile, dichloromethane, and ethanol were investigated during the course of this study. After screening different solvents, it was found that the best solvent is acetonitrile in this reaction (Table 1). We also tried to carry out this reaction without any solvent, in which the product yield was very low even with continuation of the reaction until 2 hours (entry 5, Table 1).

In contrast, microwave along with conventional thermal heating, microwave irradiation produces efficient internal heating (in core volumetric heating) by direct coupling of microwave energy with the molecules (solvents, reagents, catalysts) that are present in the reaction mixture. Microwave irradiation, therefore, raises the temperature of the whole volume simultaneously (bulk heating) whereas

* Corresponding author. Fax: +983615552935; E-mail: naeimi@kashanu.ac.ir

Table 1. Optimization of solvent effect on the reaction[a]

Entry	Solvent	Time (min)	Yield (%)
1	Ethanol	18	61
2	Acetone	17	59
3	Acetonitrile	3	94
4	Dichloromethane	15	54
5	None	120	very low

[a] Reaction of 4-methylbenzaldehyde with *o*-phenylenediamine in presence of different solvent.

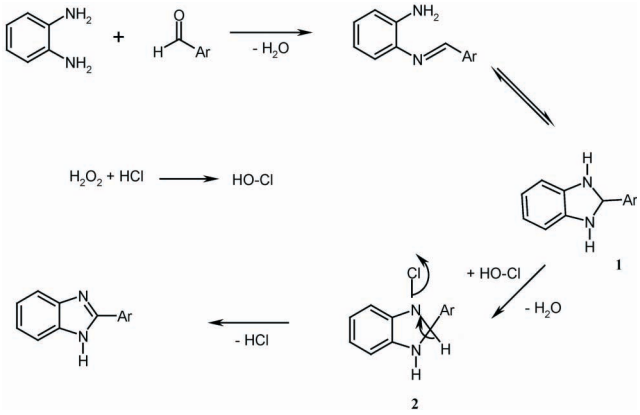
in the conventionally heated vessel, the reaction mixture in contact with the vessel wall is heated first. Since the reaction vessels employed in modern microwave reactors are typically made out of (nearly) microwave transparent materials such as borosilicate glass, quartz or Teflon, the radiation passes through the walls of the vessel and an inverted temperature gradient as compared to conventional thermal heating results. If the microwave cavity is well designed, the temperature increase will be uniform throughout the sample. The very efficient internal heat transfer results in minimized wall effects (no hot vessel surface) which may lead to the observation of so-called specific microwave effects.[21]

Then, to ascertain the scope and limitation of the present reaction, several aromatic aldehydes were reacted with *o*-phenylenediamine in the presence of HCl and H_2O_2 as oxidant system under microwave irradiation in acetonitrile solvent and the desired products including 2-substituted benzimidazole derivatives were prepared. The corresponding results are summarized in Table 2. As shown in this Table, the reaction of the various aldehydes with *o*-phenylenediamine in this reaction, were accelerated by microwave irradiation in comparison with this reaction under thermal condition. The corresponding products were obtained in excellent yields and short reaction times under microwave irradiation. While, the reaction under heating condition were produced the benzimidazoles in good yields and long reaction times. It seems this method for preparation of 2-substituted benzimidazoles has some advantages such as; highly efficient, mild and useful as compared to previously reported methods.[14-18] All compounds were confirmed by their physical and spectroscopic data and were in good agreement with those of authentic samples.[22-28]

The proposed reaction mechanism

A ratio of 7:3.5:1:1 of H_2O_2/HCl/aryl aldehyde/1,2-phenylendiamine was found to be optimum for the reaction. Regarding to the mechanism of the oxidation step, the reaction probably involves the formation of hypochlorous acid by the reaction of aqueous hydrogen peroxide with hydrochloric acid, in which then reacts with the cyclic hydrobenzimidazoles **1** to afford intermediate **2** followed by the abstraction of hydrogen to yield the corresponding benzimidazoles (Scheme II).

Scheme II



In this research, we have developed a simple, rapid and efficient method for the preparation of 2-substituted-1H-benzimidazole compounds using readily available and inexpensive reagents under microwave irradiation conditions. The corresponding products have been obtained in excellent yields, high purity and short reaction times.

EXPERIMENTAL

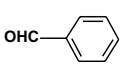
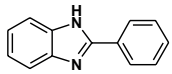
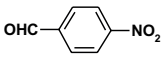
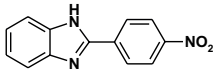
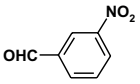
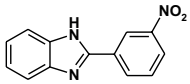
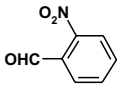
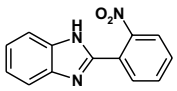
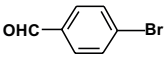
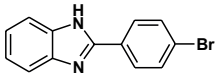
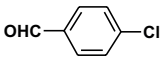
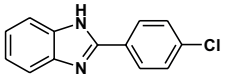
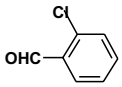
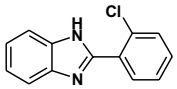
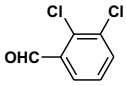
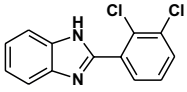
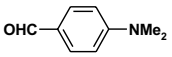
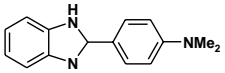
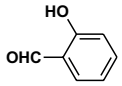
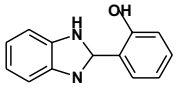
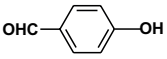
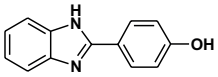
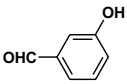
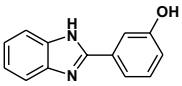
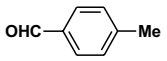
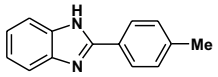
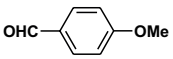
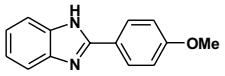
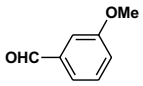
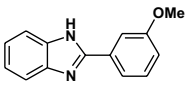
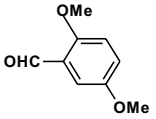
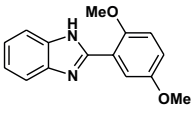
Materials

All the materials were of commercial reagent grade. The aromatic aldehydes, and *o*-phenylenediamine were purified by standard procedures and purity determined by thin layer chromatography (TLC).

Apparatus

IR spectra were recorded as KBr pellets on a Perkin-Elmer 781 spectrophotometer and an Impact 400 Nicolet FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR were recorded in DMSO solvent on a Bruker DRX-400 spectrometer with tetramethylsilane as internal reference. Melting points obtained with a Yanagimoto micro melting point apparatus are uncorrected. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company). Microwave irradiations were carried out in microwave oven specially designed for the organic synthesis (Milestone LAVIS 1000 Basic Microwave).

Table 2. Reaction of various aryl aldehydes with *o*-phenylenediamine

Entry	Substrate	Product [a]	Microwave		Heating	
			Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]
1			3.1	96	44	83
2			1.1	98	23	88
3			1.8	96	31	84
4			1.6	97	28	80
5			2	97	33	81
6			1.5	95	32	83
7			2	93	34	79
8			0.66	98	23	86
9			1.3	93	25	84
10			1.6	96	27	87
11			2	92	35	80
12			1.8	93	30	81
13			3	94	43	76
14			2.5	95	42	78
15			2	95	36	80
16			3.3	96	45	82

[a] All compounds are known and their physical and spectroscopic data were in good agreement with those of authentic samples. [b] Yields refer to pure isolated products.

Typical procedure for the Synthesis of benzimidazoles from aryl aldehydes

A solution of *o*-phenylenediamine (1.0 mmol), and aryl aldehyde (1.0 mmol) in MeCN (4 mL) was prepared. Aq. 30% H_2O_2 (7.0 mmol) and aq. 37% HCl (3.5 mmol) were added and introduced in an open Erlenmeyer flask.

The mixture was irradiated in a microwave oven. The progress of the reaction was monitored by TLC. When the starting materials had completely disappeared, the mixture was quenched by adding H_2O (10 mL), extracted with EtOAc (4 × 10 mL). The corresponding products were identified by physical and spectroscopic data.

2-Phenyl-benzimidazole

Pale yellow solid; m.p.= 289-290 °C (m.p = 288-290 °C);[22] IR (KBr)/ν (cm^{-1}) 3446 (NH), 1622 (C=N), 1590, 1445 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 7.19 (2H, m, Ar), 7.48-7.64 (5H, m, Ar), 8.17 (2H, m, Ar); ^{13}C NMR (100 MHz, DMSO)/δ ppm: 111.1, 118.6, 121.9, 126.2, 128.6, 129.5, 130.0, 134.8, 143.5, 151.0; MS: *m/z*: 193 (M-H, 100 %).

2-(4-Nitro-phenyl)-benzimidazole

Pale yellow solid; m.p. = 307-309 °C (m.p = 312-314 °C);[23] IR (KBr)/ν (cm^{-1}) 3421 (NH), 1606 (C=N), 1524, 1451 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 7.51-7.54 (2H, m, Ar), 7.83 (2H, m, Ar), 8.47 (2H, d, Ar), 8.48-8.64 (2H, d, Ar); MS: *m/z*: 239 (M^+).

2-(3-Nitro-phenyl)-benzimidazole

Yellow solid; m.p. = 309-310 °C (m.p = 310-311 °C);[22] IR (KBr)/ν (cm^{-1}) 3308 (NH), 1630 (C=N), 1531, 1482 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 7.47 (2H, m, Ar), 7.79 (2H, m, Ar), 7.92-7.95 (1H, m, Ar), 8.1-8.9 (2H, m, Ar), 9.1 (1H, s, Ar); ^{13}C NMR (DMSO, 100 MHz)/δ ppm: 114.3, 121.2, 122.1, 123.2, 130.1, 131.6, 133.6, 138.9, 148.9, 152.7; MS: *m/s*: 238 (M-H, 100%).

2-(2-Nitro-phenyl)-benzimidazole

Pale yellow solid; m.p. = 212-214 °C (m.p =209-210 °C);[23] IR (KBr)/ν (cm^{-1}) 3428 (NH), 1622 (C=N), 1530, 1458 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 7.54-7.57 (2H, m, Ar), 7.85-7.87 (2H, m, Ar), 7.99 (1H, t, Ar), 8.05 (1H, m, Ar), 8.12 (1H, d, Ar), 8.37 (1H, d, Ar); MS: *m/z*: 239 (M^+).

2-(4-Boromo-phenyl)-benzimidazole

Pale yellow solid; m.p. = 292-293 °C (m.p = 250-252 °C);[27] IR (KBr)/ν (cm^{-1}) 3449 (NH), 1628 (C=N), 1598, 1456 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 7.53 (2H, m, Ar), 7.83 (2H, m, Ar), 7.95 (2H, d, Ar), 8.28 (2H, d, Ar).

2-(4-Choloro-phenyl)-benzimidazole

Yellow solid; m.p. = 290-291 °C (m.p = 291-293 °C);[25] IR (KBr)/ν (cm^{-1}) 3442 (NH), 1598 (C=N), 1580, 1429 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 7.2 (2H, m, Ar), 7.50-7.89 (6H, m, Ar); MS: *m/z*: 229.0 $(M+H)^+$.

2-(2-Choloro-phenyl)-benzimidazole

Yellow solid; m.p. = 231-233 °C (m.p = 232-234 °C);[26] IR (KBr)/ν (cm^{-1}) 3444 (NH), 1591 (C=N), 1575, 1440 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 7.2 (2H, m, Ar), 7.50-7.89 (6H, m, Ar); MS: *m/z*: 228.5 (M^+).

2-(2,3-Dicholoro-phenyl)-benzimidazole

Yellow solid; m.p. = 224-226 °C; IR (KBr)/ν (cm^{-1}) 3095 (NH), 1624 (C=N), 1540, 1433 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 7.2 (2H, m, Ar), 7.53 (1H, m, Ar), 7.64 (2H, m, Ar), 7.82 (2H, m, Ar).

2-(N,N-dimethyl-phenyl)-benzimidazole

Yellow solid; m.p. = 277-279 °C (m.p = 294.2-296.3 °C);[24] IR (KBr)/ν (cm^{-1}) 3391 (NH), 1605 (C=N), 1518, 1459 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 6.84 (2H, d, Ar), 7.43 (2H, m, Ar), 7.70 (2H, m, Ar), 8.21 (2H, d, Ar).

2-(2-Hydroxy-phenyl)-benzimidazole

White solid; m.p. = 238-240 °C (m.p = 240-242 °C);[28] IR (KBr)/ν (cm^{-1}) 3325 (OH), 3055 (NH), 1593 (C=N), 1530, 1491 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 6.99-7.05 (2H, m, Ar), 7.27 (2H, m, Ar), 7.37 (1H, t, Ar), 7.66 (2H, m, Ar), 8.06 (1H, d, Ar), 13.19 (1H, s, OH); MS: *m/z*: 210 (M^+).

2-(4-Hydroxy-phenyl)-benzimidazole

White solid; m.p. = 254-255 °C (m.p = 254.1-256.6 °C);[24] IR (KBr)/ν (cm^{-1}) 3383 (OH), 3202 (NH), 1668 (C=N), 1600, 1457 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 6.91-7.50 (4H, m, Ar), 7.73-8.21 (4H, m, Ar), 9.7 (1H, s, OH).

2-(3-Hydroxy-phenyl)-benzimidazole

Yellow solid; m.p. = 245-247 °C; IR (KBr)/ν (cm^{-1}) 3434 (OH), 3243 (NH), 1588 (C=N), 1541, 1445 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 6.9 (1H, d, Ar), 7.18 (2H, m, Ar), 7.33 (1H, t, Ar), 7.59 (4H, d, Ar).

2-(4-Methyl-phenyl)-benzimidazole

White solid; m.p. = 260-261 °C (m.p = 261-263 °C);[26] IR (KBr)/ν (cm^{-1}) 3429 (NH), 1620 (C=N), 1587, 1433 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 2.36 (3, s, Me), 7.18 (2H, m, Ar), 7.34 (2H, d, Ar), 7.57 (2H, m, Ar), 8.06 (2H, d, Ar),

2-(4-Methoxy-phenyl)-benzimidazole

Yellow solid; m.p. = 229-230 °C (m.p = 229.2-231.1 °C);[24] IR (KBr)/ν (cm^{-1}) 3344 (NH), 1608 (C=N), 1506, 1461 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 3.89 (3H, s, Me), 7.2 (2H, d, Ar), 7.52 (2H, m, Ar), 7.79 (2H, m, Ar), 8.38 (2H, d, Ar); ^{13}C NMR (DMSO, 100 MHz)/δ ppm: 56.24, 114.06, 115.34, 115.53, 126.03, 130.62, 132,

148.91, 163.61.

2-(3-Methoxy-phenyl)-benzimidazole

Yellow solid; m.p. = 200-202 °C (m.p = 205-206 °C);[27] IR (KBr)/ν (cm^{-1}) 3437 (NH), 1596 (C=N), 1541, 1464 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 3.9 (3H, s, Me), 7.05 (1H, m, Ar), 7.19 (2H, m, Ar), 7.45 (1H, s, Ar), 7.59 (2H, m Ar), 7074 (2H, m, Ar).

2-(2,5-Dimethoxy-phenyl)-benzimidazole

Yellow solid; m.p. = 197-198 °C; IR (KBr)/ν (cm^{-1}) 3408 (NH), 1622 (C=N), 1511, 1458 (C = C, Ar); ^{1}H NMR (DMSO, 400 MHz)/δ ppm: 4.02 (3H, s, Me), 3.85 (3H, s, Me), 7.33 (2H, d, Ar), 7.55 (2H, m, Ar), 7.89 (2H, m, Ar), 8.02 (1H, s, Ar).

ACKNOWLEDGMENT

We are grateful to the University of Kashan Research Council for the partial support of this work.

REFERENCES

1. Valdez, J.; Cedillo, R.; Hernández-Campos, A.; Yépez, L.; Hernández Luis, F.; Navarrete-Vázquez, G.; Tapia, A.; Cortés, R.; Hernández, M.; Castillo, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2221.
2. Spasov, A.; Yozhitsa, I. N.; Bugaeva, L. I.; Anisimova, V. A. *Pharm. Chem. J.* **1999**, *33*, 232.
3. Kus, C.; Goker-Farm, H. *Bil. Berg*. **1994**, *19*, 23.
4. Soula, C.; Luu-Duc, C. *Lyon Pharm*. **1986**, *37*, 297.
5. Sharma, S.; Abuzar, S. *Prog. Drug Res*. **1983**, *27*, 85.
6. Song, X.; Vig, B. S.; Lorenzi, P. L.; Drach, J. C.; Townsend, L. B.; Amidone, G. L. *J. Med. Chem*. **2005**, *48*, 1274.
7. Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc*. **1979**, *101*, 6789.
8. Mortimer, C. G.; Wells, G.; Crochard, J.-P.; Stone, E. L.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem*. **2006**, *49*, 179.
9. Yamato, M. *J. Pharm. Sci. Jpn*. **1992**, *112*, 81.
10. Kumar, D.; Jacob, M. R.; Reynolds, M. B.; Kerwin, S. M. *Bioorg. Med. Chem*. **2002**, *10*, 3997.
11. Yildiz-Oren, I.; Yalcin, I.; Aki-Sener, E.; Ucarturk, N. *Eur. J. Med. Chem*. **2004**, *39*, 291.
12. Terzioglu, N.; Rijn, R. V.; Bakker, R. A.; Esch, I. J. P.; Leurs, De R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5251.
13. Figge, A.; Altenbach, H. J.; Braauer, D. J.; Tielmann, P. *Tetrahedron: Asymmetry* **2002**, *13*, 137.
14. George, B.; Papadopoulos, E. P. *J. Org. Chem*. **1977**, *42*, 441.
15. Middleton, R. W.; Wibberley, D. G. *J. Heterocycl. Chem.* **1980**, *17*, 1757-1760.
16. Geratz, J. D.; Stevens, F. M.; Polakoski, K. L.; Parrish, R. F. *Arch. Biochem. Biophys*. **1979**, *197*, 551-559.
17. Tidwell, R. R.; Geratz, J. D.; Dann, O.; Volz, G.; Zeh, D.; Loewe, H. *J. Med. Chem*. **1978**, *21*, 613-623.
18. Fairley, T. A.; Tidwell, R. R.; Donkor, I.; Naiman, N. A.; Ohemeng, K. A.; Lombardy, R. J.; Bentley, J. A.; Cory, M. *J. Med. Chem*. **1993**, *36*, 1746-1753.
19. Mavandadi, F.; Lidstro, M.; Curr, P. *Top. Med. Chem*. **2004**, *4*, 773.
20. Yu, H.; Kawanishi, H.; Koshima, H. *Heterocycl.* **2003**, *60*, 1457.
21. Kappe, C. O.; Dallinger, D.; Murphree, S. S. *Practical Microwave Synthesis for Organic Chemists*; Wiley-VCH: Weinheim, 2009; p 29.
22. Nagawade, R. R.; Shinde, D. B. *Chin. Chem. Lett*. **2006**, *17*, 453-456.
23. Ramana, D. V.; Kantharaj, E. *J. Chem. Soc., Perkin Trans*. **1995**, *2*, 1497-1501.
24. Navarrete-Vázquez, G.; Moreno-Diaz, H.; Aguirre-Crespo, F.; León-Rivera, I.; Villalobos-Molina, R.; Muñoz-Muñizd, O.; Estrada-Sotoa, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4169-4173.
25. Nagawade, R.; Shinde, D. B. *Indian J. Chem*. **2007**, *46*, 349.
26. Xiangming, H.; Huiqiang, M.; Yulu, W. *Arkivoc* **2007**, 150-154.
27. Montanari, F.; Passerini, R. *Bull. Sci. Chim. Ind. Bologna* **1953**, *11*, 42.
28. Addison, A. W.; Burke, P. J. *J. Heterocycl. Chem*. **1981**, *18*, 803-805.

