Nano Beryllium Nitride as a Source of Ammonia for the Synthesis of Highly Substituted Imidazoles

Kourosh Motevalli ¹ and Zahra Yaghoubi ²

¹ Member of Scientific Board, Applied Chemistry Department, Islamic Azad University, South Tehran Branch, Tehran, Iran, ² Member of Scientific Board, Industrial Engineering Faculty, Islamic Azad University, South Tehran Branch, Tehran, Iran,

Received: June 10 2013
Accepted: July 8 2013

ABSTRACT

This research aims at evaluating the application of nano beryllium nitride (Be₃N₂) as a suitable source of ammonia for the synthesis of 2, 4, 5-trisubstituted imidazoles. The tests revealed that heating a mixture of a benzaldehyde, a benzyl, and nano beryllium nitride in methanol leads to the formation of functionalized imidazoles in good to excellent yields.

KEYWORDS: nano beryllium nitride, imidazole, multi component reactions, synthesis, yield, ammonia

1. INTRODUCTION

Regarding the atom economy, simple reaction design, and the ability to construct compounds of desire by the introduction of several elements in a single chemical event, multi component reactions (MCR) have changed to a significant part of the set of methods currently used in combinatorial chemistry. The purification of the products of such reactions is also very easy due to the fact that all of the organic reagents used take part in the reaction and are incorporated into the target product[1]. The application of MCR to construct interesting heterocyclic scaffolds is of specific use in the preparation of various chemical libraries of ‘drug-like’ molecules.

Imidazoles constitute scaffolds in very important biomolecules, such as histamine, biotin, istidine, pilocarpine alkaloids[2], and other alkaloids, with considerable biological activities like antimicrobial, anticytotoxic or inhibition of nitric oxide synthase, or cytotoxic activities[3]. The compounds have been reported to act as inhibitors of p38 MAP kinase[4a], B-Raf kinase[4b], transforming growth factor b1 (TGF-b1) type 1 activin receptor-like kinase (ALK5)[4c], cyclooxygenase-2 (COX-2)[4d] and biosynthesis of interleukin-1 (IL-1)[4e].

Highly substituted imidazoles are prepared through a variety of methods. The most common and recent ones of which include condensation of aldehydes, benzyls, and NH₄OAc/primary amines to prepare tri- or tetrasubstituted imidazoles[5]; application of hetero-Cope rearrangement[6], reacting NH₄O₂CCF₃ with N-(2-oxo)-amides[7], condensation of arylglyoxals, primary amines, carboxylic acids, and isocyanides on Wang resin[8], and the reaction of NH₄OAc with N-alkyl-N-(β-keto)amides[9].

Ammonia is a common source of nitrogen in organic chemistry, the small scale use of which is limited due to handling issues.

It’s known by experience that this substance, i.e. Be₃N₂ was mentioned to be applicable as a source of ammonia that can be used in organic syntheses, based on the reactions below[10,11].

\[
\text{Be}_3\text{N}_2 + 6\text{H}_2\text{O} \rightarrow 2\text{NH}_3 + 3\text{Be(OH)}_2 \\
\text{Be}_3\text{N}_2 + 6\text{MeOH} \rightarrow 2\text{NH}_3 + 3\text{Be(OMe)}_2
\]

2. RESULTS AND DISCUSSION

Regarding the unrivaled pharmacological properties of imidazols, a convenient protocol, using nano beryllium nitride as the ammonia source and different aldehydes and benzyls, for the synthesis of these heterocycles is described (Scheme 1, Table 1).

According to the protocol[12], the reaction between benzyl 1, benzaldehyde 2 and nano beryllium nitride has been used as an efficient method to produce 2, 4, 5-trisubstituted imidazoles 3 in yields of 70–82% (Scheme 1, Table 1). The reactions were carried out at 80°C and were completed within 30 hours. The structure of the products 3 were established by ¹HNMR, ¹³CNMR spectroscopy and by comparison of their spectral data[13] and melting point values with those of the authentic samples reported in the literature.
Reactions at different temperatures and various molar ratios of the reactants in the presence of methanol as a solvent, proved the best operating conditions to be 80°C for reaction temperature and a molar ratio of 1:1:1.5 for aldehyde/benzyl/nano beryllium nitride reactants.

3. CONCLUSION

In summary, we have shown that the simple method introduced in this work can be effectively used for the synthesis of 2,4,5-three substituted imidazoles based on the application of Be₃N₂ as an eco-friendly, inexpensive and efficient source of ammonia, enjoying the advantage of having high yields, and simple and easy work-up operations.

| Table 1 - synthesis of 2,4,5-trisubstituted imidazole derivatives |
|-----------------|----------------|---------|------|
| 4 Ar¹ Ar²      | % Yield | mp (°C) (lit)[14,15] |
| a Ph Ph        | 82      | 268–269[267–269] |
| b 4-CIC₆H₄ Ph  | 75      | 262–263[262–264] |
| c 4-NO₂C₆H₄ Ph | 70      | 198–201[199–201] |
| d 4-NC₆H₄ Ph   | 77      | 255–257[256–259] |
| e 4-MeO₂C₆H₄ Ph| 81      | 221–223[220–223] |
| f 3-HOC₆H₄ Ph  | 72      | 259–261[258–260] |
| g CH₃CH₂CHO Ph | 80      | 226–228[225–228] |
| h 4-NO₂C₆H₄ 4-CIC₆H₄| 75 | 275[275–276] |
| i 4-MeC₆H₄ 4-CIC₆H₄| 77 | 263–265[263–264] |
| j 4-CIC₆H₄ 4-MeC₆H₄| 78 | 251[250–251] |

REFERENCES


Representative Procedure for the synthesis of 2,4,5-Triphenyl-1H-imidazole (4a): To a stirred solution of benzyl (210 mg, 1 mmol) and benzaldehyde (106 mg, 1 mmol) in MeOH (10 mL) at 0 °C was added nano beryllium nitride (0.082 mg, 1.5 mmol). The reaction vessel was sealed and heated to 80 °C for 30 h. After the cooling process, the reaction was partitioned between CH$_2$Cl$_2$ (30 mL) and H$_2$O (30 mL). The aqueous layer was acidified to pH=7 using 1 N HCl then the organic layer was separated, dried (Na$_2$SO$_4$) and concentrated in vacuo. Flash column chromatography on silica (25% EtOAc in hexanes).

Typical spectral data: 2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (4b). mp: 262–263 °C; $^1$H NMR (500.1 MHz, DMSO-d$_6$) δ: 7.12–7.43 (10H, m), 7.52 (2H, d, J = 8.5 Hz), 7.87 (2H, d, J = 8.5 Hz), 12.58 (br, NH); $^{13}$C NMR (125.8 MHz DMSO-d$_6$) δ: 12.4, 124.9, 126.2, 126.7, 127.8, 128.5, 129.0, 130.6, 133.1, 145.2; IR (cm$^{-1}$, Nujol): 3445 (NH), 3058, 1621, 1442; 4,5-Bis(4-chlorophenyl)-2-p-tolyl-1H-imidazole (4j). mp: 263–265 °C; $^1$H NMR (500.1 MHz, DMSO-d$_6$) δ: 2.32 (3H, s, CH$_3$), 7.28 (2H, 2CH, d, J = 7.7 Hz), 7.42 (2H, 2CH, d, J = 8.1 Hz), 7.53 – 7.57 (4H, 4CH, m), 7.59 (2H, 2CH, d, J = 8.1 Hz), 7.95 (2H, 2CH, d, J = 7.7 Hz), 12.68 (br, 1H, NH); $^{13}$C NMR (125.8 MHz, DMSO-d$_6$) δ: 21.2, 125.0, 126.8, 127.2, 128.1, 128.6, 129.4, 129.7, 130.3, 131.0, 132.6, 134.4, 135.9, 138.2, 146.4; IR (KBr, cm$^{-1}$): 3453(NH), 2967, 1642, 1501.