

An efficient synthesis of 5-substituted 1*H*-tetrazoles using Zn/Al hydrotalcite catalyst

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Received 2 November 2005; received in revised form 3 November 2005; accepted 23 November 2005

Available online 4 January 2006

Abstract

Zn/Al hydrotalcite is an effective heterogeneous catalyst for the (2 + 3) cycloaddition of sodium azide with nitriles to afford 5-substituted 1*H*-tetrazoles in good yields. The catalyst is recovered and reused for several cycles with consistent activity.

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Keywords: Zn/Al hydrotalcite; (2 + 3) cycloaddition; 5-Substituted 1*H*-tetrazoles; Heterogeneous catalyst

1. Introduction

Tetrazoles have a wide range of applications in materials as specialty explosives and information recording systems, in pharmaceuticals as lipophilic spacers and carboxylic acid surrogates, in coordination chemistry as ligands and also as precursors to a variety of nitrogen containing heterocycles [1]. Conventional method for the synthesis of 5-substituted 1*H*-tetrazoles is via (2 + 3) cycloaddition between an azide and a nitrile [2]. The earlier reported methods suffer from some disadvantages like use of strong Lewis acids, expensive and toxic metals and the in situ generated hydrozoic acid is highly toxic and explosive. Later Sharpless and co-workers reported an innovative and safe procedure for the synthesis of tetrazoles by the addition of sodium azide to nitriles using stoichiometric amounts of Zn(II) salts in water [3]. Pizzo and co-workers efficiently synthesized tetrazoles by the addition of TMSN₃ to organic nitriles using 10 mol% TBAF as catalyst [4]. Very recently, we reported an efficient synthesis of 5-substituted 1*H*-tetrazoles using nanocrystalline ZnO in good yields [5].

In recent years, layered double hydroxides (LDHs) or hydrotalcite-like compounds (HTs) as catalysts have received much attention in view of their unique properties [6,7]. LDHs consists of alternating cationic M(II)_(1-x) M(III)_x(OH)₂^{x+} and

anionic Aⁿ⁻·zH₂O layers, where M(II) is a divalent cation such as Mg, Cu, Ni, Co, Mn, Zn; M(III) the trivalent cation, such as Al, Fe, Cr, Ru, V, In, Ga; A the exchangeable anions [8], such as Cl⁻, CO₃²⁻, NO₃⁻; the value of the *x* is in the range from 0.1 to 0.33. In continuation of our work on the development of new synthetic methods using LDHs as novel environmentally benign recyclable catalysts [9], we herein report the synthesis of 5-substituted 1*H*-tetrazoles from a wide variety of organic nitriles with sodium azide using Zn/Al hydrotalcite catalyst (Scheme 1).

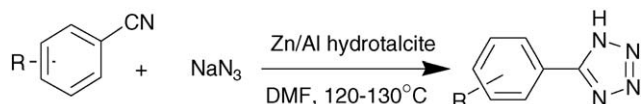
2. Experimental

ZnCl₂, AlCl₃, NaOH, NaN₃ and nitriles, were purchased from Aldrich or Fluka and used without further purification. ACME silica gel (100–200 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck-precoated silica gel 60-F254 plates. All the other solvents and chemicals were obtained from commercial sources and purified using standard methods.

2.1. Typical procedure for preparation of Zn/Al hydrotalcite

The anionic clay [Zn–Al–Cl], with a [Zn]/[Al] ratio equal 3, was synthesized by co-precipitation at a constant pH of 9.0 [10]. Mixtures of molar ZnCl₂ and AlCl₃ aqueous solutions were slowly introduced into the reactor, where the pH is maintained by the simultaneous addition of 1.0 M NaOH solution. The resulting slurry was then left under stirring for 24 h at room temperature.

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Scheme 1. Zn/Al hydrotalcite catalyzed synthesis of 5-substituted 1H-tetrazoles.

The precipitate was filtered, washed several times with distilled water and then dried at 30 °C. The zinc content in the catalyst was found to be 5.5 mmol/g. The catalyst was characterized by XRD, FTIR and it was similar to that reported earlier [10].

2.2. Typical procedure for preparation of 5-substituted 1H-tetrazole

Zn/Al hydrotalcite (0.1 g) is added to a mixture of benzonitrile (0.206 g, 2 mmol), sodium azide (0.195 g, 3 mmol) in DMF (5 mL) and stirred at 120 °C for 12 h. After completion of reaction (as monitored by TLC), the catalyst was centrifuged, washed with ethyl acetate and the centrifugate was treated with ethyl acetate (30 mL) and 5N HCl (20 mL) and stirred vigorously. The resultant organic layer was separated and the aqueous layer was again extracted with ethyl acetate (20 mL). The combined organic layers are washed with water and concentrated to give the crude solid crystalline 5-phenyltetrazole. Column chromatography was performed using silica gel (100–200 mesh) to afford pure 5-phenyltetrazole (0.245 g, 84%).

¹H NMR (200 MHz, CDCl₃ + DMSO) δ 8.04 (m, 2H), 7.61 (m, 3H); MS (70 eV) *m/z* (%) 146 (*M*⁺, 12.65%), 118 (100%), 103 (13.94%), 91 (36.70%), 77 (30.37%), 63 (26.58%), 39 (17.72%).

3. Results and discussion

In an effort to develop a better catalytic system, various reaction parameters were studied for the preparation of 5-phenyltetrazole by the reaction of benzonitrile with sodium azide and the results were summarized in Table 1. The solvent has

Table 1
Screening of reaction parameters for the formation 5-phenyltetrazole^a

| Entry | Solvent | Azide | Catalyst | Yield ^b (%) |
|-------|---------|-------------------|--------------------------|------------------------|
| 1 | Water | NaN ₃ | Zn/Al hydrotalcite | 5 |
| 2 | DMSO | NaN ₃ | Zn/Al hydrotalcite | 82 |
| 3 | NMP | NaN ₃ | Zn/Al hydrotalcite | 79 |
| 4 | DMF | NaN ₃ | Zn/Al hydrotalcite (3:1) | 84, 81 ^c |
| 5 | DMF | NaN ₃ | Mg/Al hydrotalcite (3:1) | 67 |
| 6 | DMF | TMSN ₃ | Zn/Al hydrotalcite | 66 |
| 7 | DMF | NaN ₃ | Zn(acac) ₂ | 69 ^d |
| 8 | DMF | NaN ₃ | ZnBr ₂ | 70 ^d |

^a Reaction conditions: nitrile (2 mmol), NaN₃ (3 mmol), Zn/Al hydrotalcite (0.1 g), DMF (5 mL), reaction time (12 h) and 120–130 °C.

^b Isolated yields.

^c Yield after third cycle.

^d Stoichiometric amounts are used.

a pronounced effect in these reactions (Table 1, entries 1–4), in which DMF and NMP and DMSO provided good yields. TMSN₃ was also used in the reaction with benzonitrile in DMF at 120 °C (Table 1, entry 6). Various catalysts were screened and found that Zn/Al (3:1) hydrotalcite was the effective catalyst. The controlled reaction conducted under identical conditions devoid of Zn/Al hydrotalcite gave no addition product, despite prolonged reaction times. Zn/Al hydrotalcite was recovered quantitatively by simple centrifugation and reused for three cycles with consistent activity (Table 1, entry 4).

We chose a variety of structurally divergent benzonitriles possessing a wide range of functional groups to understand the scope and the generality of the Zn/Al hydrotalcite promoted (2 + 3) cycloaddition reaction to form 5-substituted 1H-tetrazoles and the results were summarized in Table 2. Among the various nitriles tested, the aromatic benzonitriles gave moderate to good yields (Table 2, entries 1–5). 2-Chloro and 4-chlorobenzonitriles react similarly to provide the corresponding tetrazoles which shows there was no effect of substitution on benzonitrile (Table 2, entries 2 and 3).

Table 2
Zn/Al hydrotalcite mediated preparation of 5-substituted 1H-tetrazoles^a

| Entry | Substrate | Temperature (°C) | Time (h) | Yield ^b (%) |
|-------|-----------|------------------|----------|------------------------|
| 1 | | 120 | 12 | 84 |
| 2 | | 120 | 12 | 86 |
| 3 | | 120 | 12 | 81 |
| 4 | | 130 | 24 | 79 |
| 5 | | 120 | 12 | 82 |
| 6 | | 130 | 24 | 69 |
| 7 | | 120 | 5 | 91 |
| 8 | | 120 | 5 | 86 |
| 9 | | 130 | 24 | 78 |

^a Reaction conditions: nitrile (2 mmol), NaN₃ (3 mmol), Zn/Al hydrotalcite (0.1 g), DMF (5 mL) and 120–130 °C.

^b Isolated yields.

Interestingly 1,2-dicyanobenzene and 1,3-dicyanobenzene afforded mono addition product (Table 2, entries 4 and 9), whereas with Zn(II) salts di addition product was reported [3] in the literature. 4-Formylbenzonitrile gave only 1*H* tetrazole with carbonyl (aldehyde) functionality untouched (Table 2, entry 5). 4-Chlorophenyl acetonitrile provided moderate yield with long duration of time (Table 2, entry 6). Heteroaromatic nitriles such as 2-pyridinecarbonitrile and cyanopyrazine gave the corresponding tetrazoles in shorter reaction times with excellent yields (Table 2, entries 7 and 8).

4. Conclusions

In conclusion, we have developed a simple and efficient method for the preparation of 5-substituted 1*H*-tetrazoles via (2 + 3) cycloaddition using Zn/Al hydrotalcite as a heterogeneous catalyst. Various nitriles reacted with NaN₃ at 120–130 °C temperature to yield the corresponding 5-substituted 1*H*-tetrazoles with moderate to good yields (69–91%). The catalyst can be readily recovered and reused. This methodology may find widespread use in organic synthesis for the preparation of 5-substituted 1*H*-tetrazoles.

Acknowledgement

K.B. Shiva Kumar thanks UGC, India, for fellowship.

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