



Indium triflate-catalyzed one-pot synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles under solvent-free conditions

Dhiman Kundu, Adinath Majee *, Alakananda Hajra *

Department of Chemistry, Visva-Bharati University, Santiniketan, West Bengal, 731 235, India

ARTICLE INFO

Article history:

Received 21 December 2008

Revised 10 March 2009

Accepted 17 March 2009

Available online 21 March 2009

Keywords:

Indium triflate

1-Substituted-1*H*-1,2,3,4-tetrazoles

Three components, solvent-free

Cyclization

ABSTRACT

A simple, efficient, and general method has been developed for the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles via a three-component condensation of amine, trimethyl orthoformate, and sodium azide in presence of a catalytic amount of indium triflate under solvent-free conditions. The reaction proceeds smoothly to generate the corresponding 1-substituted tetrazoles in moderate to excellent yields under heating.

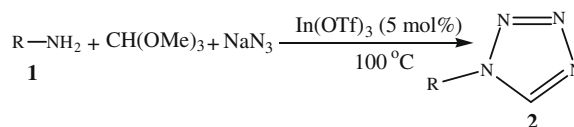
© 2009 Elsevier Ltd. All rights reserved.

One-pot catalytic conversion of organic reactions with readily available, non-toxic, and inexpensive reagents has attracted significant research interest in recent years. Multicomponent reactions with atom-economy and the identification of catalytic procedures that can be run under solvent-free conditions are ideal protocols for the development of environmental-friendly and cost-advantageous chemical processes.¹ Tetrazoles have attracted considerable interest in recent times because of their wide utility.² Among them, 1-substituted tetrazoles have received much attention and have been used in variety of synthetic and medicinal chemistry applications as well as in material science including propellants and explosives.³ They are also regarded as biologically equivalent to carboxylic acid group.⁴ Thus, synthesis of this heterocyclic nucleus is of much current importance. The well-known procedure for the synthesis of this heterocyclic nucleus is acid-catalyzed [3+2] cycloaddition between hydrazoic acid and isocyanide derivatives.⁵ However, one serious drawback of this reaction is the direct addition of large excess amounts of dangerous and harmful hydrazoic acid. The other routes include the cyclization reaction of amines or its hydrochloride salt with an orthocarboxylic acid ester and a hydrazoic acid metal salt in the presence of acetic acid.⁶ Other recent reported methods are acid-catalyzed cycloaddition between isocyanides and trimethylsilyl azide, ytterbium triflate and acidic ionic liquid-catalyzed cyclizations involving an amine, trimethyl orthoformate, and sodium azide.⁷ Each of these reported methods have one or more disadvantages such as the use of high boiling

solvents that are difficult to recover, toxic and explosive reagents, harsh conditions, tedious work-up using volatile solvents, and special efforts to prepare the catalyst. In view of these, the search for finding a cost-effective, mild and simple selective protocol for the synthesis of 1-substituted tetrazoles is still relevant.

In recent years, indium(III) compounds have evolved as mild and water-tolerant Lewis acids imparting high regio-, stereo-, and chemoselectivity in various organic transformations.⁸ Compared to conventional Lewis acids, indium(III) compounds have advantages of water stability, recyclability, and operational simplicity. Particularly, indium triflate is found to be a more effective catalyst than conventional Lewis acids in promoting various transformations.⁹ Our own work also found indium(III) compounds to be very efficient catalysts for two- and three-component coupling reactions.¹⁰ We wish to report here another remarkable catalytic activity of indium triflate for the one-pot condensation of sodium azide, amines, and trimethyl orthoformate to 1-substituted tetrazoles under solvent-free conditions (Scheme 1).

The experimental procedure is very simple.¹¹ Preliminary experiments were carried out in order to determine the best reaction conditions. The reaction of aniline (2 mmol), trimethyl orthoformate (2.4 mmol), and sodium azide (2 mmol) was carried



Scheme 1.

* Corresponding authors. Tel.: +91 3463 261526; fax: +91 3463 262728 (A.H.).
E-mail addresses: adinath.majee@visva-bharati.ac.in (A. Majee), alakananda.hajra@visva-bharati.ac.in, ahajra75@yahoo.com (A. Hajra).

Table 1
Effect of catalysts and solvents on the formation of tetrazole **2a**^a

Entry	Catalyst	Solvent	Time (h)	Yield of 2a ^b (%)
1	In(OTf) ₃	CH ₃ CN	2	85
2	In(OTf) ₃	1,2-Dichloroethane	2	82
3	In(OTf) ₃	2-Methoxyethanol	2	72
4	In(OTf) ₃	Neat	2	90
5	InCl ₃	Neat	4	65
6	Zn(OTf) ₂	Neat	4	75
7	Zn(ClO ₄) ₂	Neat	4	60
8	Mg(ClO ₄) ₂	Neat	4	72

^a Conditions: Benzaldehyde (2.0 mmol), trimethyl orthoformate (2.4 mmol), and sodium azide (2.0 mmol) in presence of a catalytic amount of catalyst (5 mol %) at 100 °C.

^b Isolated yield.

out in various solvents as well as neat in presence of different catalysts.

The results reported in Table 1 revealed that In(OTf)₃ (5 mol %) was better suited to afford the tetrazole in excellent yield under neat conditions at 100 °C (Table 1, entry 4).

The use of other organic solvents afforded the desired product in lower yields. Low conversions (60–72%) were obtained when other Lewis acid catalysts such as InCl₃, Zn(OTf)₂, Zn(ClO₄)₂, and Mg(ClO₄)₂ were employed. This method does not require any additives or anhydrous conditions and no precautions need to be taken to exclude moisture from the reaction media.

After optimizing the reaction conditions, we next examined the generality of this condition using trimethyl orthoformate, sodium azide, and several amines. The results are summarized in Table 2. Amines carrying different functional groups were subjected to the coupling reactions and in all cases the desired product was obtained in high yields. It was observed that under similar conditions, a wide range of anilines containing electron-withdrawing as well as electron-donating groups such as fluoro, chloro, methoxy, methyl, ester, and nitro underwent condensation in short reaction times with excellent isolated yields. The catalytic system also worked well with heterocyclic amine such as 2-amino pyridine and furfurylamine to generate the corresponding products with good yields of 75% and 83% (entries 11 and 12). Even for ethyl amino carboxylate, a good yield of the desired product (80%) was ob-

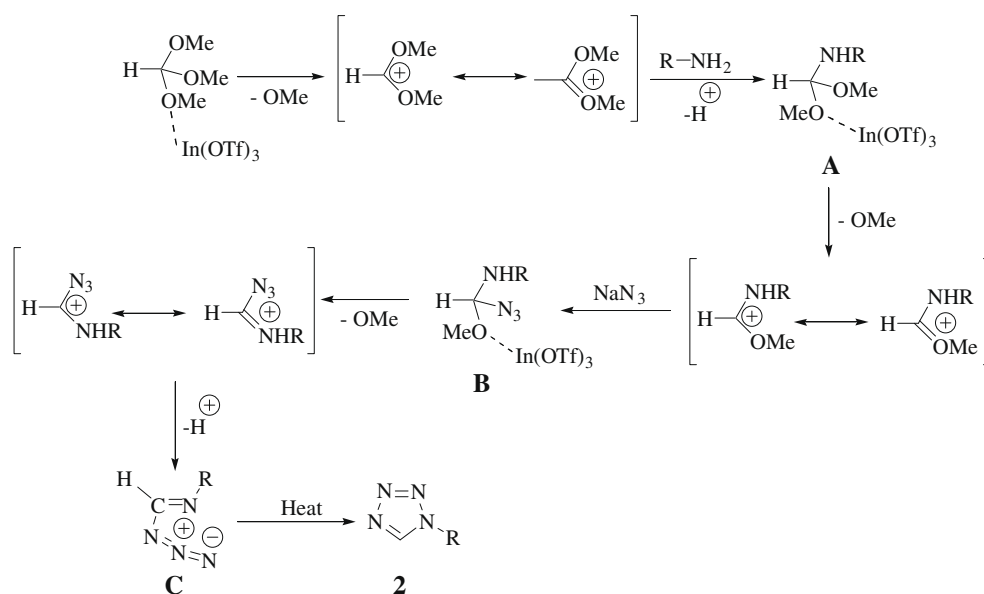
Table 2
Synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles

Entry	R	Products	Time (h)	Yield ^a (%)
1	C ₆ H ₅	2a	2	90
2	4-MeC ₆ H ₄	2b	1.5	92
3	2,3-Me ₂ C ₆ H ₃	2c	1.5	88
4	2-MeO-C ₆ H ₄	2d	1.5	89
5	2-ClC ₆ H ₄	2e	2	90
6	4-FC ₆ H ₄	2f	2	85
7	2-Cl-3-FC ₆ H ₃	2g	2.5	84
8	4-CO ₂ Et-C ₆ H ₄	2h	2.5	80
9	3-NO ₂ -C ₆ H ₄	2i	2.5	80
10	4-Vinylaniline	2j	2	82
11	2-C ₅ H ₄ N	2k	3	78
12	Furfurylamine	2l	2.5	75
13	(<i>S</i>)-1-Phenylethylamine	2m	3	81
14	C ₆ H ₅ CH ₂	2n	3.5	85
15	ⁿ Bu	2o	3.5	75
16	Cyclohexyl	2p	3.5	80
17	^t Bu	2q	3.5	70

^a Yields refer to those of pure isolated products fully characterized by spectral and analytical data.

tained without observing the formation of the other side products (entry 8). Encouraged by the above results, we continued our task to explore the reactivity of different aliphatic amines with trimethyl orthoformate and sodium azide under similar reaction conditions. The catalytic system worked well with aliphatic amines such as *n*-butylamine, cyclohexylamine, and *tert*-butylamine to generate the corresponding products of 75%, 80%, and 70% (entries 15–17).

The reusability of the catalyst is an important benefit especially for commercial applications. Thus, the recovery and reusability of In(III) triflate were investigated. After completion, the reaction mixture was diluted with cold water (5 mL) and extracted with ethyl acetate (10 mL × 3) to obtain the desired product. The catalyst was recovered almost quantitatively after removal of water under reduced pressure. The catalyst was used in the reaction and it showed the same activity as a fresh catalyst without any loss of its activity. After five recycles, the catalyst still had a high activity and gave the desired product in fairly good yield (83%, entry 3, Table 2).

**Scheme 2.** Proposed mechanism for the formation of tetrazole **2**.

A proposed mechanism for the 1-substituted tetrazole-forming reaction is shown in Scheme 2. It is clear from the sequence of steps that the role of indium triflate is limited to activate methoxy groups and to cleave C–O bonds to generate carbenium ions that are resonance stabilized by neighboring hetero atom O or N, facilitating sequential nucleophilic displacements by amine and azide anions. This would explain the formation of intermediates **A** and **B**. Indium triflate-assisted elimination of methanol from **B** leads to the proposed intermediate¹² **C** which, upon cyclization yields the final heterocycle **2**.

In comparison with the Yb(OTf)₃-catalyzed reaction^{7b} (20 mol % catalyst, 2-methoxyethanol as solvent), In(OTf)₃ has three clear advantages—it uses only 5 mol % of catalyst in a solvent-free reaction that requires less reaction time and provides improved yield.

In summary, indium triflate was found to be a novel and highly efficient Lewis acid catalyst for the synthesis of 1-substituted-1H-1,2,3,4-tetrazoles via the condensation of amines, trimethyl orthoformate, and sodium azide. The significant advantages offered by this method are: (i) solvent-free reaction, (ii) high yields, (iii) no waste production, (iv) non-toxic metal catalyst, and (v) simple operation. Another advantage of this method is its efficiency for the high yield synthesis of tetrazoles from aliphatic amines. Further studies on the application of the present methodology to the synthesis of biologically active compounds are under investigation.

Acknowledgments

A.H. is pleased to acknowledge the financial support from DST (Grant No. SR/FTP/CS-107/2006). We are thankful to DST-FIST and UGC-SAP. D.K. thanks CSIR for his fellowship. We also express our sincere thanks to Professor B. C. Ranu, Department of Chemistry, Indian Association for the Cultivation of Science, for his advice and constant encouragement.

References and notes

- (a) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025; (b) Hobbs, H. R.; Thomas, N. R. *Chem. Rev.* **2007**, *107*, 2786.
- Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, UK, 1996; Vol. 4.
- (a) Brown, M. U.S. Patent 3,338,915, **1967**; *Chem. Abstr.* **1968**, 87299; (b) Ostrovskii, V. A.; Pevzner, M. S.; Kofmna, T. P.; Shcherbinin, M. B.; Tselinskii, I. V. *Targets Heterocycl. Syst.* **1999**, *3*, 467; (c) Hiskey, M.; Chavez, D. E.; Naud, D. L.; Son, S. F.; Berghout, H. L.; Bome, C. A. *Proc. Int. Pyrotech. Semin.* **2000**, *27*, 3; (d) Burger, A. *Prog. Drug Res.* **1991**, *37*, 287; (e) Schelenz, T.; Schafer, W. *J. Fuel Prakt. Chem.* **2000**, *342*, 91; (f) Ruelke, H.; Friedel, A.; Martin, E.; Kottke, K.; Graefe, I.; Kuehmstedt, H. *Pharmazie* **1991**, *46*.
- Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. *Prog. Med. Chem.* **1980**, *17*, 151.
- (a) Zimmerman, D. M.; Olofson, R. A. *Tetrahedron Lett.* **1969**, *58*, 5081; (b) Fallon, F. G.; Herbst, R. M. *J. Org. Chem.* **1957**, *22*, 933.
- (a) Kamiya, T.; Saito, Y. U.S. Patent 3,767,667, **1973**; (b) Litkei, G.; Patonay, T.; Patonay-Peli, E.; Khilya, V. P. *Pharmazie* **1989**, *44*, 791.
- (a) Jin, T.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 9435; (b) Su, W.; Hong, Z.; Shan, W.; Zhang, X. *Eur. J. Org. Chem.* **2006**, 2723; (c) Potewar, T. M.; Siddiqui, S. A.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron Lett.* **2007**, *48*, 1721.
- (a) Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739; (b) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015; (c) Cintas, P. *Synlett* **1995**, 1087; (d) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633; (e) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959; (f) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347; (g) Auge, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739; (h) Hoppe, H. A. F.; Lloyd-Jones, G. C.; Murray, M.; Peakman, T. M.; Walsh, K. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 1545.
- (a) Nakamura, M.; Endo, K.; Nakamura, E. *Org. Lett.* **2005**, *7*, 3279; (b) Ghosh, R.; Maiti, S. J. *Mol. Catal. A: Chem.* **2007**, *264*, 2007.
- (a) Ranu, B. C.; Dey, S. S.; Hajra, A. *Tetrahedron* **2002**, *58*, 2529; (b) Ranu, B. C.; Samanta, S.; Hajra, A. *Synlett* **2002**, 987; (c) Ranu, B. C.; Hajra, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 355; (d) Ranu, B. C.; Hajra, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2262; (e) Ranu, B. C.; Samanta, S.; Hajra, A. *J. Org. Chem.* **2001**, *66*, 7519; (f) Ranu, B. C.; Hajra, A.; Jana, U. *Tetrahedron Lett.* **2002**, *41*, 531; (g) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270; (h) Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141; (i) Ranu, B. C.; Majee, A. *J. Chem. Soc., Chem. Commun.* **1997**, 1225.
- Typical procedure for the synthesis of 1-(2,3-dimethylphenyl)-1H-1,2,3,4-tetrazole (2c)*: A mixture of 2,3-dimethylaniline (242 mg, 2 mmol), trimethyl orthoformate (255 mg, 2.4 mmol), and sodium azide (130 mg, 2 mmol) was stirred in presence of indium triflate (56 mg, 5 mol %) at 100 °C for 1.5 h (TLC). After completion, the reaction mixture was diluted with cold water (5 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. The residue was concentrated and recrystallized from EtOAc–hexane (9:1) to afford the pure product as a white solid (285 mg, 88%), mp 140–141 °C. IR: ν = 2918, 2856, 1670, 1579, 1465, 1303 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.03 (s, 1H), 7.13–7.08 (m, 1H), 6.98–6.91 (m, 2H), 2.34 (s, 3H), 2.24 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 148.5, 143.8, 137.5, 127.5, 125.9, 125.1, 116.0, 20.4, 13.4. Anal. Calcd for C₉H₁₀N₄: C, 62.05; H, 5.79; N, 32.16. Found: C, 61.86; H, 5.61; N, 32.04.
- Finnegan, W. G.; Henry, R. A.; Lofquist, R. *J. Am. Chem. Soc.* **1958**, *80*, 3908.