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A novel method for the synthesis of 5-substituted 1*H*-tetrazole from oxime and sodium azide

Umakant B. Patil, Kedar R. Kumthekar, Jayashree M. Nagarkar *

Department of Chemistry, Institute of Chemical Technology (Deemed University), Nathalal Parekh Marg, Matunga(E), Mumbai 400 019, India

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ABSTRACT

A simple and efficient protocol is developed for the synthesis of 5-substituted 1*H*-tetrazoles from various oximes and sodium azide (NaN_3) by using copper acetate as a catalyst.

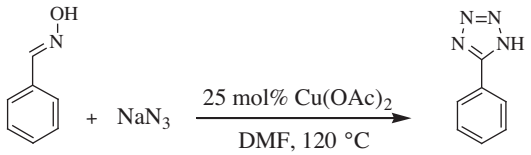
Tetrazoles are heterocyclic compounds having a five membered ring containing one carbon and four nitrogen atoms. Such heterocyclic systems are not found in nature. Tetrazoles have a wide range of applications in pharmaceutical chemistry[1] especially in drug in isosteric replacement of carboxylic acid moiety.[2] Biphenyl tetrazoles are used for the synthesis of sartan family drugs,[3] and also as ligands in the synthesis of imidoylazides.[4] Tetrazole compounds are widely used as propellants and explosives.[5] In crop protection they are used as plant growth regulators[6], herbicides, and fungicides.[7] In addition to this they possess antibiotic[8], anti-allergic[9], antagonists,[10] antihypertensive,[11] and antiviral activities.[12] Recently tetrazole moieties were widely used for binding aryl thiotetrazolylacetanilides with HIV-1 reverse transcriptase.[13]

Various methods have been reported for the synthesis of 5-substituted 1*H*-tetrazole, most of which are based on the addition of sodium azide (NaN_3) or trimethylsilyl azide ($TMSN_3$) to nitrile group. The reactions were carried out by using catalysts such as copper triflates[14a], $CdCl_2$,[14b] $Fe(OAc)_2$[14c] zinc(II) salts,[14d] Bronsted acid catalyst,[14e] various Lewis acid catalysts such as $AlCl_3$[15], BF_3–OEt_2,[16] $FeCl_3$[17], TBAF,[18] and by using some heterogeneous catalysts such as COY zeolites[19], mesoporous ZnS nanospheres,[20a] Cu_2O,[20b] and $CuFe_2O_4$ nanoparticles.[21] Acid catalysts are also used for the synthesis of tetrazole via cycloaddition of isocyanide to hydrazoic acid.[14b] The reported methods suffer from drawbacks such as use of Lewis acids, expensive and toxic metals, harsh reaction conditions, and formation of highly volatile and toxic hydrazoic acid as by product.[20a] Normally tetrazoles are synthesized by using toxic and expensive phenyl and substituted phenyl nitriles as precursors. Hence replacement of nitriles and use of comparatively cheaper and easily available catalyst, are the two motives which prompted us to carry out this work.

Herein we report a novel, simple, convenient, and greener protocol for the synthesis of 5-substituted 1*H*-tetrazole by reaction of organic oxime with solid sodium azide (NaN_3) in the presence of 25 mol % of copper acetate ($Cu(OAc)_2$) as a catalyst and DMF as solvent.

The reaction of (NZ)-*N*-benzylidenehydroxylamine with sodium azide was chosen as a model reaction (Scheme 1). Initially in an effort to develop an efficient catalyst various copper based catalysts were scanned for the preparation of 5-substituted[31] 1*H*-tetrazole, where $Cu(OAc)_2$ gave the maximum yield of 98% (Table 1, entry 6).

The reaction was optimized for various reaction parameters such as temperature, solvent, and catalyst loading. The oxime remains unconsumed when the reaction was done at room temperature (Table 2, entry 1). The effect of temperature on the yield of product was monitored from 80 to 140 °C (Table 2, entries 2–4). However, no further increase in the yield was obtained by increasing the temperature from 120 to 140 °C. Hence 120 °C was chosen as optimum reaction temperature.



Scheme 1. Synthesis of 5-substituted 1*H*-tetrazoles from oxime using $Cu(OAc)_2$ as catalyst and DMF as solvent.

* Corresponding author. Tel.: +91 22 3361 1111/2222; fax: +91 22 3361 1020.
E-mail addresses: jm.nagarkar@ictmumbai.edu.in, jayashreenagarkar@yahoo.co.in (J.M. Nagarkar).

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Table 1
Effect of catalysts on the formation of 5-substituted 1*H*-tetrazole[a]

Entry	Catalyst	Yield[b] (%)
1	$CuSO_4$	75
2	$Cu(NO_3)_2$	65
3	CuO	52
4	CuI	10
5	$Cu(acac)_2$	68
6	$Cu(OAc)_2$	98
7	$CuCl_2.H_2O$	10

[a] Reaction conditions: benzaldoxime (1 mmol), sodium azide (1.5 mmol), DMF (3 mL), catalyst (25 mol %) at 120 °C temperature for 12 h.
[b] Isolated yield.

Table 2
Effect of temperature on the formation of 5-substituted 1*H*-tetrazole[a]

Entry	Temperature (°C)	Yield[b] (%)
1	Room temp	Nil
2	80	28
3	100	61
4	120	98
5	140	98

[a] Reaction conditions: benzaldoxime (1 mmol), sodium azide (1.5 mmol), DMF (3 mL), $Cu(OAc)_2$ catalyst (25 mol %) at 120 °C temperature for 12 h.
[b] Isolated yield of product.

Table 3
Effect of solvent on the formation of 5-substituted 1*H*-tetrazole[a]

Entry	Solvent	Yield[b] (%)
1	None	20
2	H_2O	25
3	NMP	69
4	DMSO	55
5	DMF	98

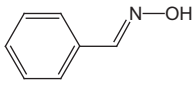
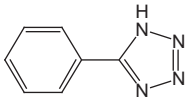
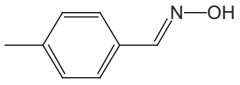
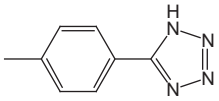
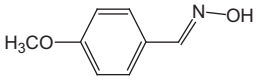
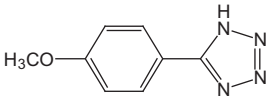
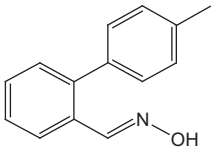
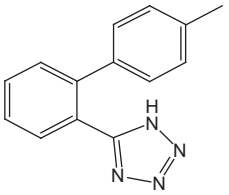
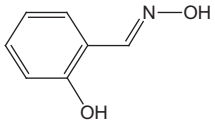
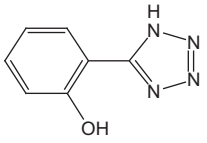
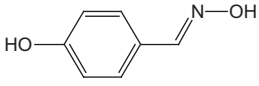
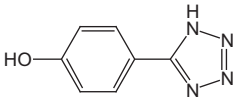
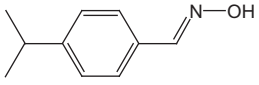
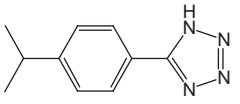
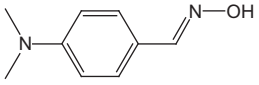
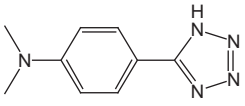
[a] Reaction conditions: benzaldoxime (1 mmol), sodium azide (1.5 mmol), DMF (3 mL), $Cu(OAc)_2$ catalyst (25 mol %) at 120 °C temperature for 12 h.
[b] Isolated yield of product.

Table 4
Effect of catalyst loading for synthesis of 5-substituted 1*H*-tetrazole[a]

Entry	Catalyst (mol %)	Yield[b] (%)
1	10	34
2	15	40
3	20	70
4	25	98
5	30	98

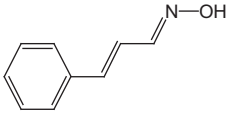
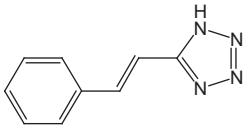
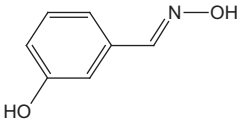
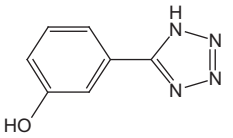
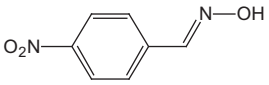
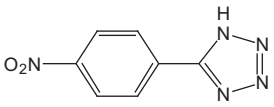
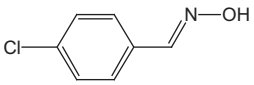
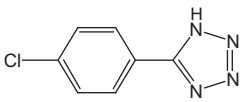
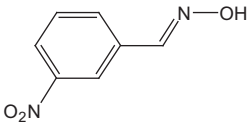
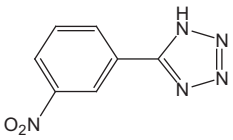
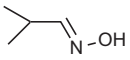
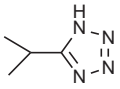
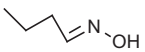
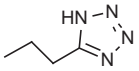
[a] Reaction conditions: benzaldoxime (1 mmol), sodium azide (1.5 mmol), DMF (3 mL), $Cu(OAc)_2$ catalyst at 120 °C temperature for 12 h.
[b] Isolated yield of product.

Table 5
Preparation of 5-substituted 1*H*-tetrazole by using various oximes

Entry	Substrate[a]	Product	Yield[b] (%)
1[14d,18]			98
2[20b,23]			90
3[22]			97
4[18,25]			90
5[24,28]			81
6[24,28]			91
7[26]			70
8[27,28]			72

(*continued on next page*)

Table 5 (*continued*)

Entry	Substrate[a]	Product	Yield[b] (%)
9[29]			40
10[16]			43
11[27,20a]			81
12[27,20a]			90
13[20a]			70
14[30]			Trace
15[30]			9

[a] Reaction conditions: benzaldoxime (1 mmol), sodium azide (1.5 mmol), DMF (3 mL), $Cu(OAc)_2$ (25 mol %) at 120 °C temperature for 12 h.
[b] Isolated yield of product.

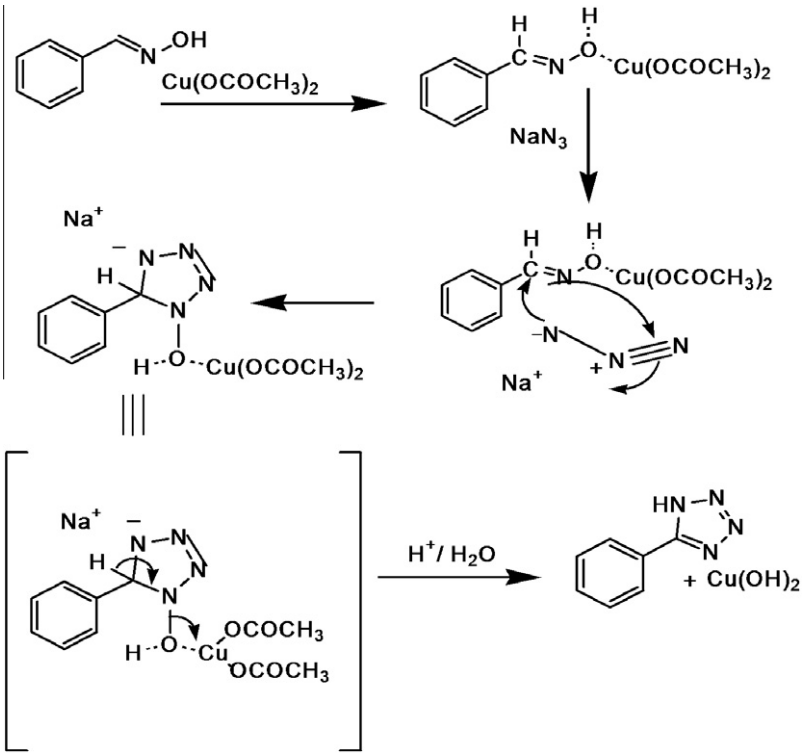


Figure 1. Plausible mechanism for tetrazole synthesis using $Cu(OAc)_2$.

An attempt to catalyze the reaction in the absence of solvent resulted in very low yield (Table 3, entry 1). Among the various solvents studied, DMF was found to be the best solvent (Table 3, entries 2–5) giving maximum yield of desired product.

Catalyst concentration was optimized by varying its concentration from 10 to 30 mol % (Table 4, entries 1–5). Increase in the product yield was observed for 10 to 25 mol % of catalyst amount. Hence 25 mol % was considered as an optimum catalyst concentration. (Table 4, entry 4)

Various 5-substituted 1*H*-tetrazoles were efficiently synthesized using this protocol. It was observed that the oximes and NaN_3 were easily converted into the desired product with excellent yield (Table 5). The oximes containing electron donating groups at *para* and *ortho* positions showed higher yield (Table 5, entries 2–6) while bulkier group at *para* position reduces the yield (Table 5, entries 7 and 8). Allylic oxime, and electron donating group at *meta* position gave lower yield (Table 5, entries 9 and 10). The reaction of oxime having an electron withdrawing group at *para* position gave better yield (Table 5, entries 11 and 12) while the electron withdrawing group at meta position gave a moderate yield. (Table 5, entry 13). Since aliphatic oximes are less reactive trace yields are obtained (Table 5, entries 14 and 15.).

Synthesis of nitrile from oxime by using $Cu(OAc)_2$ is reported[22] However, in the present work nitrile formation does not take place because of the nucleophilic attack of azide ion on the electron deficient carbon atom, instead cycloaddition takes place giving tetrazole, hence two steps process of tetrazole formation from oxime can be replaced by using one step protocol. Here $Cu(OAc)_2$ activates the C=N bond by co-coordinating with oxygen atom of oxime. This may facilitate the cycloaddition of NaN_3 across C=N bond which on acid hydrolysis gives the 5-substituted 1*H*-tetrazole product (Fig. 1).

In conclusion, we have developed a novel, greener, and atom economical protocol for the synthesis of 5-substituted 1*H*-tetrazoles by using oxime and sodium azide in the presence of $Cu(OAc)_2$ as an efficient catalyst. Replacement of toxic nitrile precursors by oximes is the novelty of this protocol. Higher yields, simple work-up procedure, easily available and cheaper catalyst are the added advantages of this protocol.

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References and notes

1. *Comprehensive Heterocyclic Chemistry*; Butler, R. N., Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford UK, 1984; Vol. 5, p 791.
2. Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379–3393.
3. Guo-xi, W.; Bao-ping, S.; Zong-ling, R. *Synth. Commun.* **2008**, *20*, 3577–3581.
4. (a) Modarresi-Alam, A. R.; Keykha, H.; Khamooshi, F.; Dabbagh, H. A. *Tetrahedron* **2004**, *60*, 1525–1530; (b) Modarresi-Alam, A. R.; Khamooshi, F.; Rostamizadeh, M.; Keykha, H.; Nasrollahzadeh, M.; Bijanzadeh, H. R.; Kleinpeter, E. *J. Mol. Struct.* **2007**, *841*, 61–66.
5. (a) Ostrovskii, V. A.; Pevzner, M. S.; Kofmna, T. P.; Shcherbinin, M. B.; Tselinskii, I. V. *Targets. Heterocycl. Syst.* **1999**, *3*, 467; (b) Hiskey, M.; Chavez, D. E.; Naud, D. L.; Son, S. F.; Berghout, H. L.; Bome, C. A. *Proc. Int. Pyrotech. Semin.* **2000**, *27*, 3–14.
6. Jursic, B. S.; Leblanc, B. W. *J. Heterocycl. Chem.* **1998**, *35*, 405–408. and references cited therein.
7. Sandmann, G.; Schneider, C.; Boger, P. Z.; Naturforsch, C. *Bioscience* **1996**, *51*, 534–539.
8. Andrus, A.; Partridge, B.; Heck, J. V.; Christensen, B. G. *Tetrahedron Lett.* **1984**, *25*, 911–914.
9. Peet, N. P.; Baugh, L. E.; Sunder, S.; Lewis, J. E.; Matthews, E. H.; Olberding, E. L.; Shah, D. N. *J. Med. Chem.* **1986**, *29*, 2403–2409.
10. Castro, J. L.; Ball, R. G.; Broughton, H. B.; Russell, M. G. N.; Rathbone, D.; Watt, A. P.; Baker, R.; Chapman, K. L.; Fletcher, A. E.; Smith, A. J.; Marshal, G. R.; Ryecroft, W.; Matassa, V. G. *J. Med. Chem.* **1996**, *39*, 842–849.
11. Wexler, R. R.; Greenlee, W. J.; Irvin, J. D.; Goldberg, M. R.; Prendergast, K.; Smith, R. D.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1996**, *39*, 625–656.
12. Wittenberger, S. *J. Org. Prep. Proced. Int.* **1994**, *26*, 499–531.
13. Gagnon, A.; Landry, S.; Coulombe, R.; Jakalian, A.; Guse, I.; Thavonekham, B.; Bonneau, P. R.; Yoakim, C.; Simoneau, B. *Bioorg. Med. Chem.* **2009**, *19*, 1199–1205.
14. (a) Bosch, L.; Vilarrasa, J. *Angew. Chem.* **2007**, *46*, 3926–3930; (b) Venkateshwarlu, G.; Premalatha, A.; Rajanna, K. C.; Saiprakash, P. K. *Synth. Commun.* **2009**, *39*, 4479–4485; (c) Bonnamour, J.; Bolm, C. *Chem. Eur. J.* **2009**, *15*, 4543–4545; (d) Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945–7950; (e) Bakunova, S. M.; Bakunov, S. A.; Patrick, D. A.; Suresh Kumar, E. V. K.; Ohemeng, K. A.; Bridges, A. S.; Wenzler, T.; Barszcz, T.; Jones, S. K.; Werbovetz, K. A.; Brun, R.; Tidwell, R. R. *J. Med. Chem.* **2009**, *52*, 2016–2035.
15. Matthews, D. P.; Green, J. E.; Shuker, A. J. *J. Comb. Chem.* **2000**, *2*, 19–23.
16. Kumar, A.; Narayanan, R.; Shechter, H. *J. Org. Chem.* **1996**, *61*, 4462–4465.
17. Nasrollahzadeh, M.; Bayat, Y.; Habibi, D.; Moshaee, S. *Tetrahedron Lett.* **2009**, *50*, 4435–4438.
18. Amantini, D.; Beleggia, R.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2004**, *69*, 2896–2898.
19. Braun, J.; Keller, W. *Ber. Dtsch. Chem. Ges.* **1932**, *65*, 1677–1685.
20. (a) Lang, L.; Li, B.; Liu, W.; Jiang, Li.; Xu, Z.; Yin, G. *Chem. Commun.* **2010**, *46*, 448–450; (b) Jin, T.; Kitahara, Kamijo S.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 2824–2827.
21. Sreedhar, B.; Kumar, A. S.; Yadav, D. *Tetrahedron Lett.* **2011**, *52*, 3565–3569.
22. Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.* **2009**, *51*, 4479–4481.
23. Curran, D. P.; Hadida, S.; Kim, S. Y. *Tetrahedron* **1999**, *55*, 8997.
24. Zhou, Y.; Yao, C.; Ni, R.; Yang, G. *Synth. Commun.* **2010**, *40*, 2624–2632.
25. Kamble, R. R.; Biradar, D. B.; Meti, G. Y.; Taj, T.; Gireesh, T.; Khazi, I. A.; Vaidyanathan, S. T.; Mohandoss, R.; Sridhar, B.; Parthasarathi, V. *J. Chem. Sci.* **2011**, *123*, 393–401.
26. Colman, J. *Chem. Ber.* **1897**, *2010*, 30.
27. Rama, V.; Kanagaraj, K.; Pitchumani, K. *J. Org. Chem.* **2011**, *76*, 9090–9095.
28. Mochizuki, H.; Hasui, T.; Kawamoto, M.; Ikeda, T.; Adachi, C.; Taniguchi, Y.; Shirota, Y. *Macromolecules* **2003**, *36*, 3457–3464.
29. Shie, J. J.; Fang, J. M. *J. Org. Chem.* **2002**, *68*, 1158–1160.
30. He, J.; Le, B.; Chen, F.; Xu, Z.; Yin, G. *J. Mol. Cat. Chem.* **2009**, *304*, 135–138.
31. *General process for the preparation of 5-substituted 1H-tetrazoles:* A mixture of oxime (1 mmol), sodium azide (1.5 mmol), catalyst (25 mol %), and DMF (3 mL) was taken in a 25 ml round bottomed flask and heated at 120 °C temperature for 12 h. under vigorous stirring. After completion of the reaction (observed on TLC) the reaction mass was cooled to rt. 5 ml of water was added followed by 5 mL of 2 N HCl. The mixture was stirred for 10 min. and the product was extracted with dichloromethane (3 × 10 mL). The organic layer was washed with water and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure to obtain the product. The crude product was purified on silica gel column by using pet ether and ethyl acetate as solvent to obtain the pure product. (98%). The obtained product was analyzed by FTIR, ^{1}H NMR and mass spectra.