



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

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ABSTRACT

A simple and efficient protocol is developed for the synthesis of 5-substituted 1H-tetrazoles from various oximes and sodium azide (NaN₃) by using copper acetate as a catalyst.

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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 chemistry¹ 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 regulators⁶, herbicides, and fungicides.⁷ In addition to this they possess antibiotic⁸, anti-allergic⁹, antagonists,¹⁰ antihypertensive,¹¹ and antiviral activities.¹² Recently tetrazole moieties were widely used for binding aryl thio-tetrazolylacetanilides with HIV-1 reverse transcriptase.¹³

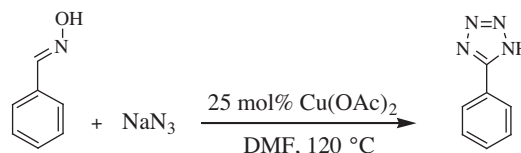
Various methods have been reported for the synthesis of 5-substituted 1H-tetrazole, most of which are based on the addition of sodium azide (NaN₃) or trimethylsilyl azide (TMSN₃) to nitrile group. The reactions were carried out by using catalysts such as copper triflates^{14a}, CdCl₂,^{14b} Fe(OAc)₂,^{14c} zinc(II) salts,^{14d} Bronsted acid catalyst,^{14e} various Lewis acid catalysts such as AlCl₃,¹⁵ BF₃–OEt₂,¹⁶ FeCl₃,¹⁷ TBAF,¹⁸ and by using some heterogeneous catalysts such as COY zeolites¹⁹, mesoporous ZnS nanospheres,^{20a} Cu₂O,^{20b} and CuFe₂O₄ 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 1H-tetrazole by reaction of organic oxime with solid sodium azide (NaN₃) 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-substituted³¹ 1H-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 1H-tetrazoles from oxime using Cu(OAc)₂ as catalyst and DMF as solvent.

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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 ₂ O	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 ₂ O	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

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