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Indium(III) Chloride Catalyzed Synthesis of 5-Substituted 1*H*-Tetrazoles from Oximes and Sodium Azide

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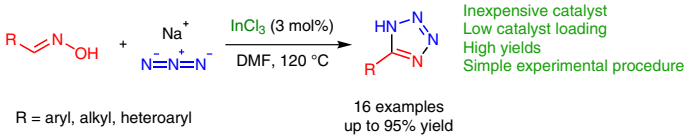

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Abstract A simple and efficient protocol has been developed for the synthesis of 5-substituted 1*H*-tetrazole derivatives in good to excellent yields from various oximes and sodium azide by using indium(III) chloride as a Lewis acid catalyst. The present method has significant advantages, such as an inexpensive catalyst, low catalyst loading, mild reaction conditions, and simple experimental procedures.

Key words tetrazoles, Lewis acids, catalysis, indium trichloride, sodium azide

Tetrazoles are privileged heterocyclic scaffolds that have numerous applications, especially in the field of pharmaceutical chemistry, where they can act as isosteric replacements of the carboxylic acid moiety.[1] They also have applications in general organic chemistry, coordination chemistry, photography, and agriculture.[2] Tetrazole moieties are found in various biologically active molecules, including antiinflammatory,[3a] antiallergic,[3b] antiviral,[3c] antibiotic,[4a] antitubercular,[4b] antineoplastic,[5] and antihypertensive agents.[6] In particular, tetrazoles are present in an important category of drugs, the sartans (for example, losartan),[7a] and they have also been used as ligands in the preparation of imidoylazides.[7b]

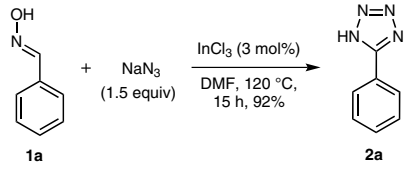
Various methods for the synthesis of tetrazoles from nitriles, amides, thioamides, imidoyl chlorides, heterocumulenes, ketones, amines, alkenes, or isocyanides have been reported.[8,9] Numerous catalysts have been used in syntheses of tetrazoles, include copper triflates,[10a] $CdCl_2$,[10b] $Fe(OAc)_2$,[10c] $ZnCl_2$,[11a] $ZnBr_2$,[11b,c] acids,[11d] $AlCl_3$,[12a] $BF_3{\cdot}OEt_2$,[12b] $FeCl_3$,[13a] TBAF,[13b] or Et_4NCl.[13c] Moreover, various heterogeneous catalysts such as COY zeolites,[14a] mesoporous ZnS nanospheres,[14b] Cu_2O,[14c] or $CuFe_2O_4$ nanoparticles[15a] have also been employed in the synthesis of 1*H*-tetrazoles from nitriles. Some of the reported methods suffer from drawbacks, such as use of expensive metal catalysts, inferior yields of the desired product, formation of side products, water sensitivity, harsh reaction conditions, the use of azide complexes such as tin or silicon azides, or the formation of toxic hydrazoic acid as a byproduct.[14b,15b] Consequently, there is still a need to develop catalytic, environmentally benign, efficient protocols for the preparation of tetrazoles.

$InCl_3$ has received considerable attention as an inexpensive readily available catalyst for performing various organic transformations with high selectivity.[16,17] $InCl_3$ has been previously reported to be an efficient catalyst for the synthesis of 5-substituted 1*H*-tetrazoles from nitriles.[18] However, the procedures include certain drawbacks, such as the danger associated with using NaN_3 in a microwave reactor, limited heterocycle substrate scope, and, most importantly, the requirement for high levels of the catalyst.

Our main objective was to replace the nitrile with an oxime as a better alternative starting material. From literature reports, we noticed that only a limited number of protocols are available for the synthesis of tetrazoles from oximes, and that this area remains largely unexplored. To the best of our knowledge, only catalysts such as *p*-toluenesulfonic acid,[19a] $Cu(OAc)_2$,[19b] and $CuFe_2O_4$[19c] have only been reported for the preparation of 1*H*-tetrazoles from oximes.

In a continuation of our studies into the development of novel synthetic methods,[20] we wish to report the conversion of oximes into 5-substituted 1*H*-tetrazoles by using a catalytic amount of $InCl_3$ (Scheme 1).

To investigate the catalytic efficiency of $InCl_3$ and to determine the most appropriate reaction conditions, we performed a model reaction with a mixture of benzaldoxime (**1a**; 1 mmol) and sodium azide (1.5 mmol) under various reaction conditions (Table 1). When 5 mol% of $InCl_3$ was



Scheme 1 Synthesis of 5-phenyl-1*H*-tetrazole

added, the reaction proceeded smoothly, and the desired 5-phenyl-1*H*-tetrazole (**2a**) was obtained in 92% yield (Table 1, entry 1). The yield remained high when the quantity of $InCl_3$ was reduced from 5 mol% to 3 mol% (entry 2). However, a further reduction in the amount of catalyst led to a protracted reaction time and a decreased yield (entry 3). In the absence of the catalyst, the reaction did not proceed even after an extended reaction time (entry 4). We also examined the effect of water and toluene as solvents under the same reaction conditions (entries 5 and 6). Among the solvents tested, DMF was found to be the best in terms of speed of conversion and yield. Hence, 3 mol% of $InCl_3$ and DMF (entry 2) were selected as the optimal reaction conditions for synthesis of 1*H*-tetrazoles.

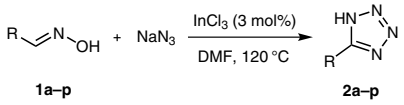
Table 1 Optimization of the Synthesis of 5-Phenyl-1*H*-tetrazole[a]

Entry	$InCl_3$ (mol%)	Solvent	Time (h)	Yield[b] (%)
1	5	DMF	15	92
2	3	DMF	15	90
3	1	DMF	20	72
4	0	DMF	48	–
5	3	H_2O	24	35
6	3	Toluene	24	trace

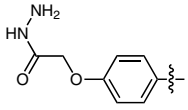
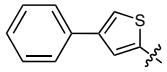
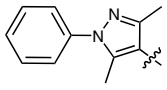
[a] Reaction conditions: benzaldoxime (**1a**; 1 mmol), NaN_3 (1.5 mmol), $InCl_3$, 120 °C.
[b] Isolated yield.

With the optimized reaction conditions in hand, we explored the scope of the protocol for the synthesis of 5-substituted 1*H*-tetrazoles from various substituted aldoximes. Aromatic oximes containing electron-donating groups at the *para*-position of the aromatic ring gave the corresponding 1*H*-tetrazoles in high yields with reduced reaction times (Table 2, entries 2–4); whereas aromatic oximes substituted with electron-withdrawing groups at the *para*-position required extended reaction times although the yields of the desired products remained unaffected (Table 1, entries 5–7). An aromatic aldoxime bearing chlorine substitution at the *para*- and *meta*-positions was well tolerated although, the yield was decreased to a certain extent (Table 2, entry 8); while an *ortho*-fluorine substituent demonstrated greater influence on the reaction time and yield of the desired product dropped markedly (Table 2, entry 9). In comparison with nitrile-based approaches, substrates bearing electron-donating groups result in the best yields with shortest reaction times (Table 2, entries 2–4), whereas substrates bearing electron-withdrawing groups reacted more slowly and gave lower yields (entries 5–7), possibly due to a reduction in the rate of formation of the aromatic tetrazole ring. A hydrazide substituent was found to be stable under the reaction conditions, and the corresponding product was obtained in high yield (entry 10). Attempts to use aliphatic oximes gave insignificant yields of the corresponding products (entries 11–13). Reactions using heteroaromatic substrates such as pyridine or thiophene aldoximes gave good yields in reduced reaction times (entries 14–16), whereas furfuryl oxime gave the desired product in an inferior yield, even after 30 hours (entry 17). The reaction using 3,5-di-

Table 2 $InCl_3$-Catalyzed Synthesis of 5-Substituted 1*H*-Tetrazoles[a]



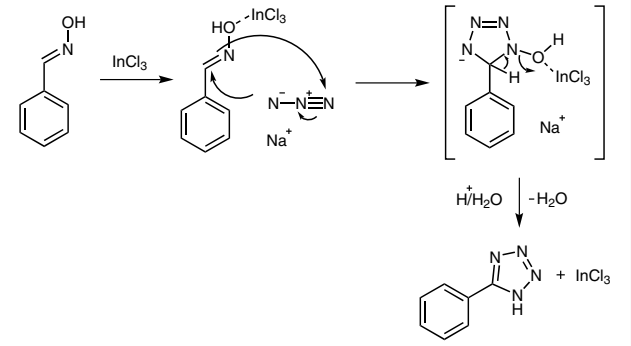
1a–p **2a–p**

Entry	R	Time (h)	Product	Yield[b] (%)
1	Ph	15	**2a**	92
2	4-Tol	10	**2b**	95
3	4-$MeOC_6H_4$	12	**2c**	90
4	4-HOC_6H_4	14	**2d**	82
5	4-$O_2NC_6H_4$	21	**2e**	84
6	4-FC_6H_4	18	**2f**	90
7	4-BrC_6H_4	20	**2g**	82
8	3,4-$Cl_2C_6H_3$	18	**2h**	78
9	2-FC_6H_4	28	**2i**	45
10		11	**2j**	72
11	Pr	28	**2k**	47
12	Bu	30	**2l**	40
13	*i*Bu	48	**2m**	20
14	3-pyridyl	14	**2n**	89
15	2-thienyl	13	**2o**	77
16		14	**2p**	83
17	2-furyl	30	**2q**	25
18		24	**2r**	-

[a] Reaction conditions: aldoxime (1 mmol), NaN_3 (1.5 mmol), $InCl_3$ (3 mol%), DMF (5 mL), 120 °C.
[b] Isolated yield.

methyl-1-phenyl-1*H*-pyrazole 4-oxime did not proceed (entry 17), possibly due to the steric effects of the methyl substituents in the *ortho*-positions of the substrate.

The synthesis of nitriles from oximes by using $InCl_3$ has been previously reported.[21] However in this conversion, we propose that nitrile formation does not occur as an initial step. Instead, nucleophilic attack by the azide on the electron-deficient carbon atom occurs, followed by cycloaddition and elimination to afford the tetrazole. In this process, the $InCl_3$ serves as a Lewis acid, activating the C=N bond by coordinating to the oxygen atom of the oxime. This might facilitate the cycloaddition of NaN_3 across the C=N bond (Scheme 2).



Scheme 2 Plausible mechanism for the $InCl_3$-catalyzed synthesis of 5-substituted 1*H*-tetrazoles

We also compared the efficiency of $InCl_3$ with other Lewis acids such as $SnCl_4$, $FeCl_3$, $ZnCl_2$, $B(C_6F_5)_3$, and $BF_3{\cdot}OEt_2$ for the synthesis of 5-phenyl-1*H*-tetrazole (Table 3). We found that $InCl_3$ was superior to other Lewis acids in terms of the yield and reaction time.

Table 3 Comparative Study of Various Lewis Acids in the Synthesis of 5-Phenyl-1*H*-tetrazole[a]

Entry	Lewis acid	Yield[b] (%)	Time (h)
1	$InCl_3$	90	15
2	$SnCl_4$	32	24
3	$FeCl_3$	25	24
4	$ZnCl_2$	45	24
5	$B(C_6F_5)_3$	–	24
6	$BF_3{\cdot}OEt_2$	–	24

[a] Reaction conditions: benzaldoxime (**1a**; 1 mmol), NaN_3 (1.5 mmol), Lewis acid (3 mol%), DMF (5 mL), 120 °C.
[b] Isolated yield.

In summary, we have established a simple and efficient protocol for the synthesis of 5-substituted 1*H*-tetrazoles by using a range of aromatic oximes and NaN_3 in the presence of $InCl_3$ as a Lewis acid catalyst.[22] The advantages of the present protocol include compatibility with many functional groups, use of a mild and an inexpensive catalyst, a simple experimental procedure, a low catalyst loading, and high yields.

Acknowledgment

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(22) **5-Substituted 1*H*-Tetrazoles 2a–r: General Procedure**

$InCl_3$ (3 mol%) was added to a stirred solution of the appropriate aldoxime (1 mmol) and NaN_3 (1.5 mmol) in DMF (5 mL), and the mixture was heated to 120 °C. When the reaction was complete (TLC), the mixture was cooled to r.t., H_2O (5 mL), 2 M aq HCl (10 mL), and EtOAc (10 mL) were successively added, and the mixture was stirred vigorously for 15 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with H_2O, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography [silica gel, EtOAc–hexane (9:1)].

2-[4-(1*H*-Tetrazol-5-yl)phenoxy]acetohydrazide (2j)

White solid; yield: 403 mg (72%); mp 197–199 °C. IR (KBr): 3432, 3318, 2869, 2645, 1614, 1521, 1450, 1280, 1172, 1108, 836 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 9.36 (br s, 1 H), 7.92 (d, *J* = 8.8 Hz, 2 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 4.49 (s, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.6, 159.4, 157.4, 127.2, 124.3, 114.6, 66.2. HRMS: *m/z* [M + H]$^+$ calcd for $C_9H_{11}N_6O_2$: 235.0938; found: 235.0939.

5-(4-Phenyl-2-thienyl)-1*H*-tetrazole (2p)

White solid; yield: 466 mg (83%); mp 240–242 °C. IR (KBr): 3220, 2260, 1574, 1478, 1261, 1153, 1066, 886, 778 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.21 (s, 1 H), 8.07 (s, 1 H), 7.74 (d, *J* = 7.2 Hz, 2 H), 7.68 (d, *J* = 7.2 Hz, 2 H) 7.45–7.33 (m, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.7, 141.6, 140.8, 134.6, 128.9, 127.4, 127.2, 125.7, 125.6. HRMS: *m/z* [M + H]$^+$ calcd for $C_{11}H_9N_4S$: 229.0542; found: 229.0543.