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$TiCl_3$ catalyzed one-pot protocol for the conversion of aldehydes into 5-substituted 1H-tetrazole

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Abstract: An efficient protocol has been explored for the one-pot synthesis of tetrazole derivatives with wide functional group compatibility in moderate to very high yields starting from aliphatic and aromatic substituted aldehydes. The reaction proceeds via non-isolated oxime and nitrile intermediates. The structures of the products were confirmed by IR and NMR spectroscopy. A plausible reaction mechanism is also provided.

Keywords: Aldehyde, Hydroxylamine hydrochloride, 5-substituted-1H-tetrazole, sodium azide, $TiCl_3$, cycloaddition reaction.

Introduction

Tetrazoles are a class of heterocycles which are receiving considerable attention due to wide range of applications associated with it and the literature having tetrazole chemistry are growing rapidly.[1] .Tetrazoles are reported to possess a huge biological activities such as antifungal[2], antibacterial [3], analgesic[4], antiviral, anti-inflammatory, antiulcer [5], and antihypertensive activities[6].Synthetic tetrazole derivatives have also been reported to possess antidiabetic[7], anti-HIV[8] activities and used for treatment of asthma[9]. 5-substituted-1H-tetrazoles can act as lipophilic spacer and carboxylic acid surrogates[10] and used in explosives[11], function as ligands in coordination chemistry[12].In addition, some famous drugs (Fig.1) Pemiroplast, candesartan, valsartan, losartan, and zolarsartan[13] contain tetrazolyl moieties. Traditional synthesis of 5-substituted 1H-tetrazole has been reported to proceed via [3+2] cycloaddition of

azide ion with nitrile[14].This procedure suffers from a few drawbacks, e.g. expensive and toxic metal organic azide and nitrile and probability of forming hydrazoic acid which is explosive. There are several catalyst in literature ,e.g. $BF_3.OEt_2$[15], $Pd(OAc)_2/ZnBr_2$[16], $AlCl_3$[17], $Yb(OTf)_3$[18] etc, but there are still a few drawbacks, e.g, tedious separation and recovery of the catalysts.Recently several heterogeneous catalytic system such as nanocrystalline ZnO, Zn/Al HT[19], $FeCl_3/SiO_2$, [20], Cu_2O[21], $CdCl_2$ [22], metal-modified montmorillonites and zeolite were extensively reported[23]. Many metals, such as Fe, Cu, Mo, V, Zn, Al, Mn, Co were used to improve the effectiveness of montmorillonites[24-31]. These methods also have some drawbacks, such as, these require excess amount of sodium azide, long reaction time, in spite of that, the cycloaddition is too slow to be practically useful except strong electron withdrawing groups activate the nitrile group. Due to the wide applications of the tetrazole-embedded structures, easy and economical synthetic protocols are still worth exploring[32]. One-pot protocols are particularly important as they get off the isolation of intermediate products [33].One-pot protocols for the synthesis of tetrazole have already been reported in literature using ammonia and iodine [34]. But this methodology should be avoided because this could result in the formation of hydrazoic acid and triiodide monoamine, which are explosive [35].Oximes also undergo [3+2] cycloaddition with sodium azide (NaN_3) to form 5-substituted 1H-tetrazole by copper acetate as a catalyst [36].

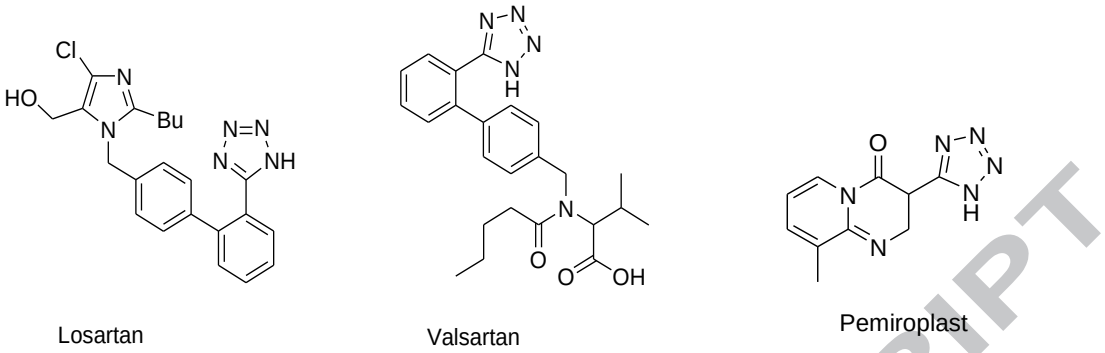
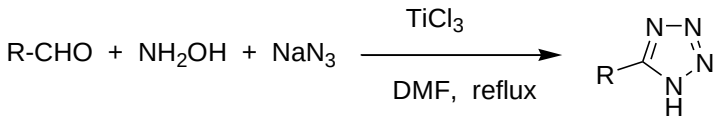


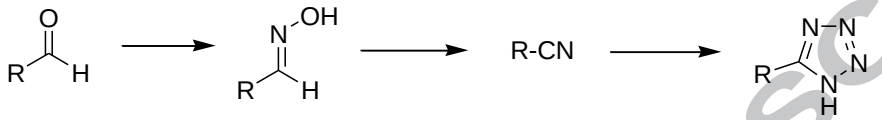
Fig.1. Pharmacologically important tetrazole drugs

In view of the availability, lower toxicity and ease of handling of aldehydes as compared to nitriles, the application of aldehydes for the synthesis of tetrazole derivatives are highly attractive and advantageous strategy. Direct transformation of aldehydes to the corresponding tetrazoles via [3+2] cycloaddition is well documented in literature [37-38].Titanium, a very abundant, inexpensive and nontoxic element, has been rarely utilized in organic synthesis. Out of several titanium compounds, a few of them ($TiCl_4$, $TiCl_3$, $TiCl_2(OR)_2$, Cp_2TiCl_2, etc.) are widely used [39]. To the best of our knowledge, $TiCl_3$ has been not yet used for the synthesis of 5-substituted 1H-tetrazole.

In this connection, herein, we report the protocol, where we used less expensive and easily available starting material aldehydes along with hydroxylamine hydrochloride and sodium azide catalysed by Titanium trichloride resulting in the formation of a number of tetrazole derivatives (1-16) from moderate to excellent yield (**Table 4**). Water solubility of catalyst, low toxicity, easy work-up, low duration and excellent yield of the products are special feature of this methodology.



Scheme 1. $TiCl_3$ catalyzed one-pot protocol for the conversion of aldehydes into 5-substituted 1H- tetrazole



Scheme 2. Proposed reaction intermediate for the synthesis of 5-substituted 1H-tetrazole

Results and discussion: The synthesis of tetrazoles (1-16) was achieved by the addition of hydroxylamine hydrochloride, sodium azide, Titanium tri chloride in DMF to various aldehydes and heating at reflux condition to afford the corresponding tetrazoles **(Scheme 1)** after work-up under acidic condition**.** The effect of temperature (Table1), solvent (Table 2) and amount of catalyst (Table 3) were monitored. It was found that DMF was the best solvent (entry 4, Table 2). We also optimized the amount of catalyst and it was found to be 20 mol% (entry 4, Table 3). For the generalization of the reaction, we applied optimized condition i.e. hydroxylamine hydrochloride (1.2 mmol), sodium azide (1.5 mmol) and $TiCl_3$ catalyst (20 mol %) under reflux condition to different aldehyde (1mmol) and got 42-95% yield at 3.5-6h (Table 4). This strategy applies to all types of aldehydes (aliphatic, aromatic and heterocyclic). The best result was found for aldehydes having electron withdrawing groups. The direct transformation of aldehydes into nitriles is well documented in literature with different reaction conditions [40-42]. Spectroscopic data confirmed the formation of the expected products. The intermediate nitrile is formed first (**Scheme 2**) and then [3+2] cycloaddition reaction takes place between nitrile and azide ion.

$TiCl_3$ facilitate the cycloaddition reaction because in absence of $TiCl_3$, only nitrile is formed (Table 3, entry 6).Formation of nitrile was confirmed by conducting the reaction using 3-nitro benzaldehyde without adding NaN_3 and got 83% nitrile.Completion of reaction was tested by TLC and after acidic work-up, the desired products were achieved by column chromatography using pet ether and ethyl acetate mixture as eluent.

Table 1: Effect of temperature on the synthesis of 5-substituted 1H-tetrazole[a]

Entry	**Temperature(^{0}C)**	**Yield[b] (%)**
1	Room temp	Nil
2	60	25
3	100	62
4	130	95
5	**reflux**	**95**

[a]Reaction condition: benzaldehyde (1mmol), hydroxylamine hydrochloride (1.2 mmol), sodium azide (1.5mmol), DMF (5ml), $TiCl_3$ catalyst (20mol%) at reflux condition for 4h, [b]Isolated yield

Table 2: Effect of solvent on the synthesis of 5-substituted 1H-tetrazole[a]

Entry	**Solvent**	**Yield[b] (%)**
1	None	Nil
2	DMSO	60
3	H_2O	20
4	**DMF**	**95**
5	Acetonitrile	30
6	Toluene	Nil
7	THF	Nil

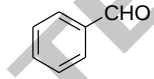
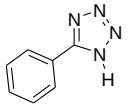
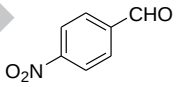
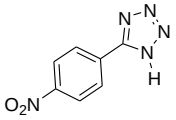
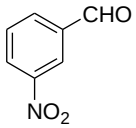
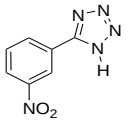
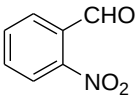
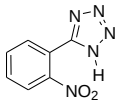
[a]Reaction condition: benzaldehyde (1mmol), Hydroxylamine hydrochloride (1.2mmol), sodium azide(1.5mmol), DMF(5ml), $TiCl_3$ catalyst (20mol%) at reflux condition for 4h, [b]Isolated yield of product

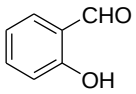
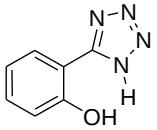
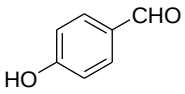
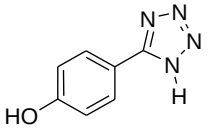
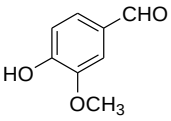
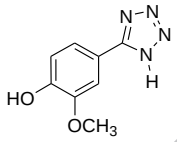
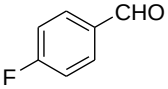
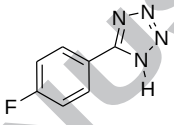
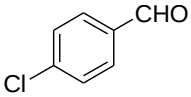
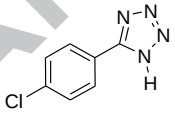
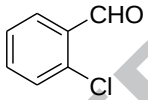
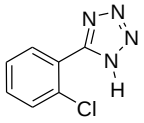
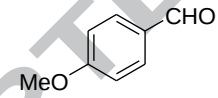
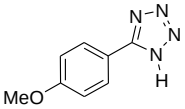
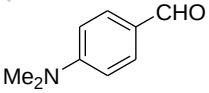
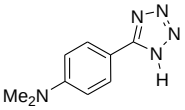
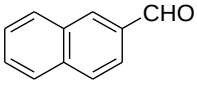
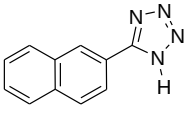
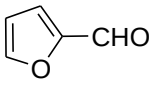
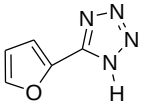
Table 3: Effect of catalyst loading for the synthesis of 5-substituted 1H-tetrazole[a]

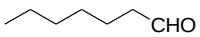
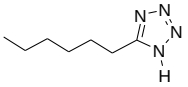
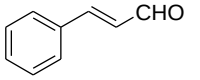
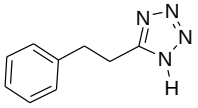
Entry	**Catalyst (mol%)**	**Yield[b] (%)**
1	5	40
2	10	67
3	15	95
4	**20**	**95**
5	30	96
6	none	nitrile

[a]Reaction condition: benzaldehyde (1mmol), Hydroxylamine hydrochloride (1.2mmol), sodium azide (1.5mmol), DMF (5ml), $TiCl_3$ catalyst at reflux condition for 4h, [b]Isolated Yield of Product

Table 4: Synthesis of 5-substituted 1H-tetrazole derivatives[a]

Entry	Reactant	Time(h)	Product	Yield(%)[b]
1		4		86
2		3.5		84
3		3		95
4		4		61

5		5		74
6		4		76
7		5		71
8		3.5		92
9		3		89
10		5		52
11		5		75
12		5.5		82
13		3.5		85
14		3		79

15		6		42
16		4		81

[a]Aldehyde (1mmol), hydroxylamine hydrochloride (1.2 mmol), sodium azide (1.5 mmol) and Titanium trichloride (20mol%) in DMF(5ml) under reflux condition, [b]Isolated yield

In summary, present methodology shows the synthesis of a nitrogen rich, bio-active heterocycle 5-substituted 1H-tetrazole directly from aldehyde, hydroxylamine hydrochloride and sodium azide catalyzed by titanium trichloride under reflux condition. The reaction is straightforward, less time consuming and easy to handle, moreover the reaction proceeds through some non-isolable reaction intermediates and products with excellent yield**.**

Conclusion

In conclusion, we have explored a lewis-acid, titanium trichloride catalyzed one-pot facile synthesis of 5-substituted 1H-tetrazole from easily available aldehyde (aromatic, aliphatic, heterocyclic), hydroxylamine hydrochloride and sodium azide under reflux condition. Advantages of this methodology are, use of less harmful organic solvent and low toxic catalyst, which are water soluble and thus causes less environmental pollution, easy work-up process and excellent yield of products**.**

General procedure for the synthesis

Aldehyde (1mmol), hydroxylamine hydrochloride (1.2mmol), sodium azide (1.5mmol) and titanium trichloride (20 mol%) were added to 5ml DMF and the mixture was kept on reflux for requisite time (Table 4). The progress of reaction was monitored by TLC and after completion of reaction, the mixture was treated with HCl (5ml dil.HCl), thereafter the mixture was added to

100ml water and extracted with ethylacetate, washed by water a few times. The extract was dried over anhydrous Na_2SO_4, purified by column chromatography on silica-gel (60-120 mesh) by pet-ether and ethyl acetate (75:25) as eluent. All the products were characterized by ^1H NMR and ^{13}C NMR spectroscopy.

Acknowledgements

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Graphical Abstract

$TiCl_3$ catalyzed one-pot protocol for the conversion of aldehydes to 5-substituted 1H- tetrazole

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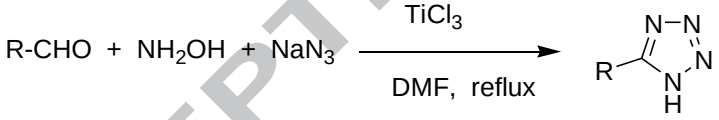

R= aryl, aliphatic, heterocyclic

HIGHLIGHTS

- Simple multi-component reaction for preparation of 5-substituted 1*H*-tetrazole from economical and easily available substrate
- Shorter reaction time
- Easy reaction set-up
- Inexpensive, reusable catalyst easily separable by simple filtration
- Functional group tolerance