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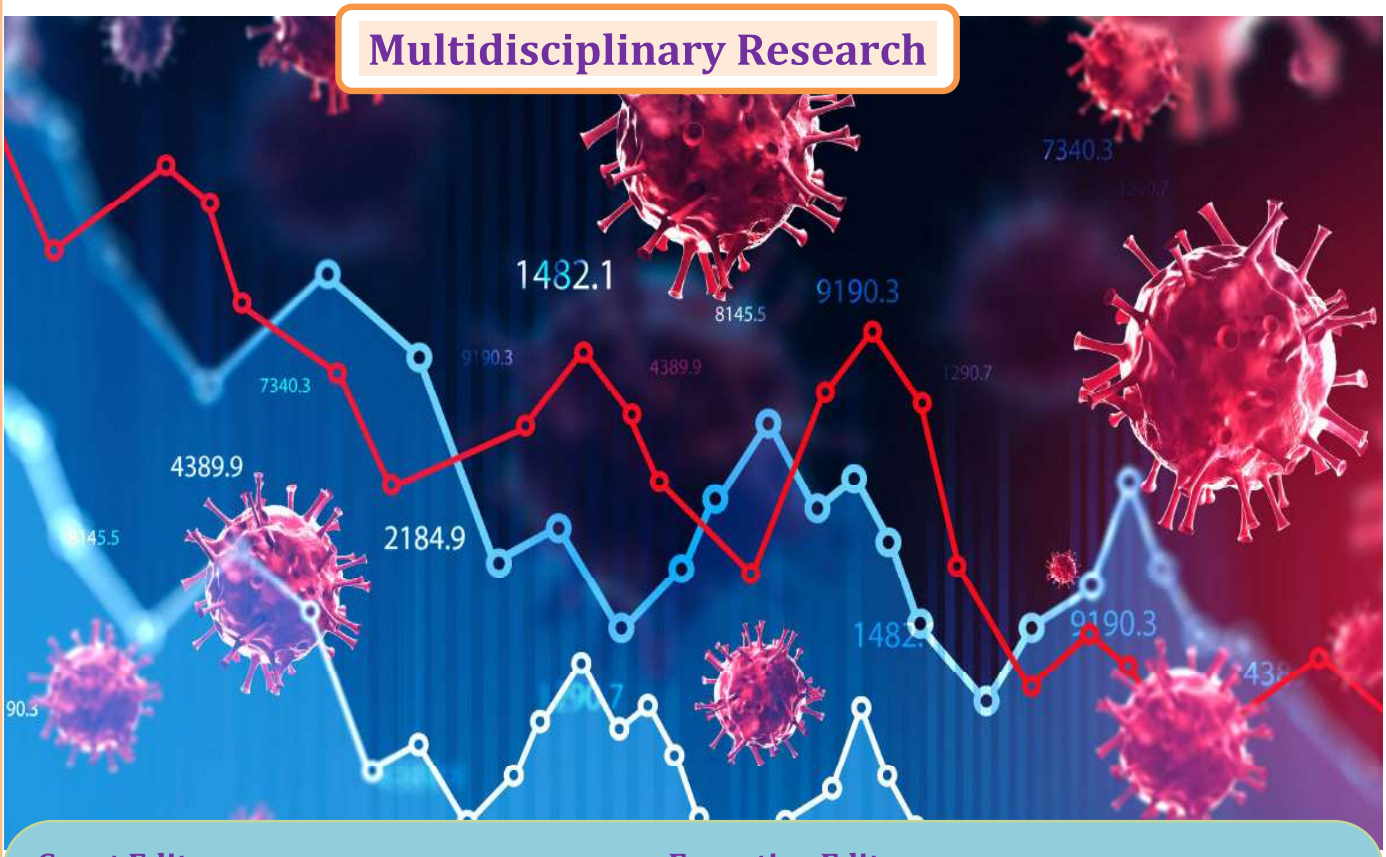

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'RESEARCH JOURNEY' International E- Research Journal
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Special Issue -256 (C) : Multidisciplinary Research
Peer Reviewed Journal
E-ISSN : 2348-7143
Dec. 2020

An Efficient Synthesis of 5-Substituted 1*H*-Tetrazole Using Eton's Reagent in Water

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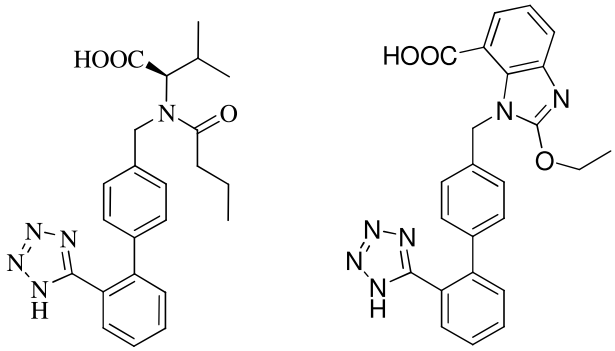
Abstract:

An efficient simple and facilemulticomponent synthesis of 5-substituted 1H-tetrazoles from aldehydes, hydroxylamine hydrochloride and sodium azide using Eton's reagent as an efficient catalyst in water under reflux condition is described. The sustainable and economic benefits of this reported protocol has several advantages such as high yields of products, simple work-up procedure, mild reactionconditions, use of water as a green solvent.

Introduction:

Organic synthesis of important small molecules has come a long way since Wohler first synthesized urea in 1828 [1]. Nitrogen-containing heterocyclic compounds are gettingmore and more attention from synthetic chemists [2-4]. Densely substitutedtetrazole derivatives are one of the most important classes of compounds widelyfound in natural products and pharmaceutical molecules owing to their profoundbioactivities [5,6].Tetrazole derivatives show bioisosterism to carboxylic acidand amide moieties and their metabolic stability. In addition the tetrazole derivatives found broad applications in various fields such as medicine, biochemistry, pharmacology and industry as materials [7-12].According to Drug bank 1H- or2H-tetrazole derivatives containing 43 drugs, out of them 23 drugs approved by FDA [13], these drugs possess antiviral, antimicrobial, hypertensive, cytostatic, and other biological activities.(fig. 1)
Multicomponent reactions (MCRs) are progressively more appreciated as efficient synthetic protocol to fast access complex products [14]. In MCRs, molecules can be assembled from more than two starting materials in a one-pot process. MCRs involve the formation of several bonds in a single operation, without isolating the intermediates, changing the reaction conditions, and often without adding further reagents. Therefore, MCRs address sustainability by step, atom, and eco-efficiency, reducing the number of intermediate steps and functional group manipulations and avoiding protective group methodologies. Syntheses involving MCRs save time and energy and proceed with high convergence.In addition, MCRs are preferably suited for combinatorial chemistry and library design, and are of enormous utility in medicinal chemistry, materials science.

Conventional synthesis of 5-substituted 1H-tetrazole has been reported to proceed via cycloaddition reaction of costly and toxic nitrile withazide ions [15]. In view of theease of handling availability, and lower toxicity of aldehydes ascompared to nitriles, the application of aldehydes for thesynthesis of tetrazole derivatives is a very attractive andvaluable approach. Some protocols were reported in literature for the synthesis of 5-substituted 1H-tetrazole from aldehyde in presence of various catalyst were used such as I_2[16], $(NH_4)_4Ce(SO_4)_4.2H_2O$ [17], $Cu(OAc)_2$[18],$TiCl_3$[19],PVA@CuSchiff base complex [20], Cu-MCM-41 [21], P_2O_5[22], and [bmim]N_3/$Cu(OAc)_2$[23]. Even though each of the reported methods has its self advantage, but the majority of reported methods are associated with some disadvantages including the use of toxic organic solvents, commercially unavailable catalysts and high reaction temperatures.To avoid such disadvantages, development efficient protocols is still in demand.



Valsartan **Candesartan**

(Antihypertensive agent)

Fig. 1 Drug containing 5-Substituted 1*H*-Tetrazole

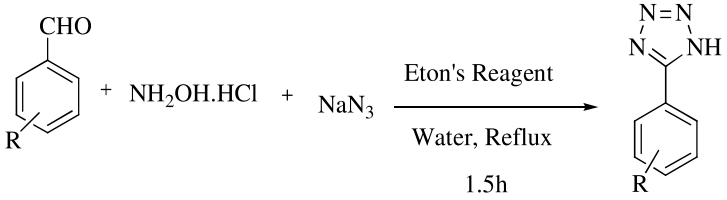
Experimental:

Material and methods:

All chemical and reagents were purchased from Sigma-Aldrich, India, and spectro-chemical companies in high purity and used without further purification. The catalystused was Sigma-Aldrich made. Infrared (IR) spectra in KBr were recorded using a PerkinElmer FTIR spectrometer 65. ^{1}H NMR spectra were recorded on BrukerAvanceII 400 MHz FT-NMR spectrometer in DMSO-d_6 as a solvent, and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internalstandard. Abbreviations used for NMR signals are s = singlet,d = doublet, t = triplet and m = multiplet. Meltingpoints were determined in open capillaries using an electrothermalMk_3 apparatus. The progresses of the reactions were monitored by TLC (thin-layer chromatography).

General procedure for the synthesis of 5-Substituted 1*H*-Tetrazole:

In a round-bottomed flask, a mixture of aldehyde (1 mmol), hydroxyl amine hydrochloride (1.5 mmol) and sodium azide(1.2mmol) in water (10 mL) was reflux in the presence of Eton's reagent (30 mole%). The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction; the reaction mixture was acidified with 5 N HCl (20 ml) the tetrazole derivatives were precipitated filtered and purified by recrystallization in a mixture of water and ethanol.



Result and Discussion:

In order to determine the optimized reaction conditions, we have usedp-nitro benzaldehyde, hydroxylamine hydrochloride and sodium azide as model substrates for the optimization of reaction conditions.Initially, the effect of various solvents was screened for synthesis of the corresponding 5-phenyl-1H-tetrazole (Table 1).Table 1 indicates, the solvent has played very important role for reaction progress. The model reaction was not completed in the absence of solvent even if the reaction time was prolonged up to 5 h (entry 1). As shown in Table

1, among the various solvents such as DMF,CH_3CN, EtOH, MeOHand water were examined among these various solvents water was selected to be the best reaction media due to its higher yield and shorter reaction time(entry 6).

To determine the catalyst loading, a model reaction wascarried out with different mole percentages of Eton's reagent in water. The reaction was performed using 10, 20, 30, 40 and 50 mol% of Eton's reagent in water under reflux condition.It was found that while increasing the amount of Eton's reagent from 10 to 20 and 30 mol%, theyields increased from 30 to 60 and 92%, respectively (Table 1, entries 2-4). Further increasingthe amount of Eton's reagent from 30 to 40 and 50 mol% does not show any significant effect on the yields(85%) of the product (Table 1, entries 5-6).

Table-1 Optimization of Solvent

Entry	Solvent	Time	Yield%
1	----	5h	---
2	DMF	3h	40
3	CH3CN	3h	45
4	EtOH	3h	55
5	MeOH	3h	55
6	Water	1.5h	92

Table 1 Optimization of catalyst loading

Entry	Amount of eton's reagent (mole %)	Time	Yield %
1	---	5h	Trace
2	10	5h	30
3	20	5h	60
4	30	1.5h	92
5	40	1.5h	85
6	50	1.5h	85

With the optimized parameters in hand, we have also performed wide substrate study with various substituted aromatic aldehydes for the synthesis of 5-Substituted 1*H*-Tetrazole derivatives (Table 3). Both electron donating and withdrawing group give good to excellent yield.

Spectral data:

1. 5-(4-nitrophenyl)-1H-tetrazole (4a): creamy solid; MP: 216-217 °C (214-215°C); reaction time 1.5 h; ^{1}H NMR (400 MHz, DMSO-d_6): 8.44 (2H, d) δ 8.32 (2H, d), ^{13}C NMR (100MHz, DMSO-d_6) δ 155.4, 148.7, 130.7, 128.2, 124.6.

Table 3 Synthesis of 5-Substituted 1*H*-Tetrazole under optimized reaction conditions

Entry	R	Time(h)	yield	M.P.	Reported M.P.
1	P-NO_2	1.5	92	216-217	214-215
2	p-Br	1.5	91	269-270	266-268
3	p-OH	1.6	90	237-238	235-236
4	m-OH	1.7	85	243-244	240-241
5	p-OMe	1.6	91	228-229	230-231
6	m-OMe	1.7	91	159-160	157-158
7	p-Cl	1.5	92	262-263	260-261

8	p-F	1.5	92	204-206	201-202
9	p-CH_3	1.3	88	250-251	247-249
10	H	1.6	90	218-219	215-217
11	p,m-di OMe	1.7	85	208-209	210-212

2. 5-(4-bromophenyl)-1H-tetrazole (4b): brown solid; MP: 269-270 °C (266-268 °C); reaction time 1.5 h; ^{1}H NMR (400 MHz, DMSO-d_6): 8.00 (2H, d), δ 7.85 (2H, d); ^{13}C NMR (100 MHz, DMSO-d6) δ 123.5,125.2, 129.3, 132.9.

Conclusion:

We have developed an environmentally benign protocol for the rapid and high yielding syntheses of 5-Substituted 1*H*-Tetrazole by using Eton's reagent from aromatic aldehyde, hydroxyl amine hydrochloride and sodium azidein water medium under reflux condition.The advantages of this protocol are mild reaction condition, good to excellent yield, minimization of the chemical wastes, use of available and cheap starting materialsand aqueous medium as the green solvent.

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