A Facile Synthesis of Novel (*Z*)-ethyl-3-(5-substituted-1-alkyl/aryl-1*H*-indol-3-yl)-2-(*1H*-tetrazol-5-yl)acrylate

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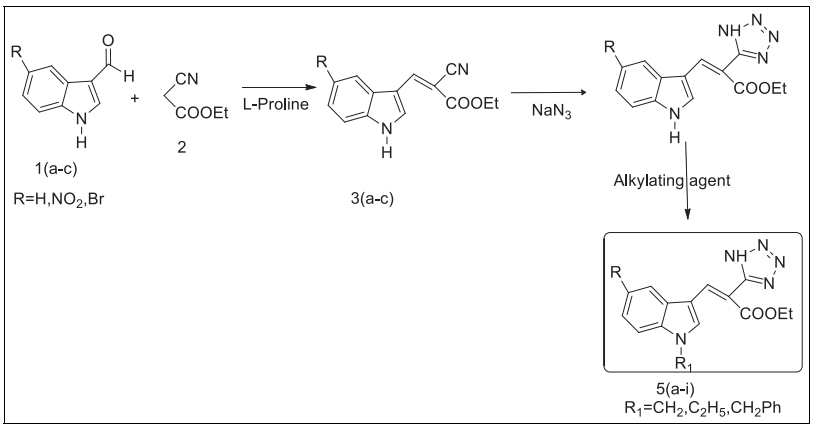
Received June 26, 2018
DOI 10.1002/jhet.3375
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).



A novel route was developed for synthesis of high potential 1*H*-tetrazoles by using conventional method. Tetrazole scaffold is a promising pharmacophore fragment, frequently used in the development of various novel drugs. Here, the novel (*Z*)-3-(*N*-alkyl-indol-3-yl)-2-(1*H*-tetrazole-5-yl)acrylates **5** (**a**–**i**) have been synthesized from (*Z*)-ethyl-3-(1*H*-indol-3-yl)2-(1*H*-tetrazol-5-yl)acrylates **4** (**a**–**c**) by using various alkylating agents such as Dimethyl Sulphate (DMS), Diethyl Sulphate (DES), and benzyl chloride; **4** (**a**–**c**) were synthesized from sodium azide in the presence of copper sulfate in dimethylformamide; **3** (**a**–**c**) have been prepared by Knoevenagel condensation of indole-3-carbaldehyde **1** (**a**–**c**) and ethylcyanoacetate **2** in the presence of L-Proline as a catalyst at room temperature in ethanol for an hour. This is an efficient and clean click chemistry method that has various advantages such as easy workup, higher yields, shorter reaction times, and more economical.

INTRODUCTION

The chemistry of heterocyclic compounds has acquired immense importance in recent years. The tetrazole functionality is metabolically stable and has a closer similarity with the acidic character of the carboxylic acid group that has been inspired medicinal chemists to synthesize substituted tetrazoles as potential medicinal agents. 5-Substituted tetrazoles are reported to possess [1] antibacterial [2], antifungal [3], antiviral, [4] analgesic [5], anti-inflammatory [6], antiulcer, and [7] antihypertensive activities. Also [8,9], this functional group has efficient roles in coordination chemistry as a ligand and in various material science applications including propellants and explosives. Furthermore [10], tetrazole moieties are important synthons in synthetic organic chemistry [11,12]. Therefore, a number of methods have been reported for the preparation of tetrazoles [13,14], one of the major synthetic routes to tetrazole formation is the [2+3] cycloaddition of an organonitrile and an azide salt [15]. The preparations of substituted tetrazoles have been the subject of intense investigation especially from the nitrile functionality, which is widely recognized as a useful intermediate in organic synthesis [16]. Synthetic, medicinal, and pharmaceutical applications of tetrazoles are well explored and documented in the literature [17]. Biphenyl tetrazoles are also well known and used to synthesize certain family drugs [18]. The other class of its use includes propellants [19], explosives, and in photography. [20] In addition to the above, it is found useful in agriculture as plant growth regulators and in crop protection [21]. Its derivatives play a key role as herbicides and fungicides [22]. The synthesis of 5-substituted-1*H*-tetrazoles was found fascinating, and many new processes and revisions of existing processes since Finnegan's invention have appeared. The basic principle of most of them is almost common, that is, cycloaddition of nitrile with an azide moiety, under the influence of several efficient catalysts and different solvent conditions. Number of new catalysts have also been investigated till date and among those which serve the purpose are [23] copper triflates [24], Fe $(OAc)_2$ [25], zinc (II) salts, and Lewis acids such as [26] $AlCl_3$ [27],

BF_3–OEt_2 [28], $FeCl_3$ [29], TBAF [30], heterogeneous catalysis COY zeolites[31], mesoporous ZnS nanospheres [32], Cu_2O, and [33] $CuFe_2O_4$ nanoparticles [25]. Acid catalysts are also used for the synthesis of tetrazoles *via* cycloaddition. Recently, many chemists have reported the use of transition elements and their salts as catalysts for the synthesis of tetrazoles [25]. Sharpless and coworkers were reported an innovative procedure for the preparation of 5-substituted-1*H*-tetrazoles from the corresponding nitriles and NaN_3 in the presence of a stoichiometric amount of 50 mol% of Zn (II) salts.

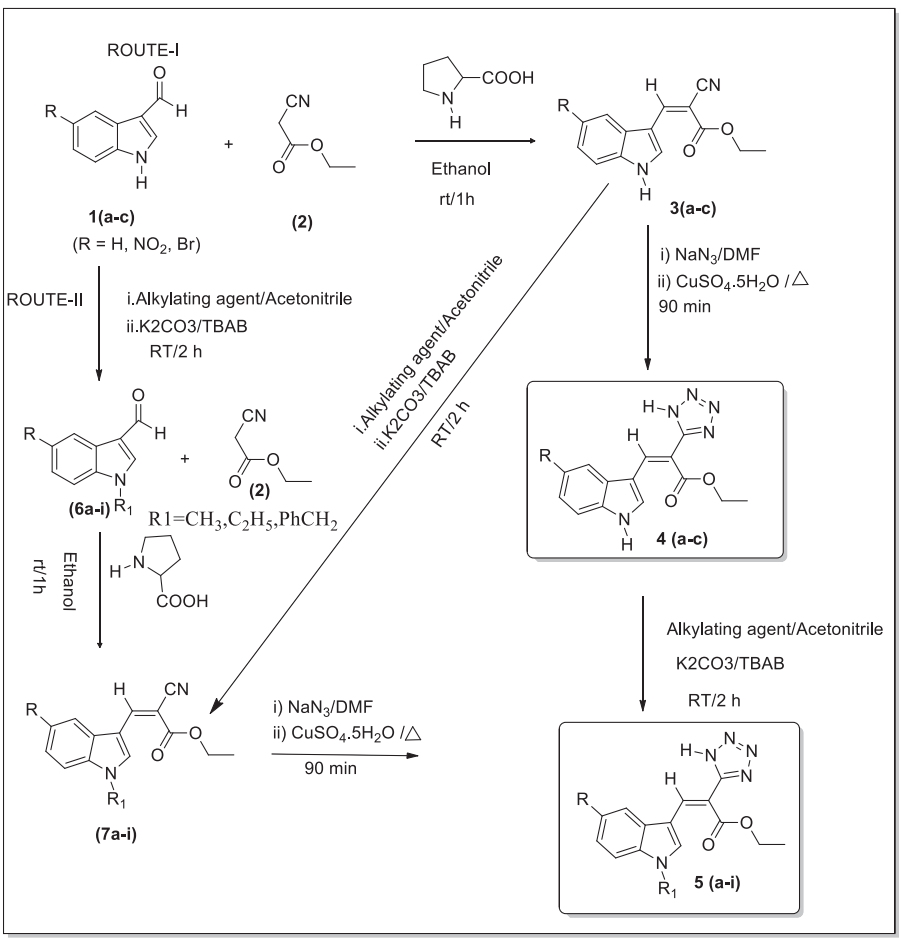
Shortly, an efficient method for the synthesis of tetrazoles was reported by the reaction of nitriles with $TMSN_3$ using 50 mol% of TBAF as catalyst. However, many of the aforementioned protocols have some disadvantages, like use of toxic metals, strong Lewis acids, expensive reagents, low yields, harsh reaction conditions, water sensitivity, and the usual separation and toxicity problems associated with small alkyl tin reagents. In addition to this, in some cases, formation of highly volatile and toxic hydrazoic acid as by product warrants the safety of the method.

Herein, we report a novel methodology for the synthesis of (*Z*)-ethyl-3-(5-substituted-1-alkyl/aryl-1*H*-indol-3-yl)-2-(1*H*-tetrazol-5-yl)acrylate derivatives and their structures were confirmed by chemical and spectroscopic methods such as FTIR, ^{1}H NMR, ^{13}C NMR, and HRMS.

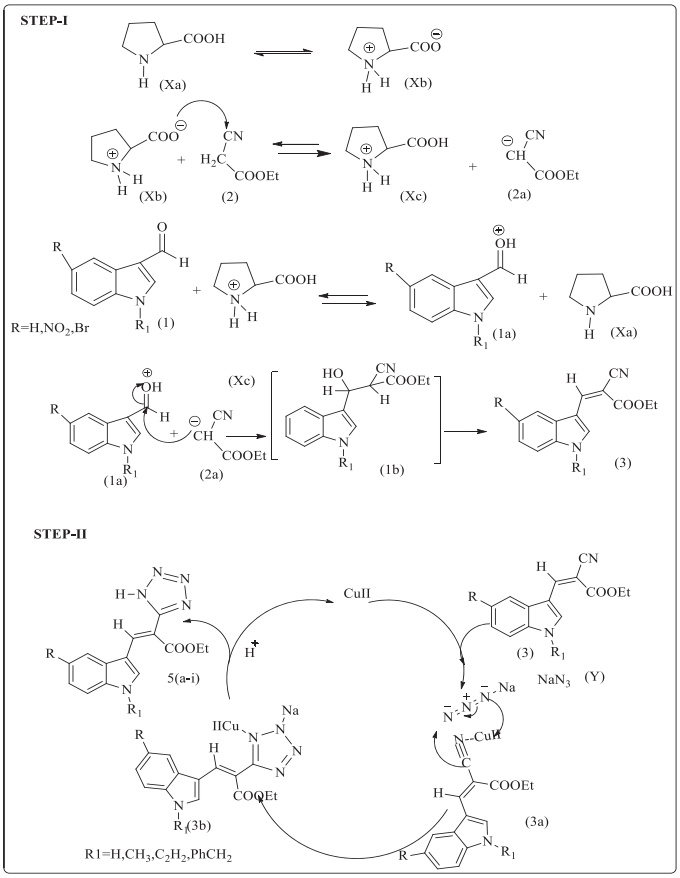
RESULTS AND DISCUSSION

The synthetic pathway for the newly synthesized compounds (*Z*)-3-(*N*-alkyl-indol-3-yl)-2-(1*H*-tetrazole-5-yl)acrylate **5** (**a**–**i**) derivatives starts from indole-3-carbaldehydes **1** (**a**–**c**), on reaction with ethylcyanoacetate **2** in the presence of L-Proline as a catalyst. The reaction has been done at room temperature in ethanol for an hour gave (*Z*)-ethyl-2-cyano-3-(1*H*-indol-3-yl)acrylates **3** (**a**–**c**); **3** (**a**–**c**) were reacted with sodium azide in dimethylformamide (DMF) containing catalytic amount of copper sulfate resulted the formation of products **4** (**a**–**c**); **4** (**a**–**c**) were reacted with various alkylating agents such as DMS, DES, and benzyl chloride gave the target

Scheme 1. Synthesis of *Z*-ethyl-3-(1*H*-indol-3-yl)2-(1*H*-tetrazol-5-yl)acrylate derivatives.



Scheme 2. Plausible mechanism for the formation of **5** (**a**–**i**) in the presence of $CuSO_4.5H_2O$.



compounds, that is, novel (*Z*)-3-(*N*-alkyl-indol-3-yl)-2-(1*H*-tetrazole-5-yl)acrylates **5** (**a**–**i**) (Scheme 1).

Another possible route for the syntheses of **5** (**a**–**i**) using (*Z*)-ethyl-2-cyano-3-(5-substituted-1-aryl/alkyl-1*H*-indol-3-yl)acrylates **7** (**a**–**i**) that were prepared from 5-substituted-1-alkyl/aryl-1*H*-indol-3-carbaldehydes **6** (**a**–**i**) and (**2**) in the presence of L-Proline as a catalyst. The reaction has been done at room temperature in ethanol for 1 h; **6** (**a**–**i**) were obtained by the same procedure mentioned earlier for the formation of **4** (**a**–**c**); **7** (**a**–**i**) were reacted with sodium azide in DMF containing catalytic amount of copper sulfate resulted the formation of the final products **5** (**a**–**i**) (Scheme 1).

The reaction conditions have been optimized for the formation of **4** (**a**–**c**) and **5** (**a**–**i**) under various conditions using different solvents such as H_2O, DMF, DMSO, ethanol, acetonitrile, and toluene. It was found that DMF is the best suitable solvent which resulting high yields of products around 90%. $CuSO_4.5H_2O$ has been chosen as the catalyst, and various molar amounts of it has been used and it was found that only 2 mol% of the catalyst is

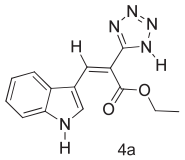
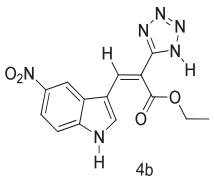
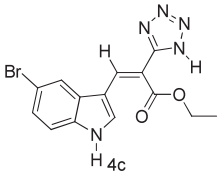
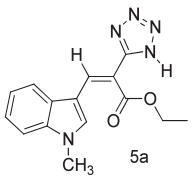
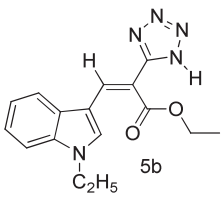
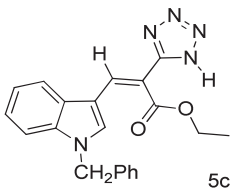
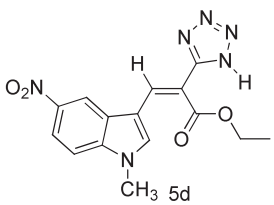
Table 1

Synthesis of **4** (**a**–**c**) and **5** (**a**–**i**) using various mol% of $CuSO_4.5H_2O$ and solvents.

S. no.	Solvent	Catalyst (mol%)	Time (h)	Temp (°C)	Yield (%)
1.	H_2O	0	24	100	0
		2			
		5			
2.	EtOH	0	24	100	0
		2			
		5			
3.	$PhCH_3$	0	24	120	0
		2			
		5			
4.	CH_3CN	0	24	120	0
		2			
		5			
5.	DMF	0	24	120	0
		2	1.5		95
		5	1.5		86
6.	DMSO	0	24	120	0
		2	2		74
		5	2		62

Table 2

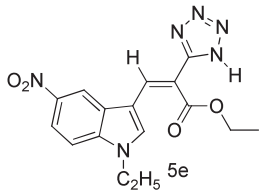
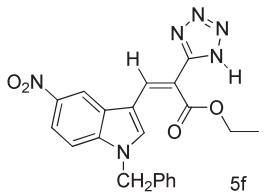
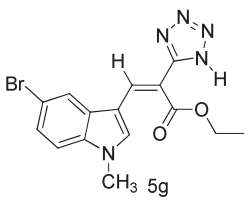
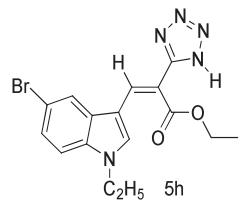
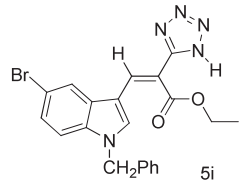
Synthesis of different structurally tetrazole derivatives of **4** (**a**–**c**) and **5** (**a**–**i**) in the presence of $CuSO_4.5H_2O$ in DMF.

S. no.	Product	Time (h)	Yield %	M.P
1	 4a	1.5	90	220–224
2	 4b	1.5	88	235–238
3	 4c	1.5	89	224–228
4	 5a	1.5	85	205–208
5	 5b	1.5	81	218–224
6	 5c	1.5	76	210–215
7	 5d	1.5	81	215–218

(*Continues*)

Table 2

(*Continued*)

S. no.	Product	Time (h)	Yield %	M.P
8	 5e	1.5	78	238–240
9	 5f	1.5	72	220–225
10	 5g	1.5	86	218–224
11	 5h	1.5	82	205–210
12	 5i	1.5	80	204–208

sufficient to obtain best results when 1:2 ratio of intermediate **3** (**a**–**c**) and sodium azide has been taken.

Generally, with the catalysis of $CuSO_4.5H_2O$ in DMSO (Table 1, entries 6), the reaction gave good yields, whereas in the absence of catalyst, (*Z*)-ethyl-3-(5-substituted-*N*-aryl/alkyl-1*H*-indol-3-yl)2-(1*H*-tetrazol-5-yl)acrylates **5** (**a**–**i**) was not obtained (Table 1, entries 1–4). On the basis of data from Table 1, the best amount of $CuSO_4.5H_2O$ as catalyst is 2 mol% (Table 1, entries 6). In an effort to develop better reaction conditions, different solvents were tested for the preparation of **5** (**a**–**i**) from the reaction of (*Z*)-ethyl-2-cyano-3-(1*H*-indol-3-yl)acrylates **3** (**a**–**c**) with sodium azide in the presence of 2 mol% of $CuSO_4.5H_2O$ (Table 1). No product was obtained when the reaction was performed in ethanol, water, toluene, and acetonitrile (Table 1, entries 1–4). As shown in Table 1, among all the different solvents tested, DMF was found to be the solvent of choice, because the excellent yield was obtained in DMF at 120°C in a very short time by applying 2 mol% of $CuSO_4.5H_2O$ and 1:2 molar ratio of (*Z*)-ethyl 2-cyano-3-(5-substituted-1-aryl/alkyl-1*H*-indol-3-yl)acrylates **7** (**a**–**i**) and sodium azide (Scheme 2, Table 1).

The formation of (*Z*)-ethyl-3-(1*H*-indol-3-yl)2-(1*H*-tetrazol-5-yl)acrylate derivatives, that is, **4** (**a**–**c**) and (*Z*)-ethyl-3-(5substituted-*N*-aryl/alkyl-1*H*-indol-3-yl)2-(1*H*-tetrazol-5-yl)acrylate derivatives **5** (**a**–**i**) were

determined by thin-layer chromatography (TLC), and the structures of these newly synthesized compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectral analysis methods.

To understand the scope and the generality of $CuSO_4.5H_2O$ promoted (3+2) cycloaddition reactions, a variety of structurally divergent *Z*-ethyl-3-(1*H*-indol-3-yl)2-(1*H*-tetrazol-5-yl)acrylates and a wide range of alkylating agents were chosen and the results are presented in Table 2.

CONCLUSION

In conclusion, an efficient and conventional method for the preparation of novel (*Z*)-ethyl-3-(5-substituted-1-alkyl/aryl-1*H*-indol-3-yl)-2-(1*H*-tetrazol-5-yl)acrylates **5** (**a**–**i**) has been presented. The synthetic method is very simple, with shorter reaction times within 0.5–1.5 h that has given excellent product yields up to 90%. This environmental friendly method is very attractive as it is very safe process with simple workup, use of inexpensive, and readily available catalyst.

EXPERIMENTAL

Melting points were determined using open capillary tubes in sulfuric acid bath, TLC were run on silica gel-G, and visualization was performed using iodine or UV light, IR spectra were recorded using PerkinElmer spectrum version 10.03.02 instrument in KBr Pellets. ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO using 400 MHz instrument. Mass spectra were recorded on an Agilent LC–MS instrument giving only M+ values in (Q + 1) mode.

All the chemicals were obtained from commercial sources and used without purification.

General procedure. Synthesis of target molecules **5** (**a**–**i**) have been done basically by following three types of reactions in both route I and route II.

1. Knovenagel condensation:
   - Route I: A mixture of indole-3-carbaldehyde **1** (**a**–**c**) (5 mmol), ethylcyanoacetate **2** (6.5 mmol, 0.69 mL), and L-Proline (40 mol%, 0.288 g) in ethanol (20 mL) was stirred at room temperature for 1 h. After completion (as shown by TLC) of the reaction, the mixture was poured into ice cold water. The separated solid was filtered, washed with water, and dried to obtain the crude product **3a** in pure form.
   - Route II: Another possible route for the preparation of **7** (**a**–**i**) from **6** (**a**–**i**) and **2**. The procedure is same as earlier.
2. Tetrazole formation:
   - Route I: A mixture of **3a** (1 mmol) and sodium azide (2 mmol) in DMF (10 mL) with catalytic amount of $CuSO_4.5H_2O$ added shown in (Table 1). The reaction mixture was refluxed for 1.5 h and the completion of the reaction indicated by TLC. The reaction mixture was poured into crushed ice, and the separated crude product was filtered. To the filtrate, 15 mL of 2N HCl was added with vigorous stirring causing the tetrazoles to precipitate. The precipitate was filtered and dried to obtain product **4** (**a**) in pure form.
   - Route II: Another possible route for the preparation of **5** (**a**–**i**) from **7** (**a**–**i**). The procedure is same as earlier.
3. N-alkylation reaction:
   - Route I: A mixture of **1** (**a**–**c**) (1 mmol), alkylating agent (3 mmol), acetonitrile (20 mL), K_2CO_3 (5 mmol), and TBAB (0.1 g) was stirred at room temperature for 2 h. The completion of reaction was checked by TLC. At the end of this period, the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (30 mL). The separated organic layer of ethyl acetate was collected and was dried over anhy. Na_2SO_4 (0.2 g) and the solvent was removed with vacuum. The obtained product was washed with hexane and recrystallized by using a suitable solvent to give pure **6** (**a**–**i**).
   - Route II: Another possible route for the preparation of **5** (**a**–**i**) from **4** (**a**–**i**) is same as earlier.

Another possible route for the preparation of **7** (**a**–**i**) from **3** (**a**–**c**) is same as earlier.

Acknowledgment. The authors are thankful to the authorities of Jawaharlal Nehru Technological University, Hyderabad, for providing laboratory facilities.

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