Journal of the Indian Chemical Society 98 (2021) 100103

Contents lists available at ScienceDirect

Journal of the Indian Chemical Society

journal homepage: www.editorialmanager.com/JINCS/default.aspx

Eco-efficient one-pot tandem synthesis of 1-aryl-1*H*-tetrazol-5-amine by CAN via *in situ* generated 1-phenylthiourea and heterocumulene

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ARTICLE INFO

Keywords:
Tetrazoles
Regioisomer
Aryl isothiocyanate

ABSTRACT

A simple, cost-effective, environmentally benign, and efficient one-pot tandem approach to the synthesis of pharmaceutically important 1-aryl-1*H*-tetrazole-5-amines 3a-k and 4a-k has been described. The reaction utilized 1-phenyl thiourea, which was generated in situ from aqueous ammonia and isocyanates 1a-k, for the formation of heterocumenes using sodium azide, triethylamine, and ceric ammonium nitrate (CAN) to obtain various aryl-substituted 1*H*-tetrazole-5-amines (3a-k) in good to excellent yields.

1. Introduction

Tetrazoles are of paramount importance to synthetic, medicinal, and pharmaceutical industries in many different ways. Additionally, multi-faceted tetrazoles are widely applied in agricultural research [1]. The tetrazole containing lead compounds can not oxidized easily by oxidants and these moieties are tough for metabolic degradation in biological systems. Due to this unique nature these compounds are extensively used in many explosives, agriculture lead compounds, and for pharmaceutical purposes [2,3]. Anionic tetrazoles have been proven to be ten fold lipophilic in nature than the corresponding carboxylates, which indicates that these analogues can pass through the cell membrane more efficiently [4]. Owing to their lipophilicity, it is enforceable to use different tetrazole derivatives as substituents of assorted functionalities. In particular, 5-substituted alkyl/aryl tetrazoles can be used as non-classical isosteres for the carboxylic acid fraction (RCO_2H) as a lead pharcaphore [5–7]. A few examples of compounds that possess the aminotetrazole moiety and exhibit various biological activities are given in Fig. 1 [8–10].

Tetrazoles are important series of the compound which are widely used in organic and inorganic chemistry to prepare various useful intermediates such as imidoylazides and lingands [11–13]. In quest of the least hazardous approach, numerous methods have been articled for the synthesis of amino tetrazolederivatives [14–23]. Most of the reported methods contend issues like to minimize the harsh reaction conditions, temperature elevation, using reagents or metal salts which are toxic as well as hazardous to environment. Fig. 2 illustrates the available synthetic methods and present work. For instance, Alam and Nasrollahzadeh prepared amino tetrazole derivatives via the reaction of cyanamide in glacial acetic acid and sodium azide for 20–30 h [15]. A tandem and regioselective synthesis of tetrazole using phenyl isothiocyanate with ammonia followed by sodium azide, molecular iodine, and triethylamine took 3 h for completion of reaction.[1]

Despite the myriad synthetic methods report outlined in the literature [24–27], the development of new efficient and shorter routes to access these compounds is of practical significance. The tandem synthetic strategy helps circumvent the separation of intermediates that may not be stable enough for isolation, as multiple transformations occur simultaneously. This approach also makes it possible to design and construct complex and active molecules using only basic chemicals as starting materials.

CAN is an eco-friendly and one of the most inexpensive commercially available reagents, which has numerous applications in organic synthesis. Owing to its one-electron oxidant Lewis acid property, high water solubility, stability, and easy work-up procedures, CAN is a very effective catalyst in the synthesis of various biologically active compounds [25–27]. Furthermore, the recent report on the synthesis of 5-substituted

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https://doi.org/10.1016/j.jics.2021.100103
Received 19 April 2021; Accepted 11 July 2021

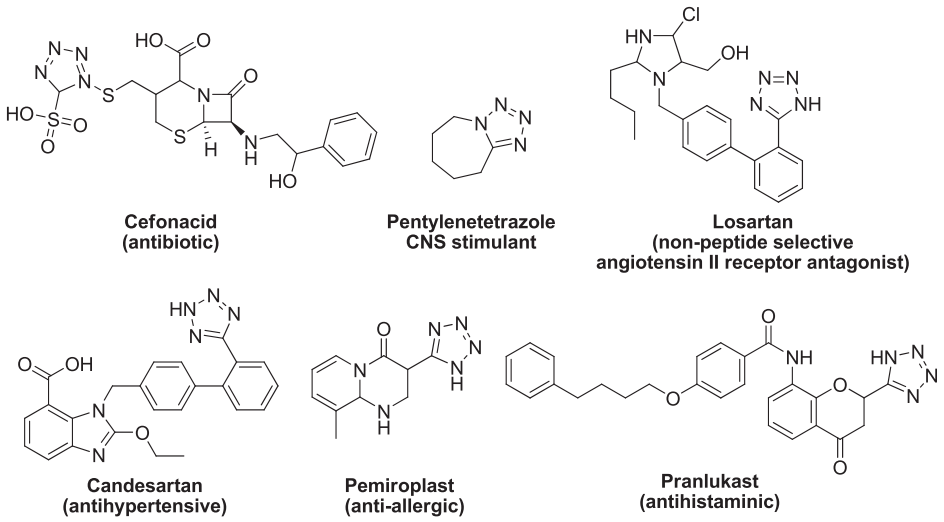


Fig. 1. Bioactive drugs containing the tetrazole ring.

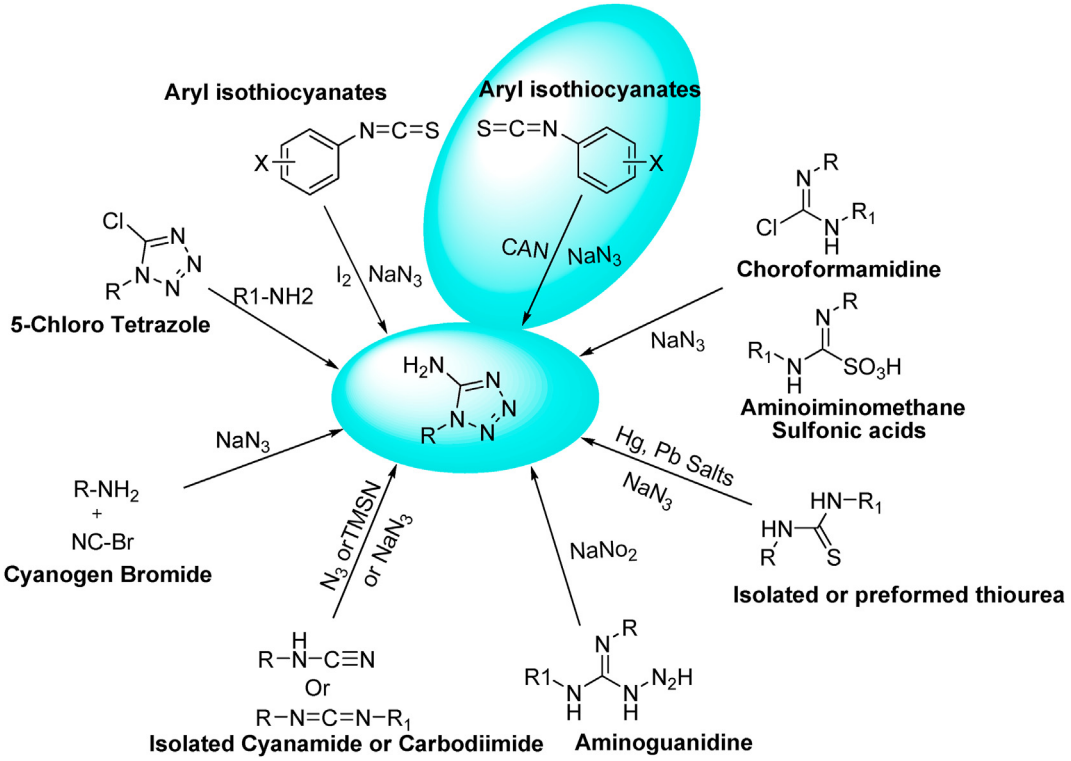
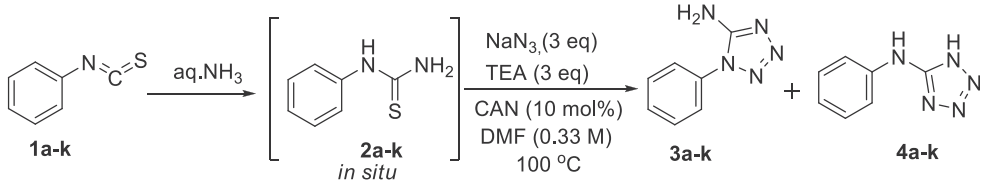


Fig. 2. Existing literature methods for the preparation of aminotetrazoles along with the present reported method [14–23].



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

1*H*-tetrazole using CAN support HY-zeolite [27] encouraged us to wield an effective tandem approach synthesizing the series ofuseful 5-amino tetrazoles by using isothiocyanates.

This one-pot tandem method involves treating phenyl isothiocyanates **1a–k** with ammonia to generate phenylthiourea **2a–k** in situ. When **2a–k** reacted with CAN in the presence of a base, cyanamides/carbodiimides were formed as intermediates. These intermediates subsequently treated with sodium azide yielded in different tetrazoles **3a–k** (Scheme 1).

Table 1
Effect of catalyst and solvent on the formation of tetrazole.

Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
CAN (5 mol%)	DMF	100	24	53
CAN (10 mol%)	DMF	100	5	96
CAN (20 mol%)	DMF	100	24	72
CAN (15 mol%)	DMSO	100	24	58
CAN (15 mol%)	1,4-Dioxane	100	24	33
CAN (15 mol%)	CAN	Reflux	8	24
CAN (15 mol%)	EtOH	Reflux	24	Trace
CAN (15 mol%)	$CHCl_3$	Reflux	24	0
CAN (15 mol%)	Water	Reflux	24	0

[a] Total yields were determined by isolation using column chromatography.

2. Experimental

2.1. General methods

Melting points (mp) of the synthesized compounds were recorded in open glass capillaries using an electrical melting point instrument and those are uncorrected. ^{1}H NMR spectra were analyzedon a Varian Mercury-VX 400 MHz NMR spectrometer (Varian, UK) in DMSO-d_6. The Infra-Red spectra were obtained on a Nicolet is 10 spectrometer (Thermo Fisher Scientific Instrument, Waltham, MA, USA) using KBr (Potassium Bromide) discs. The reactions were monitored by TLC (Thin Layer Chromatography) on silica gel 60 F-254 plates (Merck, Darmstadt, Germany). All compounds were characterized by comparing their physical and spectral properties with known literature values.

2.2. Synthetic procedure

Phenyl isothiocyanate **1a–k** (3.7 mmol) stirred for 30 min with aqueous ammonia solution (25%, 5 mL) at ice-cold temperature (~0 °C). The reaction was monitored by TLC and after complete consumption of the starting material, excess of ammonia was shelved under reduced pressure. The remained mixture was co-distilled with toluene (3 × 15 mL), subsequently, the resultant phenylthiourea **2a–k** was dried under high vacuum. After complete drying, phenyl thiourea was dissolved in anhydrous DMF (0.33 M), and NaN_3 (11.11 mmol) and CAN (10 mol%) were added sequentially portion-wise, followed by dropwise addition of triethylamine (11.11 mmol) over a period of 15 min. Afterwardthe completion of addition of triethylamine, thereafter reaction mixture was allowed to stir for 4–5 h at 100 °C. Transformation progression of the in situ generated 1-phenylthiourea **2a–k** to 1-phenyl-1*H*-tetrazol-5-ylamine was monitored by using TLC. The product was extracted with ethyl acetate (3 × 20 mL). These assorted organic layers were washed with water (3 × 20 mL) and brine solution (3 × 20 mL) and followed by Na_2SO_4 to get dried over before concentration under reduced pressure. Finally yielded crude product was purified over a column of silica gel (230–400 mesh) that was saturated with 1% triethylamine and eluted using 8:1:1 chloroform/methanol/methanolic ammonia solvent mixture to obtain tetrazoles **3a–k** and **4a–4k** in good to excellent yields. Finally structure of the desired finished products was confirmed by their MP, IR, and ^{1}H and ^{13}C NMR spectra.

3. Results and DISCUSSION

In the process of development of a tandem approach, there is a need to investigate an appropriate solvent for the reaction medium. Hence, to get better the desired product yield, the reaction conditionswere screened with distinct variables including solvent, temperature, and amount of catalyst. It was found that DMF was the most suitable reaction medium in terms of yield and reaction time. In almost all tested solvents, the reaction proceeded in the forward direction. The use of aprotic solvents such as DMF, DMSO, and 1, 4-dioxane led to good yields. On the other hand, protic solvents such as methanol and water inhibited the reaction. In case of solvents other than DMF and prolonged stirring time,

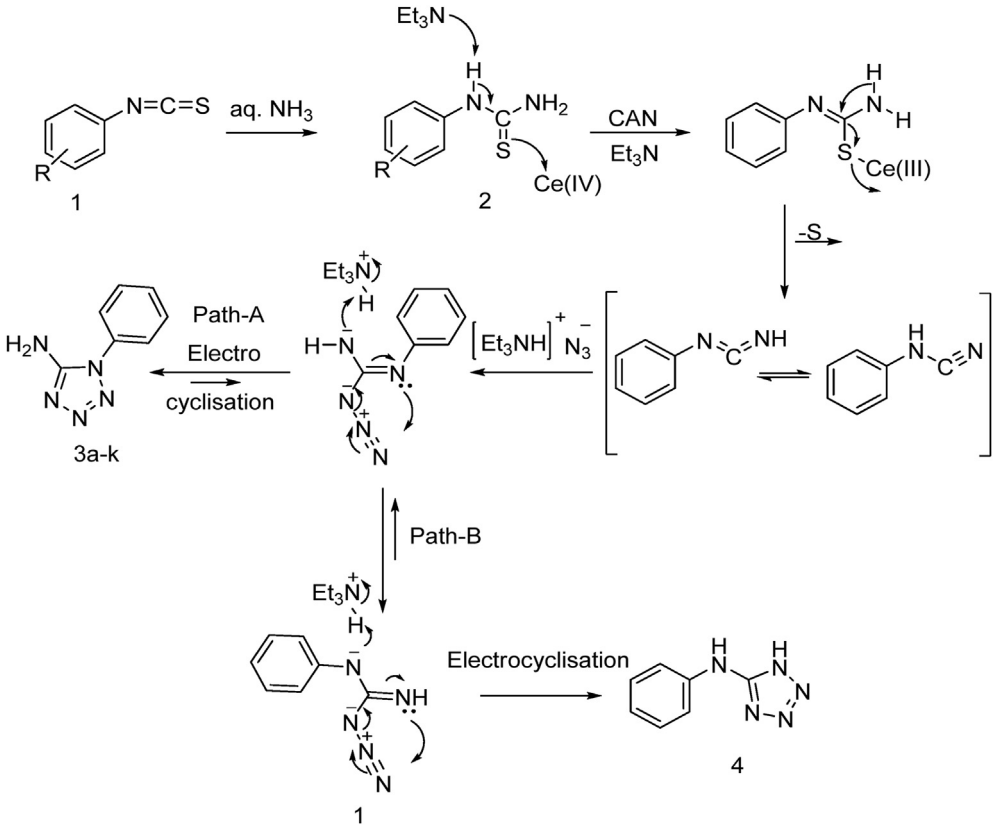
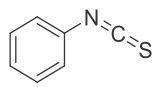
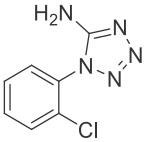
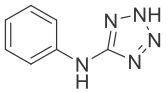
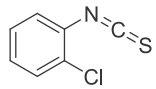
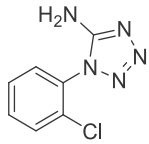
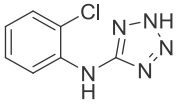
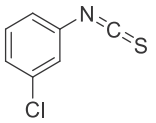
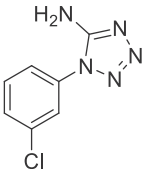
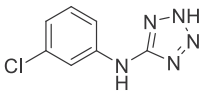
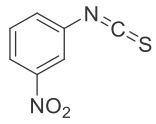
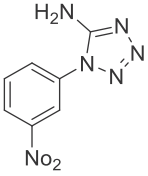
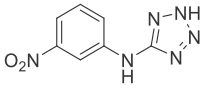
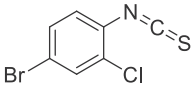
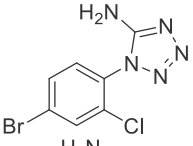
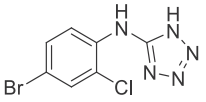
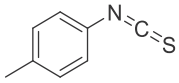
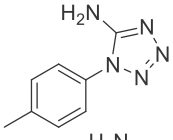
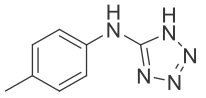
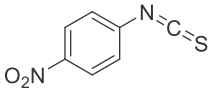
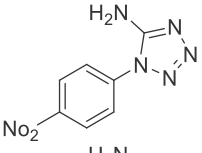
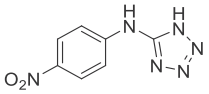
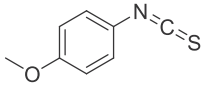
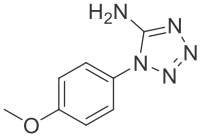
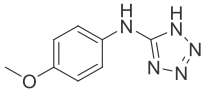
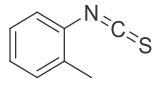
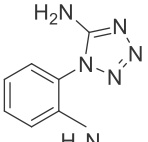
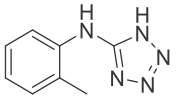
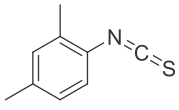
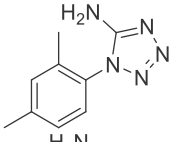
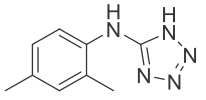
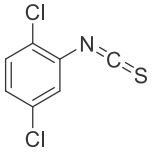
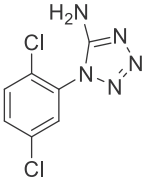
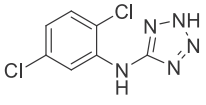


Fig. 3. Plausible reaction mechanism.

Table 2
CAN catalyzed synthesis of 1-aryl-1*H*-tetrazol-5-amine (**3a–k**) and 5-arylamino-1*H*-terazole (**4a–k**).

Entry	Isothiocyanate	Product (3a–k)[a]	Product (4a–k)[a]	Total yield (%)[b]	Ratio of regioisomers[c]
c3a				74	96:4
3b				68	91:9
3c				70	88:12
3d				93	87:13
3e				84	82:18
3f				78	94:6
3g				87	95:5
3h				81	100:0
3i				72	98:2
3j				67	100:0
3k				72	83:17

[a] Products**3a–k** and **4a–k** were characterized by their IR, and ^{1}H and^{13}C NMR.
[b] Total yields were determined by isolation using column chromatography.
[c] Ratio of 3:4 determined by ^{1}H NMR.

TLC analyses showed that there were more than two or three spots and a lesser yield of the desired amino tetrazole. Owing to the poor results in different solvents, we decided to optimize the loading of CAN (in mole percentage) to obtain better results. It was found that 10 mol% of the catalyst showed a more efficient conversion than 20 mol% of the catalyst.

The optimized three step tandem process involved the preparation of phenylthiourea using phenyl isothiocyanate (1 equiv.) and aqueous ammonia (~1 mL, 30%). The two reactants were stirred for 25–30 min in ice-cold conditions. After the total conversion of the starting material to the intermediate, the excess aqueous ammonia was shelved under reduced pressure. The reaction mixture was then co-distilled thrice with 5 mL of toluene and the distillate was dried under high vacuum. Dried phenylthiourea was then sequentially mixed with 2–3 mL of DMF, NaN_3 (3 equiv.), CAN (10 mol%), and finally triethylamine (3 equiv.). The reaction became exothermic during the dropwise addition of triethylamine over a period of 15 min (Scheme 1). Thereafter the reaction mixture was allowed to stir until the total conversion of phenylthiourea was confirmed by TLC at room temperature. An easy work-up along with excellent yields proved that this method was fairly successful (Table 1).

We have proposed a plausible mechanism for the reaction based on the literature survey and chemical behavior (Fig. 3). CAN be used as a Lewis acid, which initiates the in situ production of the intermediate cyanamides or heterocumulene from thiourea, which was itself generated in situ while isocyanates reacted with aqueous ammonia. Heterocumulene is then attacked by the azide ion to form guanylazide and subsequent electro cyclization results in the formation of 1-aryl-1*H*-tetrazol-5-amine **3a-k**. It was observed that the reaction path is dependent on the nature of the substituent on aryl cyanamide. Here, the electron-donating substrate leads to 1-aryl-1*H*-tetrazol-5-amine via path A and as the electronegativity increases, the reaction led to the formation of trace amounts of another regioisomer 5-arylamino-1*H*-tetrazole via path B.

By using thispromoted one-pot strategy, we have successfully synthesized a comprehensive series of1-aryl-1*H*-tetrazol-5-amines from their corresponding isothiocyanates as described in Table 1. Altering the distinct substituents on the aromatic ring, either electron withdrawing (chloro, bromo) or electron donating (methyl, methoxy), had no substantial effect on the reaction (Table 2). It is worth mentioning that the developed protocol underwent smoothly under the optimized reaction conditions. However, as the electronegativity of the substrate increases, the reaction tends towards the formation of another regioisomer in trace amounts.

4. Conclusion

We have developed an effective tandem process for the preparation of biologically important 1-aryl-1*H*-tetrazol-5-aminesfrom in situ generated phenylthioureas and heterocumulenes, which were prepared from the corresponding aryl isothiocyanates. Considering that multiple processes take place in one-pot and that the developed reaction methodology is environmentally sustainable, simple, and utilizes a stable and cost-effectiveness catalyst CAN, it is reasonable to conclude that this organic synthetic strategy is quite eco-efficient.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Unisynaxis Laboratories Private Limited, IDA Mallapur, Hyderabad 500076, India for providing necessary facilities.

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