Synthesis of \(N\)-heterocycles containing 1,5-disubstituted-1\(H\)-tetrazole via post-Ugi-azide reaction

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Abstract
Ugi-azide four-component reaction (UA-4CR) as development on Ugi four-component reaction (U-4CR) is the condensation reaction involving an aldehyde, an amine, an isocyanide, and an azide source. Nowadays, UA-4CR has been employed for the efficient and facile production of 1,5-disubstituted-1\(H\)-tetrazoles (1,5-DS-1\(H\)-Ts). Interestingly, the combination of 1,5-DS-1\(H\)-Ts with suitable post-transformations in a tandem manner results in the construction of various classes of heterocyclic compounds bearing 1,5-DS-1\(H\)-T moiety. This review aims to provide the application of diverse post-Ugi-azide reaction in the preparation of different \(N\)-heterocyclic compounds bearing 1,5-DS-1\(H\)-T such as substituted and fused 1,5-DS-1\(H\)-Ts.

Graphic abstract

Keywords 1,5-Disubstituted-1\(H\)-tetrazoles · 1,5-DS-1\(H\)-Ts · Post-Ugi-azide reaction · Isocyanides · Multicomponent reaction · MCRs

Introduction
In 1885, tetrazole was synthesized and characterized by the Swedish chemist, Bladin at the University of Upsala through the reaction of the anhydrous hydrazoic acid with hydrogen cyanide under pressure [1]. Since then and due to their wide range of biological activities, the synthesis of tetrazoles has attracted the attention of synthetic organic chemists, resulting in the significant development in their biology and chemistry [2]. The extensive studies on the chemistry of tetrazoles have led to the disclosure of their various use in other fields, including photographic industry, coordination chemistry, and being used as explosives, and agriculture [3]. Tetrazoles also constitute the core structure of numerous non-natural compounds which display significant biological activity [4]. Several prescribed drugs have tetrazole moiety in their structures, for example, Valsartan [5], Candesartan [6, 7], and Losartan [8, 9] as angiotensin II receptor antagonists.

On the basis of the substitution factor in the tetrazole rings, the systems can be classified into 1-, 2-, 5-monosubstituted and 1,5-, 2,5-disubstituted tetrazoles, and trisubstituted tetrazolium salts [10]. Among them, 1,5-disubstituted-1\(H\)-tetrazoles (1,5-DS-1\(H\)-Ts) have stirred up the interest

\(\text{Ugi Azide reaction}\)

**Keywords** 1,5-Disubstituted-1\(H\)-tetrazoles · 1,5-DS-1\(H\)-Ts · Post-Ugi-azide reaction · Isocyanides · Multicomponent reaction · MCRs
of the chemical community, in particular, those who are active in the field of peptide chemistry due to the metabolic resistance of bioisosteres of their cis-amide bond [11, 12]. Furthermore, the 1,5-DS-1H-T nucleus is found in many bioactive products [13] such as Cefamandole and Latamoxef which are second- and third-generation broad-spectrum cephalosporin antibiotics, respectively [14].

Several advanced methods for the production of compounds bearing the 1,5-DS-1H-T ring system based on both the [2 + 3] azide–cyanide “click” reactions and isocyanide-based multicomponent reactions (IMCRs) have been described [11, 15, 16]. IMCRs have gained significant attention during the past two decades and have emerged as efficient and powerful tools for the syntheses of several synthetic intermediates, bioactive agents, highly complex natural products and diverse drug-like compounds [17–21]. Undoubtedly, one of the most important and well-established IMCRs is Ugi four-component reaction (U-4CR) which was discovered in 1959 by an Estonian-born German chemist, Ivar Karl Ugi and reported in Angewandte Chemie for the rapid and facile construction of an N-substituted acyl aminoamide via condensation of an amine, an isocyanide, an aldehyde, and a carboxylic acid. Nowadays, this reaction is known as Ugi four-component reaction (U-4CR) [22]. A development on U-4CR involves a slight modification, in which an azide source such as azidotrimethylsilane (TMSN₃) or hydrazoic acid (HN₃) is employed instead of carboxylic acid as one of the required components in classical U-4CR. In 1961, the first Ugi-azide four-component reaction (UA-4CR) was reported by Ugi [23]. Since then, UA-4CR has been used for the facile and efficient construction of 1,5-DS-1H-Ts [24–27]. Interestingly, 1,5-DS-1H-Ts also can be prepared using various imines through Ugi-azide three-component reaction (UA-3CR) [28].

Remarkably, the UA-R can be combined with suitable post-transformations, particularly cyclization, in a cascade manner to produce various classes of heterocyclic compounds bearing 1,5-DS-1H-T moiety as scaffolds which cannot be easily synthesized by other reactions in two steps [29–33].

We are interested in heterocyclic chemistry [34–41] particularly the synthesis of heterocycles via multicomponent reactions (MCRs) [42–44]. We have reported applications of IMCRs [45–47]. Recently, we have also reported the synthesis of various N-heterocycles using the U-4CR [48]. In this review, we try to highlight the synthesis of various N-heterocycles having 1,5-DS-1H-T moiety including substituted and fused 1,5-DS-1H-Ts via post-Ugi-azide reaction.

**Synthesis of substituted 1,5-DS-1H-Ts**

In 2012, Gunawan et al. developed a unique, one-pot and two-step protocol successfully for the large-scale generation of libraries of pyrrolidinone tetrazoles 2 through the UA-4CR followed by acid-mediated lactam formation under acidic conditions. UA-4CR was initiated by mixing the appropriate tethered keto-ester methyl levulinate, isocyanides, primary amines, and TMSN₃ in MeOH at ambient temperature to afford 1,5-DS-1H-Ts 1 as Ugi adducts. The latter were then treated with 10% trifluoroacetic acid (TFA) in 1,2-dichloroethane (DCE) leading to novel peptidomimetic-like pyrrolidinone tetrazoles 2 (Scheme 1) [49].

In continuation of that work, Gunawan’s group used the above protocol to prepare the highly unique δ-lactam tetrazoles 4. Ugi 1,5-DS-1H-Ts 3 which were generated from the tethered keto-acid 5-oxohexanoic acid, isocyanides, primary amines, and TMSN₃ in MeOH at room temperature undergo intramolecular amide formation in the presence of 1,1′-carbonyldiimidazole (CDI) as the coupling reagent to give the expected products 4 (Scheme 2) [50].

γ-Oxo esters having geminal CH₂CHO and CO₂Et fragments at saturated cycle were selected as the source of aldehydes and mixed with amines, isocyanides, and TMSN₃ in EtOH at room temperature in 8–12 h (TLC control) to furnish the Ugi 1,5-DS-1H-Ts 5. The subjection of the latter to the intramolecular amide bond formation under acidic condition afforded the target compounds, 5-tetrazole substituted spirocyclic γ-lactams 6 in 50–72% (Scheme 3) [51].

A new, one-pot two-step methodology comprising UA-4CR and RNCX (X = O, S) cyclization for the rapid assembly of the novel and biologically appealing 1,5-substituted tetrazole-hydantoins and thiohydantoins 8 was described by Medda and Hulme in 2012. The reaction was initiated with the mixing of ethyl glyoxalate and amines in DCE followed

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**Scheme 1** Synthesis of pyrrolidinone tetrazoles 2

![Scheme 1](image-url)
by subjection to MWI to pre-form the resulting Schiff base. Subsequent addition of solvent TFE isocyanides and TMSN₃ with stirring at room temperature for 12 h yielded the condensation products 7 in good isolated yields. Treatment of Ugi-azide products 7 with an excess of isocyanate or isothiocyanate enabled rapid assembly of the 1,5-substituted tetrazole-hydantoin and thiohydantoin 8 in moderate to good yields, respectively (Scheme 4) [52].

Synthesis of a series of interesting isoindolin-1-ones 10 bearing a 1-substituted tetrazol-5-yl moiety in position 3 was accomplished and reported using post-Ugi-azide cyclization. The smooth UA-4CR between methyl ortho-formylbenzoate, amines, isocyanides, and TMSN₃ in MeOH for 2 days at room temperature constructed easily the desired Ugi products 9, which were cyclized by a straightforward and rapid fashion in the presence of sodium ethoxide in ethanol to give the tetrazolylisoindolinones 10. The final products were precipitated from the mother liquors in a pure form without the need for tedious workup procedures (Scheme 5) [53].

Gunawan and Hulme employed an operationally friendly strategy based on a post-condensation modification of the Ugi 1,5-DS-1H-Ts 11, which leads to tetrazolyl-indolinones 12. Methyl 2-formylbenzoate as an aldehyde source was selected and reacted with isocyanides, amines and TMSN₃ in the UA-4CR under ambient conditions to obtain the 1,5-DS-1H-Ts 11 as Ugi-azide intermediates which were
directly converted to the corresponding indolinone-tetrazole derivatives 12, without the need for the addition of acid (Scheme 6) [26].

A family of 2-tetrazolylmethyl isoindolin-1-one linked-type heterocycles 15 in moderate to good yields (10–76%) were produced under mild conditions through a one-pot UA-4CR/(N-acylation/exo-Diels–Alder)/dehydration strategy, starting from furan-2-ylmethanamine, isocyanides, aldehydes, TMSN₃, and maleic anhydride. Experimentally, the combination of furan-2-ylmethanamine with aldehydes, isocyanides, and TMSN₃ under the Ugi-azide standard conditions (MeOH, RT) provided the Ugi-azide products 13 in excellent yields after 24 h which upon treatment with maleic anhydride in toluene under a nitrogen atmosphere at room temperature in 4 h, an aromatization process was performed to give the compounds 14. At final, synthesis of novel unsymmetrical heterocycles 15 was completed in 1 h by adding p-toluensulfonic acid (PTSA) in toluene under MWI (Scheme 7) [54].

Post-Ugi-azide oxidation/oxidative-amidation cyclization cascade was used for the first time in 2016 by Foley’s group toward tetrazolyl-isatin derivatives 17. Ugi-azide adducts 16, obtained from simple mixing of ortho-aminoacetophenone, isocyanides, aldehydes, and TMSN₃ in MeOH at 25 °C in 48 h, were oxidatively cyclized via oxidation/intramolecular oxidative-amidation cascade utilizing SeO₂ under optimal conditions (dioxane, MWI, 160 °C) to construct the peptidomimetic-like isatins containing tetrazoles 17 (Scheme 8) [55].

El Kaïm et al. described the application of ortho-nitrobenzaldehyde in the UA-4CR and its post-cyclization. The Ugi 1,5-DS-1H-Ts 18, afforded from U-4CR involving ortho-nitrobenzaldehyde, amines, isocyanides, and TMSN₃, were directly heated with triethylphosphite (P(OEt)₂) as a reducing agent in DMF as the solvent at 140 °C for 10 h resulted in the formation a novel N–N bond, giving the expected tetrazolyl indazole 19 without the need of purification (Scheme 9) [30].

A novel, efficient, and robust method for the production of diversely tetrazole-containing isoindolines 21 via ligand-free palladium-catalyzed tandem C–C/C–N coupling reaction consisting of isocyanide insertion into Ugi 1,5-DS-1H-Ts.
were demonstrated. The 1,5-DS-1H-T precursor 20 was obtained in one step by the UA-4CR. Next, the reaction proceeds smoothly under mild conditions (Pd(OAc)$_2$, Cs$_2$CO$_3$, DMF, 90 °C, 1 h) in the presence of R$^3$-NC with high efficiency lead to the desired tetrazolylosindolines derivatives 21 (Scheme 10) [56].

Wu et al. synthesized diverse 1,2-disubstituted 3-(1H-tetrazol-5-yl)-2H-isindoles 23 via UA-4CR followed by AgNO$_3$-catalyzed cyclization. They used 2-alkynylbenzaldehydes amines, isocyanides, and TMSN$_3$ as the starting materials for U-4CR to form the Ugi-azide adducts 22. In the following, the latter underwent 5-exo-dig cyclization, [1, 3]-H shift, and [1,5]-H shift in the presence of AgNO$_3$ in acetonitrile at 80 °C to generate the final products 23 in moderate to excellent yields (Scheme 11) [57].

A novel and succinct two-step synthesis of a collection of 3-((tetrazol-5-yl)-3,4-dihydroquinazolin-2(1H)-ones 25 that employs the UA-4CR followed by cyclization under acidic condition was reported. UA-4CR between ethyl glyoxalate, ortho-N-Boc phenylisocyanides, aldehydes, and TMSN$_3$ in a mixture of DCE and TFE generated the unique 1,5-DS-1H-Ts 24 which undergo acid-mediated intramolecular cyclization in the presence of 10% TFA in DCE to yield 3,4-dihydroquinazolinone tetracoles 25 (Scheme 12) [58].

The UA-4CR was chosen together with Pic-tet–Spengler (PS) reaction for the construction of
2-tetrazolylmethyl-2,3,4,9-tetrahydro-1H-β-carbolines 27 under a metal-free MW-assisted one-pot process. The 1,5-DS-1H-Ts 26, formed from a combination of the commercially available tryptamine with isocyanides, aldehydes, and TMSN₃ in the UA-4CR, were subjected to cyclization in the presence of formaldehyde in a mixture of MeOH and toluene at 90 °C in 72 h to afford the expected 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1H-β-carbine derivatives 27 (Scheme 13) [59].

The stepwise combination of the UA-4CR with the PS reaction as post-condensation was used by Ghandi et al. to generate a series of quinoline-2,3,4,9-tetrahydro-1H-β-carbine-1,5-DS-1H-T derivatives 29. The reaction was initiated with the preparation of 1,5-DS-1H-Ts 28 from UA-4CR involving 2-chloroquinoline-3-carbaldehydes, tryptamine, isocyanides, and TMSN₃ under UA-4CR conditions. Upon treatment of 1,5-DS-1H-Ts 28 with formaldehyde in TFA at ambient temperature for 15 min furnished the final products 29 in moderate to good yields (Scheme 14) [60].

A one-pot two-step sequential methodology was developed through preparation of Ugi-azide adducts 30 obtained from tryptamine, aromatic aldehydes, isocyanides, and TMSN₃ in MeOH at ambient temperature and followed by PS reaction in the presence of ninhydrin and H₂SO₄ (98%) to synthesize a range of tetrazole-based tetrahydrospiro[indene-2,1′-pyrido[3,4-b]indole]-1,3-diones 31 in moderate to good yields (Scheme 15) [61].

Gordillo-Cruz et al. described the successful synthesis of nine novel 3-tetrazolylmethyl-azepino[4,5-b]indol-4-ones 33 in only two reaction steps, utilizing tryptamine. The first step of synthesis have presumably proceeded through one-pot sequential UA-4CR/N-acylation/S₉₂ process to furnish the corresponding xanthes 32 which undergo intramolecular cyclization under free radical conditions leading to the production of the resulted 3-tetrazolylmethyl-azepino[4,5-b]indol-4-ones 33 (Scheme 16) [62].

A series of six novel tris-heterocycles 1′-tetrazolylmethyl-spiro[pyrrolidine-3,3′-oxindoles] 35 were prepared in moderate to excellent yields (39–82%) in two reaction steps. The first consisted of a one-pot sequential process of the UA-4CR and PS reaction to give the 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1H-β-carbolines 34. The second was a one-pot oxidative spiro-rearrangement in the presence of NBS in THF/AcOH/H₂O (3:2:2) at −10 °C to generate the desired poliheterocycles 35 (Scheme 17) [63].
Synthesis of fused 1,5-DS-1H-Ts

For the first time in 1998, post-UA-4CR was employed as a highly convergent one-pot two-step following protocol by Bienaymé and Bouzid for the construction of stable fused tetrazoles 37. In the first step, Ugi-azide intermediate adducts 36 were prepared through the reaction between alkyl-β-(N,N-dimethylamino)-α-isocyanoacrylate, aldehydes, primary amines, and TMSN₃ in MeOH at 25 °C. In the next step, cyclization of Ugi-azide intermediate adducts 36 under diluted acidic conditions afforded the desired rigid hydrophobic tetrazoles 37. The use of TMSN₃ as a convenient source for HN₃ in MeOH has led to an increase in the versatility of this method (Scheme 18) [64].

In 2000, Nixey et al. disclosed a unique application of the TMSN₃-modified UA-4CR for the solution phase synthesis of the fused ketopiperazine-tetrazole class of molecule. UA-4CR of substituted methylisocyanoacetates with an aldehyde, primary amine, and TMSN₃ in MeOH at ambient temperature in 24 h followed by refluxing generated the expected heterocycles 38, fused tetrazolo-ketopiperazines, containing three potential diversity points in good yields (Scheme 19) [65].

Later, efficient production of 6,7-disubstituted tetrazolopiperazine building blocks 39 was reported by Umkehrer et al. in a one-pot solution phase procedure through
UA-4CR of 2-isocyanoethyltoluolsulfonate as alkylation isocyanide with aldehydes, primary amines, and TMSN₃ under UA-4AR standard conditions followed by cyclization (Scheme 20) [66].

The tricyclic tetrazolo[1,5-a]quinoloxaline 41 were constructed via one-pot reaction. 2-Fluorophenylisocyanide as a new isocyanide source was used in the UA-4CR involving aldehydes, amines, and TMSN₃ in MeOH at room temperature to provide the corresponding 1,5-DS-1H-Ts 40. Next, the latter were subjected to nucleophilic aromatic substitution (SNAr) in the presence of Cs₂CO₃ as the base in DMF as the solvent to give the desired fused 4,5-dihydtetrazolo[1,5-a]quinoloxalines 41 (Scheme 21) [67].

Recently, Patil et al. described a one-pot, short straightforward, and versatile synthesis of N-unsubstituted tetrazolo-piperidines 42. The first step of this synthesis consists of the UA-4CR using aqueous ammonia as ammonia source and as a base in this multicomponent synthesis to enable a post-cyclization reaction. Experimentally, the four components, aqueous ammonia, α-amino acid methyl ester derived isocyanides, ketones (aldehydes), and TMSN₃, selected and mixed together in MeOH/H₂O at room temperature to obtain the best yields of Ugi adducts which then were cyclized upon treatment with NH₄OH leading to the final tetrazolopyrazinones 42 in good to high yields (Scheme 22) [68].

N-Boc protected hydrazine was employed together with α-amino acid derived isocyanides in the UA-4CR followed by cyclization under the basic condition to construct the Boc-protected 7-aminotetrazolopyrazinones products 44. The reaction was commenced with the preparation of heterocycles 43 as Ugi 1,5-DS-1H-Ts from the UA-4CR between

![Scheme 20](image)

**Scheme 20** Synthesis of 6,7-disubstituted tetrazolopiperazines 39

![Scheme 21](image)

**Scheme 21** Synthesis of tricyclic tetrazolo[1,5-a]quinoloxaline 41

N-Boc protected hydrazine, α-amino acid derived isocyanides, ketones (aldehydes) and TMSN₃ in the presence of Mg(OTf)₂ in MeOH at room temperature. The post-cyclization of 43 under basic condition (NaOEt) could selectively obtain Boc-protected 7-aminotetrazolopyrazinones 44 in yield of 38–87% in a one-pot fashion (Scheme 23) [69].

In 2002, Nixey et al. developed a novel solution phase procedure utilizing UA-4CR followed by UDC strategy (involving the formation of C–N bond) to produce the fused azepine-tetrazole class of molecule. Hence, they mixed N-BOC-amino aldehydes with substituted methylisocyanoacetates, secondary amines, and TMSN₃ in methanol to obtain the Ugi 1,5-DS-1H-Ts 45. Further acid treatment of the latter with 10% TFA in CH₂Cl₂ liberated the masked internal amino nucleophile to enable partial cyclization to 7,5-fused products. Subsequent cyclization was promoted by proton scavenging in the presence of PS-diisopropylethylamine in DMF/dioxane under reflux condition leading to the desired fused azepine-tetrazoles 46 with high yield (Scheme 24) [31].

In 2010, Nayak and Batra performed the synthesis of tetrazole-fused diazepinones using a suitable isocyanide source in the UA-4CR and post-Ugi-azide cyclization. UA-4CR of substituted isonitriles as E-isomer only with primary aliphatic amines, substituted benzaldehydes/heteroaldehydes, and TMSN₃ in MeOH at an ambient temperature obtained 1,5-DS-1H-Ts 47 which were demonstrated to be appropriate substrates for constructing tetrazolo-fused diazepinones. In order to achieve the synthesis of the target compounds, the ester group in Ugi-azide products 47 was hydrolyzed either in the presence of LiOH in THF/H₂O (for methyl or ethyl ester) or in the presence of TFA in CH₂Cl₂ (for t-buty]
undergo intramolecular amide coupling reaction using EDC in NMM/CH₂Cl₂ resulted in the formation of differently substituted tetrazole-fused diazepinone 48 in good yields (Scheme 25) [7].

A novel, efficient and one-pot method for the production of heteroannulated [1,4]benzodiazepines 50 from 1,5-DS-1H-Ts 49 through a post-Ugi-azide cyclization was reported. The aforementioned tetrazole-fused diazepines represent a remarkable class of compounds which proven to act as platelet aggregation inhibitors (Scheme 26) [29].

Ugi 1,5-DS-1H-Ts 51, obtained from cyclic ketones, primary amines, methyl 2-isocyanobenzoate, and TMSN₃ under UA-4CR standard conditions, were subjected to hydrolyzation and EDAC/HOBt-mediated amide bond formation to yield the expected fused tetrazolo[1,5-α][1,4]benzodiazepines 52 in high yield and good diversity (Scheme 27) [70].
A new series of tetrazolo[1,5-α]thieno[3,2-f][1,4]diazepin-6(5H)-ones 54 were conveniently prepared through the preparation of Ugi-azide adducts 53, starting from methyl 3-isocanothiophene-2-carboxylate, piperidin-4-ones, NH₄Cl, and NaN₃ in a mixture of water and methanol. Easy isolation of the products and mild reaction conditions has made this UA-4CR an appealing and efficient reaction (Scheme 28) [71].

Gunawan et al. developed an efficient, straightforward and two-step protocol comprising UA-4CR and acid-promoted cyclization for the synthesis of arrays of tetrazolo-fused benzodiazepines 57 and benzodiazepinones 58. The protocol employs ortho-N-Boc phenylisocyanides and substituted phenylglyoxal or ethyl glyoxylate in the UA-4CR to give 1,5-DS-1H-Ts 55 and 56 equipped with the desired diversity inputs which undergo simultaneous deprotection cyclization using TFA under MWI leading to the final products 57 and 58 (Scheme 29) [58].

**Conclusion**

In this review, we tried to highlight the synthesis of substituted and fused 1,5-DS-1H-Ts by employing various post-Ugi-azide transformations. The UA-4CR is one of the essential and useful IMCRs which was discovered by Ivar Karl...
Ugi in 1961. It is used as a useful, powerful, and low-cost tool to produce a library of 1,5-DS-1H-Ts in short synthetic sequences. It is a slight modification in which a source of azide is used instead of carboxylic acid. In UA-4CRs, among solvents methanol, ethanol, and dichloromethane are the most commonly used. Combination of UA-4CR with a suitable post-transformation led to the formation of a library of heterocyclic systems bearing 1,5-DS-1H-Ts, in which a lot of them could not be readily prepared through other synthetic methods.

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