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A highly efficient tandem [3 + 2] "click" cycloaddition/6-exo-cyclization strategy for the construction of triazole fused pyrazines†

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The pharmaceutically important tetrahydro-[1,2,3]triazolopyrazine heterocyclic architecture has been synthesized via a concise tandem "click"/6-exo-dig cyclization strategy in mixed aqueous–organic media. The generality of this mild method was expanded to various amino acid based substrates. The scopes and limitations of this method are discussed in the paper.

Novel heterocyclic frameworks via concise synthetic routes from easily available starting materials are highly coveted in synthetic chemistry. A myriad of compounds containing the 1,2,3-triazole structural motif possess interesting biological properties.[1] Many natural products containing the tetrahydropyrazine framework display a broad spectrum of biological effects including antitumor activity.[2] This framework is present in the HIV protease inhibitor crixivan,[3] and other drug candidates.[4]

There are, however, only a few reports of heterocyclic systems with [1,2,3]triazole fused tetrahydropyrazine systems. The 4,5,6,7-tetrahydro [1,2,3]triazolo-[1,5-*a*]pyrazin-6-ones[5] were synthesized by the group of Chandrasekaran,[5a] Abbott Laboratories[5b] and Appella[5c] using multistep synthesis. Likewise, the 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines,[6] bearing such bicyclic fused rings were synthesized by Gurjar[6a] and Couty[6b] in multiple steps. Recently, Shen and coworkers from Merck Research Laboratories have also reported a multistep synthesis of compound containing the same the scaffold as agonists for the G-protein-coupled niacin receptor.[7] Schreiber and coworkers have synthesized the fused tetrahydrotriazolopyrazine system in a single step from aziridine through a propargylamine azide intermediate following the 'build/couple/pair' strategy of diversity-oriented syntheses.[8] A series of triazolo[1,5-

a]quinoxaline systems, a variant of the scaffold, has been synthesized by Cai via another tandem approach from *N*-(2-haloaryl)propiolamides.[9] Gulevskaya and coworkers have recently demonstrated the azide mediated tandem cyclization of (*Z*)-enediynes for the formation of the corresponding [1,2,3]-triazolo[1,5-*a*]pyridines.[10]

Inspired by the resource efficient tandem reactions,[11] we envisioned that a tandem approach combining a 1,3-dipolar [3 + 2] ("click") cycloaddition[12] followed by an intramolecular *exo*-cyclization[13] may offer a versatile route to synthesize this important fused-heterocyclic architecture from readily available synthons (Fig. 1 and Scheme 1). Thus, we have developed a simple synthetic route for the preparation of a series of 1,2,3-triazole-fused pyrazines from easily available primary amines and naturally occurring amino acids. The key step of the reaction is a mechanistically interesting tandem "click"/6-*exo*-cyclization of the *N,N*-dipropargylamine precursors as shown in Scheme 1. The reaction proceeds via a triazole–alkyne intermediate tailored for the selective 6-*exo* cyclization step.

Our preliminary efforts were dedicated towards the synthesis of compound **2a** from 4-amino benzophenone. The dipropargyl starting material **1a** was synthesized in 93% yield from the 4-amino benzophenone and propargyl bromide in dry DMF at 25 °C using K_2CO_3 as the proton scavenger (see ESI†). The structure of compound **1a** was confirmed by NMR spectroscopy, IR and mass spectrometric analysis.

Compound **1a** was heated under reflux at 80 °C for 24 h in a 1 : 1 mixture of *t*BuOH (TBA) and H_2O with sodium azide
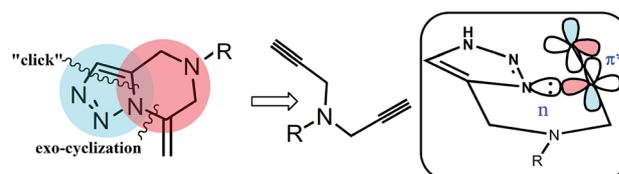
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† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for dipropargyl precursors **1a**, **3a–d**; triazole fused pyrazines compounds **2a–g**, **4a–d** and compounds **5a** and **5b**, **7a** and **7b** and **8a** and **8b**. CCDC 1026579. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra12489h

Fig. 1 Tandem approach for the synthesis of the triazole fused pyrazine system. (Box) Orbitals involved in the 6-*exo*-dig cyclization.
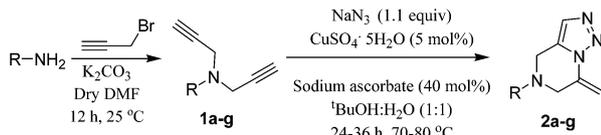
Scheme 1 General scheme for the synthesis of [1,2,3]triazolo[1,5-a]pyrazines from primary amines.

(1.1 equiv.) using CuSO$_4$·5H$_2$O (5 mol%) in presence of sodium ascorbate (40 mol%) as the reducing agent. A 1,3 dipolar cycloaddition reaction between the azide and one of the alkyne moieties formed the incipient 1,2,3 triazole ring. The triazole underwent a constrained intramolecular 6-exo-dig cycloaddition with the another alkyne moiety to furnish the desired 1,2,3 triazole-fused 4,5,6,7 tetrahydropyrazine moiety **2a** in 86% yield as the exclusive product (Scheme 1). The reaction was examined under various conditions (Table 1) and it was found that at 80 °C with 1.1 equiv. of NaN$_3$ in TBA–water (1 : 1 v/v) the best yields of **2a** were obtained from the starting materials.

To verify its generality, the procedure was tested on a variety of dipropargyl amines. The N,N-dipropargyl precursors **1b–g**[14] (see ESI†) were synthesized from a series of amines. Compounds **1b–g** were subsequently treated with sodium azide under the reaction conditions described earlier. The reactions in all the cases were found to afford the desired 1,2,3-triazole-fused 4,5,6,7-tetrahydropyrazines **2b–g** as the exclusive products in moderate to excellent yields as summarized in Table 2. The reaction was effective for a broad range of aromatic amines containing electron donating as well as electron withdrawing aromatic amines.
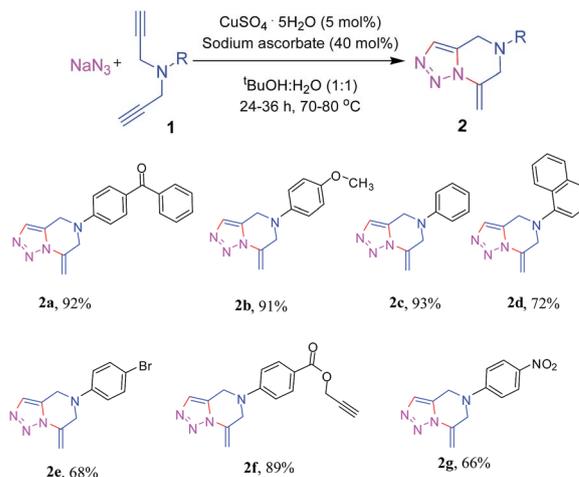
For instance, N,N-dipropargyl amines **1a**, **1f**, and **1g** with electron-withdrawing benzophenone, benzoate ester and nitrophenyl moieties furnished the target products **2a**, **2f** and **2g** in good to moderate yields (92%, 89%, and 66% respectively).

Table 2 1,3-Dipolar cycloaddition followed by intramolecular 6-exo-dig cycloaddition of diprop-2-ynylamines[a]

[a] Conditions: NaN$_3$ (1.1 equiv.), CuSO$_4$·5H$_2$O (0.05 equiv.), sodium ascorbate (0.4 equiv.), 1 : 1 mixture of tBuOH and H$_2$O; 70–80 °C; 24–36 h. (See ESI for details).

The N,N-dipropargyl amine with an electron donating methoxy group (**1b**) in the aryl unit afforded the desired product **2b** in excellent 91% yield. The case of **2f** was interesting since the additional propargyl unit linked to the carboxylate remained untouched in the reaction. The structures of these compounds were established by the 1D and 2D NMR spectroscopy. The key 2D NMR correlations for the product (**2b**) are presented schematically in Fig. 2 as an example.

The complete set of data for the structural analysis is given in the ESI.† The characteristic resonance observed at $\delta = 7.58$ corresponded to hydrogen atom of the triazole ring and the resonance at $\delta = 129.6, 130.8,$ and 46.9 ppm corresponded to olefinic carbon atoms and the methylene carbon adjacent to the double bond of the triazole ring. Additionally, characteristic resonances were observed at $\delta = 4.13$ and 4.48 ppm corresponding to methylene protons of pyrazine ring. The resonances at $\delta = 4.98$ and 6.06 in the ^{1}H NMR spectrum and the resonance at $\delta = 100.2$ in the ^{13}C NMR spectra were attributed to the methylene protons and carbon of the exocyclic double bond of pyrazine ring respectively. The methylene group of the exocyclic double bond of the pyrazine ring was confirmed by ^{1}H–^{1}H COSY, ^{1}H–^{13}C HMBC, and ^{1}H–^{1}H NOESY spectra (Fig. 2 and S28–S31, ESI†).

The success of the general strategy on a broad range of substrates for the syntheses of the 1,2,3-triazole-fused
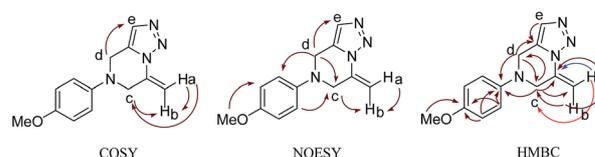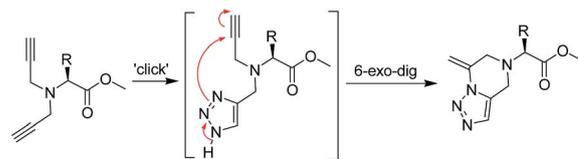
Table 1 Investigation of reaction conditions for the preparation of [1,2,3]triazolo[1,5-a]pyrazines

Entry	Conditions (1 : 1, v/v)	NaN$_3$ (equiv.)	°C[a]	Yield[b] (%)
1	THF–H$_2$O	1.0	25	23
2	THF–H$_2$O	1.0	80	41
3	THF–H$_2$O	1.1	80	46
4	TBA–H$_2$O	1.0	25	35
5	TBA–H$_2$O	1.0	80	80
6	TBA–H$_2$O	1.1	80	92
7	TBA–H$_2$O	1.5	80	81
8	TBA–H$_2$O	1.7	80	78
9	DMF–H$_2$O	1.1	80	55
10	Toluene–H$_2$O	1.1	80	29
11	CH$_3$CN–H$_2$O	1.1	80	52
12	Ethanol–H$_2$O	1.1	80	51
13	DME–H$_2$O	1.1	80	52
14	Dioxane–H$_2$O	1.1	80	56

[a] Time 24 h. [b] Isolated yield.

Fig. 2 Key 2D NMR correlations of **2b**.

tetrahydropyrazines from various aromatic primary amines motivated us to extend this synthetic protocol to naturally abundant L-amino acids. A series of methyl esters of the amino acids – alanine, valine, tryptophan and tyrosine were thus synthesized and subsequently reacted with propargyl bromide in the presence of K_2CO_3 (5 equiv.) in dry DMF at 25 °C for 12 h to form the dipropargyl precursors **3a–d** (see ESI†). It is to be noted that the methyl ester of tyrosine on treatment with propargyl bromide in the presence of K_2CO_3 afforded a product with three propargyl groups: two attached to the nitrogen, and the third one to the oxygen of the phenolic –OH group of the amino acid. Interestingly, for tryptophan, attachment of the propargyl unit to the indole-N was not observed. When subjected to our tandem "click"/*exo*-cyclization reaction conditions, substrates **3a–d** afforded compounds **4a–d** in moderate to good yields (67–85%) as summarized in Table 3.

A probable mechanism of the reaction for the formation of the triazole-fused pyrazine derivatives (series **2** and **4**) is shown in Scheme 2. Initial reaction of the diprop-2-ynylamines (series **1** and **3**) with sodium azide allows a copper(I) mediated 1,3-dipolar cycloaddition of one of the terminal alkyne groups[15] leading to the formation of a triazole-yne intermediate which subsequently undergoes a tandem intramolecular 6-*exo*-dig cycloaddition[16] through the attack of a non-bonding electron of a N of the triazole to the π* orbital of the alkyne unit (Fig. 1 and S43, ESI†) leading to the products.

Intramolecular attack of triazoles to internal alkynes in ene-diene substrates was observed leading to *endo*-cyclization.[10,17] Intramolecular *exo*-attack on an alkyne by a thiol attached to an imidazole has also recently been reported by Cai and cow-orkers.[11a] These served as an inspiration to check if the generality of our method can also be extended to non-terminal alkynes.[18] Thus compounds **5a** and **5b** bearing a methyl and an ethyl group at the alkyne terminals were prepared *via* the route used for the preparation of the dipropargyl derivatives

Table 3 1,3-Dipolar cycloaddition followed by intramolecular 6-*exo*-dig cycloaddition of diprop-2-ynylamines derived from amino acids[a]

a Conditions: NaN_3 (1.1 equiv.), $CuSO_4 \cdot 5H_2O$ (5 mol%), sodium ascorbate (40 mol%), *t*BuOH–H_2O, 1 : 1 v/v, 80 °C, *t* = 28 h, for entry 1 and 2; 36 h for entry 3 and 4.

Scheme 2 Plausible mechanism for the formation of 1,2,3-triazole-fused pyrazines.

1a–g (Scheme 3, ESI†). However, when subjected to our tandem click/*exo*-dig cyclization conditions, these non-terminal alkynes did not afford any desired product even under a series of varied drastic conditions (microwave, THF–H_2O, DMF–H_2O, toluene–H_2O, CH_3CN–H_2O, ethanol–H_2O, DME–H_2O, dioxane–H_2O and prolonged heating (up to 150 h) at elevated range of temperatures from 120–180 °C. Although these results were somewhat disheartening, it is not completely unexpected because for the "click" reaction to occur, the substrate requires a C–H bond at the terminal alkyne.[19] The classical Huisgen 1,3-dipolar cyclo-addition, which occurs in the absence of the Cu-salt at elevated temperatures, also did not work in our case.

This result led us to alter our strategy: it was anticipated that unsymmetrical alkynes (*e.g.*, **7a** or **7b**, *via* compound **6**) containing both the terminal alkyne and the internal alkyne groups would ensure the formation of the triazoles (Scheme 3, ESI†) that would to undergo the subsequent *exo*-cyclization to yield the corresponding desired pyrazine products. Surprisingly, for these cases instead of the expected '6-*exo*-dig' intramolecularly cyclized pyrazines, intermolecular, dimeric acyclic 'click' products (**8a** and **8b**) were obtained in trace quantities (Scheme 3, ESI†).

Since severe conditions failed to produce the desired inter-molecular products for the substrates with both the alkyne moieties as internal alkynes (as in the case **5a** and **5b**), and since the substrates with both terminal and internal alkynes (**7a** and **7b**) produced the products **8a** and **8b** involving only the reactions at the terminal alkynes leaving the internal alkynes intact, we were prompted to speculate that the Cu-salt might have a role for the *exo*-dig attack.[20] A plausible mechanism of the formation of the unexpected products (**8a** and **8b**), as shown in
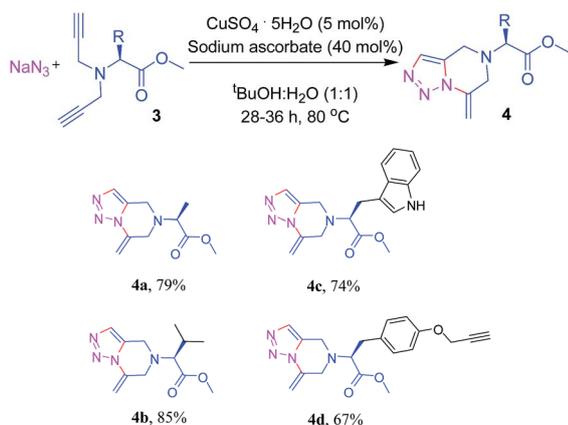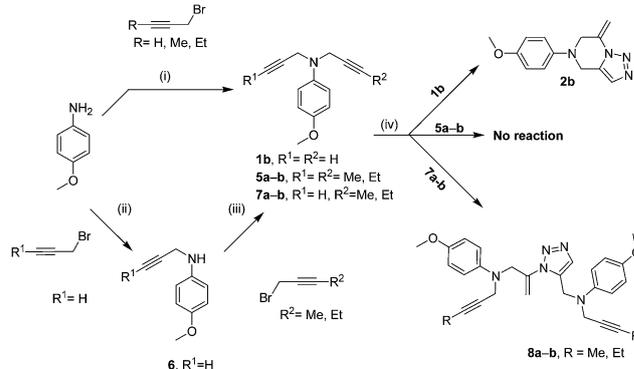
Scheme 3 Conditions: (i) K_2CO_3 (5 equiv.), dry DMF, 12 h, 25 °C (ii) K_2CO_3 (1 equiv.), dry DMF, 5 h, 25 °C (iii) K_2CO_3 (2.5 equiv.), dry DMF, 12 h, 25 °C (iv) NaN_3 (1.1 equiv.), $CuSO_4 \cdot 5H_2O$ (5 mol%), sodium ascorbate (40 mol%), *t*BuOH–H_2O, 1 : 1 v/v, 24 h, 80 °C.
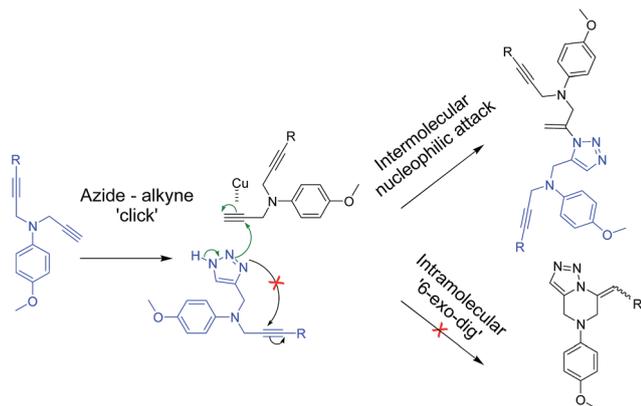
Scheme 4 Probable mechanism for the formation of intermolecular acyclic 'clicked' product through 1,3-dipolar cycloaddition reaction followed by intermolecular nucleophilic reaction.

Scheme 4, suggests that the 'click' reaction between NaN_3 and the unsubstituted propargyl group generates the 1,2,3 triazole ring in the initial step. In contrast to the intramolecular attack, the triazoles in these cases undergo an intermolecular nucleophilic attack on the terminal acetylenic moiety of another molecule, leaving the substituted propargyl group intact, thereby leading to the formation of the unexpected (1*H*-1,2,3-triazol-1-yl)allyl moiety (in **8a** and **8b**) as the exclusive products.

In conclusion, we have reported an efficient and facile synthetic approach for the syntheses of [1,2,3]triazolo[1,5-*a*]-pyrazines in excellent yields from several primary amines and amino acids using a novel, modular approach that involves a one pot 1,3-dipolar cycloaddition reaction followed by a tandem intramolecular 6-*exo*-dig cycloaddition reaction as the key step. The reaction offers high atom economy. The method is limited to the substrates bearing terminal alkynes – for the substrates with one non-terminal alkyne, the reaction yields intermolecular products in low yields. However, for the substrates where both the alkyne moieties are substituted, the reaction does not yield any product. Thus, the two step synthetic protocol permitted the construction of *N*-heterocyclic compounds from readily available primary amine or amino acid substrates which should open up many possibilities for more such heterocycles with functional diversity.

Acknowledgements

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