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

Biswajit Roy, Debashis Mondal, Joydev Hatai, and Subhajit Bandyopadhyay*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

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. Many natural products containing the tetrahydropyrazine framework display a broad spectrum of biological effects including antitumor activity. This framework is present in the HIV protease inhibitor crivixivan, and other drugs candidates.

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 were synthesized by the group of Chandrasekaran, Abbott Laboratories and Appella using multistep synthesis. Likewise, the 4,5,6,7-tetrahydro-[1,2,3] triazolo[1,5-a]pyrazines, bearing such bicyclic fused rings were synthesized by Gurjar and Couty in multiple steps. Recently, Shen and coworkers from Merck Research Laboratories have also reported a multistep synthesis of the scaffold as agonists for the G-protein-coupled niacin receptor. 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. A series of triazolo[1,5-a]quinoxaline systems, a variant of the scaffold, has been synthesized by Cai via another tandem approach from 2-(haloaryl)propiolamides. Gulevskaya and coworkers have recently demonstrated the azide mediated tandem cyclization of (Z)-enediyne for the formation of the corresponding [1,2,3]triazolo[1,5-a]pyridines.

Inspired by the resource efficient tandem reactions, we envisioned that a tandem approach combining a 1,3-dipolar [3+2] (“click”) cycloaddition followed by an intramolecular exo-cyclization 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 K2CO3 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 BuOH (TBA) and H2O with sodium azide (1.1 equiv.) using CuSO4 . 5H2O (5 mole %) in presence of sodium ascorbate (40 mole%) as the reducing agent. A 1,3 dipolar cycloaddition reaction between the azide and one of the alkyn moieties formed the incipient 1,2,3 triazole ring. The triazole underwent a constrained intramolecular 6-exo-dig cyclodition with the another alkyn 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 NaN3 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 (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.
reaction was effective for a broad range of aromatic amines containing electron donating as well as electron withdrawing aromatic amines.

![Scheme 1. General scheme for syntheses of [1,2,3]triazolo[1,5-a]pyrazines from primary amines.](image)

Table 1. Optimization of reaction conditions for the preparation of [1,2,3]triazolo[1,5-a]pyrazines

| Entry | Solvent (1:1, v/v) | NaN₃ (equiv.) | °C | Yield (%) |
|-------|-------------------|--------------|----|-----------|
| 1     | THF/H₂O           | 1.0          | 25 | 23        |
| 2     | THF/H₂O           | 1.0          | 80 | 41        |
| 3     | THF/H₂O           | 1.1          | 80 | 46        |
| 4     | TBA/H₂O           | 1.0          | 25 | 35        |
| 5     | TBA/H₂O           | 1.0          | 80 | 80        |
| 6     | TBA/H₂O           | 1.1          | 80 | 92        |
| 7     | TBA/H₂O           | 1.5          | 80 | 81        |
| 8     | TBA/H₂O           | 1.1          | 80 | 55        |
| 9     | DMF/H₂O           | 1.1          | 80 | 29        |
| 10    | Toluene/H₂O       | 1.1          | 80 | 52        |
| 11    | CH₃CN/H₂O         | 1.1          | 80 | 51        |
| 12    | Ethanol/H₂O       | 1.1          | 12 | 65        |
| 13    | DME/ H₂O          | 1.1          | 80 | 52        |
| 14    | Dioxane/H₂O       | 1.1          | 80 | 56        |

*Time 24 h. Isolated yield.

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 from primary amines.

| Entry | Nag (equiv.) | °C | Yield (%) |
|-------|--------------|----|-----------|
| 1     | 1.0          | 25 | 23        |
| 2     | 1.0          | 80 | 41        |
| 3     | 1.1          | 80 | 46        |
| 4     | 1.0          | 25 | 35        |
| 5     | 1.0          | 80 | 80        |
| 6     | 1.1          | 80 | 92        |
| 7     | 1.5          | 80 | 81        |
| 8     | 1.1          | 80 | 55        |
| 9     | 1.1          | 80 | 29        |
| 10    | 1.1          | 80 | 52        |
| 11    | 1.1          | 80 | 51        |
| 12    | 1.1          | 80 | 52        |
| 13    | 1.1          | 80 | 56        |

*a Conditions: NaN₃ (1.1 equiv.), CuSO₄ 5H₂O (5 mol%), sodium ascorbate (40 mol%), 1:1 mixture of BuOH and H₂O, 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 Figure 2 as an example.

Figure 2. Key 2D NMR correlations of 2b.

The complete set of data for the structural analysis is given in the Supporting Information (ESI†). The characteristic resonance observed at δ = 7.58 corresponded to hydrogen atom of the triazole ring and the resonance at δ = 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 δ = 4.13 and 4.48 ppm corresponding to methylene protons of pyrazine ring. The resonances at δ = 4.98 and 6.06 in the ¹H NMR spectrum and the resonance at δ = 100.2 in the ¹³C 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 ¹H-¹H COSY, ¹H-¹³C HMBC, and ¹H-¹H NOESY spectra (Fig. 2, Fig. 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 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 K₂CO₃ (5 equiv.) in dry DMF at 25 °C for 12 h to form the propargyl 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 K₂CO₃ 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 that forms the triazole-fused pyrazine derivatives (series 2 and 4) is shown in scheme 3. 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 alkyn groups leading to the formation of a triazole-yne intermediate which subsequently undergoes a tandem intramolecular 6-exo-dig cycloaddition through the attack of a non-bonding electron of a N of the triazole to the π* orbital of the alkynyl unit (Fig. 1 and Fig S43, ESI†) leading to the products.

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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 substrates bearing terminal alkynes – for substrates with one non-terminal alkyne, the reaction yields intermolecular products in low yields. For 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.

The authors gratefully acknowledge the help of Dr. Sushovan Paladhi for the determination of specific rotation, Dr. Bhaskar Pramanik for crystallography and Mr. Chiranjit Dutta with HPLC. BR is supported by an Int. Ph.D. fellowship, DM by a UGC fellowship and JH by a CSIR SRF. The authors acknowledge CSIR-India for a research grant.

Notes and references

Indian Institute of Science Education and Research (IISER) Kolkata, Mohanpur, Nadia, WB 741246, India
E-mail: sb1@iiserkol.ac.in

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–b, 7a–b, 8a–b. See DOI: 10.1039/b000000x/

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