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Facile Entry into Triazole Fused Heterocycles via Sulfamidate Derived Azido-alkynes

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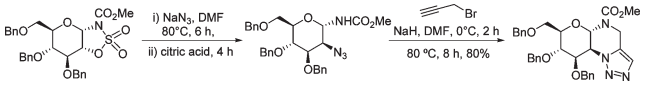

Direct synthesis of condensed triazoles from diverse sulfamidates by ring opening of sulfamidates with sodium azide followed by one-pot propargylation and cycloaddition furnished title compounds. The methodology in general has been demonstrated on diverse sulfamidates derived from amino acids, amino acid derivatives, and carbohydrates to obtain diverse triazole fused scaffolds. In one example, a condensed triazole containing amino acid has been synthesized by ring opening of a sulfamidate derivative with propargyl amine.

After the pivotal discovery by Sharpless et al.[1] that Cu(I) catalyzes the formation triazoles in a 1,4-substituted fashion, the chemistry of triazoles was brought from oblivion to renaissance. Triazole chemistry was revisited and has seen exponential growth over the years and enormous gain in popularity in diverse areas of chemistry such as organic, material, and medicinal chemistry. 1,2,3-Triazole moiety is present in many compounds exhibiting different biological properties such as antibacterial[2] (cefmatilen), anti-HIV,[3] antiallergic,[4] and inhibitory[5] (tazobactam) activities. Triazolobenzodiazepines[6] have shown high affinity toward benzodiazepine receptors. They are also emerging as powerful pharmacophores in their own right. Copper-catalyzed cycloaddition is mainly used for conjugation[7] or ligation between two molecules or in an intramolecular fashion to generate macrocycles.[8] In parallel, there has been considerable interest shown toward the synthesis of novel condensed triazoles using intramolecular version of Huisgen cycloaddition.[9] Tailor-made molecules possessing alkyne and azide moieties disposed in the same molecule when heated undergo intramolecular Huisgen cycloaddition to furnish novel, 1,5-substituted triazole fused heterocyclic systems. We have recently demonstrated this in the synthesis of 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazin-6-ones from primary amines and amino acids comprising a three-step protocol employing intramolecular [2 + 3] cycloaddition as the key step.[10] In our continued interest toward the synthesis of novel triazole fused systems, we report herein an elegant and high-yielding synthesis of diversely substituted nitrogen-rich triazole fused compounds via azido-alkynes derived from a variety of sulfamidates. The choice of azido-alkynes for the cycloaddition was quite broad, ranging from simple azido-alkynes to novel substrates derived from amino acids and carbohydrates. Constrained intramolecular [3+2] cycloaddition between azide and alkyne was used as a pivotal reaction.

Our strategy involved ring opening of diverse sulfamidates with sodium azide to furnish the corresponding azido

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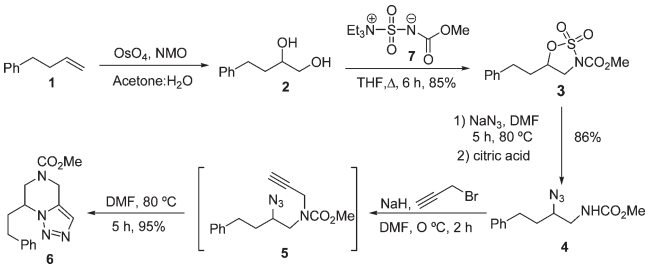
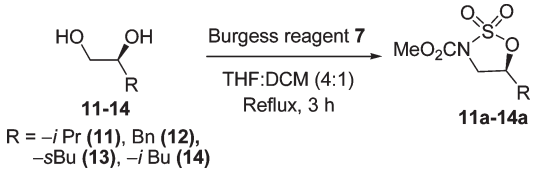
SCHEME 1. Synthesis of Triazole Fused Derivative 6 Starting from 4-Phenyl-1-butene 1



SCHEME 2. Synthesis of Sulfamidates (11a−14a) from Amino Acid Derived 1,2-Diols (11−14)



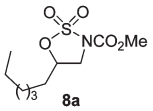
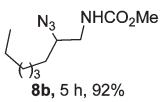
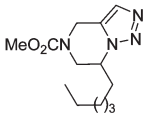
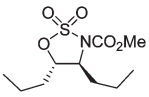
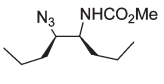
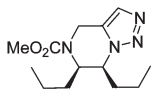
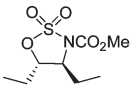
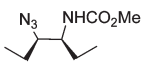
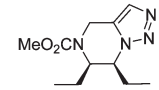
amines. When these azido amines were subjected to alkylation with propargyl bromide followed by cycloaddition in the same pot, a variety of substituted triazole fused products were formed (Scheme 1). Initially 1,2-diol from 4 phenyl-1-butene **1** was treated with Burgess reagent **7**[11] in THF to give sulfamidate **3** in 85% yield.

When **3** was treated with NaN_3 in DMF, followed by hydrolysis with citric acid, azido amine **4** was isolated. Compound **4** was then converted to the propargylated azido amine **5**. Without isolating this compound, the reaction mixture was quenched with water and was subjected to thermal cycloaddition (DMF, 80 °C, 5 h) to afford the triazole fused bicyclic compound **6** (95%).

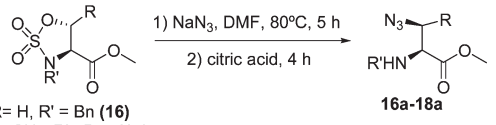
Encouraged by this result, sulfamidates **8a−10a** were synthesized from 1,2-octane diol, 4,5-octane diol and 3,4-hexane diol respectively employing Burgess reagent **7**. Ring opening of sulfamidates (**8a−10a**) with NaN_3 in DMF gave the corresponding azides **8b−10b**, respectively. Treatment of these azides (**8b−10b**) under similar conditions as described in Scheme 1 proved to be effective to furnish triazole fused compounds **8c−10c** as the only products. We next embarked on the synthesis of diverse sulfamidates derived from amino acids, amino acid derivatives, and carbohydrates. Starting from different L-amino acids such as phenylalanine, valine, leucine, and isoleucine, several enantiopure 1,2-diols (**11−14**) were synthesized.[12]

When these diols (**11−14**) were treated with Burgess reagent **7** in THF, the corresponding sulfamidates (**11a−14a**) were isolated in high yields (Scheme 2). Sulfamidates **11a−14a** were then regioselectively opened with NaN_3 to furnish the corresponding azido-amines (**11b−14b**) after hydrolysis with citric acid. The azido amines were then alkylated with propargyl bromide in the presence of NaH to furnish azido alkynes that underwent Huisgen intramolecular thermal cycloaddition smoothly in one pot to furnish

TABLE 1. Triazole Fused Derivatives (8c−10c) from Octane Diol and Hexane Diol Derived Sulfamidates (8a−10a)

Sulfamidate	azide	Triazole fused compound
 **8a**	 **8b,** 5 h, 92%	 **8c,** 7 h, 95%
 **9a**	 **9b,** 5 h, 90%	 **9c,** 7 h, 90%
 **10a**	 **10b,** 5 h, 90%	 **10c,** 7 h, 90%

SCHEME 3. Amino Acid Derived Azides (16a−18a) from Serine Derived Sulfamidates (16 and 18) and Threonine Derived Sulfamidate (17)



the corresponding amino acid derived triazole fused pryazine derivatives substituted at C-7 (**11c−14c**, respectively) in excellent yields. Sulfamidate **15a** derived from *N*-benzyl isoleucinol was reacted with NaN_3 in DMF to furnish azido amine **15b**. One-pot propargylation followed by thermal cycloaddition gave triazole fused tetrahydropyrazine derivative **15c** substituted at C-6 in 85% yield.

Synthesis of Condensed Triazoles from Serine and Threonine Derived Sulfamidates. In order to increase the diversity of substituents attached to the condensed triazoles, several amino acids containing azido-alkynes were accessed from serine and threonine derived sulfamidates[13] (**16−18**) and subjected to cycloaddition to obtain two different triazole fused skeletons. For this *N*-benzyl and *N*-Cbz serine derived sulfamidates were treated with sodium azide to give amino acid containing azides **16a** and **18a**, respectively. Ring opening of **17** with sodium azide gave threonine derived azide **17a** in 85% yield (Scheme 3).

Propargylation of **16a** followed by intramolecular cycloaddition furnished triazole fused tertrahydropyrazine derivative **16c** as the only product in excellent yield (Scheme 4). *N*-Boc deprotection from the threonine derived azide **17a**, and then one-pot alkylation with propargyl bromide and cycloaddition gave **17c** in good yield. Similarly, Cbz-protected serine derived azide **18a** when heated with dimethylacetylene dicarboxylate in $CHCl_3$ for 3 h led to the isolation of **18b** in quantitative yield. Pd/C assisted deprotection of Cbz group followed by heating the resulting mixture in DMF for 4 h led to intramolecular lactam

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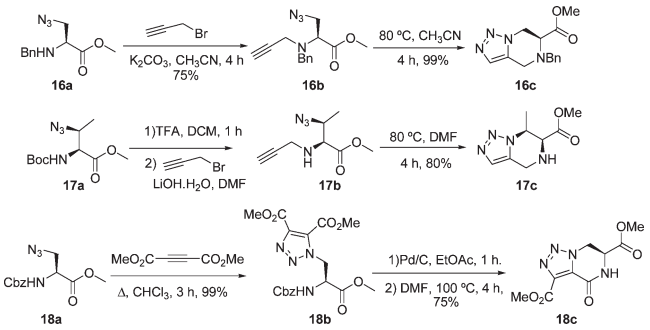
SCHEME 4. Serine and Threonine Derived Triazole Fused Bicyclic Compounds (16c−18c)



SCHEME 5. Synthesis of Sulfamidate 20a from D-Glucose Derived Diol 21

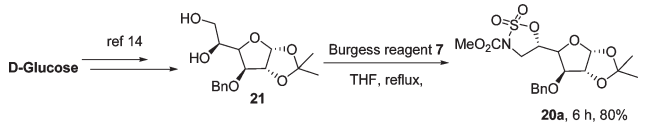
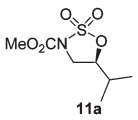
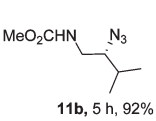
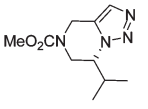
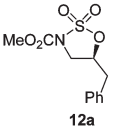
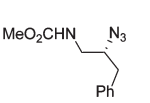
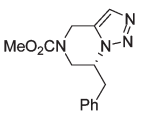
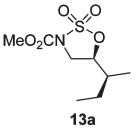
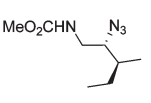
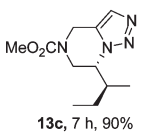
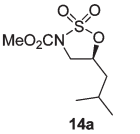
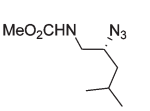
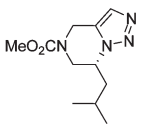
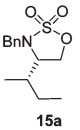
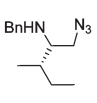
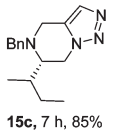


TABLE 2. Triazole Derivatives (11c−15c) from Amino Acid Derived Sulfamidates (11a−15a)[a]

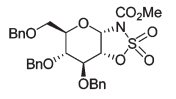
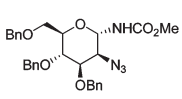
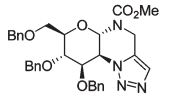
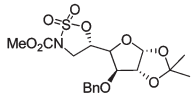
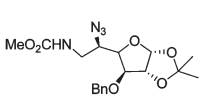
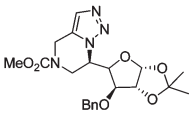
Sulfamidate	azide[b]	Triazole fused compound
 11a	 **11b,** 5 h, 92%	 **11c,** 6 h, 90%
 12a	 **12b,** 5 h, 95%	 **12c,** 7 h, 92%
 13a	 **13b,** 6 h, 94%	 **13c,** 7 h, 90%
 14a	 **14b,** 6 h, 89%	 **14c,** 7 h, 88%
 15a	 **15b,** 4 h, 90%	 **15c,** 7 h, 85%

[a]Structures of 11a-14a have been unambiguously confirmed using ^{1}H NMR analysis.[11a,16] [b]Ring-opening of sulfamidates 11a-14a with azide is stereoselective.[11]

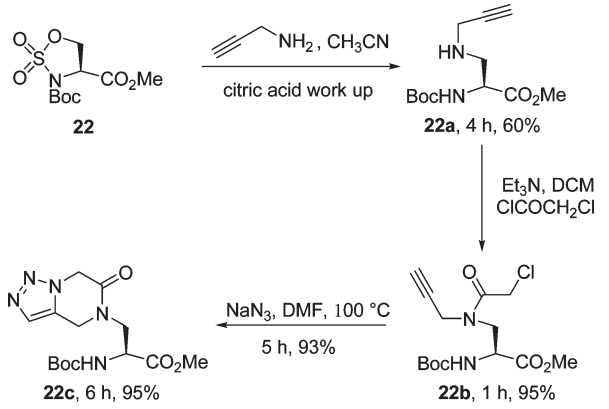
formation to yield fully decorated triazole **18c** in 75% yield (Scheme 4).

Synthesis of Condensed Triazoles Derived from D-Glucose. In continuation of our investigation to examine the efficacy of this methodology for the synthesis of carbohydrate derived condensed triazoles, we synthesized two triazole fused

TABLE 3. D-Glucose Derived Triazole Fused Derivatives (19c and 20c)

Sulfamidate	azide	Triazole fused compound
 19a	 **19b**, 6 h, 85%	 **19c**, 8 h, 80%
 20a	 **20b**, 7 h, 85%	 **20c**, 8 h, 90%

SCHEME 6. Synthesis of Condensed Triazole 22c containing Amino Acid as Pendant



compounds from D-glucose derived sulfamidates. Sulfamidate **19a** was synthesized from tribenzyl glucal in two steps.[11] When **19a** was treated with NaN_3 in DMF, it led to regioselective ring opening of sulfamidate furnishing azido-amine **19b** in good yield. Intramolecular cycloaddition was attempted after propargylation of **19b** with propargyl bromide.

We were gratified to obtain the triazole fused tricyclic compound **19c** from D-glucose in 80% yield after cycloaddition (Table 3). Selective deprotection of primary acetonide from D-glucose derived bis-acetonide gave **21**.[14]

Refluxing the diol **21** in THF with Burgess reagent **7** gave sulfamidate **20a** in 80% yield. Treatment of **20a** with NaN_3 in DMF gave azido amine **20b** in good yield. Azido amine **20b** was subjected to one-pot alkylation and cycloaddition to give novel D-glucose derived triazole fused system **20c** as the only product.

Thus, this methodology could as well be applied for the synthesis of carbohydrate derived condensed triazoles. In all of the above cases, sulfamidates were opened with azide as the nucleophile. We next attempted the ring opening of serine derived sulfamidate **22** with propargyl amine to furnish the amine **22a** in 60% yield.[15] Amine **22a** was treated with chloroacetyl chloride in DCM to give chloroacetylated propargyl amine **22b** as the only product. One-pot displacement of chlorine by azide followed by cycloaddition gave

(14) Lohman, G. J. S.; Hunt, D. K.; Hogermeier, J. A.; Seeberger, P. H. *J. Org. Chem.* **2003**, *68*, 7559.
(15) Kim, B. M.; So, S. M. *Tetrahedron Lett.* **1999**, *40*, 7687.
(16) Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, *10*, 329.

triazole fused heterocycle **22c** containing amino acid derivative as the only product.[10]

In conclusion, we have disclosed a novel and elegant route for the synthesis of condensed triazoles from diverse sulfamidate derived azido-alkynes by sequential ring opening, alkylation, and cycloaddition protocol. The applicability of this methodology has been shown on various substrates including amino acid and carbohydrate derived azido-alkynes. High yield, one-pot alkylation and cycloaddition, and easy isolation of the products are the key features of this useful methodology.

Experimental Section

General Procedure for the Synthesis of Azido Amines from Sulfamidates. To a solution of sulfamidate (1 mmol) in DMF (4 mL) was added sodium azide (3 mmol), and the mixture was stirred at 80 °C for the required time. After the disappearance of sulfamidate, saturated citric acid solution (5 mL) was added and stirred for 4 h. DMF was evaporated under vacuum, and water (10 mL) was added to the resultant slurry and extracted with DCM (2 × 20 mL). The combined organic layers were filterd through anhydrous Na_2SO_4, concentrated, and purified by flash chromatography on silica gel using mixtures of ethyl acetate/hexane as eluents to furnish the pure azido amines.

Compound 12b. Colorless oil, (0.222 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.22 (m, 5H), 5.06 (bs, 1H), 3.78−3.69 (m, 4H), 3.50−3.42 (m, 1H), 3.12−3.03 (m, 1H), 2.88 (dd, J_1 = 13.8 Hz, J_2 = 5.4 Hz, 1H), 2.78 (dd, J_1 = 13.8 Hz, J_2 = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 136.7, 129.2, 128.7, 127.0, 63.7, 52.3, 44.5, 38.5. IR (neat): 3336, 2119, 1710, 1531, 1261, 701 cm^{-1}. HRMS *m*/*z*: calcd for $C_{11}H_{14}N_4O_2$ (M + Na) 257.1014, found 257.1012. $[\alpha]^{23}_D$ −42.0 (*c* 2, $CHCl_3$).

General Procedure for the Synthesis of Condensed Triazoles. To a solution of azido-amine (1 mmol) in DMF (5 mL) at 0 °C was added sodium hydride (1.3 equiv), and the mixture stirred until the complete consumption of azido amine (TLC). Excess sodium hydride was quenched with water, and the resultant reaction mixture was heated at 80 °C for the required amount of time. DMF was evaporated under vacuum, and the resultant slurry was extracted with DCM (2 × 20 mL) and filtered through anhydrous Na_2SO_4. DCM was evaporated, and the crude product was purified by flash chromatography on silica gel using mixtures of ethyl acetate/hexane as eluents to furnish triazole fused compounds.

Compound 12c. Pale brown oil, (0.25 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.37−7.28 (m, 5H), 4.83−4.76 (m, 2H), 4.59 (d, J = 16.8 Hz, 1H), 4.13−3.90 (m, 1H), 3.79 (s, 3H), 3.61−3.49 (m, 2H), 3.06 (t, J = 11.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 135.5, 129.5, 129.0, 128.7, 127.2, 57.4, 53.2, 43.6, 39.8, 39.1. IR (neat): 3409, 1709, 1446, 1232, 765 cm^{-1}. HRMS *m*/*z*: calcd for $C_{14}H_{16}N_4O_2$ (M + H) 273.1352, found 273.1353. $[\alpha]^{23}_D$ 49.5 (*c* 2, $CHCl_3$).

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Supporting Information Available: ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.