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One-pot synthesis of 2,6-diamino-4-sulfonamidopyrimidines from sulfonyl azides, terminal alkynes and cyanoguanidine

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ABSTRACT

Ketenimine intermediates, generated in situ by the addition of copper acetylides to aryl- or alkylsulfonyl azides, are trapped by cyanoguanidine to yield 2,6-diamino-4-sulfonamidopyrimidine derivatives in moderate to good yields.

Nitrogen heterocycles are abundant in nature and are found in many natural products such as vitamins, hormones, antibiotics, and alkaloids.[1] The pyrimidine moiety is a prominent structural motif found in numerous bioactive compounds. Consequently, several methods have been developed for the construction of this ring system.[2–5] Diaminopyrimidine derivatives are widely used as key building blocks for pharmaceutical agents.[6–8]

Among several methods leading to the generation of ketenimines, the copper-catalyzed azide–alkyne cycloaddition reaction has attracted much attention because of its mild conditions.[9] The in situ generated ketenimine intermediates can be trapped by various nucleophiles.[10] In this way, frameworks of various heterocycles were successfully synthesized.[11–13] Applying this strategy, we used cyanoguanidine to trap in situ generated ketenimines and obtained 2,6-diamino-4-sulfonamidopyrimidine derivatives (Scheme 1). Herein, we report the details of this letter.[14]

First, we studied the reaction between the ketenimine intermediate generated from phenylacetylene (**1a**) and *p*-toluensulfonyl azide (**2a**) with cyanoguanidine (**3**). This reaction proceeded smoothly at room temperature and afforded N^1-(2,6-diamino-5-phenyl-4-pyrimidinyl)-4-methyl-1-benzenesulfonamide (**4a**) in an 83% yield. This result prompted us to optimize the reaction conditions for the synthesis of other 2,6-diamino-4-sulfonamidopyrimidines (see Scheme 1).

Several catalysts including CuI, CuBr, CuCl, Cu_2O, and copper powder were tested with CuI giving the best result. Among the solvents screened, tetrahydrofuran (THF) proved to be the best. Thus, the optimized reaction conditions were as follows: 10 mol % of CuI, 1 mmol of the terminal alkyne **1**, 1.2 mmol of the sulfonyl azide **2** and 1 mmol of cyanoguanidine (**3**) in THF at room temperature.

Phenylacetylene readily participated in the coupling to furnish the corresponding diaminopyrimidine derivatives in good yields (Scheme 1). Aliphatic acetylenes served as lower yielding substrates compared to phenylacetylene. Aromatic and aliphatic sulfonyl azides reacted efficiently and the corresponding products were obtained in good yields.

The structures of compounds **4a–i** were assigned from IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The ^{1}H NMR spectrum of **4a** exhibited four singlets for the methyl (2.51 ppm), NH_2 (4.28 and 4.50 ppm), and NH (8.33 ppm) protons, along with characteristic multiplets for the phenyl protons. The ^{13}C NMR spectrum of **4a** exhibited 13 signals in agreement with the proposed structure. The mass spectrum of **4a** displayed the molecular ion peak at $m/z = 355$.

A plausible mechanism for the formation of compounds **4** is given in Scheme 2. The yellow copper acetylide **5**, formed from **1** and CuI, undergoes a 1,3-dipolar cycloaddition reaction with sulfonyl azide **2**, to generate the triazole derivative **6**.[15] This intermediate can then be converted into the ketenimine derivative **7**, which is attacked by cyanoguanidine (**3**) to afford **8**. This intermediate undergoes intramolecular cyclization and tautomerization to produce **4**.

In summary, ketenimine intermediates generated by the addition of copper acetylides to sulfonyl azides are trapped by cyanoguanidine to yield 2,6-diamino-4-sulfonamidopyrimidine derivatives.

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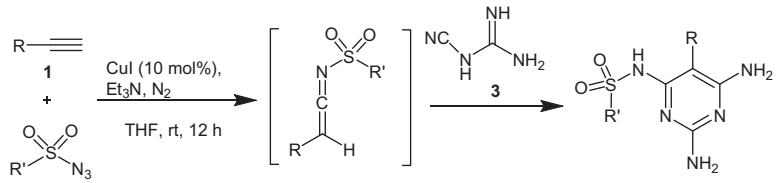
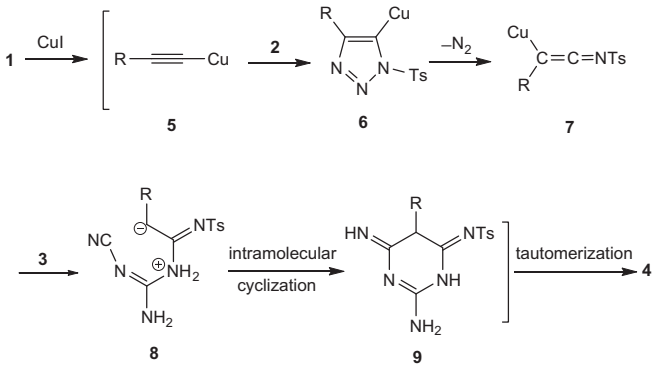


Product	R	R'	Yield (%)
4a	Ph	*p*-tolyl	83
4b	Ph	Ph	87
4c	Ph	Me	79
4d	*n*-Pr	*p*-tolyl	65
4e	*n*-Pr	Ph	63
4f	*n*-Pr	Me	60
4g	*n*-Bu	*p*-tolyl	60
4h	*n*-Bu	Ph	57
4i	*n*-Bu	Me	52

Scheme 1. Synthesis of compounds **4**.



Scheme 2. A plausible mechanism for the formation of compounds **4**.

The present method may be considered a practical route for the synthesis of functionalized sulfonamidopyrimidines. The short reaction times and readily available starting materials and catalyst are the main advantages of this methodology.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.041.

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14. *General procedure for the preparation of pyrimidines* **4a–i**: To a mixture of azide **2**, (1.2 mmol), alkyne **1** (1 mmol), CuI (0.1 mmol), and Et_3N (1 mmol) in THF (2 mL) was slowly added, under N_2 atmosphere, cyanoguanidine (**3**) (1 mmol). The mixture was stirred at room temperature. After completion of the reaction [about 12 h, TLC (EtOAc/hexane, 1:5) monitoring], the mixture was diluted with CH_2Cl_2 (2 mL) and aqueous NH_4Cl solution (3 mL), stirred for 30 min, and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 mL × 3) and the combined organic fractions dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography [silica gel (230–400 mesh; Merck), hexane/EtOAc, 5:1] to give the product.
N^1-(2,6-Diamino-5-phenyl-4-pyrimidinyl)-4-methyl-1-benzenesulfonamide (**4a**). Cream powder; mp: 280–283 °C; yield: 0.29 g (83%). IR (KBr) (ν_{max}, cm^{-1}): 3551, 3450, 3323, 3300, 3250, 1325, 1140. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 2.51 (3H, s, Me), 4.28 (2H, s, NH_2), 4.50 (2H, s, NH_2), 7.13 (2H, d, ^3J = 7.9 Hz, Ar), 7.16–7.68 (5H, m, Ph), 7.98 (2H, d, ^3J = 7.9 Hz, Ar), 8.33 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 29.3 (Me), 124.0 (CH), 124.8 (2CH), 130.6 (2CH), 135.2 (2CH), 136.0 (2CH), 136.1 (C), 147.5 (C), 151.4 (C), 153.7 (C), 154.8 (C), 156.7 (C), 158.8 (C). EI-MS: *m*/*z* (%) = 355 (M^+, 15), 339 (10), 323 (10), 278 (16), 170 (42), 155 (100), 108 (64), 91 (70), 77 (54). Anal. Calcd for $C_{17}H_{17}N_5O_2S$ (355.00): C, 57.45; H, 4.82; N, 19.70. Found: C, 57.79; H, 4.86; N, 19.81.
N^1-(2,6-Diamino-5-phenyl-4-pyrimidinyl)-1-benzenesulfonamide (**4b**). Pale-yellow powder; mp: 260–266 °C; yield: 0.29 g (87%). IR (KBr) (ν_{max}, cm^{-1}): 3545, 3453, 3333, 3300, 3255, 1323. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 4.20 (2H, s, NH_2), 4.42 (2H, s, NH_2), 7.01 (2H, t, ^3J = 7.1 Hz, Ar), 7.23 (1H, t, ^3J = 7.1 Hz, Ar), 7.48 (2H, d, ^3J = 7.1 Hz, Ar), 7.63 (2H, t, ^3J = 7.2 Hz, Ar), 7.79 (1H, t, ^3J = 7.2 Hz, Ar), 7.87 (2H, d, ^3J = 7.2 Hz, Ar), 9.00 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 124.2 (2CH), 125.3 (2CH), 126.0 (2CH), 132.8 (CH), 134.8 (CH), 135.2 (2CH), 138.1 (C), 149.6 (C), 152.9 (C), 154.8 (C), 158.4 (C), 160.1 (C). EI-MS: *m*/*z* (%) = 341 (M^+, 10), 325 (11), 309 (10), 264 (18), 156 (23), 141 (100), 108 (40), 77 (50). Anal. Calcd for $C_{16}H_{15}N_5O_2S$ (341.35): C, 56.29; H, 4.43; N, 19.37. Found: C, 56.44; H, 4.46; N, 19.51.
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