Copper-Catalyzed Tandem Synthesis of Pentasubstituted Pyridines from Sulfonoketenimides and 2-Aminoprop-1-ene-1,1,3-tricarbonitrile

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Abstract: Fully substituted pyridines were synthesized in moderate to good yields in a one-pot process by the copper-catalyzed sequential reaction of sulfonyl azides with terminal alkynes and 2-aminoprop-1-ene-1,1,3-tricarbonitrile at room temperature.

Keywords: pyridines, cyclizations, tandem reactions, copper, catalysis

Pyridine and its derivatives are an important class of six-membered heterocycles present in a number of biologically active natural products and pharmaceuticals.[1] They also have significant applications in many fields of chemistry.[2] In particular, they are useful building blocks for the preparation of chiral ligands[3] or new materials with important photo- or electrochemical properties.[4,5]

Polynitriles are versatile reagents that have been used extensively as precursors to heteroaromatics.[6] Interest in developing the synthetic potential of these compounds has recently been revived.[7] 2-Aminoprop-1-ene-1,1,3-tricarbonitrile has proved to be an excellent precursor to condensed pyridines.[8]

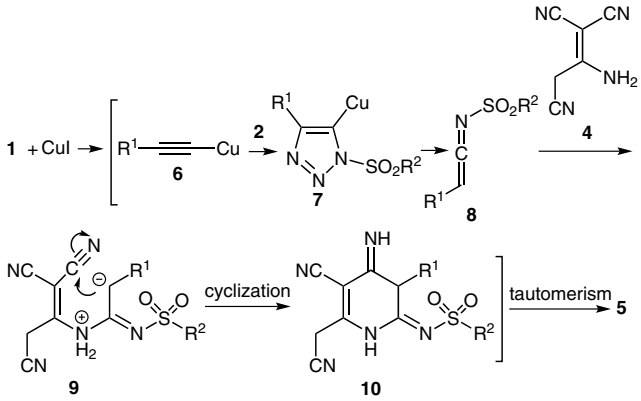
Recently, Zhou and co-workers used 2-(aminomethylene)malononitriles to trap ketenimines generated in situ to give 4-amino-2-iminopyridines or 6-amino-2-iminopyridines, depending on the reaction conditions.[9] Their report, prompted us to disclose our results on trapping sulfonoketenimides by 2-aminoprop-1-ene-1,1,3-tricarbonitrile (malononitrile dimer) to give *N*-[4-amino-5-cyano-6-(cyanomethyl)-3-(alkyl/aryl)pyridin-2-yl]-4-(alkyl/aryl)sulfonamides.[10]

Initially, we selected ethynylbenzene (**1a**), 4-toluenesulfonyl azide (**2a**), and malononitrile as model substrates, and we tested several catalysts, including copper(I) iodide, copper(I) bromide, copper(I) chloride, and copper powder, of which copper(I) iodide gave the best results. Among several solvents that we screened, dichloromethane was the best. When the reaction was performed in dichloromethane in the presence of one equivalent of triethylamine at room temperature for eight hours, the desired pyridine **5a** was obtained in 85% yield. Thus, the optimal conditions are malononitrile (2 mmol), copper(I) iodide (10 mol%), alkyne (1 mmol), and sulfonyl azide (1.2 mmol) in dichloromethane at room temperature.

Ethynylbenzene (**1a**) readily participated in the coupling reaction with various sulfonyl azides to give the corresponding *N*-sulfonamides **5a–c** in good yields (Table 1, entries 1–3); aromatic and aliphatic sulfonyl azides both reacted efficiently. Pent-1-yne and hex-1-yne also gave the corresponding sulfonamides **5d-i**, albeit in slightly lower yields (entries 4–9).

The structures of compounds **5a–i** were assigned by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and by mass spectrometric analyses. The ^{1}H NMR spectrum of **5a** exhibits four singlets for methyl (2.54 ppm), methylene (4.33 ppm), NH_2, and NH (5.78, 8.62 ppm) protons, along with characteristic multiplets for the phenyl protons. The ^{13}C NMR spectrum of **5a** shows seventeen signals, in agreement with the proposed structure. The mass spectrum of **5a** displayed a molecular ion peak at $m/z = 403$. The NMR spectra of compounds **5b–i** were similar to those of **5a**, except for the substituents, which showed characteristic signals in the appropriate regions of the spectra.

A plausible mechanism for the formation of compounds **5** is shown in Scheme 1. The copper acetylide **6**, formed from alkyne **1** and copper(I) iodide, undergoes a 1,3-dipolar cycloaddition with azide **2** to give the triazole derivative **7**.[11] This intermediate is converted into the sulfonoketenimide **8**,[12] which is attacked by amine **4** (generated in situ from malononitrile and sodium hydride) to afford intermediate **9**. This intermediate is converted into product **5** by cyclization and tautomerization.



Scheme 1

In conclusion, we have developed a sequential transformation involving sulfonoketenimide intermediates and 2-aminoprop-1-ene-1,1,3-tricarbonitrile, which provides a new route to fully substituted pyridines that have im-

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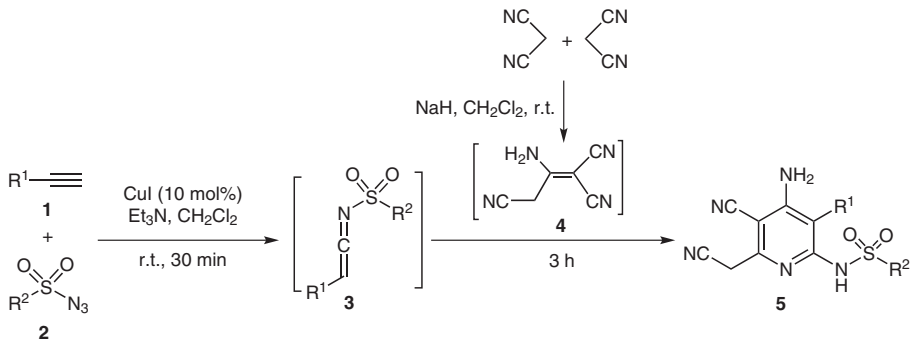
Table 1 Formation of *N*-[4-Amino-5-cyano-6-(cyanomethyl)-3-(alkyl/aryl)pyridin-2-yl]-4-(alkyl/aryl)sulfonamides **5**



Entry	R^1	R^2	Product	Yield (%)
1	Ph	4-Tol	**5a**	85
2	Ph	Ph	**5b**	81
3	Ph	Me	**5c**	78
4	Pr	4-Tol	**5d**	70
5	Pr	Ph	**5e**	68
6	Pr	Me	**5f**	64
7	Bu	4-Tol	**5g**	69
8	Bu	Ph	**5h**	63
9	Bu	Me	**5i**	60

portant applications in syntheses of biologically active and drug-like molecules.

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(10) ***N*-[4-Amino-5-cyano-6-(cyanomethyl)-3-(alkyl/aryl)pyridin-2-yl]-4-(alkyl/aryl)sulfonamides; General Procedure**

The tetracyano compound **4** was prepared by self-condensation of malononitrile (2 mmol) in CH_2Cl_2 containing NaH (1 equiv) at r.t. for 30 min. A mixture of sulfonyl azide **2** (1.2 mmol), alkyne **1** (1 mmol), CuI (10 mmol%), and Et_3N (1 mmol) in CH_2Cl_2 (3 mL) was slowly added. The mixture was stirred at r.t. under N_2 for about 3 h until the reaction was complete [TLC; EtOAc–hexane (1:5)]. The mixture was then diluted with CH_2Cl_2 (2 mL) and aq NH_4Cl (3 mL), and stirred for 10 min. The layers separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The organic fractions were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a residue that was purified by flash column chromatography [silica gel (230–400 mesh; Merck), hexane–EtOAc (5:1)].

***N*-[4-Amino-5-cyano-6-(cyanomethyl)-3-phenylpyridin-2-yl]-4-methylbenzenesulfonamide (5a)**

Cream powder; yield: 0.34 g (85%); mp 147–149 °C. IR (KBr): 3345, 3106, 2127, 1534, 1399, 1192, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.54 (s, 3 H, Me), 4.33 (s, 2 H, s, CH_2), 5.78 (s, 2 H, NH_2) 7.30–7.35 (m, 3 H, Ph), 7.67 (d, ^3J = 7.4 Hz, 2 H, Ar), 7.70 (d, ^3J = 7.8 Hz, 2 H, Ar), 8.24 (d, ^3J = 7.8 Hz, 2 H, Ar), 8.62 (s, 1 H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 24.4 (CH_2), 29.3 (Me), 116.9 (CN), 117.8 (CN), 119.0 (C), 122.5 (C), 124.9 (C), 127.0 (2 CH), 128.9 (2 CH), 130.0 (C), 131.8 (2 CH), 132.4 (2 CH), 135.6 (CH), 145.8 (C), 148.1 (C), 153.1 (C), 159.0 (C). EI-MS:

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m/z (%) = 403 [M^+] (4), 337 (18), 233 (28), 170 (71), 156 (100), 91 (57), 77 (30). Anal. Calcd for $C_{21}H_{17}N_5O_2S$ (403.46): C, 62.52; H, 4.25; N, 17.36. Found: C, 63.03; H, 4.22; N, 17.52.

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