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Copper-catalyzed one-pot synthesis of tetrasubstituted pyrazoles from sulfonyl azides, terminal alkynes, and hydrazonoyl chlorides

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ABSTRACT

Ketenimine intermediates generated by the addition of copper acetylides to sulfonyl azides are trapped by nitrile imines (generated from hydrazonoyl chlorides and triethylamine) to afford tetrasubstituted pyrazoles in moderate to good yields.

The activity of the central carbon atom of ketenimines toward various nucleophiles[1–3] has led to their application in the construction of heterocycles. Among several methods leading to the generation of ketenimines, the copper-catalyzed azide-alkyne cycloaddition has attracted significant attention because of its mild conditions.[4,5] The in situ generated ketenimine intermediates can be trapped by various nucleophiles.[6–11] Applying this strategy, Wang and co-workers[12] used hydrazones to trap in situ generated ketenimines and obtained linear addition products. This strategy was extended to sulfonamidopyrazole in the presence of a Lewis acid and an oxidant. This Letter, prompted us to describe our results on the direct one-pot synthesis of tetrasubstituted pyrazoles using hydrazonoyl chlorides as the trapping agent.

The in situ generated ketenimine intermediate **1** reacts with nitrile imine[13–15] derivative **2**, generated from a hydrazonoyl chloride **3** and Et_3N, to give the desired tetrasubstituted pyrazole **4** in moderate to good yields (Scheme 1).[16]

Several catalysts including CuI, CuBr, CuCl, Cu_2O, and copper powder were tested with CuI giving the best results. Among the solvents screened, *N*,*N*-dimethylformamide (DMF) proved to be the best. Thus, the optimized reaction conditions were 10 mol % of CuI, 1 mmol of alkyne **5**, 1.2 mmol of sulfonyl azide **6,** and 1 mmol of hydrazonoyl chloride in DMF at room temperature.

Phenylacetylene readily participates in the formation of pyrazole derivatives in good yields (Scheme 1). Aliphatic acetylenes served as low-yielding substrates compared to phenylacetylene. Aromatic and aliphatic sulfonyl azides reacted efficiently with **5** and the corresponding products **4a–n** were obtained in good yields.

The structures of compounds **4a–n** were deduced from their IR, ^1H NMR, and ^{13}C NMR spectra. For example, the ^1H NMR spectrum of **4b** exhibited two singlets for the methyl (δ 2.43) and NH (δ 8.73) protons, along with multiplets for the aromatic protons. The ^1H-decoupled ^{13}C NMR spectrum of **4b** showed 20 distinct resonances which confirmed the proposed structure. The NMR spectra of **4a** and **4c–n** were similar to those for **4b** except for the aliphatic and aryl moieties, which exhibited characteristic resonances in appropriate regions of the spectra.

A mechanistic rationalization for the reaction is given in Scheme 2. The initial event is the formation of the yellow copper acetylide **7** from **5** and CuI, which undergoes a 1,3-dipolar cycloaddition with sulfonyl azide **6**, to generate triazole **8**. This intermediate is converted into the ketenimine derivative **1**, which undergoes a [3+2] dipolar cycloaddition with nitrile imine **2** to afford **9**. Finally, intermediate **9** is converted into the product pyrazole **4** via a 1,3-H shift.

In summary, we have reported a sequential transformation involving ketenimine intermediates (generated by the addition of copper acetylides to sulfonyl azides) and nitrile imine intermediates (derived from hydrazonoyl chlorides and Et_3N), which represents a new route for the synthesis of tetrasubstituted pyrazoles. The present method may be considered as a practical route for the synthesis of functionalized pyrazoles which may show potential for further synthetic manipulations.

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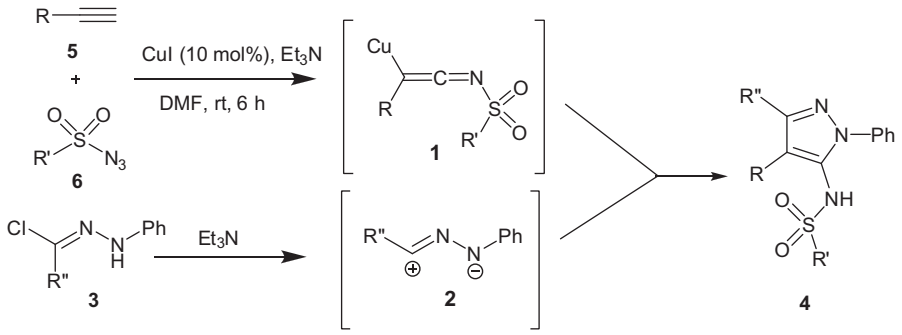
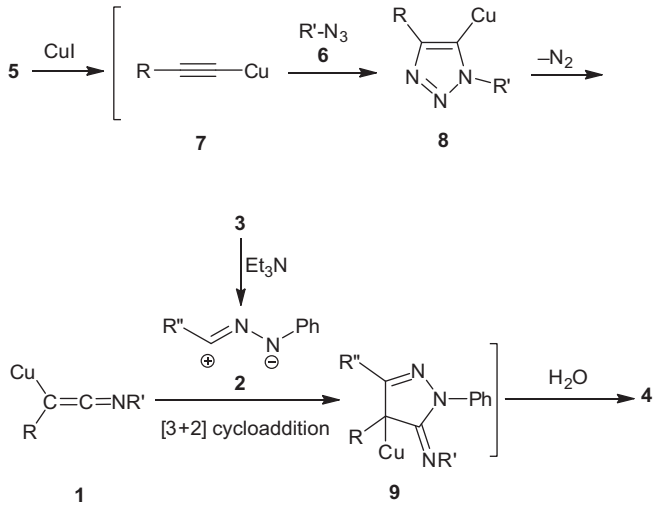


Entry	R	R'	R"	Product	Yield (%)
1	Ph	*p*-tolyl	*p*-tolyl	**4a**	91
2	Ph	Ph	*p*-tolyl	**4b**	87
3	Ph	Me	*p*-tolyl	**4c**	81
4	Ph	*p*-tolyl	4-ClC_6H_4	**4d**	90
5	Ph	Ph	4-ClC_6H_4	**4e**	85
6	Ph	Me	4-ClC_6H_4	**4f**	83
7	Ph	*p*-tolyl	Ph	**4g**	84
8	Ph	Ph	Ph	**4h**	80
9	Ph	Me	Ph	**4i**	79
10	*n*-Bu	Ph	*p*-tolyl	**4j**	69
11	*n*-Bu	*p*-tolyl	4-ClC_6H_4	**4k**	66
12	*n*-Pr	*p*-tolyl	4-ClC_6H_4	**4l**	68
13	*n*-Pr	*p*-tolyl	Ph	**4m**	65
14	*n*-Pr	Me	Ph	**4n**	60

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



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

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.083.

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16. *General procedure for the synthesis of compounds* ***4****:* The corresponding hydrazonoyl chloride **3** (1 mmol) and Et_3N (1.2 mmol) were dissolved in DMF (3 mL) and stirred for 10 min. Next, a mixture of the sulfonyl azide **6**, (1.2 mmol), alkyne **5** (1 mmol), CuI (0.1 mmol), and Et_3N (1 mmol) in DMF (2 mL) was added with stirring at room temperature under N_2 atmosphere. After completion of the reaction [about 6 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 × 3 mL) 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. The spectroscopic data for compounds **4a**, **4g**, **4h,** and **4i** were similar to those reported by Wang.[12]
N^1-[3-(4-Methylphenyl)-1,4-diphenyl-1H-pyrazol-5-yl]-1-benzenesulfonamide (***4b***)*:* Yellow solid, mp: 219–221 °C; yield: 0.40 g (87%). IR (KBr) (ν_{max}, cm^{-1}): 3738, 3431, 1595, 1507, 1255, 1110. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 2.43 (3H, s, Me), 6.97 (1H, t, ^3J = 7.2 Hz, Ar), 7.11–7.18 (5H, m, Ph), 7.25–7.30 (5H, m, Ph), 7.36 (2H, t, ^3J = 7.2 Hz, Ar), 7.48 (2H, t, ^3J = 7.3 Hz, Ar), 7.68 (2H, t, ^3J = 7.3 Hz, Ar), 7.92 (2H, d, ^3J = 8.0 Hz, Ar), 8.73 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 21.3 (Me), 113.4 (C), 120.9 (2 CH), 121.6 (C), 122.0 (CH), 125.4 (2 CH), 126.0 (C), 128.7 (2 CH), 128.8 (CH), 128.9 (2 CH), 129.0 (2 CH), 129.1 (C), 129.2 (2 CH), 129.3 (CH), 129.5 (2 CH), 131.9 (2 CH), 133.3 (C), 138.1 (C), 143.8 (C), 148.9 (C). MS: *m*/*z* (%) = 465 (M^+, 10), 309 (25), 257 (21), 157 (40), 141 (100), 91 (50), 77 (55). Anal. Calcd for $C_{28}H_{23}N_3O_2S$ (465.12): C, 72.23; H, 4.98; N, 9.03%. Found: C, 72.53; H, 5.05; N, 9.09%.