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Tandem synthesis of highly functionalized *N*-phosphorylated sulfonamido-pyrazolone derivatives

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ABSTRACT

The reaction between ketenimine intermediates, generated from terminal alkynes and sulfonyl azides, diisopropyl azodicarboxylate, and trimethyl or triphenyl phosphite, in *N*,*N*-dimethylformamide at room temperature, affords highly functionalized *N*-phosphorylated sulfonamido-pyrazolone derivatives in moderate to good yields.

Heterocyclic compounds occur widely in Nature and are essential to life. Nitrogen heterocycles are abundant existing in many natural products such as vitamins, hormones, antibiotics, and alkaloids.[1] The pyrazole ring is a prominent structural motif found in numerous pharmaceutically active compounds.[2] Much effort has been devoted to prepare this structural unit and a general method for its synthesis consists of the condensation of hydrazines with various 1,3-dicarbonyl compounds.[3–5] We have previously reported convenient methods for the preparation of functionalized pyrazole derivatives.[6–9] As an extension of these studies, we report the preparation of highly functionalized *N*-phosphorylated sulfonamido-pyrazolone derivatives.[10]

Among several methods leading to the generation of ketenimines, the copper-catalyzed azide-alkyne cycloaddition reaction has attracted significant attention because of its mild formation conditions.[11,12] The ketenimine intermediates generated in this reaction could be trapped by various nucleophiles.[13] In this way, various heterocyclic frameworks were obtained.[14–18]

In our initial investigations, phenylacetylene (**1a**), *p*-toluenesulfonyl azide (**2a**), trimethyl phosphite (**4a**), and diisopropyl azodicarboxylate (**5**) were selected as the model substrates. Several catalysts including CuI, CuBr, CuCl, Cu_2O, and copper powder were tested with CuI giving the best results. Among the several solvents screened, *N*,*N*-dimethylformamide (DMF) proved to be the best. When the reaction was performed in DMF at room temperature for five hours, it was found that the phosphorylated pyrazolone **6a** was obtained in 87% yield (Table 1). Replacement of phosphites **4** with triphenylphosphine led to a complex reaction mixture, and we were unable to isolate any pyrazolone **6** from this mixture. Thus, the optimized reaction conditions used were CuI (10 mol %), alkyne **1** (1 mmol), sulfonyl azide **2** (1.2 mmol), phosphite **4** (1 mmol), and azodicarboxylate **5** (1 mmol), in DMF at room temperature (Scheme 1).

Phenylacetylene readily participates in the coupling to furnish the corresponding *N*-phosphorylated sulfonamido-pyrazole derivatives **6** in good yields (Scheme 1). Aliphatic acetylenes served as

Table 1
Optimization of the reaction conditions for the preparation of pyrazolone **6a** from phenylacetylene (**1a**), *p*-toluenesulfonyl azide (**2a**), trimethyl phosphite (**4**), diisopropyl azodicarboxylate (**5**), and catalyst (10 mol %)

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	Cu_2O	DMF	8	20
2	Cu_2O	MeCN	8	15
3	Cu_2O	THF	8	15
4	CuCl	MeCN	8	25
5	CuCl	THF	8	20
6	CuCl	DMF	8	45
7	CuI	DMF	5	87
8	CuI	MeCN	5	64
9	CuI	THF	8	57
10	CuI	CH_2Cl_2	8	25
11	CuBr	DMF	5	80
12	CuBr	MeCN	5	55
13	CuBr	THF	8	50
14	Cu	DMF	8	–
15	Cu	MeCN	8	–
16	Cu	THF	8	–

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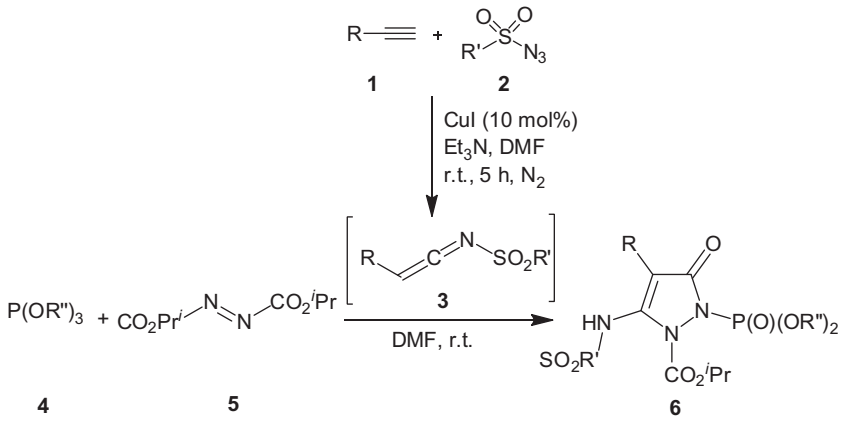


Entry	R	R'	R''	Yield (%) of **6**
a	Ph	*p*-Tol	Me	87
b	Ph	Ph	Me	80
c	Ph	Me	Me	77
d	Ph	*p*-Tol	Ph	83
e	Ph	Ph	Ph	74
f	Ph	Me	Ph	72
g	*n*-Pr	*p*-Tol	Me	69
h	*n*-Pr	Ph	Me	63
i	*n*-Pr	*p*-Tol	Ph	65
j	*n*-Bu	*p*-Tol	Me	61
k	*n*-Bu	Me	Me	58

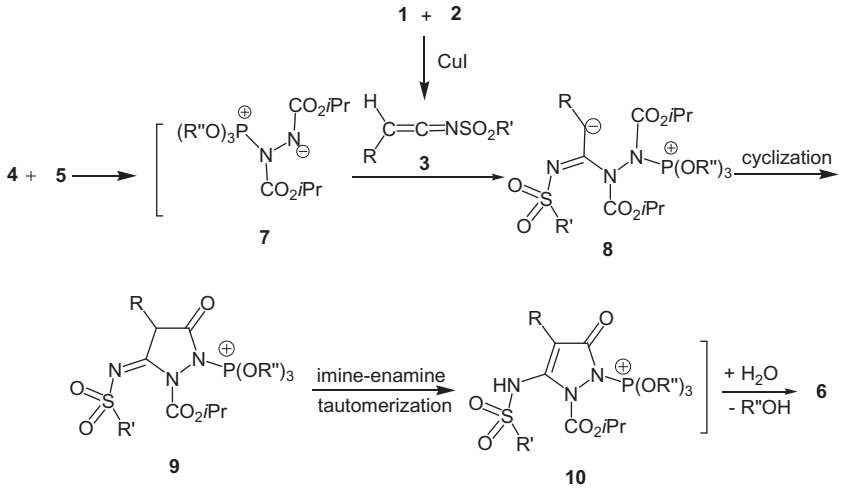
Scheme 1. Synthesis of compounds **6**.

low yielding substrates compared to phenylacetylene. Aromatic and aliphatic sulfonyl azides reacted efficiently and the corresponding products were obtained in good yields.

The structures of products **6a**–**k** were assigned by IR, ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectroscopy and from mass spectral data. For example, the ^{1}H NMR spectrum of **6a** exhibited two singlets for the methyl (2.47 ppm) and NH (8.47 ppm), and two doublets for the isopropyl (1.42 ppm, ^{3}J = 6.5 Hz), and P-OMe (3.95 ppm, $^{3}J_{PH}$ = 12.0 Hz) protons, along with characteristic multiplets for the aryl and HCO protons. The ^{13}C and ^{31}P NMR spectra of **6a** were consistent with the proposed structure (see the experimental). The NMR spectra of compounds **6b**–**k** were similar to those of **6a**, except for the substituents, which showed characteristic signals in the appropriate regions of the spectra.

A mechanism for the formation of compounds **6** is given in Scheme 2. The well-established[11,12] ketenimine intermediate **3** is attacked by the zwitterionic adduct **7**, generated from **4** and **5**, to afford **8**. Intermediate **8** undergoes intramolecular cyclization and imine-enamine tautomerization to generate **10**, which is converted into **6** by the absorption of moisture and the elimination of R″OH.

In conclusion, we have developed a tandem reaction involving the ketenimine intermediates, diisopropyl azodicarboxylate and trimethyl or triphenyl phosphite in DMF at room temperature, which affords a new route to the synthesis of functionalized *N*-phosphorylated sulfonamido-pyrazolone derivatives in moderate to good yields. The reaction described here is mild, fairly general, and efficient, thus providing a suitable pathway for the synthesis of a variety of functionalized phosphorylated pyrazolones.



Scheme 2. A possible mechanism for the formation of compounds **6**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.035.

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10. 10. *General procedure for the synthesis of compounds* ***6****:* To a mixture of acetylene **1** (1 mmol), sulfonyl azide **2** (1.2 mmol), CuI (0.1 mmol), and Et_3N (1 mmol), in DMF (3 mL) was added slowly phosphite **4** (1 mmol) and azodicarboxylate **5** (1 mmol). The mixture was stirred at room temperature. After completion of the reaction [about 5 h; TLC (EtOAc/hexane, 1:3) 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 were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic fractions were 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, 3:1] to give the product.
*Isopropyl 2-(dimethoxyphosphoryl)-5-(4-methylphenylsulfonamido)-3-oxo-4-phenyl-2,3-dihydro-1H-pyrazole-1-carboxylate (****6a****):* Pale yellow powder, mp: 112-115 °C; yield: 0.45 g (87%). IR (KBr) (ν_{max}, cm^{-1}): 3495, 1673, 1497, 1390, 1252, 1171, 1092, 1010, 926. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 1.42 (6 H, d, ^3J = 6.5 Hz, 2 Me), 2.47 (3 H, s, Me), 3.95 (6 H, d, $^3J_{P-H}$ = 12.0 Hz, 2 OMe), 5.19–5.24 (1 H, m, CHO), 7.25-7.31 (3 H, m, Ph), 7.38 (2 H, d, ^3J = 7.5 Hz, Ar), 7.48 (2 H, d, ^3J = 8.1 Hz, Ar), 7.91 (2 H, d, ^3J = 8.1 Hz, Ar), 8.47 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 22.1 (Me), 22.3 (Me), 30.0 (Me), 52.4 (d, $^2J_{PC}$ = 6.5 Hz, 2 OMe), 74.8 (CHO), 94.0 (C), 122.5 (C), 127.4 (2 CH), 128.7 (2 CH), 129.2 (CH), 130.6 (2 CH), 132.4 (2 CH), 142.1 (C), 147.3 (C), 152.3 (C=O), 160.4 (C), 175.8 (d, $^2J_{PC}$ = 4.0 Hz, C=O).^{31}P NMR (202.45 MHz, $CDCl_3$): 12.83 ppm. MS: m/z (%) = 523 (M^+, 1), 446 (8), 353 (10), 170 (20), 155 (100), 109 (31), 91 (33), 87 (32), 77 (66), 59 (21). Anal. Calcd for $C_{22}H_{26}N_3O_8PS$ (523.12): C, 50.48; H, 5.01; N, 8.03%. Found: C, 50.72; H, 5.08; N, 8.09%.
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