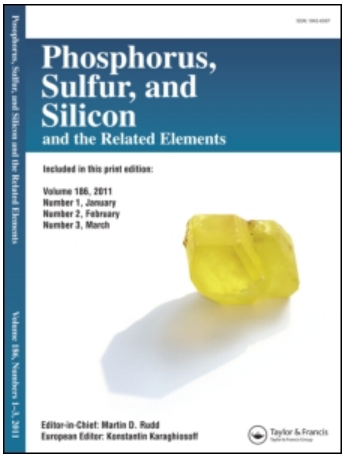


## Phosphorus, Sulfur, and Silicon and the Related Elements

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# Synthesis of a Novel Heterocyclic System: Oxazolo[3,2-*c*]pyrimidine

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# Synthesis of a Novel Heterocyclic System: Oxazolo[3,2-*c*]pyrimidine

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*Treatment of 2-chloro-4-propargyloxo-5-nitro-6-methylpyrimidine with conc. sulfuric acid gave a novel heterocyclic system 2,3-dihydro-3-methylene-7-methyl-8-nitro-5H-oxazolo [3,2-c]pyrimidine-5-one (**5**)*

**Keywords** Heterocyclization; oxazolo pyrimidine; pyrimidine; sulfuric acid

Bicyclic compounds derived from pyrimidine have critical roles in various biological processes and considerable attention has been given to the field in a search for potential antagonists.[1] It has been shown that substituted oxazolo[5,4-a]pyrimidines inhibit VEGFR 2 (vascular endotherial growth factor receptor 2, KDR) or EGFR (epidermal growth factor receptor) with/C50 values in the low nanomolar range.[2]

In spite of much interest in the synthesis of oxazolopyrimidine,[1–3] a literature survey did not disclose any references concerning the synthesis of oxazolo[3,2-*c*]pyrimidine. In continuation of our interest concerning synthesis of nitrogen heterocycles,[4] in this article we wish to report the synthesis of oxazolo[3,2-*c*]pyrimidine.

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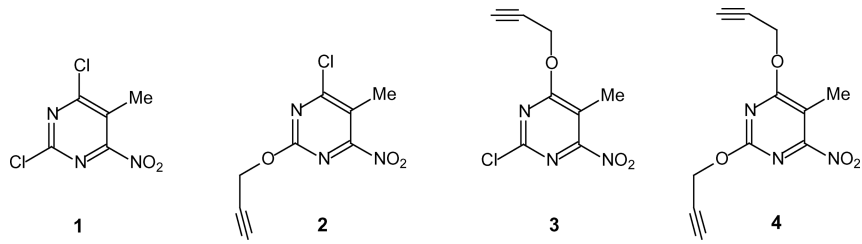


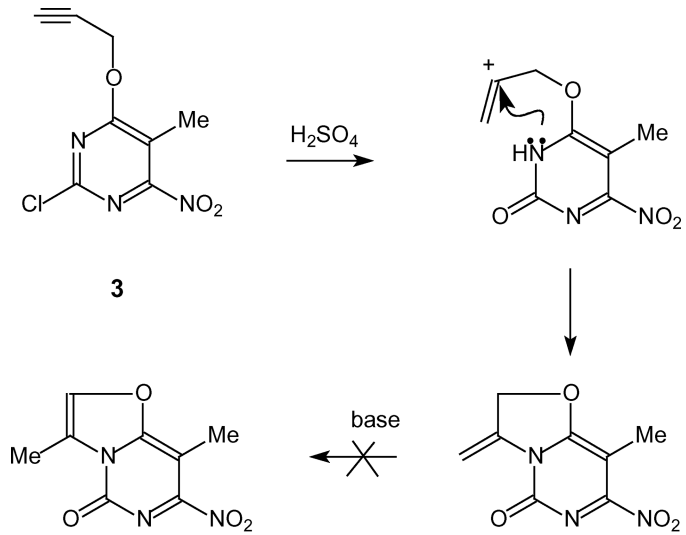

**SCHEME 1**

2,4-dichloro-5-nitro-6-methylpyrimidine was first synthesized.[5] This compound was condensed with one equivalent mole of sodium propargyl oxide (Scheme 1). The spectroscopic data ($^1$HNMR and mass spectrum) showed that only one chloro group has been replaced affording either 2-propargyloxypyrimidine **2** or 4-propargyloxypyrimidine **3**. The spectral data were not much help in deciding in favor of either product **2** or **3**. However, it is known, due to electron repultion and magnitude of this electrostatic barrier, $\gamma$-nucleophilic substitution[6] is favored over $\alpha$–nucleophilic substitution leading to the formation of **3**.

However, when compound **1** was reacted with 2, equivalents of sodium propargyl oxide compound **4** were obtained.

Over the years, others[7] and we[8] have payed attention to the catalyzed intramolecular cyclization of acetylenes. Armed with these experiences, compound **3** was treated with various bases such as sodium hydroxide, sodium methoxide, sodium amide, and triethyl amine, in ethanol. These attempt failed and in most cases starting material was recovered. We have recently reported on the regioselective acid–catalyzed ($H_2SO_4$) heterocyclization. Accordingly, compound **3** was dissolved in conc. $H_2SO_4$ at r.t. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was poured onto crushed ice, neutralized, and extracted with $CHCl_3$. Evaporation of the solvent gave a single compound. IR spectra of this compound showed signals at 1680 $cm^{-1}$, typical for amide carbonyl and 1620 $cm^{-1}$ which can be assigned to the carbon–carbon double bond. Mass spectrum of this compound showed no M + 2 paterns typical for chloro compounds. The $^1$H-NMR spectrum of the obtained compound showed a singlet for the methyl group of pyrimidine at $\delta$ 2.35 ppm, a singlet at $\delta$ 4.13 ppm for the methylene group, and two doublets for the exo methylene group at $\delta$ 5.12 and 5.61. From these data we assigned structure **5** to the obtained compound.

The most probably acid catalyzed cyclization of **3** to **5** proceeded via the formation of a vinylic carbocation and hydrolysis of the chloro group




**SCHEME 2**

at the 2 position, followed by attack of the N3 of the pyrimidine to the vinylic carbocation, which gives **5** (Scheme 2).

Compound **5**, unlike its analogues (i.e., thiazolotriazines), could not be aromatized by various bases[8,10] and acids.[9]

In summary, we have developed a new route to oxazolo[3,2-*c*]pyrimidines from available and easily prepared starting materials.

## EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus and are uncorrected. The IR spectra were obtained on a 4300 Shimadzu spectrometer. The $^1$HNMR spectra (100 MHz) were recorded on a Bruker AC 100 spectrometer. Mass spectra were scanned on a Varian CH-7 instrument at 70 eV.

### 2-Chloro-4-propargyloxy-5-nitro-6-methylpyrimidine 3

Sodium (0.23 g, 0.01 mol) was added slowly to freshly distilled propargyl alcohol (0.5 g, 0.01 mol) at $-4^\circ$C. This mixture was stirred for 5 h in which sodium was completely dissolved. To this mixture compound **1** (2.27 g, 0.01 mol) in $CHCl_3$ (5 mL) was added. The reaction mixture was stirred for 4 h at r.t. The reaction mixture was filtered. The

filtrate was evaporated and the crude was crystallized from petroleum ether (60–80) to afford the title compound. Yield: 58%. M.p.: 74–75°C, $^1$HNMR, $\delta$ ($CDCl_3$) 2.6 (s, 3H, Me), 2.9 (t, $J = 1.9$ Hz, 1H, CH), 5.15 (d, $J = 1.9$, 2H, $CH_2$), IR $\tilde{\upsilon}$ (KBr disc) 3300, 1110 $cm^{-1}$, MS, m/z, $M^+$ 225.

## 2,3-Dihydro-3-methylene-7-methyl-5H-8-nitro-oxazolo-[3,2-*c*]pyrimidin-5-one, 5

Compound **3** (2.25 g 0.01 mol) was dissolved in conc. $H_2SO_4$. The reaction mixture was stirred for 6 h at r.t. The reaction mixture was poured into crushed ice, neutralized with sodium hydroxide, and extracted with $CHCl_3$. The solvent was evaporated and the crude residue was crystallized from EtOH to give the title compound **5**.

Yield: 70%. M.p.: > 200°C, $^1$HNMR, $\delta$ ($CDCl_3$) 2.35 (s, 3H, Me), 4.13 (s, 2H, $CH_2$), 5.12 (d, $J = 2.6$, 1H, exo methylene), 5.61 (d, $J = 2.6$, 1H, exo methylene); IR $\tilde{\upsilon}$ (KBr disc) 1680, 1560 $cm^{-1}$, MS, m/z, $M^+$ 225.



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