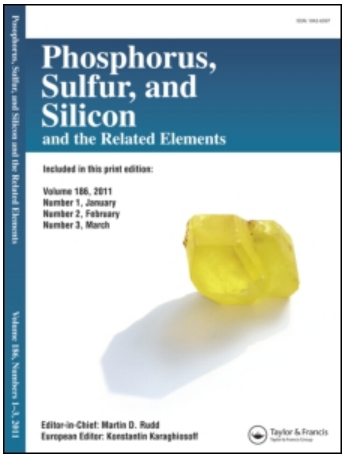

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A Novel Synthesis of Imidazo[1,2-*c*]pyrimidines

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A new method for the preparation of imidazo[1,2-c]pyrimidines is described.

Keywords Imidazole; imidazopyrimidine; pyrimidine

Guanines such as **1a** and **1b** (Figure 1) are potent phosphodiesterase (PDE) inhibitores.[1,2] Other bicyclic compounds derived from pyrimidine possess biological and pharmacological activities[3] and also find application as dyes.[4] In light of these properties, the novel synthesis of bicyclic compounds derived from pyrimidine and particularly imidazopyrimidines from the view points of chemistry and pharmacology are desirable.

In this article, we wish to report a novel and facile synthesis of imidazo[1,2-*c*]pyrimidines. Readily prepared 2,4-dichloro-5-methyl-5-nitropyrimidine **2**[5] is an attractive starting material for the preparation

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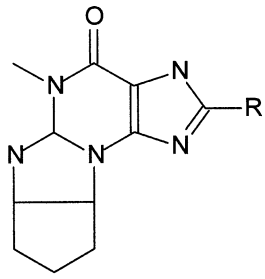


1a: R = CH_2PhCF_3
1b: R = $(CH_2)_5CH_3$

FIGURE 1

of imidazopyrimidines. The reaction of **2** with propargyl amine at r.t. gave 4-aminopropargyl derivative **3**. In this reaction, the formation of 2-propargyl derivative **4** is also possible. However, it is known due to electron repulsion and magnitude of this electrosetic barrier, that γ-nucleophilic substitution is favored,[6] leading to the formation of **3** (Figure 2).

Over the years, we and others have paied attention to the Pd,[7] base[8] and acid[35] catalyzed intermolecular cyclization of acetylenes. In order to cyclized compound **3** and keep the formed exo methylene for further transformation, we used $[PdCl_2(PhCN)_2]$[7a,b] as a catalys This reaction did not proceed. The base-catalyzed cycization of compound **3** using bases such as sodium hydroxide, sodium methoxide, and triethyl amine in ethanol also was not fruitful. However, when compound **3** was treated with conc. H_2SO_4 at -4°C, a crystalline product was obtained after a usual work up and column chromatography. The IR spectrum of this compound showed a sharp absorption band at 1680 cm^{-1}, which is typical for amide carbonyl. The mass spectrum of this compound did not show an M + 2 peak typical for chloro compounds. The ^{1}HNMR spectrum of the compound showed two methyl signals at δ2.27 and 2.8 the proton of imidazole at δ6.7 ppm, and a broad signal at

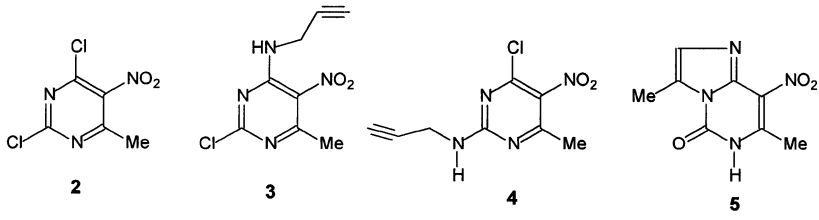


FIGURE 2

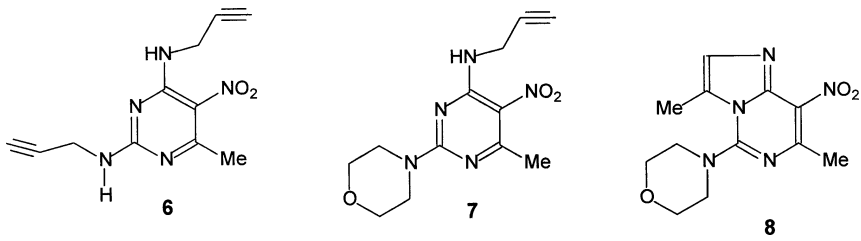


FIGURE 3

δ12.3 ppm, which can be removed by the addition of D_2O. Regarding these spectral data, we assigned structure **5** (3,7-dimethyl-8-nitro-5H-imidazo[1,2-*c*]pyrimidin-5-one) for the product of the aforementioned reaction.

Compound **3** was treated further with propargyl amine to obtain 2,4-dipropargyl amino derivative **6** (Figure 3). This compound could not be cyclized in a Pd-, base-, or acid-catalyzed reaction. When **3** reacted with morpholine, 2-morpholino-4-propargylamino-5-nitro-6-methylpyrimidine **7** was obtained. The treatment of **7** in conc. H_2SO_4 gave 3,7-dimethyl-8-nitroimidazo [1,2-*c*]pyrimidine **8**.

Most probably, the acid-catalyzed cyclization of **3** to **5** proceeds via the formation of vinylic carbocation, followed by the attack of N3 of pyrimidine to the vinylic carbocation to give a compound with exo-methylene, which subsequently undergoes isomerization-aromatization. After the addition of water, hydrolysis takes place, and chlorine is replaced by hydroxyl group (Scheme 1).

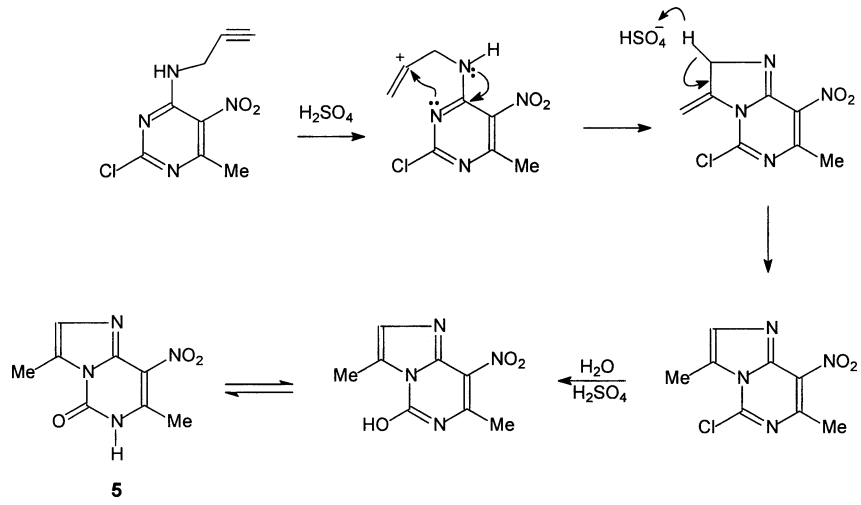
In conclusion, we have developed a new route for the synthesis of imidazo[1,2-c]pyrimidine and hope that it will find use in heterocyclic synthesis.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. IR spectra were obtained on a 4300 Shimadzu spectrometer. ^{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-propargylamino-5-nitro-6-methylpyrimidine (3)

Compound **2** (2.08 g, 0.01 mol) was dissolved in $CHCl_3$ (150 mL). To this solution and during stirring propargyl amine, 1.1 g, 0.02 mol in $CHCl_3$ (10 mL) was added in the period of 30 min. This mixture was



SCHEME 1

stirred for further 4 h at r.t. The mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude was crystallized from heptane to afford the pure titled compound. Yield: 75%. m.p.: 92–3°C, ^{1}HNMR, δ ($CDCl_3$) 2.35 (t, $J = 2.60$ Hz, 1H, ≡CH), 2.78 (s, 3H, Me), 4.48 (q, $J = 2.6$ Hz, 2H, CH_2), 8.23 (s, broad, 1H, NH); IR $\tilde{\nu}$ (KBr disc) 3400, 3300, 1600, 1510, 1290 cm^{-1}, MS, m/z, M^+ 225.

3,7-Dimethyl-8-nitro-5H-imidazo[1,2-*c*]pyrimidin-5-one (5)

Compound **3** (2.27 g, 0.01 mol) was dissolved in conc. H_2SO_4 (10 mL). The reaction mixture was kept at −4°C for 4 h. The reaction mixture was poured into crushed ice and neutralized with the addition of sodium hydroxide. The organic materials were extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude was directly subjected to column chromatography using $CHCl_3$/MeOH 90:10 as eluent to obtain the titled compound. Yield: 54%. m.p. >235°C, ^{1}HNMR, δ ($CDCl_3$) 2.27 (s, 3H, Me), 2.8 (s, 3H, Me), 6.7 (s, 1H, proton of imidazole), 12.3 (s, broad, NH, removed by treatment with D_2O); FT-IR $\tilde{\nu}$ (KBr disc) 2990, 1660, 1590 cm^{-1}, MS, m/z, M^+ 191.

2-Morpholino-4-propargylamino-5-nitro-6-methylpyrimidine (7)

Compound **3** (2.26 g, 0.01 mol) and morpholine (1.74 g, 0.02 mol) were refluxed in $CHCl_3$ (20 mL) for 11 h. The progress of the reaction was

monitored by TLC. The reaction mixture was poured in water, and separated. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was crystallized from MeOH. Yield: 65%. m.p. >157–158°C, ^{1}HNMR, δ ($CDCl_3$) 2.23 (t, J = 2.6 Hz, 1H, ≡CH), 2.69 (s, 3H, Me), 3.74 (m, 4H, 2 NCH_2), 3.89 (m, 4H, 2 OCH_2), 5.8 (dd, $J = 2.6$, 2H, CH_2), 8.7 (s, broad, 1H, NH); IR $\tilde{\nu}$ (KBr disc) 1590, 1100 cm^{-1}, MS, m/z, M^+ 275.

3,7-Dimethyl-5-morpholino-8-nitroimidazolo[1,2-*c*]pyrimidine (8)

Compound **7** (2.76 g, 0.01 mol) and conc. H_2SO_4 (10 mL) were stirred for 4 h at −4°C. After completion of the reaction, the mixture was poured into crushed ice, neutralized with NaOH, and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The crude was directly subjected to column chromatography using $CHCl_3$/MeOH (90/10) as an eluent to afford the titled compound. Yield: 40%. m.p. >216–217°C, ^{1}HNMR, δ ($CDCl_3$) 2.5 (s, 3H, Me), 2.7 (s, 3H, Me), 3.7 (m, 4H, 2 NCH_2), 3.9 (m, 4H, 2 OCH_2); MS, m/z, M^+ 276.

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