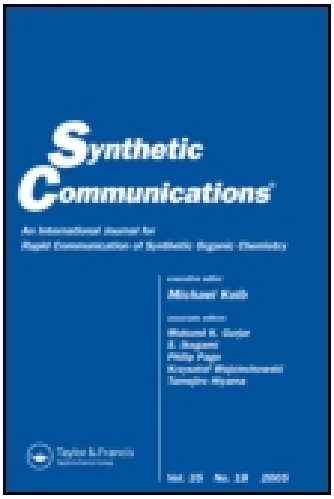

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DBU: An Efficient Base Catalyst for Synthesis of the New Oxazolo[5,4-d]pyrimidine Derivatives

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DBU: AN EFFICIENT BASE CATALYST FOR SYNTHESIS OF THE NEW OXAZOLO[5,4-D]PYRIMIDINE DERIVATIVES

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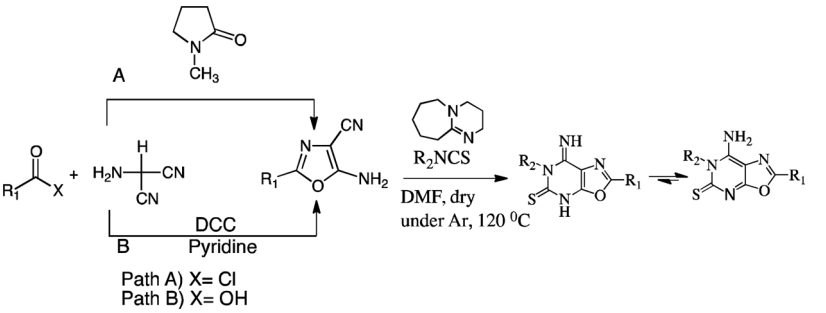
GRAPHICAL ABSTRACT



Abstract *New types of oxazolo[5,4-d]pyrimidines were synthesized via 1,8-diazabicyclo-[5,4,0]undec-7-ene-catalyzed heteroannulation of 2-substituted 5-amino-4-cyano-1,3-oxazoles with various isothiocyanates.*

Keywords Aminomalononitrile tosylate; 1,8-diazabicyclo[5,4,0]undec-7-ene; 1,3-dicyclohexylcarbodiimide; heteroannulation; isothiocyanate; oxazolopyrimidine

INTRODUCTION

The 1,3-oxazole framework represents an important structural motif in a number of biological activities and pharmaceuticals,[1] including anticancer and anti-HIV/AIDS activity.[2] Thus, a number of methods for their synthesis have been reported in the literature that mainly involve reactions of aminomalononitrile tosylate (AMNT) with various aryl or alkyl acid chlorides and acid anhydrides.[1,3] Also, oxazolopyrimidine derivatives are known subunits in many biologically active compounds, as well as in receptor tyrosine kinase such as VEGFR2 (vascular endothelial

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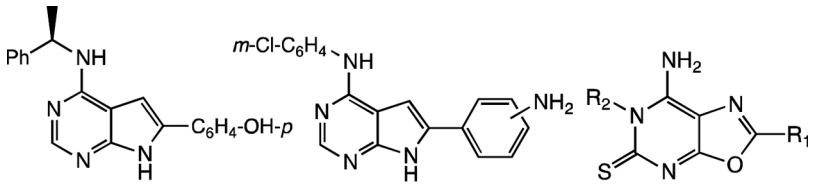


1 2 3

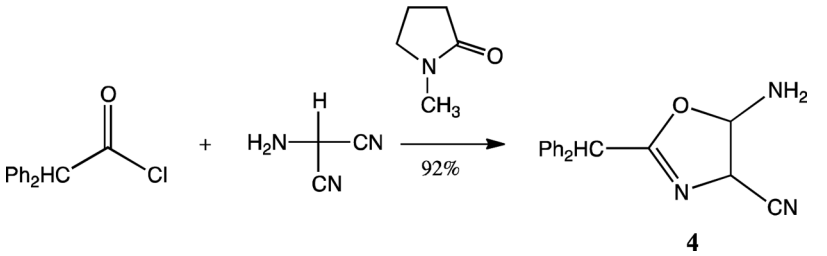
Figure 1. Pyrrolopyrimidines were shown to be potent EGFR inhibitors[5] and the proposed general structure of the oxazolopyrimidine structure.

growth factor receptor 2, KDR) or EGFR (epidermal growth factor receptor) that play crucial roles in a variety of diseases, such as cancer.[4] Recently, some pyrrolopyrimidines were shown to be potent EGFR inhibitors,[5,6,9] such as compound **1** and **2**. Thus, it is expected that the resulting compounds would show biological activity. Compound **3** depicts the general structure of the target oxazolopyrimidine (Fig. 1). Bicyclic pyrimidine ring system can be prepared by various cyclocondensation procedures such as two major routes, either starting from 5-amino 4-cyano-oxazoles or in three steps from commercially available 5-amino-4,6-dihydroxy-pyrimidine.[4–9] In connection with an ongoing synthesis program, we are interested in the development of a new route for the preparation of new types of oxazolo[5,4-d]pyrimidines via 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU)–catalyzed heteroannulation of 2-substituted 5-amino-4-cyano-1,3-oxazoles with various isothiocyanates. DBU has been recognized as a strong hindered organic base with low nucleophilicity and it finds increasing use in the synthesis.[10–13] The use of DBU is evidently advantageous over the commonly used strong bases such as lithium diisopropylamide or lithium bis(trimethylsilyl)amide (LHMDS), with which low temperatures must be employed.

To the best of our knowledge, there are no literature precedents for using DBU as the base in generation of the new oxazolo[5,4-d]pyrimidines derivatives via condensation of highly functionalized 1,3-oxazoles with various isothiocyanates.

RESULTS AND DISCUSSION

In continuation of our investigation for the synthesis of 1,3-oxazole derivatives,[14] we now introduce new types of highly functionalized 1,3-oxazoles. Thus, a solution of aminomalononitriletosylate (AMNT) in 1-methyl-2-pyrrolidinone was reacted with corresponding aryl acid chloride at room temperature (Scheme 1). The standard procedure worked especially well in yielding the desired products **4** (yield 92%), although long reaction times (around 7 days) were required. For the other procedure used to synthesize **5**, we employed aminomalononitriletosylate (AMNT) in pyridine with corresponding carboxylic acid at room temperature. The carboxyl activating reagent, 1,3-dicyclohexylcarbodiimide (DCC), was used to synthesize compounds **5** (Scheme 2). This convenient method affords 5-amino-4-cyano-2-(4-nitrophenyl)-1,3-oxazole **5** directly from acids and AMNT and avoids the prior step of preparation of acid chlorides. The DCC coupling method has broader applications. For example, 2-hydroxy oxazole can be prepared directly from



4

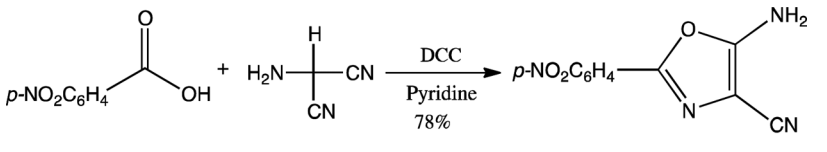
Scheme 1. Synthesis of the 5-amino-2-benzhydryl-4-cyano-1,3-oxazole (**4**).

hydroxyl acids. All new compounds communicated in this work showed good analytical and spectroscopic data (see Experimental). Furthermore, the ^{13}C NMR spectra have been assigned via heteronuclear multiple bond correlation (HMBC) and heteronuclear single quantum coherence (HSQC) experiments and are in good agreement with those previously reported for other 1,3-oxazoles.

The target oxazolopyrimidines can be synthesized via one major routes, starting from 5-amino-4-cyano-1,3-oxazoles by employing 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) under argon using aryl and alkylisothiocyanates (Scheme 3). When this reaction was repeated at room temperature, no desired product formation was observed. However, the product formation was also observed when the reaction was carried out in DMF at 60 °C using excess of DBU. The yield was inferior (50%), however, and the reaction were not completed even after overnight. Thus, refluxing all the components in presence excess of DBU in DMF at 120 °C proved to be optimum conditions for this reaction. Under these conditions, the reaction with 1,3-oxazoles (**4** and **5**) afforded the forecasted products (**6** and **7**) in good yields (81–90%).

Careful literature analysis revealed that a variety of bases with pk_a ranges from 4 to 11 have been used for some condensation reactions. We speculated that use of neutral organic bases that have high basicity, and can form a stable protonated species, may suppress other side reactions. DBU fulfills these requirements and has been used in many organic transformations in recent years.[15] it is a sterically hindered amidine base and especially useful where side reactions due to the inherent nucleophilicity of a basic nitrogen are a problem.[16] DBU is one of the strongest organic neutral base ($pk_a = 12$) and the effect of the adjacent nitrogen stabilizes the protonated species.

Relying on the concept of DBU catalysis, we believe that greater basicity and stability of DBU-H^+ effectively increases the efficiency of the reaction.[17,18] The structures of these compounds have been confirmed by spectroscopic analysis (see



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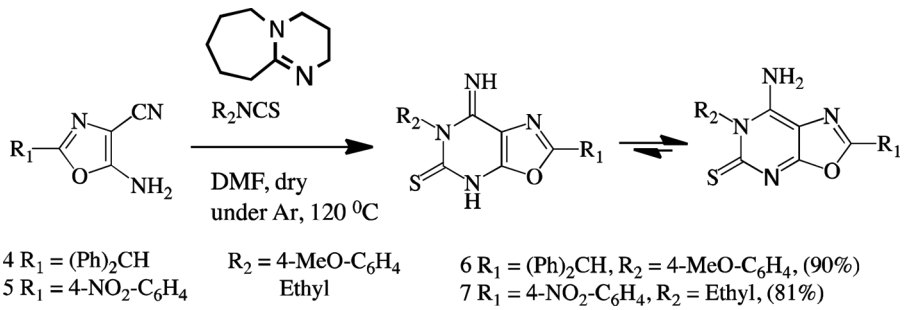
Scheme 2. Synthesis of the 5-amino-4-cyano-2-(4-nitrophenyl)-1,3-oxazole (**5**).



Scheme 3. Synthesis of the oxazolo[5, 4-d]pyrimidine-5(4H)-thiones analogs **6** and **7**.

Experimental). For example, the IR spectrum of compound **6** was devoid of the stretching vibration bands at 3341, 3310, and 2220 cm^{-1} for NH_2 and CN absorption of the precursor but instead showed new absorption bands at 3392, 3330, 1692, and 1257 cm^{-1} for NH_2, C=N, and C=S groups, respectively. The ^1H NMR spectra in dimethylsulfoxide (DMSO-d_6) showed two broad singlets at 9.90 and 5.06 due to NH_2 and CH groups respectively, as well as a singlet 3.68 corresponding to methyl group and the characteristic signals at 7.14–7.48 for phenyl groups. High-resolution mass spectra of the compound **6** showed the molecular ion peak at m/z 441.138 and 439.123 corresponding to the MH^+ and $M\text{-}H^+$, respectively.

EXPERIMENTAL

Reactions were monitored by thin-layer chromatography (TLC) using precoated silica-gel aluminum plates. Detection was done by ultraviolet (UV) (254 nm) followed by dipping in either sulfuric acid in EtOH (10%) or 0.5% phosphomolybdic acid in 95% EtOH solutions and subsequent charring at 200 °C or dipping in a 1% aqueous potassium permanganate solution and air drying. Anhydrous $MgSO_4$ was used to dry organic solutions during workup, and the removal of solvents was carried out under vacuum with a rotary evaporator. Melting points were determined on a Buchi510 and are uncorrected. IR spectra were obtained on a Bruker Alpha-P FTIR Diamond ATR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker 400 spectrometer, using tetramethylsilane as internal standard. All the assignments for proton and carbon were made via two-dimensional correlation spectroscopy (2D COSY), HSQC, and HMBC experiments. High-resolution mass spectra were obtained by a Thermo Scientific Exactive High Resolution MS (ESI probe).

Procedure for the Synthesis of 5-Amino-2-benzhydryl-4-cyano-1,3-oxazole (4)

In continuation of our investigation for the synthesis of 1,3-oxazole derivatives,[12] 1.0–1.1 equiv of the diphenylacetyl chloride was added in one portion to a stirred solution of aminomalononitrile tosylate (AMNT) (2.71 g, 8.60 mmol) in 1-methyl-2-pyrrolidinone (20 mL). The reaction mixture was stirred at room temperature until the reaction was complete. Then, the mixture was diluted with a

mixture of EtOAc and Et_2O (1:1) and washed with water, 10% aqueous $NaHCO_3$, and water. The organic layer was dried, the solvent was evaporated in vacuo, and the crude product was purified by flash silica-gel chromatography (1:1, PE/EtOAc).

5-Amino-2-benzhydryl-4-cyano-1,3-oxazole (4)

Yield (92%) as white crystals; mp 163–166 °C; IR ν_{max} 3341, 3310, 3139, 2923, 2852, 2220, 1660, 1591, 1158, 696, 744 cm^{-1};^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.70 (br s, NH_2, 2 H), 7.2–7.4 (m, $10H_{arom.}$), 5.59 (s, CH, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.34 (C5), 152.65 (C2), 139.49 (2 C, 2C1′), 128.55 (4 C, 2C3′, 2C5′), 128.44 (4 C, 2C2′, 2 C6′), 127.13 (2 C, 2 C4′), 115.44 (CN), 82.52 (C4), 49.23 (CH). HR MS: m/z calcd. for $C_{17}H_{12}ON_3$ (M-H^+) 274.099; found 274.098; m/z calcd. for $C_{17}H_{14}ON_3$(MH^+) 276.113; found 276.113.[12]

Procedure for the Synthesis of 5-Amino-4-cyano-2-(4-nitrophenyl)-1,3-oxazole (5)

4-Nitrobenzoic acid (1.39 g, 8.15 mmol) and 1, 3-dicyclohexylcarbodiimide (DCC), (1.77 g, 8.6 mmol) were added to a stirred solution of aminomalononitrile tosylate (AMNT) (2.71 g, 8.60 mmol) in pyridine (40 mL), and the reaction mixture was stirred at room temperature until the reaction was complete. The white precipitate (dicyclohexylurea) was removed by filtration and the filtrate was concentrated in vacuo to give a residue, which was purified by flash silica-gel chromatography (1:1, PE/EtOAc) to give product **5**.

5-Amino-4-cyano-2-(4-nitrophenyl)-1,3-oxazole (5)

Yield (78%) as yellow crystals: mp 274–277 °C; IR ν_{max} 3285, 3227, 2221, 1668, 1597, 1514, 1319, 1057, 852 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.26 (br s, NH_2, 2 H), 8.33 (dd, $^3J = 8.8$ Hz, H2′, H6′, 2 H), 7.95 (dd, $^3J = 8.8$ Hz, H3′, H5′, 2 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.8 (C5), 147.47 (2C, C2, C4′), 131.27 (C1′), 125.74 (2C, C2′, C6′), 124.50 (2C, C3′, C5′), 114.87 (CN), 85.54 (C4). HR MS: m/z calcd. for $C_{10}H_5O_3N_4$ (M-H^+) 229.037; found 229.036.[12]

General Method for the Synthesis of Oxazolo[5,4-d]pyrimidine-5(4H)-thiones (6 and 7)

The corresponding aryl and alkylisothiocyanates (0.8–0.95 equiv.) and the oxazoles **4** and **5** (1.0 equiv.) were added to a solution of DBU (1.0–1.1 equiv) in dry DMF (5 mL) under argon. The mixture was reacted at 120 °C until the reaction was complete. Thus, water and a solution of HCl (1 M) were added until PH 9. Then, the precipitate was filtered off and purified to give compound **6** and **7**.

7-amino-2-benzhydryl-6-(4-methoxyphenyl)-oxazolo[5,4-d]-pyrimidine-5(4H)-thione (6)

Yield (90%) as white crystals; mp 273–276 °C; IR ν_{max} 3392, 3330, 2954, 2852, 1692, 1509, 1257, 693, 738 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.90 (br s, NH_2,

2 H), 7.46 (m, 2 H4′, 2 H), 7.31 (m, 2 H3′, 2 H5′, 4 H), 7.23 (m, 2 H2′, 2 H6′, 4H), 7.15 (m, H3″, H5″, 2H), 6.73 (d, H2″, H6″, 2H), 5.06 (s, CH, 1 H), 3.68 (s, CH_3, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.27, 158.9 (C2), 154 (C3a), 150 (2 C, C7, C4″), 114 (C7a), 140 (2 C, 2C1′), 131 (2 C, C2″, C6″), 129 (4 C, 2C3′, 2C5′), 128.4 (4 C, 2 C2′, 2 C6′), 128.5 (C1″), 127 (2 C, 2 C4′), 110.86 (2C, C3″, C5″), 55 (CH_3), 50 (CH); HR MS: m/z calcd. for $C_{25}H_{21}O_2N_4S$ MH^+ 441.138; found 441.138; and m/z calcd. for $C_{25}H_{19}O_2N_4S$ $M\text{-}H^+$ 439.123; found 439.123.[12]

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SUPPLEMENTARY MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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