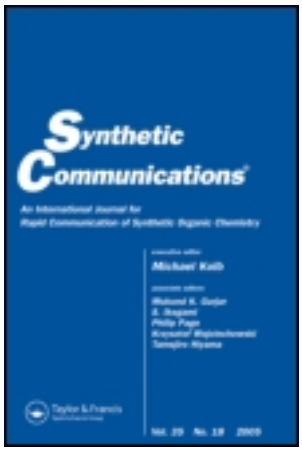

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Convenient Preparation of Novel Fused Tri-heterocyclic Compounds

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ABSTRACT

Novel pyrazolotriazolopyrimidine and dipyrazolopyrimidine fused tri-heterocyclic compounds were prepared in a convenient method and in good yields. The structures of the title compounds were confirmed by elemental analysis, ^{1}H NMR, ^{13}C NMR, IR and MS. Preliminary bioassay study showed that some compounds displayed high inhibition to mosquito (10 ppm).

Key Words: Pyrazole; Condensation; Pyrazolotriazoloyrimidine; Dipyrazolopyrimidine; Biological activity.

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INTRODUCTION

Study of fused heterocyclic compounds is an attractive field for both academic interests and the diverse applications of these compounds. Many pyrazole fused heterocyclic compounds have been found to exhibit biological activity and were widely studied in pesticide and medicine,[1–4] for example, pyrazinoxindoles are protein kinase inhibitors,[5] and pyrazolotriazolopyrimidines are antagonists of the human A_3 adenosine receptor.[6]

In this letter, we undertake the synthesis of novel fused tri-heterocyclic compounds containing a pyrazole moiety in order to get the compounds which possess novel structure and high biological activity. Our work started from 1-substituted-3-methyl-5-chloropyrazole-4-carboxylic acid **1**[7] Acylation of **1** by thionyl chloride, 1-substituted-3-methyl-5-chloropyrazole-4-carbonyl chloride **2** was got in high yields. Then **2** reacted with 3-substituted-5-aminotriazole, two kinds of 1*H*-pyrazole-4-carboxamides **3** and **4** were prepared in different condition. When heated at 80°C in DMSO with K_2CO_3, **3** or **4** was condensed to give product **5** or **6** respectively, general route is shown in Sch. 1.

DISCUSSION

The route allows facile introduction of aminotriazole or aminopyrazole substituents in the 4-position (formyl) of the 5-chloropyrazoles and flexibility for the construction of novel pyrazolotriazolopyrimidine or dipyrozolopyrimidine fused tri-heterocyclic systems. Many problems in the experiment were resulted, discusses in following.

Get Fused Tri-heterocyclic Compound

The synthesis of pyrazolo [3, 4-d] [1, 2, 4] triazolo [1, 5-a] pyrimidine **5** gave a particular problem. Our initial efforts in the presence of various basic catalysts such as DBN or NaH to obtain **5m** did not succeed under many conditions. When using sodium hydride catalyzed **3m** to synthesize fused tri-heterocyclic compound, a new compound was produced, but it was transacylated product **4m** rather than the expected product **5m**, as shown in Sch. 2. The detailed transacylation was reported in another article[8] and the study of transacylative mechanism is in progress. When **3m** with K_2CO_3 in DMSO was heated at 80°C for 6 h, to our surprised, only one product was produced, which was characterized as 1,7-diphenyl-3-methyl-1H-pyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidine-4(9H)-one **5m** by spectral data.

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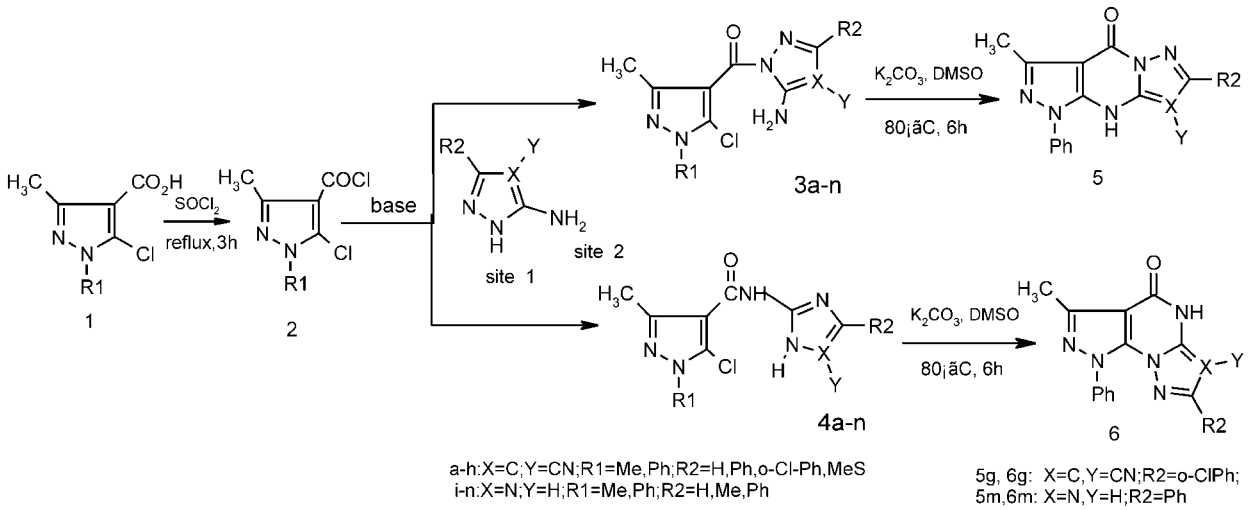

Scheme 1.

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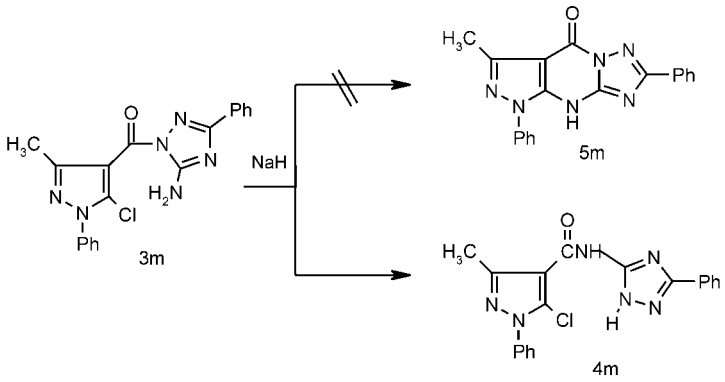

Scheme 2.

The corresponding **3g, 4m** and **4g** were reacted smoothly under identical conditions to afford the corresponding **5g, 6m** and **6g** (Sch. 1) in 88%, 81% and 98% yields, respectively.

Distinguish 5 and 6

5 and **6** have similar structures. They have very similar orders of chemical shifts in ^{1}H NMR, and their mass spectra showed the similar fragmentation pattern. But their infrared absorption displayed a slightly difference, amide-carbonyl group of **6m** absorbed at 1681 cm^{-1}, **6g** absorbed at 1693 cm^{-1}, and carbonyl group of **5m** absorbed at 1670 cm^{-1}, **5g** absorbed at 1683 cm^{-1}. The latter **5** absorbed at a lower frequency about 10 cm^{-1} than the former **6** due to the lack of conjugation. **5** and **6** can be distinguished by these.

Confirm the New Structure

Which element of the pyrimidine ring will **6m** or **6g** bearing active hydrogen adjoin, oxygen or nitrogen? The infrared spectra showed amide rather than hydroxyl group absorptions. This indicated the preponderance of the amide over the imidic acid tautomer of the compounds in their solidity, the active hydrogen adjoins nitrogen of the pyrimidine ring, as shown in Sch. 3.

Bioactivities of some new compounds were evaluated in vivo. A preliminary bioassay study showed that **6m** displayed high inhibition to mosquito (10 ppm) (no data).

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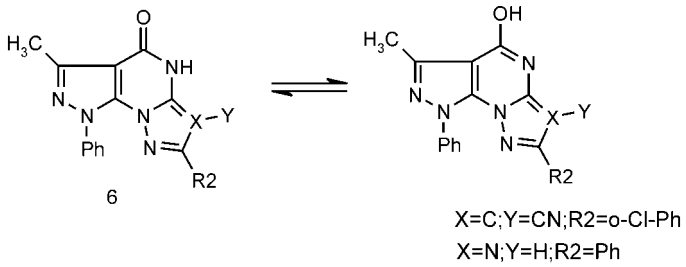

Scheme 3.

In summary, we have demonstrated a base-mediated to synthesize novel structural pyrazolotriazolopyrimidine and dipyrazolopyrimidine. These protocols are especially attractive as they allow for the synthesis of fused tri-heterocyclic systems in mild conditions. Expanding the scope of this methodology will be useful to the synthesis of other interesting heterocyclic compounds.

EXPERIMENTAL

Melting points were determined with a model Yanaco MP-500 apparatus and uncorrected. IR spectra were recorded on a Nicolet Magna-IR 750 spectrometer in Nic-Plan IR microscope-54183. ^{1}H NMR spectra were recorded on a Bruker APX400 spectrometer with TMS as internal standard. Elemental analyses were carried out on a Yanaco MT-3 instrument. Mass spectra were obtained on an HP 5989 mass spectrometer (EI).

The solvents were available commercially and were purified according to conventional methods. Substituted pyrazoleamides **3a-n** and **4a-n** were prepared according to the literature.[8]

1,7-Diphenyl-3-methyl-1H-pyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidine-4(9H)-one (5m). A solution of 1.51 g (4mmol) **3m**, 0.55 g (4 mmol) K_2CO_3, 20 ml DMSO were stirred at 80°C until compound **3m** was consumed (checked by TLC). The reaction mixture was cooled and mixed with water (50 ml), then the mixture was acidified to pH = 7 with 10% HCl, white precipitate resulted. The precipitate was filtered off, washed with water and finally recrystallized from DMF/ethanol(3/1). 1.11 g of the desired product **5m**, corresponding to 63%, was obtained. Mp > 280°C; IR (microscopy) 3261, 1670 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.52 (s, 3H, 3-CH_3), 7.38–7.92 (m, 10 H, 2 Ph); MS m/z 342 (M^+, 100), 225 (29.0), 77 (86.0). Anal. calcd. for $C_{19}H_{14}N_6O$ (342.36): C, 66.66; H, 4.12; N, 24.55. Found: C, 66.35; H, 3.95; N, 24.49.

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5g, **6g** and **6m** were prepared in the same method of **5m**.

1-phenyl-3-methyl-7-(o-chloro)phenyl-8-cyano-1H-dipyrazolo[1,5-a:3′,4′-d]pyrimidine-4(9H)-one (**5g**). White solid; mp $> 280^{\circ}$C; yield 88%; IR (microscopy) 2228, 1683 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.50 (s, 3H, 3-CH_3), 7.47–7.70 (m, 9H, 2Ph); MS m/e 400 (M^+, 100), 365 (14.0), 225 (9.0), 77 (39.0). Anal. calcd. for $C_{21}H_{13}N_6OCl$ (400.83): C, 62.93; H, 3.27; N, 20.97. Found: C, 62.73; H, 3.15; N, 20.70.

1-Phenyl-3-methyl-6-cyano-7-(o-chloro)phenyl-1H-dipyrazolo[1,5-a:4′, 3′-e]pyrimidine-4(5H)-one (**6g**). White solid; mp $> 280^{\circ}$C; yield 98%; IR (microscopy) 2228, 1693 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.54 (s, 3H, 3-CH_3), 7.47-7.70 (m, 9H, 2Ph); MS m/e 400 (M^+, 100). Anal. calcd. for $C_{21}H_{13}N_6OCl$ (400.83): C, 62.93; H, 3.27; N, 20.97. Found: C, 62.96; H, 3.25; N, 20.95.

1,8-Diphenyl-3-methyl-1H-pyrazolo[4,3-e][1,2,4]triazolo[2,3-a]pyrimidine-4(5H)-one (**6m**). White solid; mp $> 280^{\circ}$C; yield 81%; IR (microscopy) 1670cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 2.51 (s, 3H, 3-CH_3), 7.38–7.91 (m, 10H, 2Ph); MS m/e 342 (M^+, 100). Anal. calcd. for $C_{19}H_{14}N_6O$ (342.36): C, 66.66; H, 4.12; N, 24.55. Found: C, 66.47; H, 4.40; N, 24.50.

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