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# Reactions of 5-aminopyrazole with Active Methylene Compounds:Synthesis of Pyrazolo[3,4-*b*]pyridine Derivatives

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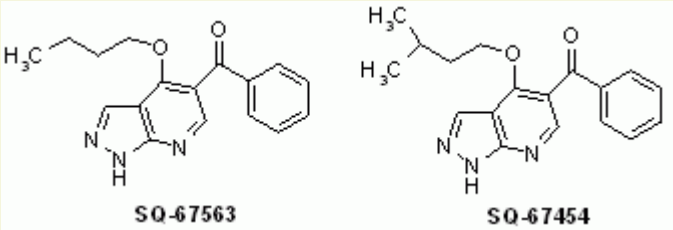
**Abstract:**

A series of pyrazolo[3,4-*b*]pyridine derivatives was synthesized by *knoevenagel condensation* of 5-aminopyrazoles aroylacetonitriles and triethyl/methylorthoesters and also by *Conrad-limpach* reaction of 5-aminopyrazole and ß-keto esters.

**Introduction:**

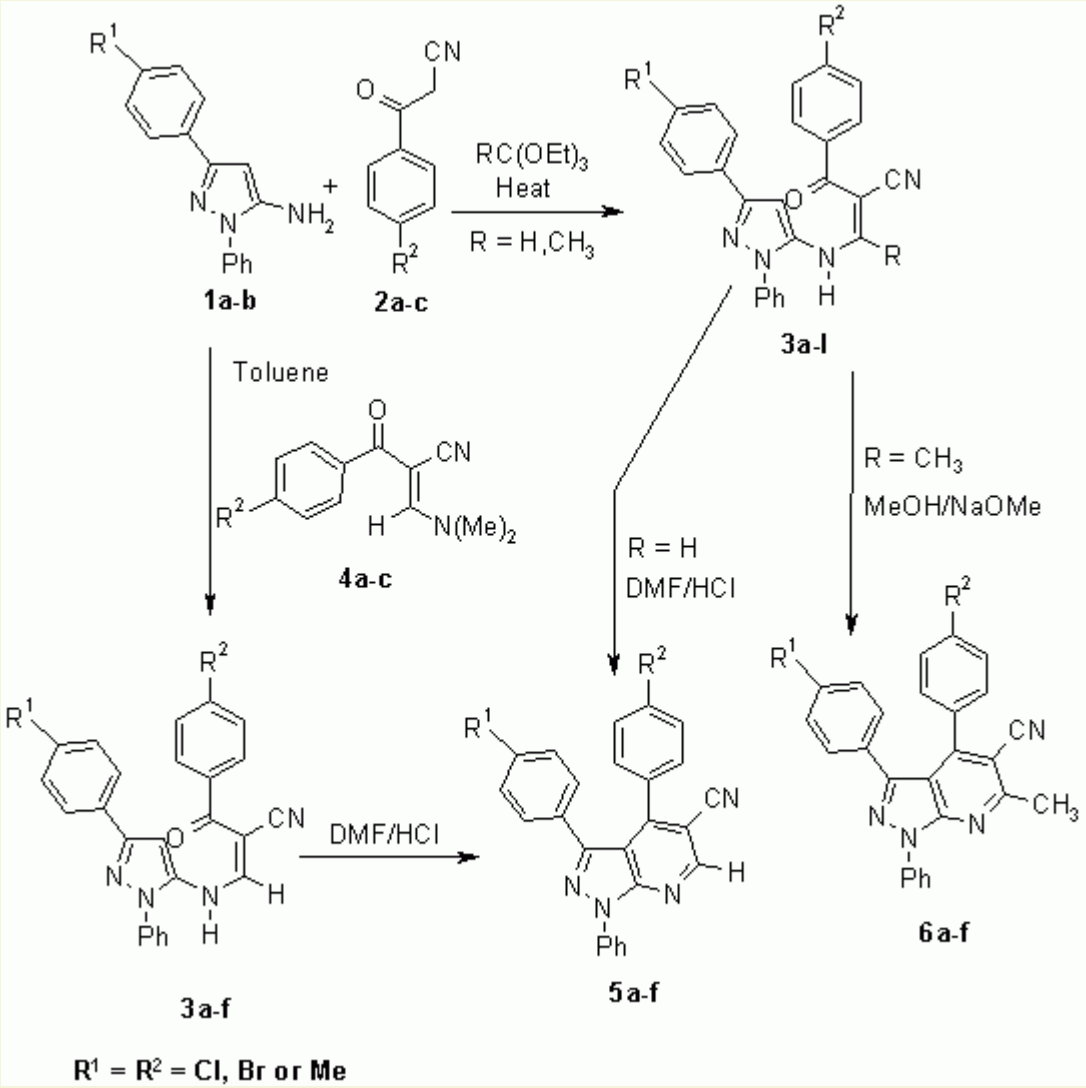
Pyridine ring annulated to the pyrazole ring i.e. pyrazolo[3,4-*b*]pyridines as aza-analogues of indazoles [1] are attractive targets in organic synthesis due to there interesting biological and pharmacological properties [2] such as vasodialotors, hypoglycemic, anti-inflammatory, analgesic and anti-pyritic, ACTH(adrenocorticotropic hormone) releasing factor (CRF(Corticotropin-releasing factor)) antagonist activity. CRF antagonists are believed to be effective in the treatment of a wide variety of stress-releated illness, such as depression, Alzheimers's disease, gastro intestinal diseases anorexia nervosa, haemorrhaged stress drug and alcohol withdrawal Symptoms, drug addition and infertility [3]. Dihydro pyrazolo[3,4-*b*]pyridines have also shown anti-hypertension activities and produced prophylactic effect as calcium antagonists in stroke-prone spontaneously hypertensive rats [4] and even been used as dyes [5] These compounds also exhibit interesting agriculture activities [6]. Recent search of literature reveals that the pyrazolo[3,4-*b*]pyridines **SQ-67563** and **SQ-67454** has been identified as a potent, selective of CDK inhibitors and are potent inhibitors of glycogen synthase kinase-3(GSK-3) [7].




**Result and Discussion:**

5-aminopyrazole were synthesized from p-substituted aroylacetonitriles, a class of compounds which was recently studied by us for other reactions [8] Pyrazolopropene/butenenitrile **3** was obtained by one pot condensation of 5-aminopyrazole **1** triethylorthoformate/acetate and aroyl acetonitriles **2** in quantitative yields. However 5-aminopyrazole **1** when refluxed in toluene with 3-aryl-2-(N,N-dimethylamino)methylene-3-oxopropanenitriles [9] afforded pyrazolopropenenitrile **3a-f** in good

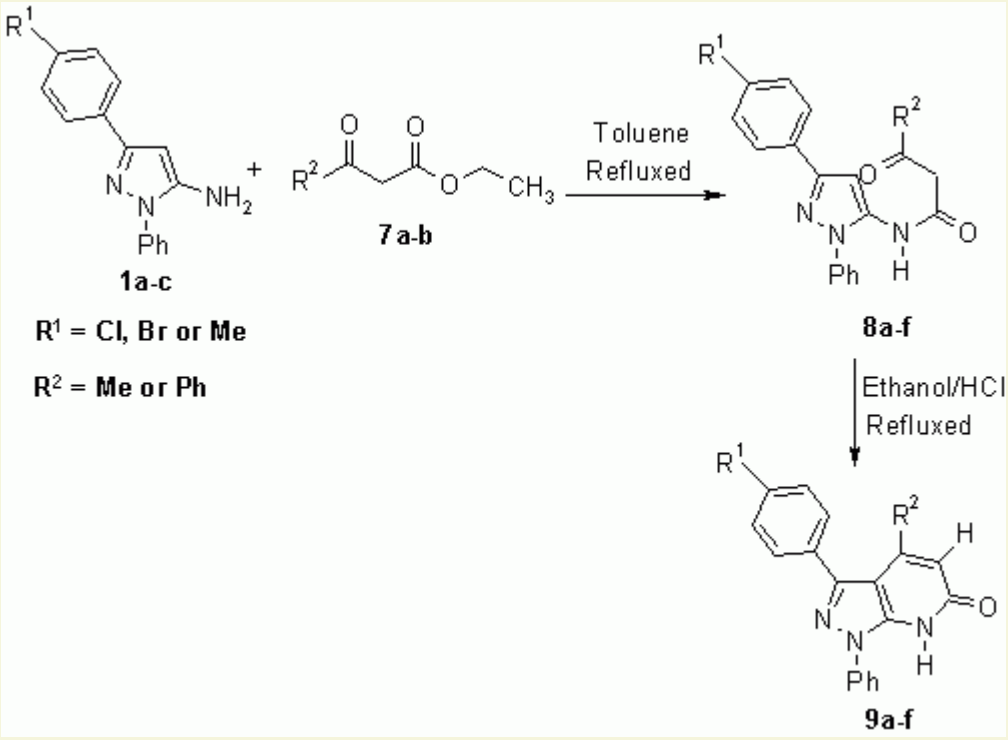
yields. pyrazolopropenenitriles could be cyclised in acidic medium to furnished 4-(aryl)-3-(aryl)-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile derivatives **5**. while pyrazolobutenenitriles could be cyclised in basic medium to furnished 4-(aryl)-3-(aryl)-6-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile **6** in good yield. (Scheme 1)




**Scheme 1**

5-aminopyrazoles **1** when condensed with ß-keto esters **2** in toluene by *conrad-limpach* reaction we isolate intermediate N-[3-(aryl)-1-phenyl-1Hpyrazol-5-yl]-3-oxo-3-phenylpropanamide/oxobutanamide **8** in quantitative yield which was could be cyclised in ethanolic HCl to furnished 3-(aryl)-4-methyl-1-phenyl-1,7-dihydro-6H-pyrazolo[3,4-*b*]pyridin-6-one or 3-(aryl)-1,4-diphenyl-1,7-dihydro-6H-pyrazolo[3,4-*b*]pyridin-6-one derivatives **9** in good yields. (Scheme 2)

All compounds were characterised by IR, NMR spectroscopy and elemental analysis.




**Scheme 2**

**Experimental Section**

*Procedure for synthesis of pyrazolopropenenitriles or pyrazolobutenenitriles(3a-l).*

A mixture of 5-aminopyrazole **1** (0.01m), aroylacetonitrile **2** (0.01m) and triethylorthoformate or triethylorthoacetate (0.012m) was heated in waterbath(80-90 °C) for 2-4 hrs(TLC monitored), cool the reaction mixture, stir the mixture in petroleum ether(40-60) for one hour,solid was separated, filtered the solid, washed with excess of petroleum ether(40-60) and recrystallized from acetonitrile or DMF.

*Procedure for synthesis of pyrazolopropenenitriles Method B (3a-f).*

A mixture of 5-aminopyrazole **1** (0.01m) and 3-aryl-2-(N,N-dimethylamino)methylene-3-oxopropanenitriles **4** (0.01m) was refluxed in toluene for 5 hours(TLC monitored),then cool the reaction mixture, filtered the solid, washed with toluene and recrystallized from acetonitrile or DMF.

*Procedure for synthesis of 4-(aryl)-3-(aryl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile derivatives (5a-f).*

A solution of pyrazolopropenenitriles **3a-f** (0.001m) and DMF/HCl(1:1v/v) was refluxed for 6 hours(TLC monitored), cool the reaction mixture, filtered the solid, washed with DMF and recrystallized from ethyl acetate.

*Procedure for synthesis of 4-(aryl)-3-(aryl)-6-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (6a-f).*

A solution of pyrazolobutenenitriles **3g-l** (0.001m), dry methanol and sodium methoxide(0.12g sodium metal in dry methanol) was refluxed for 12 hours(TLC monitored), cool the reaction mixture, filtered the solid, washed with methanol and recrystallized from ethyl acetate.

*Procedure for synthesis of N-[3-(aryl)-1-phenyl-1Hpyrazol-5-yl]-3-oxo-3-phenylpropanamide/oxobutanamide (8a-f).*

5-amino pyrazole **1** (0.01m) and ß-keto esters **7** (0.01m) was refluxed in toluene for 10 hours, cool the reaction mixture, filtered the solid and recrystallized from ethanol.

*Procedure for synthesis of 3-(aryl)-4-methyl-1-phenyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one or 3-(aryl)-1,4-diphenyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one derivatives (9a-f).*

A mixture of N-[3-(aryl)-1-phenyl-1Hpyrazol-5-yl]-3-oxo-3-phenylpropanamide/oxobutanamide **8** (0.001m) was dissolve in ethanol(10ml) then add HCl(catalytic amount) and refluxed for 3-4 hours(TLC monitored), cool the reaction mixture, filtered the solid and recrystallized from ethyl acetate.

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