FACILE SYNTHESIS OF FLUORINATED 2-ARYL-5,7 BISALKYL PYRAZOLO PYRIMIDINES FROM ARYLALKYNE NITRILES[†]

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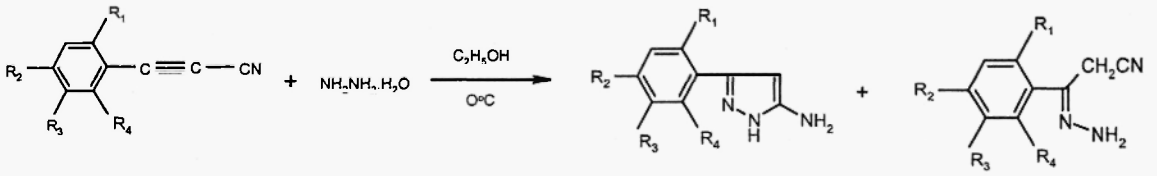
Abstract: Synthesis of pyrazolopyrimidines from fluorine substituted arylalkynenitriles is described. Arylalkynenitriles **1a-d** reacted with hydrazine to give 5-aryl-3-amino-2H-pyrazoles **2a-d**. The condensation of aminopyrazoles with 1,3-dicarbonyl compounds furnished pyrazolopyrmidines **7a-h** in good yield.

Introduction

Pyrazolopyrimidines are of considerable chemical and pharmacological importance as purine analogues,[1,2] and have antitumor, antileukemic activities. Pyrazolo[1,5-a] pyrimidines are having useful properties as antimetabolites in purine biochemical reaction.[3-5] The pyrazole containing compounds have practical applications in medicinal and agrochemical fields and the biological activity[6-8] of pyrazole and its derivatives is well documented. Pyrazole ring has shown to be the basic moiety for a number of dyes, drugs and anesthetics.[9,10] Amino and hydroxy substituted pyrazoles have been used as choline esterage inhibitors[11]. Our continued interest on the synthesis of fluorinated heterocycles,[12,13]prompted us to synthesise fluorinated aminopyrazoles and pyrazolo pyrimidines by an elegant method of nucleophilic addition of acetylenic nitriles with hydrazine. The intermediate amine pyrazole is reacted with various 1,3-dicarbonyl compounds, furnishing the pyrazolo pyrimidines.

Results and Discussion

Acetylenic nitriles are known to undergo not only 1,3-dipolar cyclo additions but also nucleophilic addition with hydrazines[14] to give aminopyrazoles or hydrazides. In the course of the chemistry of fluorinated alkynenitriles, we found that the addition of hydrazine to alkynenitrile **1** in ethanol at 0°C furnished cyclised product 3-amino-5-aryl pyrazole **2** as an exclusive product. Different fluorine substituted aryl alkynenitriles are utilized in the present investigation and obtained the cyclised pyrazoles. In contrast, 2,6-difluoro phenyl propynenitrile **1b** gave the uncyclised hydrazide **3** intermediate as the major product, the cyclised aminopyrazole **2b** being the minor component (scheme-1).



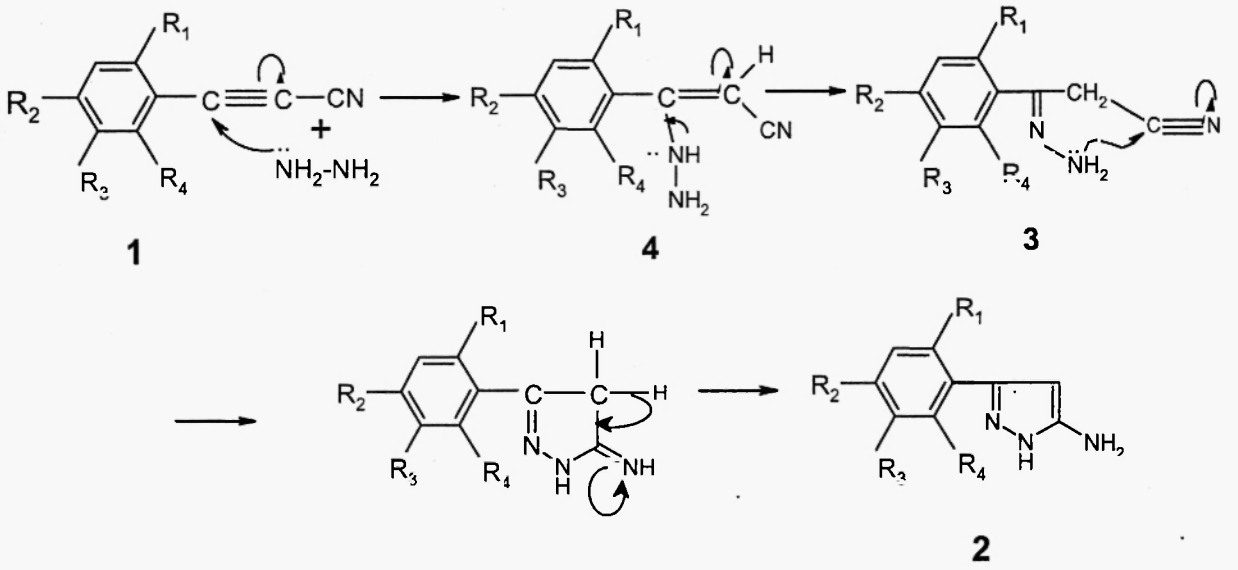
1a-d **2** **3**

a) R_1= R_3= R_4= H, R_2= F
b) R_1=R_4=F, R_2= R_3=H
c) R_1= R_2= R_3= F, R_4=H
d) R=R_2=R_3=R_4=H

Scheme-1

The IR spectra of amino pyrazoles **2a-d** showed the absence of peak in the region 2250-2260 cm-1 corresponding to nitrile group and presence of a broad absorption in the region 3410-3090cm-1 assignable to amine function. The PMR spectra of **2a-d** showed the characteristic signals at δ2.9 for two protons (-NH_2) which is exchangeable with D_2O and a singlet for pyrazole ring olefinic proton at δ5.7. The mass spectra revealed stable molecular ion and the characteristic loss of nitrogen by the fragmentation of pyrazole ring is observed in all the compounds **2a-d**. Based on the spectral data the compounds **2a-d** are characterized as fluoro substituted derivatives of 5-aryl-2H-pyrazole-3-yl-amine.

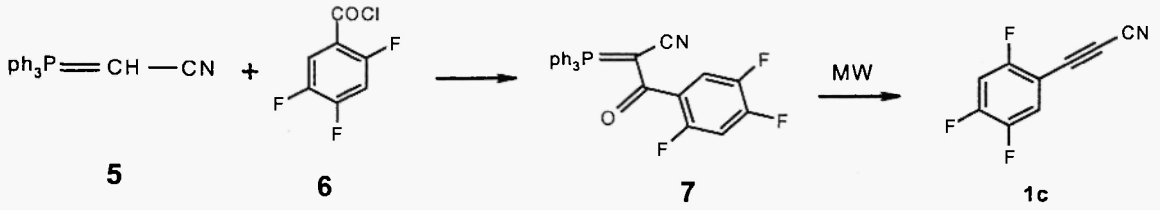
The plausible mechanism of formation of the arylamino pyrazoles **2a-d** may be explained by the initial Michael type addition of amino group on to the β-carbon of the alkynenitirle resulting in the alkenylhydrazide **4** intermediate. The latter further rearranges to give the β-cyanoalkylidene hydrazide **3**, which conveniently undergoes internal cycloaddition by the nucleophilic attack of the second amine on to the nitrile carbon to give the pyrazole imine, which upon aromatization ends up with the amino pyrazole **2a-d** as depicted in scheme-2.



Scheme – 2

The isolation of intermediate hydrazide **3** in one of the reactions **1b** along with the cyclised product confirms the mechanism showed above. The IR spectrum of 3 showed absorptions of 2240cm-1 and 3320cm-1 assignable to nitrile and amine respectively. The PMR spectrum is in agreement with the assigned structure and revealed a singlet at δ3.54 for two protons and a broad singlet at δ 5.47, which is exchangeable with D_2O, assigned to $-NH_2$ protons. The mass spectrum revealed molecular ion at *m/z* 196. The spectral data is in full agreement with the structure 3-(2,6-difluorophenyl)-3-hydrazino-propionitrile **3**.

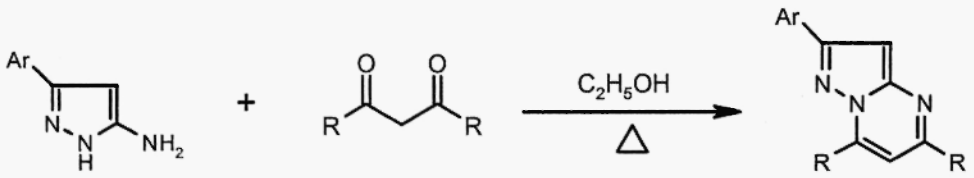
3-(2,4,5- trifluorophenyl) propynenitrile **1c** is a new compound and is prepared in good yield by the microwave irradiation of [(2,4,5-trifluorobenzoyl)-cyano methylene] triphenyl phosphorane **5c**. The oxo-ylide **7** is obtained by the acylation of cyanomethylene triphenyl phosporane **5** with 2,4,5-trifluoro benzoyl chloride in dichloromethane (scheme-3). The other acetylenic nitriles are similarly obtained from the corresponding oxo-ylides.[15]



5 6 7 1c

Scheme-3

The aminopyrazoles are active synthons and building blocks for many heterocyclic products. The presence of both primary and secondary amine functions in the same molecule is conveniently utilized in making hetero fused pyrazoles. The aminopyrazoles **2** when reacted with 1,3-dicarbonyl compound **8** in refluxing ethanol furnished the corresponding pyrazolopyrimidines **9**. The reaction is expected to go by the initial formation of a mono schiff's base which under the reaction conditions further cyclises to furnish the stable pyrazolopyrimidine **9** in good yield (scheme-4).



2 **8** **9**

a) Ar = 4-Fluorophenyl, R=CH_3.
b) Ar = 4-Fluorophenyl, R=CF_3.
c) Ar = 2,6-difluorophenyl, R=CH_3.
d) Ar = 2,6-difluorophenyl, R=CF_3.
e) Ar = 2,4,5-Trifluorophenyl, R=CH_3.
f) Ar = 2,4,5-Trifluorophenyl, R=CF_3.
g) Ar = phenyl, R=CH_3 (reported compound).
h) Ar = phenyl, R=CF_3 (reported compound).

Scheme-4

The IR spectra of compounds **9a-d** showed the disappearance of broad peak due to –NH protons in the range 3100-3400 cm^{-1} and carbonyl absorption is absent indicating that it is a cyclised product. The PMR spectra showed the characteristic protons of pyrazole and pyrimidine rings at δ 6.48 and δ6.7 respectively. The mass spectra revealed stable molecular ions and the loss of acetonitrile/trifluoro acetonitrile from molecular ion are observed in all the cases. The spectral data is in support for the assigned structure for the product **9** and characterized as 2-aryl-5,7-bisalkyl pyrazolo[1,5-a] pyrimidine **9a, 9b.**

We have, thus developed a straightforward route for the preparation of fluorinated aminopyrazoles and pyrazolo pyrimidines from aryl substituted alkyne nitriles, which are expected to be biologically important ring systems.

Experimental

General procedure for the preparation of 5-aryl-2H-pyrazole-3-yl-amine (2a-2d& 3)
Conjugated alkynenitrile **1** (0.002 mol) was dissolved in dry ethanol (2 ml), cooled to -5^0C, added hydrazine hydrate solution (0.002 mol) and allowed to stir for 1 hr. After completion of reaction ethanol was removed and the residue was dissolved in 10 ml of ethyl acetate, washed with water (5 ml), separated the organic layer and dried over sodium sulphate. The ethyl acetate solution was adsorbed on silicagel (100-200 mesh) and purified by column chromatography. Hexane and 3% ethyl acetate solvent mixture gave the corresponding amino pyrazole **2**.

5-(4-Fluorophenyl) 2H-pyrazole-3-yl-amine 2a.
Yield 85%. mp 154 °C. IR (KBr): 3410-3090, 2911, 1514 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 2.97 (br.s, 2H, NH_2), 5.70 (s, 2H), 7.02 (ddd, 2H, $^3J_{H-H}$=8.8, $^3J_{H-F}$=6.4, $^4J_{H-H}$=2.2 Hz, 2H), 7.61 (ddd, 2H, $^3J_{H-H}$=8.8, $^4J_{H-F}$=5.3, $^4J_{H-H}$=2.1 Hz, 2H). EIMS *m/z* (relative intensity) 177 (M^+, 100), 176 (12), 149 (8), 148 (75). Anal. Calcd. for $C_8H_8FN_3$ C, 61.01; H, 4.55; N, 23.72. Found: C, 60.99; H, 4.56; N, 23.71%.

5-(2,6-Difluorophenyl)- 2H-pyrazole-3-yl-amine 2b.
Yield 85%. mp 128 °C. IR (KBr): 3409-3111, 2910, 1525 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 5.41 (s, 1H), 6.26 (br.s, 2H), 7.23-7.42 (m, 3H). EIMS *m/z* (relative intensity) 195 (M^+, 80), 178 (100). Anal. Calcd. for $C_9H_7F_2N_3$ C, 55.39; H, 3.61; N, 25.53. Found: C, 55.73; H, 3.87; N, 25.70%.

5-(2,4,5-Trifluorophenyl) 2H-pyrazole-3-yl-amine 2c.
Yield 79%. mp 132 °C. IR (KBr): 3406-3100, 2911, 1514 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 3.77 (br.s, 2H), 5.92 (s, 1H), 7.02 (m, 1H), 7.43 (m, 1H). EIMS *m/z* (relative intensity) 213 (M^+, 60), 184 (45), 156 (100). Anal. Calcd. for $C_9H_6F_3N_3$ C, 50.71; H, 2.84; N, 19.71. Found: C, 50.73; H, 2.87; N, 19.70%.

5-Phenyl- 2H-pyrazole-3-yl-amine 2d.
Yield 76%.mp 145 °C. IR (KBr): 3380-3100, 2928, 1369 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 2.92 (br.s, 2H), 5.92 (s, 1H), 7.45 (s, 3H), 7.74 (m, 2H). EIMS *m/z* (relative intensity) 159 (M^+, 35), 131 (100). Anal. Calcd. for $C_9H_9N_3$ C, 67.91; H, 5.70; N, 26.90. Found: C, 67.92; H, 5.73; N, 26.88%.

3-(2,6-Difluorophenyl) 3-hydrazino propionitrile 3.
Yield 81%. mp 126 °C. IR (KBr): 3210, 2925, 2340 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 3.54 (s, 2H), 5.47 (br.s, 2H), 7.04 (m, 2H), 7.46 (m, 1H). EIMS *m/z* (relative intensity) 195 (M^+, 25), 155 (100). Anal. Calcd. for $C_9H_7F_2N_3$ C, 55.39; H, 3.62; N, 21.83. Found: C, 55.41; H, 3.65; N, 21.52%.

General procedure for the preperation of 3-(2,4,5-trifluorophenyl) propynenitrile 1c
The [(2,4,5-trifluoro benzoyl)- cyano methylene] triphenyl phosporane **7** was taken in a sealed tube and subjected to microwave irradiation for 5.5 mins. The ylide **7** was decomposed at 600Watts microwave power. The dark brown reaction mixture was cooled to room temperature, and was dissolved in dichloromethane (10 ml) and purified by column chromatography using silicagel (100-200 mesh).

2,4,5-Trifluorophenylpropynenitrile 1c.
Yield 84%. mp 38 °C. IR (KBr): 3040, 2919, 2271,2185, 1502, 1397, 1183 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 6.99-7.14 (m, 1H), 7.35-7.47 (m, 1H). EIMS *m/z* (relative intensity) 181 (M^+, 100), 130 (7),112(6), 75 (8), 55(8), 41(18). Anal. Calcd. for $C_9H_2F_3N$ C, 59.68; H, 1.11; N, 7.73. Found: C, 59.41; H, 1.65; N, 7.52%.

General procedure for the preparation of 2-aryl-5, 7-dialkyl-pyrazolo [1,5-a] pyrimidine (9a-9h).
3-Amino pyrazole (0.001 mol) was dissolved in ethanol (2 ml) and added an ethanolic solution of symmetrical 1,3-diketone (0.001 mol) at once and allowed to reflux for 3 hr. Solvent was removed from the reaction mixture and the crude material was purified by column chromatography.

2-(4-Fluorophenyl)-5,7- dimethyl-pyrazolo [1,5-a] pyrimidine 9a
Yield 81%. mp 69 °C. IR (KBr): 2923, 1607, 1463, 1266, 1150 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 2.48 (s, 3H), 2.71 (s, 3H), 6.48 (s, 1H), 6.71 (s, 1H), 7.02-7.11(m, 2H), 7.88-7.95(m, 2H). EIMS *m/z* (relative intensity) 241 (M^+, 60), 191 (11), 149 (17), 105 (35), 91(55), 57(100). Anal. Calcd. for $C_{14}H_{12}FN_3$ C, 69.70; H, 5.01; N, 17.42. Found: C, 69.72; H, 5.04; N, 17.41%.

2-(4-Fluorophenyl)-5,7- bis-trifluoromethyl-pyrazolo [1,5-a] pyrimidine 9b
Yield 77%. mp 54 °C. IR (KBr): 3041, 2923, 1598 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 7.09-7.13 (m, 2H), 7.19 (s, 1H), 7.36 (s, 1H), 7.96-8.02 (m, 2H). EIMS *m/z* (relative intensity) 349 (M^+, 90), 280 (65). Anal. Calcd. for $C_{14}H_6F_7N_3$ C, 48.15; H, 1.73; N, 12.03. Found: C, 48.15; H, 1.76; N, 12.04%.

2-(2,6-Difluorophenyl)-5,7- dimethyl-pyrazolo [1,5-a] pyrimidine 9c
Yield 83%. mp 66 °C. IR (KBr): 2933, 1617, 1463, 1265, 1155 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.74 (s, 3H), 6.27 (s, 1H), 6.95 (s, 1H), 7.05-7.10(m, 2H), 7.36-7.42(m, 1H). EIMS *m/z* (relative intensity) 259 (M^+, 55), 244 (100). Anal. Calcd. for $C_{14}H_{11}F_2N_3$ C, 64.86; H, 4.28; N, 16.21. Found: C, 64.72; H, 4.04; N, 16.41%.

2-(2,6-Difluorophenyl)-5,7- bis-trifluoromethyl-pyrazolo [1,5-a] pyrimidine 9d
Yield 78%. mp 50 °C. IR (KBr): 3031, 2925, 1600 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 7.05-7.12 (m, 3H), 7.34-7.40 (s, 1H), 7.58 (s, 1H). EIMS *m/z* (relative intensity) 367 (M^+, 80), 298 (70). Anal. Calcd. for $C_{14}H_5F_8N_3$ C, 45.79; H, 1.37; N, 11.44. Found: C, 45.15; H, 1.76; N, 11.04%.

2-(2,4,5-Trifluorophenyl)-5,7- dimethyl-pyrazolo [1,5-a] pyrimidine 9e
Yield 86%. mp 60 °C. IR (KBr): 2933, 1617, 1463, 1265, 1155 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.73 (s, 3H), 6.27 (s, 1H), 6.57 (s, 1H), 7.21-7.132 (m, 2H). EIMS *m/z* (relative intensity) 277 (M^+, 75), 262 (10). Anal. Calcd. for $C_{14}H_{10}F_3N_3$ C, 60.65; H, 3.64; N, 15.16. Found: C, 60.72; H, 3.04; N, 15.41%.

2-(2,4,5-Trifluorophenyl)-5,7- bis-trifluoromethyl-pyrazolo [1,5-a] pyrimidine 9f
Yield 77%. mp 49 °C. IR (KBr): 30412 2934, 1580 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 6.70 (s, 1H), 7.15-7.25 (m, 2H), 7.58 (s, 1H). EIMS *m/z* (relative intensity) 385 (M^+, 65), 316 (65). Anal. Calcd. for $C_{14}H_4F_9N_3$ C, 43.65; H, 1.05; N, 10.91. Found: C, 43.15; H, 1.76; N, 10.04%.

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