

Facile synthesis of fluorinated 2-aryl-5,7-bisalkyl pyrazolopyrimidines from arylalkynenitriles[†]

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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-2d**. The condensation of aminopyrazoles with 1,3-dicarbonyl compounds furnished pyrazolopyrimidines **7a-h** in good yield.

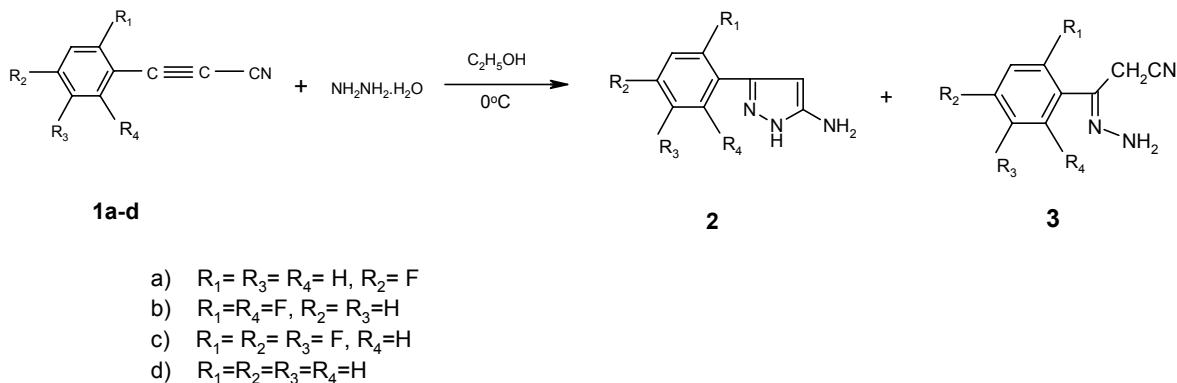
Keywords: Acetylenic nitriles, 1,3-dipolar cycloaddition, hydrazine, amino pyrazoles, 1,3-dicarbonyl compounds, pyrazolopyrimidines

Introduction

Pyrazolopyrimidines are of considerable chemical and pharmacological importance as purine analogues,^{1,2} and have antitumor, antileukemic activities. Pyrazolo [1,5-a] pyrimidines have useful properties as antimetabolites in purine biochemical reactions.³⁻⁵ The pyrazole containing compounds have practical applications in the medicinal and agrochemical field and the biological activity⁶⁻⁸ of pyrazoles and its derivatives is well documented. The 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 esterase inhibitors¹¹. Our continued interest on the synthesis of fluorinated heterocycles,^{12,13} prompted us to synthesize 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

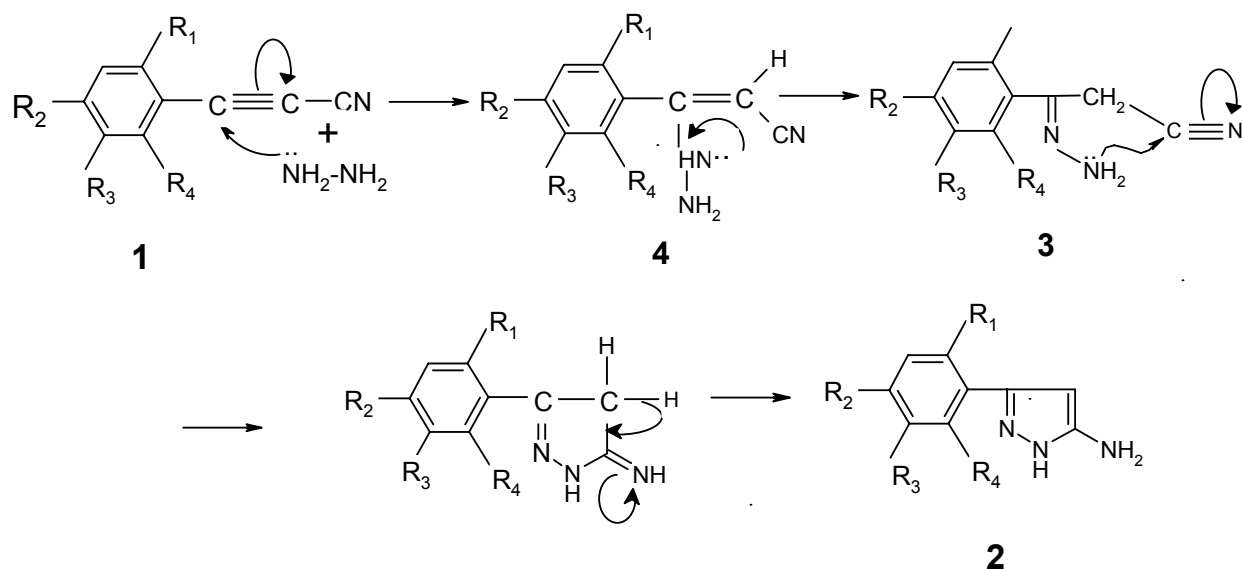
Acetylenic nitriles are known to undergo not only 1,3-dipolar cycloadditions but also nucleophilic addition with hydrazines¹⁴ to give aminopyrazoles or hydrazides. In the course of the chemistry of fluorinated alkynenitriles, we found that the addition of hydrazine to alkynenitrile **1** in ethanol at 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 to obtain the cyclized pyrazoles. In contrast, 2,6-difluoro phenyl propynenitrile **1b** gave the uncyclised hydrazide **3b** intermediate as the major product, the cyclised aminopyrazole **2b** being the minor component (Scheme 1).



Scheme 1

The IR spectra of amino pyrazoles **2a-d** showed the absence of a peak in the region 2250-2260 cm⁻¹ corresponding to the nitrile group and the presence of a broad absorption in the region 3410-3090 cm⁻¹ assignable to amine function. The NMR spectra of **2a-d** showed the characteristic signals at δ 2.9 ppm for two protons (-NH₂) which is exchangeable with D₂O and a singlet for the pyrazole ring olefinic proton at δ 5.7 ppm. The mass spectra revealed a 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-pyrazol-3-yl-amine.

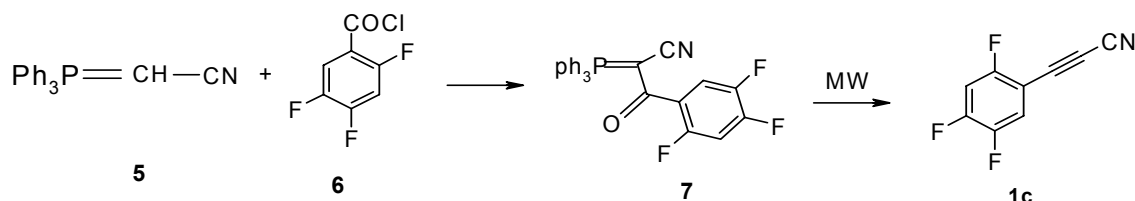
The plausible mechanism for the formation of the arylamino pyrazoles **2a-d** may be explained by the initial Michael type addition of the amino group onto the β-carbon of the alkynenitrile resulting in the alkenylhydrazide **4** intermediate. The latter further rearranges to give the β-cyanoalkylidene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



Scheme 2

The isolation of the intermediate hydrazide **3b** in one of the reactions (for **1b**) along with the cyclized product confirms the mechanism showed above. This assumption is further confirmed when compound **3b** furnished **2b** in refluxing ethanol. The IR spectrum of **3b** showed absorptions of 2240 cm^{-1} and 3320 cm^{-1} assignable to the nitrile and the amine, respectively. The NMR spectrum is in agreement with the assigned structure and revealed a singlet at δ 3.54 ppm for two protons and a broad singlet at δ 5.47 ppm, which is exchangeable with D_2O , assigned to $-\text{NH}_2$ protons. The mass spectrum revealed a molecular ion at m/z 196. The spectral data are in full agreement with the structure 3-(2,6-difluorophenyl)-3-hydrazinopropionitrile **3b**.

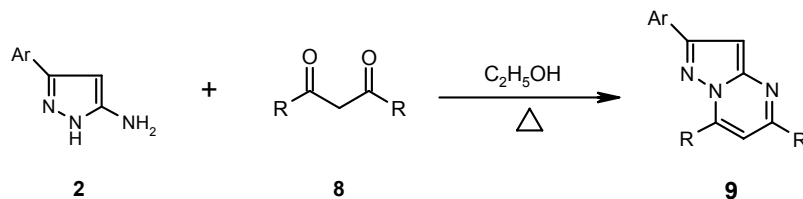
3-(2,4,5-trifluorophenyl) propynenitrile **1c** is a new compound and is prepared in good yield by microwave irradiation of [(2,4,5-trifluorobenzoyl)cyanomethylene]triphenyl phosphorane **5c**. The oxo-ylide **7** is obtained by the acylation of cyanomethylene triphenyl phosphorane **5** with 2,4,5-trifluoro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



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 a 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 cyclizes to furnish the stable pyrazolopyrimidine **9** in good yield (scheme 4).



- Ar = 4-Fluorophenyl, R=CH₃.
- Ar = 4-Fluorophenyl, R=CF₃.
- Ar = 2,6-difluorophenyl, R=CH₃.
- Ar = 2,6-difluorophenyl, R=CF₃.
- Ar = 2,4,5-Trifluorophenyl, R=CH₃.
- Ar = 2,4,5-Trifluorophenyl, R=CF₃.
- Ar = phenyl, R=CH₃
- Ar = phenyl, R=CF₃

Scheme 4

The IR spectra of compounds **9a-d** showed the disappearance of a broad peak due to –NH protons in the range 3100-3400 cm⁻¹ and a carbonyl absorption is absent indicating that cyclization occurs. The NMR spectra showed the characteristic protons of pyrazole and pyrimidine rings at δ 6.48 and δ 6.70 ppm, respectively. The mass spectra revealed stable the molecular ions and the loss of acetonitrile/trifluoro acetonitrile from molecular ion are observed in all the cases. The spectral data are in support of the assigned structure for the product **9** and is 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 pyrazolopyrimidines from aryl substituted alkynenitriles, which are expected to be biologically important ring systems.

Experimental Section

General Procedures. Melting points were determined in open glass capillaries on a Fisher Johnes melting point apparatus and are uncorrected. IR spectra were recorded on FT-IR Shimadzu Perkin-Elmer 1310 infrared spectrophotometer. ¹HNMR (200 MHz) and ¹³C NMR (50 MHz) spectra were recorded on Varian Gemini spectrometer in CDCl₃ solvent using TMS as

internal standard. Mass spectra were recorded on a VG-micro mass 7070H instrument at 70eV. Elemental analyses were carried out on EI Elemental Vario EL (Germany) apparatus.

General procedure for the preparation of 5-aryl-2H-pyrazole-3-yl-amine (2a-2d& 3).

Conjugated alkynenitrile **1** (2 mmol) was dissolved in dry ethanol (2 ml), cooled to -5°C , and hydrazine hydrate solution (2 mmol) was added 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 sulfate. 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} . ^1H NMR (200 MHz, CDCl_3): δ 2.97 (br.s, 2H, NH_2), 5.70 (s, 2H), 7.02 (ddd, 2H, $^3\text{J}_{\text{H-H}}=8.8$, $^3\text{J}_{\text{H-F}}=6.4$, $^4\text{J}_{\text{H-H}}=2.2$ Hz), 7.61 (ddd, 2H, $^3\text{J}_{\text{H-H}}=8.8$, $^4\text{J}_{\text{H-F}}=5.3$, $^4\text{J}_{\text{H-H}}=2.1$ Hz). EIMS m/z (relative intensity) 177 (M^+ , 100), 176 (12), 149 (8), 148 (75). Anal. Calcd. for $\text{C}_8\text{H}_8\text{FN}_3$ 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 8.5%. mp 128°C . IR (KBr): 3409-3111, 2910, 1525 cm^{-1} . ^1H 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 $\text{C}_9\text{H}_7\text{F}_2\text{N}_3$ 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-ylamine (2c). Yield 79%. mp 132°C . IR (KBr): 3406-3100, 2911, 1514 cm^{-1} . ^1H 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 $\text{C}_9\text{H}_6\text{F}_3\text{N}_3$ C, 50.71; H, 2.84; N, 19.71. Found: C, 50.73; H, 2.87; N, 19.70%.

5-Phenyl-2H-pyrazole-3-ylamine (2d). Yield 76%. mp 145°C . IR (KBr): 3380-3100, 2928, 1369 cm^{-1} . ^1H 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 $\text{C}_9\text{H}_9\text{N}_3$ C, 67.91; H, 5.70; N, 26.90. Found: C, 67.92; H, 5.73; N, 26.88%.

3-(2,6-Difluorophenyl)-3-hydrazinopropionitrile (3). Yield 81%. mp 126°C . IR (KBr): 3210, 2925, 2340 cm^{-1} . ^1H 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 $\text{C}_9\text{H}_7\text{F}_2\text{N}_3$ C, 55.39; H, 3.62; N, 21.83. Found: C, 55.41; H, 3.65; N, 21.52%.

General procedure for the preparation of 3-(2,4,5-trifluorophenyl)propynenitrile (1c). The [(2,4,5-trifluorobenzoyl)cyanomethylene]triphenylphosphorane **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} . ^1H 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 $\text{C}_9\text{H}_2\text{F}_3\text{N}$ 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*]pyrimidines 9a-9h. 3-Amino pyrazole (1 mmol) was dissolved in ethanol (2 ml) and added to an ethanolic solution of a symmetrical 1,3-diketone (1 mmol) at once and allowed to reflux for 3 hr. The 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} . ^1H 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 $\text{C}_{14}\text{H}_{12}\text{FN}_3$ 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} . ^1H 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 $\text{C}_{14}\text{H}_6\text{F}_7\text{N}_3$ 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} . ^1H 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 $\text{C}_{14}\text{H}_{11}\text{F}_2\text{N}_3$ 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-bistrifluoromethyl-pyrazolo[1,5-*a*]pyrimidine (9d). Yield 78%. mp 50 °C. IR (KBr): 3031, 2925, 1600 cm^{-1} . ^1H 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 $\text{C}_{14}\text{H}_5\text{F}_8\text{N}_3$ 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} . ^1H 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 $\text{C}_{14}\text{H}_{10}\text{F}_3\text{N}_3$ 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-bistrifluoromethyl-pyrazolo[1,5-*a*]pyrimidine (9f). Yield 77%. mp 49 °C. IR (KBr): 3041, 2934, 1580 cm^{-1} . ^1H 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 $\text{C}_{14}\text{H}_4\text{F}_9\text{N}_3$ C, 43.65; H, 1.05; N, 10.91. Found: C, 43.15; H, 1.76; N, 10.04%.

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