Research Article

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Regioselectivity in the reaction of 5-amino-3-anilino-1H-pyrazole-4-carbonitrile with cinnamonitriles and enaminones: Synthesis of functionally substituted pyrazolo[1,5-a]pyrimidine derivatives

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Abstract: The development of efficient methods for the synthesis of polyfunctional N-heterocycles is an important area of research in organic and medicinal chemistry. Pyrazolo[1,5-a]pyrimidine derivatives are purine analogous of biomedical importance and have been extremely studied for their broad spectrum of biological activities. Recently, they have attracted great interest in materials science owing to their photophysical properties. 3(5)-Aminopyrazoles are extensively utilized in the synthesis of condensed heterocyclic systems, particularly pyrazolo [1,5-a]pyrimidines via the reaction with 1,3-biselectrophilic reagents. However, the information available in the literature provides little in the way of reasoning their cyclization, particularly the initial attack either by the exocyclic amino group or endocyclic nitrogen. Unfortunately, the relative nucleophilicity of exo- and endocyclic nitrogen atoms in 1-unsubstituted 3(5)-aminopyrazoles is not clear and contradicting. It has been found that other factors can modulate the regioselectivity rather than basicity or steric hindrance for both active sites. The reported studies in the structure–activity relationship revealed that pyrazolo[1,5-a]pyrimidines having a substitution at fifth, sixth, and seventh positions possess potent biological activities, especially those with an amino group at the seventh position. We here developed a regioselective, high yield synthesis of 7-amino-5-arylpyrazolo [1,5-a]pyrimidine-3,6-dicarbonitriles by the reaction of N-(5-amino-4-cyano-1H-pyrazole-3-yl)-benzamide with various cinnamonitriles and enamines in pyridine at 120°C under controlled microwave heating conditions. All structures of newly synthesized compounds were established by analytical and spectral data as well as single-crystal diffraction and rationalized for their formation.

Keywords: multicomponent reaction, regioselectivity, 7-aminopyrazolo[1,5-a]pyrimidines, microwave heating, X-ray crystallography

1 Introduction

Heterocyclic compounds containing pyrazole scaffold signify a wide spectrum of pharmacological activities and constitute a common nucleus in a variety of biologically active compounds [1–6]. Pyrazolo[1,5-a]pyrimidines are potential molecules of interest [7] and have been reported to possess anticancer [8,9], antimicrobial [10,11], antiviral [12], antifungal [13], anti-inflammatory [14], as well as large range of activities [15–19]. Examples of pyrazolo[1,5-a]pyrimidine’s marketed drugs are illustrated in Figure 1.

In this regard, the nature of substituents at fifth, sixth, and seventh positions displayed a crucial role in their biological potency. It is worth mentioning that the presence of an amino group at the seventh position had an additional advantage to form hydrogen bonds with the hinge region of the receptor [20].
The nucleophilicity and reactivity of different active centers in 5-aminopyrazole scaffolds have received considerable interest over the years. Concerning nitrogen centers, several published articles argue that in some synthetic protocols ring nitrogen is the most nucleophilic center while the opposite is observed in others [21, 22]. Many different factors such as the nature of the ring substituent, temperature, pressure, solvent, catalyst type as well as the type of reaction controlling either the kinetic or thermodynamic can be utilized to modulate the selectivity of several transformations.

It has been reported that the reaction of 4-unsubstituted 3-(5)-aminopyrazoles with bidentate reagents relies on the participation of the exocyclic amino group with ring nitrogen forming pyrazolo[1,5-a]pyrimidines, pyrazolo [5,1-c]-1,2,4-triazines, pyrazolo[1,5-a]-1,3,5-triazines or the nucleophilic carbon located at C4 of the pyrazole ring leading to pyrazolo[3,4-b]pyridines [23–25]. Whereas, for C4-substituted 3-(5)-aminopyrazoles, considerable attention is required for the synthesis of bicyclic fused pyrazoloazines. Cyclization is affected by the electronic nature, either electron-donating or electron-attracting, of C-4. For example, electron-donating moieties augment the reactivity of the ring nitrogen favoring its initial attack by the bidentate reagent. However, electron-attracting substituents favor the initial attack by the less sterically hindered NH2 group.

It has been reported that the nature of the solvents plays a crucial role in such regioselective cyclocondensation. Owing to the amphoteric nature of 3(5)-aminopyrazoles, a basic solvent generates a heterocyclic anion resulting from the deprotonation of acidic-pyrole-like ring nitrogen, which enhances its reactivity. However, the acidic medium favors the exocyclic attack via protonating of the ring affording a cationic nucleus [26, 27].

Arguably, a thorough investigation to establish the chemistry and regioselectivity of 3(5)-aminopyrazoles leading to complex heterocyclic scaffolds has not been established. Nevertheless, in-depth studies will be beneficial to elucidate their reactivity, their behavior and versatility in different environments, leading to the formation of a diversity of azoloazines in order to develop efficient synthetic methodologies.

Interestingly, a wide range of chemical transformations has now been performed under controlled microwave heating conditions. As compared to conventional heating reactions, microwaves couple directly with the molecules of the entire reaction mixture. Importantly, microwave heating possesses several advantages such as spectacular acceleration of many reactions, higher yields, mild reaction conditions, and shorter reaction times [28, 29]. Moreover, several reports postulate the existence of a microwave effect as a specific radiation effect rather than the thermal one to rationalize for rate acceleration, changes in the reactivity as well as selectivity [30, 31]. Our aim was to use a variety of factors to control the regioselectivity in such reactions leading to 7-aminopyrazolo[1,5-a]pyrimidines.

2 Materials and methods

Aldehydes, malononitrile, dimethylformamide dimethylacetal, and ketones were of commercial grade, and
Pyridine was of analytically pure grade; all were purchased from Aldrich and Merck companies. $^1$H NMR (600 MHz) and $^{13}$C NMR (150 MHz) spectra were recorded using a Bruker DPX instrument ($\delta$ ppm). Mass spectra were determined by using a VG Auto spec QMS 30 and MSg (AEI) spectrometer in the EI (70 eV) mode. Melting points were recorded in a Gallen Kamp melting point apparatus and are uncorrected. X-ray crystallography was performed by using a Rigaku Rapid II and Bruker X8 Prospector single crystal X-ray diffractometer. All reactions were monitored by TLC with toluene/acetonitrile 10:5, 10:6 as an eluent and were carried out until the starting materials were completely consumed.

2.1 General procedure for the synthesis of 7-aminopyrazolo[1,5-α]pyrimidine derivatives 4a–f and 7-arylpyrazolo[1,5-α]derivatives 7a–d

A solution of compounds 1 (1 mmol), 2 (1 mmol), or 5 (1 mmol) in pyridine (10 mL) was heated under reflux in a Milestone Microwave Lab station at 120°C for 20 min. The solvent was removed under reduced pressure, and the solid formed was isolated by filtration and recrystallized utilizing an appropriate solvent (Table 1).

2.2 7-Amino-5,2-diphenylpyrazolo[1,5-α]pyrimidine-3,6-dicarbonitrile (4a)

Yield: 0.309 g (92%); $R_f$ = 0.57 (toluene/acetone 10:5); $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 6.97 (1H, t, $J$ = 6–6 H, Ar–H); 7.31 (2H, t, $J$ = 7.8 Hz Ar–H); 7.56–7.59 (m, 3H, Ar–H); 7.84, 7.85 (2H, dd, $J$ = 3.3, 4.2 Hz, Ar–H); 7.95 (2H, d, $J$ = 7.8 Hz, Ar–H); 9.02 (br, s, 2H, NH$_2$; D$_2$O exchangeable); 9.51 (s, 1H, NH, D$_2$O exchangeable). $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$: 62.76; 66.32; 70.20; 75.69; 113.32; 115.88; 118.19; 121.27; 128.38; 128.65; 128.67; 130.59; 136.67; 140.35; 149.48; 150.85; 155.63; 162.10. Analysis results for C$_{20}$H$_{12}$N$_8$O$_2$: C, 68.37; H, 3.73; N, 27.90; found: C, 68.22; H, 3.82; N, 27.88; EIMS (m/z): 351.01 [M+].

2.3 7-Amino-5-(4-nitrophenyl)-2-(phenylamino)pyrazolo[1,5-α]pyrimidine-3,6-dicarbonitrile (4b)

Yield: 0.356 g (90%); $R_f$ = 0.52 (toluene/acetone 10:5); $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$: 6.97 (1H, t, $J$ = 6.6 Hz, Ar–H); 7.31 (2H, d, $J$ = 1.2 Hz, Ar–H); 7.94 (2H, $J$ = 7.8 Hz, Ar–H); 8.09 (2H, d, $J$ = 9 Hz, Ar–H); 8.39 (2H, d, $J$ = 8.4 Hz) 9.12 (br, s, 2H, NH$_2$); 9.54 (s, 1H, NH). $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$: 66.34; 70.71; 76.11; 113.12; 115.49; 118.24; 121.36; 123.57; 128.68; 130.19; 140.28; 142.57; 148.48; 149.33; 150.72; 155.71; 159.99. Analysis results for C$_{20}$H$_{12}$N$_8$O$_2$: C, 60.60; H, 3.05; N, 28.27; found: C, 60.63; H, 3.12; N, 28.33; EIMS (m/z): 396.03 [M+].

2.4 7-Amino-5-(4-chlorophenyl)-2-(phenylamino)pyrazolo[1,5-α]pyrimidine-3,6-dicarbonitrile (4c)

Yield: 0.354 g (92%); $R_f$ = 0.75 (toluene/acetone 10:5); $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$: 6.97 (1H, t, $J$ = 7.2 Hz, Ar–H); 7.31 (2H, t, $J$ = 7.2 Hz, Ar–H); 7.64 (2H, d, $J$ = 8.4 Hz, Ar–H); 7.87 (2H, d, $J$ = 8.4 Hz, Ar–H); 7.95 (2H, d, $J$ = 8.4 Hz, Ar–H); 9.02 (br, s, 2H, NH$_2$; D$_2$O exchangeable); 9.51 (s, 1H, NH, D$_2$O exchangeable). $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$: 62.76; 66.32; 70.20; 75.69; 113.32; 115.88; 118.19; 121.27; 128.38; 128.65; 128.67; 130.59; 136.67; 140.35; 149.48; 150.85; 155.63; 162.10. Analysis results for C$_{20}$H$_{12}$N$_8$O$_2$: C, 68.37; H, 3.73; N, 27.90; found: C, 68.22; H, 3.82; N, 27.88; EIMS (m/z): 351.01 [M+].

| Compound no. | Solvent of recrystallization | Color of the product | Melting point (°C) |
|--------------|-------------------------------|----------------------|--------------------|
| 4a           | Ethanol                       | Orange crystals      | 308–310 [33]       |
| 4b           | Ethanol-dioxane               | Reddish brown crystals | >360              |
| 4c           | Ethanol                       | Yellow crystals      | 318–320            |
| 4d           | Ethanol                       | Brown crystals       | 310–312            |
| 4e           | Ethanol                       | Yellow crystals      | 288–290            |
| 4f           | Ethanol                       | Brown crystals       | 259–260            |
| 7a           | Ethanol-dioxane               | Brown crystals       | 238–240            |
| 7b           | Ethanol                       | Yellow crystals      | 268–270            |
| 7c           | Ethanol                       | Reddish brown crystals | 270–272          |
| 7d           | Ethanol                       | Orange crystals      | 168–170            |
2.5 7-Amino-5-(4-methoxyphenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3,6-dicarbinitrile (4d)

Yield: 0.354 g (93%); 1H NMR (600 MHz, DMSO-d6) δ 3.52 (3H, s, OCH3); 6.97 (1H, t, J = 7.2 Hz, Ar−H); 7.02–7.13 (1H, m, Ar−H); 7.03 (2H, t, J = 7.8 Hz, Ar−H); 7.85–7.88 (2H, m, Ar−H); 7.95 (2H, t, J = 6.6 Hz, Ar−H); 8.3 (2H, br, s, NH2); 9.48 (1H, s, NH); 13C NMR (150 MHz, DMSO-d6) δ 55.39; 60.11; 76.8; 113.42; 113.76; 114.77; 115.13; 116.06; 116.17; 121.22; 124.07; 128.41; 128.65; 128.78; 130.42; 133.31; 140.38; 149.57; 150.83; 156.62; 161.25; 161.37; 164.31. Analysis results for C20H13N5O2: C, 73.30; H, 3.39; N, 128.49; 132.71; 134.98; 140.03; 143.24; 146.22; 150.79; 155.64; 161.44. Analysis results for C20H12ClN7: C, 62.26; H, 3.14; Cl, 9.19; N, 25.41; found: C, 62.32; H, 3.18; Cl, 9.12; N, 25.58; EIMS (m/z) 385.12 [M+].

2.6 7-Amino-5-(2-chlorophenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3,6-dicarbinitrile (4e)

Yield: 0.351 g (91%); 1H NMR (600 MHz, DMSO-d6) δ 6.98 (1H, t, J = 7.8 Hz, Ar−H); 7.32 (2H, t, J = 7.8 Hz, Ar−H); 7.51 (1H, t, J = 7.2 Hz, Ar−H); 7.54 (2H, d, J = 1.8 Hz, Ar−H); 7.53 (2H, d, Ar−H); 7.56–7.592 (2H, m, Ar−H); 7.64–7.65 (1H, m, Ar−H); 7.95 (d, 2H, J = 7.8, Ar−H); 9.14 (2H, br, s, NH2); 9.565 (1H, s, NH); 13C NMR (150 MHz, DMSO-d6) δ 66.35; 70.62; 78.16; 113.10; 114.66; 116.09; 118.24; 121.40; 127.41; 128.41; 128.58; 128.72; 129.56; 130.42; 131.07; 131.45; 136.24; 140.31; 148.62; 150.79; 155.64; 161.44. Analysis results for C20H12ClN7: C, 62.26; H, 3.14; Cl, 9.19; N, 25.41; found: C, 62.24; H, 3.21; Cl, 9.23; N, 25.39; EIMS (m/z) 385.03 [M+].

2.7 7-Amino-5-(3-bromophenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3,6-dicarbinitrile (4f)

Yield: 0.386 g (90%); (toluene/acetone 10:5); 1H NMR (600 MHz, DMSO-d6) δ 6.97 (1H, t, J = 7.2 Hz, Ar−H); 7.04 (2H, t, J = 7.2 Hz, Ar−H); 7.52, 7.54 (2H, dd, J = 4.2 and 7.8 Hz, Ar−H); 7.77 (1H, t, J = 1.2 Hz, Ar−H); 7.79 (1H, d, J = 1.2 Hz, Ar−H); 7.84 (1H, t, J = 6.6 Hz, Ar−H); 7.94 (2H, d, J = 7.8 Hz, Ar−H); 7.98 (1H, t, J = 1.8 Hz, Ar−H); 9.15 (2H, br, s, NH2); 9.53 (1H, s, NH). Analysis results for C20H12ClN7: C, 55.83; H, 2.81; Br, 18.57; N, 22.79; found: C, 55.88; H, 2.29; Br, 18.66; N, 22.52; EIMS (m/z) 429.01 [M+].

2.8 7-Phenyl-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (7a)

Yield: 0.286 g (92%); 1H NMR (600 MHz, DMSO-d6) δ 6.94 (1H, t, J = 7.2 Hz, Ar−H); 7.26 (2H, t, J = 7.8 Hz, Ar−H); 7.34 (1H, d, J = 4.8 Hz, Ar−H); 7.60–7.62 (3H, m, Ar−H); 7.63 (3H, t, J = 2.4 Hz, Ar−H); 7.64–7.67 (3H, m, Ar−H); 8.12 (1H, d, J = 1.8 Hz, C6−H); 8.13 (1H, d, J = 1.2 Hz, Ar−H); 8.65 (1H, J = 4.8 Hz, C6−H); 9.59 (1H, s, NH); 13C NMR (150 MHz, DMSO-d6) δ 66.3 67.89; 109.24; 113.47; 117.95; 121.39; 128.42; 128.6; 129.44; 129.74; 131.51; 140.48; 145.9; 151.78; 152.22; 155.91. Analysis results for C20H12BrN2: C, 73.30; H, 4.21; N, 22.49; found: C, 73.22; H, 4.31; N, 22.42; EIMS (m/z) 311.17 [M+].

2.9 7-(2-Nitrophenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (7b)

Yield: 0.320 g (90%); 1H NMR (600 MHz, DMSO-d6) δ 6.90–6.93 (1H, m, Ar−H); 7.17–7.20 (2H, m, Ar−H); 7.39–7.41 (2H, m, Ar−H); 7.46 (1H, J = 4.8 Hz, Ar−H); 7.84–7.86 (1H, m, Ar−H); 7.94–7.97 (2H, m, Ar−H); 8.03–8.05 (1H, m, Ar−H); 8.39, 8.41 (1H, dd, J, 1.2, 1.2 Hz, C5−H); 8.79 (1H, J = 4.8 Hz, C6−H); 9.56 (1H, s, Ar−H); 13C NMR (150 MHz, DMSO-d6) δ 68.12; 109.70; 113.06; 117.91; 117.99; 121.66; 124.63; 128.49; 132.71; 134.98; 140.03; 144.57; 147.51; 150.51; 152.92; 156.09. Analysis results for C20H12NO2: C, 64.04; H, 3.39; N, 23.58; found: C, 64.12; H, 4.01; N, 23.67; EIMS (m/z) 356.02 [M+].

2.10 7-(4-Methylphenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (7c)

Yield: 0.289 g (89%); (toluene/acetone 10:6); 1H NMR (400 MHz, DMSO-d6) δ 2.38 (3H, s, CH3); 6.94–7.69 (9H, m, Ar−H); 8.10 (1H, d, J = 1.2 Hz, C5−H); 8.66 (1H, d, J = 4.8 Hz,
C₆-H); 9.59 (1H, s, NH). Analysis results for C₂₀H₁₅N₅O: C, 73.83; H, 4.65; N 20.52; found: C, 73.88; H, 4.62; N, 21.55.

2.11 7-(4-Methoxyphenyl)-2-(phenylamino) pyrazolo[15-a]pyrimidine-3-carbonitrile (7d)

Yield: 0.307 g (88%); (toluene/acetone 10:6); ¹H NMR (400 MHz, DMSO-d₆) δ 3.34 (3H, s, OCH₃); 6.92–7.57 (9H, m, Ar–H); 8.13 (1H, d, J = 1.2 Hz, C₅–H); 8.65 (1H, d, J = 4.8 Hz, C₆–H); 9.85 (1H, s, NH). Analysis results for C₂₀H₁₅N₅O: C, 70.37; H, 4.43; N, 20.52; found: C, 70.44; H, 4.42; N, 20.57.

3 Results and discussion

The reaction of N-(5-amino-4-cyano-1H-pyrazole-3-yl)-benzamide 1 with a variety of electrophiles was reported to afford different isomeric pyrazolo[1,5-a]pyrimidine derivatives. Thus, in an early report [32], the reaction of 1 with tetracyano ethylene in dry ethyl acetate or methylene chloride at ambient temperature for 48 h or with 2-(dicyanomethylene) indan-1, 3-dione (CNIND) in dry pyridine and heating under reflux at 100°C for 3 h afforded mainly the corresponding 5-aminopyrazolo [1,5-a]pyrimidine via the initial attachment of ring nitrogen followed by cyclization of the formed 1:1 adduct with an exocyclic amino group, which was subsequently supported by other authors. Soliman et al. [33] have similarly reported that reaction of 1 with various halo reagents, active methylene, and ketene dithiocacets under phase transfer conditions proceeds via the initial attack of the endocyclic ring nitrogen at the electrophile active site followed by cyclization of the cyclic intermediate with the exocyclic amino group. However, they revealed the initial attack by the exocyclic amino group upon reacting 1 with acetyl chloride, ethoxymethylene, malononitrile, and Lawson’s reagent followed by cyclization with the ring nitrogen. A similar pathway was reported by Ahmed et al. [34] and Dozhenko et al. [35]. Elnagdi et al. [36,37] examined the regio-orientation in the reaction of 5-aminopyrazoles with benzylidene malononitrile and enaminoes utilizing (¹⁵N, ¹H) HMBC to establish a more conclusive structure elucidation as the structure assigned for such reactions was mainly based on ¹H NMR and IR spectra. They concluded that the reaction with benzylidene malononitrile proceeds initially by the nucleophilic attack of the exocyclic amino group; however, the initial attack of the ring nitrogen occurs with enaminones. Moreover, under such basic reaction conditions, the cyano group at the C-4 pyrazole ring remained inactive. In contrast, Hebishy and co-workers [38] recently reported the reaction of N-(5-amino-4-cyanoH-pyrazol-3-yl)-benzamide with arylidene-malononitrile afforded the corresponding 5-aminopyrazolo [1,5-a]pyrimidine derivatives. Recently, the catalyst-free Biginelli-type reaction of 5-amino-3-arylpyrazole-4-carbonitrides with ylidene-1,3-dicarbonyl compounds by refluxing in DMF has been reported by Dotsenko and co-workers [39]. The authors confirmed the formation of the corresponding 4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carbonitrides via the intermediary of the aza-Michael adduct resulting from the initial attack of the ring nitrogen and subsequent cyclondensation with the exocyclic amino group. The reaction of 1 with dimedone catalyzed by tin(II) chloride dehydrate, which acts as a Lewis acid, and a low melting solvent was recently reported to afford the corresponding pyrazolo[5,4-b]quinolones via the nucleophilic attack of the exocyclic amino group on the carbonyl carbon of dimedone followed by cyclization of the formed imino form on to the cyano group and hydrolysis [40]. A similar phenomenon was reported by Schmidtke and co-authors [41].

To shed further light on this unresolved issue and in continuation of our studies in which we utilize microwave heating [42–48], we report herein the results of our investigation on the reaction of N-(5-amino-4-cyano-1H-pyrazole-3-yl)-benzamide 1 with various electrophiles under controlled microwave heating conditions. Our aim was to modulate several factors controlling regioselectivity in such reactions.

The reaction of 5-aminopyrazole derivative 1 with benzylidene malononitrile 2a in pyridine under microwave irradiation (120°C, 20 min) was found to afford selectively the corresponding 7-aminopyrazolo[1,5-a]-pyrimidine derivative 4a rather than isomeric 5-aminopyrazole 3a. The mass spectrum of 4a showed a molecular ion peak m/z = 351.01 (100%). The IR spectra (KBr) showed an amino group, two cyano groups, and C═N absorption bands at λ_max = 3,441, 3,360, 2,179, 2,200, and 1,631 cm⁻¹. ¹H NMR spectra revealed a broad singlet at δ = 9.02 ppm integrated for two protons, which was assigned to the NH₂ group at C-7. If the reaction product was isomeric 5-aminopyrazole derivatives, such amino groups will appear at a higher field shift. This low downfield shift could be rationalized for the anisotropic effect of the adjacent pyrazole ring nitrogen. In addition, it reveals signals at δ = 6.97 (1H, t, J = 6.6 Hz, Ar–H), 7.31 (2H, t, J = 7.8 Hz, Ar–H), 7.56–7.59 (m, 3H, Ar–H), 7.84–7.85 (2H, dd, J = 3.3, 4.2 Hz, Ar–H), 7.95 (2H, d, J = 7.8 Hz, Ar–H), 9.02 (1H, s, aniline-NH, D₂O exchangeable). Its ¹³C NMR spectrum showed characteristic
signals at \( \delta = 75.69 \) (pyrazole C-3), 115.88 (CN at C-6), 118.19 (CN at C-3), 121.27–140.35 (aromatic carbons), 149.48 (C-4), 155.63 (C-5), 162.1 (C-7). Furthermore, the structure of 4a was unambiguously confirmed by single-crystal X-ray diffraction [41] (Figure 2).

With these results in hand, we investigated the scope of such reactions with a variety of substituted cinnamonic nitrile derivatives. Thus, the reaction of 1 with 2b–f under the same experimental conditions afforded the corresponding 7-aminopyrazolo[1,5-a]pyrimidine derivatives 4b–f, respectively, in excellent yields. The structures of 4b–f were established from their mass spectra, \(^1\)H NMR, and \(^{13}\)C NMR spectra, which showed a similar pattern as compound 4a as well as elemental analysis. Further confirmation was achieved by single-crystal X-ray diffraction of 4d [42] (Figure 3, Scheme 1). These results were in contrast to that reported for the formation of 5-aminopyrazolo[1,5-a]pyrimidines from the reaction of 1 with arylidene malononitriles [37]

Another example of regioselectivity in the reaction of 5-aminopyrazoles with electrophilic reagents was reported [41] involving its reaction with \((E)-3-(\text{dimethylamino})-1-

arylprop-2-en-1-one\) derivatives, which afforded the corresponding 5-arylpypyrazolo[1,5-a]pyrimidines formed via the initial attack by the ring nitrogen. It is worth mentioning that such cyclocondensation is not favored in our case. Thus, the reaction of 1 with \((E)-3-(\text{dimethylamino})-1-\text{phenylprop-2-en-1-one}\) 5a afforded the corresponding 7-arylpypyrazolo[1,5-a]pyrimidine 7a. The possible formation of 5-arylpypyrazolo[1,5-a]pyrimidine 6a was ruled out based on analytical and spectral data. The mass spectra showed a molecular ion peak \(m/z = 311.17\) (43%). The \(^1\)H NMR revealed a downfield doublet at \(\delta = 8.65\) ppm and a doublet at \(\delta = 8.13\) ppm, corresponding to C_6–H and C_7–H and signals at \(\delta = 6.94\) (1H, \(J = 7.2\) Hz, Ar–H), 7.26 (2H, \(J = 7.8\) Hz, Ar–H), 7.34 (1H, d, \(J = 4.8\) Hz, Ar–H), 7.60–7.62 (3H, m, Ar–H), 7.63 (3H, t, \(J = 2.4\) Hz, Ar–H), 7.64–7.67 (3H, m, Ar–H), 8.13 (1H, d, \(J = 1.2\), Ar–H), 9.59 (1H, s, aniline–NH). If the reaction product was 6a,

Figure 2: ORTEB diagram of compound 4a (X-ray).

Figure 3: ORTEB diagram of compound 4d (X-ray).

Figure 4: ORTEB diagram of compound 6a (X-ray).

Scheme 1: The reaction of 5-aminopyrazole derivatives 1 with benzyldene malononitrile derivatives 2.
the signal assigned for C6–H will appear at a higher field shift. The $^{13}$C NMR spectrum revealed C6 and C7 carbons at $\delta = 109.24$ and 151.78, which are difficult to rationalize for if the product was 6a in addition to the characteristic signals at $\delta = 117.95$ (CN at C-3), 113.47–140.48 (aromatic carbons), 145.9 (C-4), and 152.22 (C-2).

Scheme 2: The reaction of 5-aminopyrazole derivatives 1 with enaminone derivatives 5.

Scheme 3: Mechanism of the formation of 4af and 7a–d.
Moreover, the structure of 7a was confirmed by single-crystal X-ray diffraction (Figure 4) [43]. Similarly, compound 1 reacted with 5b under the same experimental conditions to afford the newly synthesized 7-arylpyrazolo[1,5-a]pyrimidines 7b–d (Scheme 2). The structure proposed for the reaction products was established based on a similar 1H NMR and 13NMR pattern as 7a.

A proposed mechanism to account for the formation of 4a–g and 7a–d was demonstrated in Scheme 3. An initial attack of the exocyclic amino group on the activated double bond system in 2a–g afforded 1:1 adduct 10 followed by cyclization via the addition of the ring NH to the cyano group and subsequent aromatization. The same applies for the formation of 7a, which proceeds via dimethylamine elimination from the reaction of the exocyclic amino group with 5a forming intermediate 13 and subsequent cyclization via the attack of the lone pair at the carbonyl group of ring nitrogen with water loss.

4 Conclusion

In conclusion, we can reveal that ring nitrogen is the more basic center and the exocyclic amino group is the less hindered. An attack by ring nitrogen is favored with less sterically hindered electrophiles; however, the attack with the exocyclic amino group predominates with bulky electrophiles. However, no firm conclusion on which to determine the preferred tautomer form of the final product has been arrived. Here, we do believe that the nature of the substituents of the aminopyrazole scaffold plays a crucial role in such regioselectivity. The presence of a cyano group at C-4 in compound 1 reduces the donating ability of the ring nitrogen. Moreover, for the titled compound, the chains of dimers formed by pairs of ring N–H...N hydrogen bonds render it less active. We concluded that unambiguous assignment of the regioselectivity in such reactions requires advanced techniques, particularly X-ray diffraction crystallography as insufficient spectral data could be a mess resulting in incorrect conclusions.

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Appendix

Characterization data for compounds 4a, 4b, 4c, 4d, 4e, 4f, 7a, 7b, 7c, and 7d.

A1 7-Amino-5,2-diphenylpyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4a)

Orange crystals; mp: 308–310°C; yield: 0.309 g (92%); Rf = 0.57 (toluene.acetone 10:5); 1H NMR (600 MHz, DMSO-δ6) δ 6.97 (1H, t, J = 6–6 Hz, Ar–H), 7.31 (2H, t, J = 7.8 Hz, 7.56–7.59) (m, 3H, Ar–H), 7.84, 7.85 (2H, dd, J = 3.3, 4.2 Hz, Ar–H), 7.95 (2H, d, J = 7.8 Hz, Ar–H), 9.02 (br, s, 2H, NH3, D2O exchangeable), 9.51 (s, 1H, NH, D2O exchangeable); 13C NMR (150 MHz, DMSO-d6) δ = 62.76, 66.32, 70.20, 75.69, 113.32, 115.88, 118.19, 121.27, 128.38, 128.65, 128.67, 130.59, 136.67, 140.35, 149.48, 150.85, 155.63, 162.10. Analysis results for C20H12N8O2: C, 60.60; H, 3.05; N, 28.27; found: C, 60.63; H, 2.78; N, 28.27; yield: 0.309 g (92%); Rf = 0.75 (toluene.acetone 10:5); 1H NMR (600 MHz, DMSO-d6) δ 6.97 (1H, t, J = 7.2 Hz, Ar–H), 7.31 (2H, t, J = 7.2 Hz, Ar–H), 7.64 (2H, d, J = 8.4 Hz, Ar–H), 7.87 (2H, d, J = 8.4 Hz, Ar–H), 7.95 (2H, d, J = 8.4 Hz, Ar–H), 9.03 (2H, br, s, NH3), 9.52 (1H, s, NH); 13C NMR (150 MHz, DMSO-d6) δ 70.35, 75.68, 113.26, 115.78, 121.31, 128.52, 128.68, 130.53, 135.45, 140.33, 149.43, 150.79, 155.65, 160.82. Analysis results for C20H12ClN7: C, 62.26; H, 3.14; Cl, 9.19; N, 25.41; found: C, 62.32; H, 3.16; Cl, 9.12; N, 25.58; EIMS (m/z) 385.12 [M+]

A2 7-Amino-5-(4-nitrophenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4b)

Reddish brown crystals; mp: >360°C; yield: 0.356 g (90%); Rf = 0.52 (toluene.acetone 10:5); 1H NMR (600 MHz, DMSO-δ6) δ 6.97 (1H, t, J = 6.6 Hz, Ar–H), 7.31 (2H, d, J = 1.2 Hz, Ar–H), 7.94 (2H, J = 7.8 Hz, Ar–H), 8.09 (2H, d, J = 9 Hz, Ar–H), 8.39 (2H, d, J = 8.4 Hz), 9.12 (br, s, 2H, NH3), 9.54 (s, 1H, NH), 13C NMR (150 MHz, DMSO-d6) δ = 66.34, 70.71, 76.11, 113.42, 113.49, 118.24, 121.36, 123.57, 128.68, 130.19, 140.28, 142.57, 148.47, 149.33, 150.72, 155.71, 159.99. Analysis results for C20H12N8O2: C, 60.60; H, 3.05; N, 28.27; found: C, 60.63; H, 3.12; N, 28.33; EIMS (m/z) 396.03 [M+].

A3 7-Amino-5-(4-chlorophenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4c)

Yellow crystals; mp: 318–320°C; yield: 0.354 g (92%); Rf = 0.75 (toluene.acetone 10:5); 1H NMR (600 MHz, DMSO-d6) δ 6.97 (1H, t, J = 7.2 Hz, Ar–H), 7.31 (2H, t, J = 7.2 Hz, Ar–H), 7.64 (2H, d, J = 8.4 Hz, Ar–H), 7.87 (2H, d, J = 8.4 Hz, Ar–H), 7.95 (2H, d, J = 8.4 Hz, Ar–H), 9.03 (2H, br, s, NH3), 9.52 (1H, s, NH); 13C NMR (150 MHz, DMSO-d6) δ 70.35, 75.68, 113.26, 115.78, 121.31, 128.52, 128.68, 130.53, 135.45, 140.33, 149.43, 150.79, 155.65, 160.82. Analysis results for C20H12ClN7: C, 62.26; H, 3.14; Cl, 9.19; N, 25.41; found: C, 62.32; H, 3.16; Cl, 9.12; N, 25.58; EIMS (m/z) 385.12 [M+]

A4 7-Amino-5-(4-methoxyphenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4d)

Brown crystals; mp: 310–312°C; yield: 0.354 g (93%); 1H NMR (600 MHz, DMSO-d6) δ 3.52 (3H, s, OCH3), 6.97 (1H, t, J = 7.2 Hz, Ar–H), 7.02–7.13 (2H, m, Ar–H), 7.03 (2H, t, J = 7.8 Hz, Ar–H), 7.85–7.88 (2H, m, Ar–H), 7.95 (2H, t, J = 6.6 Hz, Ar–H), 8.3 (2H, br, s, NH3), 9.48 (1H, s, NH); 13C NMR (150 MHz, DMSO-d6) δ = 55.39, 60.11, 76.8, 113.42, 113.76, 114.77, 115.13, 116.06, 116.17, 121.72, 124.07, 128.41, 128.65, 128.78, 130.42, 133.31, 140.38, 149.57, 150.83, 155.62, 160.39, 161.25, 161.37, 164.31. Analysis results for C21H15N6O: C, 66.13; H, 3.96; N, 25.71; found: C, 66.22; H, 4.01; N, 25.75; EIMS (m/z) 381.11 [M+].
A5 7-Amino-5-(2-chlorophenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4e)

Yellow crystals; mp: 288–290°C; yield: 0.351 g (91%); 
$^1$H NMR (600 MHz, DMSO-d$_6$) $\delta$ 6.98 (1H, t, $J = 7.8$ Hz, Ar–H), 7.32 (2H, t, $J = 7.8$ Hz, Ar–H), 7.51 (1H, t, $J = 7.2$ Hz, Ar–H), 7.54 (2H, d, $J = 1.8$ Hz, Ar–H), 7.53 (2H, d, Ar–H), 7.565–7.592 (2H, m, Ar–H), 7.64–7.65 (1H, m, Ar–H), 7.95 (d, 2H, $J = 7.8$, Ar–H), 9.14 (2H, br, s, NH$_2$), 9.565 (1H, s, NH), $^{13}$C NMR (150 MHz, DMSO-d$_6$) $\delta$ 66.35, 70.62, 78.16, 113.10, 114.66, 116.09, 128.41, 128.41, 128.58, 128.72, 129.56, 130.42, 131.07, 131.45, 136.24, 140.31, 148.62, 150.79, 155.64, 161.44. Analysis results for C$_{20}$H$_{12}$ClN$_7$: C, 62.26; H, 3.14; Cl, 9.19; N, 25.41; found: C, 70.62, 78.16, 113.10, 114.66, 116.09, 128.41, 128.41, 128.58, 128.72, 129.56, 130.42, 131.07, 131.45, 136.24, 140.31, 148.62, 150.79, 155.64, 161.44. Analysis results for C$_{20}$H$_{12}$ClN$_7$: C, 62.26; H, 3.14; Cl, 9.19; N, 25.41; found: C, 62.24; H, 3.21; Cl, 9.23; N, 25.39; EIMS (m/z): 385.03 [M+].

![Diagram of 7-Amino-5-(2-chlorophenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4e)](image)

A6 7-Amino-5-(3-bromophenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4f)

Brown crystals; mp: 259–260°C; yield: 0.386 g (90%); (toluene/acetone 10:5); $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta$ 6.97 (1H, t, $J = 7.2$ Hz, Ar–H), 7.04 (2H, t, $J = 7.2$ Hz, Ar–H), 7.52, 7.54 (2H, dd, $J = 4.2$ and 7.8 Hz, Ar–H), 7.77 (1H, t, $J = 1.2$ Hz, Ar–H), 7.79 (1H, d, $J = 1.2$ Hz, Ar–H), 7.84 (1H, t, $J = 6.6$ Hz, Ar–H), 7.94 (2H, d, $J = 7.8$ Hz, Ar–H), 7.98 (1H, t, $J = 1.8$ Hz, Ar–H), 9.15 (2H, br, s, NH$_2$), 9.53 (1H, S, NH). Analysis results for C$_{20}$H$_{12}$BrN$_4$: C, 55.83; H, 2.81; Br, 18.57; N, 22.79; found: C, 55.88; H, 2.92; Br, 18.66; N, 22.52; EIMS (m/z): 429.01 [M+].

![Diagram of 7-Amino-5-(3-bromophenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (4f)](image)

A7 7-Phenyl-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (7a)

Brown crystals; mp: 238–240°C; yield: 0.286 g (92%); 
$^1$H NMR (600 MHz, DMSO-d$_6$) $\delta$ 6.94 (1H, t, $J = 7.2$ Hz, Ar–H), 7.26 (2H, t, $J = 7.8$ Hz, Ar–H), 7.34 (1H, d, $J = 4.8$ Hz, Ar–H), 7.60–7.62 (3H, m, Ar–H), 7.63 (3H, t, $J = 2.4$ Hz, Ar–H), 7.64–7.67 (3H, m, Ar–H), 8.12 (1H, d, $J = 1.8$ Hz, C$_{6}$–H), 8.15 (1H, d, $J = 1.2$ Hz, Ar–H), 8.65 (1H, $J = 4.8$ Hz, C$_{6}$–H), 9.59 (1H, s, NH); $^{13}$C NMR (150 MHz, DMSO-d$_6$) $\delta$ 66.3–67.89, 109.24, 113.47, 117.95, 121.39, 128.6, 129.64, 129.74, 131.51, 140.48, 145.9, 151.78, 152.22, 155.91. Analysis results for C$_{19}$H$_{16}$N$_{6}$: C, 73.30; H, 4.21; N, 22.49; found: C, 73.22; H, 4.31; N, 22.42; EIMS (m/z): 311.17 [M+].

![Diagram of 7-Phenyl-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (7a)](image)

A8 7-(2-Nitrophenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (7b)

Yellow crystals; mp: 268–270°C; yield: 0.320 g (90%); 
$^1$H NMR (600 MHz, DMSO-d$_6$) $\delta$ 6.90–6.93 (1H, m, Ar–H), 7.17–7.20 (2H, m, Ar–H), 7.39–7.41 (2H, m, Ar–H); 7.46 (1H, $J = 4.8$ Hz, Ar–H); 7.84–7.86 (1H, m, Ar–H), 7.94–7.97 (2H, m, Ar–H), 8.03–8.05 (1H, m, Ar–H), 8.39, 8.41 (1H, dd, $J = 1.2$, 1.2 Hz, C$_{6}$–H), 8.79 (1H, $J = 4.8$ Hz, C$_{6}$–H), 9.56 (1H, s, Ar–H); $^{13}$C NMR (150 MHz, DMSO-d$_6$) $\delta$ 68.12, 109.70, 113.06, 117.91, 117.99, 121.66, 124.63, 124.81, 128.49, 132.71, 134.98, 140.03, 144.57, 147.51, 150.51, 152.92, 156.09. Analysis performed for C$_{20}$H$_{12}$NO$_2$: C, 64.04; H, 3.39; N, 23.58; found: C, 64.12; H, 4.01; N, 23.67; EIMS (m/z) 356.02 [M+].

![Diagram of 7-(2-Nitrophenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (7b)](image)
A9 7-(4-Methylphenyl)-2-(phenylamino) pyrazolo[1,5-α]pyrimidine-3-carbonitrile (7c)

Reddish brown crystals; mp: 270–272°C; yield: 0.289 g (89%); (toluene/acetone 10:6); $^1$H NMR (400 MHz, DMSO-$d_6$) δ 2.38 (3H, s, CH$_3$), 6.94–7.69 (9H, m, Ar–H), 8.10 (1H, d, $J = 1.2$ Hz, C$_5$–H), 8.66 (1H, d, $J = 4.8$ Hz, C$_6$–H), 9.59 (1H, s, NH). Analysis performed for C$_{20}$H$_{15}$N$_5$: C, 73.83; H, 4.65; N, 21.52; found: C, 73.88; H, 4.62; N, 21.55.

A10 7-(4-Methoxyphenyl)-2-(phenylamino) pyrazolo [1,5-α]pyrimidine-3-carbonitrile (7d)

Orange crystals; mp: 168–170°C; yield: 0.307 g (88%); (toluene/acetone 10:6); $^1$H NMR (400 MHz, DMSO-$d_6$) δ 3.34 (3H, s, OCH$_3$), 6.92–7.57 (9H, m, Ar–H), 8.13 (1H, d, $J = 1.2$ Hz, C$_5$–H), 8.65 (1H, d, $J = 4.8$ Hz, C$_6$–H), 9.85 (1H, s, NH). Analysis results for C$_{20}$H$_{15}$N$_5$O: C, 70.37; H, 4.43; N, 20.52; found: C, 70.44; H, 4.42; N, 20.57.