A new method for the synthesis of 2,4-diamino-6-arylpyrimidines

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A method for the synthesis of 2,4-diamino-6-arylpyrimidines from guanidine and α-chlorocinnamonitriles was developed. The starting nitriles can be easily prepared by catalytic olefination reaction.

Key words: 2,4-diamino-6-arylpyrimidines, α-chlorocinnamonitriles, guanidine, catalytic olefination reaction.

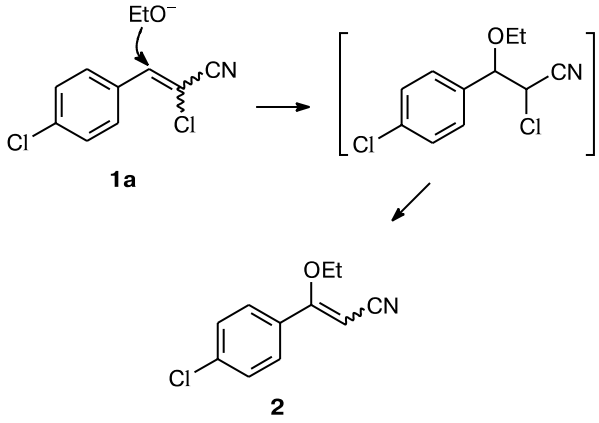
Catalytic olefination, which is essentially copper-catalyzed reactions of carbonyl compound hydrazones with polyhaloalkanes,[1] opens up the route to α-chlorocinnamonitriles from hydrazones of aromatic aldehydes and trichloroacetonitrile.[2] We assumed that the reactions of the products obtained with guanidine can afford 2,4-diamino-6-arylpyrimidines, which are valuable organic reagents[3] with a potential biological activity.[4]

Several methods for the synthesis of 2,4-diamino-6-arylpyrimidines have been documented. For instance, 2,4-diamino-6-phenylpyrimidine was obtained by condensation reactions of dicyanodiamide with acetophenone[5] and of guanidine with phenylpropiolonitrile[6] or β-bromocinnamonitriles.[7] Nucleophilic substitution for potassium amide in 4-arylpyrimidines gives the corresponding products in low yields.[8] A series of substituted diaminopyrimidines were obtained by the Suzuki reaction from 2,4-diamino-6-chloropyrimidine.[9]

The conditions of the reaction with guanidine were optimized for a model 2-chloro-3-(4-chlorophenyl)acrylonitrile (**1a**). We found that guanidine nitrate does not react with the substrate in boiling ethanol without a base. In the presence of NaOH, K_2CO_3, or NaOEt or with the use of guanidine carbonate, the product obtained was 3-(4-chlorophenyl)-3-ethoxyacrylonitrile (**2**) instead of the expected pyrimidine; *i.e.*, a nucleophilic ethoxide anion attacks the β-position of substituted acrylonitrile with subsequent elimination of hydrogen chloride (Scheme 1).

The target 2,4-diamino-6-(4-chlorophenyl)pyrimidine (**3a**) can be obtained by carrying out the reaction in DMSO or DMF; however, its yield is low. With compound **3a** as an example, we demonstrated that *tert*-butyl alcohol is the optimum solvent for the synthesis of diaminopyrimidines.

Scheme 1



Solvent	Bu^{t}OH	DMSO	DMF
Yield (%)	67	35	21

Under the optimized conditions, a series of diaminopyrimidines **3a—g** was synthesized from various nitriles **1a—g** in good yields (Table 1). The presence of electron-donating substituents (Me and OMe) in the aromatic ring substantially increases the reaction time compared to com-

Table 1. Synthesis of 2,4-diamino-6-arylpyrimidines **3a—g**

Compound	Ar	Yield (%)
3a	4-Cl-C_6H_4	67
3b	4-OMe-C_6H_4	53
3c	4-NO_2-C_6H_4	55
3d	3-NO_2-C_6H_4	36
3e	2-Naphthyl	50
3f	1-Naphthyl	55
3g	4-Me-C_6H_4	54

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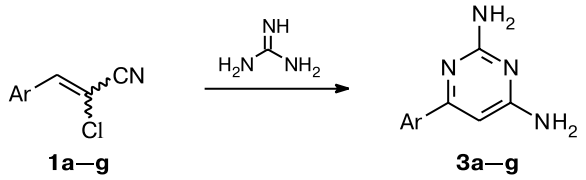
Scheme 2



1a—g **3a—g**

pounds bearing electron-withdrawing substituents (NO_2); this can be associated with the effect of the substituent on the increase or decrease in the electron density at the C(3) atom of the nitrile.

Thus, we developed the novel method for the synthesis of 2,4-diamino-6-arylpyrimidines, which can be a convenient alternative for their preparation because of the simple procedure, good yields, and accessible starting reagents.

Experimental

IR spectra were recorded on a UR-20 spectrophotometer (Nujol). ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 (^{1}H) and 100 MHz (^{13}C), respectively) in $CDCl_3$ and DMSO with Me_4Si as the internal standard. TLC was carried out with Merck 60 F_{254} plates; Merck silica gel (63—200 mesh) was used for column chromatography.

Compounds **1a**—**g** were prepared according to the previously described procedures.[2]

Synthesis of diaminopyrimidines 3a—g (general procedure). A stirred solution of an α-chlorocinnamonitrile **1a**—**g** (1 mmol) and guanidine carbonate (0.36 g, 2 mmol) was refluxed in 2 mL of *tert*-butyl alcohol for 4 to 20 h (TLC monitoring). The precipitate that formed was filtered off and washed with ethanol (2 mL). The solvent was removed in a rotary evaporator and the product was purified on a thin layer of silica gel with ethyl acetate as the eluent. Compound **3a** was identified as hydrochloride.

The IR spectra of all products contained the absorption bands of amino groups at 3470 to 3280 and 1630 cm^{-1}.

2,4-Diamino-6-(4-chlorophenyl)pyrimidine hydrochloride (3a · HCl) was obtained in 67% yield, slightly yellowish crystals, m.p. 288—289 °C (*cf.* Ref. 10: 291—292 °C), R_f 0.15 (ethyl acetate). ^{1}H NMR (DMSO-d_6), δ: 8.42, 8.20 (both br.s, 1 H each, NH); 7.90, 7.64 (both d, 2 H each, H_{arom}, J = 8.7 Hz); 6.44 (s, 1 H, CH); 3.83 (br.s, 3 H, NH_3^+).

2,4-Diamino-6-(4-methoxyphenyl)pyrimidine (3b) was obtained in 53% yield, yellow crystals, m.p. 210—212 °C (*cf.* Ref. 9: 212—215 °C), R_f 0.12 (ethyl acetate). ^{1}H NMR (DMSO-d_6), δ: 7.84, 6.98 (both d, 2 H each, H_{arom}, J = 8.7 Hz); 6.36 (br.s, 2 H, NH_2); 6.15 (s, 1 H, CH); 6.02 (br.s, 2 H, NH_2); 3.78 (s, 3 H, Me).

2,4-Diamino-6-(4-nitrophenyl)pyrimidine (3c) was obtained in 55% yield, yellow crystals, m.p. 210—215 °C, R_f 0.30 (ethyl acetate). ^{1}H NMR (DMSO-d_6), δ: 8.28, 8.11 (both d, 2 H each, H_{arom}, J = 8.9 Hz); 6.57 (br.s, 2 H, NH_2); 6.32 (s, 1 H, CH); 6.17 (br.s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6), δ: 165.32, 163.76, 159.89, 147.88, 144.53, 127.39, 123.68, 92.05 (CH, pyrimidine). Found (%): C, 51.86; H, 3.88. $C_{10}H_9N_5O_2$. Calculated (%): C, 51.95; H, 3.92.

2,4-Diamino-6-(3-nitrophenyl)pyrimidine (3d) was obtained in 36% yield, yellow crystals, m.p. 212—216 °C (*cf.* Ref. 9: 213—216 °C), R_f 0.33 (ethyl acetate). ^{1}H NMR (DMSO-d_6), δ: 8.74 (s, 1 H, H_{arom}); 8.29—8.25 (m, 2 H, H_{arom}); 7.74 (t, 1 H, H_{arom}, J = 8.0 Hz); 6.49 (br.s, 2 H, NH_2); 6.33 (s, 1 H, CH); 6.13 (br.s, 2 H, NH_2).

2,4-Diamino-6-(2-naphthyl)pyrimidine (3e) was obtained in 50% yield, yellow crystals, m.p. 108—110 °C, R_f 0.1 (ethyl acetate). ^{1}H NMR (DMSO-d_6), δ: 8.47 (s, 1 H, H_{arom}); 8.03—7.90 (m, 4 H, H_{arom}); 7.55—7.51 (m, 2 H, H_{arom}); 6.44 (br.s, 2 H, NH_2); 6.38 (s, 1 H, CH); 6.07 (br.s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6), δ: 165.25, 163.59, 161.87, 135.62, 133.52, 132.77, 128.57, 127.85, 127.50, 126.68, 126.39, 125.60, 124.03, 91.14 (CH, pyrimidine). Found (%): C, 71.58; H, 5.31. $C_{14}H_8N_4$. Calculated (%): C 71.17; H 5.12.

2,4-Diamino-6-(1-naphthyl)pyrimidine (3f) was obtained in 55% yield, yellow crystals, m.p. 123—125 °C, R_f 0.1 (ethyl acetate). ^{1}H NMR (DMSO-d_6), δ: 8.19—8.16 (m, 1 H, H_{arom}); 7.95—7.92 (m, 2 H, H_{arom}): 7.56—7.48 (m, 4 H, H_{arom}); 6.41, 6.01 (both br.s, 2 H each, NH_2); 5.92 (s, 1 H, CH). ^{13}C NMR (DMSO-d_6), δ: 164.72, 164.44, 163.13, 143.84, 137.78, 133.31, 130.33, 128.55, 128.16, 126.08, 125.86, 125.75, 125.31, 95.72 (CH, pyrimidine). Found (%): C, 71.45; H, 5.34. $C_{14}H_8N_4$. Calculated (%): C, 71.17; H, 5.12.

2,4-Diamino-6-(4-methylphenyl)pyrimidine (3g) was obtained in 54% yield, yellow crystals, m.p. 117—120 °C (*cf.* Ref. 9: 118—120 °C), R_f 0.12 (ethyl acetate). ^{1}H NMR (DMSO-d_6), δ: 7.78, 7.23 (both d, 2 H each, H_{arom}, J = 8.0 Hz); 6.30 (br.s, 2 H, NH_2); 6.17 (s, 1 H, CH); 5.91 (br.s, 2 H, NH_2); 2.32 (s, 3 H, Me).

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