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Highly efficient synthesis of 5,6-disubstituted-5*H*-pyrrolo[2,3-*b*]-pyrazine-2,3-dicarbonitriles through a one-pot palladium-catalyzed coupling reaction/cyclization in water

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ABSTRACT

A highly efficient one-pot synthesis of 5,6-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazine-2,3-dicarbonitriles is presented. The reaction of 5-(alkyl-arylamino)-6-chloropyrazine-2,3-dicarbonitriles with phenylacetylene, catalyzed by Pd–Cu, in the presence of SDS as the surfactant in water, leads to the desired products in good-to-high yields.

Pyrrolo[2,3-*b*]pyrazines have gained significant attention as they exhibit diverse biological activities and clinical applications. They show antibronchospastic effects[1] and the ability to inhibit the activity of p38 MAP kinase.[2] These compounds also inhibit cyclin-dependent kinases (CDKs), thereby exhibiting antiproliferative effects.[3,4] Due to the potential applications of CDK inhibitors as novel agents for a variety of neurodegenerative disorders such as Alzheimer's disease, this family of compounds were named the 'aloisines' following the first name (Aloiz) of Dr. Alzheimer.[3b] CDKs are involved in numerous biological processes such as cellular differentiation, transcription, apoptosis, and cell cycle control.[5,6] Furthermore, CDKs have been linked to several diseases, for example, cancer, neurodegenerative diseases, and diabetes.[7]

Several approaches for the synthesis of pyrrolo[2,3-*b*]pyrazine cores have been developed, such as condensation of a benzonitrile derivative with an α-lithiated alkyl pyrazine,[4,8] palladium-catalyzed cyclization of 2-chloro-3-(methanesulfonamido)pyrazine with substituted alkynes under thermal[9] or microwave-assisted conditions,[10] and reaction of commercially available 2,3-dichloropyrazine with α-lithiated ketones, esters, and nitriles followed by cyclization with primary amines or hydrazines.[11] However, these methods have their own shortcomings concerning yields, nature of the substituents, and the use of toxic solvents and bases. Thus, a more general and safer practical approach to the synthesis of substituted pyrrolo[2,3-*b*]pyrazines is required.

Sonogashira cross-coupling with subsequent cyclization has been successfully utilized for the synthesis of carbocyclic[12] and heterocyclic compounds.[13] The use of water or aqueous solutions represents a technique to overcome the economical and the environmental problems caused by the use of toxic and harmful organic solvents in chemical reactions.[14] Several examples of Pd-catalyzed Sonogashira reactions in aqueous medium have already been reported.[15]

In continuation of our studies[16] on the Pd-catalyzed synthesis of new heterocyclic compounds of biological significance, and in particular the efficient synthesis of pyrrolo[2,3-*b*]quinoxalines,[17] we became interested in developing a synthetic route to 5,6-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazine-2,3-dicarbonitriles in water. In order to introduce two substituents on the pyrrolo[2,3-*b*]pyrazine-fused ring system, our retrosynthetic analysis revealed the use of 5-(alkyl-arylamino)-6-chloropyrazine-2,3-dicarbonitriles and phenylacetylene as the starting materials (Scheme 1). The palladium-catalyzed cross-coupling reaction is the key step in this synthesis.

The starting materials **1a–h** were prepared from commercially available diaminomaleonitrile and oxalyl chloride in several steps via literature procedures (Scheme 2).[18]

When compounds **1a–h** were reacted with phenylacetylene (**2**) in the presence of bistriphenylphosphine palladium(II) chloride, copper(I) iodide, sodium lauryl sulfate (SDS), and potassium

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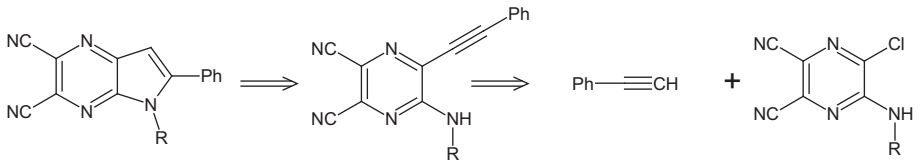
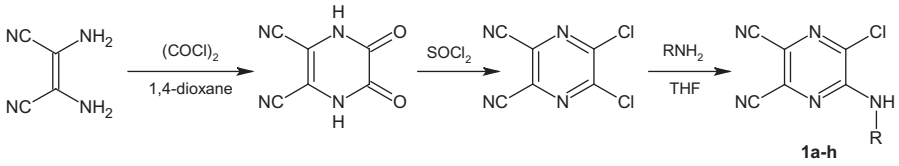
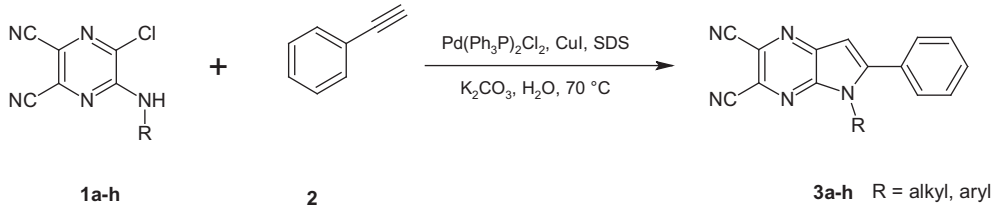


Scheme 1. Retrosynthetic analysis of 5,6-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazine-2,3-dicarbonitriles.

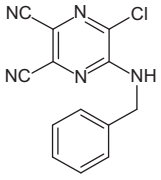
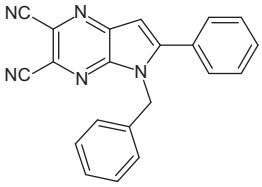
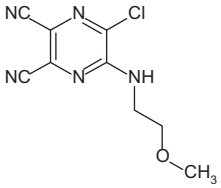
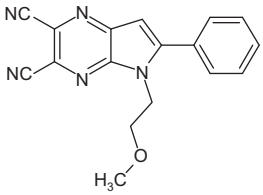
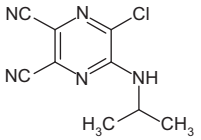
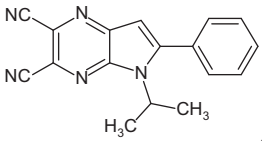
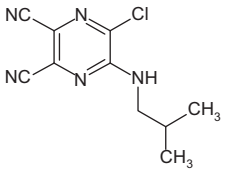
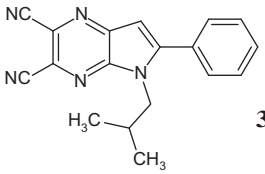


Scheme 2. Synthesis of 5-(alkyl-arylamino)-6-chloropyrazine-2,3-dicarbonitriles from diaminomaleonitrile and oxalyl chloride.



Scheme 3. Sonogashira coupling/cyclization of 5-(alkyl-arylamino)-6-chloropyrazine-2,3-dicarbonitriles with phenylacetylene. Reagents and conditions: Compound **1a**–**h** (0.556 mmol), **2** (1.11 mmol), K_2CO_3 (1.67 mmol), $Pd(Ph_3P)_2Cl_2$ (5 mol %), CuI (10 mol %), SDS (10 mol %), distilled H_2O (5 mL), 70 °C, 24 h, argon atmosphere.

Table 1
Synthesis of 5,6-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazine-2,3-dicarbonitriles

Entry	Amine **2**	Product	Mp	Yield (%)
1		 **3a**	156	87
2		 **3b**	148	82
3		 **3c**	180	75
4		 **3d**	133	68

(*continued on next page*)

Table 1 (*continued*)

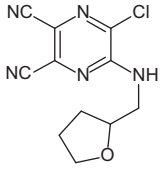
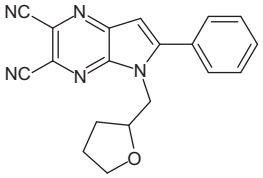
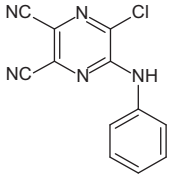
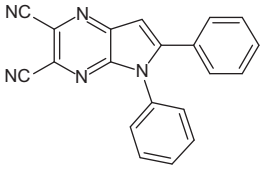
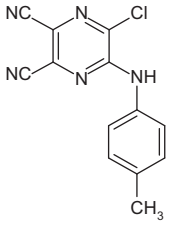
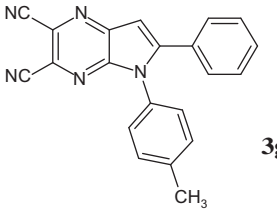
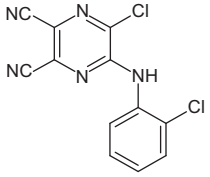
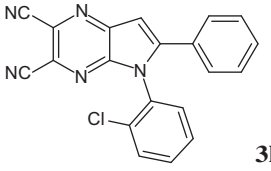
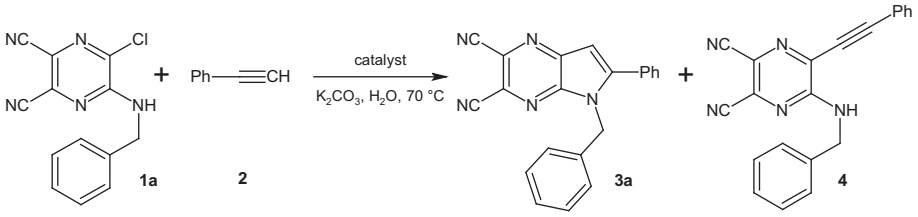
Entry	Amine **2**	Product	Mp	Yield (%)
5		 **3e**	147	78
6		 **3f**	230	96
7		 **3g**	241	93
8		 **3h**	220	90

Table 2
Effect of various catalysts on the reaction of 5-(benzylamino)-6-chloropyrazine-2,3-dicarbonitrile with phenylacetylene[a]



Entry	Catalyst	Yield[b] (%)	
		3	**4**
1	$PdCl_2$, Ph_3P, CuI	75	—
2	$Pd(Ph_3P)_2Cl_2$, CuI	87	—
3	$Pd(Ph_3P)_2Cl_2$	—	65
4	$PdCl_2$, Ph_3P	—	53
5	Pd/C, Ph_3P, CuI	20	60

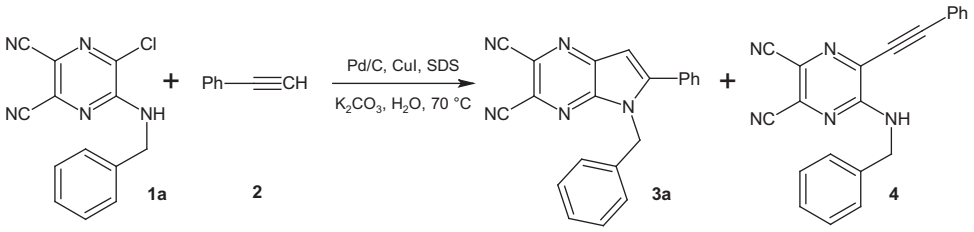
[a] Reaction conditions: **1a** (0.556 mmol), **2** (1.11 mmol), K_2CO_3 (1.67 mmol), Pd catalyst (5 mol %), CuI (10 mol %), SDS (10 mol %), distilled H_2O (5 mL), 70 °C, 24 h, argon atmosphere.

carbonate at 70 °C in water under an argon atmosphere, 5,6-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazine-2,3-dicarbonitriles **3a–h** were obtained in good-to-high yields (Scheme 3). The results are shown in Table 1.

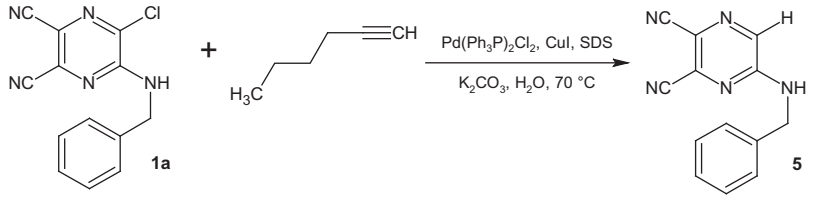
The effect of the catalyst also studied, and the results are presented in Table 2. $Pd(Ph_3P)_2Cl_2$ and CuI were found to be the best catalyst system (entry 2). Addition of copper(I) iodide was essential as the co-catalyst. The reactions carried out without CuI (entries 3 and 4), led only to 5-(benzylamino)-6-(phenylethynyl)pyrazine-2,3-dicarbonitrile (**4**) and no cyclization product was formed. When Pd/C, CuI was used as the catalyst system (entry 5), a mixture of products of **3** and **4** was formed (Scheme 4).

Potassium carbonate was found to be a suitable base for the reaction, giving cleaner products and better yields. The inclusion of the surfactant was also critical for the success of the reaction, and the yields decreased significantly when no surfactant was used.

The structural assignments of compounds **3a–h** were based on elemental analyses, and spectroscopic data. The ^1H NMR spectrum of **3d** showed an aromatic proton at δ 7.25, which was characteristic



Scheme 4. Pd/C-catalyzed reaction of 5-(alkyl-arylamino)-6-chloropyrazine-2,3-dicarbonitriles with phenylacetylene. Reagents and conditions: Compound **1a** (0.556 mmol), **2** (1.11 mmol), K_2CO_3 (1.67 mmol), Pd/C (5 mol %), CuI (10 mol %), SDS (10 mol %), distilled H_2O (5 mL), 70 °C, 24 h, argon atmosphere.



Scheme 5. Reaction of **1a** with an aliphatic alkyne to give the dechlorinated product. Reagents and conditions: Compound **1a** (0.556 mmol), hex-1-yne (1.11 mmol), K_2CO_3 (1.67 mmol), $Pd(Ph_3P)_2Cl_2$ (5 mol %), CuI (10 mol %), SDS (10 mol %), distilled H_2O (5 mL), 70 °C, 24 h, argon atmosphere.

of a fused pyrrole ring. The other five aromatic protons appeared at δ 7.63–7.79. In the aliphatic region, two doublets at δ 0.61 and δ 4.33 and a multiplet at δ 1.79 were assigned to the *iso*-butyl group.

The use of phenylacetylene was necessary as aliphatic alkynes, due to their low reactivity, gave only reduced products under the reaction conditions (Scheme 5). This was confirmed from the ^{1}H NMR spectrum of 5-benzylaminopyrazine-2,3-dicarbonitrile **5** which showed a characteristic singlet at δ 7.50 for the aromatic proton.

In conclusion, the chemistry outlined here provides a simple, one-pot, and highly efficient method for the synthesis of 5,6-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazine-2,3-dicarbonitriles in water from readily available starting materials in good-to-high yields.

General procedure for the preparation of 5,6-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazine-2,3-dicarbonitriles 3a–h

A mixture of 5-(alkyl-arylamino)-6-chloropyrazine-2,3-dicarbonitrile **1** (0.556 mmol), $Pd(Ph_3P)_2Cl_2$ (0.0278 mmol, 5 mol %), CuI (0.0556 mmol, 10 mol %), sodium lauryl sulfate (0.0389 mmol, 7 mol %), and K_2CO_3 (1.67 mmol) in H_2O (5 mL) under an argon atmosphere was treated with phenylacetylene (**2**) (1.11 mmol) slowly, and the resulting mixture was stirred at 70 °C for 24 h. After completion of the reaction, the mixture was filtered, and the remaining solid washed with H_2O and dried. The crude product was purified by column chromatography using $CHCl_3$–CH_3OH (99:1) as eluent.

5-(2-Methylpropyl)-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine-2,3-dicarbonitrile (3d)

Brown solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.61 (d, J = 6.8 Hz, 6H, $2CH_3$), 1.79 (m, 1H, CH), 4.33 (d, J = 7.6 Hz, 2H, CH_2), 7.25 (s, 1H, CH pyrrole), 7.63–7.66 (m, 3H, 3CH), 7.76–7.79 (m, 2H, 2CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 154.28, 140.66, 140.37, 130.55, 129.74, 129.20, 129.04, 126.04, 123.52, 115.58, 115.47, 102.69, 49.92, 28.16, 19.46; IR (KBr): 3120, 2950, 2200 (CN), 1523, 1478, 1458, 756 cm^{-1}; Anal. Calcd for $C_{18}H_{15}N_5$: C, 71.74; H, 5.02; N, 23.24. Found: C, 71.75; H, 4.99; N, 23.25.

5-(Benzylamino)pyrazine-2,3-dicarbonitrile (5)

White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.60 (d, J = 6.2 Hz, 2H, CH_2), 7.16–7.39 (m, 5H, 5CH), 7.50 (s, 1H, CH pyrazine), 8.22 (t, J = 6.2 Hz, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 153.66, 145.56, 139.94, 129.98, 128.28, 127.88, 127.26, 120.22, 115.21, 114.67, 43.97; IR (KBr): 3300 (NH), 3100, 2900, 2210 (CN), 1605, 1546, 1490, 995 cm^{-1}; Anal. Calcd for $C_{13}H_9N_5$: C, 66.37; H, 3.86; N, 29.77. Found: C, 66.36; H, 3.85; N, 29.79.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.016.

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