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Pot, atom and step economic (PASE) synthesis of 5-isoxazolyl-5*H*-chromeno[2,3-*b*]pyridine scaffold

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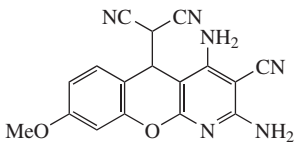
The new multicomponent reaction of salicylaldehydes, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and 3-phenylisoxazol-5(4*H*)-one gives substituted 2,4-diamino-5-(5-oxo-3-aryl-2,5-dihydroisoxazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles (50–74% yields), which are promising for biomedical applications.

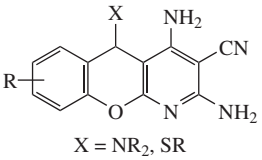
The design of functional organic and hybrid molecular systems has shown outstanding recent growth and is a high priority in the development of new technologies and novel functional materials.[1] In this context the concept of 'privileged medicinal structures or scaffolds' has emerged as one of the guiding principles of drug discovery design.[2] These scaffolds commonly consist of rigid hetero ring system that assigns well-defined orientation of appended functionalities for target recognition.[3]

Among various types of chromene systems, 2-amino-4*H*-chromenes are of particular utility since they belong to privileged medicinal scaffolds, and used for the treatment of viral hepatitis,[4] Alzheimer's disease,[5] cardiovascular disorders, epilepsy, inflammatory bowel syndrome,[6] hypertension and atherosclerosis.[7]

Increasing interest to 2-amino-4*H*-chromene derivatives bearing nitrile group is connected with their application in the treatment of human inflammatory diseases such as carcinoma,[8] arthritis,[9] leukemia,[10] and in cancer therapy.[11,12] Thus, the corresponding cyano-functionalized chromeno[2,3-*b*]pyridine **1** originating from 2-amino-4*H*-chromene scaffold was found to inhibit mitogen-activated protein kinase-activated protein kinase 2 (MK-2) and suppress the expression of TNFα in U937 cells.[13]



1



X = NR_2, SR

2

The known procedures for the synthesis of chromeno[2,3-*b*]-pyridine type **1** employ piperidine-catalysed interaction between (2-amino-3-cyano-4*H*-chromen-4-yl)malononitriles and malononitrile under reflux in ethanol.[14] Recently we have found more simple way to **1** directly from salicylic aldehydes and three equivalents of malononitrile.[15]

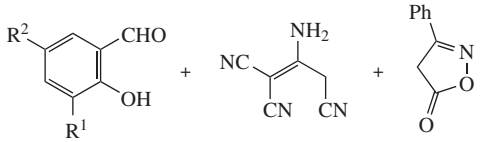
Multicomponent reaction (MCR) strategy has sufficient advantages over conventional linear-type synthesis due to its flexible, convergent and atom efficient nature.[16,17] The combination of pot, atom and step economy (PASE) in the synthesis provides a new line of approach towards developing environmentally friendly synthetic technologies.[18]

The MCR methods have been reported for the synthesis of only 5-S or 5-N substituted chromeno[2,3-*b*]pyridine derivatives of type **2** from malononitrile or its dimer, salicylaldehydes and thiols[19,20] or amines,[21] respectively.

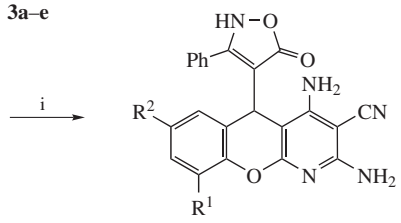
In the present study we report the first multicomponent synthesis of 5-C substituted chromeno[2,3-*b*]pyridines from salicylaldehydes, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and 3-phenylisoxazol-5(4*H*)-one (Scheme 1).

The first phase included development of a method for the preparation of 2,4-diamino-5-(5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile **4a** (Table 1).

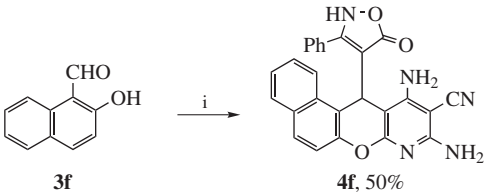
Catalyst-free reflux of salicylaldehyde **3a**, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and 3-phenylisoxazol-5(4*H*)-one in ethanol



3a–e



4a $R^1 = R^2 = H$, 74%
4b $R^1 = OMe$, $R^2 = H$, 65%
4c $R^1 = H$, $R^2 = Cl$, 72%
4d $R^1 = H$, $R^2 = Br$, 70%
4e $R^1 = R^2 = Cl$, 72%



3f **4f**, 50%

Scheme 1 *Reagents and conditions*: i, aldehyde **3** (3 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (3 mmol), 3-phenylisoxazol-5(4*H*)-one (3 mmol) and Py (5 ml), reflux.

Table 1 Multicomponent transformation of salicylaldehyde **3a**, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and 3-phenylisoxazol-5(4*H*)-one into chromeno-[2,3-*b*]pyridine **4a**.[a]

Entry	Solvent	Base (mol%)	*T*/°C	*t*/h	Isolated yield of **4a** (%)
1	EtOH	–	78	0.5	–
2	EtOH	AcONa (10)	78	0.5	7[b]
3	EtOH	AcONa (10)	78	4	10[b]
4	PrOH	AcONa (10)	97	4	15[b]
5	EtOH	Pyridine (10)	78	4	28
6	PrOH	Pyridine (10)	97	4	36
7	Pyridine	–	115	4	74
8	Pyridine	–	115	2	67

[a] Aldehyde **3a** (3 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (3 mmol), 3-phenylisoxazol-5(4*H*)-one (3 mmol) and solvent (5 ml). [b] ^{1}H NMR yields.

for 30 min (entry 1, Table 1) did not afford **4a**. In the presence of 10 mol% of NaOAc as catalyst and ethanol or 1-propanol as solvent, chromeno[2,3-*b*]pyridine **4a** was obtained in low yields even upon 4 h refluxing (entries 2–4). The use of 10 mol% pyridine in alcohols increased the yield of up to 28 and 36% (entries 5, 6). Best results were achieved on using pyridine as a solvent (entries 7, 8), when the product **4a** was obtained in 74 and 67% yield in 4 and 2 h, respectively.

Under optimum conditions thus found (entry 7, Table 1) other salicylaldehydes **3b–f** were similarly converted into corresponding chromeno[2,3-*b*]pyridines **4b–f** (Scheme 1).†

The crystal structure of compound **4a** (Figure 1)‡ was determined from X-ray powder diffraction (XRD) and verified using described approach.[22]

The possible mechanism of the chromeno[2,3-*b*]pyridines **4** formation is shown in Scheme 2. It is conceivable that the initial

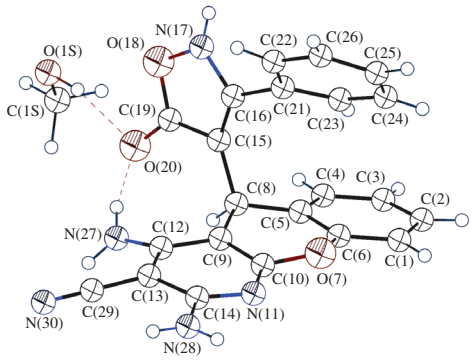
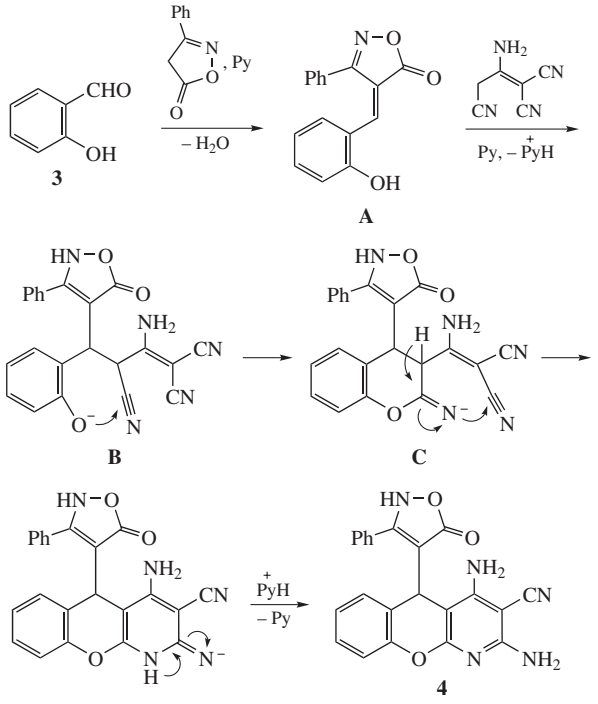


Figure 1 Molecular structure of **4a**·MeOH in crystal. Atoms are represented by spheres indicating their isotropic thermal displacements (p = 50%).

† *General (typical) procedure*. Aldehyde **3** (3 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (3 mmol), 3-phenylisoxazol-5(4*H*)-one (3 mmol) were refluxed in pyridine for 4 h. After the reaction was finished, the solid was filtered, washed with methanol and dried to isolate pure substituted 5-isoxazolyl-5*H*-chromeno[2,3-*b*]pyridine **4**. For characteristics of products **4a–f**, see Online Supplementary Materials.

‡ *Crystal data for* **4a**·MeOH. Crystals of $C_{23}H_{19}N_5O_4$ (M = 429.43) are triclinic, space group $P\bar{1}$ (no. 2), a = 15.1775(6), b = 6.8201(2) and c = 10.2028(4) Å, α = 86.114(2)°, β = 71.252(2)°, γ = 85.230(2)°, V = = 995.66(6) Å^3, Z = 2, T = 298 K, μ(CuKα_1) = 0.839 mm^{-1}, d_{calc} = = 1.432 g cm^{-3}. At average Δd of 0.01 Å (K_1 = 15) the refinement converged to $R_p/R_P/R_{WP}/R_{WP}/R_{Bragg}$ values of 3.802/13.935/5.609/15.099/1.780% with $R_{exp}/R_{exp'}$ of 1.163/3.132%, GOF = 4.822 (Figure S1, Online Supplementary Materials).

CCDC 1411988 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.



Scheme 2

step is formation of the Knoevenagel product **A** from condensation of aldehyde **3** and 3-phenylisoxazol-5(4*H*)-one. Then, a nucleophilic attack of the malononitrile dimer results in anion **B** formation. The subsequent intramolecular cyclization of **B** affords the intermediate anion **C**. The second intramolecular nucleophilic attack followed by tautomerization and aromatization produces chromeno[2,3-*b*]pyridines **4**.

In conclusion, the found procedure utilizes simple equipment; it is easily carried out and is valuable from the viewpoint of environmentally benign diversity-oriented large-scale processes. This efficient technique for 5-isoxazolyl-5*H*-chromeno[2,3-*b*]-pyridine scaffold formation represents the novel synthetic concept – PASE synthesis, which provides a new line of approach towards developing environmentally friendly synthetic technologies.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.11.008.

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