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PASE facile and efficient multicomponent approach to the new type of 5-C-substituted 2,4-diamino-5*H*-chromeno[2,3-*b*]pyridine scaffold

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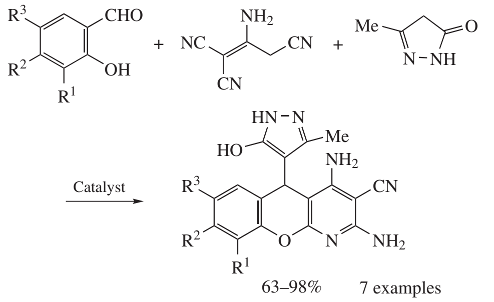
The new multicomponent reaction comprises the triethylamine catalyzed assembling of salicylaldehydes, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and 3-methyl-2-pyrazolin-5-one in small amount of propanol, which affords substituted 2,4-diamino-5-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles in 63–98% yields. This process is in agreement with PASE principles and opens the way to new chromeno[2,3-*b*]pyridine scaffold containing 3-methyl-2-pyrazolin-5-one fragment, which is promising for various biomedical applications.



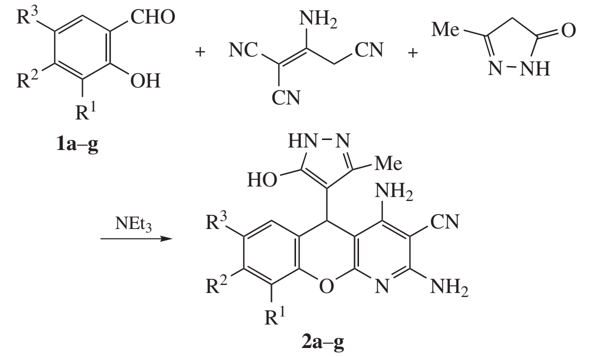
The application of pot, atom and step economy (PASE) principles in the organic synthesis reduces the number and amount of reagents as well as solvents and wastes. At the same time, reducing the number of stages also makes these processes far less harmful.[1] When many bonds are constructed in one reaction step, the simplified whole process becomes advantageous by saving time and improving other practical aspects in connection with the modern environmental demands.[2]

Chromenopyridine is recognized as an important scaffold in medicinal chemistry since compounds incorporating it show a large spectrum of pharmacological properties.[3–5] Among them, 5-carbon substituted 2,4-diaminochromeno[2,3-*b*]pyridines suppress expression of TNFα in U937 cells as perspective anticancer agents.[6] On the other hand, among the nitrogen-containing heterocycles functionally substituted 2-pyrazolin-5-ones have also received considerable attention in the field of medicinal chemistry.[7] Therefore, modification of chromeno[2,3-*b*]pyridine scaffold with 3-methyl-2-pyrazolin-5-one fragment might combine properties of both scaffolds and enhance the pharmacological activity.

In last decade, we have accomplished various types of PASE multicomponent transformations of carbonyl compounds and C–H acids.[8–13] Recently we have performed assembling of salicylaldehydes, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and 3-phenylisoxazol-5(4*H*)-one,[14] or 1,3-cyclohexanedione.[15] It is noteworthy that the development of eco-friendly green synthetic methods and the elimination of organic solvents in chemical processes is an important goal in organic chemistry.[16] Thus, solvent-free[17,18] and on-water methods have serious advantages as compared with usual in solvent methods.[19,20]

In this paper, we report our results on the novel multicomponent assembling of salicylaldehydes **1a**–**g**, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and 3-methyl-2-pyrazolin-5-one into the earlier unknown 2,4-diamino-5-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **2a**–**g** (Scheme 1, Table 1). Initially, the synthesis of compound **2a** has been carried out under solvent-free and ‘on-water’ reaction conditions[†] (Table 1, entries 1–4), however, in only 9–45% yields.

Nowadays, solvent-assisted (‘on-solvent’) methods due to their flexibility, high rates and selectivity find more application in comparison with solvent-free ones.[21] These ‘on-solvent’ methodologies[22–24] have been suggested for multicomponent



a $R^1 = R^2 = R^3 = H$ (98%)
b $R^1 = R^2 = H, R^3 = Me$ (94%)
c $R^1 = MeO, R^2 = R^3 = H$ (90%)
d $R^1 = R^3 = H, R^2 = OH$ (89%)
e $R^1 = R^2 = H, R^3 = Br$ (68%)
f $R^1 = R^2 = H, R^3 = NO_2$ (63%)
g $R^1 = R^3 = Cl, R^3 = H$ (64%)

Scheme 1

[†] *Solvent-free procedure*. A mixture of salicylaldehyde **1** (3 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (3 mmol, 0.4 g) and 3-methyl-2-pyrazolin-5-one (3 mmol, 0.3 g) with or without catalyst was heated for 1 h. The crude solid was then analyzed by ^{1}H NMR spectroscopy.

[‡] *‘On-solvent’ procedure*. Triethylamine (0.3 mmol) was added to a stirred emulsion of salicylaldehyde **1** (3 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (3 mmol, 0.4 g) and 3-methyl-2-pyrazolin-5-one (3 mmol, 0.3 g) in propanol (2 ml) at ambient temperature. The resulting mixture was refluxed for 1 h, cooled, transferred on filter, washed with methanol (2×3 ml) and dried to isolate pure compound **2**. In some cases additional crystallization from DMSO was needed.

Table 1 Multicomponent assembling of salicylaldehyde **1a**, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and 3-methyl-2-pyrazolin-5-one into chromeno[2,3-*b*]pyridine **2a**.^{a,b}

Entry	Solvent	Catalyst	t/h	T/°C	Yield of **2a** (%)
1	Solvent-free^a	–	1	80	9^c
2	Solvent-free^a	KF	1	80	15^c
3	Solvent-free^a	AcONa	1	80	19^c
4	H_2O	–	1	80	45^c
5	MeCN	–	1	82	37^c
6	MeCN	Morpholine	1	82	59^c
7	MeCN	Piperidine	1	82	63^c
8	MeCN	Et_3N	1	82	67^c
9	Pyridine	–	1	116	72^d
10	EtOH	Et_3N	1	78	83^d
11	PrOH	Et_3N	1	98	98^d
12	PrOH	Et_3N	0.5	98	71^d

^{a}Salicylaldehyde **1a** (3 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (3 mmol), 3-methyl-2-pyrazolin-5-one (3 mmol) were heated with 10 mol% of catalyst or without catalyst. ^{b}The same amounts of the reactants were heated under reflux in solvent (2 ml) with 10 mol% of catalyst or without catalyst. ^{c}NMR data. ^{d}Isolated yield.

reactions in minimum quantity of solvent. For example, in reagent mixtures or emulsions the components are not fully dissolved, and this would increase the efficiency of the total synthetic processes.

Therefore, the next experiments have been carried out with minimum quantity of solvent (2 ml) in emulsions under 'on-solvent' conditions. Reactions in MeCN in the presence of amines as catalysts afforded **2a** in 59–67% yields (Table 1, entries 6–8). The best results were obtained in boiling propanol with 10 mol% of Et_3N (1 h reaction time). Under these optimal conditions, product **2a** was formed in excellent 98% yield (entry 11) and a series of new substituted chromeno[2,3-*b*]pyridines **2a–g** was obtained in 63–98% yields (see Scheme 1).‡ The structures of compounds **2a–g** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry data. The structure of compound **2a** was also confirmed by X-ray powder diffraction study (Figure 1).§

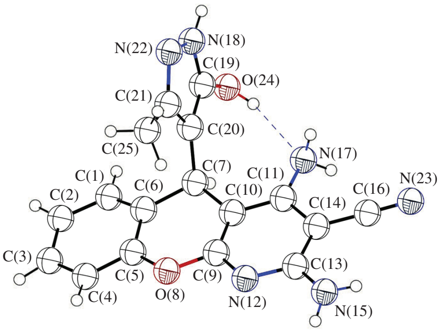
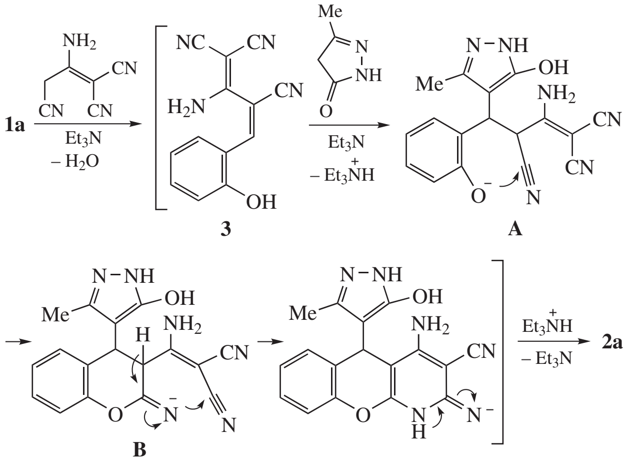


Figure 1 Molecular structure of chromeno[2,3-*b*]pyridine **2a** in crystal. Atoms are represented by spheres indicating their isotropic thermal displacements (p = 50%).

Based on the current results and the mechanistic data on multicomponent formation of chromenopyridine moiety from carbonyl compounds and C–H acids,[25, 26] the following mechanism for our process can be suggested by the example of transformation of salicylaldehyde **1a** (Scheme 2). The initial step is formation of the Knoevenagel adduct **3** from substrate **1a** and 2-aminoprop-1-ene-1,1,3-tricarbonitrile. Next, the nucleophilic attack of 3-methyl-2-pyrazolin-5-one results in anion **A**, whose subsequent intramolecular cyclization leads to anion **B**. The second intramolecular cyclization followed by tautomerization and aromatization produces chromeno[2,3-*b*]pyridine **2a**.



Scheme 2

Thus, highly efficient PASE 'on-solvent' reaction of salicylaldehydes, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and 3-methyl-2-pyrazolin-5-one catalyzed by triethylamine in small amount of propanol leads to earlier unknown substituted 2,4-diamino-5-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles. This new process opens an effective and facile 'one-pot' way to obtain a novel type of substituted chromeno[2,3-*b*]pyridines, the promising compounds for the treatment of human inflammatory TNFα-mediated diseases, cancer, tubercular, rheumatic therapy, and different biomedical applications. This procedure utilizes simple equipment; it is easily carried out and is valuable from the viewpoint of environmentally benign diversity-oriented large-scale processes. The elaborated technique represents the novel synthetic concept, PASE 'on-solvent' multicomponent strategy, 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.2018.07.010.

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*2,4-Diamino-5-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile* **2a**. White solid; 0.98 g (98%); mp 338–339 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.64 (s, 3H, Me), 4.93 (s, 1H, CH), 6.23 (s, 2H, NH_2), 6.40 (s, 2H, NH_2), 7.02–7.15 (m, 3H, Ar), 7.18–7.28 (m, 1H, Ar), 10.88 (br. s, 2H, NH+OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 9.7, 27.0, 70.8, 89.6, 105.6, 115.8, 116.4, 123.7, 123.9, 127.7, 129.4, 137.8, 149.9, 156.8, 158.4, 159.1, 159.2. IR (KBr, ν/cm^{-1}): 3402, 3185, 2202, 1641, 1600, 1566, 1488, 1395, 1259, 1063. MS, m/z (%): 334 [M$^+$] (35), 301 (3), 237 (100), 195 (15), 171 (32), 128 (3), 98 (65), 79 (34), 52 (18), 39 (24). Found (%): C, 60.89; H, 4.15; N, 25.08. Calc. for $C_{17}H_{14}N_6O_2$ (%): C, 61.07; H, 4.22; N, 25.14.

For characteristics of compounds **2b–g**, see Online Supplementary Materials.

§ *Crystal data for* **2a**: $C_{17}H_{14}N_6O_2$ (M = 334.34), triclinic, space group $P\bar{1}$ (no. 2), a = 6.47435(7), b = 10.13429(13) and c = 13.01634(14) Å, α = 117.0736(9)°, β = 95.5182(8)°, γ = 82.7553(6)°, V = 753.659(16) Å^3, Z = 2, T = 298 K, μ(Cu$K\alpha_1$) = 0.844 mm^{-1}, d_{calc} = 1.473 g cm^{-3}. At average Δd of 0.010 Å (K_1 = 44) the refinement converged to $R_\text{P}/R'_\text{P}/R_\text{WP}/R'_\text{WP}/R_\text{Bragg}$ values of 2.345 / 6.921 / 3.364 / 7.543 / 1.143% with $R_\text{exp}/R'_\text{exp}$ of 1.098 / 2.461%, GOF = 3.065.

CCDC 1821376 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.

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