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Regioselective synthesis of two types of highly substituted 2-pyridones through similar multicomponent reactions

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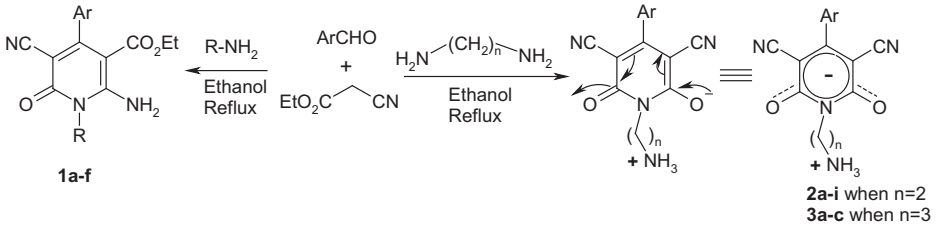
ABSTRACT

The refluxing of a mixture of ethylcyanoacetate, aromatic aldehydes, and primary monoamines in ethanol produces highly substituted 2-amino-6-pyridones such as 2-amino-1-(alkyl)-5-cyano-6-oxo-4-(aryl)-1,6-dihydropyridine-3-ethylcarboxylates in one-pot. On the other hand the refluxing of a mixture of ethylcyanoacetate, aromatic aldehydes, and primary diamines (1,2-ethylenediamine/1,3-propylenediamine) in ethanol furnishes symmetrical zwitterionic 2-pyridones such as 1-(2-amino-ethyl/3-amino-propyl)-6-hydroxy-2-oxo-4-(aryl)-1,2-dihydropyridine-3,5-dicarbonitriles. The result shows that primary diamines and monoamines react differently in the reactions, which provides new mechanistic insight into the regioselective synthesis of these biologically important compounds.

Apart from having environmental and economically positive implications, one-pot multicomponent coupling reactions (MCRs) have been proven to be a very elegant and rapid way to access complex structures in a single synthetic operation from simple building blocks. They also address fundamental principles of synthetic efficiency and reaction design, and show atom-economy and selectivity.[1] In this context, Hantzsch reaction for the synthesis of dihydropyridines (DHPs) shows interesting features of MCR. More than a century ago the first 1,4-DHPs were obtained by Hantzsch.[2] After that a number of modified methods under improved conditions have been reported.[3] Hantzsch 1,4-dihydropyridine derivatives are often regarded as the models of the natural reduced nicotinamide-adenine dinucleotide (NADH) coenzyme which functions as redox reagent in biological reactions.[4] In our strategy, DHP which is formed as an intermediate, subsequently undergoes spontaneous oxidation to form 2-pyridones. 2-Pyridones have been used as lead compounds for the preparation of several drugs such as selective anticancer agents,[5] antiviral agents,[6] or inhibitors of Aβ-peptide aggregation, which play an important role in amyloid formation in Alzheimer's disease.[7] 2-Pyridones are important intermediates for the synthesis of polycyclic compounds having biological significance as illustrated by the recent synthetic approaches toward the camptothecin family of antitumor agents.[8] 2-Pyridones have been prepared by numerous methods,[9] for



Scheme 1. Synthesis of hexasubstituted 2-pyridones **1**–**3**.

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Table 1
Formation of 2-pyridones **1a–f** using primary monoamines

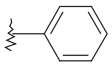
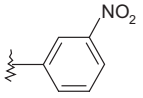
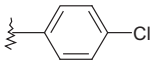
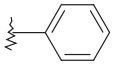
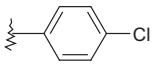
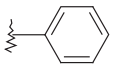
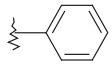
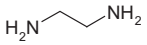
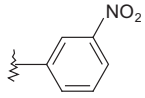
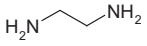
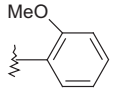
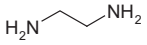
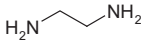
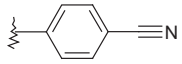
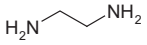
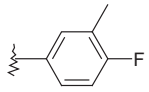
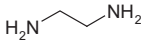
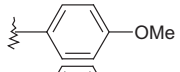
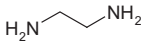
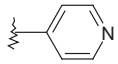
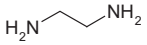
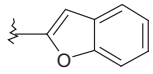
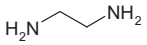
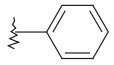
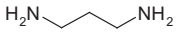
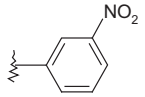
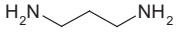
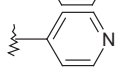
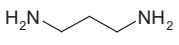
Entry	Ar of ArCHO	Amines (R-NH_2)	Products	Yield (%)	Melting point (°C)
1		Benzylamine	**1a**	71	202
2		Benzylamine	**1b**	69	158
3		Benzylamine	**1c**	67	184
4		*n*-Propylamine	**1d**	61	192
5		*n*-Propylamine	**1e**	63	234
6		*n*-Butylamine	**1f**	68	204

Table 2
Formation of products **2** and **3** using primary diamines

Entry	Ar of ArCHO	Diamines	Products	Time (min)	Yield (%)	Melting point (°C)
1			**2a**	90	52	>320
2			**2b**	60	54	315
3			**2c**	90	49	320
4			**2d**	90	50	314
5			**2e**	45	53	>320
6			**2f**	45	51	319
7			**2g**	90	47	288
8			**2h**	60	49	>320
9			**2i**	60	48	>320
10			**3a**	90	50	>320
11			**3b**	75	51	318
12			**3c**	60	52	>320

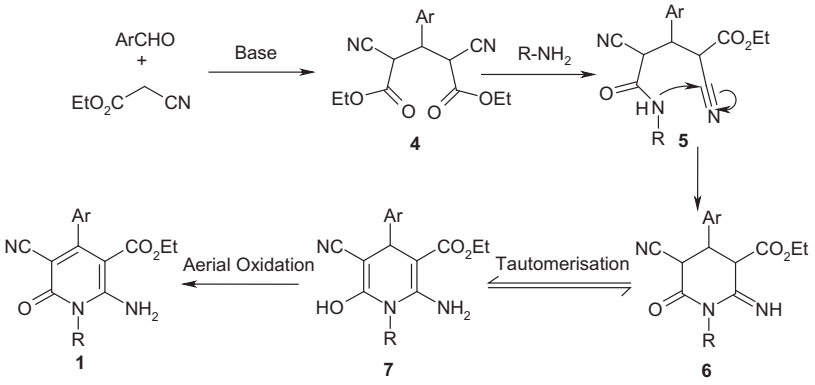
example, oxidation of an N-substituted pyridinium salt,[10] by Knoevenagel-type reactions,[11] such as cross-condensation of cyanoacetoamide and β-dicarbonyl compounds with basic catalysts or by the reaction of 2-pyrones with amides. Despite this large number of existing methods for their synthesis, new procedures are continuously being developed.[12]

Herein we like to introduce an approach for the synthesis of two types of highly substituted 2-pyridones, such as 2-amino-1-(alkyl)-5-cyano-6-oxo-4-(aryl)-1,6-dihydropyridine-3-ethylcarboxylates (**1a–f**) and 1-(2-amino-ethyl/3-amino-propyl)-6-hydroxy-2-oxo-4-(aryl)-1,2-dihydropyridine-3,5-dicarbonitriles (**2** or **3**) using primary monoamines and primary diamines as product determining factor (Scheme 1). The significance of the protocol relies on the construction of the pyridin-2(1*H*)-one skeleton with dense substitution patterns in one-pot. When an ethanolic solution of primary monoamines, aromatic aldehydes, and ethylcyanoacetate in 1:1:2 molar

proportion is refluxed for 16 h, 2-pyridones **1** are formed (Scheme 1 and Table 1).[13] But interestingly when primary diamines (1,2-ethylenediamine/1,3-propylenediamine) are used instead of primary monoamines, the symmetrical zwitterionic 2-pyridones (**2** or **3**) are precipitated out from the reaction mixture within 45 min–2 h under similar reaction condition (Scheme 1 and Table 2).[13] Some pirfenidone analogs which are antifibrotic agents and structurally close to compounds **1** such as 2-amino-1-(aryl)-5-cyano-6-oxo-4-(aryl)-1,6-dihydropyridine-3-ethylcarboxylates have been synthesized previously through stepwise procedure.[14]

The Knoevenagel condensation of aromatic aldehydes and ethylcyanoacetate, followed by Michael addition in the basic medium leads to adduct **4** (Scheme 2). Subsequently the primary amine attacks the ester carbonyl of adduct **4** to produce amide intermediates **5**. Then the intramolecular nucleophilic attack of amide nitrogen to the cyano group generates six-membered nitrogenous heterocycles **6** in a regioselective way. Probably, the sterically hindered secondary amide nitrogen prefers to attack the less hindered linear cyano group compared to ester carbonyl, although ester carbonyl is more reactive than cyano group. Subsequently the tautomerization of compound **6** leads to 1,4-DHP **7** which spontaneously oxidizes to 2-pyridones **1** under the reaction conditions, confirmed by X-ray crystallography (Fig. 1).[15] All the compounds are also characterized by ^{1}H and ^{13}C NMR spectroscopy.[16] It has been observed that this multicomponent reaction does not take place with aromatic primary amines due to their low nucleophilicity.

The synthesis of symmetrical 2-pyridones **2** or **3** comprises of an interesting mechanistic path way (Scheme 3). The intermediate **4** so formed (Scheme 2) undergoes a nucleophilic attack by diamine (1,2-ethylenediamine/1,3-propylenediamine) to the ester carbonyl to produce acyclic intermediate **8**. Then most likely the reaction involves an intramolecular nucleophilic attack on the remaining ester carbonyl to generate nine/ten-membered lactam intermediate **9**. Subsequently intramolecular nucleophilic attack of the amide nitrogen on the other amide carbonyl generates bicyclic intermediate **10** which produces monocyclic compound **11** through ring opening. After that the intermediate **11** follows the same reaction pathway as discussed earlier (Scheme 2) to produce intermediate **12** which furnishes zwitterionic 2-pyridones **13** through proton exchange. It was not possible to isolate any of the intermediates **4**–**12** under the reaction conditions. This is the



Scheme 2. Reaction mechanism of three-component one-pot cyclization in the formation of **1** with primary monoamines.

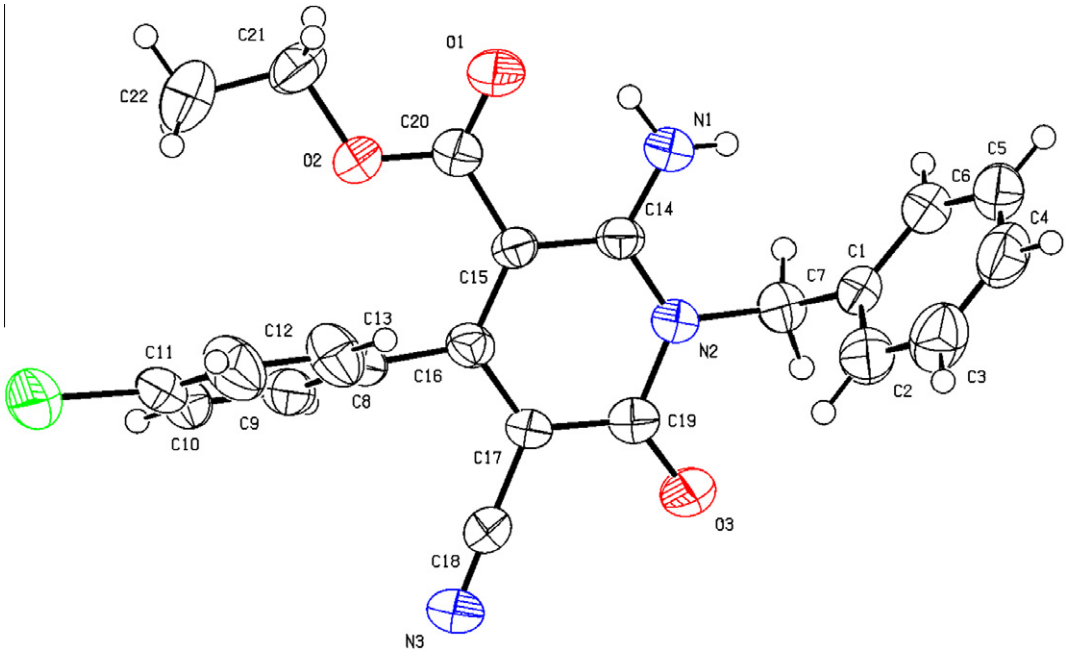
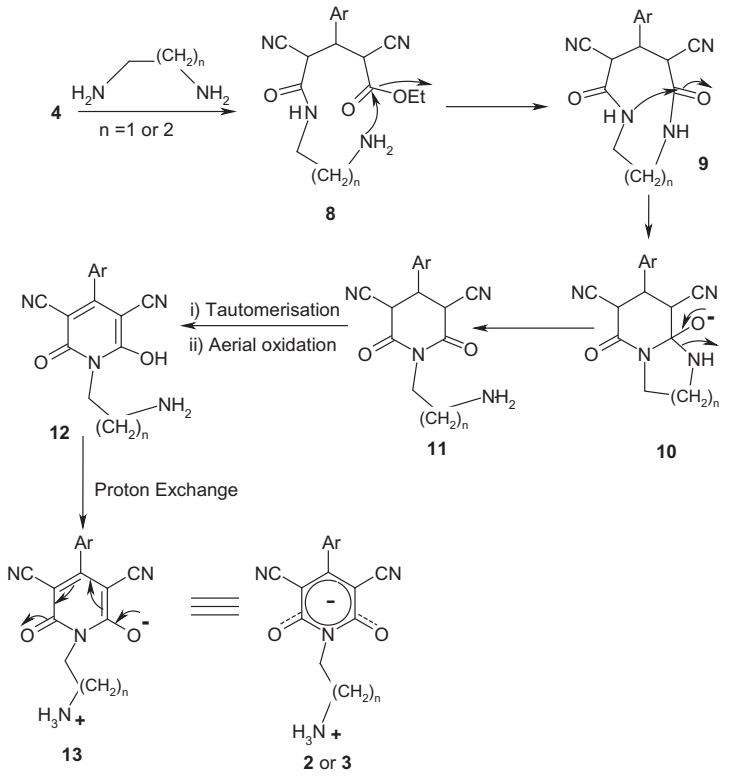


Figure 1. ORTEP diagram of compound **1c** with atom numbering scheme. Thermal ellipsoids are shown at the 50% probability. Color code: red, oxygen; blue, nitrogen; green, chlorine; large white, carbon; small white, hydrogen.



Scheme 3. Reaction mechanism of three-component one-pot cyclization for the formation of zwitterionic **2** and **3** with primary diamines.

first example of formation of zwitterions where highly acidic phenolic hydroxyl group participates in generating zwitterion with primary amine. The zwitterion **13** mainly exists as delocalized compounds **2** or **3** confirmed by NMR[16] and X-ray crystallography[15] (Fig. 2). It is obvious from the NMR spectra that only one amino group of ethylenediamine/propylenediamine is involved in the reaction. The second amino group becomes nonreactive for further reaction since it loses its nucleophilicity through protonation in products **2** or **3**. The zwitterionic compounds **2** or **3** are precipitated out from the reaction mixture due to its high polarity. Generally in ^{1}H NMR spectra the protons of the aliphatic amino groups come at δ ~0.5–3 ppm. In the products **2** or **3** due to strong electron-withdrawing effect of positively charged nitrogen atom, the attached three protons become deshielded (δ 6.0–8.0 ppm).

Figure 2 shows the crystal structure of **2a** where nitrogen atom N1 is quaternary and positively charged. The 2-pyridone ring is found planar indicating all the atoms in the ring are sp^2 hybridized. In the crystal structure the C9–O2 and C10–O1 bond distances are almost same, 1.23 and 1.24 Å, respectively. This indicates that the 2-pyridone ring in product **2a** is symmetrical which is further confirmed by ^{13}C NMR spectroscopy where the carbon atoms of two cyano groups (C12 and C13), the two ring carbon atoms attached to cyano groups (C8 and C11), and the two amide carbons (C9 and C10) are found pair wise equivalent.

The formation of zwitterionic compound **2a** and its charge distribution is evident from the solvent mediated crystal packing. The packing diagram in Figure 2 shows that each **2a** molecule forms hydrogen bonds with three water molecules such

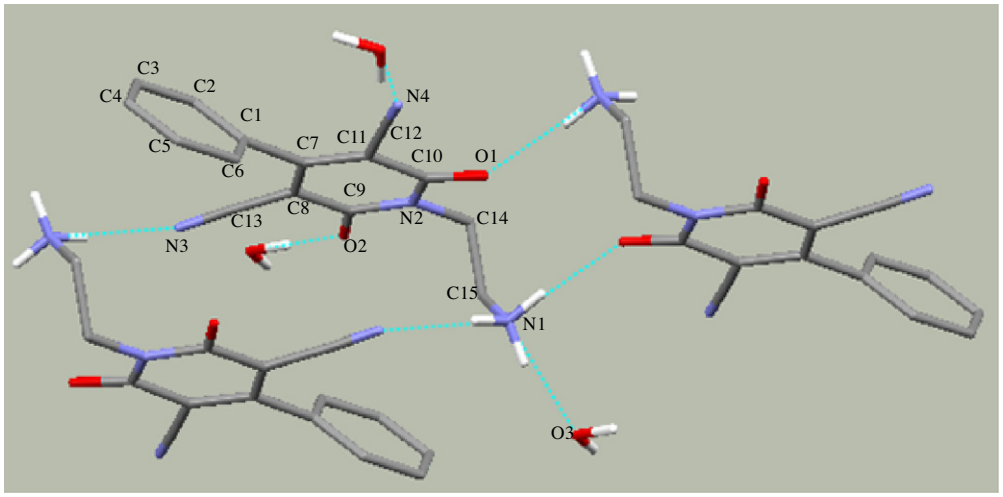


Figure 2. Crystal structure and packing diagram of compound **2a** (hydrogen bondings are shown in dotted line).

as –CN···H–OH, –CO···H–OH, and $–N^+–H···OH_2$. Remaining one –CN and one –CO of **2a** form hydrogen bonds with $–N^+–H$ groups of neighboring molecules as a result the compounds **2a** are aligned in an antiparallel fashion. This arrangement allows further electrostatic interactions between the oppositely charged groups of two closely packed **2a** molecules. It is interesting to note that a small molecule like **2a** is capable of forming seven intermolecular hydrogen bonds.

In summary, a multicomponent reaction involving ethylcyanoacetate, amines, and aromatic or heteroaromatic aldehydes to form hexasubstituted 2-pyridones has been developed. The process, which can include an additional component in a multicomponent protocol, allows the incorporation of two series of potentially bio-active 2-pyridones. The result shows that primary diamines and monoamines react differently in the reactions, which provides new mechanistic insight into the regioselective synthesis of these biologically important compounds. Further studies for the synthesis of similar compounds from other amines and active methylene compounds are currently underway to explore their biological activities and various aspects of molecular aggregation. The highly efficient binding motifs as observed in crystal structure of **2a** might be useful for the realization of water-stable supramolecular materials in future.

Acknowledgements

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Supplementary data

Supplementary data (IR, ^1H, ^{13}C data of compounds **1**, **2** and **3** and crystallographic data for **2b**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.010.

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13. *Typical procedure for preparation of 2-amino-1-benzyl-5-cyano-6-oxo-4-phenyl-1,6-dihydro-pyridine-3-ethylcarboxylate (**1a**)*: A mixture of benzaldehyde (1 mL, 9.8 mmol), ethylcyanoacetate (2.1 mL, 19.6 mmol) and benzylamine (1.1 mL, 9.8 mmol) is refluxed in ethanol (6.0 mL) for 16 h. The cold reaction mixture is poured into ice-cold water and extracted with ethylacetate. Then it is purified by column chromatography over silica gel (71% yield). *Typical procedure for the preparation of 1-(2-amino-ethyl)-6-hydroxy-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (**2a**)*: A mixture of benzaldehyde (2.3 mL, 22.5 mmol), ethylcyanoacetate (3.2 mL, 30 mmol) and 1,2-ethylenediamine (1 mL, 15 mmol) was refluxed in ethanol (6.0 mL) until a white solid product was precipitated out from the reaction mixture (time is mentioned in Table 2). The white solid product **2a** was isolated through filtration and thorough washing with methanol (52% yield). Then the compound **2a** was crystallized from a mixture of dimethylsulphoxide and water. *Typical procedure for the preparation of 1-(3-amino-propyl)-6-hydroxy-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (**3a**)*: A mixture of benzaldehyde (1.9 mL, 18 mmol), ethylcyanoacetate (2.6 mL, 24 mmol) and 1,3-propylenediamine (1 mL, 12 mmol) was refluxed in ethanol (6.0 mL) until a white solid product was precipitated out from the reaction mixture (time is mentioned in Table 2). Then the white solid product **3a** was isolated through filtration and thorough washing with methanol (50% yield).
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15. Crystallographic data for the structure **1c** and **2a** in this Letter have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 869051, 861220 respectively. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 01223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
16. *2-Amino-1-benzyl-5-cyano-6-oxo-4-phenyl-1,6-dihydro-pyridine-3-ethylcarboxylate (**1a**)*: ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.24 (m, 10H), 5.35 (s, 2H), 3.74 (qt, J = 7.2 Hz, 2H), 0.57 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 161.7, 159.6, 156.3, 143.1, 138.5, 133.1, 129.5, 128.6, 128.0, 126.7, 126.6, 116.0, 92.2, 92.0, 60.6, 45.7, 12.7. IR (in KBr): 3371(b), 2216, 1672 cm^{-1}; Anal. Calcd for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found C, 70.71; H, 5.11; N, 11.22. *1-(2-Amino-ethyl)-6-hydroxy-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (**2a**)*: ^1H NMR (300 MHz, DMSO-d_6): δ 7.64–7.29 (m, 5H), 6.60 (br s, $–NH_3$), 4.06 (t, J = 5.1 Hz, 2H), 2.96 (t, J = 5.1 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.4, 160.5, 136.1, 129.6, 128.0, 127.5, 118.9, 82.0, 38.6, 37.7; IR (in KBr): 3052(b), 2205, 1633 cm^{-1}; Anal. Calcd for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19. Found C, 64.23; H, 4.27; N, 19.92. *1-(3-Amino-propyl)-6-hydroxy-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (**3a**)*: ^1H NMR (300 MHz, DMSO-d_6): δ 7.44–7.35 (m, 8H), 3.87 (t, J = 6.3 Hz, 2H), 2.72 (t, J = 7.2, 2H), 1.82–1.77 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.0, 160.1, 136.1, 129.4, 128.3, 127.9, 118.6, 81.7, 37.0, 36.1, 25.9; IR (in KBr): 3057(b), 2207, 1635 cm^{-1}; Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found C, 65.24; H, 4.73; N, 18.98.