Substituent-Dictated Concise Synthesis of 4,6-Disubstituted *N*-Alkyl-2-pyridones and 2-Aminopyridines[1]

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Abstract: Functionalized *N*-alkyl-2-pyridones and 2-aminopyridines are useful precursors for the synthesis of various heterocyclic compounds of therapeutic importance. In this paper we have delineated and illustrated a direct methodology for the synthesis of 6-aryl-*N*-hydroxyethyl-4-methylsulfanyl-2-pyridones through the ring transformation of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones by ethanolamine. Surprisingly, the analogous reaction with 6-aryl-3-cyano-4-piperidin-1-yl-2*H*-pyran-2-ones afforded 2-aminopyridines in high yield instead of the corresponding 2-pyridones.

Keywords: *N*-alkyl-2-pyridone, 2-aminopyridine, ethanolamine, pyran-2-one, ring transformation reaction

Substituted *N*-alkyl-2-pyridones and 2-aminopyridines in a flexible or rigid conformation are common structural features found in many biologically important synthetic and natural products.[2] Molecules embedded with these scaffolds are known to exhibit diverse pharmacological activities as neuropeptide Y1 receptor antagonists,[3] muscle relaxants,[4] antitumor,[5] antifungal,[6] and antiviral[7] activities, free radical scavenging,[8] hypotensive,[9] and cardiotropic[10] activities, and inactivation of voltage-dependent K^+ channels.[11] From a chemical perspective, several dialkylaminopyridines such as DMAP, 4-pyrrolidinopyridine (PPY) and their analogues have been extensively used as catalysts in acylation and alkylation[12] reactions. In addition, 2-aminopyridines and 2-pyridinones are key intermediates in the synthesis of a variety of heterocyclic compounds of therapeutic importance.[13]

In general, the alkylation of 2-pyridone leads to both N- and O-alkylated product and the regioselectivity depends on the nature of the base, the structure of the alkyl halide, substituents on the pyridone ring, and the solvent employed.[14] Selective N-alkylation of 2-pyridone predominates in the presence of sodium salts but an increase in the size of alkyl halide favors O-alkylation. Numerous synthetic methodologies are available for the synthesis of 2-pyridones[15–22] but the methods for direct access to *N*-alkyl-2-pyridones are rare. Similarly, various approaches are known in the literature for the synthesis of aminopyridines.[23–25] Recently, we reported a regioselective approach to access 2-pyridones and 2-aminopyridines through nucleophile-induced ring transformation of 2*H*-pyran-2-ones using urea as the nucleophilic source.[26] Though palladium-catalyzed amination has been shown[27,28] to be of immense value as an alternative approach to preparing aminopyridines, the applicability of several of these methods suffers from a lack of generality, intolerance of many functional groups, or incompatibility with ring or *N*-alkyl chain substitution. Due to the difficulty in selective N-alkylation of 2-pyridone and the limitations of existing methodologies, we sought to develop a general synthetic route, which could directly provide N-alkylated pyridones and 2-aminopyridines. Herein, we report a one-pot synthesis of *N*-hydroxyethyl-2-pyridones and 2-aminopyridines through nucleophile-induced ring transformation of 2*H*-pyran-2-ones by ethanolamine.

The 2*H*-pyran-2-ones **1a**–**e** used as parent precursors have been conveniently prepared by the reaction of methyl 2-cyano-3,3-di(methylsulfanyl)acrylate with acetophenones as described earlier.[29] The unique features of the 2*H*-pyran-2-one **1** is the presence of three electrophilic centres; C2, C4, and C6 where the latter two are highly susceptible to nucleophiles due to the extended conjugation and the presence of the electron-withdrawing substituent at position three on the pyran ring. Our approach to synthesize *N*-alkyl-2-pyridones **2a**–**e** involved the reaction of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones **1a**–**e** with ethanolamine in ethanol at reflux temperature (Scheme 1). The reaction was monitored by TLC, which was complete in one to four hours. The resulting mixture was cooled to room temperature and left overnight. The white crystalline solid was filtered off and characterized as 6-aryl-3-cyano-4-(2-hydroxyethylamino)-2*H*-pyran-2-ones **3a**–**e**. The filtrate was evaporated to dryness and the desired pyridone (Table 1) was isolated in good yield by passing the crude material through a column using chloroform as an eluent.[30,31]

In order to confirm that the isolated products **2a**–**e** were 1-(2-hydroxyethyl)-4-methylsulfanyl-6-phenyl-1*H*-pyridin-2-ones and not 2-(6-aryl-2-imino-4-methylsulfanyl-2*H*-pyridin-1-yl)ethanols **4a**–**e**, an independent reaction with 3-carbomethoxy-4-methylsulfanyl-6-phenyl-2*H*-pyran-2-one (**5**) was carried out as shown in Scheme 2. After the usual work-up, we isolated two products 6-phenyl-*N*-hydroxyethyl-4-methylsulfanyl-2-pyridone (**6**) and 3-carbomethoxy-4-(2-hydroxyethylamino)-6-phenyl-2*H*-pyran-2-ones (**7**). The spectroscopic data of compound **6** exactly matched the data of compound **2a** suggesting that the assigned structures for compounds **2a**–**e** were correct.

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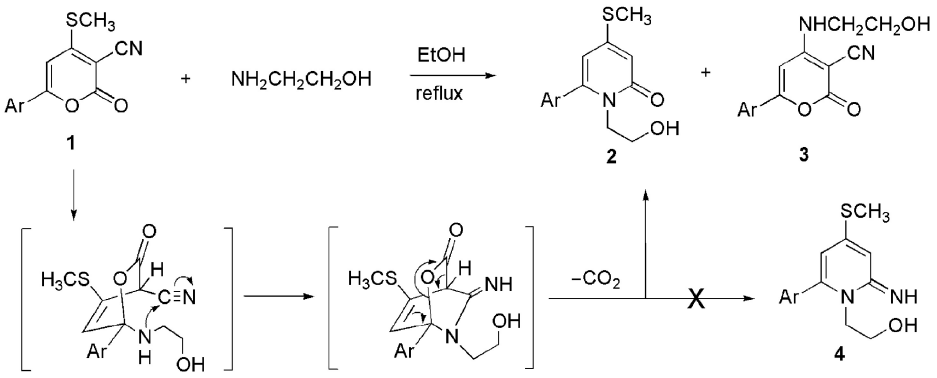


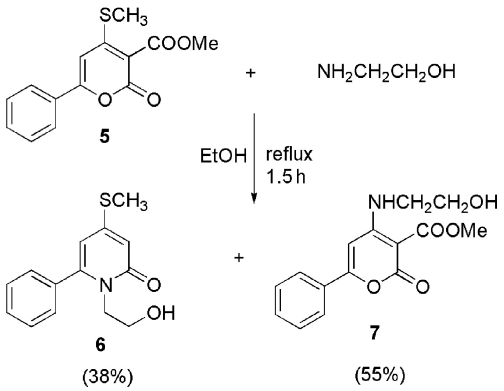
Scheme 1

Table 1 Synthesis of Pyridone

Compound	Ar	Reaction time (h)	Yield[a] (%)	
			2	**3**
a	C_6H_5	1.0	47	51
b	4-FC_6H_4	2.5	42	46
c	4-ClC_6H_4	2.0	40	51
d	4-BrC_6H_4	2.0	39	55
e	4-$CH_3C_6H_4$	3.5	41	53

[a] All the reactions were carried out at 80 °C in ethanol.

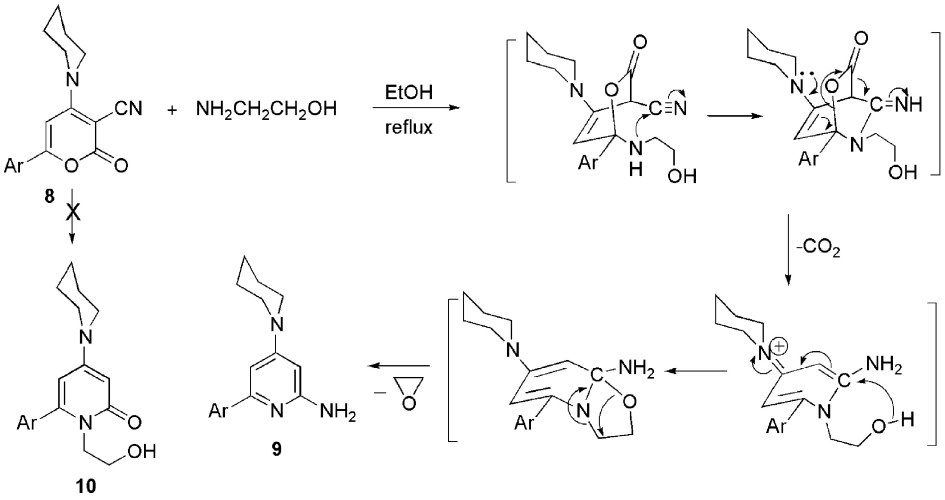
A plausible reaction mechanism for the formation of 6-aryl-*N*-hydroxyethyl-4-methylsulfanyl-2-pyridones **2** is depicted in Scheme 1. The reaction is possibly initiated by attack of the amino functionality of ethanolamine on the highly vulnerable electrophilic center C6 of 2*H*-pyran-2-one, followed by intramolecular cyclization involving the secondary amine and the nitrile functionality present at position 3 of 2*H*-pyran-2-one, this is followed by decarboxylation to give *N*-(2-hydroxyethyl)-1*H*-pyridin-2-ylideneamine intermediate. The imino group of the intermediate was readily hydrolyzed to the corresponding carbonyl functionality to afford 6-aryl-*N*-hydroxyethyl-4-methylsulfanyl-2-pyridone in good yield.[31]



Scheme 2

The lack of selectivity between compounds **2** and **3** under these reaction conditions prompted us to examine the course of the reaction in different solvents such as DMF, DMSO, benzene, and pyridine as well as vary the reaction temperatures. Unfortunately, all such efforts led to a mixture of compounds with different side products as indicated by TLC of various reaction mixtures. Even after many attempts, we could not selectively prepare 2-pyridones **2a**–**e** from 2*H*-pyran-2-ones **1a**–**e**. From the reaction mechanism described in Scheme 1, we found that the methylsulfanyl group at position 4 on the 2*H*-pyran-2-one **1** is playing a leading role in the formation of side product **3** due to the presence of the electron-withdrawing group at position 3 on the pyran ring and the good leaving group ability of the methyl sulfanyl group.

In order to prepare 2-pyridones exclusively, we attempted to reduce the electrophilicity at position 4 of lactone **1** by replacing a methyl sulfanyl group with a secondary amine. We then prepared 6-aryl-2-oxo-4-piperidin-1-yl-2*H*-pyran-3-carbonitriles **8a**–**f** by refluxing a solution of lactone **1** with piperidine in methanol for six to eight hours. Surprisingly, when we carried out the reaction with lactones **8a**–**f** and ethanolamine under the same reaction conditions as described in Scheme 1, we isolated new compounds 6′-aryl-3,4,5,6-tetrahydro-2*H*-[1,4′]bipyridinyl-2′-ylamines **9a**–**f** in high yields instead of the corresponding pyridones (Scheme 3). The 2-aminopyridines (Table 2) are the sole products of the reaction and are easily isolated by column chromatography and were characterized by spectroscopic means.[31] Distinctive characteristics of 2-aminopyridine **9d** include two sharp NH_2 signals in the IR spectrum at 3352 and 3456 cm^{-1} and a broad singlet in the ^1H NMR spectrum at 4.30 ppm for two protons, which disappeared after a D_2O shake. The replacement of the SMe group in **1** with a piperidine functionality did not yield 2-pyridones **10**, which showed that the functional groups (methylsulfanyl, piperidine) at position 4 in 2*H*-pyran-2-ones **1** dictated the direction of the reaction either towards the formation of 2-pyridones or 2-aminopyridines.



Scheme 3

Table 2 Synthesis of 2-Aminopyridine

Compound	Ar	Reaction time (h)	Yield[a] (%)
			9
a	C_6H_5	12	88
b	4-BrC_6H_4	12	87
c	4-ClC_6H_4	11	92
d	4-MeC_6H_4	10	90
e	4-$MeOC_6H_4$	11	90
f	Thienyl	12	84

[a] All the reactions were carried out at 80 °C in ethanol.

The possible reaction mechanism for the formation of 2-aminopyridines is depicted in Scheme 3. The reaction is initiated by attack of the amino functionality of ethanolamine at the C6 position of the 2*H*-pyran-2-one, followed by intramolecular cyclization involving secondary amine and nitrile functionality to give a bicyclic intermediate and decarboxylation. The intermediate underwent intramolecular cyclization followed by elimination to yield 2-aminopyridines **9a**–**f** in high yields.

In conclusion, our procedure for the preparation of *N*-alkyl-2-pyridones and 2-aminopyridines from the reaction of 2*H*-pyran-2-ones and ethanolamine is simple and convenient. A reaction of functionalized 4-methylsulfanyl-2*H*-pyran-2-ones with ethanolamine yielded 2-pyridones, while under the same reaction conditions, 4-(piperidin-1-yl)-2*H*-pyran-2-ones afforded 2-aminopyridines exclusively. This one-pot method is of significant importance due to its short reaction time, flexibility of introducing different substituents, and easy work-up.

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(30) **Synthesis of 6-aryl-*N*-hydroxyethyl-4-methylsulfanyl-2(1*H*)-pyridones 3a–e and 6-aryl-3-carbomethoxy/cyano-4-(2-hydroxyethyl-amino)-2*H*-pyran-2-ones 2a–e; General procedure:** A mixture of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones (**1**, 1 mmol) and ethanolamine (1.2 mmol) was refluxed in EtOH for 1–4 h. After completion, the reaction was cooled to r.t. and left overnight. The white crystalline solid **3** was filtered off and washed with EtOH. The filtrate was evaporated to dryness and pure compound **2** was isolated by column chromatography using $CHCl_3$ as an eluent.

(31) **Spectroscopic and elemental analyses data of selected compounds. 2a**: white solid; mp 140–142 °C; IR (KBr): 1630 (CO), 3427 cm^{-1} (OH); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, SCH_3), 3.72–3.75 (m, 2 H, CH_2), 4.03 (t, J = 4.9 Hz, 2 H, CH_2), 4.16 (t, J = 4.9 Hz, 1 H, OH), 6.03 (d, J = 2.0 Hz, 1 H, CH), 6.33 (d, J = 2.0 Hz, 1 H, CH), 7.28–7.33 (m, 2 H, ArH), 7.43–7.48 (m, 3 H, ArH); MS (FAB): m/z = 262 (M^+ + 1); Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.07; H, 5.92; N, 5.25. **3a**: white solid; mp 248–250 °C; IR (KBr): 1687 (CO), 2216 (CN), 3271 (NH), 3401 cm^{-1} (OH); ^1H NMR (200 MHz, DMSO-d_6): δ = 3.57 (s, 4 H, 2 CH_2), 4.90 (br s, 1 H, OH), 7.04 (s, 1 H, CH), 7.55–7.58 (m, 3 H, ArH), 7.93–7.97 (m, 2 H, ArH), 8.30 (br s, 1 H, NH); MS (FAB): m/z = 257 (M^+ + 1); Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.65; H, 4.51; N, 10.83. **7**: white solid; mp 236–237 °C; IR (KBr): 1657, 1688 (CO), 3403 cm^{-1} (OH); ^1H NMR (200 MHz, DMSO-d_6): δ = 3.63–3.66 (m, 4 H, 2 CH_2), 3.74 (s, 3 H, OCH_3), 5.08 (br s, 1 H, OH), 6.97 (s, 1 H, CH), 7.53–7.58 (m, 3 H, ArH), 7.96–8.00 (m, 2 H, ArH), 10.05 (br s, 1 H, NH); MS (FAB): m/z = 290 (M^+ + 1); Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.31; H, 5.26; N, 4.48. **9a**: white solid; mp 124–126 °C; IR (KBr): 3370 (NH), 3469 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.56–1.60 (m, 4 H, 2 CH_2), 1.65–1.68 (m, 2 H, CH_2), 3.34–3.37 (m, 4 H, 2 CH_2), 4.51 (br s, 2 H, NH_2), 5.84 (d, J = 2.0 Hz, 1 H, PyH), 6.59 (d, J = 2.0 Hz, 1 H, PyH), 7.38–7.42 (m, 3 H, ArH), 7.84–7.88 (m, 2 H, ArH); MS (FAB): m/z = 254 (M^+ + 1); Anal. Calcd for $C_{16}H_{19}N_3$: C, 75.85; H, 7.56; N, 16.59. Found: C, 75.38; H, 7.06; N, 16.37.