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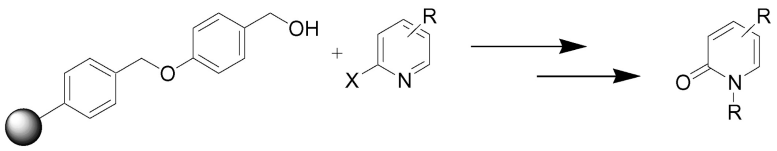

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Preparation of N-Alkylated Pyridones via Selective N-Alkylation of 2-Alkoxypyridines on Solid Phase

Marcus C. Ruda,*[,†,‡] Jan Bergman,[‡,§] and Jinchang Wu[†]

Karo Bio AB, Novum, SE-14157 Huddinge, Sweden, Unit for Organic Chemistry, CNT, Department of Biosciences at Novum, Karolinska Institute, Novum Research Park, SE-141 57 Huddinge, Sweden, and Södertörn University College, SE-141 04 Huddinge, Sweden

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Regioselective solid-phase synthesis of N-alkylated 2-pyridones has been carried out starting from 2-halopyridines. Variously substituted 2-halopyridines were linked to a Wang resin in quantitative yields to afford 2-alkoxypyridines. The coupled products were then reacted with a variety of alkyl halides, resulting in tandem alkylation and cleavage from the resin to generate N-alkylated pyridones with no detectable traces of O-alkylated products. The scope and limitations of this exceptionally selective reaction have been studied.

Introduction

Heterocyclic steroid mimetics have attracted considerable attention because of their unique structural features and intriguing biological activities.[1−4] In the course of our research, we were interested in employing solid-phase parallel synthetic methods in the preparation of azasteroids libraries with a 2-pyridone heterocyclic ring as bioisosteric replacement for the carbocylic A-ring of steroids. The anticancer activities of derivatives of the naturally occurring camptothecin family, a class of topoisomerase inhibitors, have prompted the development of methods for selective N-alkylation of pyridones.[5,6] Total synthesis approaches to the natural product cerpagin, which possesses analgesic, antiinflammatory, antiulcer, and tranquilizer properties, have also fueled development of selective methods for N-alkylation.[7−9]

To our knowledge, no entirely satisfactory methodology for such N-alkylation of 2-pyridones has been published. Two different solution-phase approaches to the synthesis of N-alkylated pyridones have been described; however, both of these methods suffer from a number of significant limitations. The first shortcoming is the competition between N- and O-alkylation, and the second drawback is the low yields with unactivated alkyl halides.

In the first method, a 2-pyridone is treated with base to generate a 2-oxypyridine anion that is then alkylated by adding an alkyl halide. Although this method is applicable to a wide variety of electrophiles (including activated, unactivated, and sterically hindered alkyl halides) and the regioselectivity of the reaction can be enhanced under carefully controlled conditions (such as treatment with sodium hydride as base, lithium bromide as a Lewis acid in a mixture of DMF and DME[10] or cesium fluoride in DMF[11]), the method often produces mixtures of both N- and O-alkylated products because of the ambident nucleophilic property of the intermediate anion in the reaction. Separation of such a mixture is often tedious. In the second method, a 2-alkoxypyridine is employed as the starting material for synthesis of an N-alkylated pyridone.[12] The nitrogen atom in alkoxypyridine attacks an alkyl halide to generate a pyridinium salt where the counterion subsequently displaces the alkyl side chain from the alkoxy group to afford an *N*-alkyl-2-pyridone. The advantage of this approach is that the reaction proceeds in high yield and is very regioselective. However, this method has not been thoroughly studied, and so far, only activated alkyl halides have been used together with unsubstituted 2-alkoxypyridines. A potential drawback of this reaction is that the alkyl halide that is produced as a side product can also N-alkylate the remaining unreacted alkoxypyridine, leading to a mixture of products. Hence, it is likely that this method is limited to electrophiles that are more reactive than the alkyl halide that is produced as a byproduct of the reaction.

In this paper, we have employed a modification of the second approach for the synthesis of N-alkylated pyridones by linking the alkoxy group of the synthetic intermediate alkoxypyridine to a solid support. We generate the intermediate alkoxypyridine by treating a benzyl alcohol resin (Wang resin) with a base followed by addition of a 2-halopyridine with heating. To the best of our knowledge, there is only one example of linking 2-halopyridine to a solid support reported in the literature.[13] In addition, a method for the linkage of 4-pyridones via a Mitsunobu reaction has been reported[14] that is also known to be applicable for 2-pyridones.[15]

We first studied a model solution-phase reaction by alkylation of 2-benzyloxypyridine with propyl iodide. However, when we attempted to N-alkylate 2-benzyloxypyridine with propyl iodide in DCM, only *N*-benzyl-2-pyridone was

* To whom correspondence should be addressed. Phone: +46-8-608-6103. Fax: +46-8-774-8261. E-mail: marcus.ruda@karobio.se.
† Karo Bio AB.
‡ Karolinska Institute.
§ Södertörn University College.

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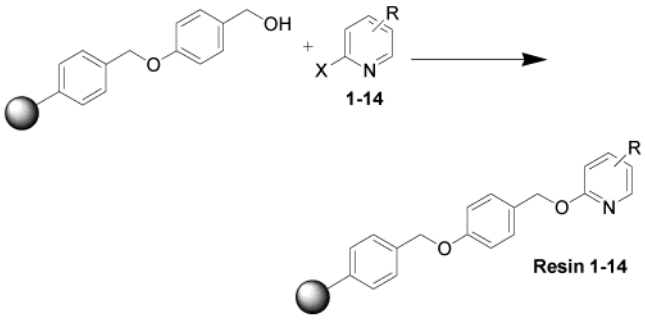
Table 1. Yields for the Loading of 2-Halopyridines to Wang Resin

product	yield,[a] %	product	yield,[a] %
resin **1**	100	resin **8**	100
resin **2**	100	resin **9**	100
resin **3**	100	resin **10**	100
resin **4**	100	resin **11**	50
resin **5**	100	resin **12**	
resin **6**	100	resin **13**	100
resin **7**	100	resin **14**	

[a] Yield based on analysis by ^{1}H MAS NMR.

Scheme 1[a]



[a] Reaction conditions: *t*-BuOK, DMF, 80 °C, 3 h.

isolated with none the desired *N*-propyl-2-pyridone detectable by NMR in the crude reaction mixture. The undesirable outcome of this reaction was a result of the highly electrophilic benzyl iodide byproduct generated in situ reacting much more quickly with alkoxypyridine than propyl iodide. However, when the benzyloxy side chain was replaced with a benzyloxy group covalently linked to a solid support (i.e., a Wang resin), only the desired *N*-propyl-2-pyridone was obtained. Presumably the undesirable side reaction between the benzylic iodide and unreacted 2-benzyloxypyridine, which are both linked to solid support, is suppressed because of steric constraints imposed by the solid support. Furthermore, any side product that is produced is trapped on the solid support and not easily cleaved from the resin under reaction conditions that would normally be used. Thus, performing the alkylation on solid-phase eliminates an undesirable side product and makes possible regioselecitive N-alkylation with less reactive alkyl halides. This encouraging result prompted a more thorough investigation of the scope and limitations of the N-alkylation of 2-alkoxypyridines on solid phase using Wang resin.

Results and Discussion

A variety of 2-halopyridines were linked to Wang resin in the presence of *t*-BuOK in DMF at 80 °C. The attachment of 2-halopyridines to Wang resin proceeded smoothly in quantitative yield in most cases, as shown in Table 1 and Scheme 1. However, with pyridines containing acidic protons, such as compounds **12** and **14**, the attachment failed. Under the same conditions, the reaction of Wang resin with 4-amino-2-chloropyridine (**11**) only yielded 50% of resin **11**. The products of resins were analyzed by ^{1}H magic-angle spinning (MAS) NMR. The yields of the reaction were determined by integration of the peaks representing the

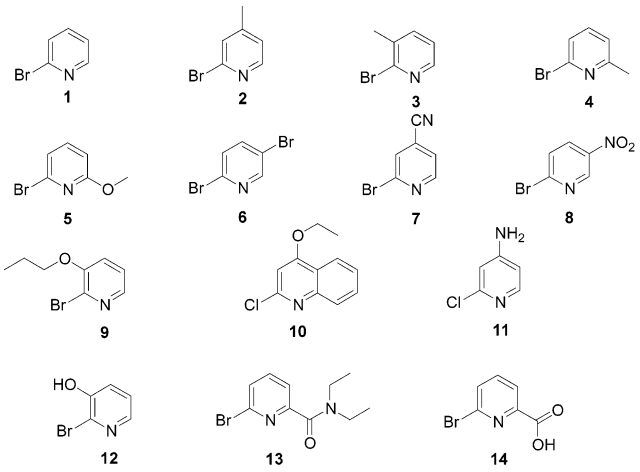
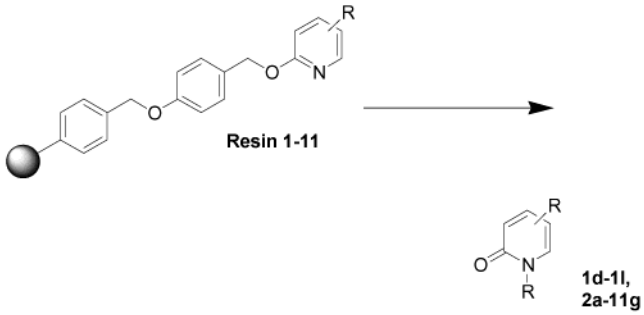


Figure 1. 2-Halopyridines.

Scheme 2[a]



[a] Reaction conditions: Sealed tube, DCM, 24 h, alkyl halide (**A**−**L**).

methylene protons of the benzyl alcohol on the Wang resin and methylene protons of polymer-bound 2-benzyloxypyridine.

To probe the sensitivity of the alkylation cleavage reaction to electronic effects, differently substituted 2-halopyridines were selected (Figure 1).

The tandem alkylation and cleavage steps were performed by treating the swelled Wang resin in DCM with an alkyl halide in a sealed tube at 120 °C (Scheme 2). Although Bowman et al.[12] used acetonitrile and sodium iodide in a related transformation in solution phase, DCM was chosen as the solvent in our reactions because DCM promotes better swelling of the Wang resin compared to acetonitrile. In addition, a mixture of N- and O-alkylated as well as unalkylated pyridones was formed when the reaction was conducted with the Wang resin bonded alkoxypyridine (resin **1**) and propyl iodide in the presence of sodium iodide as additive at 120 °C. The most likely explanation for this undesirable outcome is that sodium iodide cleaved the 2-alkoxypyridine from the resin to generate a free pyridone anion that reacted with propyl iodide to afford both O- and N-alkylated pyridones. Fortunately, running the reaction in the absence of sodium iodide afforded predominantly the desired N-alkylated pyridine. Unalkylated pyridone was also formed, but no O-alkylated product was observed. When the reaction temperature was decreased from 120 to 80 °C, only the N-alkylated product was observed. When substituted 2-halopyridines were used, the unalkylated pyridone cleavage product in addition to the desired N-alkylated pyridone was obtained. Presumably, traces of water in the reaction mixture

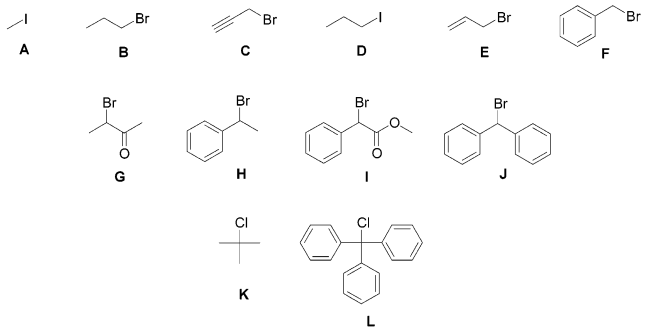


Figure 2. Alkyl halides.

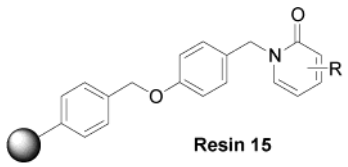


Figure 3. Site−site reaction product.

caused cleavage of unalkylated pyridine from the resin. Hence, in all subsequent reactions, the resin was dried prior to linking with the 2-halopyridines by mixing with anhydrous toluene followed by azeotropic evaporation of the solvent, which substantially reduced the amount of unalkylated side product.

When the resins, after the tandem alkylation and cleavage steps, were analyzed with MAS NMR, the undesired product resin **15** (Figure 3) was detected. Presumably, this product is formed via a site−site reaction[16] between benzylic halide, which is formed during the reaction, and unreacted 2-benzyloxypyridine (resins **1**−**11**).

Electronic effects of substituents have a substantial impact on the reaction. The parent pyridine **1** and the pyridines with an electron-donating substituent (**2**−**4**, **9**) reacted successfully with both activated and unactivated alkyl halides (see Table 2). Pyridines with a moderately electron-withdrawing substituent (**6**, **7**) could be alkylated only with activated alkyl halides (**A**, **C**, **E**, **F**; Figure 2), and pyridines bearing strong electron-withdrawing groups (**8**) generally reacted very poorly with all alkyl halides being used.

Steric hindrance of the alkylating agents has a significant influence on the yields of the alkylation reaction. Though halides such as **H**−**L** are benzylic bromides that are activated in view of the electronic effect, the bulkiness of these reagents prevented reaction with any pyridine derivative. Similar negative steric influence for the selective N-alkylation of 2-pyridones has been noted in the literature.[17] Pyridines with heteroatoms at the 4- or 6-postion (**5**, **10**, **11**) gave low yields under the conditions in our method. Possibly the heteroatom on the ring stabilized the oxypyridinium salt and thus prevented the second step for the cleavage of the product from resin.

In general, pure product was obtained by a simple washing and evaporation without need for chromatographic separation.

Conclusion

We have developed a method to link pyridines to solid phase by using 2-halopyridines and Wang resin. These solid-supported pyridines have been employed for the selective alkylation to yield N-alkylated pyridones. Though with limitation, this method provides a new strategy for the regioselective synthesis of N-alkylated 2-pyridones. Further application of the solid-supported pyridines for the synthesis of azasteroid libraries is under investigation in our laboratories and will be reported in due course.

Experimental Section

General. Proton magic-angle spinning (MAS) NMR spectra were obtained on Bruker 600 MHz and Varian 500 MHz instruments. The MAS NMR samples were prepared by swelling a few milligrams of each sample inside the NMR tube by the addition of $CDCl_3$. Proton NMR spectra were measured on a JEOL 270 MHz, Bruker 300 MHz, and Bruker 500 MHz instruments. The ^{13}C NMR spectra were measured on a JEOL 270 MHz at 67 MHz.

Alkyl halides, 2-halopyridines, and solvents were purchased from Aldrich, Lancaster, SPECS and BioSPECS, or TCI and were used without further purification. Wang resin (100−200 mesh, 1% cross-linked, 0.91 mmol/g) was purchased from NovaBiochem. The starting material 6-bromopicolinoyl-*N*,*N*-diethylamide (**13**) was synthesized from the corresponding acid via its acyl chloride, and 2-bromo-3-propoxypyridine (**9**) was prepared from the corresponding 3-hydroxypyridine by the treatment with sodium hydride and propyl iodide.

2-Bromo-3-propoxypyridine (9). 2-Bromo-3-hydroxypyridine (0.5 g, 2.87 mmol) was dissolved in dry DMF (10 mL), and then NaH (161 mg, 4.02 mmol) was added at room temperature. After 30 min of stirring under N_2 atmosphere,

Table 2. Yields[a] (%) for Cleavage of Resins **1**−**10** with Alkyl Halides (**A**−**G**)

	A	B	C	D	E	F	G
resin **1**	*b*	*b*	*b*	19	79	58	17
resin **2**	39	33	62	13	58	59	39
resin **3**	62	*c*	17[e] (1:2)[d]	*c*	51	35	81
resin **4**	85	*c*	27[e] (1:2)[d]	*c*	78	24[e] (2:1)[d]	33[e] (1.3:1)[d]
resin **5**	3.5	*b*	*c*	*c*	18	8[e] (1.4:1)[d]	*c*
resin **6**	63	*c*	60	*c*	62	53	*c*
resin **7**	48	*f*	33	*c*	41	31	*f*
resin **8**	8[e] (1:2)[d]	*b*	*f*	*f*	14[e] (1:2.5)[d]	*c*	*f*
resin **9**	86	22	63	*c*	79	61	*c*
resin **10**	56	*b*	11[e] (1:4.4)[d]	*c*	15[e] (1:4)[d]	12[e] (1:2)[d]	3[e] (1:2.2)[d]

[a] Overall isolated yield (loading + cleavage). Loading yields appear to be 100% on the basis of ^1H MAS NMR (see Table 1). All the products were analyzed with ^1H NMR and ES-MS. [b] Not attempted. [c] Product could only be detected by ES-MS. [d] Alkylated product versus unalkylated product. [e] Yield of the N-alkylated product. [f] No product detected.

after which time evolution of H_2 bubbles ceased, propyl iodide (505 μL, 4.02 mmol) was added and then the reaction mixture was heated at 80 °C for 3 h. The reaction was quenched with the addition of 0.5 mL of water, and the volume of DMF was reduced by evaporation and then extracted with water and DCM. Flash chromatography on silica gel, eluting with EtOAc−heptane (1:9), gave 569 mg (2.63 mmol, 92%) of 2-bromo-3-propoxypyridine. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (t, 3H, J = 7.6 Hz), 1.76−1.83 (m, 2H), 3.92 (t, 2H, J = 6.3 Hz), 7.05 (d, 1H, J = 8.2 Hz), 7.12 (dd, 1H, J = 8.2 and 4.4 Hz) and 7.87 (d, 1H, J = 4.4 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) δ 10.5, 22.4, 70.8, 119.6, 123.5, 133.0, 140.9 and 152.5; ES-MS m/z 216, 218 ($(M + H)^+$).

6-Bromopyridine-2-*N*,*N*-diethylcarboxamide (13). A solution of 6-bromopicolinic acid (300 mg 1.48 mmol), oxalyl chloride (108 μL, 1.24 mmol), and anhydrous DCM (5 mL) was stirred at room temperature. After evolution of carbon dioxide ceased, *N*,*N*-diethylamine (448 μL, 4.33 mmol) was added dropwise and the mixture was allowed to stir overnight. The reaction mixture was extracted with 1 M NaOH and DCM to give 266 mg (70%) of 6-bromopyridine-2-*N*,*N*-diethylcarboxamide. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.02 (t, 3H, J = 7.1 Hz), 1.05 (t, 3H, J = 7.1 Hz), 3.16 (q, 2H, J = 7.1 Hz), 3.34 (q, 2H, J = 7.1 Hz) and 7.31−7.52 (m, 3H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 12.7, 14.1, 40.4, 43.4, 122.0, 124.9, 128.7, 139.3, 140.3, 155.5 and 166.6; ES-MS m/z 257, 259 ($(M + H)^+$).

General Procedure for Coupling 2-Halopyridines to the Wang Resin. To 550 mg of Wang resin in 15 mL of anhydrous DMF was added 5 equiv of *t*-BuOK under argon atmosphere. After 10 min of stirring, a solution of 6 equiv of 2-halopyridine in 5 mL of anhydrous DMF was added and the mixture was heated to 80 °C for 3 h. The resin was sequentially washed with DMF, THF, MeOH, and DCM and dried under a flow of argon. The resin was analyzed by ^{1}H MAS NMR.

Resin 1. ^{1}H MAS NMR (500 MHz, $CDCl_3$) δ 4.92 (br s, $-CH_2-O-$), 5.31 (s, $-CH_2-O-$), 6.75 (s), 6.81 (s), 7.49 (s), and 8.16 (s).

Resin 2. ^{1}H MAS NMR (600 MHz, $CDCl_3$) δ 2,22 (s, $-CH_3$), 4.92 (br s, $-CH_2-O-$), 5.30 (s, $-CH_2-O-$), 6.58 (s), 6.65 (s), and 8.01 (s).

Resin 3. ^{1}H MAS NMR (600 MHz, $CDCl_3$) δ 2.17 (s, $-CH_3$), 4.91 (br s, $-CH_2-O-$), 5.33 (s, $-CH_2-O-$), 6.73 (s), 7.32 (s), and 7.98 (s).

Resin 4. ^{1}H MAS NMR (600 MHz, $CDCl_3$) δ 2.46 (s, $-CH_3$), 4.93 (br s, $-CH_2-O-$), 5.31 (s, $-CH_2-O-$), 6.55 (s), and 6.68 (s).

Resin 5. ^{1}H MAS NMR (600 MHz, $CDCl_3$) δ 3.89 (s, $-OCH_3$), 4.93 (br s, $-CH_2-O-$), 5.30 (s, $-CH_2-O-$), 6.28 (s), and 6.32 (s).

Resin 6. ^{1}H MAS NMR (600 MHz, $CDCl_3$) δ 4.93 (br s, $-CH_2-O-$), 5.28 (s, $-CH_2-O-$), 7.57 (s), and 8.20 (s).

Resin 7. ^{1}H MAS NMR (600 MHz, $CDCl_3$) δ 4.93 (br s, $-CH_2-O-$), 5.33 (s, $-CH_2-O-$), and 8.26 (s).

Resin 8. ^{1}H MAS NMR (600 MHz, $CDCl_3$) δ 4.94 (br s, $-CH_2-O-$), 5.31 (s, $-CH_2-O-$), 6.76 (s), 8.27 (s), and 9.07 (s).

Resin 9. ^{1}H MAS NMR (600 MHz, $CDCl_3$) δ 1.00 (s, $-CH_3$), 1.81 (s, $-CH_2-$), 3.92 (s, $-CH_2-O-$), 4.93 (br s, $-CH_2-O-$), 5.43 (s, $-CH_2-O-$), 6.77 (s), 7.43 (br s), and 7.72 (s).

Resin 10. ^{1}H MAS NMR (600 MHz, $CDCl_3$) δ 1.43 (s, $-CH_3$), 4.09 (s, $-CH_2-O-$), 4.93 (br s, $-CH_2-O-$), 5.47 (s, $-CH_2-O-$), 6.22 (s), 7.43 (s), 7.56 (s), 7.81 (s), and 8.08 (s).

Resin 11. ^{1}H MAS NMR (600 MHz, $CDCl_3$) δ 4.13 (br s, $-CH_2-O-$), 4.93 (br s, $-CH_2-O-$), 6.26 (br s), 6.39 (br s), and 7.86 (br s).

Resin 13. ^{1}H MAS NMR (600 MHz, $CDCl_3$) δ 1.18 (s, $-CH_3$), 1.27 (s, $-CH_3$), 3.36 (s, $-CH_2-N-$), 3.56 (s, $-CH_2-N-$), 4.94 (br s, $-CH_2-O-$), 5.32 (s, $-CH_2-O-$), 6.79 (s), and 7.60 (s).

General Procedure for N-Alkylation of Polymer-Supported 2-Benzyloxypyridines. The resin was first dried by placing 50 mg in a 15 mL Supelco screw-top reaction vial with 10 mL of anhydrous toluene followed by azeotropic evaporation of the solvent at 40 °C with a Speedvac (model number AES2010). This drying cycle was repeated an additional two times. The reaction vessel containing the dried resin was then charged with 3 mL of DCM followed by 200 μL of alkyl halide, flushed with argon, and sealed with a Supelco 18 mm screw cap with a PTFE liner. The reaction mixture was heated to either 120 °C for 24 h for alkyl halides without α-protons or 80 °C for 48 h with alkyl halides with α-protons. The mixture was transferred to a filter column and was washed sequentially with DCM (2 × 1 mL), 10% MeOH in DCM (1 mL), MeOH (1 mL), and DCM (2 × 1 mL). The solvent was evaporated, and the residue was directly analyzed by NMR.

The reaction mixture containing benzyl bromide had to be purified from the excess of benzyl bromide. The DCM solution from the reaction was added to a dry packed silica gel column (2 g). The column was first eluted with 15 mL of DCM to get rid of the benzyl bromide, and the product was eluted with 6 mL of 10% MeOH in DCM. The MeOH−DCM solvent mixture was evaporated, and the residue was analyzed with NMR and ES-MS.

1-Propyl-1*H*-pyridine-2-one (1d). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.4 Hz), 1.71−1.82 (m, 2H), 3.88 (t, 2H, J = 7.4 Hz), 6.13 (dt, 1H, J = 6.7 and 1.2 Hz), 6.55 (d, 1H, J = 9.6 Hz), and 7.20−7.40 (m, 2H); ES-MS m/z 138 ($(M + H)^+$).

1-Allyl-1*H*-pyridine-2-one (1e). ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.82 (d, 2H, J = 5.9 Hz), 5.31 (d, 1H, J = 17.8 Hz), 5.38 (d, 1H, J = 10.4 Hz), 5.90−6.09 (m, 1H), 6.84 (t, 1H, J = 6.8 Hz), 7.58 (d, 1H, J = 9.2 Hz), and 7.75−7.86 (m, 2H); ES-MS m/z 136 ($(M + H)^+$).

1-Benzyl-1*H*-pyridine-2-one (1f). ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.13 (s, 2H), 6.12 (t, 1H, J = 6.1 and 1.2 Hz), 6.60 (d, 1H, J = 9.1 Hz), and 7.20−7.38 (m, 7H); ES-MS m/z 186 ($(M + H)^+$).

1-(1-Methyl-2-oxopropyl)-1*H*-pyridine-2-one (1g). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.54 (d, 3H, J = 7.3 Hz), 2.21 (s, 3H), 5.51 (q, 1H, J = 7.3 Hz), 6.24 (t, 1H, J = 6.8 Hz), 6.59 (d, 1H, J = 9.2 Hz), 7.19 (d, 1H, J = 6.8 Hz), and 7.35 (t, 1H, J = 7.9 Hz); ES-MS m/z 166 ($(M + H)^+$).

1,4-Dimethyl-1*H*-pyridine-2-one (2a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.56 (s, 3H), 6.10 (d, 1H, J = 6.7 Hz), 6.46 (s, 1H), and 7.23 (d, 1H, J = 6.8 Hz); ES-MS m/z 124 ($(M + H)^+$).

4-Methyl-1-propyl-1*H*-pyridine-2-one (2b). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.4 Hz), 1.67−1.81 (m, 2H), 2.15 (s, 3H), 3.84 (t, 2H, J = 7.4 Hz), 5.98 (dd, 1H, J = 6.9 and 1.7 Hz), 6.35 (s, 1H), and 7.11 (d, 1H, J = 6.9 Hz); ES-MS m/z 152 ($(M + H)^+$).

4-Methyl-1-prop-2-ynyl-1*H*-pyridine-2-one (2c). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.47 (t, 1H, J = 2.6 Hz), 4.73 (d, 2H, J = 2.6 Hz), 6.12 (dd, 1H, J = 7.0 and 1.8 Hz), 6.41 (s, 1H), and 7.52 (d, 1H, J = 7.0 Hz); ES-MS m/z 148 ($(M + H)^+$).

1-Allyl-4-methyl-1*H*-pyridine-2-one (2e). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.20 (s, 3H), 4.56 (d, 2H, J = 4.8 Hz), 5.18 (d, 1H, J = 17.1 Hz), 5.26 (d, 1H, J = 10.1 Hz), 5.91−5.97 (m, 1H), 6.10 (d, 1H, J = 6.0 Hz), 6.53 (s, 1H), and 7.18 (d, 1H, J = 6.5 Hz); ES-MS m/z 150 ($(M + H)^+$).

1-Benzyl-4-methyl-1*H*-pyridine-2-one (2f). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 5.13 (s, 2H), 6.01 (dd, 1H, J = 7.0 and 1.8 Hz), 6.44 (s, 1H), 7.15 (d, 1H, J = 7.0 Hz), and 7.28−7.38 (m, 5H); ES-MS m/z 200 ($(M + H)^+$).

4-Methyl-1-(1-methyl-2-oxopropyl)-1*H*-pyridine-2-one (2g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (d, 3H, J = 7.3 Hz), 2.20 (s, 3H), 2.21 (s, 3H), 5.48 (q, 1H, J = 7.3 Hz), 6.12 (d, 1H, J = 7.0 Hz), 6.41 (s, 1H), and 7.08 (d, 1H, J = 7.0 Hz); ES-MS m/z 180 ($(M + H)^+$).

1,3-Dimethyl-1*H*-pyridine-2-one (3a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.57 (s, 3H), 6.10 (t, 1H, J = 6.7 Hz), 7.18 (d, 1H, J = 6.6 Hz), and 7.21 (d, 1H, J = 6.6 Hz); ES-MS m/z 124 ($(M + H)^+$).

3-Methyl-1-prop-2-ynyl-1*H*-pyridine-2-one (3c). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.46 (t, 1H, J = 2.6 Hz), 4.77 (d, 2H, J = 2.6 Hz), 6.17 (t, 1H, J = 6.8), 7.22 (d, 1H, J = 6.8 Hz), and 7.50 (d, 1H, J = 5.7 Hz); ES-MS m/z 148 ($(M + H)^+$).

1-Allyl-3-methyl-1*H*-pyridine-2-one (3e). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (s, 3H), 4.58 (d, 2H, J = 5.7 Hz), 5.18 (d, 1H, J = 17.2 Hz), 5.25 (d, 1H, J = 10.1 Hz), 5.92−6.00 (m, 1H), 6.10 (t, 1H, J = 6.6 and 6.3 Hz), 7.13 (d, 1H, J = 5.6 Hz), and 7.19 (d, 1H, J = 5.7 Hz); ES-MS m/z 150 ($(M + H)^+$).

1-Benzyl-3-methyl-1*H*-pyridine-2-one (3f). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 5.17 (s, 2H), 6.09 (t, 1H, J = 6.8 Hz), and 7.17−7.38 (m, 7H); ES-MS m/z 200 ($(M + H)^+$).

3-Methyl-1-(1-methyl-2-oxopropyl)-1*H*-pyridine-2-one (3g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (d, 3H, J = 6.9 Hz), 2.16 (s, 3H), 2.25 (s, 3H), 5.26 (bq, 1H, J = 6.9 Hz), 6.79 (bs, 1H), 7.41 (bs, 1H), and 7.89 (bs, 1H); ES-MS m/z 180 ($(M + H)^+$).

1,6-Dimethyl-1*H*-pyridine-2-one (4a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.61 (s, 3H), 6.21 (d, 1H, J = 6.8 Hz), 6.61 (d, 1H, J = 8.8 Hz), and 7.34 (t, 1H, J = 6.9 and 8.8 Hz); ES-MS m/z 124 ($(M + H)^+$).

6-Methyl-1-prop-2-ynyl-1*H*-pyridine-2-one (4c). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (t, 1H, J = 2.5 Hz), 2.52 (s, 3H), 4.87 (d, 2H, J = 2.5 Hz), 6.05 (d, 1H, J = 6.4 Hz), 6.48 (d, 1H, J = 9.2 Hz), and 7.23 (t, 1H, J = 9.1 and 6.9 Hz); ES-MS m/z 148 ($(M + H)^+$).

1-Allyl-6-methyl-1*H*-pyridine-2-one (4e). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 4.72 (s, 2H), 5.00 (d, 1H, J = 17.1 Hz), 5.19 (d, 1H, J = 10.1 Hz), 5.92−5.97 (m, 1H), 6.02 (d, 1H, J = 5.1 Hz), 6.48 (d, 1H, J = 8.5), and 7.22 (t, 1H, J = 8.4 and 6.0); ES-MS m/z 150 ($(M + H)^+$).

1-Benzyl-6-methyl-1*H*-pyridine-2-one (4f). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 5.38 (s, 2H), 6.05 (d, 1H, J = 10.7 Hz), 6.57 (d, 1H, J = 9.1 Hz), and 7.16−7.40 (m, 6H); ES-MS m/z 200 ($(M + H)^+$).

6-Methyl-1-(1-methyl-2-oxopropyl)-1*H*-pyridine-2-one (4 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (d, 3H, J = 7.1 Hz), 2.19 (s, 3H), 2.35 (s, 3H), 5.20 (q, 1H, J = 7.1 Hz), 6.62 (d, 1H, J = 8.1 Hz), 6.71 (d, 1H, J = 7.3 Hz), and 7.47 (t, 1H, J = 8.1 and 7.3 Hz); ES-MS m/z 180 ($(M + H)^+$).

6-Methoxy-1-methyl-1*H*-pyridine-2-one (5a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 (s, 3H), 3.89 (s, 1H), 5.52 (d, 1H, J = 7.6 Hz), 6.21 (d, 1H, J = 8.9), and 7.29 (t, 1H, J = 7.6 Hz in side $CDCl_3$ peak); ES-MS m/z 140 ($(M + H)^+$).

1-Allyl-6-methoxy-1*H*-pyridine-2-one (5e). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.71 (s, 2H), 5.10 (d, 1H, J = 16.9 Hz), 5.14 (d, 1H, J = 10.9 Hz), 5.51 (d, 1H, J = 8.0 Hz), 5.86−5.94 (m, 1H), 6.22 (d, 1H, J = 9.2), and 7.29 (t, 1H, J = 8.7 and one under the solvent); ES-MS m/z 166 ($(M + H)^+$).

1-Benzyl-6-methoxy-1*H*-pyridine-2-one (5f). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.03 (s, 2H), 5.52 (d, 1H, J = 12.8 Hz), 6.29 (t, 1H, J = 12.8 Hz), and 7.17−7.38 (m, 6H); ES-MS m/z 216 ($(M + H)^+$).

5-Bromo-1-methyl-1*H*-pyridine-2-one (6a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.53 (s, 3H), 6.50 (d, 1H, J = 9.7 Hz), 7.36 (dd, 1H, J = 2.3 and 9.6 Hz), and 7.42 (d, 1H, J = 2.1 Hz); ES-MS m/z 188, 190 ($(M + H)^+$).

5-Bromo-1-prop-2-ynyl-1*H*-pyridine-2-one (6c). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56 (t, 1H, J = 2.5 Hz), 4.72 (d, 2H, J = 2.5 Hz), 6.51 (d, 1H, J = 9.0 Hz), 7.39 (dd, 1H, J = 9.0 and 1.5 Hz), and 7.78 (s, 1H); ES-MS m/z 212, 214 ($(M + H)^+$).

1-Allyl-5-bromo-1*H*-pyridine-2-one (6e). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (d, 2H, J = 4.8 Hz), 5.24 (d, 1H, J = 17.0 Hz), 5.31 (d, 1H, J = 10.1 Hz), 5.88−5.96 (m, 1H), 6.51 (d, 1H, J = 9.5), 7.35 (d, 1H, J = 9.5 Hz), and 7.37 (s, 1H); ES-MS m/z 214, 216 ($(M + H)^+$).

1-Benzyl-5-bromo-1*H*-pyridine-2-one (6f). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (s, 2H), 6.56 (d, 1H, J = 15.9 Hz), and 7.31−7.46 (m, 7H); ES-MS m/z 264, 266 ($(M + H)^+$).

1-Methyl-2-oxo-1,2-dihydropyridine-4-carbonitrile (7a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.56 (s, 3H), 6.27 (d, 1H, J = 6.8 Hz), 6.91 (s, 1H), and 7.4 (d, 1H, J = 6.9 Hz); ES-MS m/z 135 ($(M + H)^+$).

2-Oxo-1-prop-2-ynyl-1,2-dihydropyridine-4-carbonitrile (7c). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59 (t, 1H, J = 2.6 Hz), 4.76 (d, 2H, J = 2.6 Hz), 6.37 (dd, 1H, J = 7.1 and 1.8 Hz), 6.93 (s, 1H), and 7.82 (d, 1H, J = 7.1 Hz); ES-MS m/z 159 ($(M + H)^+$).

1-Allyl-2-oxo-1,2-dihydropyridine-4-carbonitrile (7e). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (d, 2H, J = 5.3 Hz), 5.25 (d, 1H, J = 17.2 Hz), 5.34 (d, 1H, J = 10.0 Hz), 5.90−5.95 (m, 1H), 6.29 (d, 1H, J = 6.8 Hz), 6.93 (s, 1H), and 7.38 (d, 1H, J = 6.8 Hz); ES-MS m/z 161 ((M + H)$^+$).

1-Benzyl-2-oxo-1,2-dihydropyridine-4-carbonitrile (7f). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (s, 2H), 6.26 (dd, 1H, J = 7.0 and 1.8 Hz), 6.96 (d, 1H, J = 1.5 Hz), and 7.30−7.43 (m, 6H); ES-MS m/z 211 ((M + H)$^+$).

1-Methyl-5-nitro-1*H*-pyridine-2-one (8a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 6.58 (d, 1H, J = 10.0 Hz), 8.11 (dd, 1H, J = 10.0 and 3.0 Hz), 8.63 (d, 1H, J = 3.0 Hz); ES-MS m/z 155 ((M + H)$^+$).

1-Allyl-5-nitro-1*H*-pyridine-2-one (8e). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (d, 2H, J = 5.7 Hz), 5.36 (d, 1H, J = 17.2 Hz), 5.43 (d, 1H, J = 10.2 Hz), 5.93−5.99 (m, 1H), 6.59 (d, 1H, J = 10.1 Hz), 8.10 (d, 1H, J = 10.0 Hz), and 8.59 (s, 1H); ES-MS m/z 181 ((M + H)$^+$).

1-Methyl-3-propoxy-1*H*-pyridine-2-one (9a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.3 Hz), 1.76−1.83 (m, 2H), 3.62 (s, 3H), 3.91 (t, 2H, J = 6.5 Hz), 6.17 (t, 1H, J = 7.0 Hz), 6.71 (d, 1H, J = 7.0 Hz), and 6.97 (d, 1H, J = 7.0 Hz); ES-MS m/z 168 ((M + H)$^+$).

3-Propoxy-1-propyl-1*H*-pyridine-2-one (9b). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, 6H, J = 7.4 Hz), 1.74−1.83 (m, 2H), 1.84−1.92 (m, 2H), 3.87 (t, 2H, J = 6.8 Hz), 3.92 (t, 2H, J = 7.4 Hz), 6.05 (t, 1H, J = 7.0 Hz), 6.59 (dd, 1H, J = 1.6 and 7.0 Hz), and 6.85 (dd, 1H, J = 1.6 and 7.0 Hz); ES-MS m/z 196 ((M + H)$^+$).

3-Propoxy-1-prop-2-ynyl-1*H*-pyridine-2-one (9c). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, 3H, J = 6.8 Hz), 1.90 (m, 2H), 2.44 (t, 1H, J = 2.1 Hz), 3.91 (t, 2H, J = 7.8 Hz), 4.79 (d, 2H, J = 2.1 Hz), 6.16 (t, 1H, J = 7.2 Hz), 6.61 (d, 1H, J = 7.2 Hz), and 7.22 (d, 1H, J = 7.2 Hz); ES-MS m/z 192 ((M + H)$^+$).

1-Allyl-3-propoxy-1*H*-pyridine-2-one (9e). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, 3H, J = 7.5 and 7.4 Hz), 1.83−1.89 (m, 2H), 3.87 (t, 2H, J = 6.6 and 6.2 Hz), 4.60 (d, 2H, J = 4.9 Hz), 5.19 (d, 1H, J = 17.2 Hz), 5.23 (d, 1H, J = 10.3 Hz), 5.91−5.98 (m, 1H), 6.09 (t, 1H, J = 7.0 and 6.9 Hz), 6.60 (d, 1H, J = 6.6 Hz), and 6.86 (d, 1H, J = 6.0 Hz); ES-MS m/z 194 ((M + H)$^+$).

1-Benzyl-3-propoxy-1*H*-pyridine-2-one (9f). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.02 (t, 3H, J = 7.4 Hz), 1.80−1.92 (m, 2H), 3.86 (t, 2H, J = 6.9 Hz), 5.16 (s, 2H), 6.04 (t, 1H, J = 7.3 and 6.9 Hz), 6.57 (dd, 1H, J = 7.3 and 1.7 Hz), 6.88 (dd, 1H, J = 6.9 and 1.7 Hz), and 7.26−7.33 (m, 5H); ES-MS m/z 244 ((M + H)$^+$).

4-Ethoxy-1-methyl-1*H*-quinolin-2-one (10a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (t, 3H, J = 6.9 Hz), 3.68 (s, 3H), 4.17 (q, 2H, J = 6.9 Hz), 6.03 (s, 1H), 7.23 (t, 1H, J = 7.9 Hz), 7.34 (d, 1H, J = 7.9 Hz), 7.58 (t, 1H, J = 7.9 Hz), and 8.01 (d, 1H, J = 7.9 Hz).

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