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Specific N-Alkylation of Hydroxypyridines Achieved by a Catalyst- and Base-Free Reaction with Organohalides

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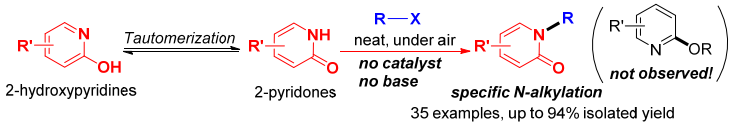
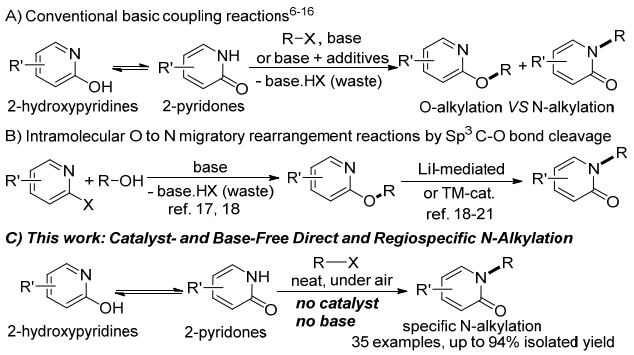


Abstract: A specific N-alkylation of 2-hydroxypyridines is achieved by reacting with organohalides under catalyst- and base-free conditions. The observed HX-facilitated conversion of pyridyl ether intermediates to 2-pyridone products may account for the success and specific N-alkylation of the reaction under the unexpectedly simple conditions. This new reaction may provide a useful alternative for the synthesis of 2-pyridones and analogous structures due to its >99% N-selectivity, relatively broad scopes of both substrates, and no mandatory use of catalysts and bases.

N-Substituted 2-pyridones and analogous pyridone structures not only present frequently in biologically and pharmacologically active molecules[1] as well as natural products having potent antitumor and antivirus activities,[2] they are also versatile reagents in synthesis[3] such as in Diels-Alder reactions[4] and material sciences.[5] Therefore, much attention has been focused on the synthesis of N-substituted pyridones over the past decades. Conventionally, N-alkyl 2-pyridones have been prepared by reacting 2-hydroxypyridines with alkyl halides under basic conditions (Scheme 1A).[6] The use of a base is required in these methods, but this can generate inorganic salts as waste. Meanwhile, formation of the competing O-alkylated byproducts is also inevitable due to the inherent ambident nature of the intermediate anions derived from the 2-hydroxypyridine and 2-pyridone tautomers (Scheme 1A).[7] In some cases, O-alkylation can

even become the dominant reaction.[6e] Therefore, N-selectivity is always an issue to be addressed. Hence, various modified methods were developed to enhance the selectivity of the target N-alkylation reaction. For example, CsF,[8] LiBr,[9] NaI,[10] and TBAX (tetrabutylammonium halides)[11] were reported as effective additives. Alternative reaction conditions like ionic liquid[12] and microwave irradiation,[13] and the Mitsunobu method[14] were also reported. Moreover, mechanistic aspects of the reaction were also investigated to understand the nature of N- and O-alkylation reactions.[15] More recently, Ren and co-workers reported that Tween 20 (2% w/w) could also be used as an effective additive to improve the N-selectivity of the conventional basic reaction.[16] Even though, generation of the O-alkylated byproducts could not be avoided completely by these modifications.



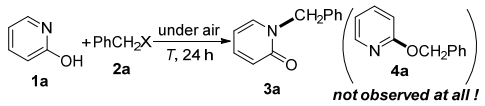
Scheme 1. Methods for N-Substituted 2-Pyridone Synthesis.

On the other hand, since 2-pyridyl ethers can be obtained by basic reaction of 2-halopyridines with alcohols,[17,18] intramolecular O to N migratory rearrangement reactions of 2-pyridyl ethers have also been developed recently to achieve N-substituted 2-pyridones and analogous pyridone structures (Scheme 1B).[18-21] For example, the Anderson group developed a transition-metal-free LiI-mediated method;[18] Dong and co-workers disclosed the first efficient catalytic migration reaction using Ru catalyst;[19] Shibata and co-workers reported an Ir-catalyzed rearrangement method for 2-pyridyl ethers bearing secondary O-alkyl groups.[20] Other transition metal catalysts such as Pt, Ag, Au, and Pd were also found to be active catalysts for similar transformations.[21] More recently, You and co-workers developed an elegant Ir-catalyzed asymmetric allylic amination of 2-hydroxypyridines with allylic methyl carbonates for enantioselective synthesis of N-substituted 2-pyridones.[22] Although these methods generally gave high selectivities of the N-substituted 2-pyridones, these reactions are in effect two-step

procedures because the 2-pyridyl ether substrates have to be prepared first.[17,18] Additionally, these methods are limited by high loadings of the additives and the use of expensive noble metal catalysts. Therefore, an efficient, practical, and highly N-selective one-step transition metal-free method is still highly desirable in the field. Recently, a few transition-metal-catalyzed additions of hydroxypyridines to unsaturated compounds have been developed to address some of the above issues.[23] Herein we report another advance in the research, that is, the anticipated specific N-alkylation reaction of 2-hydroxypyridines can be achieved by reacting 2-hydroxypyridines with organohalides under catalyst- and base-free conditions (Scheme 1C). In comparison with the known methods, this new reaction may provide a useful alternative for the synthesis of 2-pyridones and analogous structures due to its >99% N-selectivity, the relatively broad scopes of both the hydroxyheterocycle and organohalide substrates, and no mandatory use of bases.

We serendipitously encountered this new reaction during our ongoing studies on N-, C-, O-, and S-alkylation reactions[24] and the need to obtain pyridyl ethers.[17d] As shown in Table 1, initially, 2-hydroxypyridine **1a** and $PhCH_2Br$ (**2a**-Br) were directly heated under the air atmosphere without solvent and base (entry 1). Under these conditions we originally reasoned that no reaction would occur. To our surprise, the reaction afforded a considerable yield of a new product, which was later determined to be N-benzyl 2-pyridone **3a**. Realizing that a selective N-alkylation reaction might have occurred with possible formation of the O-alkylated ether **4a**,[6,8-16] we repeated the reaction to determine the N/O selectivity. To our surprise again, **4a** could not be observed at all by TLC and GC-MS analysis (entry 1, **3a**/**4a** >99/1, **3a** and **4a**[17] can be easily distinguished[25]). This result suggested that *this is a specific N-alkylation reaction of 2-hydroxypyridine realized by only one step under the catalyst- and base-free conditions!* Realizing that this new finding may serve as a good alternative for synthesis of the N-substituted 2-pyridones and analogous pyridone structures,[6,8-16,18-21] we further optimized the reaction conditions.

Table 1. Conditions Screening and Optimization.[a]



entry	$PhCH_2X$ (equiv.)	*T*	**3a**/**4a** [b]	**3a**%[c]
1	$PhCH_2Br$ (1.2)	60 °C	>99/1	60
2	$PhCH_2Br$ (1.2)	80 °C	>99/1	71
3	$PhCH_2Br$ (1.2)	100 °C	>99/1	79
4	$PhCH_2Br$ (1.2)	120 °C	>99/1	76
5	$PhCH_2Br$ (1.0)	100 °C	>99/1	75
6	***$PhCH_2Br$ (1.5)***	***100 °C***	***>99/1***	***84***
7	$PhCH_2Br$ (2.0)	100 °C	>99/1	83
8	$PhCH_2Cl$ (2.0)	100 °C	>99/1	56
9[d]	$PhCH_2Br$ (1.5)	100 °C	>99/1	77
10[e]	$PhCH_2Br$ (1.5)	100 °C	>99/1	13~82
11[f]	$PhCH_2Br$ (1.5)	100 °C	>99/1	87

[a] Unless otherwise noted, the neat mixture of 2-hydroxypyridine **1a** (2 mmol) and benzyl halide **2a** sealed under air in a 10 mL Schlenk tube was directly heated for 24 h. [b] Ratios determined by GC-MS analysis. [c] Yields based on **1a**. [d] 12 h. [e] Normal solvents like toluene, EtOH, DMF, 1,4-dioxane, THF, MeOH, DCE, DCM, CH_3CN (1 mL) were investigated. [f] Under N_2.

As shown in Table 1, temperature screening showed that 100 °C is optimal (entries 1-4). Screening of $PhCH_2Br$ loading (entries 3, 5-7) showed that 1.5 equiv. is the best (entry 6). No improvement of the product yield was observed even with more $PhCH_2Br$ (entry 7). Using $PhCH_2Cl$ instead of $PhCH_2Br$ gave a decreased yield of **3a** (entry 8), showing that the bromide is more reactive than the chloride. Screening of reaction time showed that 24 h is necessary (entry 9). The effect of solvent was also investigated but only lower yields were obtained with the normal solvents tested (entry 10). When the reaction was performed under nitrogen, a slightly higher yield of **3a** was obtained (entry 11), which suggests that this reaction is insensitive to air. Therefore, entry 6 was chosen as the optimal conditions as the operation of the reaction can be greatly simplified by performing the reaction under air. It should also be pointed out that no **4a** was observed in all these reactions.

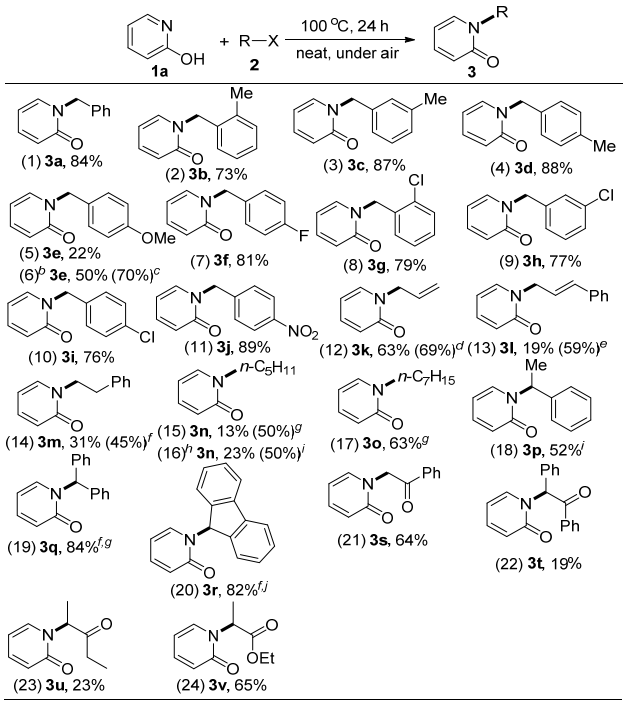
The optimized conditions (Table 1, entry 6) were then extended to various organohalides to

test the scope of this new method. As shown in Table 2, similar to $PhCH_2Br$ (entry 1), most electron-rich and –deficient benzylic bromides including the sterically-hindered ones (entries 2 and 8) and the one with a very reactive nitro group (entry 11) could also afford the target N-substituted 2-pyridones in good to high yields (entries 2-4, 7-11). In the reaction of *p*-$MeOC_6H_4CH_2Br$, the yield of the product **3e** was very low, which may be attributed to the observed instability of the bromide in the reaction (entry 5). Alternatively, when the more stable chloride *p*-$MeOC_6H_4CH_2Cl$ was used instead, the reaction gave a much higher yield of **3e** (50%) under N_2, which could be enhanced further to 70% by performing the reaction at a higher temperature of 120 ^oC (entry 6). Using allyl bromide as the alkylating reagent also afforded the N-allyl 2-pyridone **3k** in an acceptable yield (entry 12). Possibly due to the more unstable and reactive nature of the allyl bromide, the reaction was performed better at a lower temperature, giving a higher yield of **3k** (entry 12, the result in parenthesis). This is especially the case with the reaction of cinnamyl bromide, which was even less effective under the standard conditions (entry 13). Thus, an acceptable yield of the product was obtained at an even lower temperature of 60 ^oC (entry 13, the result in parenthesis).

This method could also be extended to less reactive alkyl bromides, but the yields were generally lower (entry 14-17). Nevertheless, we found that the yields of the products could be improved by running the reactions at a higher temperature (entry 14), using the corresponding more reactive alkyl iodide (entry 16), or by adding TBAI (tetrabutylammonium iodide) as the additive (entries 15-17). Similarly, the reactions of the sterically more bulky secondary alkyl bromides were also ineffective under the standard conditions, thus requiring a higher reaction temperature or additive TBAI to obtain moderate to high yields of the products (entries 18-20). Due to the higher melting points of the substrates and high viscosity of the reaction mixture, the reaction of 9-bromofluorene was better carried out by using DMF as the solvent (entry 20). Moreover, functionalized bromides could also be used as the alkylating reagents in this specific N-alkylation reaction. Thus, the reaction of bromoacetophenone afforded a moderate 64% yield of the target **3s** (entry 21), while the more bulky phenyl-substituted bromoacetophenone and 2-bromopentan-3-one only afforded lower yields of **3t** and **3u** (entries 22-23). Surprisingly, the similarly bulky secondary bromide, ethyl 2-bromopropanoate, showed very high reactivity in the reaction, giving a much higher yield of the product (entry 24) than the preceding secondary

bromides (entries 22-23).

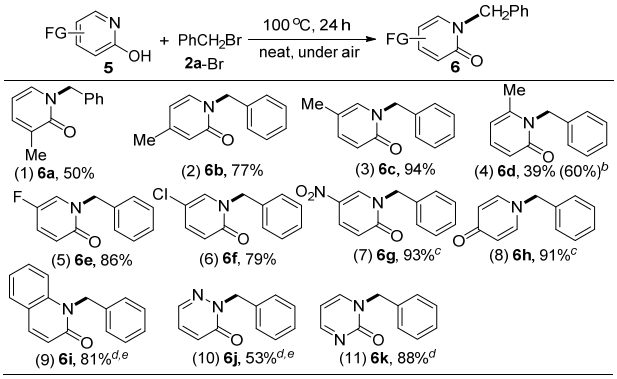
Table 2. Scope of the Organohalides.[a]



[a] Unless otherwise noted, the corresponding RBr was used. See entry 6 of Table 1 for detailed conditions. Yields based on **1a**. [b] The corresponding RCl was used instead under N_2. [c] 120 °C. [d] N_2, 80 °C. [e] N_2, 60 °C. [f] N_2, 130 °C. [g] N_2, 1.0 equiv. TBAI added. [h] The corresponding RI was used instead under N_2. [i] 0.5 equiv. TBAI added. [j] DMF (0.5 mL) added.

The scope of the hydroxyheterocycles (**5**) was our next concern. Substituted 2-hydroxypyridines were firstly investigated. As shown in Table 3, 2-hydroxypyridines with electron-donating or -withdrawing groups at the 3-, 4-, 5-, 6-positions all afforded the target products **6a-g** in moderate to high yields under the standard or modified conditions (entries 1-7). The yields of the products of 3- and 6-methyl 2-hydroxypyridines were relatively lower under the standard conditions most possibly due to the steric hindrance derived from the adjacent methyl groups (entries 1 and 4). Similar to the case of 9-bromofluorene (Table 2, entry 20), the reaction of 5-nitro-2-hydroxypyridine also required the addition of DMF as the solvent, and a high yield of the product **6g** was obtained (Table 3, entry 7).

Table 3. Scope of the Hydroxyheterocycles.[a]

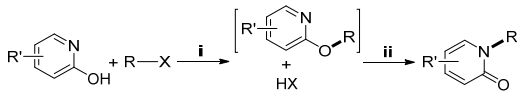


[a] Unless otherwise noted, see entry 6 of Table 1 for detailed conditions. Yields based on **5**. [b] 48 h. [c] DMF (1 mL) added. [d] N_2, 1.0 equiv. TBAI. [e] 130 °C.

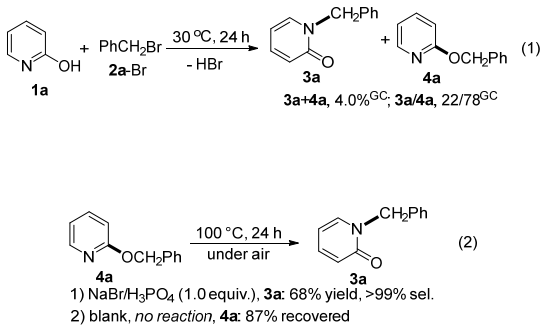
We then investigated 3- and 4-hydroxypyridines. In the case of 3-hydroxypyridine, no product was observed at all; whereas, 4-hydroxypyridine could afford a high yield of the target N-benzyl 4-pyridone **6i** in DMF (Table 3, entry 8). This is clearly due to the mismatched positions of the N and OH moieties in 3-hydroxypyridine that can not fulfill the dearomatization of the hydroxypyridine structure to the pyridone structure. In addition, other hydroxyheterocycles such as 2-hydroxyquinoline, 3-hydroxypyridazine, and 2-hydroxy pyrimidine could also react with benzyl bromide to give moderate to high yields of the products in the presence of TBAI (entries 9-11).

Preliminary mechanistic studies revealed that the O-alkylated pyridyl ether **4** was most likely generated as the initial product, being the key intermediate of this specific N-alkylation reaction (Scheme 2, step i), because **4a** was observed as the major product in the reaction of **1a** and **2a** at a lower temperature of 30 °C (eq. 1). **4a** could then be effectively converted into **3a** in >99% selectivity upon heating in the presence of another byproduct HX (Scheme 2, step ii), as this was also confirmed by the reaction of **4a** with the *in situ* generated HBr from NaBr and H_3PO_4 (eq. 2, entry 1).[26] In contrast, no reaction occurred at all in the absence of HBr with recovery of 87% **4a** (eq. 2, entry 2),[27] revealing the key role of HBr in the conversion of pyridyl ether intermediate **4** to product **3**. These interesting results (eq. 2) and complete production of **3a** at higher temperatures (Table 1) can account for why the present reaction can undergo a specific

N-alkylation reaction to effectively afford 2-pyridone products under the unexpectedly simple catalyst- and base-free conditions.



Scheme 2. Possible Reaction Paths.



In conclusion, we serendipitously discovered and then developed a specific N-alkylation method for one-step and efficient synthesis of the useful N-substituted 2-pyridones and analogous pyridone structures, which can be easily achieved by reacting hydroxyheterocycles with organohalides under catalyst- and base-free conditions. In comparison with known methods, this new reaction may be a good advance in the field and a useful alternative for the synthesis of 2-pyridones and analogous structures due to its >99% N-selectivity, the relatively broad scopes of both the hydroxyheterocycle and organohalide substrates, and no mandatory use of bases. Preliminary mechanistic studies revealed that byproduct HX may work to facilitate the complete conversion of the pyridyl ether intermediates to the pyridone products, which can well explain why no base is needed in this new method. Deeper mechanistic studies of this interesting reaction is our next concern as it may help to further enhance the reaction efficiency of some less reactive and bulky substrates and broaden the scope of the substrates.

Experimental Section

General. Unless otherwise noted, the chemicals were purchased from Energy Chemical,

Alfa Aesar, TCI, and other chemical companies and used without further purification. 2-Bromo-1,2-diphenylethan-1-one and 2-bromopentan-3-one (used in entries 22-23 in Table 2) were prepared by the literature method.[28] Unless otherwise specified, all reactions were carried out in sealed Schlenk tubes (10 mL) under the air atmosphere and monitored by TLC and/or GC-MS. Products were purified by column chromatography on silica gel using petroleum ether and ethyl acetate as the eluent. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance-III 500 instrument (500 MHz for ^{1}H and 125.4 MHz for ^{13}C NMR spectroscopy) using $CDCl_3$ as the solvent. Chemical shifts for ^{1}H and ^{13}C NMR were referred to internal Me_4Si (0 ppm) as the standard. Mass spectra were measured on a Shimadzu GC-MS-QP2010 Plus spectrometer (EI). HRMS (ESI) analysis was measured on a Bruker micrOTOF-Q II instrument. Melting points were measured on microcomputer melting point apparatuses WRS-1C (Shanghai Shenguang) and X-4 (Beijing Taike).

Typical Procedure for N-Alkylation of 2-Hydroxypyridines with Organohalides. To a 10 mL Schlenk tube was add 2-hydroxypyridine **1a** (190 mg, 2.0 mmol) and benzyl bromide **2a**-Br (356 μL, 3.0 mmol, 1.5 equiv.) under air. The mixture was then sealed and directly heated for 24 h. The reaction was monitored by TLC and GC-MS. The reaction mixture was purified by flash column chromatography using hexane/EtOAc (2/1) as eluent to give 1-benzylpyridin-2(1H)-one **3a** (313 mg, 84%) as a white solid.

1-Benzylpyridin-2(1H)-one ***(3a)***.[19] White solid (313 mg, 84%). Mp 72.3-72.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.28 (m, 7H), 6.63 (d, J = 9.5 Hz, 1H), 6.15 (t, J = 6.5 Hz, 1H), 5.14 (s, 1H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.7, 139.5, 137.3, 136.4, 128.9, 128.1, 128.0, 121.1, 106.3, 51.9. MS (EI): *m/z* (%) 186 (7), 185 (52), 184 (33), 92 (9), 91 (100), 89 (7), 80 (7), 79 (25), 51 (7).

1-(2-Methylbenzyl)pyridin-2(1H)-one ***(3b)***.[18a] White solid (290.6 mg, 73%). Mp 85.2-85.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.30 (m, 1H), 7.23-7.16 (m, 3H), 7.07 (m, 1H), 7.02 (m, 1H), 6.62 (m, 1H), 6.14-6.11 (m, 1H), 5.12 (s, 2H), 2.26 (s, 3H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.8, 139.4, 136.8, 136.7, 133.8, 130.8, 128.8, 128.3, 126.5, 120.8, 106.3, 49.6, 19.1. MS (EI): *m/z* (%) 199 (16), 198 (13), 197 (45), 196 (14), 182 (10), 181 (18), 105 (64), 104 (100), 103 (24), 79 (10).

1-(3-Methylbenzyl)pyridin-2(1H)-one ***(3c)***.[18a] Colorless oil (346.2 mg, 87%). ^{1}H NMR (500

MHz, $CDCl_3$): δ 7.21-7.19 (m, 2H), 7.15-7.11 (m, 1H), 7.02-7.0 (m, 3H), 6.54-6.50 (m, 1H), 6.07-6.04 (m, 1H), 5.03-5.00 (m, 2H), 2.25-2.22 (m, 3H). $^{13}C\{1H\}$NMR (125.4 MHz, $CDCl_3$): δ 162.6, 139.4, 138.5, 137. 5, 136.4, 128.8, 128.7, 125.1, 120.9, 106.1, 51.7, 21.3. MS (EI): *m/z* (%) 199 (26), 198 (31), 197 (90), 196 (57), 106 (10), 105 (100), 103 (13), 98 (10), 79 (20, 77 (10).

1-(4-Methylbenzyl)pyridin-2(1H)-one ***(3d)***.[18a] White solid (350.2 mg, 88%). Mp 73.1-73.2 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 (ddd, J_1 = 9.0 Hz, J_2 = 6.5 Hz, J_3 = 2.0 Hz, 1H), 7.30 (dd, J_1 = 7.0 Hz, J_2 = 2.0 Hz ,1H), 7.20 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.5 Hz, 2H), 6.78 (d, J = 9.5 Hz, 1H), 6.22 (t, J = 6.5 Hz, 1H), 5.13 (s, 2H), 2.33 (s, 3H). $^{13}C\{1H\}$NMR (125.4 MHz, $CDCl_3$): δ 162.6, 139.9, 138.1, 137.2, 132.9, 129.6, 128.3, 120.8, 107.2, 52.1, 21.1. MS (EI): *m/z* (%) 199 (18), 198 (20), 197 (61), 196 (26), 106 (9), 105 (100), 104 (14), 103 (10), 79 (11), 77 (7).

1-(4-Methoxybenzyl)pyridin-2(1H)-one ***(3e)***.[18a] White solid (301 mg, 70%). Mp 75.3-75.8 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.31 (ddd, J_1 = 15.5 Hz, J_2 = 6.5 Hz, J_3 = 2.0 Hz, 1H), 7.26 (dd, J_1 = 7.0 Hz, J_2 = 2.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.63 (d, J = 9.0 Hz, 1H), 6.14 (t, J = 6.5 Hz, 1H), 5.10 (s, 2H), 2.33 (s, 3H). $^{13}C\{1H\}$NMR (125.4 MHz, $CDCl_3$): δ 162.7, 139.4, 137.8, 137.1, 133.3, 129.6, 128.2, 121.1, 106.3, 51.7, 21.1. MS (EI): *m/z* (%) 215 (6), 214 (6), 213 (24), 212 (5), 122 (12), 121 (100), 120 (18), 91 (5), 78(3), 77 (4), 51 (1).

1-(4-Fluorobenzyl)pyridin-2(1H)-one ***(3f)***.[19] White solid (328.6 mg, 81%). Mp 84.5-85.2 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.35-7.27 (m, 4H), 7.01 (t, J = 8.5 Hz, 2H), 6.65 (d, J = 9.0 Hz, 1H), 6.18 (t, J = 6.5 Hz, 1H), 5.10 (s, 2H). $^{13}C\{1H\}$NMR (125.4 MHz, $CDCl_3$): δ 163.5, 162.6, 161.6, 139.8, 137.1, 132.0 (J = 3.8 Hz), 130.0 (J = 8.8 Hz), 121.1, 115.8 (J = 21.3Hz),106.9 ,51.6. MS (EI): *m/z* (%) 203 (13), 202 (16), 201 (54), 200 (21), 110 (9), 109 (100), 108 (13), 107 (6), 83 (9), 79 (10).

1-(2-Chlorobenzyl)pyridin-2(1H)-one ***(3g)***.[18a] White solid (346 mg, 79%). Mp 71.8-72.3 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37-7.28 (m, 6H), 6.61 (t, J = 8.5 Hz, 1H), 6.7-6.13 (m, 1H), 5.23 (d, J = 5.5 Hz, 2H). $^{13}C\{1H\}$NMR (125.4 MHz, $CDCl_3$): δ 162.7 139.7, 137.6, 133.7, 133.4, 130.0, 129.6, 129.3, 127.3, 121.1, 106.3, 49.6. MS (EI): *m/z* (%) 184 (46), 183 (100), 182 (24), 155 (6), 127 (11), 89 (8).

1-(3-Chlorobenzyl)pyridin-2(1H)-one ***(3h)***.[19] White solid (337.2 mg, 77%). Mp 73.0-73.2

°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (ddd, J_1 = 9.0 Hz, J_2 = 6.5 Hz , J_3 = 2.0 Hz, 1H), 7.29-7.27 (m, 4H), 7.19-7.18 (m, 1H), 6.66 (d, J = 9.0 Hz, 1H), 6.20 (td, J_1 = 6.5 Hz, J_2 = 1.5, 1H), 5.11(s, 2H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.5, 139.7, 138.3137.2, 134.8, 130.2, 128.2, 128.1, 126.2, 121.3, 106.7, 51.6. MS (EI): *m/z* (%) 219 (45), 218 (48), 217 (92), 216 (65), 126 (17), 125 (100), 124 (19), 89 (20), 79 (29).

1-(4-Chlorobenzyl)pyridin-2(1H)-one ***(3i)***.[19] White solid (332.8 mg, 76%). Mp 83.4-84.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.24 (m, 6H), 6.70 (d, J = 9.0 Hz, 1H), 6.21 (t, J = 6.5 Hz, 1H), 5.12 (s, 2H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.6, 139.8, 137.2, 134.9, 133.9, 129.5, 129.0, 121.2, 106.7, 51.5. MS (EI): *m/z* (%) 219 (27), 218 (22), 217 (55), 216 (25), 127 (36), 126 (16), 125 (100), 124 (16), 89 (14), 79 (16).

1-(4-Nitrobenzyl)pyridin-2(1H)-one ***(3j)***. White solid (405.4 mg, 89%). Mp 141.5-141.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.38-7.35 (m, 1H), 7.31 (d, J = 6.5 Hz, 1H), 6.62 (d, J = 9.5 Hz, 1H), 6.22 (t, J = 8.0 Hz, 1H), 5.21 (s, 2H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.4, 147.7, 143.6, 140.1, 137.3, 128.6, 124.0, 121.5, 107.0, 51.9. MS (EI): *m/z* (%) 230 (18), 229 (31), 228 (72), 227 (100), 226 (47), 182 (25), 106 (26), 89 (34), 79 (28), 78 (20). HRMS Calcd for $C_{12}H_{11}N_2O_3$ (M+H): 231.0764; found: 231.0829.

1-Allylpyridin-2(1H)-one ***(3k)***.[10] Colorless oil (186.4 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.32 (m, 1H), 7.28-7.26 (m, 1H), 6.60 (m, 1H), 6.22-6.18 (m, 1H), 6.00-5.91 (m, 1H), 5.28-5.25 (m, 1H), 5.21-5.16 (m, 1H), 4.59-5.57 (m, 2H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.4, 139.5, 137.1, 132.5, 121.0, 118.4, 106.2, 51.0. MS (EI): *m/z* (%) 211 (22), 210 (42), 209 (9), 120 (36), 118 (10), 117 (100), 116 (66), 115 (99), 96 (46), 91 (21).

1-Cinnamylpyridin-2(1H)-one ***(3l)***.[21f] Colorless oil (249 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$: δ 7.36-7.21 (m, 7H), 6.60-6.54 (m, 2H), 6.32-6.27 (m, 1H), 6.17-6.15 (m, 1H), 4.70 (d, J = 6.5 Hz, 2H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.5, 139.6, 137.2, 136.0, 134.0, 128.6, 128.1, 126.6, 123.6, 120.9, 106.3, 50.7. MS (EI): *m/z* (%) 211 (12), 210 (30), 118 (10), 117 (100), 116 (64), 115 (96), 114 (8), 96 (45), 78 (6), 51 (5).

1-Phenethylpyridin-2(1H)-one ***(3m)***.[19] White solid (179.2 mg, 45%). Mp 86.7-87.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.26 (m, 3H), 7.24-7.21 (m, 1H), 7.14 (d, J = 7.5 Hz, 2H), 6.90 (dd, J_1 = 7.0 Hz, J_2= 1.5 Hz, 1H), 6.63 (d, J = 9.0 Hz, 1H), 6.02 (t, J = 6.5 Hz, 1H), 4.15 (t, J =

7.0 Hz, 2H), 3.06 (t, *J* = 7.0 Hz, 2H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.5, 139.6, 137.9, 128.7, 126.7, 120.8, 105.7, 52.0, 35.0. MS (EI): *m/z* (%) 199 (11), 105 (11), 104 (100), 103 (7), 80 (13), 79 (4), 78 (15), 77 (7), 53 (9), 51 (5).

1-Pentylpyridin-2(1H)-one ***(3n)***.[13] Colorless oil (165 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.31 (ddd, J_1 = 9.0 Hz, J_2 = 7.0 Hz, J_3 = 2.0 Hz, 1H), 7.28 (d, *J* = 6.0 Hz, 1H), 6.62 (d, *J* = 9.0 Hz, 1H), 6.18 (t, *J* = 6.5 Hz, 1H), 3.93 (t, *J* = 7.5 Hz, 2H), 1.78-1.72 (m, 2H), 1.38-1.32 (m, 4H), 0.90 (m, 3H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.6, 139.4, 137.5, 121.0, 106.1, 50.0, 29.0, 28.8, 22.3, 13.9. MS (EI): *m/z* (%) 164 (36), 147 (35), 147 (35), 135 (22), 122 (20), 96 (50), 78 (30), 67 (33), 55 (8), 53 (14).

1-Heptylpyridin-2(1H)-one ***(3o)***.[13] Colorless oil (347.2 mg, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.30 (m, 1H), 7.28-7.27 (m, 1H), 6.58 (d, *J* = 9.5 Hz, 1H), 6.17 (t, *J* = 7.0 Hz, 1H), 3.92 (t, *J* = 7.5 Hz,2H), 1.77-1.71 (m, 2H), 1.33-1.27 (m, 8H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.6, 139.2, 137.5, 121.0, 105.8, 49.9, 31.6, 29.3, 28.9, 26.6, 22.5, 14.0. MS (EI): *m/z* (%) 193 (27), 192 (69), 191 (41), 176 (46), 175 (69), 136 (39), 122 (35), 109 (100), 96 (51), 95 (56), 78 (12), 53 (3).

1-(1-Phenylethyl)pyridin-2(1H)-one ***(3p)***.[18a] White solid (207 mg, 52%). Mp 79.4-80.3 °C. ^{1}H NMR (500 MHz, CDCl3): δ 7.38-7.31 (m, 6H), 7.14 (d, *J* = 6.0 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 1H), 6.46 (q, *J* = 7.0 Hz, 1H), 6.19 (t, *J* = 6.5 Hz, 1H), 1.73 (d, *J* = 7.0 Hz, 3H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.4, 139.8, 139.3, 134.4, 128.9, 128.1, 127.5, 120.4, 107.3, 53.1, 19.0. MS (EI): *m/z* (%) 199 (19), 198 (19), 197 (12), 105 (100), 95 (19), 79 (13), 78 (11), 77 (15), 51 (2).

1-Benzhydrylpyridin-2(1H)-one ***(3q)***.[15a] White solid (438.4 mg, 84%). Mp 240.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.38-7.32 (m, 6H), 7.21 (d, *J* = 7.0 Hz, 1H), 7.13 (d, *J* = 7.0 Hz, 4H), 6.87 (d, *J* = 9.0 Hz , 1H), 6.25 (t, *J* = 7.0 Hz , 1H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.5, 139.9, 138.2, 136.1, 128.9, 128.8, 128.2, 120.3, 107.2, 62.7. MS (EI): *m/z* (%) 261 (7), 260 (9), 259 (31), 258 (12), 167 (45), 166 (100), 165 (57), 164 (50), 163 (25), 152 (18), 151 (11), 115 (2), 77 (0.5), 51 (0.2).

1-(9H-fluoren-9-yl)pyridin-2(1H)-one ***(3r)***. White solid (424.7 mg, 82%). Mp 221.7-222.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.46-7.42 (m, 4H), 7.33-7.29 (m, 4H), 6.77 (d, *J* = 9.0 Hz, 1H), 6.48 (dd, J_1 = 7.0 Hz, J_2 = 2.0 Hz, 1H), 5.97-5.94 (m, 1H).

^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 163.5, 143.2, 141.2, 139.5, 134.6, 129.2, 128.1, 125.3, 120.8, 120.3, 106.5, 59.3. MS (EI): *m/z* (%) 259 (8), 258 (10), 257 (37), 256 (15), 167 (6), 166 (53), 165 (100), 164 (79), 163 (20), 115 (3). HRMS Calcd for $C_{18}H_{14}NO$ (M+H): 260.1070; found: 260.1083.

1-(2-Oxo-2-phenylethyl)pyridin-2(1H)-one ***(3s)***.[29] White solid (272.6 mg, 64%). Mp 150.4-151.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 7.0 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.40 (ddd, J_1 = 9.5 Hz , J_2 = 6.5 Hz, J_3 = 1.5 Hz ,1H), 7.23 (dd, J_1 = 6.5 Hz, J_2 = 2.0 Hz ,1H), 6.63 (d, J = 9.5 Hz, 1H), 6.24 (t, J = 6.5 Hz, 1H), 5.38 (s, 2H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 192.3, 162.4, 140.2, 138.4, 134.8, 134.0, 128.9, 128.2, 120.7, 106.3, 54.4. MS (EI): *m/z* (%) 212 (7), 211 (13), 184 (14), 118 (11), 106 (8), 105 (100), 104 (9), 80 (8), 77 (28),53 (6).

1-(3-Oxobutan-2-yl)pyridin-2(1H)-one ***(3t)***. White solid (110.1 mg, 19%). Mp 170.9-171.6 °C. ^{1}H NMR (500 MHz, CDCl3): δ 8.0 (d, J = 7.5 Hz, 2H), 7.75 (s, 1H), 7.55-7.52 (m, 1H), 7.43-7.34 (m, 8H), 7.07 (d, J = 7.0 Hz, 1H), 6.65 (d, J = 9.0 Hz, 1H), 6.15 (t, J = 7.0 Hz, , 1H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 194.7, 162.5, 139.8, 136.4, 135.2, 133.7, 133.5, 130.2, 129.8, 129.5, 129.0, 128.8, 119.9, 105.8, 63.5. MS (EI): *m/z* (%) 289 (33), 287 (21), 286 (74), 285 (38), 278 (11), 269 (13), 205 (17), 184 (49), 183 (86), 166 (27), 165 (34), 164 (19), 105 (100), 78 (20), 77 (17). HRMS Calcd for $C_{19}H_{16}NO_2$ (M+H): 290.1181; found: 290.1204.

1-(3-Oxopentan-2-yl)pyridin-2(1H)-one ***(3u)***. Colorless oil (82.4 mg, 23%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (ddd, J_1= 14.0 Hz, J_2 = 6.5 Hz, J_3= 2.0 Hz, 1H), 7.22 (dd, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 1H), 6.59 (d, J = 9.0 Hz, 1H), 6.24 (td, J_1 = 7.0 Hz, J_2 = 1.5 Hz , 1H), 5.56 (q, J = 7.5 Hz, 1H), 2.53 (qd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 2H), 1.54 (d, J = 7.0 Hz, 3H), 1.06 (t, J = 7.0 Hz, 3H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 207.1, 162.2, 139.6, 134.5, 120.6, 106.5, 58.6, 33.0, 15.5, 7.5. MS (EI): *m/z* (%) 179 (14), 178 (18), 150 (41), 149 (23), 123 (59), 122 (100), 121 (45), 104 (14), 95 (31), 78 (29). HRMS Calcd for $C_{10}H_{14}NO_2$ (M+H): 180.1019; found: 180.1043.

Ethyl-2-(2-oxopyridin-1(2H)-yl)propanoate ***(3v)***.[14c,15b] Colorless oil (253.6 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.30 (m, 2H), 6.58 (d, J = 9.0 Hz, 1H), 6.23 (t, J = 6.5 Hz, 1H), 5.54 (q, J = 7.5 Hz, 1H), 4.19 (q, J = 7.0 Hz, 2H), 1.62 (d, J = 7.0 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 170.6, 162.2, 139.6, 134.9, 120.6, 106.4, 61.8, 53.7, 16.7, 14.1. MS (EI): *m/z* (%) 195 (16), 194 (48), 149 (68), 148 (50), 123 (20), 122 (100), 121

(20), 95 (29), 78 (19).

1-Benzyl-3-methylpyridin-2(1H)-one ***(6a)***.[19] White solid (199 mg, 50%). Mp 65.7-66.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.24 (m, 4H), 7.15 (d, J = 8.0 Hz, 2H), 6.56 (d, J = 9.5 Hz, 1H), 6.04 (d, J = 6.5 Hz, 1H), 5.35 (s, 2H), 2.26 (s, 3H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 164.0, 146.7, 139.2, 136.4, 128.8, 127.3, 126.5, 117.8, 107.0, 47.2, 20.6. MS (EI): *m/z* (%) 200 (8), 199 (53), 198 (26), 182 (3), 122 (5), 93 (20), 91 (100, 65 (16), 53 (3).

1-Benzyl-4-methylpyridin-2(1H)-one ***(6b)***.[19] White solid (306.4 mg, 77%). Mp 64.5-64.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.26 (m, 5H), 7.15 (d, J = 7.0 Hz, 1H), 6.47 (s, 1H), 6.02-6.0 (m, 1H), 5.1 (s, 2H), 2.17 (s, 3H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.6, 151.3, 136.5, 136.2, 128.9, 128.1, 127.9, 119.4, 109.1, 51.5, 21.2. MS (EI): *m/z* (%) 200 (9), 199 (28), 198 (37), 197 (100), 196 (79), 122 (11), 93 (36), 91 (88), 65 (10).

1-Benzyl-5-methylpyridin-2(1H)-one ***(6c)***.[19] White solid (374.2 mg, 94%). Mp 67.6-67.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20-7.17 (m, 5H), 7.05-7.03 (m, 1H), 6.97 (s, 1H), 6.44 (d, J = 9.5 Hz, 1H), 4.99 (s, 2H), 1.89 (s, 3H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 161.8, 142.2, 136.7, 134.9, 128.7, 127.9, 127.7, 120.4, 51.6, 16.9. MS (EI): *m/z* (%) 199 (24), 198 (31), 197 (86), 196 (60), 195 (9), 122 (13), 93 (26), 92 (10), 91 (100), 65 (10).

1-Benzyl-6-methylpyridin-2(1H)-one ***(6d)***.[18a] White solid (238.8 mg, 60%). Mp 103.1-103.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 731-7.24 (m, 4H), 7.15 (d, J = 7.5 Hz , 2H), 6.56 (d, J = 9.0 Hz, 1H), 6.04 (d, J = 6.5 Hz , 1H), 5.35 (s, 2H), 2.26 (s, 3H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 163.0, 136.71, 136.67, 134.7, 130.1, 128.8, 128.1, 127.9, 105.9, 52.2, 17.4. MS (EI): *m/z* (%) 199 (14), 198 (31), 197 (100), 196 (52), 184 (8), 183 (18), 122 (16), 93 (20), 92 (9), 91 (91), 65 (8), 51 (0.5).

1-Benzyl-5-fluoropyridin-2(1H)-one ***(6e)***. White solid (349.2 mg, 86%). Mp 121.4 -122.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.24 (m, 6H), 7.17 (m, 1H), 6.63-6.60 (dd, J_1 = 10.0 Hz , J_2 = 5.5 Hz, 1H), 5.10 (s, 2H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 160.8, 148.4 (J = 231.3 Hz), 135.6, 131.39 (J = 23.8 Hz), 129.1, 128.38, 128.36, 122.4 (J = 36.4 Hz), 121.7 (J = 6.3 Hz), 52.2. MS (EI): *m/z* 203 (10), 202 (19), 201 (66), 200 (31), 91 (100), 65 (8), 51 (1). HRMS Calcd for $C_{12}H_{11}FNO$ (M+H): 204.0819; found: 204.0835.

1-Benzyl-5-chloropyridin-2(1H)-one ***(6f)***.[19] White solid (346 mg, 79%). Mp 89.2-89.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.25 (m, 7H), 6.61 (d, J = 9.5 Hz, 1H), 5.10 (s, 2H).

^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 161.1, 140.5, 135.6, 134.7, 129.1, 128.4, 128.3, 121.9, 112.7, 52.2. MS (EI): *m/z* (%) 221 (9), 220 (8), 219 (27), 218 (12), 184 (1), 92 (8), 91 (100), 89 (4), 65 (13), 51 (3).

1-Benzyl-5-nitropyridin-2(1H)-one ***(6g)***.[30] White solid (427.5 mg, 93%). Mp 99.8-101.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (d, J = 3.0 Hz, 1H), 8.07 (dd, J_1 = 10.0 Hz, J_2 = 3.0 Hz, 1H), 7.42-7.34 (m, 5H), 6.60 (d, J = 10.0 Hz, 1H), 5.19 (s, 2H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 161.5, 138.9, 134.3, 133.1, 130.9, 129.4, 129.0, 128.6, 119.8, 53.2. MS (EI): *m/z* (%) 230 (7), 229 (8), 228 (34), 227 (9), 182 (5), 153 (2), 124 (4), 91 (100), 65 (7), 51 (1).

1-Benzylpyridin-4(1H)-one ***(6h)***.[31] White solid (336.8 mg, 91%). Mp 108.7-109.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 7.5 Hz, 2H), 7.35-7.31 (m, 3H), 7.18 (d, J = 6.5 Hz, 2H), 6.43 (d, J = 7.5 Hz, 2H), 5.02 (s, 2H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 178.4, 140.6, 134.7, 129.3, 129.0, 127.6, 118.5, 60.3. MS (EI): *m/z* (%) 185 (5), 184 (22), 92 (8), 91 (100), 90 (8), 89 (2), 77 (2), 65 (14), 51 (2).

1-Benzylquinolin-2(1H)-one ***(6i)***.[32] Colorless oil (380.8 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 9.5Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.30-7.16 (m, 7H), 6.80 (d, J = 9.5 Hz, 1H), 5.55 (s, 2H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 162.5, 139.5, 136.4, 130.6, 128.82, 128.78, 127.3, 126.6, 122.2, 121.7, 121.0, 115.0, 45.9. MS (EI): m/z (%) 235 (18), 234 (29), 233 (100), 232 (67), 214 (8), 158 (20), 157 (10), 130 (23), 129 (96), 128 (42), 91 (79).

2-Benzylpyridazin-3(2H)-one ***(6j)***.[33] White solid (197.1 mg, 53%). Mp 35-36 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77-7.76 (m, 1H), 7.43 (d, J = 7.0 Hz, 2H), 7.34-7.28 (m, 3H), 7.16 (dd, J_1 = 9.5 Hz, J_2 = 4.0 Hz, 1H), 6.94 (d, J = 9.5Hz, 1H), 5.33 (s, 2H). ^{13}C{1H}NMR (125.4 MHz, CDCl3): δ 160.4, 136.23, 136.19, 131.1, 130.2, 128.7, 128.6, 127.9, 55.2. MS (EI): *m/z* (%) 186 (45), 185 (100), 184 (22), 157 (16), 130 (14), 106 (21), 104 (13), 92 (13), 91 (53), 82 (45), 77 (6).

1-Benzylpyrimidin-2(1H)-one ***(6k)***.[18a] White solid (327.3 mg, 88%). Mp 128.1-128.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58-8.56 (m, 1H), 7.62-7.59 (d, J = 4.5 Hz, 1H), 7.39-7.32 (m, 5H), 6.28-6.26 (m, 1H), 5.10 (s, 2H). ^{13}C{1H}NMR (125.4 MHz, $CDCl_3$): δ 165.8, 156.3, 147.3, 134.7, 129.2, 128.74, 104.2, 54.0. MS (EI): *m/z* (%) 186 (49), 185 (13), 157 (4), 92 (10), 91 (100), 89 (6), 81 (15), 80 (9), 65 (22), 77 (2).

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Notes

The authors declare no competing financial interest.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/xxxxxxxxx.

Comparison data of product **3a** and byproduct **4a**, preliminary mechanistic studies, and copies of ^{1}H NMR and $^{13}C\{^{1}H\}$NMR spectra of the products.

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25. **3a** and **4a** (the N- and O-isomers) are greatly different in R_f value in TLC analysis, the retention time and MS in GC-MS analysis, and ^{1}H and ^{13}C NMR spetra. See the SI for detailed comparison of **3a** and **4a**.

26. No unreacted **4a** was observed in the reaction. So the selectivity of **3a** is also >99%. The observation of mall amounts of **1a** and dibenzyl ether generated by decomposition of **4a** may account for the moderate yield of **3a**. See the SI for detail.

27. No **3a** was observed in the reaction. See the SI for detail. This result is consistent with the literature methods that conversion of **4a** to **3a** requires a catalyst or a promoter (ref. 18-21).

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