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# Mild and Regioselective *N*-Alkylation of 2-Pyridones in Water

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Supporting Information

**ABSTRACT:** A mild and regioselective *N*-alkylation reaction of 2-pyridones in water has been developed. Tween 20 (2% w/w) was added to create a micellar system for improved solubility of starting materials, which leads to enhanced reaction rates. The protocol demonstrated a wide substrate scope with good isolated yields (40−94%) for all of the 24 examples evaluated. High regioselectivity favoring *N*-alkylation over *O*-alkylation was observed for benzyl halides (>5:1), primary alkyl halides (>6:1), and bulky and less reactive secondary alkyl halides (>2.4:1).


*N*-Alkylated 2-pyridones and close analogues are important components both in natural products[1−4] and in many active pharmaceuticals.[5] Due to their ambident nucleophilic nature, regioselective control of *N*- versus *O*-alkylation of 2-pyridones has intrigued chemists for over half a century.[6] Even though impressive progress has been made in the development of new methodologies (*vide infra*) to induce regioselectivity for *N*-alkylated 2-pyridones as well as in the mechanistic understanding of these alkylations,[7] there are no reports of a general and straightforward method on selective *N*-alkylation of 2-pyridones, especially with bulky secondary alkyl groups.

Alkylation has been traditionally performed by treating alkyl halides with metal salts of 2-pyridones, either preformed or formed *in situ*.[8] The regioselectivity of *N*- versus *O*-alkylation depends on a variety of factors including the nature of the metals, the structure of the alkyl halides, substituents on the 2-pyridone ring, solvents,[9] and temperature. Modifications of the reaction conditions have been developed to improve the conversion and regioselectivity of these alkylations. The use of CsF furnished *N*-alkylated products from activated alkyl halides (benzyl or allyl chlorides) with the *N*-/*O*-alkylation ratios of up to 13:1 under mild conditions (DMF, 30 °C). However, *O*-alkylation was favored for unactivated secondary alkyl halides.[10] Addition of LiBr to mixtures of NaH, DMF, and DME afforded *N*-propargylated products with alkylation ratios of up to 12:1. However, the ratio was low for benzyl and alkyl halides under the same reaction conditions.[11]

Mitsunobu reaction conditions do not provide improved regioselectivity for *N*-alkylated products. *N*-/*O*-alkylation ratios of up to 4:1 were obtained for activated primary alcohols such as benzyl alcohol. Unactivated primary alcohols generally yielded mixtures of *N*- and *O*-alkylated products, while secondary alcohols favored *O*-alkylation instead.[12,13]

Several other strategies have been reported to give high regioselectivity. However, the requirements for special catalysts or starting materials limit the substrate scopes and render these methods less practical. Metal-catalyzed *N*-allylation of 2-pyridone[14,15] proved high yielding. Selective *N*-alkylation of 2-pyridones was observed for alkoxypyridines[16,17] with activated alkyl halides. A cationic Ir(I) complex catalyzes *O*- to *N*-alkyl migration for 2-alkoxypyridines.[18] In the presence of Mg(O*t*-Bu)$_2$, *N*-selective alkylation of 2-pyridones was achieved with 2-halo-carboxylic acids.[19] *N*-Alkylated 2-pyridones could be obtained through nucleophilic ring opening of oxazolinium intermediates, which are tedious to prepare.[20]

Herein, we report a mild, practical, and regioselective *N*-alkylation reaction of 2-pyridones with both activated and unactivated alkyl halides. In addition, the method has been developed in water, the environmentally friendly solvent, which makes the methodology even more attractive.

To address ever-increasing environmental concerns,[21] a growing number of advances in chemical synthesis and catalysis have been reported utilizing water as solvent. One focus of our group is to develop reactions in aqueous reaction conditions; these reactions can be facilitated by micelles formed in water from readily available surfactants. We favor the choice of polysorbates (also known as Tween) because of their low cost, availability, high stability, and relatively nontoxic profile.[22] Micelles form nanoreactor environments in water due to the hydrophobic effects that favor the compartmentalization of organic reagents thus improving the solubility and the local concentration of reagents.[23] As a consequence, unique enhancement of reactivity, chemo-, region-, and stereoselectivities can be achieved in aqueous micellar systems.[24]

Based on the C−H arylation using the Tween/water micellar system we developed,[25] we have explored the challenges in the synthesis of *N*-alkylated 2-pyridones and exploited the effects of this micellar system on the conversion and regioselectivity of the alkylation of 2-pyridones. We started this endeavor by reacting 5-bromo-2-pyridone (**1a**) with benzyl bromide (**2a**) using $K_2CO_3$ as the base (Table 1). To our delight, we observed high conversion (76%) to the alkylated products (**3a**[26] and **4a**) after 3 h at ambient temperature in Tween 20/water (2% w/w). Based on HPLC analysis, *N*-/*O*-alkylation ratio (**3a**/**4a** ratio) was 10:1 (entry 1). We then evaluated the effects of different bases

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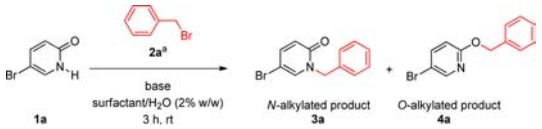
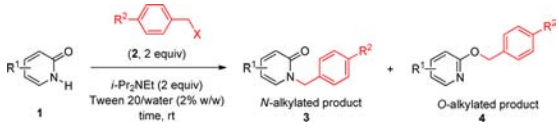
**Table 1. Optimization of Reaction Conditions for *N*-Alkylation of 2-Pyridone**




| entry | base (equiv) | surfactant | conversion[b] (HPLC) | 3a/4a ratio[b] (HPLC) |
|---|---|---|---|---|
| 1 | $K_2CO_3$ (1.2 equiv) | Tween 20 | 76% | 10:1 |
| 2 | $Cs_2CO_3$ (1.2 equiv) | Tween 20 | 69% | 8:1 |
| 3 | $Et_3N$ (1.2 equiv) | Tween 20 | 57% | 5:1 |
| 4 | *i*-$Pr_2$NEt (1.2 equiv) | Tween 20 | 85% | 12:1 |
| 5 | *i*-$Pr_2$NEt (1.2 equiv) | Tween 80 | 84% | 10:1 |
| 6 | *i*-$Pr_2$NEt (1.2 equiv) | none | 37% | 6:1 |
| 7 | *i*-$Pr_2$NEt (2.0 equiv) | Tween 20 | 94% | 14:1 |
| 8 | *i*-$Pr_2$NEt (5.0 equiv) | Tween 20 | 95% | 14:1 |

[a]The same equivalent of benzyl bromide (**2a**) as the base was used. [b]Conversion and *N*-/*O*-alkylation ratio were determined by HPLC peak areas at 214 nm for 2-pyridone and the regio-isomer products (**3a** and **4a**) in the reaction mixture.

**Table 2. Scope of 2-Pyridones and Benzyl Halides for the Regioselective *N*-Alkylation Reaction in Water**




| entry | 1 | 2 | time | conversion[a] (HPLC) | 3/4 ratio[b] (NMR) | isolated yield of 3 |
|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | 3 h | 94% | 14:1 | **3a**, 83% |
| 2 | **1b** | **2a** | 3 h | 93% | 15:1 | **3b**, 81% |
| 3 | **1c** | **2a** | 3 h | 96% | 17:1 | **3c**, 80% |
| 4 | **1d** | **2a** | 18 h | 90% | >19:1 | **3d**, 89% |
| 5 | **1e** | **2a** | 6 h | 100% | >19:1 | **3e**, 94% |
| 6 | **1f** | **2a** | 18 h | 90% | 5:1 | **3f**, 52% |
| 7 | **1g** | **2a** | 18 h | 80% | 8:1 | **3g**, 66% |
| 8 | **1a** | **2b** | 3 h | 100% | 12:1 | **3h**, 90% |
| 9 | **1a** | **2c** | 3 h | 100% | 14:1 | **3i**, 94% |
| 10 | **1a** | **2d** | 3 h | 100% | 17:1 | **3j**, 93% |
| 11 | **1a** | **2e** | 6 days | 97% | 8:1 | **3a**, 86% |

[a]Conversion was determined by HPLC peak areas at 214 nm for 2-pyridone and the regio-isomer products in the reaction mixture. [b]*N*-/*O*-alkylation ratio was determined by comparing integrations of characteristic protons for product **3** and **4** in $^1$H NMR spectrum of the concentrated reaction mixture

including $Cs_2CO_3$ (entry 2), $Et_3N$ (entry 3), and *i*-$Pr_2$NEt (entry 4), and discovered that *i*-$Pr_2$NEt provided the highest conversion and regioselectivity (*N*-/*O*-alkylation ratio). Use of Tween 80 as the surfactant provided similar conversion as that of Tween 20, but with lower *N*-/*O*-alkylation ratio (10:1, entry 5). In the absence of a Tween surfactant, the reaction was sluggish and the regioselectivity was poor (entry 6), which is consistent with our observations in previous studies[25] and the reported benefits of surfactants in solubility improvement and reaction rate acceleration.[24]

Interestingly, Mayr showed that the nucleophilicity of 2-pyridone is greatly decreased in aqueous solution.[7] Under micellar alkylation conditions, however, the nucleophilicity reduction of 2-pyridone **1a** was not observed, further demonstrating the utility of the reaction environment created by micelles relative to simple aqueous solutions. When the amounts of *i*-$Pr_2$NEt and benzyl bromide **2a** were increased to 2 equiv, both the conversion and regioselectivity were improved (entry 7). Further increasing the amounts of *i*-$Pr_2$NEt and benzyl bromide provided negligible improvement in conversion (entry 8).

With the optimized reaction condition identified, we evaluated the substrate scope. As shown in Table 2 (entries 1−7), a variety of substituted 2-pyridones (**1a**−**1g**) bearing both electron-



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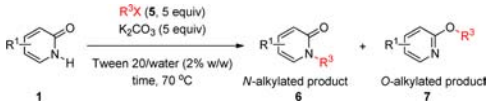
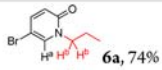
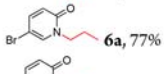
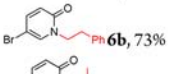
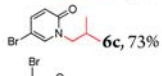
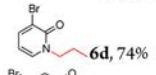
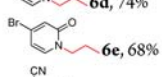
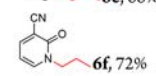
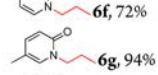
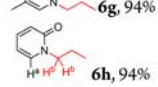
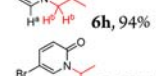
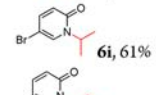
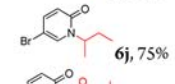
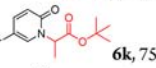
**Table 3. Scope of Aliphatic Halides and 2-Pyridones for the Regioselective *N*-Alkylation Reaction in Water**




| entry | 1 | 5 | time | conversion[a] (HPLC) | 6/7 ratio[b] (NMR) | isolated yield of 6 |
|---|---|---|---|---|---|---|
| 1 |  1a |  5a | 24 h | 100% | >19:1 |  6a, 74% |
| 2 |  1a |  5b | 18 h | 100% | >19:1 |  6a, 77% |
| 3 |  1a |  5c | 18 h | 100% | 6:1 |  6b, 73% |
| 4 |  1a |  5d | 48 h | 80% | >19:1 |  6c, 73% |
| 5 |  1d |  5b | 60 h | 100% | >19:1 |  6d, 74% |
| 6 |  1c |  5b | 24 h | 100% | >19:1 |  6e, 68% |
| 7 |  1e |  5b | 24 h | 100% | >19:1 |  6f, 72% |
| 8[c] |  1f |  5b | 60 h | 100% | >19:1 |  6g, 94% |
| 9[c] |  1g |  5b | 60 h | 100% | >19:1 |  6h, 94% |
| 10[c] |  1a |  5e | 18 h | 92% | 3:1 |  6i, 61% |
| 11[c] |  1a |  5f | 48 h | 93% | 7:1 |  6j, 75% |
| 12[c] |  1a |  5g | 18 h | 100% | 10:1 |  6k, 75% |
| 13[c] |  1e |  5e | 48 h | 74% | 2.4:1 |  6l, 40% |

[a]Conversion was determined by HPLC peak areas at 214 nm for 2-pyridone and the regio-isomer products in the reaction mixture. [b]*N*-/*O*-alkylation ratio was determined by comparing integrations of characteristic protons for products **6** and **7** in $^1$H NMR spectra of the concentrated reaction mixture. [c]Ten equivalents of halides (**5**) and ten equivalents of $K_2CO_3$ were used.

donating and electron-withdrawing substituents were well tolerated with high conversion (>80%). The *N*-/*O*-alkylation ratios ranged from 5:1 to >19:1 as determined by integration of the characteristic protons for products **3** and **4** in $^1$H NMR spectra of the concentrated reaction mixtures. The desired *N*-alkylated products (**3a**−**3g**) were isolated in good yields (52−94%). The regiochemistry (*N*-alkylation) was confirmed by 2D NMR for the representative compound **3a** based on the observation of ROESY cross-peaks between $H^a$ and $H^b$ in **3a** (Supporting Information). Electron withdrawing substituents at the 3-position deactivate 2-pyridones (**1d** and **1e**) toward alkylation, and prolonged reaction time was required for good conversions (entries 4 and 5). 2-Pyridones with electron donating/neutral groups (**1f** and **1g**) were also less reactive and resulted in lower isolated yields with compromised regioselectivities of the *N*-alkylated products, even after prolonged reactions (entries 6 and 7). Limited scope of benzyl halide was then explored (Table 2, entries 8−11) using 5-bromo-2-pyridone (**1a**). *para*-Substituted benzyl bromides (**2b**−**2d**) with electron-donating and electron-withdrawing substituents were well tolerated yielding good conversions, alkylation ratios, and isolated yields. *N*-Alkylated products (**3h**−**3j**) were the predominant regioisomers isolated in high yields (90−94%) after 3 h of reaction at room temperature. The *N*-/*O*-alkylation ratios were determined to range from 12:1 to 17:1 by $^1$H NMR analysis. In addition, benzyl chloride (**2e**) also afforded *N*-alkylated product with high yield (86%) and regioselectivity (8:1), albeit the reaction rate was slower.

To further evaluate the efficiency of the reaction condition, we examined the *N*-alkylation of 2-pyridones with unactivated primary and secondary aliphatic halides. Not surprisingly, reaction was sluggish under the aforementioned conditions optimized for activated benzyl halides. The reaction could be accelerated by elevating the temperature to 70 °C as well as increasing the amount of both base and halides to five equivalents. However, the elevated temperature resulted in the formation of unknown side products. Fortunately, the formation of side products could be suppressed by switching the base from *i*-$Pr_2NEt$ to $K_2CO_3$. As shown in Table 3 (entries 1−4), 5-bromo-2-pyridone (**1a**) reacted with primary bromide **5a** and primary iodides **5b**−**5d** to afford *N*-alkylated products (**6a**−**6c**) in high isolated yields. Except for iodide **5c**, which afforded *N*-/*O*-alkylation ratio of 6:1, *N*-alkylated products were the only regio-isomers detected in $^1$H NMR spectra of the concentrated reaction mixtures for halides **5a**, **5b**, and **5d**. The reaction showed high tolerability to the electronic properties of substitutions on 2-pyridones, as demonstrated by the reactions between 2-pyridones (**1d**−**1h**) and *n*-propyl iodide (**5b**) (entries 5−9). Even though 2-pyridones **1f** and **1g** showed moderate yields when reacting with benzyl bromide (**2a**) (Table 2, entries 6 and



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7), excellent isolated yields (94%) were achieved when ten equivalents of *n*-propyl iodide (**5b**) and $K_2CO_3$ were used with the prolonged reaction time of 60 h at 70 °C (Table 3, entries 8 and 9). In order to further confirm the regio-chemistry (*N*- versus *O*-alkylation), 2D NMR experiments have been conducted for the representative compounds **6a** and **6h**. The ROESY cross-peaks between $H^a$ and $H^b$ of both compounds (entries 1 and 9) were observed (Supporting Information), providing strong evidence for *N*-alkylation products. In addition, $^{13}C$ NMR spectrum of **6h** was observed to be identical to literature data,[27] which provided further evidence for our regiochemistry assignments. We then further explored the scope of unactivated secondary alkyl halides, which has presented a long-lasting, unresolved challenge to the organic chemistry community. To our delight, our reaction condition employing the Tween/water micellar system was well tolerated for unactivated secondary iodides (isopropyl iodide **5e** and isobutyl iodide **5f**) with different substitutions on the 2-pyridone (Table 3, entries 10, 11, and 13). The desired *N*-alkylation products (**6i**, **6j**, and **6l**) were obtained in moderate to good isolated yields, and reasonable regioselectivities were observed based on $^1H$ NMR analysis of concentrated reaction mixtures. Activated alkyl bromide **5g** (*tert*-butyl 2-bromopropanoate) afforded a higher *N*-/*O*-alkylation ratio (10:1) with good isolated yield (75%, entry 12). In the IR spectra, strong bands between 1643 and 1670 $cm^{-1}$ (characteristic for C═O) were observed for all products (**3a**−**3j** and **6a**−**6l**), further supporting the structure assignment of *N*-alkylation.

In summary, we have developed a mild and regioselective *N*-alkylation reaction of 2-pyridones. Our methodology allows the use of water as the "green" reaction solvent and employs Tween 20 to create a micellar system to effectively enhance the nucleophilicity of 2-pyridones to afford *N*-alkylated products with high regioselectivity. Our protocol demonstrated wide substrate scope including unactivated secondary alkyl halides, which have presented a long-lasting challenge for the organic chemistry community. Good isolated yields (40−94%) were obtained for all 24 examples evaluated. Further application of this new methodology to regioselective alkylations of alternate ambident nucleophiles is under current investigation.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and analytical data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01628.

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### Notes

The authors declare no competing financial interest.

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