CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.201301350

Nickel-Catalyzed Direct Alkylation of Heterocycles with α-Bromo Carbonyl Compounds: C3-Selective Functionalization of 2-Pyridones

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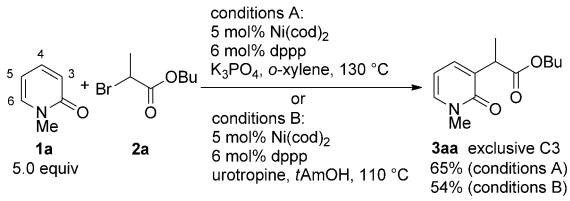
Pyridone derivatives constitute an important class of compounds in pharmaceutical and medicinal chemistry.[1] In particular, acetic acids that contain 2-pyridone cores at the position α to carbonyl groups show unique biological activity.[2] The palladium, nickel, and copper-catalyzed α-arylation of carbonyl compounds with halogenated pyridones appear to be attractive approaches to the target molecules.[3] However, the reaction with electron-rich heterocyclic halides is still restricted in efficiency and selectivity.[4] The metal-promoted C–H functionalization chemistry of heterocycles has recently received significant attention, and the traditional homolytic radical aromatic substitution (HAS) is now revisited as an efficient and direct functionalization methodology for heterocycles.[5] For example, Ru- and Ir-based photoredox catalysts are applied to the HAS of electron-rich indoles and pyrroles with α-halo carbonyl compounds and provides a complementary access to α-heterocyclic acetic acid derivatives.[6,7] However, these photocatalysis reactions still suffer from a somewhat narrow substrate scope of α-halo carbonyls; only highly activated systems, such as 2-bromomalonate esters, can be used owing to the limitation of their redox potentials. Although the HAS reaction with xanthates has been reported, preactivation of α-haloacetates into the corresponding xanthates is inevitable, and an excess amount of peroxide is required.[8] Thus, there remains a challenge to develop the HAS-type direct alkylation of electron-rich heterocycles with less activated α-halo carbonyl compounds. Herein, we report a nickel-catalyzed HAS-type reaction with α-bromoacetates. The nickel catalyst enables the alkylation of 2-pyridones, as well as indoles, benzofuran, and coumarin, to directly form the corresponding α-heterocyclic acetic acids. Moreover, in the reactions of 2-pyridones, unique C3 selectivity is observed.

We first chose *N*-methyl-2-pyridone (**1a**) and butyl 2-bromopropanoate (**2a**) as model substrates and extensively screened various reaction parameters, such as catalysts, ligands, bases, and solvents.[9] It was found that a $Ni(cod)_2$/dppp (cod = 1,5-cyclooctadiene, dppp = 1,3-bis(diphenylphosphino)propane) catalyst system with K_3PO_4 as a base promoted the reaction of **1a** with **2a** in heated *ortho*-xylene to afford the alkylated 2-pyridone **3aa** in good yield (Scheme 1, conditions A). A combination of hexamethylenetetramine (urotropine) and 2-methyl-2-butanol (*t*AmOH) also gave a comparable yield (Scheme 1, conditions B). Particularly notable is that the C–C bond formation occurred exclusively at the C3 position of 2-pyridone and no regioisomers were detected. Such a high C3 selectivity is not trivial,[10] and C5- and C6-selective functionalizations are possible under Pd[11] and Ni/Al bimetallic[12] catalysts, respectively.



Scheme 1. Reaction conditions for nickel-catalyzed C3-selective alkylation of *N*-methyl-2-pyridone (**1a**) with butyl 2-bromopropanoate (**2a**).

By using the conditions A or B shown in Scheme 1, we performed the direct alkylation of an array of 2-pyridone derivatives with **2a** (Table 1). Regardless of the substitution pattern on the pyridone ring, the exclusive C3 selectivity was uniformly observed. Namely, 4-methyl, 5-methyl, and 6-methyl-2-pyridones (**1c–e**) also underwent the alkylation, and the corresponding C3-alkylated products **3ca–ea** were obtained as the single regioisomers (Table 1, entries 3–8). On the other hand, when the methyl group was introduced to the C3 position, no reaction took place (Table 1, entries 1 and 2). In addition to the simple methyl group, a trifluoromethyl group at the C4 or C5 positions was tolerated, albeit with somewhat lower efficiencies (Table 1, entries 9 and 10). The nickel catalysis accommodated the benzyl substituent on nitrogen, which can be a useful synthetic handle for further manipulations after an appropriate deprotection (Table 1, entry 11). A benzene-fused *N*-methyl-2-quinolinone (**1i**) was also available for use (Table 1, entry 12). Moreover, an oxygen analogue, coumarin (**1j**), could be employed for the alkylation reaction; as shown in the reaction with 2-pyridones, the C3-alkylated coumarin (**3ja**) was

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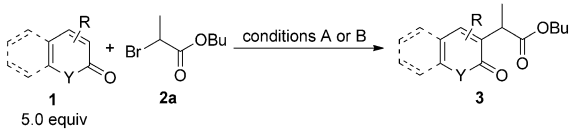
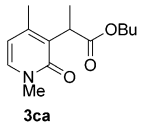
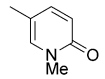
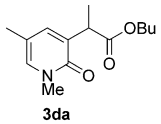
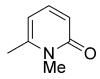
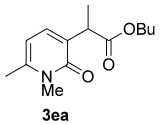
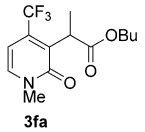
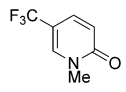
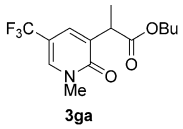
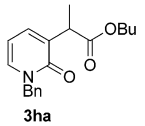
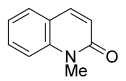
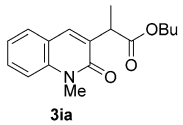
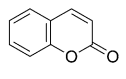
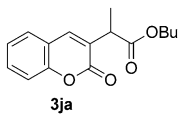
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201301350.

Table 1. Nickel-catalyzed direct alkylation of various 2-pyridones **1** with butyl 2-bromopropanoate (**2a**).[a]



Entry	1	Conditions	3	Yield [%][b]
1		A		
2	 **1b**	B	No reaction	
3		A		55
4	 **1c**	B	 **3ca**	53
5		A		56
6	 **1d**	B	 **3da**	63
7		A		41
8	 **1e**	B	 **3ea**	51
9	 **1f**	A	 **3fa**	48
10	 **1g**	B	 **3ga**	34
11	 **1h**	B	 **3ha**	49
12	 **1i**	B	 **3ia**	56
13		A		69
14	 **1j**	B	 **3ja**	70

[a] Reaction conditions A: $Ni(cod)_2$ (0.025 mmol), dppp (0.030 mmol), K_3PO_4 (0.60 mmol), **1** (2.5 mmol), **2a** (0.50 mmol), *ortho*-xylene (3.0 mL), N_2, 130 °C, 6–8 h; reaction conditions B: $Ni(cod)_2$ (0.025 mmol), dppp (0.030 mmol), urotropine (0.60 mmol), **1** (2.5 mmol), **2a** (0.50 mmol), *t*AmOH (3.0 mL), N_2, 110 °C, 4–6 h. [b] Yield of isolated product. Bn = benzyl.

formed as the sole product (Table 1, entries 13 and 14). In this reaction, an excess amount of the 2-pyridone **1** was essential for a synthetically useful yield, but about half the quantity of **1** was recovered, unreacted, by simple extraction with chloroform after the coupling reaction (see the Experimental Section for details).

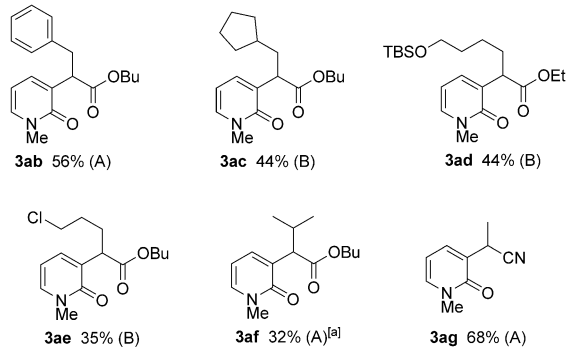
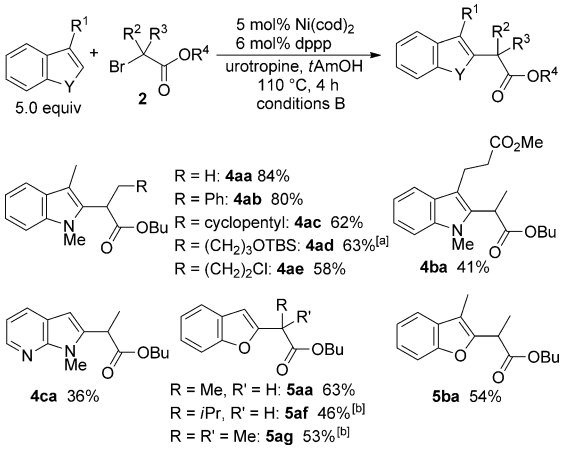


Figure 1. Products of nickel-catalyzed direct alkylation of *N*-methyl-2-pyridone (**1a**) with various α-bromocarbonyl compounds. [a] With 10 mol% of $Ni(cod)_2$ and 12 mol% of dppp for 10 h. TBS = *tert*-butyldimethylsilyl.

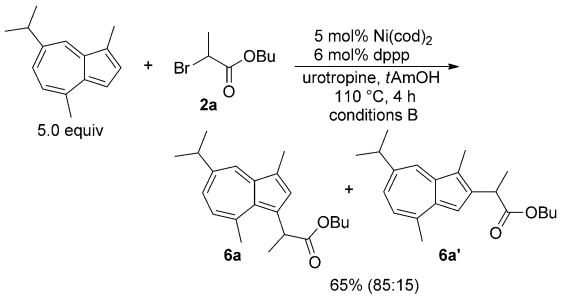
We next investigated the scope of α-bromocarbonyl coupling partners with *N*-methyl-2-pyridone (**1a**; Figure 1). α-Bromoesters with phenyl and cyclopentyl substituents at the β position also reacted regioselectively with **1a** to form the coupling products **3ab** and **3ac** in acceptable yields. The nickel catalysis was compatible with silyl ether and alkyl chloride functionalities (**3ad** and **3ae**); however, the bulky *i*Pr-substituted substrate showed somewhat lower reactivity (**3af**). Additionally, α-bromopropanenitrile worked as a suitable alkyl donor, giving the corresponding alkylated product **3ag** in good yield. However, α-bromoamides, α-bromoketones, α-chlorocarbonyls, and primary alkyl halides were inaccessible substrates under the standard conditions (data not shown).

The above nickel catalyst systems can be applied to the direct alkylation of electron-rich heterocycles other than 2-pyridones (Scheme 2). *N*,3-Dimethylindole was coupled with a variety of α-bromoesters to afford the corresponding α-indolylacetates in moderate to good yields (Scheme 2, **4aa**–**ae**). The tryptophan methyl ester and pyrrolopyridine also



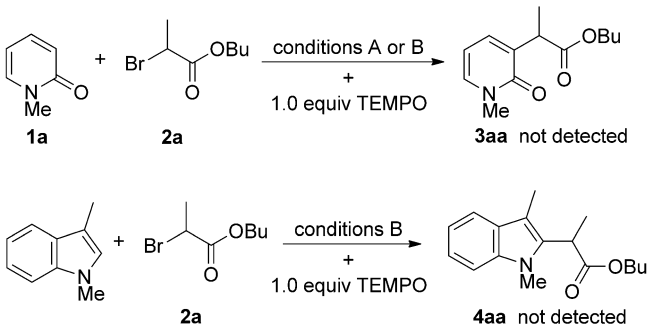
Scheme 2. Nickel-catalyzed direct alkylation of electron-rich heterocycles with various α-bromocarbonyl compounds. [a] With 10 mol% of $Ni(cod)_2$ and 12 mol% of dppp for 10 h. [b] The corresponding ethyl ester was used.

participated in the reaction (Scheme 2, **4ba** and **4ca**).[13] Moreover, benzofuran and 3-methylbenzofuran were transformed into the α-benzofurylesters in acceptable yields (**5**). It is worth noting that the coupling of benzofuran with sterically hindered *i*Pr- and dimethyl-substituted bromoesters was possible (Scheme 2, **5af** and **5ag**). In the cases of pyrrolopiridine and benzofuran, the C–C bond formation occurred regioselectively at the C2 position of the pyrrole and furan ring, respectively. Significantly, the direct alkylation of guaiazulene was successful (Scheme 3), indicating that this nickel catalyst can provide a new and facile access to functionalized azulene derivatives.[14]

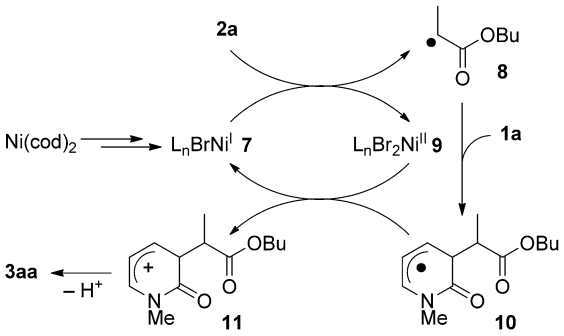


Scheme 3. The direct alkylation of guaiazulene.

To get some mechanistic insight, we carried out the catalytic reactions in the presence of a radical inhibitor. The addition of 2,2,6,6,-tetramethylpiperidine-1-oxyl (TEMPO) completely suppressed the nickel catalysis for both 2-pyridone and indole (Scheme 4). On the basis of the above results and literature information,[15–18] although the detailed mechanism is not yet clear, we propose the reaction course of *N*-methyl-2-pyridone (**1a**) and **2a** shown in Scheme 5. A single electron transfer from an initially formed Ni^{I} species **7** to **2a** gives an alkyl radical intermediate **8** with the concomitant generation of Ni^{II} complex **9**. Subsequent addition of **8** to **1a** proceeds through a SOMO/HOMO interaction, in which the C–C bond is formed selectively at the C3 position on the pyridone ring because of the relatively large

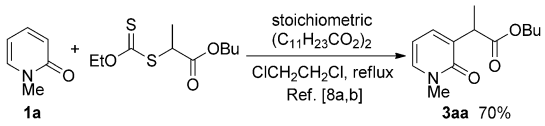


Scheme 4. Nickel catalysis of 2-pyridone and indole in the presence of the radical initiator TEMPO.



Scheme 5. Plausible mechanism.

atomic contribution of HOMO at the C3 atom[19] and preferable resonance stabilization of the resultant adduct **10**. The alkylated product **3aa** is then formed from the oxidation of **10** by Ni^{II} complex **9** and rearomatization of **11** through a deprotonation. The oxidation process concurrently regenerates the starting Ni^{I} complex to complete the catalytic cycle.[20] The postulated HAS-type mechanism can explain the observed regioselectivity in the functionalization of indoles, benzofurans, and azulene, as well as 2-pyridones.[21] Indeed, upon exposure of *N*-methyl-2-pyridone (**1a**) to the conventional peroxide-promoted HAS conditions[8a,b] with the corresponding xanthate, the same regioselectivity was observed (Scheme 6).[22] Thus, the presented



Scheme 6. Reaction of *N*-methyl-2-pyridone (**1a**) under conventional peroxide-promoted HAS conditions.

catalysis can be regarded as a peroxide-free, nickel-catalyzed HAS-type reaction of heterocycles with less reactive α-halocarbonyls. However, an alternative involving a Ni^{0}/Ni^{I} redox system cannot be completely excluded. Further investigation is essential for clarification of the detailed mechanism.

In conclusion, we have developed a nickel-catalyzed direct alkylation of electron-rich heterocycles with α-bromocarbonyl compounds. The nickel catalysis can provide a peroxide-free catalytic system for the HAS-type reaction with less reactive α-halocarbonyls. Moreover, the HAS-type reaction is found to be capable of the unique C3-selective direct functionalization of 2-pyridones.

Experimental Section

Nickel-catalyzed direct alkylation of *N*-methyl-2-pyridone (1a) with butyl 2-bromopropanoate (2a): 1,3-Bis(diphenylphosphino)propane (dppp, 12 mg, 0.030 mmol), K_3PO_4 (127 mg, 0.60 mmol), and dibenzyl (ca.

30 mg, internal standard) were placed in a two-necked reaction flask (20 mL), and the flask was taken into a glove box filled with nitrogen. Ni(cod)$_2$ (6.9 mg, 0.025 mmol) in xylene (2.0 mL) was then added and the flask was sealed with a septum and taken out of the glove box. After the suspension was stirred for 15 min at ambient temperature, a solution of *N*-methyl-2-pyridone (**1a**, 273 mg, 2.5 mmol) and butyl 2-bromopropanoate (**2a**, 105 mg, 0.50 mmol) in xylene (1.0 mL) was added. The reaction was heated to 130 °C and stirred for 6 h. The resulting mixture was quenched with water and then extracted four times with ethyl acetate. The combined organic layers were dried over sodium sulfate. Concentration in vacuo and subsequent purification by column chromatography on silica gel with dichloromethane/ethyl acetate (1:1, v/v) as an eluent gave the alkylated 2-pyridone (**3aa**, 77 mg, 0.32 mmol) in 65% yield. The residual water layer was extracted four times with chloroform and remaining *N*-methyl-2-pyridone (**1a**) was recovered (139 mg, 1.3 mmol).

Acknowledgements

This work was partly supported by Grants-in-Aid from MEXT and JSPS, Japan. K.H. acknowledges The Uehara Memorial Foundation for financial support. We thank Mr. Tomoyuki Yao for his initial experimental assistance.

Keywords: alkylation · homolytic radical aromatic substitution · nickel · pyridones · synthetic methods

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Received: April 10, 2013
Published online: May 2, 2013

