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Direct C3-alkenylation of pyridin-4(1*H*)-one via oxidative Heck coupling

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ABSTRACT

Oxidative Heck coupling of pyridin-4(1*H*)-one via palladium(II)-catalyzed C–H bond activation has been achieved in moderate to good yields. The coupling occurred selectively at C3 position. Pivalic acid was found to be an effective additive to promote this alkenylation.

1. Introduction

During the last few decades, major progress has been achieved in transition metal catalyzed carbon(sp2)–carbon(sp2) bond-formation.[1] Among them, Heck reaction between halogenated arenes with alkenes is recognized as one of the most powerful methods to construct alkenylated arenes.[2] More recently, the more economical and straightforward C–C bond formation via palladium(II)-catalyzed C–H bond cleavage between unpreactivated arenes or heteroarenes and olefins, known as oxidative Heck coupling, has been becoming an exceedingly valuable process in contemporary organic synthesis since this methodology generally avoids the need of the preactivation of arene species.[3] Up to date, lots of efforts have been devoted to the direct alkenylation of various heteroaromatic scaffolds through the oxidative Heck coupling to build diverse molecular library.[4]

Pyridin-4(1*H*)-one is a common motif found in a variety of bioactive natural products and versatile synthetic molecules.[5] Typically, the compounds bearing 2-hydroxymethyl-5-hydroxyl pyridin-4(1*H*)-one scaffold are demonstrated to show some interesting bioactivities (Fig. 1),[6] which has attracted much attention in the synthetic community during the past several years. For example, Ge et al. reported an efficient alkenylation of quinolones[7] and enaminones[8] via an oxidative Heck reaction. Very recently, Hong and co-workers also disclosed a direct alkenylation of various chromones via a palladium(II)-catalyzed C–H functionalization reaction.[9] As a continuation of our research on nitrogen-containing heteroarenes,[10] we wish to utilize an oxidative Heck coupling reaction to realize the C3-alkenylation of 2,5-disubstituted pyridin-4(1*H*)-one, leading to diverse chemical libraries for biological screening. We herein report our results.

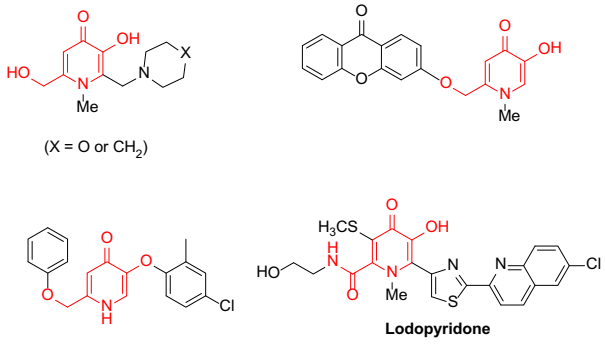

Fig. 1. Representative examples of bioactive compounds bearing 2,5-disubstituted pyridin-4(1*H*)-one.

2. Results and discussion

Our initial investigation focused on the coupling of 5-methoxy-2-(methoxymethyl)-1-methylpyridin-4(1*H*)-one **1a** with *n*-butyl acrylate **2a** as summarized in Table 1.[11] **1a** could be readily achieved from Kojic acid through double methylation of hydroxyl groups

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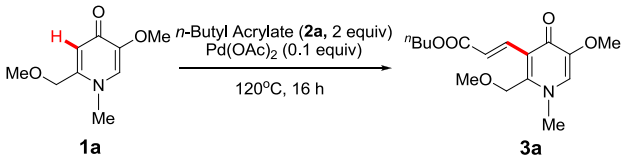
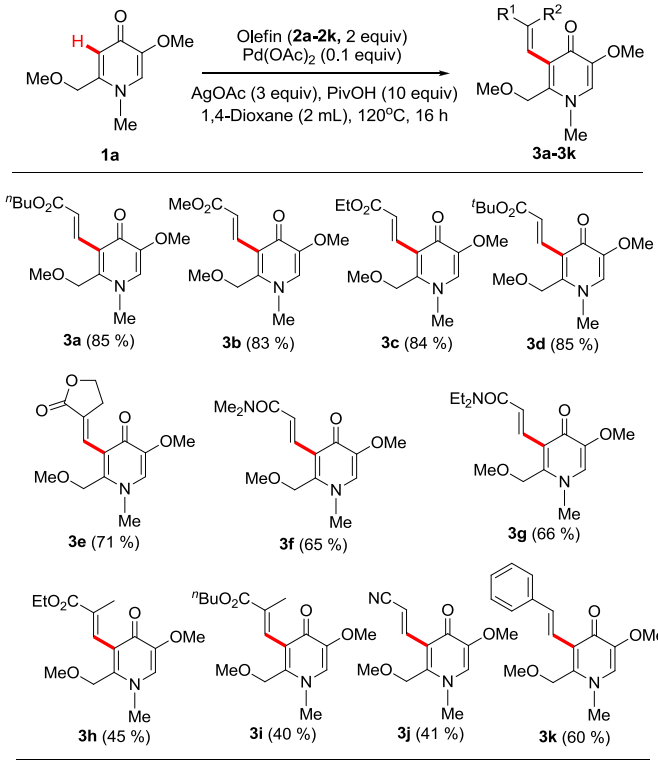
Table 1
Screening of reaction conditions[a,11]



Entry	Oxidant (2 equiv)	Solvent (2 mL)	Additive (equiv)	Yield (%)[b]
1	AgOAc	DMF	—	27
2	$Cu(OAc)_2$	DMF	—	Trace
3	Ag_2CO_3	DMF	—	19
4	BQ	DMF	—	Trace
5	$K_2S_2O_8$	DMF	—	Trace
6	AgOAc	DMA	—	25
7	AgOAc	CH_3CN	—	20
8	AgOAc	AcOH	—	17
9	AgOAc	DMSO	—	Trace
10	AgOAc	1,4-Dioxane	—	54
11	AgOAc	1,4-Dioxane	Cs_2CO_3 (2)	0
12	AgOAc	1,4-Dioxane	K_2CO_3 (2)	Trace
13	AgOAc	1,4-Dioxane	TEA (2)	0
14	AgOAc	1,4-Dioxane	PivOH (2)	63
15	AgOAc	1,4-Dioxane	PivOH (10)	79[c]
16[d]	AgOAc	1,4-Dioxane	PivOH (10)	75
17[e]	AgOAc	1,4-Dioxane	PivOH (10)	64
18	AgOAc[f]	1,4-Dioxane	PivOH (10)	85[c]

[a] Reaction conditions: **1a** (0.5 mmol), *n*-butyl acrylate (**2a**, 1 mmol), $Pd(OAc)_2$ (0.05 mmol), oxidant (1 mmol), and additive in solvent (2 mL) at 120 °C for 16 h.
[b] ^1H NMR yields using dibromomethane (δ=4.80) as an internal standard.
[c] Isolated yields.
[d] 100 °C.
[e] 110 °C.
[f] AgOAc (1.5 mmol) was used.

Table 2
Olefin scope[a,b]



[a] Reaction conditions: **1a** (0.5 mmol), olefin (**2a-2k**. 1 mmol), $Pd(OAc)_2$ (0.05 mmol), AgOAc (1.5 mmol) and PivOH (5 mmol) in 1,4-dioxane (2 mL) at 120 °C for 16 h.
[b] Isolated yields.

with Me_2SO_4, followed by amination with $MeNH_2$.[12] Initial screening revealed that the use of AgOAc as an oxidant provided the desired alkenylated product **3a** in higher yield than other oxidants (entries 1–5). NOESY spectrum of **3a** proved that the alkenylation selectively occurred at the C3 position.[13] Subsequent screening on solvent suggested that the yield could be promoted to 54% when 1,4-dioxane was used (entries 6–10). The screening on additive effect indicated basic additives were detrimental to this alkenylation (entry 11–13), while PivOH could dramatically increased the coupling efficiency, resulting in the yield of **3a** to 79% (entry 14–15). This could be explained by the fact that palladium–PivOH combinations could lower the energy of C(sp2)–H bond cleavage, leading to excellent reactivity in C–H activation reactions.[14] Replacing $Pd(OAc)_2$ with other commonly used Pd(II) catalysts or changing the reaction temperature gave no further improved results (entries 16–17). Finally, we were pleased to find that the yield of **3a** could be increased to 85% by increasing the loading of AgOAc (entry 18).

With the established condition in hand, we examined various olefins to demonstrate the reaction scope as shown in Table 2. Generally, all olefins could react smoothly to provide the desired cross-coupling products in moderate to good yields. For example, the good yields of the corresponding products (**3a**–**e**) maintained when the substrate **1a** was coupled with acrylates, while the yields of the alkenylation with acrylamides slightly dropped (**3f**, **3g**). More sterically hindered α-methyl acrylates afforded the desired products in relatively low yields (**3h**, **3i**). In addition, the coupling with other olefins, such as acrylonitrile, styrene, could also provide the corresponding products (**3j**, **3k**) in moderate yields.

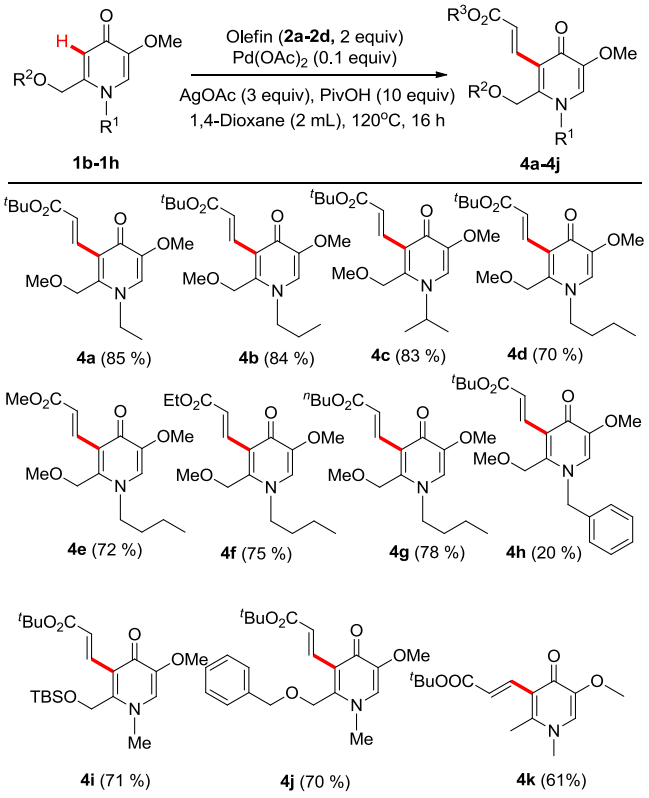
Next, the effective conditions were extended to a variety of substrates bearing N1- and C2-substutions and the results were shown in Table 3. We observed that steric hindrance at the N1-position has some impact on the yield of the alkenylated product. Beside methyl, small alkyl groups like ethyl, *n*-propyl or *i*-propyl did not influence the effectiveness of this reaction, affording the desired product in good yields (**4a**–**c**), while *n*-butyl substitution slightly declined the yields (**4d**–**g**). Very interestingly, benzyl substitution at N1-position dramatically decreased the coupling yield (**4h**). TBS and Bn groups on C2 position, or removal of the methoxyl group were found to be well tolerated under the optimized conditions, providing the desired products in good yields (**4i**–**k**).

Finally, we proposed a plausible mechanism for the C3-alkenylation of pyridin-4(1*H*)-one as illustrated in Fig. 2. The reaction is initiated by the nucleophilic attack of pyridin-4(1*H*)-one at C3 position. Such regioselectivity is controlled by the inherent electronic bias of the pyridin-4(1*H*)-one substrate itself,[7,15] rather than by the oxygen atom at the 2-methoxymethyl group since 2-methyl substrate still showed good regioselectivity (**4k**, Table 3). Deprotonation by the pivalate ligand gave C3-palladated intermediate **A**, which smoothly inserts into the olefin to produce intermediate **B**. Finally, **B** undergoes a reductive elimination to provide the desired coupled product and Pd(0), which is reoxidized to Pd(II) by AgOAc to complete the catalytic cycle.

3. Conclusion

In conclusion, we have developed a general protocol for the direct C3-alkenylation of 2,5-disubstituted pyridin-4(1*H*)-one in moderate to good yields via Pd(II)-catalyzed C–H bond activation. The coupling reaction selectively occurred at C3 position. Furthermore, PivOH could dramatically improve the coupling efficiency. Further application of this methodology to the functionalization of

Table 3
Substrate scope[a,b]



[a] Reaction conditions: **1b-1h** (0.5 mmol), olefin (**2a-2d**, 1 mmol), $Pd(OAc)_2$ (0.05 mmol), AgOAc (1.5 mmol) and PivOH (5 mmol) in 1,4-dioxane (2 mL) at 120 oC for 16 h.
[b] Isolated yields.

pyridin-4(1*H*)-one, as well as the study on their biological activities, are ongoing in our laboratory, which will be reported in due course.

4. Experimental section

4.1. General information

Melting point (mp) was measured on a microscopic melting point apparatus. ^1H and ^{13}C NMR spectra were collected on BRUKER AV-300 (300 MHz) spectrometer using $CDCl_3$ as solvent. Chemical shifts of ^1H NMR were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ=0.00 ppm) with the solvent resonance as an internal standard ($CDCl_3$: δ=7.26 ppm). Data are reported as follows: chemical shift in ppm (δ), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant (Hertz), and integration. Chemical shifts of ^{13}C NMR were reported in ppm with the solvent as the internal standard ($CDCl_3$: δ=77.0 ppm). Infrared spectra (IR) were recorded on a Thermo Scientific iS10 FT/IR spectrometer; absorptions are reported in reciprocal centimeters. High Resolution Mass measurement was performed on Agilent QTOF 6520 mass spectrometer with electron spray ionization (ESI) as the ion source.

4.2. General experimental procedure

A reaction tube was charged with 5-methoxypyridin-4(1*H*)-one substrate (0.5 mmol, 1.0 equiv), olefin (1.0 mmol, 2 equiv), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 10 mol %), AgOAc (250 mg, 1.5 mmol, 3.0 equiv), pivalic acid (5 mmol, 10 equiv), and 1,4-dioxane (2 mL). The mixture was vigorously stirred at 120 °C (oil temperature). After stirring for 16 h, the mixture was cooled to room temperature, diluted with ethyl acetate, and filtered. The filtrate was concentrated in vacuo to give dark yellow residue, which was purified by flash chromatography on silica gel to afford the cross-coupling product.

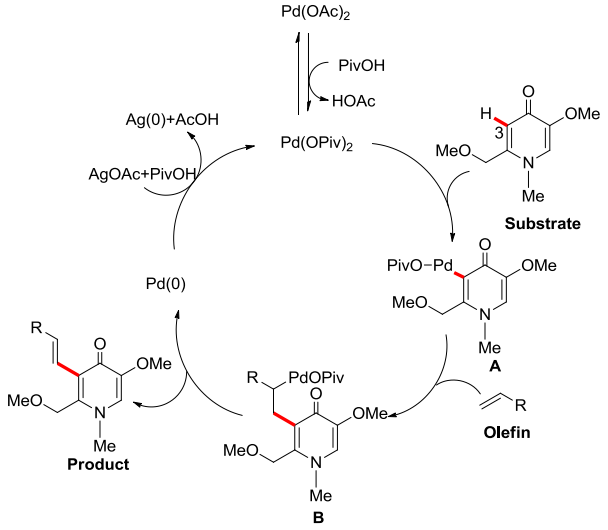


Fig. 2. Proposed reaction mechanism.

4.3. Characterization data of products

*4.3.1. n-Butyl 3-(5-methoxy-2-(methoxymethyl)-1-methyl-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**3a**).* Yellowish solid, mp 96–98 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J=7.3 Hz, 3H), 1.36–1.49 (m, 2H), 1.63–1.72 (m, 2H), 3.44 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 4.18 (t, J=6.6 Hz, 2H), 4.50 (s, 2H), 6.91 (s, 1H), 7.28 (d, J=15.6 Hz, 1H), 7.75 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 167.2, 148.2, 142.7, 135.8, 122.1, 121.3, 120.7, 65.4, 63.1, 57.4, 55.3, 41.1, 29.7, 18.1, 12.6 ppm; IR (KBr) 2958, 1701, 1627, 1561, 1301, 1268, 1135, 1097, 956, 865 cm^{-1}; HRMS (ESI) calcd for $[C_{16}H_{23}NO_5+H]^+$ 310.1649, found 310.1654.

*4.3.2. Methyl 3-(5-methoxy-2-(methoxymethyl)-1-methyl-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**3b**).* Yellow solid, mp 180–182 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.43 (s, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 4.46 (s, 2H), 6.98 (s, 1H), 7.24 (d, J=15.6 Hz, 1H), 7.72 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 168.5, 149.2, 143.8, 137.2, 123.0, 121.8, 121.6, 66.4, 58.4, 56.3, 51.4, 42.1 ppm; IR (KBr) 3128, 1715, 1625, 1570, 1396, 1307, 1167, 1090, 1041, 981, 870 cm^{-1}; HRMS (ESI) calcd for $[C_{13}H_{17}NO_5+H]^+$ 268.1179, found 268.1180.

*4.3.3. Ethyl 3-(5-methoxy-2-(methoxymethyl)-1-methyl-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**3c**).* Yellow solid, mp 162–164 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, J=7.0 Hz, 3H), 3.43 (s, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 4.23 (q, J=7.0 Hz, 2H), 4.46 (s, 2H), 6.97 (s, 1H), 7.23 (d, J=15.6 Hz, 1H), 7.72 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 168.0, 149.2, 143.7, 136.9, 123.1, 122.4, 121.8, 66.4, 60.2, 58.4, 56.3, 42.1, 14.3 ppm; IR (KBr) 2985, 2932, 1710, 1628, 1565, 1298, 1276, 1250, 1099, 1043, 980, 956, 868 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{19}NO_5+H]^+$ 282.1336, found 282.1341.

*4.3.4. tert-Butyl 3-(5-methoxy-2-(methoxymethyl)-1-methyl-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**3d**).* Yellowish solid, mp 146–148 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H), 3.43 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 4.47 (s, 2H), 6.95 (s, 1H), 7.15 (d, J=15.6 Hz, 1H), 7.63 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0,

167.4, 149.2, 143.5, 135.7, 124.7, 123.5, 122.2, 80.0, 66.4, 58.4, 56.5, 42.1, 28.2 ppm; IR (KBr) 2920, 1693, 1628, 1563, 1300, 1273, 1151, 1135, 1099, 956 cm^{-1}; HRMS (ESI) calcd for $[C_{16}H_{23}NO_5+H]^+$ 310.1649, found 310.1654.

*4.3.5. 5-Methoxy-2-(methoxymethyl)-1-methyl-3-((2-oxodihydrofuran-3(2H)-ylidene)methyl)pyridin-4(1H)-one (**3e**).* Yellow solid, mp 146–148 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 3H), 3.69 (s, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 4.63 (s, 2H), 4.71 (s, 2H), 7.02 (s, 1H), 7.48 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 170.9, 148.5, 147.5, 141.7, 131.5, 125.5, 124.4, 70.4, 67.1, 58.5, 56.5, 41.8, 21.7 ppm; IR (KBr) 2920, 1747, 1630, 1555, 1297, 1136, 1081, 1049, 949, 850 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{17}NO_5+H]^+$ 280.1179, found 280.1181.

*4.3.6. 3-(5-Methoxy-2-(methoxymethyl)-1-methyl-4-oxo-1,4-dihydropyridin-3-yl)-N,N-dimethylacrylamide (**3f**).* Yellow solid, mp 152–154 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.17 (s, 3H), 3.43 (s, 3H), 3.79 (s, 3H), 3.79 (s, 3H), 4.54 (s, 2H), 6.94 (s, 1H), 7.65 (d, J=14.8 Hz, 1H), 8.21 (d, J=14.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 168.1, 149.3, 143.6, 133.4, 122.9, 122.2, 122.0, 66.0, 58.5, 56.4, 42.1, 37.3, 35.7 ppm; IR (KBr) 2920, 1649, 1624, 1553, 1403, 1298, 1158, 1091, 1050, 953 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{20}N_2O_4+H]^+$ 281.1496, found 281.1499.

*4.3.7. N,N-Diethyl-3-(5-methoxy-2-(methoxymethyl)-1-methyl-4-oxo-1,4-dihydropyridin-3-yl)acrylamide (**3g**).* Yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, J=7.2 Hz, 3H), 1.26 (t, J=7.2 Hz, 3H), 3.43 (s, 3H), 3.49 (q, J=7.2 Hz, 4H), 3.78 (s, 6H), 4.54 (s, 2H), 6.94 (s, 1H), 7.68 (d, J=14.8 Hz, 1H), 8.18 (d, J=14.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 167.1, 149.2, 143.5, 133.3, 122.7, 122.5, 121.9, 66.0, 58.5, 56.3, 42.3, 42.1, 40.9, 14.9, 13.2 ppm; IR (KBr) 2917, 1634, 1594, 1556, 1461, 1299, 1274, 1091, 1049, 749, 599 cm^{-1}; HRMS (ESI) calcd for $[C_{16}H_{24}N_2O_4+H]^+$ 309.1809, found 309.1812.

*4.3.8. Ethyl 3-(5-methoxy-2-(methoxymethyl)-1-methyl-4-oxo-1,4-dihydropyridin-3-yl)but-2-enoate (**3h**).* Yellow solid, mp 96–98 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J=7.5 Hz, 3H), 1.75 (s, 3H), 3.34 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 4.24 (q, J=7.0 Hz, 2H), 4.34 (s, 2H), 7.13 (s, 1H), 7.49 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 167.5, 148.9, 140.9, 133.2, 133.2, 124.6, 124.4, 67.8, 60.7, 58.3, 56.4, 41.5, 14.4, 14.2 ppm; IR (KBr) 2922, 1704, 1627, 1554, 1400, 1300, 1261, 1146, 1050, 1035, 753 cm^{-1}; HRMS (ESI) calcd for $[C_{15}H_{21}NO_5+H]^+$ 296.1492, found 296.1494.

*4.3.9. n-Butyl 3-(5-methoxy-2-(methoxymethyl)-1-methyl-4-oxo-1,4-dihydropyridin-3-yl)but-2-enoate (**3i**).* Yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J=6.6 Hz, 3H), 1.40–1.47 (m, 2H), 1.66–1.71 (m, 2H), 1.75 (s, 3H), 3.33 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 4.18 (t, J=5.7 Hz, 2H), 4.34 (s, 2H), 7.08 (s, 1H), 7.48 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 167.6, 149.0, 140.9, 133.3, 133.1, 124.7, 124.4, 67.8, 64.7, 58.3, 56.5, 41.6, 30.6, 19.2, 14.5, 13.7 ppm; IR (KBr) 2959, 2931, 1708, 1626, 1564, 1297, 1253, 1143, 1119, 1096, 750 cm^{-1}; HRMS (ESI) calcd for $[C_{17}H_{25}NO_5+H]^+$ 324.1805, found 324.1810.

*4.3.10. 3-(5-Methoxy-2-(methoxymethyl)-1-methyl-4-oxo-1,4-dihydropyridin-3-yl)acrylonitrile (**3j**).* Light yellow solid, mp 212–214 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.47 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 4.45 (s, 2H), 6.92 (s, 1H), 7.35 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 149.8, 144.0, 142.2, 122.7, 120.1, 119.8, 100.9, 66.0, 58.8, 56.5, 42.4 ppm; IR (KBr) 3185, 2207, 1625, 1609, 1560, 1400, 1290, 1137, 1097, 961, 858 cm^{-1}; HRMS (ESI) calcd for $[C_{12}H_{14}N_2O_3+H]^+$ 235.1076, found 235.1077.

*4.3.11. 5-Methoxy-2-(methoxymethyl)-1-methyl-3-styrylpyridin-4(1H)-one (**3k**).* Brown solid, mp 138–140 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.41 (s, 3H), 3.76 (s, 3H), 3.76(s, 3H), 4.43 (s, 2H), 7.00 (s, 1H), 7.10–7.35 (m, 5H), 7.47 (s, 1H), 7.50 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 147.5, 139.7, 136.8, 133.0, 127.5, 126.5, 126.1, 125.6, 123.0, 121.2, 66.9, 57.2, 55.6, 40.7 ppm; IR (KBr) 3133, 1626, 1544, 1399, 1301, 1147, 1087, 744, 690, cm^{-1}; HRMS (ESI) calcd for $[C_{17}H_{19}NO_3+H]^+$ 286.1439, found 286.1438.

*4.3.12. tert-Butyl 3-(1-ethyl-5-methoxy-2-(methoxymethyl)-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**4a**).* Sepia oil; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, J=6.2 Hz, 3H), 1.51 (s, 9H), 3.45 (s, 3H), 3.80 (s, 3H), 4.07 (q, J=6.2 Hz, 2H), 4.48 (s, 2H), 7.05 (s, 1H), 7.14 (d, J=15.6 Hz, 1H), 7.65 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 167.4, 149.7, 142.9, 135.9, 124.5, 122.3, 121.6, 79.9, 66.1, 58.4, 56.5, 49.5, 28.1, 16.3 ppm; IR (KBr) 2978, 2926, 1699, 1627, 1567, 1310, 1275, 1152, 1095, 768, 760, 744 cm^{-1}; HRMS (ESI) calcd for $[C_{17}H_{25}NO_5+H]^+$ 324.1805, found 324.1806.

*4.3.13. tert-Butyl 3-(5-methoxy-2-(methoxymethyl)-4-oxo-1-propyl-1,4-dihydropyridin-3-yl)acrylate (**4b**).* Yellow solid, mp 114–116 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, J=7.4 Hz, 3H), 1.51 (s, 9H), 1.78–1.91 (m, J=7.6 Hz, 2H), 3.44 (s, 3H), 3.79 (s, 3H), 3.94 (t, J=7.7 Hz, 2H), 4.47 (s, 2H), 7.01 (s, 1H), 7.15 (d, J=15.6 Hz, 1H), 7.65 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 167.4, 149.4, 143.0, 135.9, 124.6, 122.3, 122.1, 79.9, 66.1, 58.4, 56.5, 55.9, 28.2, 24.5, 10.9 ppm; IR (KBr) 2976, 2931, 1699, 1626, 1567, 1368, 1310, 1275, 1260, 1152, 1095, 956, 753, 748 cm^{-1}; HRMS (ESI) calcd for $[C_{18}H_{27}NO_5+H]^+$ 338.1962, found 338.1959.

*4.3.14. tert-Butyl 3-(1-isopropyl-5-methoxy-2-(methoxymethyl)-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**4c**).* Yellow solid, mp 104–106 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, J=6.8 Hz, 6H), 1.51 (s, 9H), 3.44 (s, 3H), 3.84 (s, 3H), 4.53 (s, 2H), 4.72–4.81 (m, J=6.8 Hz, 1H), 7.03 (d, J=15.6 Hz, 1H), 7.14 (s, 1H), 7.68 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 167.4, 149.4, 143.0, 135.9, 124.5, 122.3, 122.1, 79.9, 66.1, 58.4, 56.5, 55.9, 28.2, 24.5, 10.9 ppm; IR (KBr) 2983, 1628, 1574, 1276, 1261, 1150, 768, 760, 756, 741 cm^{-1}; HRMS (ESI) calcd for $[C_{18}H_{27}NO_5+H]^+$ 338.1962, found 338.1968.

*4.3.15. tert-Butyl 3-(1-butyl-5-methoxy-2-(methoxymethyl)-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**4d**).* Yellow solid, mp 94–96 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, J=7.3 Hz, 3H), 1.37–1.44 (m, J=7.3 Hz, 2H), 1.51 (s, 9H), 1.74–1.84 (m, J=7.3 Hz, 2H), 3.44 (s, 3H), 3.80 (s, 3H), 3.96 (t, J=7.8 Hz, 2H), 4.47 (s, 2H), 7.00 (s, 1H), 7.16 (d, J=15.6 Hz, 1H), 7.65 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 167.4, 149.4, 143.0, 135.9, 124.6, 122.4, 122.1, 79.9, 66.2, 58.4, 56.6, 54.3, 33.2, 28.2, 19.8, 13.6 ppm; IR (KBr) 2924, 1632, 1275, 1261, 1151, 768, 760, 744 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{29}NO_5+H]^+$ 352.2118, found 352.2124.

*4.3.16. Methyl 3-(1-butyl-5-methoxy-2-(methoxymethyl)-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**4e**).* Yellow solid, mp 98–100 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, J=7.2 Hz, 3H), 1.36–1.46 (m, J=7.4 Hz, 2H), 1.75–1.82 (m, J=7.5 Hz, 2H), 3.44 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.96 (t, J=7.7 Hz, 2H), 4.48 (s, 2H), 7.00 (s, 1H), 7.25 (d, J=15.6 Hz, 1H), 7.76 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 168.6, 149.6, 143.2, 137.3, 122.2, 121.9, 66.2, 58.5, 56.5, 54.3, 51.4, 33.2, 19.8, 13.6 ppm; IR (KBr) 2954, 2924, 1686, 1628, 1567, 1401, 1266, 1127, 1093, 1053, 764, 750 cm^{-1}; HRMS (ESI) calcd for $[C_{16}H_{23}NO_5+H]^+$ 310.1649, found 310.1650.

*4.3.17. Ethyl 3-(1-butyl-5-methoxy-2-(methoxymethyl)-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**4f**).* Yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J=7.2 Hz, 3H), 1.31 (t, J=7.0 Hz, 3H), 1.38–1.44 (m, J=7.3 Hz, 2H), 1.75–1.85 (m, J=7.3 Hz, 2H), 3.45 (s, 3H), 3.79 (s, 3H), 3.98 (t, J=7.8 Hz, 2H), 4.24 (q, J=7.2 Hz, 2H), 4.47 (s, 2H), 7.02 (s, 1H),

7.21 (d, J=15.6 Hz, 1H), 7.64 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 168.1, 149.4, 143.2, 137.1, 122.4, 122.0, 121.9, 66.1, 60.1, 58.4, 56.4, 54.3, 33.1, 19.7, 14.2, 13.5 ppm; IR (KBr) 2987, 1699, 1627, 1567, 1275, 1260, 1094, 770, 741 cm^{-1}; HRMS (ESI) calcd for $[C_{17}H_{25}NO_5+H]^+$ 324.1805, found 324.1810.

*4.3.18. n-Butyl 3-(1-butyl-5-methoxy-2-(methoxymethyl)-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**4g**).* Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92–1.01 (m, 6H), 1.39–1.43 (m, 4H), 1.62–1.69 (m, J=7.1 Hz, 2H), 1.77–1.82 (m, J=6.8 Hz, 2H), 3.45 (s, 3H), 3.79 (s, 3H), 3.97 (t, J=7.7 Hz, 2H), 4.18 (t, J=6.6 Hz, 2H), 4.47 (s, 2H), 7.00 (s, 1H), 7.25 (d, J=15.6 Hz, 1H), 7.74 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 168.2, 149.5, 143.2, 137.0, 122.5, 122.0, 121.9, 66.1, 64.1, 58.4, 56.5, 54.3, 33.2, 30.7, 19.8, 19.1, 13.6, 13.6 ppm; IR (KBr) 2960, 1704, 1627, 1568, 1275, 1261, 1129, 767, 760, 744 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{29}NO_5+H]^+$ 352.2118, found 352.2123.

*4.3.19. tert-Butyl 3-(1-benzyl-5-methoxy-2-(methoxymethyl)-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**4h**).* Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H), 3.40 (s, 3H), 3.75 (s, 3H), 4.42 (s, 2H), 5.26 (s, 2H), 6.98 (s, 1H), 7.05 (d, J=6.5 Hz, 2H), 7.17 (d, J=15.6 Hz, 1H), 7.28–7.39 (m, 3H), 7.69 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 167.3, 149.5, 143.5, 135.5, 129.3, 129.1, 128.4, 126.4, 125.9, 125.3, 122.9, 80.1, 66.3, 58.5, 57.2, 56.6, 28.2 ppm; IR (KBr) 2980, 1697, 1627, 1570, 1275, 1151, 752, 748, 739 cm^{-1}; HRMS (ESI) calcd for $[C_{22}H_{27}NO_5+H]^+$ 386.1962, found 386.1968.

*4.3.20. tert-Butyl 3-(2-(((tert-butyldimethylsilyl)oxy)methyl)-5-methoxy-1-methyl-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**4i**).* Light yellow solid, mp 186–189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.90 (s, 9H), 1.49 (s, 9H), 3.76 (s, 3H), 3.83 (s, 3H), 4.69 (s, 2H), 6.97 (s, 1H), 7.00 (d, J=15.7 Hz, 1H), 7.61 (d, J=15.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 166.8, 149.0, 145.5, 136.0, 124.8, 123.4, 121.5, 79.9, 58.3, 56.4, 41.9, 28.2, 25.7, 18.1, −5.4 ppm; IR (KBr) 3102, 2957, 2931, 2858, 1709, 1628, 1561, 1293, 1261, 1154, 840, 765, 750 cm^{-1}; HRMS (ESI) calcd for $[C_{21}H_{35}NO_5Si+H]^+$ 410.2357, found 410.2361.

*4.3.21. tert-Butyl 3-(2-((benzyloxy)methyl)-5-methoxy-1-methyl-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**4j**).* Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, 9H), 3.71 (s, 3H), 3.77 (s, 3H), 4.55 (s, 2H), 4.59 (s, 2H), 6.90 (s, 1H), 7.13 (d, J=15.6 Hz, 1H), 7.31–7.35 (m, 5H), 7.65 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 167.2, 149.2, 143.5, 136.6, 136.0, 128.6, 128.3, 128.2, 124.6, 123.4, 122.3, 80.0, 73.1, 64.4, 56.4, 42.1, 28.2 ppm; IR (KBr) 2982, 1699, 1628, 1558, 1276, 1261, 1152, 771, 759, 740, 701 cm^{-1}; HRMS (ESI) calcd for $[C_{22}H_{27}NO_5+H]^+$ 386.1962, found 386.1969.

*4.3.22. tert-Butyl 3-(5-methoxy-1,2-dimethyl-4-oxo-1,4-dihydropyridin-3-yl)acrylate (**4k**).* Light yellow solid, mp 218–220 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H), 2.39 (s, 3H), 3.66 (s, 3H), 3.75 (s, 3H), 6.86 (s, 1H), 7.34 (d, J=15.6 Hz, 1H), 7.53 (d, J=15.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 168.2, 148.6, 146.6, 136.4, 123.1, 122.6, 119.8, 79.9, 56.5, 43.0, 28.2, 16.2 ppm; IR (KBr) 2979, 1686, 1638, 1611, 1558, 1301, 1266, 1133, 962, 759, 863 cm^{-1}; HRMS (ESI) calcd for $[C_{15}H_{21}NO_4+H]^+$ 280.1549, found 280.1551.

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Supplementary data

Supplementary data including detailed results of reaction condition screening and reaction scope investigation, along with ^{1}H NMR and ^{13}C NMR spectra of **3a**–**k**, **4a**–**j**, and NOESY spectrum of **3a**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.11.061.

References and notes

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11. Please see Supplementary data for the detailed results of reaction condition screening.
12. Please see Supplementary data for the preparation of pyridin-4(1*H*)-one substrates.
13. Please see Supplementary data for the copy of the NOESY spectrum of **3a**.
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