Synthesis of 4-Quinolones through Nickel-Catalyzed Intramolecular Amination on the β-Carbon of *o*-(*N*-Alkylamino)propiophenones

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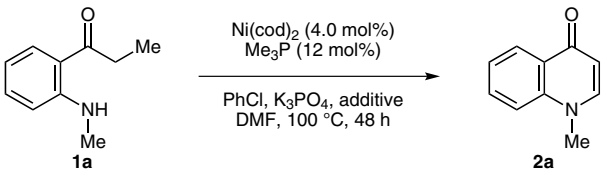
Abstract: *o*-(*N*-Alkylamino)propiophenones are converted into 4-quinolones in the presence of chlorobenzene, potassium phosphate, morpholine, and nickel(0) catalyst. The reaction proceeds through the nickel-catalyzed formation of β-enaminones from *o*-(*N*-alkylamino)propiophenones and morpholine, followed by the intramolecular transamination.

Key words: nickel, cyclization, amination, ketones, oxidation

Synthesis of 4-quinolones is an important issue in organic synthesis because the skeleton is often seen in a variety of pharmaceutically valuable compounds.[1] Conrad–Limpach reaction[2] or Camps cyclization[3] has been classically utilized for the synthesis of the 4-quinolones. Some researchers are interested in the synthesis of 4-quinolones from *o*-haloaryl alkynyl ketones[4a] or isatoic anhydrides[4b] by using transition-metal catalysts. Herein we report a novel access to 4-quinolones from *o*-(*N*-alkylamino)propiophenones, which are easily prepared from *N*-alkylanilines.[5,6] The present reaction involves the catalytic carbon–nitrogen bond formation of ethyl ketones on the β-carbon.[7]

Recently, we reported that ethyl ketones are converted into β-enaminones by using a nickel catalyst, chlorobenzene, and potassium phosphate.[7,8] In the reaction, the ethyl ketone undergoes catalytic dehydrogenation to give α,β-unsaturated ketone. The generated enone undergoes the 1,4-addition of an amine and subsequent reoxidation of the resulting β-aminoketone to produce the β-enaminone. We thought that the reaction of aryl ethyl ketones having an amino group at the *ortho* position might afford pharmaceutically valuable 4-quinolones through tandem dehydrogenation–1,4-addition–reoxidation sequence. A mixture of *o*-(*N*-methylamino)propiophenone (**1a**), chlorobenzene, and potassium phosphate in DMF was heated at 100 °C for 48 hours in the presence of a catalytic amount of $Ni(cod)_2$ and trimethylphosphine (Table 1, entry 1). Although **1a** completely disappeared, no 4-quinolone **2a** was detected by ^1H NMR analysis. In the reaction, the oligomerization of α,β-unsaturated ketone intermediate was observed. The nucleophilicity of the internal *N*-arylamino group might not be enough for the intramolecular 1,4-addition leading to the formation of the desired 4-quinolone. The amino group of 3-amino-1-[*o*-(*N*-methylamino)phenyl]prop-2-en-1-one **3** is known to be exchanged with internal *N*-arylamino group (Scheme 1).[9] Therefore, we thought that the reaction of **1a** with a secondary amine would afford the 4-quinolone **2a** under the same conditions as shown in Scheme 1. Namely, the present reaction was hypothesized to proceed via dehydrogenative coupling of **1a** and a secondary amine followed by the intramolecular transamination of β-enaminone **3**.

Table 1 Effect of Amine in the Intramolecular Nickel-Catalyzed Cyclization of *o*-(*N*-methylamino)propiophenone (**1a**)[a]



Entry	Additive	Yield (%)[b]
1	–	0
2	morpholine	82
3	piperidine	74
4	pyrrolidine	<5
5	dibutylamine	36
6	diisopropylamine	21
7[c]	morpholine	87

[a] Reactions were conducted on a 0.5 mmol scale in 0.2 mL of DMF. The ratio of **1a**/$Ni(cod)_2$/Me_3P/PhCl/K_3PO_4/additive was 25:1:3:100:100:50.
[b] The isolated yield of **2a**.
[c] The reaction was conducted by using 10 mol% of morpholine.

Hence, the cyclization of **1a** was conducted in the presence of a secondary amine (Table 1, entries 2–6). Morpholine was the most effective for the production of **2a**, which was obtained in 82% yield (Table 1, entry 2).[10] Use of piperidine in place of morpholine decreased the yield of **2a** (Table 1, entry 3). In contrast to six-membered ring amines, pyrrolidine failed to produce **2a** (Table 1, entry 4). Acyclic amines were not suitable for the present reaction (Table 1, entries 5 and 6). The reaction proceeded efficiently even when the amount of morpholine was decreased from 200 mol% to 10 mol% (Table 1, entry 7).

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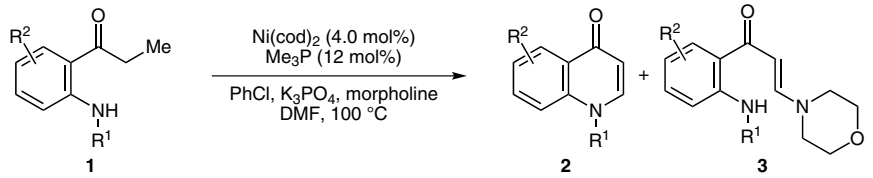
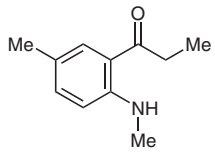
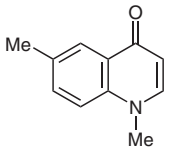
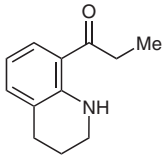
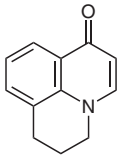
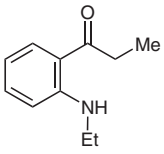
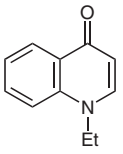
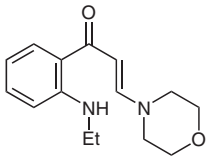
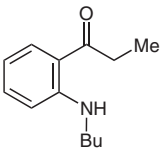
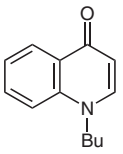
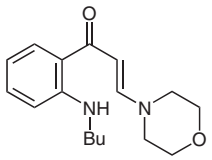
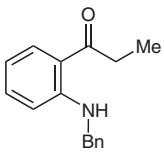
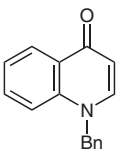
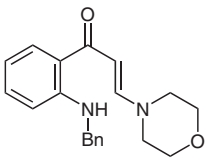
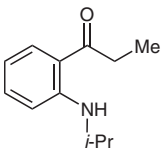
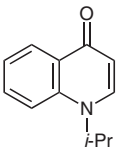
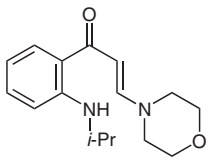
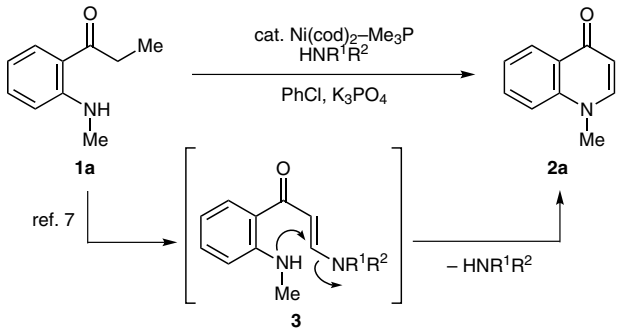
Table 2 Effect of the Substituent on a Nitrogen Atom of **1**[a]



1 **2** **3**

Entry	*o*-(*N*-Alkylamino)propiophenone **1**	Time (h)	4-Quinolone **2**	Yield of **2** (%)[b]	β-Enaminone **3**	Yield of **3** (%)[c]
1	 **1b**	48	 **2b**	93	–	–
2	 **1c**	48	 **2c**	81	–	–
3	 **1d**	48	 **2d**	not detected	 **3d**	trace
4[d]		48		73		9
5[d]	 **1e**	48	 **2e**	71	 **3e**	9
6[d]	 **1f**	48	 **2f**	70	 **3f**	trace
7[d]	 **1g**	120	 **2g**	10	 **3g**	75
8[d,e]		48		72		trace

[a] Reactions were conducted on a 0.5 mmol scale in 0.2 mL of DMF. The ratio of **1** (0.5 mmol)/$Ni(cod)_2$/Me_3P /PhCl /K_3PO_4/morpholine was 100:4:12:400:400:10 unless otherwise noted.
[b] The isolated yield of 4-quinolone **2**.
[c] The isolated yield of β-enaminone **3**.
[d] The reaction was conducted by using 2 equiv of morpholine.
[e] To the crude reaction mixture was added EtOH (1.0 mL) and a drop of AcOH, and then the resulting solution was refluxed for 4 d.



Scheme 1 A new synthetic route from **1a** to 4-quinolone **2a** via the formation of β-enaminone **3**

The reaction conditions were applied to the cyclization of various *o*-(*N*-alkylamino)propiophenones (Table 2). The reaction of **1b** with 10 mol% of morpholine proceeded to give 4-quinolone **2b** in high yield (Table 2, entry 1). Tetrahydroquinoline **1c** was smoothly cyclized to give tricyclic 4-quinolone **2c** in 81% yield (entry 2). However, the reaction of *o*-(*N*-ethylamino)propiophenone (**1d**) failed to afford **2d** (Table 2, entry 3), but **2d** was successfully formed by using two equivalents of morpholine (Table 2, entry 4). In the reaction, β-enaminone **3d**, which is considered as an intermediate for the formation of **2d**, was recovered in 9% yield. The method using two equivalents of morpholine was applicable to the reaction of *N*-butylated substrate **1e** (Table 2, entry 5). The *N*-benzyl-protected 4-quinolone **2f** was obtained in 70% yield (Table 2, entry 6). In contrast, the reaction of **1g**, possessing the bulkier isopropyl group on the nitrogen atom, gave undesirable β-enaminone **3g** as the major product (Table 2, entry 7). The compound **3g** scarcely underwent transamination even when the reaction was conducted for 120 hours. The corresponding 4-quinolone **2g** was obtained from **3g** by treatment of the crude mixture with acetic acid (Table 2, entry 8).[9] No cyclization of *o*-(*N*-methylamino)butyrophenone occurred because 1,4-addition of morpholine was hindered by the steric repulsion of the methyl group on the β-carbon of the generated internal α,β-unsaturated ketones.

In conclusion, we successfully developed the nickel-catalyzed intramolecular amination of *o*-(*N*-alkylamino)propiophenones on the β-carbon. The reaction offers a new synthetic route to pharmaceutically valuable 4-quinolones. The cyclization occurred through tandem catalytic formation of β-enaminone from *o*-(*N*-alkylamino)propiophenone and an external secondary amine–intramolecular transamination sequence.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) **Typical Procedure for the Transformation of 1a into 2a**
In a nitrogen-filled drybox, a 4 mL screw-capped vial was charged with $Ni(cod)_2$ (5.6 mg, 0.020 mmol), K_3PO_4 (424.5 mg, 2.0 mmol), and DMF (0.2 mL). After a magnetic stir bar was added, the vial was fitted with a septum cap and removed from the drybox. A solution of trimethylphosphine in THF (60 μL, 1 M solution, 0.060 mmol), chlorobenzene (0.20 mL, ρ = 1.106 g/mL, 1.97 mmol), *o*-(*N*-methylamino)-propiophenone (**1a**, 81.3 mg, 0.50 mmol), and morpholine (4.5 μL, ρ = 0.996, 0.05 mmol) were added. The resulting mixture was heated at 100 °C for 48 h. The reaction mixture was filtered through a Celite pad to remove the insoluble inorganic salt. The filtrate was concentrated and purified by silica gel column chromatography (EtOAc–MeOH = 5:1) to give 4-quinolone **2a** (69.1 mg, 87%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.81 (s, 3 H), 6.28 (d, *J* = 7.7 Hz, 1 H), 7.37–7.48 (m, 2 H), 7.51 (d, *J* = 7.7 Hz, 1 H), 7.69 (ddd, *J* = 8.7, 7.1, 1.6 Hz, 1 H), 8.48 (dd, *J* = 8.2, 1.6 Hz, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 40.6, 109.9, 115.3, 123.7, 126.7, 126.9, 132.1, 140.5, 143.7, 178.2.

