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A Cu(I)-Catalyzed C-H α -Amination of Aryl Ketones. Direct Synthesis of Imidazolinones

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Abstract

This paper describes an α -amination process of aryl ketones using CuCl as catalyst and di-*tert*-butyldiaziridinone as the nitrogen source. A variety of imidazolinone derivatives are prepared in moderate yields under mild conditions. A possible catalytic cycle is proposed for this reaction.

Amines and their derivatives are very important functional moieties contained in many natural products, pharmaceutical agents, and chemical materials. A variety of efficient methods have been developed to introduce nitrogens.¹ The formation of C-N bonds by direct C-H amination is highly attractive, and great progress has been achieved in this area.^{2,3} In our studies on amination with diaziridinones, recently we have found that esters (**1**) can be directly aminated at the α position to form hydantoins (**3**) with di-*tert*-butyldiaziridinone (**2**)^{4–7} and CuCl (Scheme 1).⁸ In further investigation on C-H amination with di-*tert*-butyldiaziridinone (**2**), we have found that aryl ketone **4** can also be aminated at the α position to form imidazolinone **5** directly using CuCl as catalyst (Scheme 1). Imidazolinones are important moieties that are present in various biologically active compounds,⁹ such as MurB inhibitor^{9b} and CGRP receptor antagonist^{9d} (Figure 1). In general, imidazolinones can be prepared by cyclization of α -amino derivatives of ketones, aldehydes, and related compounds,^{9,10} or by derivatization of imidazolinones.¹¹ The current direct α -amination of ketones provides a valuable alternative method for the synthesis of imidazolinones. Herein we wish to report our studies on this subject.

When acetophenone **4a** was initially treated with di-*tert*-butyldiaziridinone (**2**) and 5 mol% of CuCl-P(*n*-Bu)₃ (1:1) in CDCl₃ at 65 °C in an NMR tube for 12 h, imidazolinone **5a** was formed in 39% yield. The yield can be improved to 46% using 5 mol% of CuCl-P(*n*-Bu)₃ (1:2) in dry 1,2-dichloroethane and by slow addition of di-*tert*-butyldiaziridinone over 8 h (Table 1, entry 1). As shown in Table 1, various substituted acetophenones were successfully α -aminated to give the corresponding imidazolinone derivatives in moderate yields (Table 1, entries 2–7) (the X-ray structure of **5b** is shown in Supporting Information). The substituent on the aryl ring appears to have little influence on the reaction. Methyl 2-naphthyl ketone and methyl 2-thienyl ketone were also effective substrates that yielded the corresponding α -amination products with moderate yields (Table 1, entries 8 and 9). Butyrophenone was also α -aminated to afford the

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Supporting Information Available: The spectroscopic and analytic data of compounds **5b–g**, **i**, **j**, the X-ray data of compounds **5b** and **6** along with the ¹H and ¹³C NMR spectra of imidazolinone products **5** and **6** (46 pages). This material is available free of charge via the internet at <http://pubs.acs.org>.

imidazolinone albeit in low yield (Table 1, entry 10). In all these cases, the relatively low yields obtained are largely due to relatively low conversions of ketone substrates. When the reaction was carried out at a larger scale (4.0 mmol), slightly lower yields were obtained (Table 1, entries 1 and 8). The aryl group of the ketone substrate appears to be important, and α,β -unsaturated ketones such as (*E*)-4-phenylbut-3-en-2-one and dialkyl ketones such as octan-2-one are not effective substrates under the current reaction conditions. The deprotection of the resulting imidazolinone product was also investigated with compound **5a**. Treating **5a** with CF₃CO₂H at 65 °C for 5 h led to a selective removal of one *tert*-butyl group to give compound **6** in 97% yield (Scheme 2).^{4a,d,8} The structure of **6** was confirmed by the X-ray analysis (see Supporting Information). However, removal of two *tert*-butyl groups under more forcing conditions led to a mixture of unidentified products. More effective deprotection procedures need to be further developed.

While an exact reaction mechanism awaits further study, a plausible catalytic cycle similar to the formation of hydantoin is proposed in Scheme 3.⁸ The N-N bond of di-*tert*-butyldiaziridinone (**2**) is probably reduced initially by CuCl to form species **7**^{4c,12–15} or **7a**, which then abstracts a hydrogen or proton from ketone **4** to form **8**. Species **8** undergoes a reductive elimination to give compound **9** and regenerate CuCl catalyst.^{16,17} Imidazolinone **5** is formed by cyclization of compound **9** and loss of water under the reaction conditions.

In summary, a variety of aryl ketones can be successfully α -aminated to directly form imidazolinones in moderate yields using CuCl as catalyst and di-*tert*-butyldiaziridinone (**2**) as nitrogen source under mild reaction conditions. The current α -amination process can be potentially useful for the synthesis of biologically active imidazolinone derivatives.

Experimental Section

Representative α -amination procedure on 0.4 mmol scale (Table 1, entry 1)

To a 1.5 mL vial equipped with a stir bar was added CuCl (0.002 g, 0.02 mmol). The sealed vial was evacuated and filled with Ar three times, followed by addition of 1,2-dichloroethane (0.10 mL) and tri-*n*-butylphosphine (0.01 mL, 0.04 mmol). After the mixture was stirred at room temperature for 10 min, acetophenone (**4a**) (0.048 g, 0.40 mmol) was added. The reaction mixture was warmed to 65 °C using an oil bath with stirring, and di-*tert*-butyldiaziridinone (**2**) (0.136 g, 0.80 mmol) was added by syringe pump over 8 h. The reaction mixture was stirred at this temperature for an additional 4 h and purified by flash chromatography (silica gel, petroleum ether:ethyl ether = 5:1) to give imidazolinone **5a** as a white solid (0.050 g, 46%). mp. 128–129 °C; IR (film) 1669 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.31 (s, 5H), 6.05 (s, 1H), 1.54 (s, 9H), 1.42 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 153.7, 134.9, 130.5, 127.88, 127.85, 122.8, 108.2, 58.3, 54.7, 30.4, 28.3; HRMS Calcd for C₁₇H₂₄N₂O (M⁺): 272.1889. Found: 272.1890.

Representative α -amination procedure on 4.0 mmol scale (Table 1, entry 8)

To a 10 mL round-bottomed flask equipped with a stir bar was added CuCl (0.020 g, 0.20 mmol) and methyl 2-naphthyl ketone (**4h**) (0.68 g, 4.0 mmol). The sealed flask was evacuated and filled with Ar three times, followed by addition of 1,2-dichloroethane (1.0 mL) and tri-*n*-butylphosphine (0.10 mL, 0.40 mmol). After stirring at room temperature for 10 min, the reaction mixture was warmed to 65 °C using an oil bath, and then di-*tert*-butyldiaziridinone (**2**) (1.36 g, 8.0 mmol) was added by syringe pump over 8 h. The reaction mixture was stirred at this temperature for an additional 4 h and purified by flash chromatography (silica gel, petroleum ether:ethyl ether = 5:1) to give unreacted methyl 2-naphthyl ketone (**4h**) (0.22 g) and imidazolinone **5h** (0.455 g, 49%) as a white solid. mp. 117–118 °C; IR (film) 1677 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.86–7.76 (m, 4H), 7.52–7.42 (m, 3H), 6.13 (s, 1H), 1.57

(s, 9H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.9, 133.1, 132.8, 132.4, 129.0, 128.3, 128.0, 127.8, 127.1, 126.6, 126.4, 122.9, 108.8, 58.5, 54.8, 30.4, 28.3; HRMS Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}$ (M^+): 322.2045. Found: 322.2044.

Deprotection of 5a (Scheme 2)

A mixture of **5a** (0.30 g, 1.1 mmol) and $\text{CF}_3\text{CO}_2\text{H}$ (3.0 mL) was stirred at 65 °C under argon atmosphere for 5 h, concentrated, and purified by flash chromatography (silica gel, diethyl ether) to give compound **6** as a white solid (0.23 g, 97%). mp. 170–171 °C; IR (film) 3151, 1676 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 11.90 (s, 1H), 7.54 (d, J = 7.8 Hz, 2H), 7.35 (dd, J = 7.8, 7.2 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 6.65 (d, J = 2.7 Hz, 1H), 1.64 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.0, 129.9, 128.9, 126.6, 123.2, 121.7, 105.0, 55.0, 28.5; HRMS Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$ (M^+): 216.1263. Found: 216.1265.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Biologically active compounds containing imidazolinones.

Scheme 1.
 α -Amination of ester and ketone.

Scheme 2.
Selective deprotection of imidazolinone 5a

Scheme 3.
A proposed catalytic cycle for the α -amination.

Table 1

Cu(I)-Catalyzed α -Amination of Ketones^a

Entry	Substrate (4)
1	4a
2	4b
3	4c

Entry	Substrate (4)
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4
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5
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Entry

Substrate (4)

6

4f

7

4g

Entry	Substrate (4)
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8	
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9	
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Entry	Substrate (4)
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10	
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4j

^a All reactions were carried out with ketone (0.4 mmol), 1,2-di-*tert*butyldiaziridinone (**2**) (0.80 mmol) (added slowly over 8 h with syringe pump), CuCl-P(*n*-Bu)₃ (1:2) (0.02 mmol) in DCE (0.1 mL) at 65 °C under argon for 12 h unless otherwise stated. For entries 6 and 9, 60 °C was used.

^b Isolated yield based on ketone.

^c The reaction was carried out with 4 mmol of the ketone.