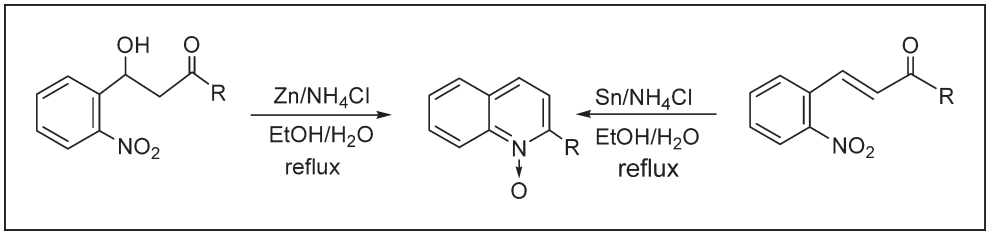
Chemoselective Synthesis of Quinoline *N*-Oxides from 3-(2-Nitrophenyl)-3-hydroxypropanones

Kentaro Okuma,* Jun-ichi Seto, Noriyoshi Nagahora, and Kosei Shioji

Department of Chemistry, Faculty of Science, Fukuoka University, Jonan-ku, Fukuoka 814-0180, Japan
*E-mail: kokuma@fukuoka-u.ac.jp

Received January 20, 2010
DOI 10.1002/jhet.485
Published online 25 August 2010 in Wiley Online Library (wileyonlinelibrary.com).



The reaction of 3-(2-nitrophenyl)-3-hydroxypropanones with Zn/NH_4Cl gave the corresponding quinoline *N*-oxides in 80–90% yields. The reaction initiated the reduction of nitro group to afford the corresponding hydroxylamine, which intramolecularly condensed and followed by dehydration to give quinoline *N*-oxide. Although treatment of 2-nitrochalcone with Zn/NH_4Cl in $EtOH/H_2O$ resulted in the formation of quinoline *N*-oxide in low yield, the reaction of 2-nitrochalcone with Sn/NH_4Cl in refluxing $EtOH/H_2O$ afforded quinoline *N*-oxide in 80% yield.

J. Heterocyclic Chem., **47**, 1372 (2010).

INTRODUCTION

Quinoline ring framework can be found in many synthetic and natural compounds of biological importance. Especially, quinoline *N*-oxides (**1**) are important compounds because of their biological activity [1]. The quinoline *N*-oxide core unit has been found in drugs exerting microsomal Na, K-ATPase [2], antiviral [3], or antimalarian activities [4]. The synthetic method of quinoline *N*-oxide mainly devoted to the oxidation of the corresponding quinolines, which were synthesized from 2-aminochalcones or 2-nitrochalcones and Sn/HCl or with Pd/C hydrogenation and cyclization [5]. We have also reported the synthesis of quinolines by the reaction of 2-aminochalcones with NIS or I_2 [6]. Direct palladium-catalyzed arylation of quinoline *N*-oxides to 2-arylquinoline *N*-oxides was recently reported [7]. Although Baylis-Hilman adducts reacted with trifluoroacetic acid to give 3,4-substituted quinoline *N*-oxides in 49–82% yields [8], there are few reports on the direct synthesis of quinoline *N*-oxides from chalcones or 3-hydroxy ketones, which afforded mixtures of quinolines and quinoline *N*-oxides [9]. These results prompted us to investigate the direct synthesis of quinoline *N*-oxides from 3-hydroxy ketones (**2**) or 2-nitrochalcones. Herein, we would like to report a direct synthesis of quinoline *N*-oxides from easily available 3-hydroxy ketones **2** and 2-nitrochalcones.

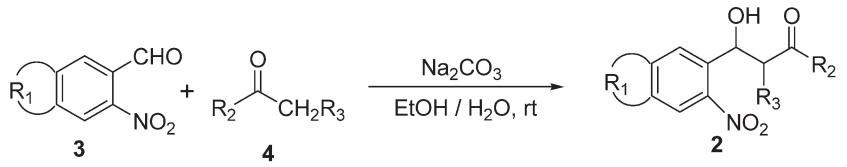
RESULTS AND DISCUSSION

3-Hydroxy ketones **2** were synthesized by the reaction of 2-nitrobenzaldehydes (**3**) and acetophenones (**4**) in the presence of sodium carbonate by the method recently described by Wang et al. [10] (Scheme 1).

We first tried the metal mediated reductive cyclization of 3-hydroxy-3-(2-nitrophenyl)-1-phenylpropan-1-one **2a** whether 2-phenylquinoline *N*-oxide **1a** or 2-phenylquinoline **5a** would be formed. The results were shown in Table 1. Treatment of **2a** with Sn/HCl resulted in the formation of *N*-oxide **1a** and **5a** in 26 and 60% yields, respectively (entry 1). When Zn/HCl was allowed to react with ketone **2a**, *N*-oxide **1a** was obtained in 46% yield (entry 2). When Sn/NH_4Cl was treated with **2a** at 60°C for 12 h, *N*-oxide **1a** and quinoline **5a** were obtained in 7 and 6% yields, respectively (entry 4). Finally, when Zn/NH_4Cl was used as reducing reagents at 60°C, *N*-oxide **1a** was exclusively obtained in 85% yield (entry 6).

As the optimum conditions (4 equiv Zn/ 3 equiv of NH_4Cl, $EtOH/H_2O$, 60°C) were determined, we then tried other 3-hydroxy ketones **2** to investigate the scope and limitation of this method. Treatment of 3-hydroxy-3-(2-nitrophenyl)-1-*p*-tolylpropan-1-one (**2b**) with Zn/NH_4Cl in $EtOH/H_2O$ resulted in the formation of 2-(*p*-tolyl)quinoline *N*-oxide (**1b**) in 90% yield (entry 2). When methyl, methoxy, or chloro groups were substituted on aromatic ring (ketones **2c**–**e**), the corresponding

Scheme 1



3a: R_1 =H, H
3b: R_1 =OCH_2O

4a: R_2 = Ph, R_3 = H
4b: R_2 = 4-MeC_6H_4, R_3 = H
4c: R_2 = 3-MeC_6H_4, R_3 = H
4d: R_2 = 2-MeC_6H_4, R_3 = H
4e: R_2 = 4-$MeOC_6H_4$, R_3 = H
4f: R_2 = 4-ClC_6H_4, R_3 = H
4g: R_2 =2-naphthyl, R_3 = H
4h: R_2 = 2-OH, 5-Br C_6H_3, R_3 = H
4i: R_2 = Ph, R_3 =Br
4j: R_2 = Me, R_3 = H

2a: R_1 = H, R_2 = Ph, R_3 = H 72%
2b: R_1 = H, R_2 = 4-MeC_6H_4, R_3 = H 72%
2c: R_1 = H, R_2 = 3-MeC_6H_4, R_3 = H 57%
2d: R_1 = H, R_2 = 2-MeC_6H_4, R_3 = H 68%
2e: R_1 = H, R_2 = 4-$MeOC_6H_4$, R_3 = H 66%
2f: R_1 = H, R_2 = 4-ClC_6H_4, R_3 = H 74%
2g: R_1 = H, R_2 = naphthyl, R_3 = H 61%
2h: R_1 = H, R_2 = 2-OH, 5-BrC_6H_2, R_3 = H 74%
2i: R_1 = H, R_2 = Ph, R_3 = Br 52%
2j: R_1 = H, R_2 =Me, R_3 =H 66%
2k: R_1 =OCH_2O, R_2 = 4-Ph, R_3 = H 50%

N-oxides **1c–e** were obtained in high yields (entries 2–6). Naphthyl substituted ketone **2g** also afforded 2-naphtylquinoline *N*-oxide **1g** (entry 7). Interestingly, 4-hydroxy-4-(2-nitrophenyl)butan-2-one **2j** also reduced and cyclized to afford 2-methylquinoline *N*-oxide (**1j**) in 86% yield (entry 10). Other quinolines were obtained in high yields (Table 2). Thus, general synthesis of *N*-oxides **1** from easily available 3-hydroxy ketones **2** under mild conditions was achieved.

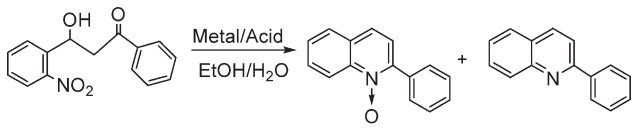
The reaction might proceed as follows: 3-hydroxy ketone **2a** was reduced by Zn/NH_4Cl to give hydroxylamine **6a** which was easily cyclized under these conditions and dehydrated to give quinoline *N*-oxide **1a** (Scheme 2).

The present method has some advantage over direct Pd-catalyzed arylation of quinoline *N*-oxides [7], which requires $Pd(OAc)_2$ as a catalyst and refluxing toluene for 16 h in 55–91% yields. Additionally, 3 equiv of starting quinoline *N*-oxides were required. The present method requires shorter reaction time (5–6 h) and relatively lower temperature (60°C).

We then tried the reductive cyclization of 2-nitrochalcone (**7a**) whether *N*-oxide **1a** would be exclusively formed. Previously, Barros et al. [9] have reported the reductive cyclization of 2-nitrochalcones with $SnCl_2$/HCl, which led to the mixtures of 2-substituted quinoline *N*-oxides **1** and quinolines **5** in moderate yields. To the best of our knowledge, only one report on the practical synthesis of *N*-oxide **1** from chalcone **7** was appeared, whereas yields were low [11]. Thus, the method of exclusive formation of *N*-oxides **1** from **7** must be required. When chalcone **7a** was treated with Sn/HCl at RT for 1 h, quinoline **5a** was isolated in 80% yield (Table 3, entry 1). Treatment of chalcone **7a**, Pd/C (0.1 equiv), and H_2 gas in ethanol (5 h), followed by refluxing for 13 h resulted in the formation of quinoline

Table 1

Reaction of **2a** with metal and acid.



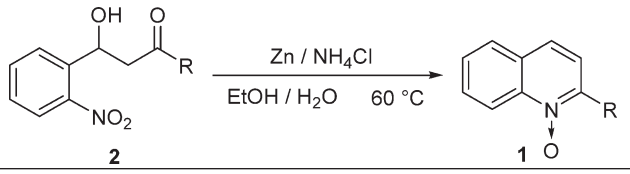
2a **1a** **5a**

Entry	Metal (eq)	Acid (eq)	Temperature (°C)	Time (h)	**1a** Yield (%)	**5a** Yield (%)
1	Sn (3)	HCl (4)	60	1	26	60
2	Zn (3)	HCl (4)	RT	18	46	0[a]
3	Fe (3)	HCl (4)	RT	12	61	14
4	Sn (3)	NH_4Cl (3)	60	12	7	6[b]
5	Sn (3)	NH_4Cl (3)	Reflux	2	40	20[c]
6	Zn (4)	NH_4Cl (3)	60	5	85	0
7	Fe (5)	NH_4Cl (3)	Reflux	24	0	0[d]

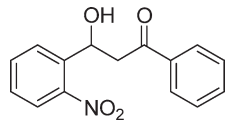
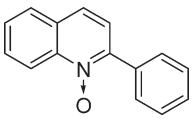
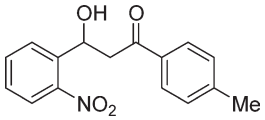
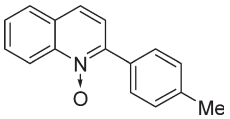
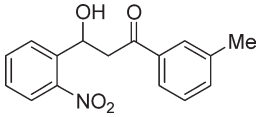
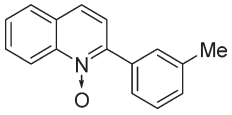
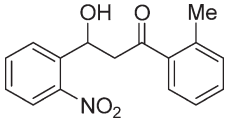
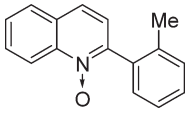
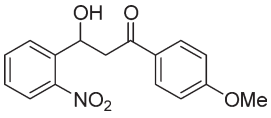
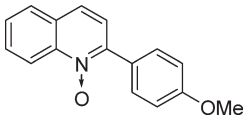
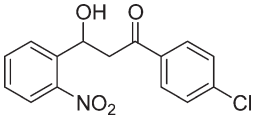
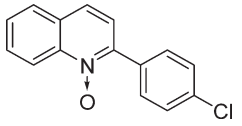
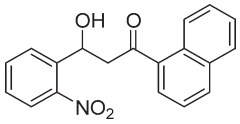
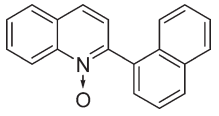
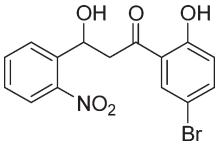
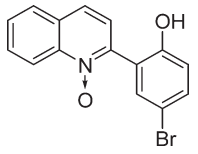
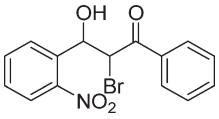
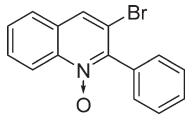
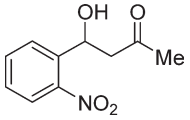
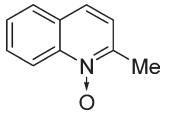
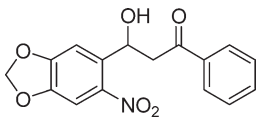
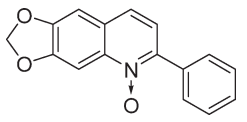
[a] Starting **2a** was recovered in 36% yield.
[b] Starting **2a** was recovered in 69% yield.
[c] Starting **2a** was recovered in 25% yield.
[d] Starting **2a** was recovered in 90% yield.

Table 2

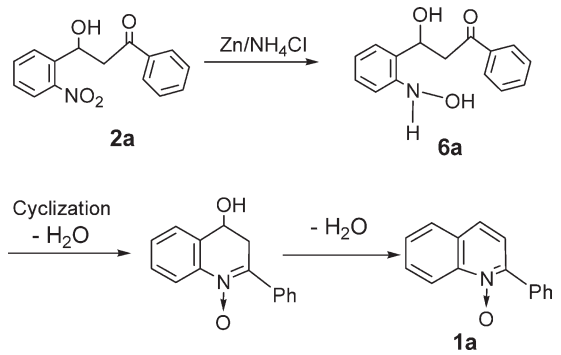
Reductive cyclization of 2-hydroxy ketones **2**.



2 **1**

Entry	Substrate		Time (h)	Product		Yield (%)
1		**2a**	5		**1a**	85
2		**2b**	6		**1b**	90
3		**2c**	6		**1c**	88
4		**2d**	6		**1d**	90
5		**2e**	6		**1e**	89
6		**2f**	5		**1f**	82
7		**2g**	5		**1g**	80
8		**2h**	5		**1h**	89
9		**2i**	4		**1i**	89
10		**2j**	5		**1j**	86
11		**2k**	5		**1k**	85

Scheme 2. Reaction mechanism.



5a in 78% yield (entry 4). In both case, no quinoline *N*-oxide **1a** was obtained. When Zn/NH_4Cl was treated with **7a** at 60°C, *N*-oxide **1a** was obtained in 21% yield along with 15% of starting chalcone **7a** (entry 5). When the reaction was carried in refluxing ethanol for 24 h by using Sn/NH_4Cl as a reducing reagent, *N*-oxide **1a** and quinoline **5a** were obtained in 80% and 4% yields, respectively (entry 8). Prolonged heating resulted in the further reduction of **1a**–**5a** (entries 9–10). Other substituted nitrochalcones **7b–d** also afforded quinoline *N*-oxides **1** in good yields, however, small amount of starting chalcones **7b–d** were still remained unreacted (entries 11–13).

By using metal/HCl as reducing reagents, 2-nitrochalchone **7a** was reduced to give hydroxylamine **8a**. Since carbonyl moiety at trans position of hydroxylamine **8a** prevent intramolecular cyclization, part of which further reduced to give aniline **9a**, then cyclized to afford quinoline **5a** (entries 1–4). On the other hand, by using Sn/NH_4Cl, which have lower reducing ability than Sn/HCl, as reducing reagents, target quinoline *N*-oxides **1a** were obtained in acceptable yields, while careful tuning of the reaction time must be required (Scheme 3). Compared to the reductive cyclization of 3-hydroxy ketones **2** (Table 2), the reduction of 2-nitrochalcones required prolonged reaction time.

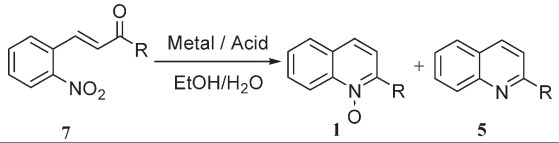
In summary, we have synthesized 2-substituted quinoline *N*-oxides by one-pot process from 3-hydroxylpropanones or 2-nitrochalcones. This procedure provides a general synthesis of quinoline *N*-oxides from easily available 3-hydroxypropanones or 2-nitrochalcones.

EXPERIMENTAL

General. All chemicals were obtained from commercial suppliers and were used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and flash column chromatography was performed with silica (Merck, 70-230 mesh). NMR spectra (^1H at 400 MHz; ^{13}C at 100 MHz) were recorded in $CDCl_3$, and chemical shifts are expressed in ppm relative to internal TMS ($\delta = 0.00$) and $CDCl_3$ ($\delta = 77.00$) for ^1H- and ^{13}C-NMR. Melting points were uncorrected.

Table 3

Hydroamination of 2-nitrochalcones with metal.

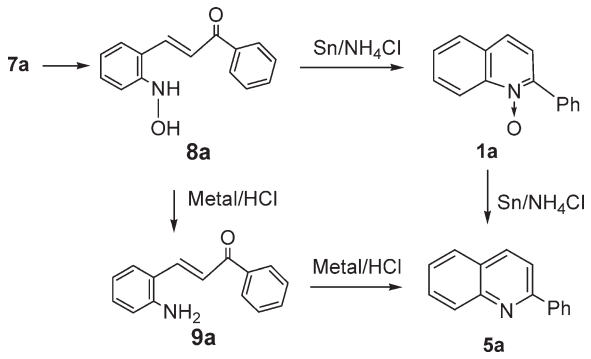


7 1 5

Entry	R	Metal (equiv)	Acid	Temperature (°C)	Time (h)	Yield (%) 1	Yield (%) 5
1	Ph	Sn (3)	HCl	Rt	1	0	80
2	Ph	Zn (3)	HCl	Rt	4	0	42
3	Ph	Fe (3)	HCl	Rt	24	0	0
4	Ph	Pd/C (0.1)	–	reflux	18	0	78
5	Ph	Zn (3)	NH_4Cl	60	4	21	3
6	Ph	Sn (3)	NH_4Cl	60	28	20	0
7	Ph	Sn (3)	NH_4Cl	reflux	20	75[a]	0
8	Ph	Sn (3)	NH_4Cl	reflux	26	80	4
9	Ph	Sn (3)	NH_4Cl	reflux	33	78	12
10	Ph	Sn (3)	NH_4Cl	reflux	72	0	87
11	4-MeC_6H_4	Sn (3)	NH_4Cl	reflux	24	82[b]	0
12	4-ClC_6H_4	Sn (3)	NH_4Cl	reflux	22	80[c]	0
13	1-naphtyl	Sn (3)	NH_4Cl	reflux	24	82[d]	0

[a] Starting chalcone **7a** was recovered in 5% yield.
[b] 1-(4-Methylphenyl)-3-(2-nitrophenyl)-2-en-1-one **7b** was recovered in 4% yield.
[c] 1-(4-Chlorophenyl)-3-(2-ntrophenyl)-2-en-1-one **7c** was recovered in 3% yield.
[d] 1-Naphtyl-3-(2-nitrophenyl)prop-2-en-1-one **7d** was recovered in 4% yield.

Scheme 3



Materials. Benzaldehydes **3a–3b** and ketones **4a–4j** were purchased from TCI and Aldrich. Zn powder (<50 nm) was purchased from Aldrich. Sn powder (200 mesh) was purchased from Wako.

Preparation of 3-hydroxy-3-(2-nitrophenyl)-1-phenylpropan-1-one (2a). To a solution of acetophenone (1.20 g, 10.0 mmol) and sodium carbonate (0.55 g, 5.2 mmol) in water (60 mL) was added a solution of 2-nitrobenzaldehyde (1.51 g, 10.0 mmol) in ethanol (15 mL) in dropwise. After stirring for 17 h at RT, the reaction mixture was extracted with dichloromethane (10 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give brown solid, which was chromatographed over silica gel by elution with hexane-ethyl acetate (5:1) to afford green crystals of **2a** (1.95 g, 7.2 mmol). mp 106–107°C (ref. [11] mp 106–107°C). ^{1}H-NMR ($CDCl_3$) δ = 8.00–7.96 (m, 4H), 7.71 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.60 (t, *J* = 7.4, 1.2 Hz, 1H), 7.45–7.50 (m 3H), 5.86 (dd, *J* = 9.3, 2.4 Hz, 1H), 4.01 (d, *J* = 3.1 Hz, 1H), 3.73 (dd, *J* = 17.7, 2.4 Hz, 1H), 3.22 (dd, *J* = 17.7, 9.3 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ = 200.2, 147.5, 138.8, 138.6, 136.6, 134.1, 134.0, 129.0(2C), 128.7, 128.5(2C), 128.4, 124.7, 66.2, 46.7.

Other reactions were carried out in a similar manner.

3-Hydroxy-1-(4-methylphenyl)-3-(2-nitrophenyl)propan-1-one (2b). Yield: 72%. Deep green crystals. mp 70–71°C. ^{1}H-NMR ($CDCl_3$) δ = 7.97–8.00 (m, 2H), 7.86 (d, *J* = 7.9 Hz, 2H), 7.69 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.46 (dd, *J* = 7.8, 7.6 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 2H), 5.84 (dd, *J* = 9.4, 2.4 Hz, 1H), 4.06 (br, 1H), 3.71 (dd, *J* = 17.6, 2.4 Hz, 1H), 3.17 (dd, *J* = 17.6, 9.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ = 199.9, 147.5, 145.1, 138.9, 134.1, 134.0, 129.7, 128.7(2C), 128.6(2C), 128.5, 124.7, 66.2, 46.5, 22.0. Calcd for $C_{16}H_{15}NO_4$; C, 67.36; H, 5.30; N, 4.91. Anal Found; C, 67.38; H, 5.36; N, 4.92.

3-Hydroxy-1-(3-methylphenyl)-3-(2-nitrophenyl)propan-1-one (2c). Yield: 57%. Deep green oil. ^{1}H-NMR ($CDCl_3$) δ = 8.00–7.98 (m, 2H), 7.78–7.75 (m, 2H), 7.70 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.47 (ddd, *J* = 7.8, 7.6, 1.4 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.36 (dd, *J* = 7.6, 7.5 Hz, 1H), 5.86 (dd, *J* = 9.3, 2.2 Hz, 1H), 4.04 (br, 1H), 3.73 (dd, *J* = 17.6, 2.2 Hz, 1H), 3.20 (dd, *J* = 17.6, 9.3 Hz, 1H), 2.41(s, 3H). ^{13}C-NMR ($CDCl_3$) δ = 191.0, 148.8, 143.0, 138.8, 137.7, 134.2, 133.9, 131.6, 130.6, 129.6, 129.5, 128.8, 127.8, 126.2, 25.2, 21.6. Calcd for $C_{16}H_{15}NO_4$(-H_2O); C, 71.90; H, 4.90; N, 5.24. Anal Found; C, 71.76; H, 5.12; N, 5.12.

3-Hydroxy-1-(2-methylphenyl)-3-(2-nitrophenyl)propan-1-one (2d). Yield: 68%, greenish brown crystals, mp 55–56°C. ^{1}H-NMR ($CDCl_3$) δ = 8.00–7.96 (m, 2H), 7.72–7.66 (m, 2H), 7.46 (ddd, *J* = 7.7, 7.6, 1.2 Hz, 1H), 7.40 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 7.28–7.23 (m, 2H), 5.8 4(dd, *J* = 9.3, 2.0 Hz, 1H), 4.00 (br 1H), 3.64 (dd, *J* = 17.6, 2.0 Hz, 1H), 3.15 (dd, *J* = 17.6, 9.3 Hz, 1H), 2.56(s, 3H). ^{13}C-NMR ($CDCl_3$) δ = 203.9, 147.5, 139.1, 138.9, 137.0, 134.0, 132.4, 132.3, 129.2, 128.6, 128.5, 126.1, 124.7, 66.4, 49.2, 21.8. Calcd for $C_{16}H_{15}NO_4$ (-H_2O); C, 71.90; H, 4.90; N, 5.24. Anal Found; C, 71.84; H, 5.12; N, 5.11.

3-Hydroxy-1-(4-metoxyphenyl)-3-(2-nitrophenyl)propan-1-one (2e). Yield: 66%, pale yellow crystals, mp 128–129°C (ref. [12] mp 128–129°C). ^{1}H-NMR ($CDCl_3$) δ = 8.00–7.93 (m, 4H), 7.69 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.46 (ddd, *J* = 7.6, 7.8, 1.4 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 2H), 5.83 (dd, *J* = 9.4, 2.4 Hz, 1H), 4.20 (d, *J* = 2.6 Hz, 1H), 3.88 (s, 3H), 3.70 (d, *J* = 17.4, 2.4 Hz, 1H), 3.14 (dd, *J* = 17.4, 9.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ = 198.8, 164.4, 147.6, 138.9, 134.0, 130.9(2C), 129.6, 128.7, 128.5, 124.6, 114.1(2C), 66.4, 55.8, 46.1.

1-(4-Chlorophenyl)-3-hydroxy-3-(2-nitrophenyl)propan-1-one (2f). Yield: 74%, deep green crystals, mp 92–93°C. ^{1}H-NMR ($CDCl_3$) δ = 7.99 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.98 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.70 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.49–7.43 (m, 3H), 5.85 (dd, *J* = 9.3, 2.2 Hz, 1H), 3.87 (d, *J* = 3.0 Hz, 1H), 3.68 (dd, *J* = 17.6, 2.2 Hz, 1H,) 3.19 (dd, *J* = 9.3, 17.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ = 198.8, 147.5, 140.6, 138.7, 134.9, 134.1, 129.9(2C), 129.3(2C), 128.6, 128.6, 124.7, 66.1, 46.8. Calcd for $C_{15}H_{12}ClNO_4$; C, 58.93; H, 3.96; N, 4.58. Anal. Found; C, 58.69; H, 4.11; N, 4.52.

3-Hydroxy-1-naphthyl-3-(2-nitrophenyl)propan-1-one (2g). Yield: 61%, greenish brown oil, ^{1}H-NMR($CDCl_3$) δ = 8.73 (d, *J* = 8.6 Hz, 1H), 8.03–7.98 (m, 3H), 7.94 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.89 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.74 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 7.64 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H), 7.57 (ddd, *J* = 8.2, 8.2, 1.2 Hz, 1H), 7.51–7.44 (m, 2H), 5.94 (dd, *J* = 9.3, 2.2 Hz, 1H), 4.04 (d, *J* = 3.1 Hz, 1H), 3.82 (dd, *J* = 17.5, 2.2 Hz, 1H), 3.31 (dd, *J* = 175, 9.3 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ = 204.1, 147.5, 138.9, 134.9, 134.2, 134.1, 133.8, 130.4, 128.8, 128.8, 128.7, 128.6, 128.5, 126.9, 125.9, 124.7, 124.6, 66.7, 49.8. Calcd for $C_{19}H_{15}ClNO_4$ (+H_2O); C, 67.25; H, 5.05; N, 4.13. Anal Found; C, 67.49; H, 4.77; N, 4.04.

1-(5-Bromo-2-hydroxyphenyl)-3-hydroxy-3-(2-nitrophenyl)propan-1-one (2h). Yield: 74%, purple crystals, mp 92–93°C. ^{1}H-NMR ($CDCl_3$) δ = 11.9 (s, 1H), 8.02 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.98 (d, *J* = 7.9, 1.3 Hz, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.73 (ddd, *J* = 7.9, 7.8, 1.3 Hz, 1H), 7.57 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.50 (ddd, *J* = 7.9, 7.8, 1.4 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 1H), 5.90 (dd, *J* = 9.2, 2.1 Hz, 1H), 3.66 (dd, *J* = 17.8, 2.1 Hz, 1H), 3.41(br, 1H), 3.30(dd, *J* = 17.8, 9.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ = 204.7, 161.7, 147.4, 139.8, 138.4, 134.3, 132.4, 128.9, 128.6, 124.8, 120.9, 120.6, 111.0, 65.5, 46.9. Calcd for $C_{15}H_{12}NO_3$; C, 67.25; H, 5.05; N, 4.13. Anal. Found; C, 67.49; H, 4.77; N, 4.04.

2-Bromo-3-hydroxy-3-(2-nitrophenyl)-1-phenylpropan-1-one (2i). Yield: 52%, colorless crystals, mp 103–104°C. ^{1}H-NMR ($CDCl_3$) δ = 8.06 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 2H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.67 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.55 (dd, *J* = 7.9, 7.6 Hz, 1H), 7.45–7.40 (m, 3H), 5.02 (d, *J* = 5.0 Hz, 1H), 4.83 (d, *J* = 5.0 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ = 191.4, 147.4, 135.2, 134.3, 134.2, 130.3, 129.8,

129.5, 129.0(2C), 128.5(2C), 124.9, 60.3, 58.1. Anal. Calcd for $C_{15}H_{12}NO_3$ (-HBr); C, 66.91; H, 4.12; N, 5.20. Found; C, 66.84; H, 4.38; N,5.24.

4-Hydroxy-4-(2-nitrophenyl)butan-2-one (2j). Yield: 66%, yellow crystals, mp 55–56°C (ref. [13] mp 52–55°C). ^{1}H-NMR ($CDCl_3$) δ = 7.91 (d, *J* = 7.9 Hz, 1H), 7.68 (dd, *J* = 7.9, 7.7 Hz, 1H), 7.45 (dd, *J* = 8.1, 7.7 Hz, 1H), 5.69 (dd, *J* = 9.4, 2.0 Hz, 1H), 3.15 (dd, *J* = 17.8, 2.0 Hz, 1H), 2.73 (dd, *J* = 17.8, 9.4 Hz, 1H), 2.24(s, 3H). ^{13}C-NMR ($CDCl_3$) δ = 209.1, 147.4, 138.6, 134.1, 128.5, 128.4, 124.7, 65.9, 51.3, 30.7.

3-Hydroxy-3-(*b*-nitrobenzo[1,3]dioxol-5-yl)-1-phenylpropan-1-one (2k). Yield: 50%, pale yellow crystals, mp 96–97°C. ^{1}H-NMR($CDCl_3$) δ = 7.96 (d, *J* = 7.4 Hz, 2H), 7.60 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.54 (s, 1H), 7.48 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.43 (s, 1H), 6.13 (s, 2H), 5.88 (dd, *J* = 9.2, 2.0 Hz, 1H), 4.03 (d, *J* = 2.2 Hz, 1H), 3.72 (dd, *J* = 17.6, 2.0 Hz, 1H), 3.11 (dd, *J* = 17.6, 9.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ = 200.3, 152.9, 147.4, 141.3, 136.8, 136.6, 134.0, 129.0(2C), 128.5(2C), 107.4, 105.4, 103.2, 66.4, 46.7. Anal. Calcd for $C_{16}H_{13}NO_6$; C, 60.95; H, 4.16; N, 4.44. Found; C, 60.67; H, 4.36; N, 4.40.

Reductive cyclization of 2a by using tin and hydrochloric acid. To a solution of **2a** (0.136 g, 0.5 mmol) and conc HCl (0.17 mL, 0.20 mmol) in EtOH (12 mL) was added Sn powder (0.178 g, 1.5 mmol) in one portion. After being stirred for 1h at 60°C, the reaction mixture was evaporated, washed with water, and extracted with CH_2Cl_2 (5 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give pale green oily solid, which was chromatographed over silica gel by elution with dichloromethane to afford 2-phenylquinoline *N*-oxide **1a** (0.029 g, 0.13 mmol) and 2-phenylquinoline **5a** (0.062 g, 0.30 mmol). mp 79–80°C (ref. [1] mp 78–79°C).

2-Phenylquinoline *N*-oxide **1a**: yield: 89%, pale yellow crystals, mp 74–75°C (ref. [14] mp 76°C). ^{1}H-NMR ($CDCl_3$) δ = 8.87 (d, *J* = 8.8 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 2H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.80–7.75 (m 2H), 7.65 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.55–7.45 (m 4H). ^{13}C-NMR ($CDCl_3$) δ = 144.9, 142.2, 133.5, 130.5, 129.6(2C), 129.5, 129.5, 128.4(2C), 128.3, 128.0, 125.2, 123.3, 120.2.

Reductive cyclization of 2j by using zinc and ammonium chloride. To a solution of 4-hydroxy-4-(2-nitropohenyl)-2-butanone **2j** (0.142 g, 0.50 mmol) and ammonium chloride (0.080 g, 1.5 mmol) in ethanol-water (1:1, 40 mL) was added zinc powder (0.098 g, 1.5 mmol) in one portion. After stirring for 6 h at 60°C, the reaction mixture was poured into water (20 mL), and extracted with dichloromethane (10 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give pale yellow solid, which was recrystallized from methanol to afford 2-methylquinoline *N*-oxide **1j** (0.094 g, 0.43 mmol) colorless crystals. mp 54–55°C (ref. [15] mp 76°C). ^{1}H-NMR ($CDCl_3$) δ = 8.80 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.76 (dd, *J* = 8.6, 8.2 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.60 (dd *J* = 8.6, 8.2 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 2.73 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ = 146.0, 141.8, 130.5, 129.4, 128.2, 128.0, 125.4, 123.2, 119.8, 19.0.

Other reactions were carried out in a similar manner.

2-(4-Methylphenyl)quinoline *N*-oxide (1b). Yield: 90%, orange crystals, mp 112–113°C (ref. [7] mp 127–128°C). ^{1}H-NMR ($CDCl_3$) δ = 8.86 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.77 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.62 (dd *J* = 8.4, 7.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 2.43 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ = 145.4, 142.5, 139.9, 130.8, 129.9, 129.7(2C), 129.7(2C), 129.2, 128.5, 128.2, 125.5, 123.5, 120.5, 21.7.

2-(3-Methylphenyl)quinoline *N*-oxide (1c). Yield: 88%, orange crystals, mp 110–111°C. ^{1}H-NMR ($CDCl_3$) δ = 8.87 (d, *J* = 8.8 Hz, 1H), 7.88–7.62 (m, 5H), 7.64 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.42 (dd *J* = 7.6, 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 2.45(s, 3H). ^{13}C-NMR ($CDCl_3$) δ = 145.5, 142.6, 138.2, 133.7, 130.8, 130.5, 130.3, 129.8, 128.6, 128.5, 128.2, 126.9, 125.3, 123.7, 120.6, 21.7. Anal. Calcd for $C_{13}H_{15}NO_4$; C, 81.86; H, 5.57; N, 5.95. Found; C, 81.52; H, 5.41; N, 5.78.

2-(2-Methylphenyl)quinoline *N*-oxide (1d). Yield: 90%, orange crystals, mp 109–110°C (ref. [7] mp 103–104°C).^{1}H-NMR ($CDCl_3$) δ = 8.85 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.82–7.71 (m, 2H), 7.66 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.43–7.29 (m, 5H), 7.62 (dd, *J* = 7.8, 7.8 Hz, 1H), 2.27 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ = 146.7, 142.0, 137.7, 133.9, 130.4, 130.1, 129.9, 129.3, 129.1, 128.4, 128.0, 125.9, 124.6, 123.8, 120.3, 19.7.

2-(4-Methoxylphenyl)quinoline *N*-oxide (1e). Yield: 89%, pale yellow crystals, mp 123–124°C (ref. [7] mp 125–126°C). ^{1}H-NMR ($CDCl_3$) δ = 8.86 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.78 (ddd, *J* = 8.0, 8.0, 1.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.63 (ddd *J* = 8.4, 8.0, 1.2 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 2H), 3.89(s, 3H). ^{13}C-NMR ($CDCl_3$) δ = 160.7, 144.9, 142.5, 131.5(2C), 130.7, 129.5, 128.4, 128.1, 125.9, 125.4, 123.3, 120.4, 113.9(2C), 55.6.

2-(4-Chlorophenyl)quinoline *N*-oxide (1f). Yield: 82%, greenish yellow crystals mp 170–171°C. ^{1}H-NMR ($CDCl_3$) δ = 8.84 (d, *J* = 8.8 Hz, 1H), 7.98–7.94 (m, 2H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.80 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.66 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.52–7.48 (m, 3H). ^{13}C-NMR ($CDCl_3$) δ = 144.1, 142.6, 135.8, 132.1, 131.2(2C), 131.0, 129.9, 128.9, 128.8(2C), 128.3, 125.6, 123.1, 120.5. Anal. Calcd for $C_{15}H_{10}ClNO_4$; C, 70.46; H, 3.94; N, 5.48. Found; C, 70.51; H, 4.18; N, 5.53.

2-(1-Naphthyl)quinoline *N*-oxide (1g). Yield: 80%, colorless crystals, mp 168–169°C (ref. [7] mp 168–169°C). ^{1}H-NMR ($CDCl_3$) δ = 8.88 (d, *J* = 9.3 Hz, 1H), 8.02–7.91 (m, 3H), 7.85–7.77 (m, 2H), 7.69(ddd, *J* = 8.1, 6.8 and 1.2 Hz, 1H), 7.60(d, *J* = 5.6 Hz, 2H), 7.60(d, *J* = 5.6 Hz 2H), 7.55–7.41(m, 4H). ^{13}C-NMR ($CDCl_3$) δ = 145.6, 142.1, 133.4, 132.1, 130.7, 130.5, 130.1, 129.9, 128.6, 128.6, 128.1, 127.7, 126.9, 126.2, 125.4, 125.4, 124.7, 124.5, 20.4.

2-(5-Bromo-2-hydroxyphenyl)-quinoline *N*-oxide (1h). Yield: 89%, pale yellow crystals, mp 167–168°C (ref. [9] mp 167–168°C). ^{1}H-NMR ($CDCl_3$) δ = 11.30 (s, 1H, OH), 8.91 (d, *J* = 8.8 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.92 (dd *J* = 8.5, 7.9 Hz, 1H), 7.75 (dd, *J* = 8.2, 7.9 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.62 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ = 159.4, 147.5, 141.1, 135.3, 133.6, 132.2, 129.9, 129.4, 129.2, 128.3, 124.2, 123.5, 122.7, 120.3, 112.0.

3-Bromo-2-phenylquinoline *N*-oxide (1i). Yield: 89%, yellow crystals mp 124–125°C (ref. [16] mp 125–127°C). ^{1}H-NMR ($CDCl_3$) δ = 8.64 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 7.6

Hz, 1H), 7.60–7.52 (m, 4H), 7.52 (dd, J = 7.8, 7.8 Hz, 2H), 7.44 (dd, J = 7.4, 7.2 Hz, 1H), 7.27 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ = 130.1(2C), 129.9, 129.8, 129.7, 129.0, 128.7(2C), 128.6, 128.2, 128.0, 127.6, 127.1, 120.0, 111.3.

6-Phenyl-[1,3]dioxolo[4,5-g]quinoline *N*-oxide (1k). Yield: 85%, pale yellow crystals, mp 224–225°C. ^{1}H-NMR ($CDCl_3$) δ = 8.22 (s, 1H), 7.91 (dd, J = 8.2, 1.2 Hz, 2H), 7.58 (d, J = 8.6 Hz, 1H), 7.52–7.44 (m, 3H), 7.35 (d, J = 8.6 Hz, 1H), 7.09 (s, 1H), 6.17 (s, 2H). ^{13}C-NMR ($CDCl_3$) δ = 152.2, 149.5, 133.9, 129.8(2C), 129.5, 129.4, 128.7, 128.4(2C), 127.0, 124.7, 121.9, 103.4, 102.6, 98.5. Anal. Calcd for $C_{16}H_{11}NO_3$; C, 72.45; H, 4.18; N, 5.28. Found; C, 72.28; H, 4.43; N, 5.27.

Reductive cyclization of 2-nitrochalcone with Sn/HCl. To a solution of 2-nitrochalchone **7a** (0.253 g, 1.0 mmol) and conc. HCl (0.33 mL, 4.0 mmol) in EtOH (15 mL) was added Sn powder (0.356 g, 3.0 mmol) in one portion. After stirring for 1h at RT, the reaction mixture was evaporated to afford dark solid, which was extracted with EtOAc (5 mL × 3), dried over sodium sulfate, filtered, and evaporated to afford yellow solid. Chromatographic separation of the solid (SiO_2, EtOAc:hexane = 1:1) gave 2-phenylquinoline **5a** (0.164 g, 0.80 mmol).

Reductive cyclization of 2-nitrochalcone with Pd/C. To a solution of 2-nitrochalcone **7a** (0.253 g, 1.0 mmol) in EtOH (15 mL) was added Pd/C (10%, 0.053 g, 0.05 mmol) in one portion. After stirring for 3 h under hydrogen atmosphere, the reaction mixture was refluxed for 8h, and evaporated to give dark brown oily crystals, which was chromatographed over silica gel by elution with EtOAc:Hexane (1:5) to give **5a** (0.160 g, 0.78 mmol).

Reductive cyclization of 2-nitrochalcone with Sn/NH_4Cl. To a solution of 2-nitrochalcone **7a** (0.127 g, 0.50 mmol) and ammonium chloride (0.080 g, 1.5 mmol) in ethanol-water (1:1, 40 mL) was added tin powder (0.178 g, 1.5 mmol) in one portion. After refluxing for 26 h, the reaction mixture was poured into water (20 mL), and extracted with dichloromethane (10 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give pale yellow crystals, which was chromatographed over silica gel to afford 2-phenyllquinoline *N*-oxide **1a** (0.088 g, 0.40 mmol) and 2-phenylquinoline **5a** (0.004 g, 0.02 mmol).

Other reactions were carried out in a similar manner.

2-(4-Methylphenyl)quinoline *N*-oxide **1b** (0.109 g, 0.41 mmol): mp 112–113°C. 2-(4-Chlorophenyl)quinoline *N*-oxide **1f** (0.115 g, 0.40 mmol): mp 170–171°C. 2-Naphtylquinoline *N*-oxide **1g** (0.124 g, 0.41 mmol): mp 168–169°C.

REFERENCES AND NOTES

[1] (a) Fakhfakh, M. A.; Fournet, A.; Prina, E.; Mouscadet, J. -F.; Franck, X.; Hocquemiller, R.; Figadere, B. Bioorg Med Chem 2003, 11, 5013; (b) Banath, J. P.; Olive, P. L. Cancer Res 2003, 63, 4347; (c) Kanou, M.; Saeki, K.; Kato, T.; Takahashi, K.; Mizutani, T. Fund Clin Pharmacol 2002, 16, 513.

[2] Andreev, V. P.; Korvacheva, E. G.; Nizhnik, Y. P. Pharm Chem J 2006, 40, 347.

[3] Albrecht, T.; Spleelman, D. J.; Ramanujam, V. M. S.; Lund, H. W.; Legator, M. S.; Trieff, N. M. Terat Carcin Mut 1980, 1, 161.

[4] (a) Werbel, L. M.; Kersten, S. J.; Turner, W. R. Eur J Med Chem 1993, 28, 837; (b) Mouaddib, A.; Joseph, J.; Hasnaoui, A.; Merour, Y. -J. Synthesis 2000, 549.

[5] (a) Horino, H.; Inoue, N. Tetrahedron Lett 1979, 20, 329; (b) Horaguchi, T.; Hosokawa, N.; Tanemura, K.; Suzuki, T. J. Heterocycl Chem 2002, 39, 61.

[6] Okuma, K.; Yasuda, T.; Shioji, K.; Yokomori, Y. Bull Chem Soc Jpn 2007, 80, 1824.

[7] Campeau, L. C.; Stuart, D. R.; Leclerc, J. -P.; Bertrand-Laperte, M.; Villemure, E.; Sun, H. -Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. J. Am Chem Soc 2009, 131, 3291.

[8] Lee, K. Y.; Kim, J. M.. Kim, J. N. Tetrahedron 2003, 59, 385.

[9] (a) Barros, A. I. R. N. A.; Silva, A. M. S. Tetrahedron Lett 2003, 44, 5893; (b) Barros, A. I. R. N. A.; Dias, A. F.; Silva, A. M. S. Monatsh Chem 2007, 138, 585; (c) Muchowski, J. M.; Naddox, M. L. Can J Chem 2004, 82, 461.

[10] Wang, G. -W.; Zhang, Z.; Dong, Y. -W. Org Proc Res Dev 2004, 8, 18.

[11] Baik, W. K.; Kim, D. I.; Hyu, J.; Chung, W. -J.; Kim, B. H.; Lee, S. W. Tetrahedron Lett 1997, 38, 4579.

[12] Mei, K.; Zhang, S.; He, S.; Li, P.; Jin, M.; Xue, F.; Luo, G.; Zhang, H.; Song, L.; Duan, W.; Wang, W. Tetrahedron Lett 2008, 49, 2681.

[13] Chimni, S. S.; Mahajan, D. Tetrahedron 2005, 61, 5019.

[14] White, J. D.; Yager, K. M.; Stappenbeck, F. J. Org Chem 1993, 58, 3466.

[15] Bjorsvik, H. -R.; Gambarotti, C.; Jensen, V. R.; Gonzalez, R. R. J. Org Chem 2005, 70, 3218.

[16] Hayashi, E.; Miyashita, A. Yakugaku Zasshi 1976, 96, 968.