A New Convenient Method for the Synthesis of 2*H*-1,4-Benzoxazine Derivatives from Nitroketones *via* Intramolecular Reductive Cyclization

Meyoung Ju Joung,[a] Jin Hee Ahn,[a, 1] Hoe Moon Kim,[a] Kee Won Kim,[b] Jae Hoon Kang,[b] Seok Joon Lee,[b] and Nung Min Yoon[a]*

[a]Department of Chemistry, Sogang University, 1 Shinsu-dong, Mapo-ku, Seoul 121-742, Korea
Fax: +82(2)701-0967; E-mail: nungmin@ccs.sogang.ac.kr
[b]Ildong Pharmaceutical Co. Ltd., 260-5, Eonnam-ri, Kuseong-eup, Yongin, Kyongki-do 449-915, Korea
Fax : +82(31)287-1800
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Dedicated to Professor Herbert C. Brown on the occasion of his 90th birthday.

Potentially bioactive 2*H*-1,4-benzoxazine derivatives could be conveniently prepared in one step from the corresponding nitroketones using 10% palladium on carbon with triethylamine in the presence of hydrogen (Pd/C-TEA-H_2) system. Several other tertiary amines such as nicotine, pyridine, and quinoline also could be used, but TEA gave the best results.

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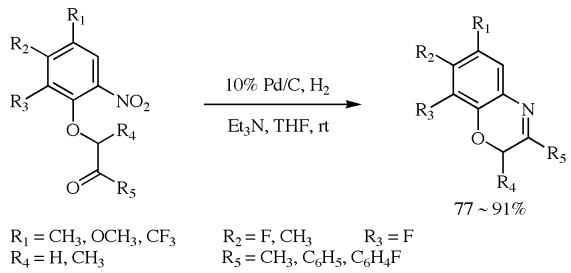
Introduction.

2*H*-1,4–Benzoxazine is a useful prochiral cyclic imine [2-4] for the synthesis of chiral cyclic amines, and especially 3-aryl-2*H*-1,4–benzoxazines are found to have an anti-inflammatory activity [5]. The 2*H*-1,4–benzoxazines have been classically prepared by base [6] or acid [7] catalyzed intramolecular condensation of 2-aminophenoxyketones or directly by the reaction of 2-aminophenol with phenacyl bromide derivatives under basic condition [8-10]. However, the direct synthesis of cyclic imines from the corresponding nitroketones by reductive cyclization would be more attractive. Such reductive cyclizations were reported using Ni $(COD)_2$ [11] or Zn in AcOH [12] and Pd/C [13] or PtO_2 [14] under hydrogen atmosphere. However these methods provided low yields or were restricted only to the highly conjugated aromatic system. Alternatively, the synthesis of 3-phenyl-2*H*-1,4-benzoxazine derivatives from 2-nitrophenoxyacetophenones has been reported using 5% Pd/C and sodium phosphinite as hydrogen donor in a two-phase system of water/THF in good yields [15], but the product cyclic imines were contaminated with the corresponding overreduced cyclic amines in our hands [16]. Now we report here a general convenient method for the synthesis of 2*H*-1,4-benzoxazine derivatives from nitroketones without contamination with the overreduced cyclic amines.

Recently, during our investigation for the synthesis of 7,8-difluoro-3-methyl-2*H*-1,4-benzoxazine, which is a prochiral substrate to make 7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine, an optically active key intermediate of antibacterial agent, levofloxacin [2], we could develop a useful method for the preparation of the cyclic imine from 3,4-difluoro-2-(2-oxopropyloxy)nitrobenzene quantitatively using 10% Pd/C under hydrogen atmosphere (1 atm) in the presence of triethylamine (TEA) in THF at room temperature. Encouraged by the result, we applied this method to the synthesis of 2*H*-1,4-benzoxazine derivatives including 3-aryl-2*H*-1,4-benzoxazine as shown in Scheme 1.

Scheme 1



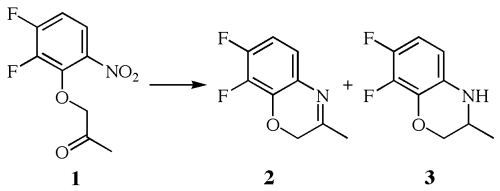
Results and Discussions.

It has been known that amines such as quinoline or TEA are effective for selective hydrogenation such as hydrogenation of acetylenes to *cis* olefins [17] and reduction of imidoyl chloride to the corresponding imine [18]. Based on the assumption that tertiary amines should partially poison the surface of Pd catalyst, we investigated the effects of tertiary amines in the reductive cyclization of nitroketone **1** for the synthesis of cyclic imine derivatives (Table 1). In the absence of tertiary amine (entry 1), an overreduction to the corresponding cyclic amine **3** took place preferentially. The use of tertiary amines such as triethylamine, nicotine, pyridine or quinoline (entry 2-7) provided the cyclic imine **2** as the major product although yields and ratios of **2** and **3** depended on the tertiary amine, it's amount and the reaction time. The best result was obtained in the presence of 1 equivalent of TEA (entry 2).

Based on these preliminary results, the synthesis of 3-aryl-2*H*-1,4-benzoxazines and other diverse 2*H*-1,4-benzoxazines was investigated under the optimum condition (entry 2 in Table 1). The starting materials were prepared by the reactions of commercially available 2-nitrophenol

Table 1

The Reductive Cyclization of Nitroketone **1** in the Presence of Tertiary Amine [a]



1 **2** **3**

Entry	Tertiary Amine (equiv.)	Time (h)	Yield (%) [b] **2**	Yield (%) [b] **3**
1	none	2	5	95
2	Et_3N (1.0)	0.5	>99	<0.1
3	Et_3N (2.0)	1	98	2
4	Nicotine (0.3)	18	95	0.7
5	Nicotine (0.5)	24	97	1
6	Pyridine (5.0)	3	92	1
7	Quinoline (1.0)	1	70	0.5

[a] The nitroketone **1** (4 mmol, 0.924 g) was hydrogenated in THF (10 mL) at 1 atm using 10% Pd/C (1 wt %, 9.24 mg) at room temperature; [b] GC Yield.

derivatives with α-chloroketone moieties [19]. The reductive cyclizations were carried out over 1 wt % of 10% Pd/C with 1 equivalent of TEA under hydrogen atmosphere (1 atm) in THF at room temperature. Reaction progress was monitored either by GC or TLC, and as soon as the starting material disappeared, the reaction mixture was filtered to give the crude imine, usually as a sole product, which was then purified by short column chromatograph. When the reaction was allowed to proceed further after the disappearance of starting materials, the proportion of the corresponding overreduced cyclic amine increased. The crude imine seemed to decompose slowly during purification process. The results are summarized in Table 2.

In Table 2, as mentioned above, the treatment of 3,4-difluoro-2-(2-oxopropyloxy)nitrobenzene (**1**) with 1 wt % of 10% Pd/C and 1 equivalent of TEA provided 7,8-difluoro-3-methyl-2*H*-1,4-benzoxazine (**2**) in 90% yield by the one step procedure. On the other hand, that imine **2** has been prepared from the corresponding nitroketone in two different methods. One method [3] involves three steps with 81% overall yield; (a) a protection of the carbonyl group of 3,4-difluoro-2-(2-oxopropyloxy)nitrobenzene with ethylene glycol, (b) a reduction of nitro group into amine and (c) a deprotection of the carbonyl group and concomitant condensation. Another method [4] is also a three step procedure with 82% overall yield; (a) a reduction to the saturated amine, 7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine, (b) a *N*-bromination of the saturated amine and (c) a base-induced elimination to cyclic imine.

Table 2

The Reductive Cyclization of Nitroketones Using 10% Pd/C–H_2 with Et_3N in THF at Room Temperature [a]

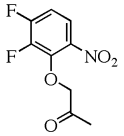
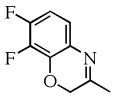
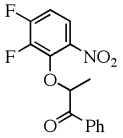
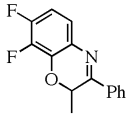
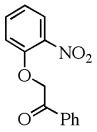
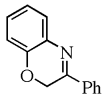
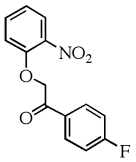
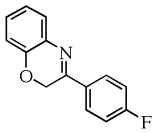
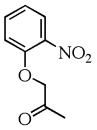
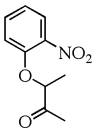
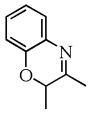
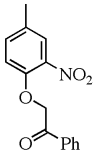
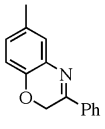
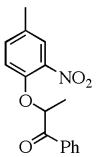
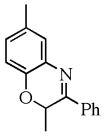
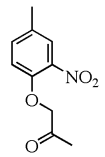
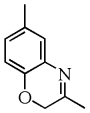
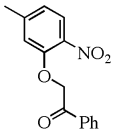
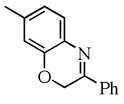
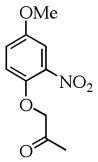
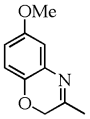
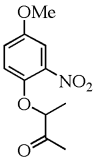
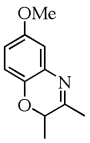
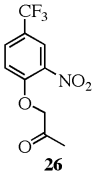
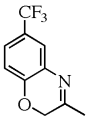
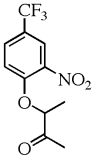
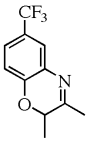
Substrate	Product	Yield (%) [b]
 **1**	 **2**	90
 **4**	 **5**	91
 **6**	 **7**	88
 **8**	 **9**	90
 **10**	 **11**	91
 **12**	 **13**	85 [c]
 **14**	 **15**	80
 **16**	 **17**	90

Table 2 (continued)

Substrate	Product	Yield (%) [b]
 **18**	 **19**	86 [c]
 **20**	 **21**	77
 **22**	 **23**	91
 **24**	 **25**	89
 **26**	 **27**	87
 **28**	 **29**	80

[a] The nitroketone (4 mmol) in THF (10 mL) was hydrogenated at 1 atm using 1 wt % of Pd/C with Et_3N (4 mmol) at room temperature; [b] Isolated Yield; [c] 10 wt % of Pd/C with Et_3N was used.

The nitroketone **4** (R_4 = Me and R_5 = Ph) was also successfully cyclized under the above-mentioned optimum condition to afford the cyclized product (**5**) in quantitative isolated yield of 91%. A number of methodologies for the synthesis of 3-phenyl-2*H*-1,4-benzoxazines (R_5 = Ph) has been developed under basic conditions in 55 ~ 85% yields [8-10], or using 5% Pd/C and sodium phosphinite as hydrogen donor in 80% yield [15]. With our system, the nitroketones **6** (R_5 = Ph) and **8** (R_5 = C_6H_4F) were effectively hydrogenated to afford 3-aryl-2*H*-1,4-benzoxazines **7** and **9** in 88% and 90% yields exclusively. In addition, the reductive cyclization of nitroketone **10** (R_5 = Me) readily proceeded to give the cyclic imine **11** in 91% yield.

We explored a number of nitroketones by modifying the substituent of the benzene ring (R_1 or R_2) such as methyl group (**14**, **16**, **18**, and **20**), electron donating group (OMe, **22** and **24**) or electron withdrawing group (CF_3, **26** and **28**), and also by variations of R_4 or R_5 group in the ketone such as methyl (**12**, **16**, **24**, and **28**) or phenyl (**14**, **16**, and **20**) group. Generally the 2*H*-1,4-benzoxazines were prepared within 30 minutes to 7 hours in good yields, however in some cases (**12** and **18**), a 10 wt % of Pd/C was needed to complete the reactions.

Throughout the survey, the nitroketones containing a phenyl group at R_5 position were found to be more reactive than other nitroketones (R_5 = Me) to the reductive cyclization and quickly hydrogenated within 30 minutes, presumably due to the affinity of phenyl group to the surface of Pd/C. Apparently, the Pd/C-H_2-TEA system would be not only an alternative convenient method for the synthesis of 3-aryl 2*H*-1,4-benzoxazines from aryl nitroketones, but also the new general convenient method for the synthesis of 2*H*-1,4-benzoxazines derivatives.

Conclusion.

In conclusion, the convenient method for the synthesis of potentially bioactive, prochiral 2*H*-1,4-benzoxazine derivatives directly from the corresponding nitroketones was developed using 10% Pd/C-TEA-H_2 in THF system in one step. The appropriate poisoning of Pd/C with TEA turned out to be essential for the exclusive formation of cyclic imines in good yields.

EXPERIMENTAL

Preparation of Nitroketone: General Procedure [19].

To a solution of 2-nitrophenol (10 mmol) in acetone (40 mL) were added KI (10 mmol) and powdered K_2CO_3 (18 mmol), then chloroketone (27 mmol; 10 mmol in the case of R_5 = Ph). After stirring vigorously until the starting material disappeared at room temperature or under reflux, the reaction mixture was filtered with acetone, and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, ethyl acetate/hexane) and then recrystallization from ethyl acetate-hexane gave a nitroketone as a solid (**12** is an oil) in good yields.

Preparation of Cyclic Imine: General Procedure.

To a solution of nitroketone (4.0 mmol) in dried THF (10 mL) were added dried TEA (0.56 mL, 4.0 mmol) and 10% palladium carbon (1 wt % or 10 wt % of nitroketone) under 1 atm of hydrogen gas at room temperature. The reaction was monitored by

Table 3
Spectral Data of 1,4-Benzoxazine

Product	^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	GCMS (EI) *m*/*z* (%)
2 [a]	2.14 (s, 3 H), 4.58 (s, 2 H), 6.66 - 6.79 (m, 1 H), 6.91 - 7.02 (m, 1 H)	183 (M^+, 100), 168 (39), 140 (9), 114 (38), 88 (24)
5 [b]	1.18 (d, 3 H, *J* = 6.46), 4.52 (q, 1 H, *J* = 6.46), 6.72 – 6.75 (m, 1 H), 6.90 – 6.95 (m, 1 H), 7.37 – 7.60 (m, 5 H)	259 (M^+, 100), 244 (69), 231 (20), 215 (15), 115 (16), 91 (12)
7 [c]	5.08 (s, 2 H), 6.91 – 7.21 (m, 3 H), 7.43 – 7.94 (m, 6 H)	209 (M^+, 87), 180 (24), 103 (100), 77 (33)
9 [d]	5.02 (s, 2 H), 6.92 (d, 1 H, *J* = 7.97), 7.03 - 7.19 (m, 4 H), 7.41 (d, 1 H, *J* = 7.55), 7.91 – 7.96 (m, 2 H)	227 (M^+, 100), 198 (14), 121 (46), 101 (19)
11 [e]	2.15 (s, 3 H), 4.54 (s, 2 H), 6.81 – 7.27 (m, 4 H)	147 (M^+, 100), 132 (40), 118 (27), 78 (85)
13 [f]	1.40 (d, 3 H, *J* = 6.87), 2.17 (s, 3 H), 4.65 (q, 1 H, *J* = 6.87), 6.83 – 7.13 (m, 4 H)	161 (M^+, 100), 146 (96), 133 (54), 91 (33), 79 (23)
15 [g]	2.33 (s, 3 H), 5.04 (s, 2 H), 6.81 (d, 1 H, *J* = 8.24), 6.96 (d, 1 H, *J* = 8.24), 7.36 - 7.49 (m, 4 H), 7.90 – 7.93 (m, 2 H)	223 (M^+, 100), 194 (9), 180 (3), 103 (16), 77 (7)
17 [h]	1.39 (d, 3 H, *J* = 6.87), 2.34 (s, 3 H), 5.50 (q, 1 H, *J* = 6.87), 6.82 (d, 1 H, *J* = 8.10), 6.97 (d, 1 H, *J* = 8.10), 7.44 – 7.49 (m, 4 H), 7.94 – 7.98 (m, 2 H)	237 (M^+, 100), 222 (76), 209 (14), 115 (26), 91 (16)
19 [i]	2.14 (s, 3 H), 2.29 (s, 3 H), 4.51 (s, 2 H), 6.73 (d, 1 H, *J* = 8.13), 6.90 (d, 1 H, *J* = 8.13), 7.07 (s, 1 H)	161 (M^+, 100), 146 (35), 132 (18), 118 (24), 91 (53), 77 (8)
21 [j]	2.34 (s, 3 H), 5.04 (s, 2 H), 6.75 - 6.86 (m, 2 H), 7.31 - 7.49 (m, 4 H), 7.88 - 7.93 (m, 2 H)	223 (M^+, 100), 208 (3), 194 (14), 180 (8), 103 (46), 77 (20)
23 [k]	1.38 (s, 3 H), 3.81 (s, 3 H), 4.39 (s, 2 H), 6.19 - 6.26 (m, 2 H), 6.89 - 6.90 (m, 1 H)	177 (M^+, 100), 162 (40), 134 (24), 122 (14), 108 (20)
25 [l]	1.38 (d, 3 H, *J* = 6.87), 2.17 (s, 3 H), 3.78 (s, 3 H), 4.60 (q, 1 H, *J* = 6.87), 6.66 – 6.87 (m, 3 H)	191 (M^+, 90), 176 (100), 163 (32), 148 (15), 122 (10), 79 (12)
27 [m]	2.17 (s, 3 H), 4.62 (s, 2 H), 6.89 (d, 1 H, *J* = 8.52), 7.35 (d, 1 H, *J* = 8.52), 7.51 (s, 1 H)	215 (M^+, 100), 200 (36), 186 (9), 173 (10), 147 (28), 127 (9), 75 (6)
29 [n]	1.42 (d, 3 H, *J* = 6.87), 2.19 (s, 3 H), 4.72 (q, 1 H, *J* = 6.87), 6.91 (d, 1 H, *J* = 8.38), 7.35 (d, 1 H, *J* = 8.38), 7.52 (s, 1 H)	229 (M^+, 25), 214 (34), 201 (27), 91 (30), 75 (55), 63 (53), 55 (100)

[a] *Anal.* Calcd for $C_9H_7NOF_2$: C, 59.02; H, 3.85; N, 7.65. Found: C, 59.06; H, 3.83; N, 7.69;^{1}H NMR, mass, and microanalysis spectra were in agreement with those reported in literature [3]. [b] *Anal.* Calcd for $C_{15}H_{11}NOF_2$: C, 69.49; H, 4.28; N, 5.40. Found: C, 69.41; H, 4.29; N, 5.47. [c] *Anal.* Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.32; H, 5.32; N, 6.61. ^{1}H NMR, mass, and microanalysis spectra were in closely agreement with those reported in literature [8, 20]. [d] *Anal.* Calcd for $C_{14}H_{10}NOF$: C, 74.00; H, 4.44; N, 6.16. Found: C, 73.93; H, 4.50; N, 6.15. [e] *Anal.* Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.48; H, 6.14; N, 9.58. [f] *Anal.* Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.67; H, 6.94; N, 8.66. [g] *Anal.* Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.67; H, 5.84; N, 6.28. ^{1}H NMR, mass spectra were in agreement with those reported in literature [15]. [h] *Anal.* Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.84; H, 6.46; N, 5.91. ^{1}H NMR, mass spectra were in agreement with those reported in literature [15]. [i] *Anal.* Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.48; H, 6.89; N, 8.66. [j] *Anal.* Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.60; H, 5.91; N, 6.25. [k] *Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.53; H, 6.26; N, 8.00. [l] *Anal*. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.11; H, 6.80; N, 7.34. [m] *Anal.* Calcd for $C_{10}H_8NOF_3$: C, 55.82; H, 3.75; N, 6.51. Found: C, 55.77; H, 3.74; N, 6.43. [n] *Anal.* Calcd for $C_{11}H_{10}NOF_3$: C, 57.64; H, 4.40; N, 6.11. Found: C, 57.60; H, 4.39; N, 6.14.

TLC and GC. The reaction was completed within 30 minutes for 3-aryl-2*H*-1,4-benzoxazines and within 7 hours for other 2*H*-1,4-benzoxazines. As soon as the starting material disappeared, the reaction mixture was filtered with cold CH_2Cl_2, and the filtrate was evaporated under reduced pressure. Purification of the residue by short column chromatography (SiO_2, ethyl acetate/hexane/TEA 1:10:0.5) provided the cyclic imine as a white solid or yellowish oil.

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