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2-ARYLQUINOLINE SYNTHESIS FROM Cbz-PROTECTED 2-AMINOCHALCONE MEDIATED BY BF_3•Et_2O

Tomohiro Maegawa,* Misa Nogata, Takaya Honda, Akira Nakamura, and Yasuyoshi Miki*

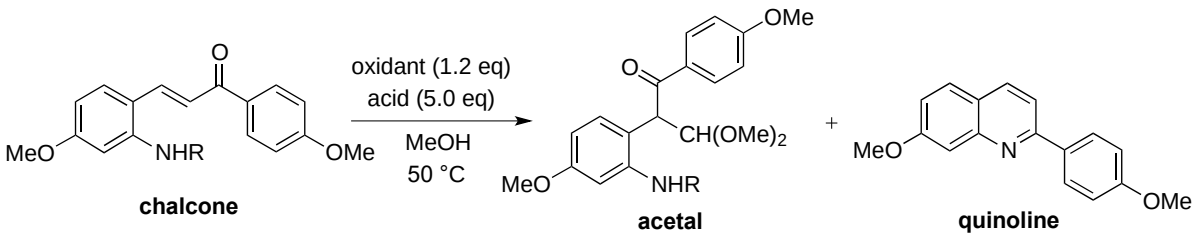
School of Pharmaceutical Sciences, Kindai University, 3-4-1 Kowakae, Higashi-Osaka, Osaka, 577-8502, Japan; E-mail: y_miki@phar.kindai.ac.jp
Research Organization of Science and Technology, Research Center for Drug Discovery and Pharmaceutical Science, 1-1-1 Nojihigashi, Kusatsu, Shiga 525-8577, Japan

Abstract – A novel approach to producing the quinoline skeleton from 2-aminochalcone was developed. Treatment of benzyloxycarbonyl (Cbz)-protected 2-aminochalcones with BF_3·Et_2O afforded quinoline derivatives via the deprotection of the Cbz group and isomerization of olefin in a one-pot reaction. The reaction of various 2-aminochalcones proceeded to give the corresponding 2-arylquinoline derivatives in good yields. This method is applicable to the rapid synthesis of dubamine.

The quinoline skeleton is a component of natural products and pharmaceuticals with useful bioactivities.[1] For example, dubamine has antibacterial activity[2] and 2-phenyl-5,6,7-trimethoxyquinoline has anticancer activity.[3] Many methods for synthesizing the quinoline skeleton have been reported,[1] but few from 2-aminochalcones. The reported methods from 2-aminochalcones used *N*-iodosuccinimide,[4] I_2,[4] or *hν*[5] to isomerize the olefin for cyclization. *N*-Benzenesulfonyl-protected 2-aminochalcone was also used for the construction of quinoline, but its double bond was reduced by hydrogenation for cyclization, and then polyphosphoric acid-mediated cyclization was conducted under an oxygen atmosphere for quinoline ring formation.[6] In most of these cases, an independent isomerization step is necessary for cyclization. We focused on the reactivity of chalcones with hypervalent iodine reagents for the construction of heterocycles, such as isoflavone derivatives.[7] 2-Hydroxychalcone derivatives was chosen as a substrate and reacted with $PhI(OCOCF_3)_2$ affording the acetal as a rearranged product. The treatment of the acetal with Lewis acid gave the isoflavone derivatives and further transformation led to the natural product, (±)-pterocarpin. Then, we planned to apply this method to *N*-containing heterocycles and investigated the

rearrangement reaction of 2-aminochalcones with hypervalent iodine reagents. The reaction was performed using $PhI(OAc)_2$ and $BF_3{\cdot}Et_2O$ or H_2SO_4 in MeOH, and the rearrangement reaction proceeded depending on the protective group on the amino group (Table 1). With a trifluoroacetyl group on the amino group, the rearranged product was obtained in good yield (Entries 1 and 2). With a benzyloxycarbonyl (Cbz) group, however, no rearranged product was obtained and instead quinoline was formed in good yield (Entry 3). The use of $BF_3{\cdot}Et_2O$ gave better quinoline ring formation than the use of H_2SO_4 (Entries 3 and 4). Next, we conducted this reaction in the absence of $PhI(OAc)_2$, and the quinoline ring was formed in even better yield (Entry 5). The decrease in the equivalent of $BF_3{\cdot}Et_2O$ led to prolongation of the reaction time or a decrease in the yield. Conducting the reaction at room temperature also decreased the yield.

Table 1. Reaction of 2-aminochalcone with $PhI(OAc)_2$ and acid



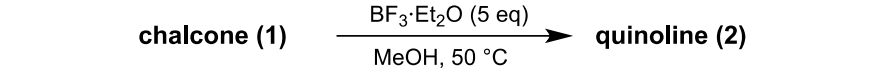
Entry	R	Oxidant	Acid	Acetal (%)	Quinoline (%)
1	$COCF_3$	PIFA	$BF_3{\bullet}Et_2O$	95	-
2	$COCF_3$	PIDA	H_2SO_4	80	-
3	Cbz	PIDA	$BF_3{\bullet}Et_2O$	-	77
4	Cbz	PIDA	H_2SO_4	-	48
5	Cbz	-	$BF_3{\bullet}Et_2O$	-	87

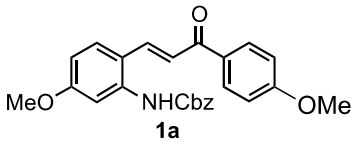
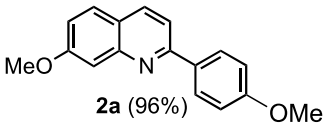
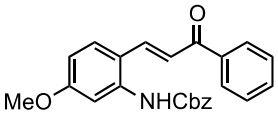
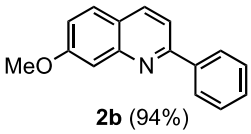
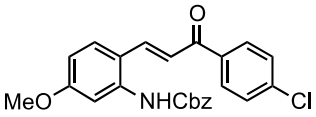
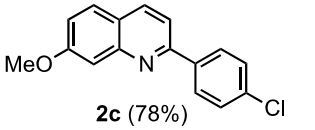
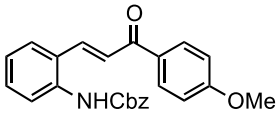
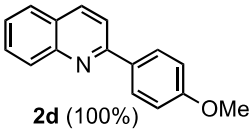
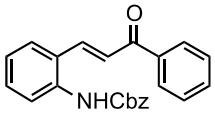
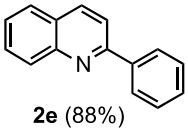
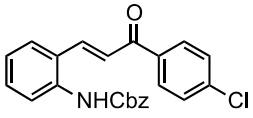
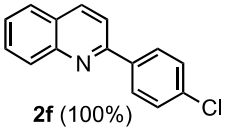
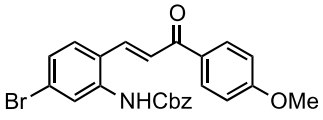
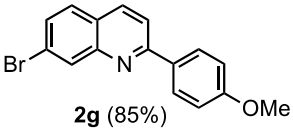
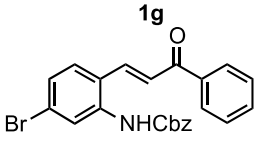
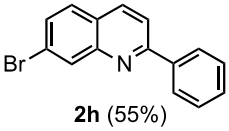
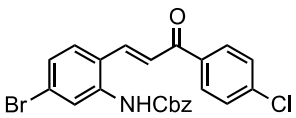
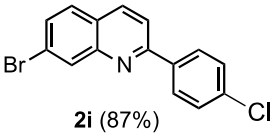
Very recently, Willis and co-workers reported similar transformation of *N*-Boc aminochalcone to quinoline by the treatment with CF_3CO_2H.[8] The feature of their method is the Rh-catalyzed hydroacylation with aldehydes and alkynyl anilines for preparing the aminochalcones. The MeS group is necessary within aldehydes to prevent the side reaction in the hydroacylation and it may limit the scope of substrate.

Next, we examined the generality of the substrate for the quinoline formation reaction under the optimized conditions in hand (Table 2). First, we investigated the reaction of chalcone with the methoxy group on an aniline ring. The reaction of **1a** and **1b**, which have an electron-donating group or a non-substituent on the benzene ring on the benzoyl side, respectively, provided the corresponding quinoline in high yield (Entries 1 and 2). The reaction of **1c**, with chlorine on the benzene ring on the

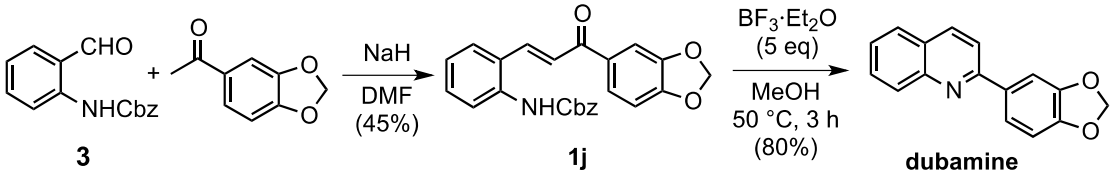
benzoyl side, yielded the quinoline in slightly lower yield (78%) because of its low solubility in MeOH (Entry 3). For chalcones with no substituent on the aniline ring, the reactions successfully proceeded in high yield irrespective of the substituent on the benzene ring on the benzoyl side (Entries 4–6). The chalcones with bromine on the aniline ring underwent the quinoline formation reaction, but the reaction times were longer than for other chalcones. This is because these chalcones have low solubility in MeOH, especially chalcone **1h**, leading to a low yield (55%) after stirring for 5 days.

Table 2. Reaction of 2-aminochalcones to quinolines using $BF_3{\cdot}Et_2O$ in MeOH



Entry	Chalcone	Time	Quinoline (Yield)
1	 **1a**	12 h	 **2a** (96%)
2	 **1b**	3 h	 **2b** (94%)
3	 **1c**	6 h	 **2c** (78%)
4	 **1d**	1 h	 **2d** (100%)
5	 **1e**	1 h	 **2e** (88%)
6	 **1f**	2 h	 **2f** (100%)
7	 **1g**	5 d	 **2g** (85%)
8	 **1h**	5 d	 **2h** (55%)
9	 **1i**	19 h	 **2i** (87%)

Finally, we applied our method to the synthesis of dubamine. Several syntheses of dubamine have been reported, but most of them utilized transition metal-catalyzed cross-coupling reactions,[9] such as a Pd-catalyzed cross-coupling reaction between a halide and boronic acid, tin, and sulfonate, including oxidative coupling. Other methods for synthesizing dubamine without a transition metal catalyst have also been reported,[10] but there are no reports on the synthesis of quinolines from 2-aminochalcones. We reacted *N*-Cbz-protected 2-aminobenzaldehyde **3** and commercial 3,4-methylenedioxyacetophenone giving the corresponding chalcone **1j** in 45% yield. Quinoline formation from **1j** successfully proceeded to afford dubamine in 80% yield.



In conclusion, we developed a novel approach to produce quinolones from *N*-Cbz-protected 2-aminochalcones under BF_3·Et_2O-mediated conditions in good to high yield. A variety of 2-aminochalcones can be synthesized easily from the corresponding 2-aminobenzaldehydes and ketones. Our method with BF_3·Et_2O in MeOH is effective using *N*-Cbz-protected aminochalcones for the cyclization to quinolines, whereas the previous quinoline synthesis from 2-aminochalcones used NIS, I_2, and *hv* for isomerization.

EXPERIMENTAL

Typical procedure for quinoline synthesis by the cyclization of *N*-Cbz-protected 2-aminochalcones with BF_3·Et_2O: At room temperature, BF_3·Et_2O was added to a suspension of chalcone **1** in MeOH, which was then stirred at 50 °C. Saturated aq. $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with water and dried over Na_2SO_4. The combined organic layer was then concentrated under reduced pressure to give a residue, which was purified by silica-gel column chromatography to afford the quinoline derivatives. Compounds **2a**,[11] **2b**,[10f] **2d–f**,[12] **2h**,[13] and dubamine[10b] are known compounds and the spectral data were in full agreement with the reported data.

7-Methoxy-2-(4-methoxyphenyl)quinoline (2a)[11]

a yellow solid; mp 143-145 °C; ^{1}H-NMR($CDCl_3$) δ: 3.89 (3H, s, OMe), 3.98 (3H, s, OMe), 7.04 (2H, d, *J* = 8.8 Hz), 7.15 (1H, dd, *J* = 2.8, 8.8 Hz, H-6), 7.47 (1H, d, *J* = 2.0 Hz, H-8), 7.67-7.70 (2H, m, arom), 8.08-8.12 (3H, m, arom). ^{13}C-NMR($CDCl_3$) δ: 55.3, 55.4, 107.4, 114.1, 116.3, 119.0, 122.0, 128.3, 128.7, 132.4, 136.2, 149.9, 157.1, 160.6, 160.8.

7-Methoxy-2-phenylquinoline (2b)[10f]

a yellow solid; mp 52-54 °C; ^{1}H-NMR($CDCl_3$) δ: 3.98 (3H, s, OMe), 7.18 (1H, dd, *J* = 2.6, 8.6 Hz, H-6), 7.46-7.54 (4H, m, arom), 7.70-7.75 (2H, m, arom), 8.13-8.15 (3H, m, arom). ^{13}C-NMR($CDCl_3$) δ: 55.5, 107.5, 116.8, 119.4, 122.3, 127.4, 128.4, 128.7, 129.1, 136.3, 139.8, 149.9, 157.6, 160.8.

2-(4-Chlorophenyl)-7-methoxyquinoline (2c)

a yellow solid; mp 75-76 °C; ^{1}H-NMR($CDCl_3$) δ: 3.98 (3H, s, OMe), 7.20 (1H, dd, *J* = 2.4, 8.8 Hz, H-6), 7.48-7.50 (3H, m, arom), 7.69-7.72 (2H, m, arom), 8.08-8.15 (3H, m, arom). ^{13}C-NMR($CDCl_3$) δ: 55.5, 107.5, 116.4, 119.7, 122.4, 128.4, 128.7, 128.9, 135.3, 136.5, 138.2, 149.9, 156.2, 161.0. HRMS (EI) *m/z*: Calcd for $C_{16}H_{13}ON^{37}Cl$: 272.0656. Found: 272.0627.

2-(4-Methoxyphenyl)quinoline (2d)[12]

a yellow solid; mp 124-126 °C; ^{1}H-NMR($CDCl_3$) δ: 3.89 (3H, s, OMe), 7.05 (2H, d, *J* = 8.8 Hz), 7.50 (1H, t, *J* = 7.2 Hz), 7.71 (1H, t, *J* = 7.8 Hz), 7.79-7.85 (2H, m, arom), 8.13-8.19 (4H, m, arom).

2-Phenylquinoline (2e)[12]

a yellow solid; mp 83-85 °C; ^{1}H-NMR($CDCl_3$) δ: 7.47-7.55 (4H, m, arom), 7.73 (1H, t, *J* = 7.0 Hz), 7.83 (1H, d, *J* = 8.4 Hz), 7.89 (1H, d, *J* = 8.4 Hz), 8.16-8.24 (4H, m, arom).

2-(4-Chlorophenyl)quinoline (2f)[12]

a yellow solid; mp 101-103 °C; ^{1}H-NMR($CDCl_3$) δ: 7.49-7.56 (3H, m, arom), 7.74 (1H, dt, *J* = 1.5, 7.7 Hz), 7.82-7.86 (2H, m, arom), 8.11-8.14 (3H, m, arom), 8.23 (1H, d, *J* = 8.8 Hz).

7-Bromo-2-(4-methoxyphenyl)quinoline (2g)

a yellow solid; mp 183-185 °C; ^{1}H-NMR($CDCl_3$) δ: 3.89 (3H, s, OMe), 7.05 (2H, d, *J* = 9.2 Hz), 7.57 (1H, dd, *J* = 1.4, 8.6 Hz), 7.66 (1H, d, *J* = 8.8 Hz), 7.84 (1H, d, *J* = 8.8 Hz), 8.12-8.14 (3H, m, arom), 8.32 (1H, d, *J* = 1.6 Hz). ^{13}C-NMR($CDCl_3$) δ: 55.4, 114.2, 118.7, 123.5, 125.4, 128.6, 128.9, 129.3, 131.6, 131.8, 136.4, 148.9, 157.6, 161.0. HRMS (EI) *m/z*: Calcd for $C_{16}H_{12}ON^{81}Br$: 315.0082. Found: 315.0092.

7-Bromo-2-phenylquinoline (2h)[13]

a white solid; mp 125-126 °C; ^{1}H-NMR($CDCl_3$) δ: 7.48-7.56 (3H, m, arom), 7.61 (1H, dd, *J* = 2.0, 8.8 Hz, H-6), 7.69 (1H, d, *J* = 8.8 Hz), 7.90 (1H, d, *J* = 8.4 Hz), 8.12-8.20 (3H, m, arom), 8.37 (1H, d, *J* = 2.0 Hz).

7-Bromo-2-(4-chlorophenyl)quinoline (2i)

a white solid; mp 162-165 °C; ^{1}H-NMR($CDCl_3$) δ: 7.49-7.52 (2H, m, arom), 7.62 (1H, dd, *J* = 1.8, 8.6 Hz), 7.69 (1H, d, *J* = 8.8 Hz), 7.86 (1H, d, *J* = 8.8 Hz), 8.10-8.12 (2H, m, arom), 8.19 (1H, d, *J* = 8.8 Hz), 8.34 (1H, d, *J* = 2.0 Hz). ^{13}C-NMR($CDCl_3$) δ: 118.7, 123.8, 125.7, 128.6, 128.7, 129.0, 129.9, 131.9, 135.9, 136.7, 137.4, 148.7, 156.7. HRMS (EI) *m/z*: Calcd for $C_{15}H_9N^{79}Br^{35}Cl$: 317.9685. Found: 317.9667.

Dubamine[10b]

a yellow solid; mp 93-95 °C; ^{1}H-NMR($CDCl_3$) δ: 6.04 (2H, s, OC*H*$_2$O), 6.95 (1H, d, *J* = 8.0 Hz), 7.50 (1H, t, *J* = 7.4 Hz), 7.65-7.75 (3H, m, arom), 7.78-7.81 (2H, m, arom), 8.13 (1H, d, *J* = 8.8 Hz), 8.18 (1H, d, *J* = 8.8 Hz).

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