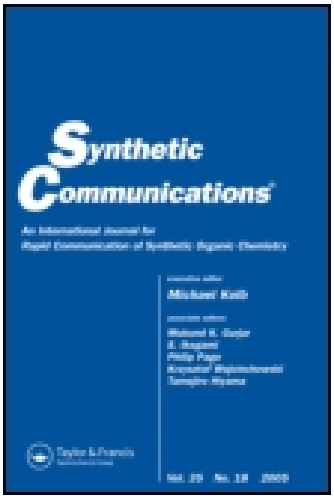

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Efficient One-Pot Synthesis of Hydroxyflavanones by Cyclization and O-Demethylation of Methoxychalcones

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Efficient One-Pot Synthesis of Hydroxyflavanones by Cyclization and *O*-Demethylation of Methoxychalcones

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Abstract: An efficient one-pot method for the synthesis of hydroxyflavanones is described. Methoxychalcones are treated with 36% HBr to afford cyclization and regioselective *O*-demethylation products (**2a**–**i**) while cyclization and complete *O*-demethylation products (**3a**–**e**) are obtained in the presence of 45% HI.

Keywords: Cyclization, *O*-demethylation, hydrobromic acid, hydroiodic acid, hydroxyflavanones, methoxychalcones

INTRODUCTION

Flavanones attract the attention of researchers as physiologically active substances with a wide range of biological activities. They have been found use as radical scavenging agents,[1] inhibitors of nitric oxide production,[2] antiproliferative agents,[3] apoptosis-inducing agents,[4] inhibitors of aromatase,[5] and inhibitors of trypsin.[6] It is also known that flavanones have been used to construct flavonoid-related molecules such as flavones[7] and other heterocyclic compounds.[8] Flavanone is usually obtained by cyclization of 2′-hydroxychalcones in acidic or alkaline media such as acetic acid,[9] sulfuric acid,[3] phosphoric acid,[10] or triethylamine.[11] Sodium

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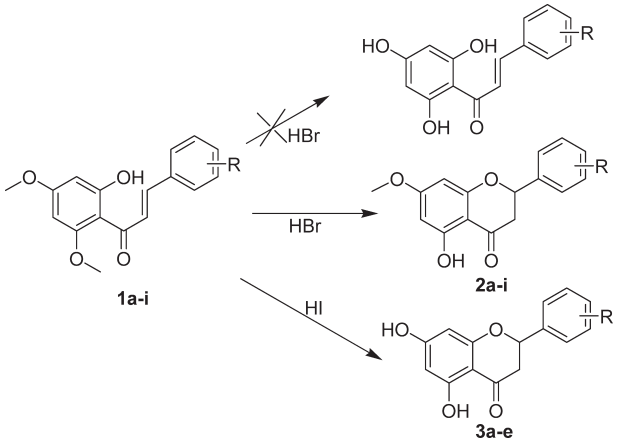
acetate is also used for this purpose.[12] However, these procedures led to low conversions and yields, even prolonging the reaction time. On the other hand, biologically active flavanones always bear free hydroxy groups on the backbone. For synthesis of hydroxyflavanone, it is need to protect free hydroxy groups, followed by deprotection. The regular approaches to synthesis of hydroxyflavanones when using methoxychalcones as starting material use these two steps, cyclization and *O*-demethylation.

In the course of our continuing studies on the antitumor activities of flavonoids,[13] we occasionally found when treating 2-chloro-2′-hydroxy-4′,6′-dimethoxychalcone **1a** with 36% hydrobromic acid, no intented product (2′,4′,6′-trihydroxychalcone) was obtained. Further research revealed that 2′-chloro-5-hydroxy-7-methoxy-flavanone **2a** was the main product (Scheme 1). On the basis of this unexpected result, here we are gratified to report an efficient and convenient method for the cyclization and *O*-demethylation of polymethoxychalcones into corresponding hydroxyflavanones in glacial acetic acid in the presence of hydrogen halide in one pot.

RESULTS AND DISCUSSION

With the discovery of this new route, the cyclization and *O*-demethylation of **1a** were explored. Initial efforts focused on optimizing the proportion of substrate **1a** to 36% hydrobromic acid. The proportions of substrate **1a** to 36% hydrobromic acid were from 1 mmol:0.3 mL to 1 mmol:1.5 mL under refluxing for 1 h. The above reaction was successfully carried out, and better results were obtained when the proportion was 1 mmol:1.2–1.5 mL (Table 1, entries 3 and 4). Also we investigated the duration for the reaction. As can be seen from Table 1, the best yield was achieved when



Scheme 1. Hydrogen halide–mediated direct conversion of methoxychalcones to hydroxyflavanones.

Table 1. Selection of the reaction conditions for preparation of **2a**

Entry	Sub./36% HBr (mmol/mL)	Time (hr)	Yield (%)[a]
1	1:0.3	1	59
2	1:0.6	1	67
3	1:1.2	1	75
4	1:1.5	1	76
5	1:1.2	0.25	69
6	1:1.2	0.5	78
7	1:1.2	1.25	74

[a]Isolated yield.

the proportion of **1a** to 36% hydrobromic acid was 1:1.2 (mmol/mL) with heating for 0.5 h (Table 1, entry 6).

In the presence of 36% hydrobromic acid, the *O*-demethylation sequence was regioselective, yielding 2′-chloro-5-hydroxy-7-methoxyflavanone **2a** only. Otherwise, when 36% hydrobromic acid was replaced by 45% hydroiodic acid, the result of cyclization and *O*-demethylation was slightly different from this, yielding 2′-chloro-5,7-dihydroxyflavanones **3a** as the main product. The optimization of reaction conditions by using 45% hydroiodic acid solution was further investigated (Table 2). When the proportion of **1a** to 45% hydroiodic acid was increasd up to 1:20, the reaction became complicated and the amount of the desired product was reduced. For comparison, the yield was higher when the proportion of **1a** to 45% hydroiodic acid was 1:16 (mmol/mL) with refluxing for 2 h (Table 2, entry 3).

To establish the scope of these two reactions, a number of methoxychalcones were subjected to cyclization and *O*-demethylation in glacial acetic acid in the presence of hydrogen halide, and the results are given in Table 3. As can be seen from Table 3, all methoxychalcones with electron-donating as well as

Table 2. Selection of the reaction conditions for preparation of **3a**

Entry	Sub./45% HI (mmol/mL)	Time (h)	Yield (%)[a]
1	1:8	2	64
2	1:12	2	64
3	1:16	2	68
4	1:20	2	54
5	1:24	2	44
6	1:16	1	61
7	1:16	1.5	63
8	1:16	2.5	67

[a]Isolated yield.

Table 3. Cyclization and *O*-demethylation of methoxychalcones into corresponding hydroxyflavanones

R	Product	Yield (%)[a]	Product	Yield (%)[a]
2-Cl	**2a**	78	**3a**	68
H	**2b**	65	**3b**	60
4-CH_3	**2c**	63	**3c**	71
4-Cl	**2d**	64	**3d**	63
4-$N(CH_3)_2$	**2e**	75	**3e**	73
2-OCH_3	**2f**	43		
4-OCH_3	**2g**	40		
3,4-OCH_2O	**2h**	51		
3-NO_2	**2i**	63		

[a]Isolated yield.

electron-withdrawing substituents except other methoxyl groups on the B ring underwent cyclization and *O*-demethylation smoothly to give their corresponding hydroxyflavanones in 60–78% yields. We also observed that applying 36% hydrobromic acid protocol to substrates with a methoxyl group on the B ring resulted in poor conversions (40–51%). The desired products (**3f**–**h**) could not be obtained in the presence of 45% hydroiodic acid. We speculated that the main product was a dehydrated product of two molecules of hydroxyflavanone (see attachment 1) after further research. As for compound **3i**, which has nitro group on B ring, we also could not get it, because the reaction mixture was easy to turn brown and black and might form polymers.

CONCLUSIONS

In conclusion, we have elaborated an efficient and convenient method for the one-pot synthesis of hydroxyflavanones. It is noteworthy that when using methoxychalcones as starting materials, cyclization and regioselective *O*-demethylation products are yielded using 36% hydrobromic acid, whereas cyclization and complete *O*-demethylation products are obtained in the presence of 45% hydroiodic acid. Compared with other synthetic methods, this protocol has the advantage of an easy workup, more efficient cyclization and *O*-demethylation procedures, and moderate to high yields in a one-pot synthesis of hydroxyflavanones.

EXPERIMENTAL

Reagents and solvents were commercially available and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker

Advance DMX 400-MHz spectrometer with $SiMe_4$ as the internal standard in DMSO-d_6. Melting points were determined on a B-540 Buchi melting-point apparatus and are uncorrected. Infrared spectra were recorded on a Bruck Vector 200 spectrophotometer (Brucker Optic GmbH, Germany). Electrospray ionization mass spectrometry (ESI) were measured on a Esquire-LC-00075 spectrometer (Germany). Column chromatography was performed on silica gel (200–300 mesh).

Representative Procedure for Preparation of 2a

To a solution of chalcones **1a** (1 mmol) in glacial acetic acid (20 mL), 36% HBr solution (1.2 mL) was added. The mixture was refluxed under N_2 for 30 min. After the reaction mixture was cooled to room temperature, solvent was evaporated in vacuo. Water (30 mL) was added to the residue, and the mixture was neutralized to pH 7 with saturated sodium bicarbonate solution. The solution was extracted with dichloromethane (20 mL × 3) and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. The crude product was further purified by column chromatography on silica gel with petroleum ether and acetone (30:1) as eluent to give hydroxyflavanones **2a**.

Data for **2a**

White crystalline solid, mp 120–123 °C. IR (KBr): 3053, 2924, 2852, 1664, 1575, 1442, 1304, 1191, 1157, 1092, 745 cm^{-1}; ESI-MS: 305 (M + 1); ^1H NMR (400 MHz, DMSO-d_6): δ 12.11 (s, 1H, 5-OH), 7.78 (d, 1H, $J = 7.6$ Hz, Ar-3′-H), 7.49–7.41 (m, 3H, Ar-4′-H, 5′-H and 6′-H), 6.18 (s, 1H, 8-H), 6.16 (s, 1H, 6-H), 5.90 (dd, 1H, $J = 13.2$ Hz, 2.8 Hz, 2-H), 3.90 (s, 3H, OCH_3), 3.02–2.98 (m, 2H, 3-Ha and 3-Hb); ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.8 (C═O), 168.3 (C-7), 164.2 (C-8a), 160.4 (C-5), 136.1 (C-1′), 131.5 (C-2′), 129.7 (C-3′), 129.6 (C-4′), 127.4 (C-6′), 127.0 (C-5′), 103.9 (C-4a), 102.5 (C-6), 92.8 (C-8), 66.4 (C-2), 56.0 (O-CH_3), 45.7 (C-3).

Representative Procedure for Preparation of 3a

To a solution of chalcones **1a** (1 mmol) in glacial acetic acid (20 mL), 45% HI solution (16 mL) was added. The reaction mixture was refluxed under N_2 for 2 h. After the reaction mixture was cooled to room temperature, solvent was evaporated in vacuo. Water (25 mL) was added to the residue and neutralized to pH 7 with saturated sodium bicarbonate solution. The solution was extracted with dichloromethane (20 mL × 3) and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated.

The crude product was further purified by column chromatography on silica gel with petroleum ether and acetone (10:1) as eluent to give hydroxyflavanones **3a**.

Data for **3a**

White crystalline solid, mp 270–272 °C. IR (KBr): 3117, 3017, 2924, 2850, 1637, 1601, 1577, 1481, 1303, 1168, 1089, 761 cm^{-1}; ESI-MS: 291 (M + 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.12 (s, 1H, 5-OH), 10.80 (s, 1H, 7-OH), 7.75 (d, 1H, $J = 7.6$ Hz, Ar-3′-H), 7.45-7.41 (m, 3H, Ar-4′-H, 5′-H and 6′-H), 6.01 (s, 1H, 8-H), 5.99 (s, 1H, 6-H), 5.67 (dd, 1H, $J = 13.2$ Hz, 2.8 Hz, 2-H), 3.12–3.08 (m, 2H, 3-Ha and 3-Hb); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 196.4 (C═O), 162.5 (C-7), 161.0 (C-8a), 159.4 (C-5), 137.1 (C-1′), 130.5 (C-2′), 129.1 (C-3′), 128.9 (C-4′), 128.0 (C-6′), 126.6 (C-5′), 102.7 (C-4a), 94.5 (C-6), 93.8 (C-8), 66.7 (C-2), 47.5 (C-3).

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