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K_2CO_3-Catalyzed Synthesis of Chromones and 4-Quinolones through the Cleavage of Aromatic C−O Bonds

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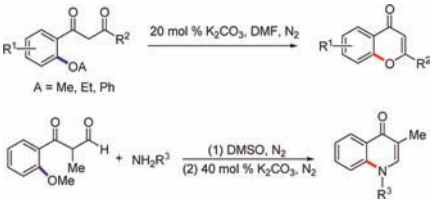
ABSTRACT



Phenol-derived electrophiles are favorable substrates because phenols are naturally abundant or can be readily prepared from other aromatic compounds. However, the cleavage of aromatic C−O bonds is a great challenge because of their high energy. K_2CO_3-catalyzed intramolecular cyclization of 1-(2-alkoxyphenyl)-3-akylpropane-1,3-dione and 3-(alkylimino)-1-(2-methoxyphenyl)-2-methylpropan-1-one derivatives via the selective cleavage of aromatic C−O bonds is reported. The corresponding chromone and 4-quinolone derivatives were obtained in reasonable yields.

Transition-metal-catalyzed aromatic nucleophilic substitutions are ubiquitous in modern organic synthesis,[1] and most of the reactions use aryl halides as electrophiles because of their high reactivity.[2] However, aryl halides are far less available from natural sources, and they are certainly not used as coupling partners in biosynthesis pathways.[3] In addition, some drawbacks accompany the reactions by using aryl halides as electrophiles. For example, aryl halides and halide byproducts are environmentally unfriendly, and some of aryl halides are often unavailable and difficult to prepare. Therefore, it is highly desirable to develop some alternatives of aryl halides. Phenol-derived electrophiles are favorable substrates because phenols are naturally abundant or can be readily prepared from other easily accessed aromatic species, and over 50000 phenol derivatives are commercially available.[3,4] However, the cleavage of aromatic C−O bonds often is not easy because of a higher aryl C−O bond energy relative to C−X (X = Cl, Br, I) bonds in aryl halides.[5] Therefore, activations of C−O bonds in phenols are required. Typically, phenols are converted into corresponding sulfonates,[6] sulfamates,[7] phosphates,[8] carboxylates,[9] and carbamates[10] to improve cleavage of aromatic C−O bonds together with assistance

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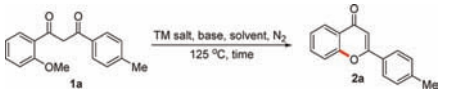
of expensive transition metals. Recently, the selective cleavage of aromatic C−O bonds from alkyl aryl ethers has been investigated in the presence of transition metals,[11] particularly nickel catalysts.[12] Herein, we report base-catalyzed synthesis of chromone and 4-quinolone derivatives via selective cleavage of aromatic C−O bonds.

As shown in Table 1, intramolecular cyclization of 1-(2-methoxyphenyl)-3-*p*-tolylpropane-1,3-dione (**1a**) to 2-*p*-tolyl-4*H*-chromen-4-one (**2a**) was chosen as the model reaction to optimize the reaction conditions including transition-metal salts, bases, and solvents under nitrogen atmosphere. Four solvents were tested in the presence of highly pure K_2CO_3 (here, K_2CO_3 with 99.997% purity was used from Alfa Aesar Co.[13] in order to avoid the involvement of other metals in the reaction) (entries 1−4), and DMSO (entry 1) and DMF (entry 2) gave better results. DMF provided the highest yield (95%). The effect of bases was investigated (entries 5−8), and K_2CO_3 provided the highest efficiency (compare entries 2, 5−8). Interestingly, organic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), also afforded the target product (**2a**) in 71% yield (entry 8), and use of the organic base further avoided involvement of other metals. The solvent in the resulting solution of entry 2 was removed, the residue was determined by inductively coupled plasma mass spectroscopy (ICP-MS), and only trace amounts of Ni (8.41 ppm), Pd (1.98 ppm), Rh (0.47 ppm), Ru (0.63 ppm), and Cu (2.52 ppm) were found. We changed the amount of K_2CO_3 (entries 9−11), and a small amount of K_2CO_3 also afforded the target product (**2a**) in higher yields. The results showed that K_2CO_3 acted as the catalyst in this reaction. When volume of DMF was changed to 1 mL from 2 mL, a 86% yield was provided (entry 11). The reaction under air gave a low yield (17%) with some byproduct appearing (entry 12). We attempted cyclization of 1-(2-methoxyphenyl)-3-*p*-tolylpropane-1,3-dione (**1a**) in the presence of different transition-metal salts, and the results showed that addition of these transition-metal salts decreased the efficiency of this reaction (entries 13−15). Therefore, the standard reaction condition for the base-catalyzed synthesis of chromone derivatives is as follows: 20 mol % of K_2CO_3 as the catalyst and DMF as the solvent under nitrogen atmosphere.

Table 1. Intramolecular Cyclization of 1-(2-Methoxyphenyl)-3-*p*-tolylpropane-1,3-dione (**1a**) to 2-*p*-Tolyl-4*H*-chromen-4-one (**2a**): Optimization of Conditions[a]



entry	tm salt[b]	base (equiv)	solvent	time (h)	yield[c] (%)
1		K_2CO_3 (1)	DMSO	24	90
2		K_2CO_3 (1)	DMF	24	95
3		K_2CO_3 (1)	1,4-dioxane	24	trace
4		K_2CO_3 (1)	NMP	24	57
5		Cs_2CO_3 (1)	DMF	24	81
6		K_3PO_4 (1)	DMF	24	64
7		KOH (1)	DMF	24	18
8		DBU (1)	DMF	24	71
9		K_2CO_3 (0.8)	DMF	40	88
10		K_2CO_3 (0.4)	DMF	40	86
11		**K_2CO_3 (0.2)**	**DMF**	**40**	**84 (86[d])**
12		K_2CO_3 (0.2)	DMF	40	17[d,e]
13	CuI	K_2CO_3 (0.2)	DMF	40	68[d]
14	$NiCl_2$	K_2CO_3 (0.2)	DMF	40	73[d]
15	$Pd(OAc)_2$	K_2CO_3 (0.2)	DMF	40	5[d]

[a] Reaction conditions: 1-(2-methoxyphenyl)-3-*p*-tolylpropane-1,3-dione (0.5 mmol), base (0.5 mmol), solvent (2 mL), tm salt (no addition of tm salt for entries 1−16; 0.05 mmol for 17−20) under nitrogen atmosphere in a sealed Schlenk tube. Reaction temperature (125 °C). Reaction time (24 or 40 h). [b] tm = transition metal. [c] Isolated yield. [d] Solvent (1 mL). [e] Under air.

We investigated the substrate scope of the base-catalyzed intramolecular cyclization. As shown in Table 2, the examined substrates provided good to excellent yields. For substituent R^1, the substrates with electron-withdrawing groups showed higher reactivity than those with electron-donating groups (compare entries 2−5). For substituent R^2, the substrates containing electron-donating groups on aromatic rings provided higher yields than those containing electron-withdrawing and neutral groups on aromatic rings, and the reactivity decreased when R^2 was an aliphatic alkyl (entry 6). In general, the intramolecular cyclization afforded slightly lower yields when 2-methoxyl was replaced with 2-ethanoxyl (entry 7) or 2-phenoxyl (entries 8−12). It is well-known that the chromone derivatives are important natural products and have exhibited various biological and medicinal activities,[14] and the acid-catalyzed synthesis of chromones is a common strategy via the reaction of 1-(2-hydroxyphenyl)-3-akylpropane-1,3-dione derivatives.[15] The present base-catalyzed intramolecular nucleophilic substitution is a transition-metal-free process, and this transition-metal-free method solves the problem that trace amount of toxic transition-metals remained in the

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(13) K_2CO_3 (99.997%), Mg (2 ppm), Na (8 ppm), other elements including Al, Sb, As, Ba, Bi, B, Cd, Ca, Cr, Co, Cu, In, Fe, Pb, Li, Mn, Mo, Ni, P, Si, Te, Sn, Ti, V, Zn, Zr (sought but not detected) (the data were provided by Alfa Aesar Co.).

(14) (a) Havsteen, B. H. *Pharmacol. Ther.* **2002**, *96*, 67–202. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930. (c) deAzevedo, W. F.; Mueller-Dieckmann, H. J.; Schulze-Gahmen, U.; Worland, P. J.; Sausville, E.; Kim, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 2735–2740.

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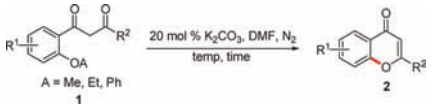
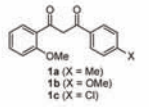
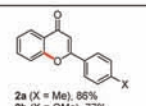
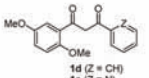
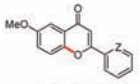
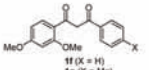
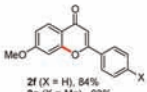
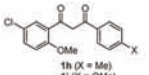
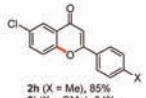
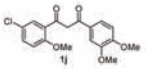
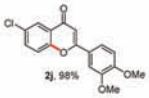
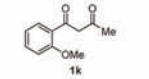
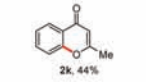
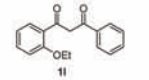
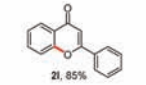
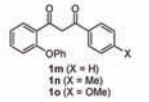
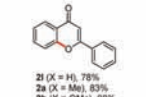
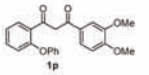
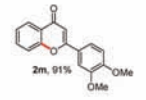
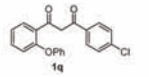
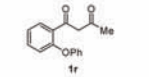
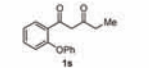
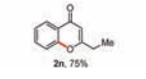
Table 2. K_2CO_3-Catalyzed Intramolecular Cyclization Leading to Chromone Derivatives[a]



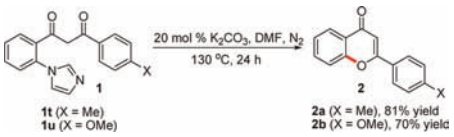
entry	1	temp (°C)	time (h)	2, yield[b]
1	 1a (X = Me) 1b (X = OMe) 1c (X = Cl)	125 (for 1a) 125 (for 1b) 125 (for 1c)	40 (for 1a) 24 (for 1b) 40 (for 1c)	 2a (X = Me), 86% 2b (X = OMe), 77% 2c (X = Cl), 82%
2	 1d (Z = CH) 1e (Z = N)	160 (for 1d) 160 (for 1e)	48 (for 1d) 48 (for 1e)	 2d (Z = CH), 75% 2e (Z = N), 61%
3	 1f (X = H) 1g (X = Me)	160 (for 1f) 160 (for 1g)	48 (for 1f) 48 (for 1g)	 2f (X = H), 84% 2g (X = Me), 93%
4	 1h (X = Me) 1i (X = OMe)	125 (for 1h) 125 (for 1i)	40 (for 1h) 24 (for 1i)	 2h (X = Me), 85% 2i (X = OMe), 94%
5	 1j	125	31	 2j, 98%
6	 1k	125	31	 2k, 44%
7	 1l	160	48	 2l, 85%
8	 1m (X = H) 1n (X = Me) 1o (X = OMe)	125 (for 1m) 125 (for 1n) 125 (for 1o)	24 (for 1m) 34 (for 1n) 24 (for 1o)	 2l (X = H), 78% 2a (X = Me), 83% 2b (X = OMe), 98%
9	 1p	125	24	 2m, 91%
10	 1q	125	24	2c, 88%
11	 1r	125	24	2k, 70%
12	 1s	125	24	 2n, 75%

[a] Reaction conditions: dione (**1**) (0.5 mmol), K_2CO_3 (0.1 mmol), DMF (1 mL) under nitrogen atmosphere in a sealed Schlenk tube. [b] Isolated yield.

final target products after purification by the previous isolation procedures. Therefore, the present transition-metal-free and aryl-halide-free base-catalyzed method is environmentally friendly.

Similarly, we attempted intramolecular cyclization of 1-(2-(1*H*-imidazol-1-yl)phenyl)-3-*p*-tolylpropane-1,3-dione

Scheme 1. K_2CO_3-Catalyzed Intramolecular Cyclization of Substituted 1-(2-(1*H*-Imidazol-1-yl)phenyl)-3-phenylpropane-1,3-diones Leading to Flavones



(**1t**) and 1-(2-(1*H*-imidazol-1-yl)phenyl)-3-(4-methoxyphenyl)propane-1,3-dione (**1u**), and the corresponding chromones **2a** and **2b** were obtained in 81 and 70% yields, respectively (Scheme 1). In the previous organic synthesis, aromatic compounds with nitrogen-containing groups as leaving groups were limited. For example, diazo compounds were used as electrophiles,[16] but preparation of the diazo compounds needed environmentally unfriendly HNO_2 as the partner. In addition, aryl ammonium salts were also applied in the coupling reactions, and transition-metal catalysts were required.[17] It is well-known that cleavage of the aromatic C−N bonds in neutral arylamines is very difficult, so the present finding is different from traditional aromatic nucleophilic substitution reactions.

In our previous research on the synthesis of chromone derivatives from substituted 1-(2-halophenyl)-3-*p*-tolylpropane-1,3-diones,[18] we performed various control experiments in order to explore the base-mediated mechanism. The results showed that the substrates containing 2-bromo or chloro almost exhibited similar reactivity. Here, alkoxyl and 1*H*-imidazol-1-yl were used as the leaving groups, and the reactions worked well. Obviously, the present reaction mechanism is different from the traditional nucleophilic substitution reactions of aryl C−X (X = halo and their alternates). A possible mechanism on the base-catalyzed intramolecular nucleophilic substitutions of **1** leading to chromone derivatives (**2**) is proposed in Scheme 2. Enolization of the α-carbonyl group in **1** leads to intermediate **I** in the presence of base (K_2CO_3), and intrmolecular cycloaddition of **I** gives **II**. Rearomatization of **II** by elimination of KY provides the target product (**2**). Treatment of KY with $KHCO_3$ regenerates K_2CO_3 leaving HY.

Inspired by the excellent results above, we investigated reactions of 3-(2-methoxyphenyl)-2-methyl-3-oxopropanal with primary amines leading to 4-quinolone derivatives (See Table 3). The whole process was divided into two steps: coupling of aldehyde with primary amine first formed imine intermediate, 3-(alkylimino)-1-(2-methoxyphenyl)-2-methylpropan-1-one (**III**), and then intramolecular cyclization of the imine yielded 4-quinolone derivative (see Scheme 3). Formation of imines was performed in DMSO

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Scheme 2. Possible Mechanism on Base-Catalyzed Intramolecular Cyclization of **1** Leading to Chromone Derivative (**2**)

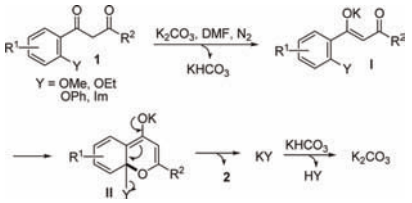
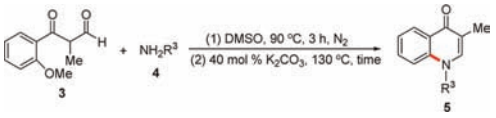
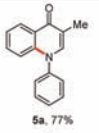
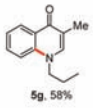
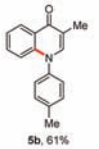
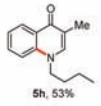
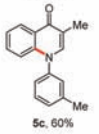
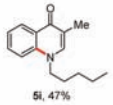
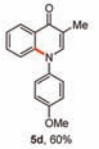
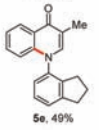
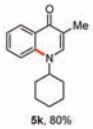
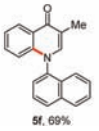
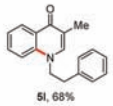


Table 3. Reactions of 3-(2-Methoxyphenyl)-2-methyl-3-oxopropanal with Primary Amines Leading to 4-Quinolone Derivatives under Catalysis of K_2CO_3[a]

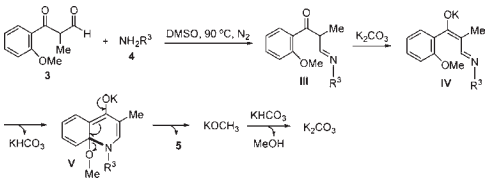


entry	time (h)	5, yield[b]	entry	time (h)	5, yield[b]
1	48	 5a, 77%	7	24	 5g, 58%
2	48	 5b, 61%	8	24	 5h, 53%
3	48	 5c, 60%	9	24	 5i, 47%
4	48	 5d, 60%	10	24	 5j, 58%
5	48	 5e, 49%	11	24	 5k, 80%
6	48	 5f, 69%	12	24	 5l, 68%

[a] Reaction conditions: 3-(2-methoxyphenyl)-2-methyl-3-oxopropanal (**3**) (0.5 mmol), amine (**4**) (0.55 mmol), K_2CO_3 (0.2 mmol), DMSO (1 mL) under nitrogen atmosphere in a sealed Schlenk tube. [b] Isolated yield.

at 90 °C under nitrogen atmosphere. After completeness of imine formation (TCL determination) (about 3 h), 40 mol % K_2CO_3 was added to the resulting solution, and the following reaction was carried out at 130 °C under nitrogen atmosphere. To our delight, the corresponding 4-quinolone derivatives were obtained in moderate yields. Both aromatic and aliphatic amines were effective in the reactions, and no evident difference was observed. As chromone derivatives, 4-quinolone derivatives were of biological and medicinal function.[19] Therefore, the present method will find wide application in chemistry, biology, and medicine.

Scheme 3. Possible Mechanism on Coupling of **3** with **4** Followed Intramolecular Cyclization under Base-Catalysis Leading to 4-Quinolone Derivative (**5**)



According to the previous results, a possible mechanism for synthesis of 4-quinolone derivatives is suggested in Scheme 3. Reaction of aldehyde **3** with primary amine **4** provides imine **III**, and then enolization of carbonyl group in **III** leads to **IV** in the presence of base (K_2CO_3). Intramolecular cycloaddition of **IV** gives **V**. Rearomatization of **V** by elimination of $KOCH_3$ provides the target product **5**. Treatment of $KOCH_3$ with $KHCO_3$ regenerates K_2CO_3 leaving CH_3OH.

In summary, we have developed a convenient and efficient base-catalyzed method for synthesis of chromone and 4-quinolone derivatives. The protocol uses K_2CO_3 as the catalyst, readily available substituted 1-(2-alkoxyphenyl)-3-akylpropane-1,3-diones 3-(2-methoxyphenyl)-2-methyl-3-oxopropanal, and primary amines as the starting materials, the reactions underwent the selective cleavage of the aromatic C−O bonds, and the corresponding chromone and 4-quinolone derivatives were obtained in reasonable yields. The method did not need the aid of any transition metal which avoided contamination of toxic metals to the products. Thus, the inexpensive and environmentally benign approaches to heterocycles will find wide application and attract much attention in academic and industrial research.

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Note Added after ASAP Publication. Errors were corrected in Table 3, Scheme 3, TOC/Abstract graphic; this reposted May 17, 2012.

Supporting Information Available. Synthetic procedures, characterization data, and ^1H and ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org. The authors declare no competing financial interest.

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The authors declare no competing financial interest.