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An efficient synthesis of 4-chromanones

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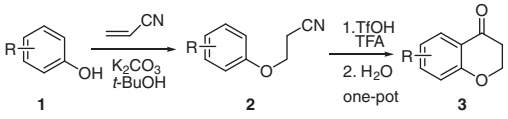
ABSTRACT

A two step efficient and practical synthesis of a variety of 4-chromanones is described. Phenols undergo a Michael addition to acrylonitriles in the presence of catalytic amounts of potassium carbonate and *tert*-butanol to generate the corresponding 3-aryloxypropanenitriles in 50–93% yields. Treatment of the resulting aryloxypropionitriles with 1.5 equiv of TfOH and 5 equiv of TFA, followed by an aqueous work up afforded 4-chromanones in moderate to excellent yields.

The synthesis of chromanones is of great interest in the field of organic chemistry because they exhibit a wide variety of well-documented biological activity,[1] including antiviral,[2] antimicrobial,[3] antiarrhythmic,[4] and antidiabetic.[5] The preparation of chromanone was conventionally carried out by intramolecular acylation of β-phenoxyproprionic acids in the presence of strong Brønsted acids[6] or by a Fries rearrangement followed by intramolecular cyclization.[7] Methods reported in the literature for the preparation of chromanones involve Friedel–Crafts acylation followed by intramolecular cyclization using base[8]; Friedel–Crafts acylation involving an enone and phenol followed by a cesium fluoride catalyzed Michael addition[9]; Friedel–Crafts acylation of 3-aryloxypranoic esters in the presence of strong Brønsted acids[10]; condensation of phenol with a Meldrum's acid derivative in the presence of $Yb(OTf)_3$.[11] These methods, however, only give moderate yield of 4-chromanones, and hence a more general and efficient method for preparing 4-chromanones in high yield needs to be developed.

In 2001, Colquhoun[12] reported a two-step synthesis of dixanthones by cyclization of 2-aryloxybenzonitriles via intramolecular superacid-promoted Houben–Hoesch reaction.[13] This two step sequence required a large amount of expensive trifluoromethanesulfonic acid (40 equiv) and prolonged reaction time (5 days) to afford xanthone–iminium triflates in about 81% yield. The resulting iminium triflates were hydrolyzed in 75% sulfonic acid under reflux conditions for 24 h and provided the dixanthones in only 18% yield as shown in the few examples reported. Reinvestigating for the feasibility of the protocol, we found that the intramolecular Houben–Hoesch reaction of 3-aryloxypropanenitriles could be highly efficient using only 1.5 equiv of trifluoromethanesulfonic acid and 5 equiv of trifluoroacetic acid, followed by aqueous work up at room temperature in a one-pot protocol and provided the corresponding desired 4-chromanones in excellent yield. Herein we wish to report this mild, practical, and general synthetic protocol for the preparation of 4-chromanones (Scheme 1).

The synthetic sequence starts from the Michael addition of phenols **1** to acrylonitrile. Oxa-Michael addition reactions of **1** to acrylonitrile have been widely reported for decades. The reaction was generally promoted by sodium,[14] sodium methoxide, and sodium *tert*-butoxide,[15] potassium hydride,[16] potassium *tert*-butoxide,[17] Triton B or benzyltrimethylammonium hydroxide,[18] potassium hydroxide,[19] and trialkylphospine.[20] However, these conditions have their limitations such as low to moderate yields, incompatibility with some functional groups, restrictions in some Michael acceptors, and requirement of chromatographic purification. After screening conditions for the Michael addition, we found that conducting the addition in acrylonitrile under reflux in the presence of potassium carbonate and *tert*-butanol gave the best results in terms of conversion, purification/isolation, and yield.



Scheme 1.

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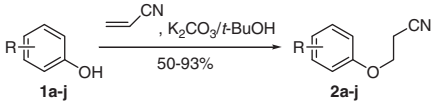
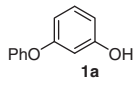
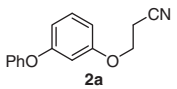
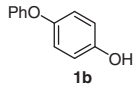
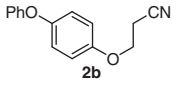
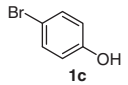
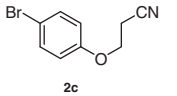
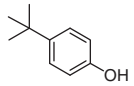
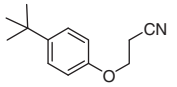
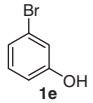
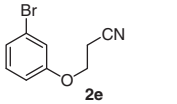
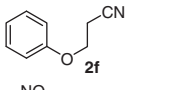
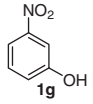
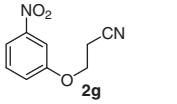
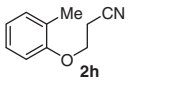
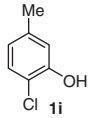
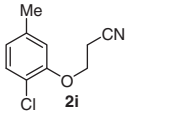
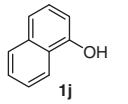
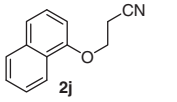
Further optimization of the reaction defined the optimal conditions: treatment of 1 equiv of the phenols **1a–1j** with 10 equiv of acrylonitrile in the presence of 10 mol % of potassium carbonate and 10 mol % of *tert*-butanol under reflux for 24–36 h.

Isolation of the Michael adducts and recovery of the excess acrylonitrile was fairly straightforward. The reaction mixture was cooled to room temperature and quenched with 0.08 equiv of phosphoric acid and concentrated to recover the excess acrylonitrile. It is worthwhile to note that without quenching the potassium carbonate, adducts **2a–2j** generally reversed back to phenols **1a–1j** and acrylonitrile during concentration. The resulting crude 3-aryloxypropanenitriles **2a–2j** were diluted with toluene, which was washed with 1 N NaOH (aq)/DMSO (4:1, 2×) and 10 wt % of phosphoric acid (1×). The organic layer was concentrated to give analytically pure 3-aryloxypropanenitriles **2**. As shown in Table 1, a variety of phenols **1a–j**, including those with a simple phenyl ring (entry 6), electron rich substituted phenols (entries 1–2, 4 and 8), halogen-substituted phenols (entries 3, 5, and 9), electron deficient phenol (entry 7), and a naphthalenol (entry 10) reacted with acrylonitrile smoothly to provide 3-aryloxypropanenitriles **2a–j** in good to excellent yields (Table 1).[21]

Table 1
Preparation of 3-aryloxy propanenitriles **2a–2j**



1a-j 2a-j

Entry	Substrate	Michael addition product	Isolated yield (%)
1	 1a	 2a	83
2	 1b	 2b	81
3	 1c	 2c	70
4	 1d	 2d	93
5	 1e	 2e	50
6	 1f	 2f	87
7	 1g	 2g	53
8	 1h	 2h	89
9	 1i	 2i	52
10	 1j	 2j	92

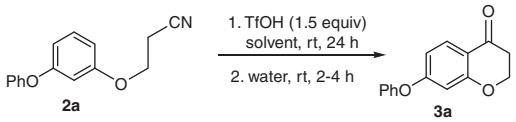
With the desired 3-aryloxypropanenitriles **2a–j** in hand, a one-pot protocol for the synthesis of 4-chromanones was investigated. Our initial studies involved the treatment of 1 equiv of 3-(3-phenoxyphenoxy)propanenitrile **2a** with 1.5 equiv of trifluoromethanesulfonic acid in a variety of solvents (Table 2) at room temperature for 24 h followed by hydrolysis of the resulting iminium triflates by the addition of 10 equiv of water at room temperature. Without solvent, the reaction gave 86% conversion and 74% yield of the desired chromanone **3a** (entry 1). In organic solvents typical for the Friedel–Crafts reaction, for example, dichloromethane (entry 2), toluene (entry 3), chlorobenzene (entry 4) and 1,2-dichloroethane (entry 5), 72–90% of **2a** was consumed and provided 60–79% of the desired product **3a**. The cyclization didn't occur in 85% phosphoric acid while the starting material **2a** was fully recovered (entry 8). Substrate **2a** completely decomposed in 96% sulfonic acid (entry 7). To our delight, the cyclization gave full conversion in either trifluoroacetic acid or methanesulfonic acid with the desired product **3a** obtained in 97% and 90% yield, respectively (entries 6 and 9).

The scope of this new protocol was investigated and all substrates shown in Table 1 were converted to 4-chromanones **3a–3j** in 11–98% yield (Table 3). In the optimized conditions, substrates were dissolved in 5 equiv of trifluoroacetic acid, and then, 1.5 equiv of TfOH was added dropwise at 0–5 °C. The cyclization of 3-aryloxy-propanenitriles **2a–2j** to iminium triflate intermediates was typically completed after stirring at 0–5 °C and at room temperature for 16–24 h, and the subsequent hydrolysis of imini um triflates to 4-chromanones **3a–3j** was achieved at room temperature in one-pot protocol via the addition of 2 equiv of water.[22]

Employing the above protocol, a variety of 3-aryloxypropanenitriles **2a–2j** was converted to 4-chromanones **3a–3j**. Functional groups such as bromo, chloro, phenoxy, and alkyl were well tolerated under the reaction conditions. Interestingly, an electron-donating group at the meta-position (entry 1) gave high selectivity and excellent yield of product **3a**. However, a bromo substituted group at the meta-position (entry 5) gave ~1:1 mixture of chromanoes **3e–4e**. As expected, substitution at the aromatic ring with strong electron-withdrawing group (entry 7) afforded low yield of product **3g**. 3-(Naphthalen-1-yloxy)propanenitrile **2j** was also efficiently converted to 4-chromanones **3j** in good yield.

In summary, we have developed a practical, efficient, and scalable one-pot synthesis of a variety of 4-chromanones by cyclization of 3-aryloxypropanenitriles via intramolecular superacid-promoted Houben–Hoesch reaction. The reaction proceeds under mild conditions and produces 4-chromanones in excellent purity with yields ranging from 11% to 98%. Additionally, we developed a practical protocol for the preparation of 3-aryloxy-propanenitriles via the Oxa-Michael addition reactions of phenols to

Table 2
Solvent effect for the TfOH-mediated Friedel–Crafts reaction

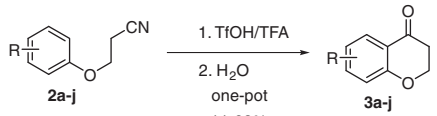


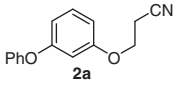
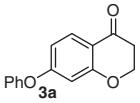
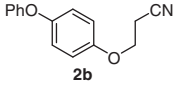
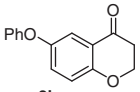
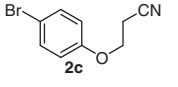
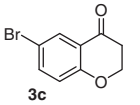
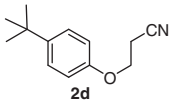
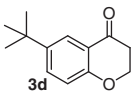
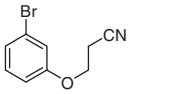
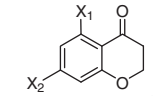
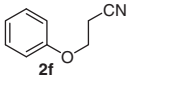
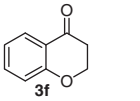
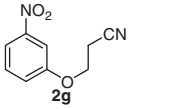
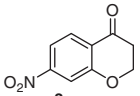
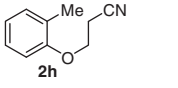
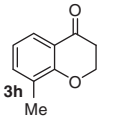
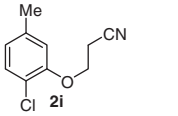
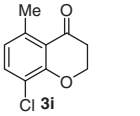
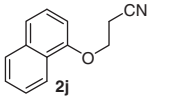
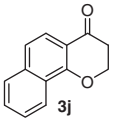
2a 3a

Entries	Solvent	Conversion (%)	Assay yield (%)*
1	Neat	86	74
2	Dichloromethane	83	73
3	Toluene	75	62
4	Chlorobenzene	90	79
5	1,2-Dichloroethane	72	60
6	Trifluoroacetic acid	100	97
7	96% sulfonic acid	100	0
8	85% phosphonic acid	0	0
9	Methanesulfonic acid	100	90

* The assay yield was measured by HPLC against to standard.

Table 3
Preparation of chromanones **3a–3j** via Friedel–Crafts reaction



Entry	Substrate	Chromanone	Isolated yield
1	 **2a**	 **3a**	95
2	 **2b**	 **3b**	90
3	 **2c**	 **3c**	58
4	 **2d**	 **3d**	85
5	 **2e**	 **3e**: X_1 = H, X_2 = Br (47%) **4e**: X_1 = Br, X_2 = H (53%)	73
6	 **2f**	 **3f**	85
7	 **2g**	 **3g**	11
8	 **2h**	 **3h**	98
9	 **2i**	 **3i**	98
10	 **2j**	 **3j**	60

acrylonitrile. We believe that the facile methodology will find applications in the fields of organic and medicinal chemistry.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.018.

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21. *General procedure for the preparation of 3-aryloxypropanenitriles* **2a–2j***:* To a 250 mL 3-necked round-bottomed flask, equipped with an overhead stirrer, thermocouple, water-cooled condenser, and nitrogen inlet, was charged aryl phenol (8.90 mmol) and acrylonitrile (58.6 mL, 890 mmol), 5 mol % potassium carbonate (0.62 g, 4.45 mmol), and 10 mol % of *tert*-butanol (0.66 g, 8.90 mmol). The resulting slurry was refluxed for 8 h. The remaining 5 mol % of potassium carbonate(0.62 g, 4.45 mmol) was added to the reaction mixture. After being stirred in reflux for 36 h, the reaction mixture was cooled to rt, and 8 mol % of 85% phosphorous acid (0.82 g,7.12 mmol) was added, and stirred for 0.5 h. The excess acrylonitrile was distilled off under atmospheric pressure. The resulting oily crude product was diluted with toluene (75 mL).The solution was washed with 1 N NaOH (aq)/DMSO (4:1,80 mL × 1). After phase separation, the aqueous layer was extracted with toluene (25 mL). The combined organic layers were washed with 1 N NaOH (aq)/DMSO (4:1, 20 mL × 2),and 10 wt % phosphorous acid (10 mL × 1). The organic layer was concentrated and dried under vacuum to give desired 3-aryloxypropanenitriles **2a–2j** in 50–93% yield (typical ⩾95%purity).
22. *General procedure for the preparation of 4-chromanones* **3a–3j***:* To a 25 mL 2-necked round-bottomed flask, equipped with thermocouple and nitrogen inlet, was charged 3-aryloxypropanenitriles **2a–2j** (12.6 mmol) in 5 equiv of TFA(4.86 mL, 63.0 mmol) solution. To the resulting solution was slowly added 1.5 equiv of TfOH (1.67 mL, 17.7 mmol) at 0–5 °C. The resulting solution was stirred at 0 °C for 5 h, and then at ambient temperature for 16–24 h until the conversion of the reaction was >99%. The reaction mixture was cooled to 0 °C. Then, 2 equiv of water (0.41 mL, 25.2 mmol) was added dropwise at 0–10 °C. The resulting solution was stirred at room temperature for 1–5 h. The reaction mixture was transferred to a separation funnel and diluted with toluene (20 mL) and water (10 mL). After phase separation, the aqueous layer was extracted with toluene (6 mL × 1). The combined organic layers were washed with water (9 mL × 1) and concentrated. The pure 4-chromanones **3a**, **3b**, **3d**, **3f**, **3h**, and **3i** obtained by crystallization of their corresponding crude products in isopropanol (IPA) and the pure chromanones **3c**, **3–4e**, **3g** and **3j** were obtained by Biotage chromatographic purification (EtOAc/hexanes from 10% to 80%).