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One-Pot Synthesis of 3,5-Disubstituted and Polysubstituted Phenols from Acyclic Precursors

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Supporting Information

ABSTRACT: A new strategy for the synthesis of 3,5-disubstituted phenols is established through one-pot Robinson annulation of α,β-unsaturated ketones with α-fluoro-β-ketoesters followed by in situ dehydrofluorination and tautomerization. This method has been extended to the synthesis of polysubstituted phenols and applied in the preparation of biologically active compounds.

Substituted phenols are important structures in pharmaceutical, agricultural, and fine chemicals, as well as synthetic polymers.[1] Shown in Figure 1 are the biologically active 3,5-disubstituted phenols luteinizing hormone (LH) receptor inhibitor LUF5771,[2] the leukotriene B4 (LTB4) receptor inhibitor RO5101576,[3] and the CD40 function inhibitor **I**.[4] Among the substituted phenols, regiospecific synthesis of 3,5-disubstituted phenols is a challenging task because electrophilic aromatic substitution of phenols is unfavorable at the *meta* (3 and 5) positions.[5] Alternative synthetic methods using nonaromatic precursors have been developed,[6] which include benzannulations of vinylketenes,[7] carbenes,[8] or alkyenes,[9] carbonyl insertion of vinylcyclopropenes,[10] Diels–Alder-based cycloaromatization of alkynes,[11] [3 + 3] cyclocondensations involving 1,3-dicarbonyl compounds,[12] dienone–phenol rearrangements,[13] dehydrogenative aromatization of cyclohexenones,[14] and eliminative aromatization of cyclohexenones.[15] However, not all of these methods are regiospecific for 3,5-disubstituted phenols. In addition, some reactions require special substrates such as silyl enol ethers or reactive intermediates such as ketenes and carbenes and need transition-metal catalysis. The development of straightforward and efficient methods for 3,5-disubstituted phenols is still highly desirable. Introduced here is a new [3 + 3] cyclocondensation strategy for the synthesis of 3,5-disubstituted phenols through in situ dehydrofluorinative aromatization of Robinson annulation products. This one-pot synthesis employs readily available substrates without transition-metal catalysis.

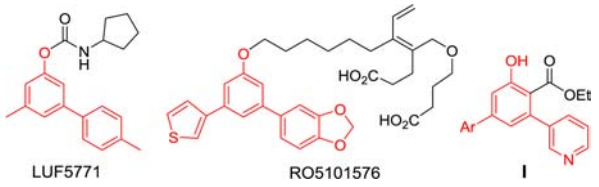
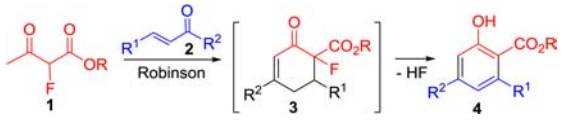


Figure 1. Representative bioactive 3,5-biaryl phenols.

In our recent effort to develop a one-pot synthesis of organofluorine molecules,[16] we reported Robinson annulations of α-fluoro-β-ketoesters **1** and α,β-unsaturated ketones **2** for the synthesis of fluorinated cyclohexenes **3** (Scheme 1).[17] The fluorination of β-ketoesters with Selectfluor and sequential Robinson annulation were carried out as a one-pot synthesis. Interestingly, we noticed that if isolated α-fluoro-β-ketoesters **1** were used for the Robinson annulation,[18] a significant amount of **3** underwent dehydrofluorination and tautomerization to form phenol **4**. Since there are very limited examples in the literature on regiospecific synthesis of 3,5-disubstituted phenols through eliminative aromatization of cyclohexenones,[19] we envisioned that the Robinson annulation followed by in situ dehydrofluorination[20] could be developed as new method for the synthesis of 3,5-disubstituted phenols.

Scheme 1. One-Pot Robinson and Dehydroflourination



The development of reaction conditions for the synthesis of α-hydroxybenzoate **4a** through one-pot reactions was carried out using commercially available α-fluoro-β-ketoester **1a** and chalcone **2a** as the substrates (Table 1). After screening a series of bases including Cs_2CO_3, Na_2CO_3, NaOH, KOH, and Et_3N and exploring the reaction temperature (70–120 °C) and time (0.5–4 h), it was found that using 1 equiv of Cs_2CO_3 at 70 °C for 30 min afforded **4a** in up to 89% yield (entry 1). It was also found that increased reaction time or temperature caused decarboxylation of **4a** to form 3,5-disubstituted phenol **5a** (entries 2–4). If the reaction was carried out using 2 equiv of Cs_2CO_3 at 120 °C for 4 h, **4a** was fully decarboxylated to form **5a** in 91% yield (entry

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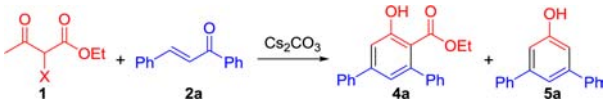
Table 1. Optimization of Reaction Conditions[a]



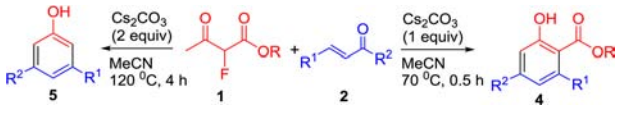
entry	X	Cs_2CO_3 (equiv)	solvent	temp (°C)	time (h)	4a[b] (%)	5a[b] (%)
1	F	1	MeCN	70	0.5	89	trace
2	F	1	MeCN	90	2	71	21
3	F	1	MeCN	100	0.5	63	31
4	F	1	MeCN	120	4	8	85
5	F	2	MeCN	120	4	trace	91
6	F	2	DMF	120	4	23	63
7	F	2	DMSO	120	4	16	77
8	F	2	PhMe	120	4	14	45
9	Cl	2	MeCN	120	4	trace	trace
10	Br	2	MeCN	120	4		

[a]Reaction conditions: **1** (0.6 mmol), **2a** (0.5 mmol). [b]Isolated yield.

5). DMF, DMSO, and toluene were found to be ineffective solvents for this reaction (entries 6–8). Reactions with chlorinated or brominated substrates were conducted to confirm that the dehydrohalogenation only happens to the fluorinated substrates (entries 9 and 10).

To explore the scope of this new reaction, different α-fluoro-β-ketoesters **1** and α,β-unsaturated ketones **2** were employed for the preparation of a series of α-hydroxybenzoates **4** and the corresponding decarboxylated phenols **5** (Table 2). Using 1 equiv of Cs_2CO_3 at 70 °C for 30 min, reactions of **2** with either electron-donating groups (Me, OMe, and OH) (**2b–e**) or

Table 2. Synthesis of Phenols 4 and Decarboxylated Phenols 5[a]



entry	R (1)	R^1	R^2	2	4[b] (%)	5[b] (%)
1	Et (**1a**)	Ph	Ph	**2a**	89 (**4a**)	91 (**5a**)
2	Et (**1a**)	Ph	4-MePh	**2b**	86 (**4b**)	87 (**5b**)
3	Et (**1a**)	4-MePh	Ph	**2c**	85 (**4c**)	85 (**5c**)
4	Et (**1a**)	4-MeOPh	Ph	**2d**	82 (**4d**)	80 (**5d**)
5	Et (**1a**)	4-OHPh	Ph	**2e**	80 (**4e**)	81 (**5e**)
6	Et (**1a**)	4-ClPh	Ph	**2f**	92 (**4f**)	93 (**5f**)
7	Et (**1a**)	4-FPh	Ph	**2g**	92 (**4g**)	93 (**5g**)
8	Et (**1a**)	4-NO_2Ph	Ph	**2h**	92 (**4h**)	93 (**5h**)
9	Et (**1a**)	Ph	4-CF_3Ph	**2i**	93 (**4i**)	94 (**5i**)
10	Et (**1a**)	Ph	3-CF_3Ph	**2j**	94 (**4j**)	92 (**5j**)
11	Et (**1a**)	Ph	2-CF_3Ph	**2k**	92 (**4k**)	90 (**5k**)
12	Et (**1a**)	3-pyridyl	Ph	**2l**	90 (**4l**)	93 (**5l**)
13	Et (**1a**)	1-naphthyl	Ph	**2m**	85 (**4m**)	88 (**5m**)
14	Et (**1a**)	2-furanyl	Me	**2n**	87 (**4n**)	89 (**5n**)
15	Et (**1a**)	2-thienyl	Me	**2o**	89 (**4o**)	90 (**5o**)
16	Et (**1a**)	Ph	Me	**2p**	79 (**4p**)	80 (**5p**)
17	Et (**1a**)	Me	Me	**2q**	80(**4q**)	83(**5q**)
18	Et (**1a**)	Ph	*c*-C_6H_{12}	**2r**	80 (**4r**)	85 (**5r**)
19	Et (**1a**)	Ph	*c*-C_3H_6	**2s**	78 (**4s**)	79 (**5s**)
20	Et (**1a**)	Ph	*t*-Bu	**2t**	75 (**4t**)	77 (**5t**)
21	*t*-Bu (**1b**)	Ph	Ph	**2a**	87 (**4u**)	90 (**5u**)
22	Bn (**1c**)	Ph	Ph	**2a**	89 (**4v**)	92 (**5v**)

[a]Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol). [b]Isolated yield.

electron-withdrawing groups (NO_2, CF_3, F, and Cl) (**2f–i**) at the *para*-, *meta*-, and *ortho*-positions of the benzene rings (**2i–k**) afforded α-hydroxybenzoates **4** in 80–94% yields (entries 1–11). Reactions of **2** with heteroaromatic rings such as 3-pyridyl (**2l**), 1-naphthyl (**2m**), 2-furanyl (**2n**), and 2-thienyl (**2o**) also proceeded smoothly (entries 12–15). It is noteworthy that the CD40 function inhibitor **I** shown as **4l** in Scheme 1 was prepared in 90% yield through this one-pot reaction process (entry 12). Reactions of α,β-unsaturated ketones **2** with nonaromatic R^1 and R^2 groups, such as Me (**2n–q**), cyclohexyl (**2r**), cyclopropyl (**2s**), and *t*-Bu (**2t**), also generated the corresponding phenols in good to excellent yields (entries 14–20). In addition, α-fluoro-β-ketoesters **1** with a bulky R group such as *t*-Bu (**1b**) or Bn (**1c**) also worked well to give product in 87% and 92% yields, respectively (entries 21 and 22). The substrates shown in Table 2 were also used for the corresponding decarboxylation using 2 equiv of Cs_2CO_3 at 120 °C for 4 h. The desired 3,5-disubstituted phenols **5** were produced in 77–94% yield.

Using readily available α-fluoro-α,β-unsaturated ketones **6** as starting materials, this method has easily been applied to the synthesis of 4-fluorophenols **7** and the corresponding decarboxylated 4-fluorophenols **8** in good to excellent yields (Table 3). Structures of both **7c** and **8d** have been confirmed by X-ray

Table 3. Synthesis of *p*-Fluorophenols 7 and 8[a]

entry	R	6	7[b] (%)	8[b] (%)
1	Ph	**6a**	87 (**7a**)	90 (**8a**)
2	1-naphthyl	**6b**	83 (**7b**)	81 (**8b**)
3	4-CF_3Ph	**6c**	90 (**7c**)	93 (**8c**)
4	4-NO_2Ph	**6d**	89 (**7d**)	90 (**8d**)
5	4-ClPh	**6e**	86 (**7e**)	89 (**8e**)
6	4-MePh	**6f**	82 (**7f**)	84 (**8f**)
7	2-pyridyl	**6g**	85 (**7g**)	93 (**8g**)
8	2-thienyl	**6h**	87 (**7h**)	91 (**8h**)

[a]Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol). [b]Isolated yield.

crystal structure analysis (Figure 2). To our knowledge, there are only two reported methods for the synthesis of 3,5-disubstituted 4-fluorophenols by [3 + 3] cycloaddition of 1,3-bis(silyl enol ethers)[21] and Pd-catalyzed displacement of 4-bromo-3,5-disubstituted phenols with CsF.[22]

The new method has also been extended to the synthesis of polysubstituted phenols using γ-substituted ketoesters and/or α-substituted unsaturated ketones. Thus, the reactions of methyl 2-fluoro-3-oxopentanoate **9a** or methyl 2-fluoro-3-oxohexanoate **9b** with chalcone **2a**, α-fluoro-α,β-unsaturated ketone **6a**, or α-methyl-α,β-unsaturated ketone **10** afforded tetra- and pentasubstituted phenols **11** and the corresponding decarboxylated phenols **12** in 26–93% yields (Scheme 2).

In addition to the synthesis of the CD40 function inhibitor **I** shown as **4l** in Table 1, we also applied the method for a gram-scale synthesis of another biologically active compound LUF5771 (Scheme 3). As shown in Table 2, entry 2, the reaction of **1a** and **2b** with 2 equiv of Cs_2CO_3 at 120 °C for 4 h afforded the 3,5-disubstituted phenol **5b**. Without separation from the reaction mixture, compound **5b** was reacted with

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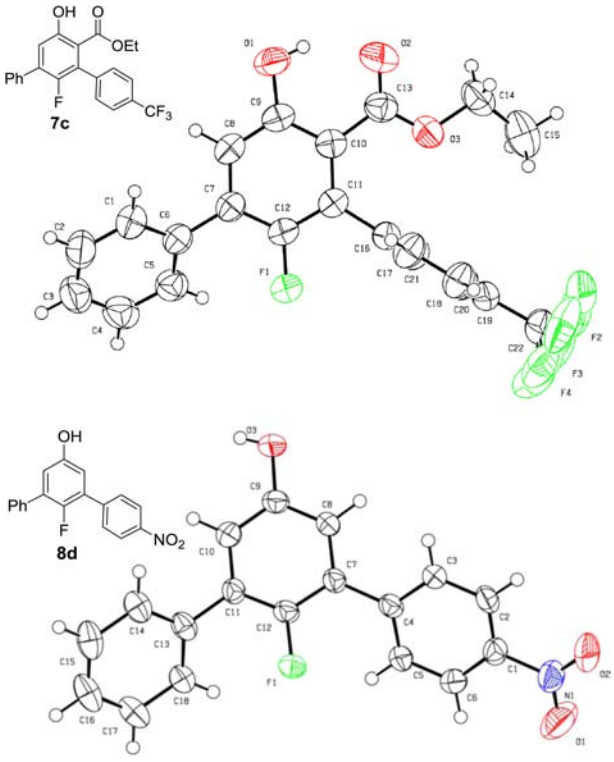
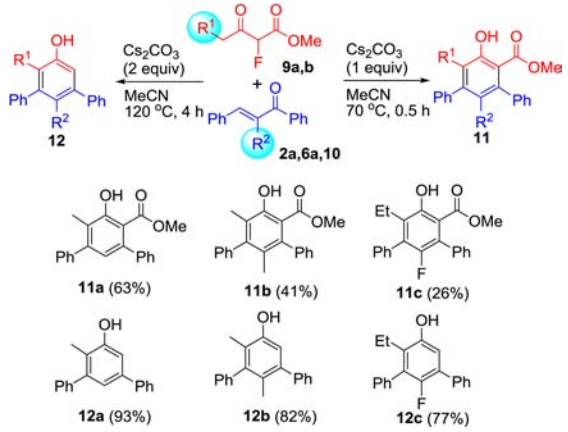


Figure 2. X-ray crystal structures of **7c** and **8d**.

Scheme 2. Synthesis of Polysubstituted Phenols 11 and 12



Scheme 3. One-Pot Synthesis of LUF5771

cyclopentylisocyanate to afford LUF5771 in 76% yield (Scheme 3).

In summary, we have developed a new [3 + 3] cyclocondensation method for the synthesis of 3,5-disubstituted phenols by the reaction of readily available α-fluoro-β-ketoesters and α,β-unsaturated ketones. Straightforward and highly efficient one-pot synthesis of α-hydroxybenozoates and corresponding decarboxylated phenols has been accomplished through a one-pot reaction process involving tandem Robinson annulation, dehydrofluorination, aromatization, and decarboxylation. The new method has been employed for the synthesis of 4-fluorophenols and polysubstituted phenols. The method has also been applied to the one-pot synthesis of bioactive compounds such as the CD40 function inhibitor and the luteinizing hormone (LH) receptor inhibitor LUF5771.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for all new compounds and X-ray data for **7c** and **8d** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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