Tandem [4 + 1 + 1] annulation and metal-free aerobic oxidative aromatization: straightforward synthesis of highly substituted phenols from one aldehyde and two ketones†

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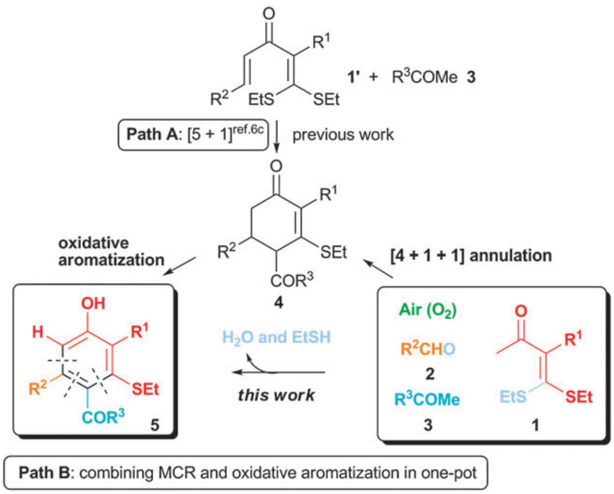
Polysubstituted phenols are efficiently assembled from one aldehyde and two different methyl ketones in a one-pot operation *via* a newly base-induced regiospecific [4 + 1 + 1] annulation and sequential metal-free oxidative aromatization using molecular oxygen (from air) as the sole oxidant at room temperature.

Phenols are important building blocks for constructing pharmaceuticals, polymers, natural products, and oxygenated heterocycles.[1] Consequently, the establishment of new efficient synthetic methods for highly substituted phenols, with selective control of substitution patterns, from readily available and simple acyclic substrates continues to be actively pursued.[1–4] In this area, although several attractive methods, such as Dötz benzannulation, a formal [3 + 2 + 1] cycloaddition of Fischer carbene complexes with alkynes,[2a–c] have proven to be powerful and efficient methods for the facile construction of various phenol derivatives,[1–4] these methods are restricted to alkynes and the regioselectivity depends on the structure of the alkyne substrates. To the best of our knowledge, there is no report in the construction of highly substituted phenols *via* multicomponent reactions (MCRs)[5] involving three or more different starting materials.

Previously, we developed a [5C + 1C] annulation of five-carbon 1,5-dielectrophiles (Scheme 1, for example, compounds **1′**) with nitroalkanes for the synthesis of polysubstituted phenols.[6a,b] In a recent report, we also successfully synthesized 2-cyclohexenones **4** based on this [5C + 1C] annulation using methyl aryl ketones **3** as the one-carbon nucleophiles (Scheme 1, Path A).[6c] This result prompts us to pursue a more convenient [4C + 1C + 1C] annulation procedure suitable for the synthesis of phenols by combining the significant advantages of MCRs like cheap and easily available starting materials and product diversity.[5] In the present work, we choose a kind of four-carbon 1,4-dipolar synthons **1** as the four carbon component in a multicomponent reaction which allows the straightforward synthesis of highly substituted phenols from three different starting materials including a 1,4-dipolar synthon **1**, an aldehyde **2** and a methyl ketone **3** under mild conditions (Scheme 1, Path B). Notably, we also emphasize a novel metal-free oxidative aromatization of 2-cyclohexenones leading to phenols using molecular oxygen from air as the sole oxidant under basic conditions.[7,8]



Scheme 1 Strategy for the synthesis of highly substituted phenols.

Initially, the reaction of 2-(bis(ethylthio)methylene)-1-phenylbutane-1,3-dione **1a**, benzaldehyde **2a**, and acetophenone **3a** was employed as a model reaction to screen reaction conditions for the three-component reaction. Among the various basic systems tested, including *t*-BuOK/THF, *t*-BuOK/DMF, *t*-BuOK/MeCN, NaOH/DMF, and NaOMe/DMF, *t*-BuOK/DMF proved the most efficient. The reaction of **1a** (1.0 mmol), **2a** (1.1 mmol) and **3a** (1.1 mmol) in dry DMF (10 mL) in the presence of *t*-BuOK (2.0 equiv.) at room temperature for 35 h gave 2-cyclohexenone **4a** in 62% yield (Table 1, entry 1). It was found that the addition order of reagents has a significant influence on the yield of **4a** (entries 1–4). In the case of addition order D, *i.e.*, treatment of **2a** (1.1 mmol) and **3a** (1.1 mmol) with *t*-BuOK (1.0 equiv.) under solvent-free conditions at room temperature for 1.0 h and then adding **1a** (1.0 mmol) and additional *t*-BuOK (1.0 equiv.) in 10 mL of dry DMF and reacting for another 19 h, cyclohexenone **4a** was obtained in 82% yield (entry 4).

The above results (entries 1, 3 and 4) support the design strategy outlined in Scheme 1 for developing the [4 + 1 + 1] annulation (Path B), a more convenient route to 2-cyclohexenones.[6c] Fortunately, it was found that phenol **5a** could be obtained simply by increasing the amount of *t*-BuOK. As can be seen from the comparison (entries 5–11), the best results were obtained by using 4.0 equivalent of *t*-BuOK and by following the addition order D. Under the optimized conditions, *i.e.*, the mixture of **2a** (1.1 mmol) and **3a** (1.0 mmol) was treated with *t*-BuOK (0.5 mmol) at room temperature under solvent-free condition for 0.5 h and then adding **1a** (1.0 mmol in 10 mL of

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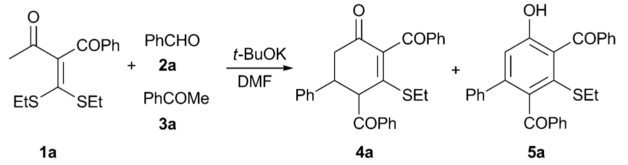
† Electronic supplementary information (ESI) available: Detailed experimental procedures, analytical and spectral data for all the compounds **5a–p**. See DOI: 10.1039/c0cc02313b

Table 1 Screening of reaction conditions[a]

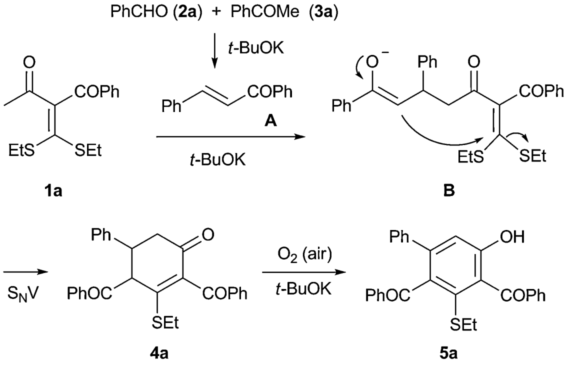


Entry	Addition order[b]	t-BuOK (eq.)	T/°C	t/h	Yield[c] (%) 4a	Yield[c] (%) 5a
1	A	2.0	rt	35	62	0
2	B	2.0	rt	35	20	0
3	C	2.0	rt	20	65	0
4	D	2.0	rt	20	82	0
5	D	3.0	rt	12	34	38
6	**D**	**4.0**	**rt**	**3.0**	**0**	**67**
7	A	4.0	rt	3.0	41	12
8	B	4.0	rt	3.0	32	0
9	C	4.0	rt	3.0	15	14
10	D	5.0	rt	2.5	0	66
11	D	4.0	60	2.0	0	63

[a] **1a** (1.0 mmol), **2a** (1.1 mmol), **3a** (1.1 mmol), dry DMF (10 mL). [b] Addition order A: a mixture of **1a**, **2a** and **3a** in dry DMF was treated with *t*-BuOK; addition order B: a mixture of **1a** and **2a** in dry DMF was treated with *t*-BuOK and then reacted with **3a**; addition order C: a mixture of **2a** and **3a** in dry DMF was treated with *t*-BuOK and then reacted with **1a**; addition order D: a mixture of **2a** and **3a** was treated with *t*-BuOK under solvent-free conditions and then reacted with **1a** and additional *t*-BuOK in dry DMF. [c] Isolated yield based on **1a**.

dry DMF) and *t*-BuOK (3.5 mmol) and reacting for another 2.5 h, the 2,3,4,5-tetrasubstituted phenol **5a** was obtained in 67% isolated yield (entry 6).

Based on the experimental results summarized in Table 1, the formation of phenol **5a** should be reasonably expressed as a [4 + 1 + 1] annulation/oxidative aromatization or [4 + 1 + 1] oxidative aromatization process as indicated in Scheme 2. This MCR arises from the base-mediated aldol condensation of, for example, preferably acetophenone **3a** with benzaldehyde **2a**, leading to chalcone intermediate **A**. Under basic conditions, subsequent intermolecular Michael addition of acetyl ketene dithioacetal **1a** to intermediate **A** leads to intermediate **B** and then furnishes 2-cyclohexenone **4a** through intramolecular Michael addition followed by elimination of ethanethiol (S_NV).[6] Finally, **5a** is produced by oxidative aromatization of **4a** using molecular oxygen as the sole oxidant (exposed to the open air).

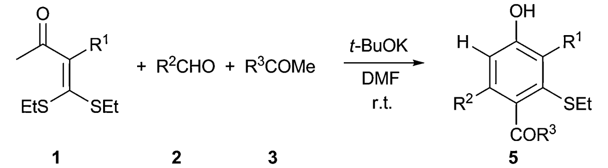


Scheme 2 Proposed mechanism for the formation of phenols **5**.

The regiospecific preparation of highly substituted phenols is one of the challenging problems in organic synthesis.[1–4,6] To the best of our knowledge, the synthesis of phenol **5a** provides the first example of multicomponent synthesis of highly substituted phenols which combines an aldehyde and two different methyl ketones. It is worth noting that the oxidative aromatization step after the [4 + 1 + 1] annulation is very important for the successful implementation of the [4 + 1 + 1] oxidative aromatization strategy since similar conditions are used in both cases. It is true that the utilization of molecular oxygen as a terminal oxidant in oxidative transformations is a highly attractive strategy in current organic synthesis, while there remain challenges.[7–9] The oxidative aromatization reaction of 2-cyclohexenones is an important transformation for the synthesis of phenol derivatives. In general, the reaction requires the use of oxidants (such as MnO_2, *N-tert*-butylbenzenesulfinimidoyl chloride, or molecular iodine, *etc.*), or is achieved by aerobic oxidative aromatization *via* catalytic dehydrogenation in the presence of metal catalyst, for example, catalytic amounts of $VOSO_4$ and 50 mol% HBr aq. (48%) or $CuBr_2$/LiBr mixture.[8,9] By comparison, the aerobic oxidative aromatization of 2-cyclohexenone **4a** as described above preceded smoothly under basic condition without the assistance of metal catalyst. So, it provides a very important means by which 2-cyclohexenones can be easily aromatized to the corresponding phenols under more simple and lower cost reaction conditions.[7–9]

Considering the significant combination of the MCR and oxidative aromatization, the scope of this process was investigated under the optimized conditions (Table 1, entry 6) and

Table 2 Synthesis of phenols **5**[a]‡



Entry	R^1	R^2	R^3	t/h	5	Yield[b] (%)
1	PhCO	Ph	Ph	3.0	**5a**	67
2	PhCO	4-ClC_6H_4	Ph	3.0	**5b**	77
3	PhCO	4-$NO_2C_6H_4$	Ph	3.0	**5c**	58
4	PhCO	4-MeC_6H_4	Ph	3.0	**5d**	55
5	PhCO	3,4-$CH_2O_2C_6H_3$	Ph	5.0	**5e**	62
6	PhCO	4-$MeOC_6H_4$	Ph	3.0	**5f**	54
7	PhCO	2-furyl	Ph	3.0	**5g**	73
8	PhCO	Cy	Ph	3.0	—	—[c]
9	PhCO	4-ClC_6H_4	4-ClC_6H_4	3.0	**5h**	69
10	PhCO	4-ClC_6H_4	4-MeC_6H_4	3.0	**5i**	65
11	PhCO	4-ClC_6H_4	2-furyl	3.0	**5j**	54
12	PhCO	4-ClC_6H_4	Me	3.0	—	—[c]
13	CO_2Et	4-ClC_6H_4	Ph	3.0	**5k**	70
14	CN	4-ClC_6H_4	Ph	3.0	**5l**	55
15	MeCO	4-ClC_6H_4	Ph	3.0	**5m**	51
16	4-$MeOC_6H_4$	4-ClC_6H_4	Ph	3.0	**5n**	68
17	H	Ph	Ph	3.0	**5o**	55
18	H	4-ClC_6H_4	Ph	4.0	**5p**	40

[a] General reaction conditions: **1** (1.0 mmol), **2** (1.1 mmol), **3** (1.1 mmol), *t*-BuOK (4.0 equiv.), DMF (10 mL), rt. [b] Isolated yield based on **1**. [c] Complex mixture was obtained.

the results are summarized in Table 2.[10] Clearly, the results suggest a wide scope of substituents at the α-position of acetyl ketene dithioacetals **1**, including benzoyl (entries 1–12), ethoxycarbonyl (entry 13), cyano (entry 14), acetyl (entry 15), aryl (entry 16), and hydrogen (entries 17 and 18). Accordingly, a wide range of aldehydes **2** bearing phenyl (entries 1 and 17), electron-deficient (entries 2, 3, 9–16, 18), electron-rich (entries 4–6) aromatic and hetero aromatic groups (entry 7) are suitable aldehyde components for this tandem procedure. By comparison, the reaction with cyclohexanecarbaldehyde led to an inseparable mixture (entry 8). In the case of methyl ketones, all aryl methyl ketones **3** tested afforded the desired highly substituted phenols **5** in good yields except that the reaction with acetone gave a complex mixture (entry 12).

In conclusion, a facile multicomponent synthesis of highly substituted phenols has been developed starting from readily available acyclic precursors under mild conditions. In the first stage, the [4 + 1 + 1] annulation of an aldehyde and two different methyl ketones, involving an aldol condensation/intermolecular Michael addition/intramolecular Michael addition/elimination of ethanethiol sequence, is highly chemo- and regioselective since the two ketones show different reactivities. In the second stage, the 2-cyclohexenones (the [4 + 1 + 1] annulation products) are efficiently converted to the corresponding phenols through a metal-free dehydrogenation oxidation using molecular oxygen from air as the oxidant. This work provides (1) a new entry to highly substituted 2-cyclohexenones; (2) a new entry to highly substituted phenols; and more importantly, (3) a new and low cost approach for efficient transformation of 2-cyclohexenones to the corresponding phenol derivatives using molecular oxygen from air as the only oxidant. Further studies are in progress.

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Notes and references

‡ General procedure for the multicomponent synthesis of poly substituted phenols **5** (taking **5a** as an example): to a well-stirred mixture of benzaldehyde **2a** (0.11 mL, 1.1 mmol) with acetophenone **3a** (0.128 mL, 1.1 mmol) was added *t*-BuOK (56 mg, 0.5 mmol) at room temperature. After the reaction mixture was stirred at room temperature for 0.5 h, a mixture of 2-(bis(ethylthio)methylene)-1-phenylbutane-1,3-dione **1a** (294 mg, 1.0 mmol) and *t*-BuOK (392 mg, 3.5 mmol) in dry DMF (10 mL) was added and the resulting reaction mixture was stirred at room temperature for additional 2.5 h. After completion of the reaction as indicated by TLC, the reaction was quenched by saturated sodium chloride aqueous (20 mL), neutralized with dilute HCl aqueous, and extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with water (3 × 20 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, eluent, petroleum ether–diethyl ether: 3/1, v/v) to give (3-(ethylthio)-5-hydroxybiphenyl-2,4-diyl) bis(phenylmethanone) **5a** (293 mg, 67%) as a yellow oil.

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