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Metal-free direct *C*-arylation of 1,3-dicarbonyl compounds and ethyl cyanoacetate: A platform to access diverse array of *meta*-functionalized phenols

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Base mediated, highly convenient strategy for the direct *C*-arylation of 1,3-dicarbonyls and cyanoacetate with various phenol derivatives as aryl partners is presented. The present work excel in forming C–C bond at the *meta*-position of the phenols which is traditionally challenging to functionalize. This protocol further leads the way to have scalable, straightforward access to phenol assimilated heterocycles which have powerful applications both in synthetic chemistry and medicinal research.

C-arylation has drawn extensive and revolutionized attention as one of the significant methods for the C–C bond formation, which provides an easy access to complex organic frameworks that manifest a wide range of pharmacological activities.[1] The chemistry of 1,3-diones is a cornerstone of organic synthesis by virtue of their eloquent reactivity of functional group. The enolate arylation of 1,3-dicarbonyl compounds and ethyl cyanoacetate were usually carried out by transition metals[2] but rarely by organocatalysts.[3] Particularly, Stoltz[4a] *et al.* isolated the small amount of *C*-arylation product during aryne insertion reaction into the C–H σ–bond of 1,3-diones. Wang[4b] *et al.* studied the α-arylation of dicarbonyls with CuBr-trichloroacetic acid as a catalyst. Owning to the potential application[5] of 2-aryl 1,3-dicarbonyls, a convenient and practical and strategy for the direct α-arylation of 1,3-dicarbonyl compounds and cyanoacetates is still challenging.

During our studies on dearomatization of phenols, we found that the *in situ* generated reactive intermediates[6] bearing rich functional groups could potentially participate in various addition reactions. It occurred to us that the addition of 1,3-dicarbonyl compounds and cyanoacetate to 2-methoxy-phenols-derived *ortho*-benzoquinone monoketals would provide α-arylated products. If this is realised, it would pave a way to highly prudent methodology to furnish *meta*-functionalized phenols. The synthesis of *meta*-substituted phenols possesses a significant challenge of bypassing the normal *ortho*/*para* directing group effect of hydroxyl functionality. Recent reported methods for *meta*-functionalization are mainly based on transition metal catalysis and template-based strategies.[7] Although efficient, these methods often require lengthy synthetic routes, high temperature and prolonged reaction time.

Herein, we disclose our results on base-mediated *C*-arylation of 1,3-diones and cyanoacetate with commercially available, innocuous 2-methoxyphenols as aryl partners. These phenols can be easily dearomatized to the corresponding benzoquinone derivatives, also known as masked *o*-benzoquinones (MOBs). Thus *in situ* generated conjugated cyclohexadienones were then subjected to Michael attack by C–H activated acids to access *meta*-selective C–H functionalized products under very mild conditions. Further remarkability of this approach has been proven by extending it for the synthesis of various phenol functionalized *N*- and *O*-heterocyclic scaffolds *viz.*, pyrazole, isoxazole, coumarin, and triazolone derivatives by utilizing β-diketones as essential building blocks. Some of these heterocyclic compounds that are counted among the most potent biologically active scaffolds[8–11] are shown in Figure 1.

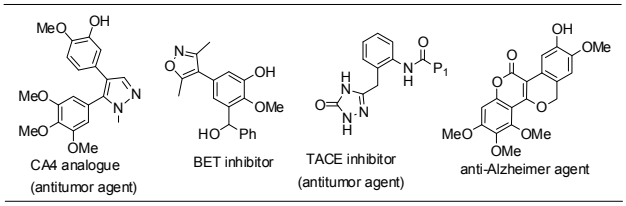

Fig. 1 Pharmaceutically active agents containing heterocyclic scaffolds.

The feasibility of the enolate arylation reaction of 1,3-diones is investigated by attempting the reaction between 4-bromo-2-methoxyphenol (**1a**) and acetylacetone (**3**). In the initial step, the dearomatization of 4-bromoguaiacol was

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Electronic Supplementary Information (ESI) available: [Experimental procedures, spectroscopic data, copies of ^{1}H NMR and ^{13}C NMR and cif file of crystal structure of **19** (CCDC 1585102)]. See DOI: 10.1039/x0xx00000x

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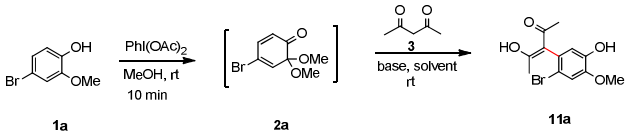
carried out with diacetoxyiodobenzene (DIB, 1.2 equiv) in methanol to generate *o*-benzoquinone monoketal **2a**. This transformation then facilitated the Michael addition of C–H activated acid **3** in the presence of Et_3N (1 equiv) to enable the synthesis of product **11a** with desired substitution in 60% yield (Table 1, entry 1). The base additive was found to be crucial for the reaction (entry 2). Fortified by above results, other reaction parameters such as the choice of base, solvent and temperature were screened. It was observed that with most of the commonly used bases such as Cs_2CO_3, K_2CO_3, NaOH, KO^{t}Bu, DABCO, the reaction went on to completion successfully (entries 3–7). Among these, Et_3N was proved to be efficient base for this enolate arylation. In order to circumvent the nucleophilic attack of MeOH on MOB, after dearomatization event, methanol was first removed from the reaction mixture by rotatory evaporator *in vacuo* and the reaction was continued by diluting the residue in another solvent followed by the addition of base and dicarbonyl compound (entries 8–11). To our delight, when the reaction was carried out in toluene, the arylated product **11a** was obtained in enhanced yield of 62% (entry 11). An increment of the product yield was observed by increasing the amount of Et_3N to 2.0 equiv (entries 12 and 13). However, increasing the stoichiometry of acetylacetone also showed a positive effect on the yield (entries 14 and 15). However, elevating the temperature has no substantial effect on the reaction (entry 16).

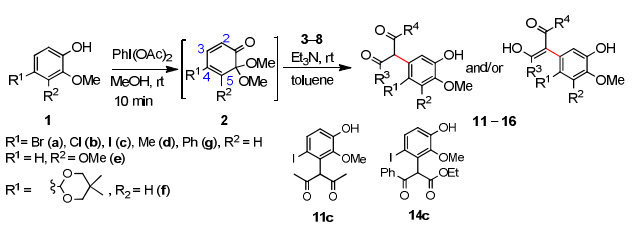
Table 1 Screening of reaction conditions[a]

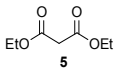
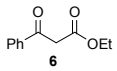


Entry	Acetylacetone (equiv)	Solvent	Base (1 equiv)	Yield[b] (%)
1	1	MeOH	Et_3N	60
2	1	MeOH	-	nr
3	1	MeOH	KO^{t}Bu	61
4	1	MeOH	K_2CO_3	58
5	1	MeOH	Cs_2CO_3	63
6	1	MeOH	NaOH	nd
7	1	MeOH	DABCO	55
8	1	DCM	Et_3N	40
9	1	CAN	Et_3N	55
10	1	THF	Et_3N	50
11	1	Toluene	Et_3N	62
12[c]	1	Toluene	Et_3N	65
13[d]	1	Toluene	Et_3N	68
14[d]	**1.2**	**Toluene**	**Et_3N**	**72**
15[d]	2.0	Toluene	Et_3N	73
16[d, e]	1.2	Toluene	Et_3N	61

[a] Reaction conditions: **1a** (0.30 mmol), DIB (0.36 mmol), acetylacetone (**3**, 0.45 mmol), base, solvent (3 mL) stirred at rt, in air for 3 h. [b] Pure and isolated yields. nd: Not determined. nr: No reaction. [c] Performed with 1.5 equiv of Et_3N at room temperature for 24 h. [d] Performed with 2.0 equiv of Et_3N at room temperature for 24 h. [e] Carried out with 1.5 equiv of Et_3N at 80 °C.

Table 2 Reactions of substituted guaiacols with various 1,3-dicarbonyl compounds **3–8**[a]



Entry	1	1,3-dicarbonyl compound	Time	Yield (%)[b] Keto form	Yield (%)[b] Enol form
1	**1a**	 **3**	3 h	–	**11a**/72
2	**1a**	 **4**	3 h	**12a**/71[c]	
3	**1a**	 **5**	5 h	**13a**/68	–
4	**1a**	 **6**	6 h	**14a**/80	–
5	**1a**	 **7**	3 h	–	**15a**/82
6	**1a**	 **8**	4 h	**16a**/86	–
7	**1c**	**3**	3 h	[d]**11c**/71	–
8	**1b**	**5**	6 h	**13b**/65	–
9	**1c**	**6**	5 h	[d]**14c**/76	–
10	**1b**	**7**	2 h	–	**15b**/80
11	**1b**	**8**	3 h	**16b**/85	–
12	**1d**	**3**	50 min	**11d**/78	–
13	**1d**	**5**	2 h	**13d**/Traces	
14	**1d**	**6**	2 h	**14d**/80[c]	
15	**1d**	**7**	3 h	**15d**/85	–
16	**1d**	**8**	4 h	–	**16d**/86
17[e]	**1e**	**3**	4 h	**11e**/60	–
18[e]	**1e**	**5**	7 h	**13e**/61	–
19[e]	**1e**	**6**	6 h	**14e**/62	–
20[e]	**1e**	**7**	5 h	–	**15e**/70
21[e]	**1e**	**8**	5 h	–	**16e**/76
22	**1f**	**3**	4 h	**11f**/81	–
23	**1f**	**6**	5 h	**14f**/74	–
24	**1g**	**5**	6 h	**13g**/52[c]	

[a] Reaction conditions: **1** (0.3 mmol), DIB (0.36 mmol), 1,3-dicarbonyl compound (**3–6**, 0.45 mmol), Et_3N (0.67 mmol), solvent (3 mL) stirred at rt. [b] Pure and isolated yields. [c] Combined yield of both keto and enols forms. [d] Michael addition took place at C-5 of 4-iodo MOB **2c**. [e] Reaction was performed at 80 °C.

Having established the optimum reaction conditions, we were keen to study the generality of this protocol. A number of acyclic and cyclic dicarbonyls were subjected to react with variously substituted 2-methoxyphenols under these conditions. Thus the reactions of dicarbonyls **3–8** and 2-methoxyphenols **1a–1e** furnished the arylated *meta*-

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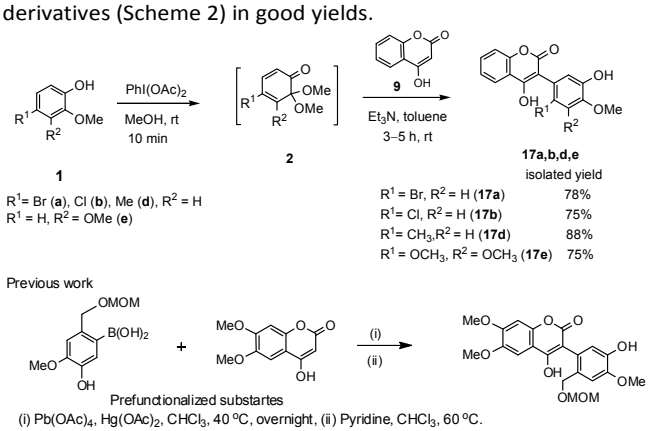
functionalized phenols successfully in good to high yields revealing the validity of standard established reaction conditions for α-arylation of 1,3-diones (Table 2). As shown, the alicyclic 1,3-dicarbonyl compounds afforded the products **11a**-**e**–**14a**-**e** in good to high yields. A minor drop in the yield of compounds **13a**,**b**,**e** arising from less acidic diethyl malonate (**5**) may be noted. A dynamic equilibrium between keto and enol forms has been observed in case of compound **12a** and **14d**. Furthermore, the cyclohexadienone **2e** derived from 2,3-dimethoxyphenol (**1e**) is less reactive and hence the Michael addition was performed at 80 °C (entries 17–21). Enthrallingly, cyclic 1,3-diketones **7** and **8** can also be employed in this base mediated transformation to furnish the desired products **15a,b,d,e** and **16a,b,d,e**, respectively, in good to excellent yields of 70–86%. The vanillin-derived acetal **1f** worked equally good and furnished **11f** and **12f** (entries 22 and 23). The electron-withdrawing phenyl group in **1g** resulted in the formation of **13g** in a reduced yield of 52% (entry 24). The current protocol did not work with *p*-methoxy phenols.

It was envisioned that positions 3 and 5 of *in situ* generated MOBs are susceptible for nucleophilic attack. Interestingly, the site for Michael attack in this transformation is directed by the substituent present on cyclohexadienone system. Unlike the reaction of 4-bromo, 4-chloro, 4-methyl and 5-methoxy guaiacol derivatives **1a,b,d,e**, where the nucleophiles attacked on C-3 of the corresponding MOBs, the reaction of 4-iodoguaiacol (**1c**) proceeded *via* Michael attack on C-5 of its oxidized species **2c** to furnish the products **11c** and **14c** in good yields.

As 1,3-diketones are widely known to show commendable keto-enol tautomerism, it is worth to mention the effect of substituents on phenols and ketones on the tautomerism of the corresponding products. Thus, the reaction of 2-methoxy-4-methylphenol (**1d**) with **6** and **9** under the optimal conditions furnished the products **14d** and **17d** as a 3:1 mixture of keto and enol tautomers. It was observed that pronucleophiles such as diethyl malonate (**5**) provided products predominately in keto form, whereas ethyl acetoacetate (**4**) furnished the product dominating enol form.

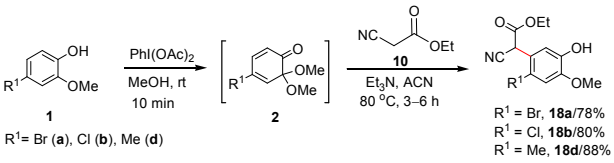
Spurred by the great synthetic medicinal interest of substituted coumarin, especially benzopyranocoumarins for the treatment of neurodegenerative diseases such as Alzheimer's disease, the versatility of this approach was extended to the 4-hydroxycoumarin (**9**). Thus, we carried out the reaction of substituted guaiacols with **9** under previously established conditions. Delightfully, all the products **17a,b,d,e** obtained in excellent yields of 75–88% (Scheme 1). These compounds are quite similar to the precursors of benzopyranocoumarins, worked as potent anti-Alzeimer agents and were prepared through metal catalysis starting from pre-functionalized substrates and in multi-step processes[12] (Scheme 1).

After this, we stepped ahead to explore the reactivity of ethyl cyanoacetate (**10**). The initial attempts for *meta*-substitution with optimized reaction conditions were unsuccessful due to its low reactivity. However, when we performed the reaction of **1a** with **10** in acetonitrile at 80 °C, the *meta*-substituted product **18a** was obtained in 78% isolated yield. All the substrates reacted well under these conditions and furnished the substituted ethyl cyanoacetate derivatives (Scheme 2) in good yields.



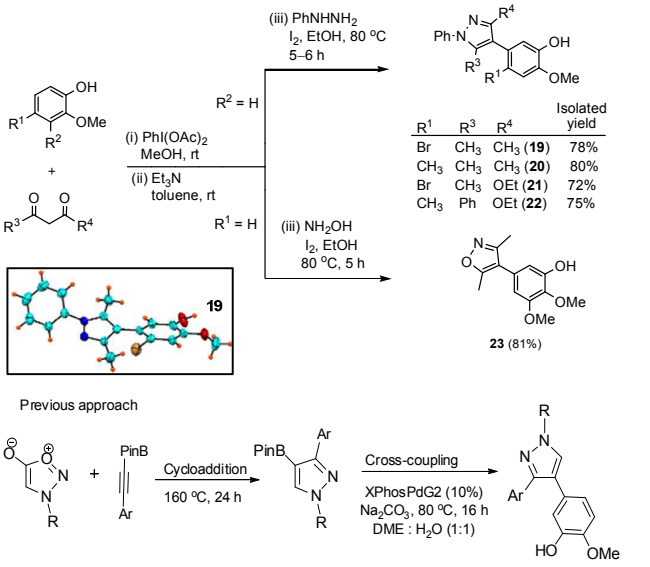
Scheme 1 Reactions of 2-methoxyphenol derivatives with 4-hydroxycoumarin.

It is worth mentioning here that the arylated ethyl cyanoacetates worked as excellent starting materials to generate stable quaternary stereocenter *via* C–C bond formation[13].



Scheme 2 Reactions of guaiacol derivatives with ethyl cyanoacetate.

Having successfully developed an efficient protocol for *meta*-substituted phenols, we turned our focus on the utility of these obtained compounds to access phenol functionalized novel heterocyclic scaffolds in one-pot manner. Condensation of α-arylated diketones with phenylhydrazine and hydroxylamine in presence of iodine led to the formation of corresponding pyrazoles **19**–**22** and isoxazole **23**, respectively, in high yields (Scheme 3).



Scheme 3 Synthesis of phenol substituted pyrazoles and oxazoles.

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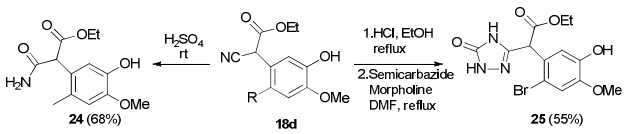
The synergism of phenol with pyrazole and isoxazole leads to some novel analogues of combretastatin A4 (antitumor agent)[14] and dimethylisoxa-zole[15a] motif that act as BET inhibitor (epigenetic target), respectively.

The reactivity profile of α-arylated ethyl cyanoacetate **18d** has been further expanded through the manipulation of the cyano group, by readily converting it into other functionalities. Thus the treatment of **18d** with sulfuric acid gave carboxylic amide **24**. Interestingly, carboxylic amides appear in a variety of drugs, fabrics, plastics, lubricants and fertilizers.[16] The cyano group can also be transformed to triazolone **25**. Of particular note, the triazolones have been established as potent biological active templates[17] for antitumor and antihamelogic activity (Scheme 4).



Scheme 4 Transformation of ethyl cyanoacetate substituted products.

In summary, we have illustrated a novel approach to access *meta*-substituted phenols *via* an efficient, metal-free, base mediated protocol. The present work involves a simple dearomatization strategy of 2-methoxy phenols as readily available aryl source for the α-arylation of 1,3-dicarbonyls and cyanoacetate through C–C bond formation. Underlining the utility of the obtained products, one-pot, straightforward, clean, high yielding routes for the synthesis of phenol substituted heterocycles such as pyrazoles, isoxazoles, coumarins, triazolones and carboxylic amide were demonstrated, that leads the way for the endowment of important biological scaffolds.

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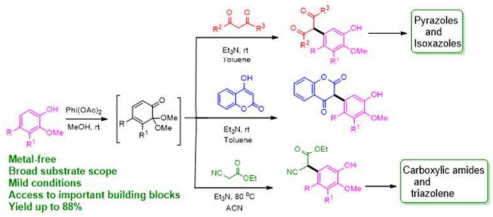
Metal-free direct *C*-arylation of 1,3-dicarbonyl compounds and ethyl cyanoacetate: A platform to access diverse array of *meta*-functionalized phenols



338x190mm (96 x 96 DPI)