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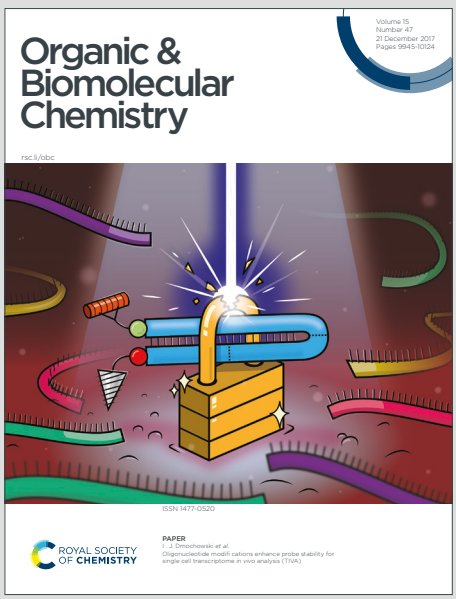

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ARTICLE

Iron-catalyzed regioselective alkylation of 1,4-quinones and coumarins with functionalized alkyl bromides

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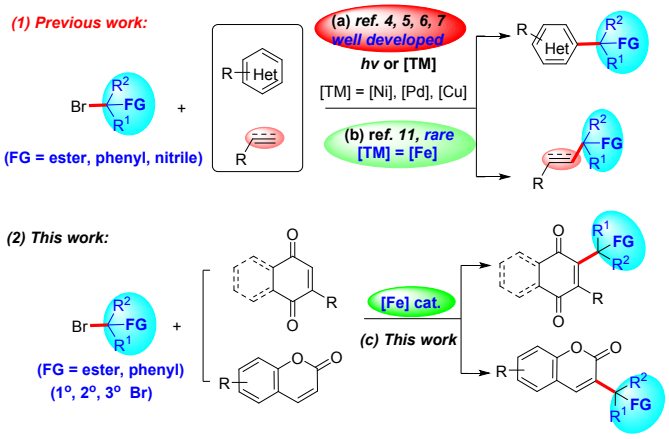
A simple and efficient Fe-catalyzed regioselective alkylation of 1,4-quinones and coumarins, using functionalized alkyl bromides as alkylating reagents, has been developed. The reaction proceeds under mild conditions with addition of alkyl bromides to a wide range of 1,4-quinone and coumarin derivatives with broad substrate scope and densely functional group tolerance in good yields. Further application of these strategies could be accessed to important biologically active antimalarial lead drugs, such as Plasmodione in gram scale in single step for medicinal purposes.

Introduction

The introduction of alkyl groups into molecules of medicinal interest has been recognized as a significant strategy in drug discovery, due to their unique chemical properties and biological activities.[1] Among the numerous methods, using commercially available and bench stable coupling partners should be a desirable project to pursue. Functionalized alkyl halides, especially the readily available α-bromocarbonyl compounds, are among the most ubiquitous chemical blocks, have been studied extensively as one of the most straightforward strategies for the preparation of alkylating compounds.[2] In this context, great efforts have been devoted in cross-coupling reactions[3] between alkenes, alkynes and heteroarenes by Ru-, Ir-based photoredox strategies[4] or transition metals with Ni-,[5] Pd-,[6] or Cu-[7] catalytic systems (a, Scheme 1).

As the most abundant transition metal on earth with low cost, nontoxic and environmentally benign nature, the utilization of iron catalysts in synthetic chemistry should have powerful advantages.[8] Although iron-catalyzed cross-coupling of Grignard reagents[9] as well as the atom transfer radical polymerization (ATRP) reaction[10] with alkyl halides has been well established. However, Fe-catalyzed reactions to construct alkyl groups are remain to be addressed. In 2017, Thomas and Shaver developed an elegant iron-catalyzed atom transfer radical elimination (ATRE) reaction to facilitate a formal Heck cross-coupling with styrenes and functionalized alkyl bromides.[11a] Later on, similar strategies were disclosed by Nishikata and co-workers with tertiary alkyl bromides for heteroaromatic or vinylic C–H alkylations to construct all carbon quaternary centers[11b] (b, Scheme 1). Although impressive achievements have been made,[11] other types of substrate scope upon alkyl halides with iron catalyst in synthetic chemistry were still highly desirable.

The 1,4-quinone[12a-b] and coumarin[12c-e] scaffolds are frequently studied in natural products, biological systems and pharmaceutical chemistry.[12] Therefore, particular attention has been paid in the development of new methods for the construction of alkyl-containing compounds in this area.[13, 14] Inspired by these seminal works[11, 13, 14] and our continuous interest in radical chemistry,[15] herein, we wish to report a general iron-catalyzed protocol for the synthesis of alkylated 1,4-quinones and coumarins with functionalized alkyl bromides with high regioselectivity (c, Scheme 1).



Scheme 1. Selected strategies for the alkylation with functionalized alkyl bromides

Results and discussion

To test this possibility, we began our initial study with 2-methylnaphthalene-1,4-dione (**1a**) in the reaction with ethyl 2-bromopropanoate (**2a**) as the model substrates to optimize the reaction conditions.[13] To our delight, the desired product **3a** was isolated in 48% yield when the reaction was performed in the presence of $FeCl_2$ (10 mol%) and DIPEA (2.0 equiv) in 1,4-dioxane at 100 °C for 24 h (entry 1, Table 1). Control experiments revealed that iron catalyst and DIPEA were all indispensable, and no desired product was detected in the absence of neither of them (entries 2-3).

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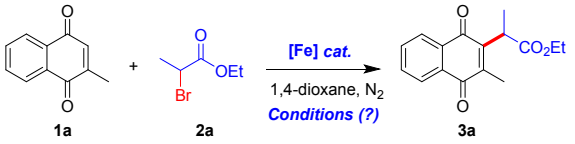
Other solvents (see ESI for details), such as, DCE (27%), toluene (36%), CH_3CN (28%), or DMSO (n.d.) was proven less effective. Screening of other Fe(II) and Fe(III) species, suggested that $FeCl_2$ (48%, entry 1, Table 1) was superior to other iron catalysts (entries 5-9, Table 1). Gratifyingly, increasing the temperature (115 °C) could improve the yield of **3a** to 57% (entry 10). Finally, decreasing the amount of $FeCl_2$ and base, a significant higher of the yield was obtained (69%, entry 16). Thus, we wonder whether a catalytic amount of iron-catalyst could cooperate with substrate **1a** under the reaction conditions. From these experiments, we determined the optimized catalytic reaction conditions: $FeCl_2$ (5.0 mol%), DIPEA (1.5 equiv) in 1,4-dioxane at 115 °C for 28 h.

Table 1. Optimization of the reaction conditions[a]

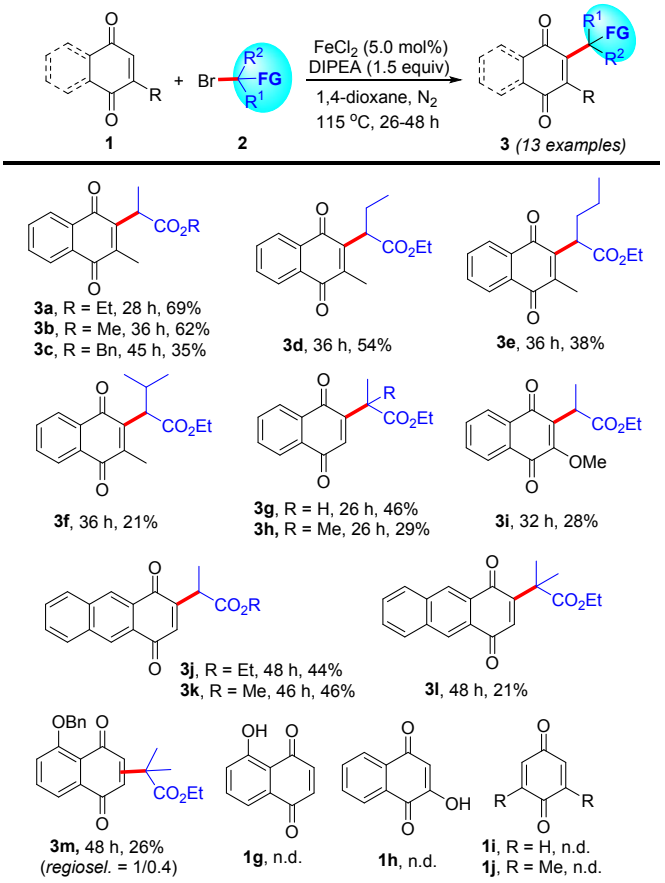


1a 2a 3a

Entry	Catalyst (mol%)	Base (equiv)	T (°C) / t (h)	Yield (%)[b]
1	$FeCl_2$ (10)	DIPEA (2.0)	100 / 24	48
2	$FeCl_2$ (10)	--	100 / 18	n.d.
3	--	DIPEA (2.0)	100 / 30	n.d.
4	$FeCl_2$ (10)	DIPEA (2.0)	85 / 30	< 5
5	$FeCl_3$ (10)	DIPEA (2.0)	100 / 24	46
6	$Fe(acac)_3$ (10)	DIPEA (2.0)	100 / 22	20
7	$Fe(acac)_2$ (10)	DIPEA (2.0)	100 / 22	24
8	$Fe(OTf)_2$ (10)	DIPEA (2.0)	100 / 24	36
9	$Fe(OAc)_2$ (10)	DIPEA (2.0)	100 / 24	25
10	$FeCl_2$ (10)	DIPEA (2.0)	115 / 24	57[c]
11	$FeCl_2$ (10)	DABCO (2.0)	115 / 22	n.d.
12	$FeCl_2$ (10)	NEt_3 (2.0)	115 / 22	19
13	$FeCl_2$ (10)	PMDTA (2.0)	115 / 22	n.d.
14	$FeCl_2$ (10)	Na_2CO_3 (2.0)	115 / 22	22
15	$FeCl_2$ (7.5)	DIPEA (2.0)	115 / 24	68[c]
16	***$FeCl_2$ (5.0)***	***DIPEA (1.5)***	***115 / 28***	***69***[c]
17	$FeCl_2$ (5.0)	DIPEA (1.5)	115 / 28	60[c, d]
18	$FeCl_2$ (3.0)	DIPEA (1.5)	115 / 28	59[c]

[a] Reaction conditions: In N_2 atmosphere, **1a** (1.0 equiv, 0.20 mmol), **2a** (2.0 equiv, 0.40 mmol), [Fe], base (2.0 equiv, 0.40 mmol) in 1,4-dioxane (1.5 mL) at 100 °C for 18-28 h; [b] Isolated yield; [c] 0.40 mmol scale of **1a** was used; [d] **2a** (1.5 equiv) was used. Unless otherwise noted, DIPEA = *N,N*-Diisopropylethylamine; DABCO = Triethylenediamine; PMDTA = Pentamethyldiethylenetriamine; n.d. = not detected.

With the optimized conditions in hand, the scope of 1,4-quinones and alkyl bromides was investigated first (Scheme 2). Alkyl bromides with ester groups derivate from various substituents, such as, Et, Me, Bn were examined, all could undergo the alkylation reaction smoothly, and generate the corresponding products **3a-3i** in moderate yields in 21-69%. It should be noted that, an obvious substituent effect was observed in electronic and steric properties with alkyl bromides[7i] during the formation of **3e-3f** and **3h-3i**. Then the substitution effect of the aromatic rings of 1,4-quinones was examined. Anthracene-1,4-dione (**1e**) also reacted smoothly to give the desired products **3j-3l** in moderate yields. 1,4-Quinone (**1f**) bearing a BnO-group was also tolerated, albeit with low yield (**3m**, 26% yield and 1/0.4 regioselectivity). Unfortunately, 1,4-quinones **1g-1j**; alkyl bromides **2h-2j**, such as ethyl 2-bromoacetate or bromocyclohexane, could not be used as substrates to give the desired products, and complete decomposition of the starting materials were observed.

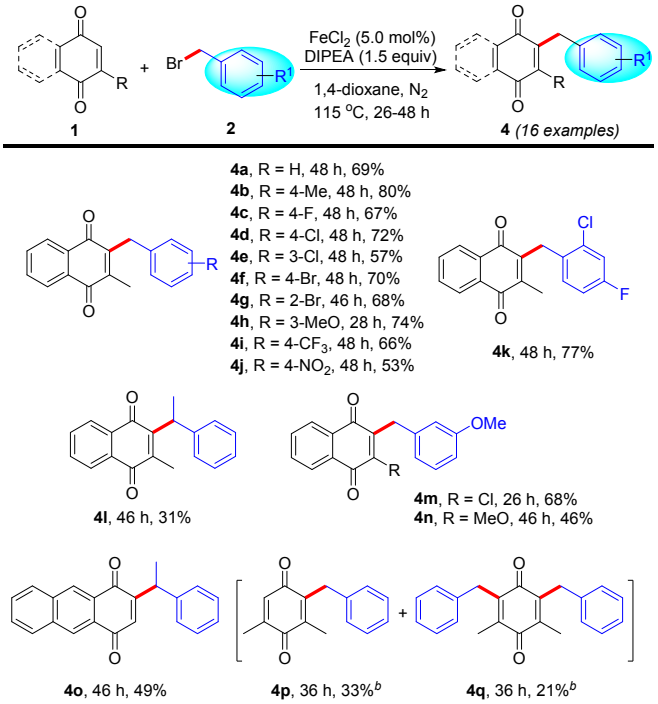


Scheme 2. Substrate scope of 1,4-quinones with alkyl bromides[a]

[a] Reaction conditions: In N_2 atmosphere, **1** (1.0 equiv, 0.20 mmol), **2** (2.0 equiv, 0.40 mmol), $FeCl_2$ (5.0 mol%), DIPEA (1.5 equiv, 0.30 mmol) in 1,4-dioxane (1.5 mL) at 115 °C for 26-48 h; n.d. = not detected.

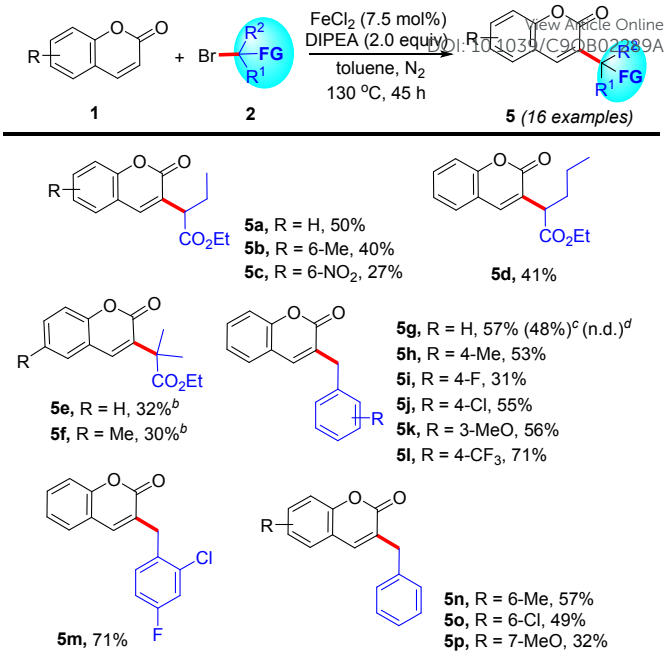
We then turned our interest to benzyl bromides, which could lead to important biologically active molecules, such as benzylmenadione analogs, identified as potent and fast-acting antimalarial lead drug in pharmaceutical industry[16] (Scheme 3).

It was showed that, benzyl bromides bearing different substituents, either electron-donating (*e.g.*, Me, OMe) or electron-withdrawing groups (F, Cl, Br, CF_3), even the strong electron-withdrawing group (4-NO_2), at different positions of the benzene ring, could be functionalized as the competent coupling partners to generate the desired product **4a-4o** in moderate to good yields in 31-80% successfully. Notably, *ortho*-substituted effect was not found during the formation of **4g** and **4k** (68% and 77%). However, product **4l** was formed in lower yield (31%), likely due to the steric effects. When 2,6-dimethylcyclohexa-2,5-diene-1,4-dione was tested under standard conditions, a complicated mixture containing bis-benzylated products including **4p** and **4q** were obtained in 33% and 21% yield, respectively.



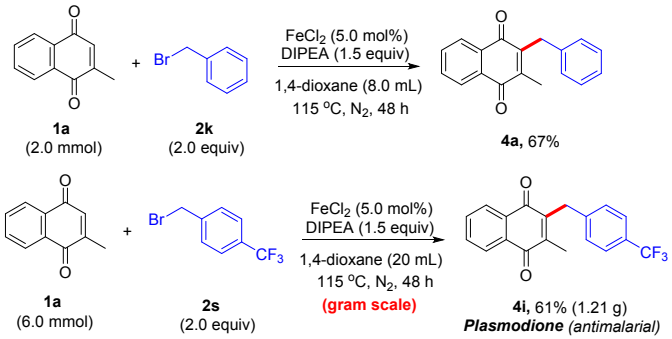
Scheme 3. Substrate scope of 1,4-quinones with benzyl bromides[a]
[a] Reaction conditions: In N_2 atmosphere, **1** (1.0 equiv, 0.20 mmol), **2** (2.0 equiv, 0.40 mmol), $FeCl_2$ (5.0 mol%), DIPEA (1.5 equiv, 0.30 mmol) in 1,4-dioxane (1.5 mL) at 115 °C for 26-48 h; [b] 100 °C.

Encouraged by these results, we then studied the feasibility of the current reaction with a range of coumarins for further expansion of the substrate scope[14, 15e] (Scheme 4). Numerous coumarins with different electronic properties and substitution patterns (**1k-1o**) were successful in providing the desired products **5a-5p** in moderate to good yields in 27-71%.



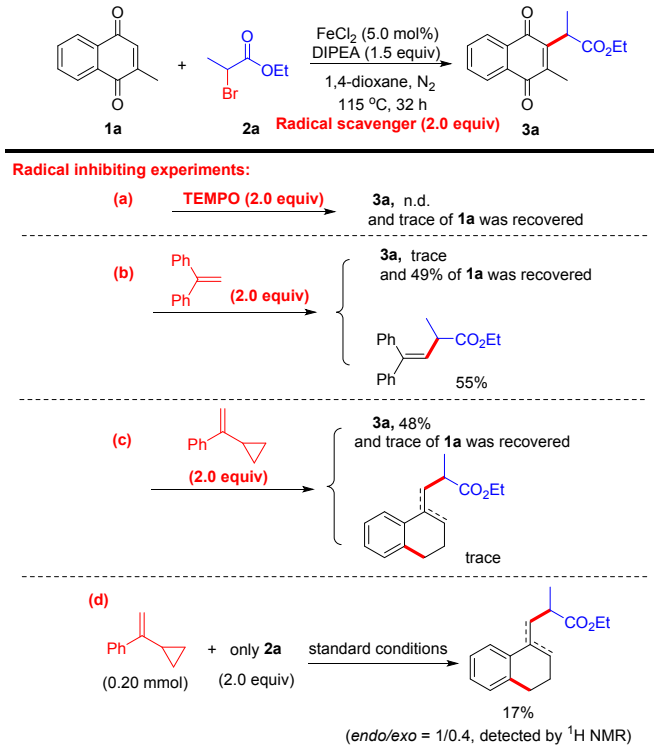
Scheme 4. Substrate scope of coumarins with alkyl bromides[a]
[a] Reaction conditions: In N_2 atmosphere, **1** (1.0 equiv, 0.20 mmol), **2** (2.0 equiv, 0.40 mmol), $FeCl_2$ (7.5 mol%), DIPEA (2.0 equiv, 0.40 mmol) in toluene (2.0 mL) at 130 °C for 45 h; [b] in 1,4-dioxane/ toluene (2.0 mL, v/v = 1/1); [c] in 1,4-dioxane; [d] 115 °C; n.d. = not detected.

It is noteworthy that, the reaction could be performed at large scale without significant loss of the yield (Scheme 5). A simple 10-fold scale reaction in the formation of **4a** (2.0 mmol scale, 67% yield) or a gram-scale reaction for the preparation of antimalarial lead drug Plasmodione analogs[16] **4i** (1.21g scale, 61% yield) was performed successfully with these commercially available and bench stable coupling partners in good results.



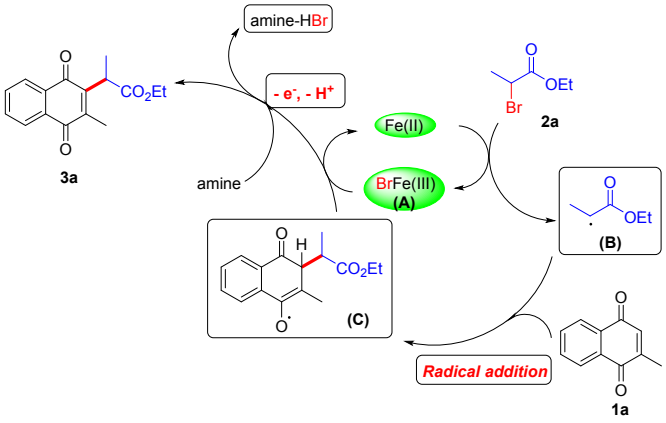
Scheme 5. Large-scale synthesis

Several control experiments were conducted to probe the reaction mechanism. For example, some radical scavengers, such as, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was performed to gain insights into the mechanism of the reaction.[11] The reactions were completely inhibited by TEMPO, and almost no desired product **3a** was generated (a, Scheme 6). Importantly, the alkyl radical was trapped by 1,1-diphenylethylene or (1-cyclopropylvinyl)benzene,[15d-e, 17] albeit in low yield (b-d, Scheme 6, and ESI for details), indicating that radical intermediates were involved in the reaction.[11, 17]



Scheme 6. Mechanistic study

Based on these results and previous established reports,[11] a plausible reaction pathway was proposed in Scheme 7. Initially, functionalized alkyl bromide **2a** is reduced by the Fe(II)-catalyst to afford Fe(III)-species **A** and alkyl radical **B**. Then, radical addition of **B** to the C-3 position of 1,4-quinone **1a** generates radical intermediate **C**.[13j] Ultimately, **C** undergoes single electron transfer (SET) oxidation[11b] by **A** and proton elimination in the presence of the amine,[11b] leads to the desired product **3a**, with concurrent regeneration of the Fe(II)-catalyst.



Scheme 7. Plausible mechanism

Conclusions

In summary, we have developed a highly efficient Fe-catalyzed regioselective alkylation of 1,4-quinones and coumarins with functionalized alkyl bromides as alkylating reagents. The reaction proceeds under mild conditions with addition of alkyl bromides to a wide range of 1,4-quinone and coumarin derivatives with broad substrate scope and densely functional group tolerance in good yields. Further application of these strategies could be utilized for the preparation of important biologically active antimalarial lead drugs, such as Plasmodione in gram scale in single step for medicinal purposes.

Conflicts of interest

There are no conflicts to declare.

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