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Regioselective reaction of quinones with Reformatsky reagent: $(BrZnCH_2CO_2Et{\cdot}THF)_2$

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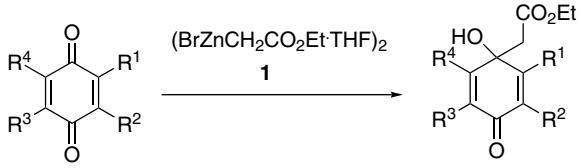
Abstract—Reformatsky reactions of *p*-quinones with crystalline reagent $(BrZnCH_2CO_2Et{\cdot}THF)_2$ were investigated and took place successfully, providing β-hydroxy esters in high yield. Notably, in the case of 2,6-disubstituted-*p*-quinones, regioselective Reformatsky reactions occurred to give corresponding β-hydroxy esters in good yields.

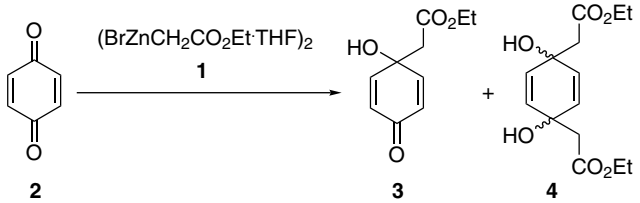
Quinol esters are important intermediates in the biosynthesis and metabolism of phenolic natural products.[1] They are also very useful precursors in the synthesis of naturally occurring quinones and alkaloides.[2] With regard to the preparation of quinol esters, addition reactions with organolithium reagents have been extensively investigated.[3] An indium-mediated reaction of quinones has also been developed.[4] In contrast, there has been little use of organozinc compounds such as Reformatsky reagents in the synthesis of quinol esters, despite that the Reformatsky reaction has been investigated extensively during the years.[5] Perhaps widespread prejudice that 'the classical zinc-mediated Reformatsky reaction with *p*-benzoquinone gives *p*-qinole ester in only low yield' has precluded investigations in this area.[6] On the other hand, with regard to Reformatsky reagents, syntheses of crystalline *tert*-butyl bromozincacetate and the reactions using its Reformatsky reagent are reported.[7] Recently, we isolated a crystalline powder of ethyl bromozincacetate: $(BrZnCH_2CO_2Et{\cdot}THF)_2$ (**1**).[8] Applicability under a variety of reaction conditions as well as an improvement of yield was expected. In this letter, we report that the Reformatsky reaction of quinones with **1** took place with high regioselectivity to give quinole esters in good yields (Scheme 1).



Scheme 1. Highly selective Reformatsky reaction of quinones with $(BrZnCH_2CO_2Et{\cdot}THF)_2$.

First, the reaction of *p*-benzoquinone (**2**) with crystalline Reformatsky reagent **1** in Et_2O was examined (entry 1 in Table 1). This Reformatsky reaction took place nearly

Table 1. Reformatsky reaction of *p*-benzoquinone with **1**[a]



2 **3** **4**

Entry	**1** (equiv)	Solvent	Reaction ratio[b] **3**:**4**	Isolated yield (%)
1	0.6	Et_2O	93:7	**3**, 78
2	0.6	THF	90:10	**3**, 70
3	1.5	THF	0:100	**4**, 66

[a] Reaction conditions: **1** (2–5 mmol), **2** (3.3 mmol), solvents (8.5–17.5 mL), 20–25 °C, 1–3 h.
[b] ^1H NMR analysis of crude products.

Keywords: Reformatsky reaction; Regioselectivity; Quinones; Quinol esters.
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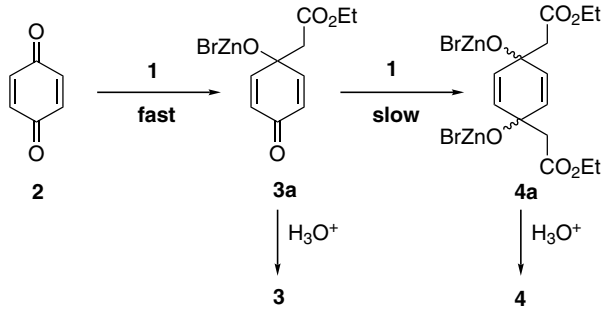
selectively, and the corresponding monoalcohol **3** was obtained in 78% yield.

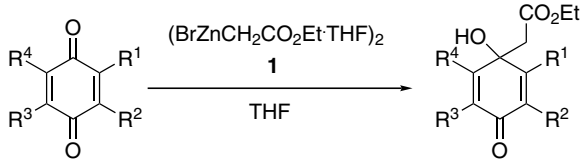
As the classical Reformatsky reaction of **2** is reported to provide *p*-quinol ester in low yield (26%),[6a] this result indicates that **1** is useful for a Reformatsky reaction. Siegel et al. suggested that this reaction took place selectively because of the insolubility of intermediate **3a**, although **3** was formed in only low yield in Et_2O (Scheme 2). In fact the reaction mixture was a suspension. Next, we attempted the reaction of **2** with **1** in THF, which would solve **3a** (entry 2).[9] Interestingly, this reaction proceeds smoothly to give **3** in 70% yield despite being homogeneous. In addition, when the amount of **1** was increased to 1.5 equiv, a double addition product (**4**) was obtained in 66% yield (entry 3). These results suggest that the reaction from **2** to **3a** is considerably faster than that from **3a** to **4a** (Scheme 2).

Table 2 summarizes representative results of the Reformatsky reaction of various *p*-benzoquinones with **1**. 2,5-Disubstituted-*p*-benzoquinones with methyl or chloro groups were employed successfully for the Reformatsky reaction (entries 2 and 3). The reaction with 2,3,5,6-tetrasubstituted-*p*-benzoquinones such as tetramethyl-*p*-benzoquinone and tetrachloro-*p*-benzoquinone proceeded smoothly to provide the corresponding monoalcohols, **7** and **8**, respectively, in good yield.



Scheme 2. A possible pathway for the Reformatsky reaction of *p*-benzoquinone with **1**.

Table 2. Reformatsky reaction of various *p*-benzoquinones with **1**[a]

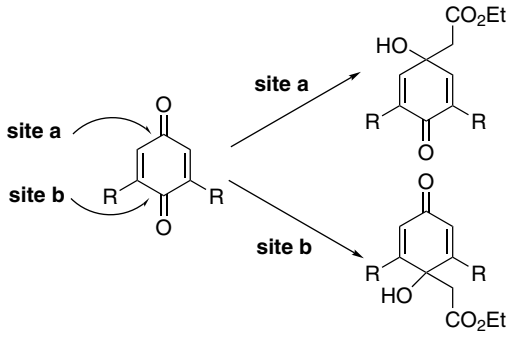


Entry	Quinone				Product	Isolated yield (%)
	R^1	R^2	R^3	R^4		
1	H	H	H	H	**3**	70
2	Me	H	Me	H	**5**	87
3	Cl	H	Cl	H	**6**	92
4	Me	Me	Me	Me	**7**	94
5	Cl	Cl	Cl	Cl	**8**	94

[a] Reaction conditions: **1** (2 mmol), quinones (3.3 mmol), THF (9 mL), 20–25 °C, 1h.

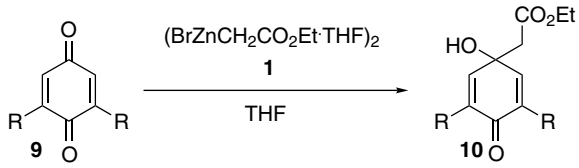
We have also investigated the Reformatsky reaction of 2,6-disubstituted-*p*-benzoquinones with **1**. The addition of not only one or two carbonyl units but also of an α,β-unsaturated carbonyl unit (1,2- or 1,4-addition) is expected (Scheme 3). Therefore, the direct addition of organometallic compounds to unsymmetrical quinones exhibited low regioselectivity.[10] To produce 1,2-adducts of 2,6-disubstituted-*p*-benzoquinones, the protection of quinone with TMSCN, and deprotection had to be carried out.[11]

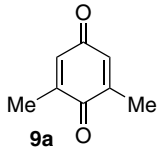
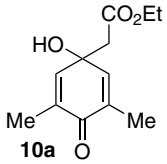
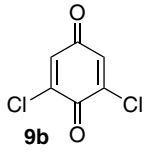
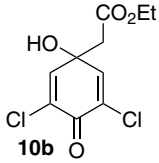
The reaction of 2,6-disubstituted-*p*-benzoquinones **9** with crystalline Reformatsky reagent **1** was examined (Table 3). In the case of 2,6-dimethyl-*p*-benzoquinone (**9a**) and 2,6-dichloro-*p*-benzoquinone (**9b**), the reaction took place regioselectively, and the corresponding product **10a** and **10b** was produced in 80% and 74% yields, respectively (entries 1 and 2).[12] It is noteworthy that the direct addition of **1** to unsymmetrical quinones at



Scheme 3. Reformatsky reaction of 2,6-disubstituted-*p*-benzoquinones.

Table 3. Reformatsky reaction of 2,6-disubstituted-*p*-benzoquinones with **1**[a]



Entry	Quinones	Product	Yield (%)
1			80[b]
2			74[c]

[a] Reaction conditions: **1** (2 mmol), **9** (3.3 mmol), THF (9 mL), 20–25 °C, 1 h.
[b] Isolated yield.
[c] NMR yield.

room temperature proceeds regioselectively in good yield, although **9a** and **9b** contain two or more different reactive sites for addition.

In summary, we have developed a highly selective Reformatsky reaction of quinones with crystalline Reformatsky reagent **1**. The results suggest that the reaction using crystalline Reformatsky reagent is synthetically very useful. We are currently examining the application of this reagent to different classes of substrates.

Acknowledgements

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10. Preparation of ethyl(1-hydroxy-4-oxocyclohexa-2,5-dien-1-yl)acetate (**3**). Under nitrogen atmosphere, 6 mL of THF was added to 1.22 g (2 mmol, 0.6 equiv) of $(BrZnCH_2CO_2Et{\cdot}THF)_2$. Under argon atmosphere, a solution of 0.36 g (3.33 mmol) of *p*-benzoquinone in 2.5 mL of THF was added dropwise while stirring at 0–5 °C. The mixture was stirred at 20–25 °C for 1 h. Five milliliters of 1 N hydrochloric acid was added dropwise at 20 °C or lower, followed by dilution with 25 mL of ethyl acetate. Then, the layers were separated. The organic layer was washed successively with 5 mL (×2) of 1 N hydrochloric acid, 5 mL of water, 5 mL (×2) of an aqueous saturated sodium bicarbonate solution, and 5 mL (×2) of an aqueous saturated sodium chloride solution. After washing, the organic layer was dried with anhydrous magnesium sulfate. After concentration under reduced pressure, purification with silica gel column (developing solvent; ethyl acetate/*n*-hexane = 1/3, 1/2) afforded 0.46 g of **3** (yield 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, $J = 7.1$ Hz, 3H), 2.70 (s, 2H), 4.19 (q, $J = 7.1$ Hz, 2 H), 4.36 (s, 1H), 6.17 (d, $J = 10.1$ Hz, 2H), 6.98 (d, $J = 10.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 44.2, 61.8, 67.7, 128.4, 149.9, 170.8, 185.6; IR (NaCl) 3327, 1728, 1668, 1622 cm^{-1}; MS (EI), $m/z = 196$ (M^+); Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 60.94; H, 6.00.
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12. Preparation of ethyl(1-hydroxy-3,5-dimethyl-4-oxocyclohexa-2,5-dien-1-yl)acetate (**10a**). Under nitrogen atmosphere, 6 mL of THF was added to 1.22 g (2 mmol, 0.6 equiv) of $(BrZnCH_2CO_2Et{\cdot}THF)_2$. Under argon atmosphere, a solution of 0.45 g (3.33 mmol) of 2,6-dimethyl-*p*-benzoquinone in 3 mL of THF was added dropwise while stirring at 0–5 °C. The mixture was stirred at 20–25 °C for 1 h. Five milliliters of 1 N hydrochloric acid was added dropwise at 20 °C or lower, followed by dilution with 25 mL of ethyl acetate. Then, the layers were separated. The organic layer was washed successively with 5 mL (×2) of 1 N hydrochloric acid, 5 mL of water, 10 mL (×2) of an aqueous saturated sodium bicarbonate solution, and 5 mL (×2) of an aqueous saturated sodium chloride solution. After washing, the organic layer was dried with anhydrous magnesium sulfate. After concentration under reduced pressure, purification with silica gel column (developing solvent; ethyl acetate/*n*-hexane = 1:3) afforded 0.60 g of **10a** (yield 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, $J = 7.2$ Hz, 3H), 1.89 (s, 6H), 2.64 (s, 2H), 3.87 (s, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 6.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 15.7, 44.0, 61.0, 67.2, 144.2, 144.3, 170.8, 186.3; IR (KBr) 3408, 1732, 1631 cm^{-1}; MS (EI), $m/z = 224$ (M^+); Anal. Calcd for $C_{12}H_{18}O_4$: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.28.