Convenient Synthesis of Quinol Esters by Indium-mediated Reformatsky Reaction of Quinones

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Indium-mediated Reformatsky reaction of *para*-quinones gives good yields of *para*-quinols under mild conditions. Naturally occurring quinol esters such as jacaranone are conveniently prepared in a one-pot synthesis.

Functionalized quinols are not only important intermediates in the biosynthesis and metabolism of natural phenols[1] but are also useful synthetic precursors to naturally occurring quinones and alkaloids.[2] The direct addition of organometallic reagents to quinones is unfavourable for the selective synthesis of quinols, because it generally gives a complex mixture of products with poor yields of the desired quinols.[3] The selective protection of one of the carbonyl groups of substituted *p*-quinones with trimethylsilyl cyanide has been developed by Evans[4] and the resulting protected quinones have been demonstrated to be excellent substrates for organometallic addition.[2,5] Later, it was shown that organo-lithium and -magnesium reagents add at low temperature to unprotected quinones to give good yields of quinols.[3,6]

We have recently reported that the organoindium reagent derived from an iodoacetate ester and indium metal reacts with aldehydes and ketones to give β-hydroxy esters.[7] We found that this indium enolate couples with unprotected quinones under mild reaction conditions to give good yields of quinol esters. Naturally occurring quinol esters such as jacaranone were conveniently prepared by this method.

1 **2**

Reagents and conditions: i, $ICH_2CO_2R^5$, In, DMF, room temperature; ii, water

1	R^1	R^2	R^3	R^4
a	H	H	H	H
b	$-[CH{=}CH]_2-$		H	H
c	$-[CH{=}CH]_2-$		Me	H
d	$-[CH{=}CH]_2-$		OMe	H

2	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	Me
b	H	H	H	H	Et
c	$-[CH{=}CH]_2-$		H	H	Me
d	$-[CH{=}CH]_2-$		Me	H	Me
e	$-[CH{=}CH]_2-$		H	Me	Me
f	$-[CH{=}CH]_2-$		OMe	H	Me

Results and Discussion

Quinones **1** were treated with indium enolates prepared from iodoacetates and indium powder in dimethylformamide (DMF) at room temperature for 5–24 h. Aqueous work-up and purification by chromatography gave pure quinol esters **2**. Results are summarized in Table 1. *p*-Benzoquinone **1a** reacted with methyl and ethyl indioacetates to give jacaranone **2a**[8] and the corresponding ethyl ester **2b**,[9] respectively. These quinol esters are naturally occurring, antitumour compounds. 2-Methyl-1,4-naphthoquinone **1c** gave two isomeric products **2d** and **2e**, and the major one was identified as the 2-methyl isomer **2e** based on ^1H NMR analysis. 2-Methoxy-1,4-naphthoquinone **1d** gave a high yield of the 3-methoxyquinol **2f** exclusively, and the corresponding 2-methoxy isomer was not formed, presumably owing to the strong electron-donating nature of the methoxy group. It is worth noting here that only the 2-methoxy isomer was formed, and compound **2f** could not be obtained, by Evans' carbonyl-protection methodology.[10]

Classical zinc-mediated Reformatsky reaction on *p*-benzoquinone is known, but the yield of the *para*-quinol is low (26%).[11] Although direct coupling of lithium enolates with unprotected quinones at low temperature has been developed recently,[3,6] our indium-based procedure is superior to the existing methods in respect of (i) no hazardous reagents such as butyllithium or lithium diisopropylamide are employed, (ii) the yields are generally good, (iii) reaction conditions are mild, and (iv) experimental operations are simple. Therefore, the present indium-mediated Reformatsky reaction of quinones provides a convenient method for the synthesis of functionalized quinols.

Experimental

M.p.s were determined on a Mitamura Riken micro melting point apparatus and are uncorrected. IR spectra of solids (KBr) and oils (neat) were recorded on a JASCO A-102 spectrophotometer. ^1H NMR spectra were obtained for solutions in $CDCl_3$ on a Hitachi R-90 (90 MHz) or a Varian XL-200 (200 MHz) spectrometer with Me_4Si as internal standard; *J*-values are given in Hz. Elemental analyses were performed at the Elemental Analysis Centre of Kyoto University.

Synthesis of Quinols **2**; *Typical Procedure*.—Methyl iodoacetate (360 mg, 1.8 mmol) was added to a stirred suspension of

Table 1 Synthesis of quinols **2**

Quinone	R^5 in $ICH_2CO_2R^5$	Reaction time (*t*/h)	Product	Yield (%)
1a	Me	12	**2a**	51
1a	Et	24	**2b**	69
1b	Me	5	**2c**	69
1c	Me	19	**2d**	23
			2e	63
1d	Me	17	**2f**	89

indium powder (99.99%; stabilized by 0.5% MgO; 138 mg, 1.2 mmol) in DMF (2 cm^3) under argon. An exothermic reaction occurred immediately. The mixture was stirred at room temperature for 30 min. *p*-Benzoquinone **1a** (108 mg, 1 mmol) was added as a solid in one portion and the reaction mixture was stirred for 12 h. Water (50 cm^3) was added and the product was extracted with dichloromethane (30 cm^3 × 3). The extracts were washed with water (100 cm^3), dried with anhydrous sodium sulphate, and evaporated. The residue was purified by preparative TLC [silica gel; CH_2Cl_2–Et_2O (9:1)] to give jacaranone **2a** (93 mg, 51%) as crystals from chloroform–hexane, m.p. 80–81 °C (lit.,[8a] 76–77 °C). Other quinols (**2b–f**) were similarly prepared and purified.

Ethyl (1-hydroxy-4-oxocyclohexa-2,5-dien-1-yl)acetate **2b**. Crystals from chloroform–hexane, m.p. 72–74 °C (lit.,[9] 71 °C).

Methyl (1,4-dihydro-1-hydroxy-4-oxonaphthalen-1-yl)acetate **2c**. Crystals from ethyl acetate–hexane, m.p. 125–127 °C (lit.,[10] 127–128 °C).

Methyl (1,4-dihydro-1-hydroxy-2-methyl-4-oxonaphthalen-1-yl)acetate **2d**. Crystals from CCl_4, m.p. 117–118 °C (Found: C, 68.2; H, 5.7. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%); ν_{max}/cm^{-1} 3450, 1734, 1662 and 1642; δ_H 1.99 (3 H, d, *J* 2, Me), 2.68 (1 H, d, *J* 16, C*H*H), 3.00 (1 H, d, *J* 16, CH*H*), 3.69 (3 H, s, OMe), 4.30 (1 H, s, OH), 6.97 (1 H, q, *J* 2, olefin), 7.46 (1 H, t, *J* 8, ArH), 7.63 (1 H, t, *J* 8, ArH), 7.74 (1 H, d, *J* 8, ArH) and 8.09 (1 H, d, *J* 8, ArH).

Methyl (1,4-dihydro-1-hydroxy-3-methyl-4-oxo-1-naphthalene)acetate **2e**. Oil (lit.,[10] m.p. 65–66 °C).

Methyl (1,4-dihydro-1-hydroxy-2-methoxy-4-oxonaphthalen-1-yl)acetate **2f**. Crystals from acetonitrile, m.p. 167–169 °C (Found: C, 64.1; H, 5.35. $C_{14}H_{14}O_5$ requires C, 64.1; H, 5.4%); ν_{max}/cm^{-1} 3380, 1730, 1624 and 1614; δ_H 2.80 (1 H, d, *J* 16, C*H*H), 3.08 (1 H, d, *J* 16, CH*H*), 3.62 (3 H, s, OMe), 3.86 (3 H, s, OMe), 4.46 (1 H, s, OH), 5.74 (1 H, s, olefin), 7.50 (1 H, t, *J* 8, ArH), 7.67 (1 H, t, *J* 8, ArH), 7.78 (1 H, d, *J* 8, ArH) and 8.12 (1 H, d, *J* 8, ArH).

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