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A new mild and rapid deprotecting method for aryl cyclohex-2-en-1-yl ethers to phenols

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Abstract—Cyclohex-2-en-1-yl ether can be used as a new protecting group of mono and disubstituted phenols. The cleavage of the cyclohex-2-en-1-yl ether is mild, rapid with excellent yields.

Protecting groups of phenols or polyphenols have been widely used in synthetic organic chemistry,[1,2] many hydroxy protecting groups are known, the most often used being esters,[3] carbonates,[4] ethers removable in acid or basic conditions,[5] but also allyl[6–9] or benzyl[10] groups which can be deprotected by reductive procedures, including catalytic hydrogenation or dissolved metals.

In this paper we report the use of cyclohex-2-en-1-yl entity as a good protecting group for phenols as ethers not previously described. The cleavage of cyclohex-2-en-1-yl ether in acid medium was generally rapid and mild. The scope of this protection method was studied with different mono and disubstituted phenols or catechol.

Hydrogen chloride in anhydrous ethyl ether was used to cleave the cyclohex-2-en-1-yl ether link. The starting ether derivatives (Table 1, entries 1–5) were easily obtained in excellent yields (92–98%)[11] from monophenols substituted either with electron-withdrawing (2-Br, 2-$CONH_2$, 4-NO_2) or electron-donating groups (4-C_2H_5, 4-OCH_3). The cleavage of these cyclohex-2-en-1-yl ether derivatives was rapid and easy, to give the corresponding phenol products with good yields (Table 1, entries 1–5). We can notice that for the deprotection of the nitro derivative (Table 1, entry 5), the reaction time increased (60 min), probably caused by the strongly electron-withdrawing effect of the nitro group compared to bromo and acetamido groups of the corresponding products in entries 1–2. The cleavage of the cyclohex-2-en-1-yl ether derivatives in entries 3–4, with electron-donating groups was rapid and easy.

In the series of disubstituted phenols (Table 1, entries 6–11), the deprotection of cyclohex-2-en-1-yl ether was also easy in the presence of a free hydroxy group, an other ether link and even with other protecting groups such as esters or allyl ethers.

The deprotection method was applied to methyl-4-(cyclohex-2-en-1-yloxy)-3-hydroxy benzoate[12] to give the corresponding methyl-3,4-dihydroxybenzoate (Table 1, entry 6). The starting material of this reaction was synthesized with methyl-3,4-hydroxybenzoate in the presence of 3-bromocyclohexene and K_2CO_3 in acetone at room temperature to give moderate yield of 40%.[12] Increasing the temperature to reflux led to the formation of methyl-3,4-bis (cyclohex-2-en-1-yloxy)-benzoate with a high yield of 87%.

The diether compounds (Table 1, entries 7–11) were synthesized from methyl-4-(cyclohex-2-en-1-yloxy)-3-hydroxybenzoate in the presence of an excess of 3-bromocyclohexene and K_2CO_3 in acetone with excellent yields (89–97%).[11,13] In the same conditions cleavage with hydrogen chloride in anhydrous ether, the diether products gave selectively methyl-3-alkoxy-4-hydroxy benzoate (Table 1, entries 7–9). When the substrates in entries 10[11] and 11[13] (Table 1) were treated in analogous conditions, the allyl ether and the acetate group were not cleaved and only the cyclohex-2-en-1-yl ether was cleaved to yield the corresponding products.

The selective cleavage of cyclohex-2-en-1-yl ether could be due to the more stability of the corresponding carbocation formed in acid medium.

Keywords: phenol deprotection.

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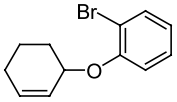
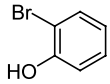
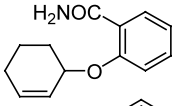
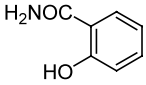
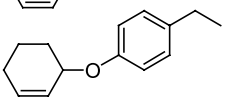
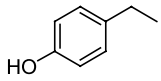
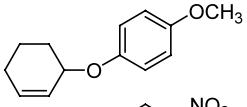
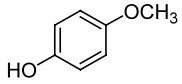
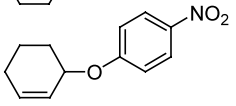
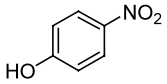
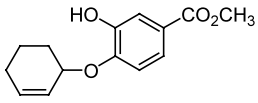
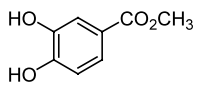
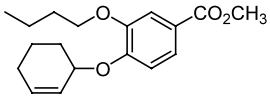
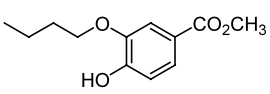
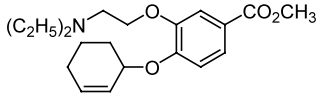
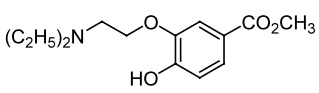
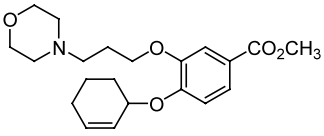
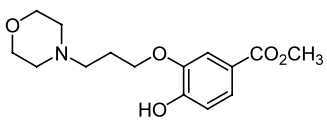
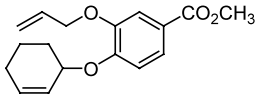
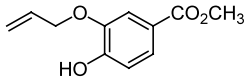
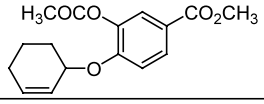
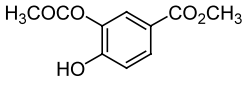
Table 1. Cyclohex-2-en-1-yl ethers deprotection to mono and disubstituted phenols or catechol (entries 1–11)

Entry	Substrate	Time (mn)	Product	Yield %
1		1		94
2		1		98
3		1		99
4		1		95
5		30		85
6		1		94
7		60		99
8		1		98
9		1		99
10		360		70
11		180		95

General procedure: To a solution of cyclohex-2-en-1-yl ether compound (10 mmol) in anhydrous diethyl ether (20 mL), a solution of diethyl ether saturated with gaseous hydrogen chloride was added. The mixture was stirred at room temperature. On completion of the reaction, as indicated by TLC, the solution was evaporated under reduced pressure to give the final product without purification.

In summary, we have developed a rapid and mild efficient method for deprotection of cyclohex-2-en-1-yl ether in presence of other functional groups. This method will find application in organic synthesis with phenols, which require different protecting groups.

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11. General procedure to synthesize the monoether (Table 1, entries 1–5) or the diether compounds (entries 7–10): Phenol derivative (1 mmol) was added to a mixture of acetone (10 mL), K_2CO_3 (3 mmol) and the desired halogeno reagent (3 mmol). The solution was refluxed for 2 h, filtered and evaporated under reduced pressure. The oily residue was washed with petroleum ether (40–60) and recrystallized. Yield (89–98%).
12. Synthesis of methyl-4-(cylohex-2-en-1-yloxy)-3-hydroxy benzoate (entry 6): to a mixture of methyl-3,4-dihydroxybenzoate (1 mmol) and K_2CO_3 (1 mmol) in acetone (30 mL), 3-bromocyclohexene (1 mmol) in acetone (5 mL) was added. The mixture was stirred at room temperature for one day. The solution was filtered and the filtrate evaporated under reduced pressure. The oily residue was washed with water and petroleum ether (40–60) to give a solid, which was recrystallized from diisopropyl ether. Yield 40%; mp 109–111°C; IR 3384 (OH) 1693 (CO); ^{1}H NMR ($CDCl_3$): δ 1.60–2.30 (6H, m, $(CH_2)_3$), 3.90 (3H, s, OCH_3), 4.92 (1H, m, CH), 5.80 (1H, s, OH), 5.85 (1H, m, CH=), 6.05 (1H, m, CH=), 6.82 (1H, d, $J=8.05$ Hz, CH_{Ar}), 7.56–7.63 (2H, m, 2 CH_{Ar}).
13. Synthesis of methyl-4-(cyclohex-2-en-1-yloxy)-3-acetyl benzoate (entry 11): methyl-4-(cyclohex -2-en-1-yloxy)-3-hydroxybenzoate (1 mmol) in acetic anhydride (10 mL) was refluxed for 2 h. The solution was evaporated under reduced pressure. Water (10 mL) and ethyl acetate (10 mL) were added to the residue. The organic layer was dried, evaporated under reduced pressure to give an oily product. Yield 91%; IR 1770 (CO) 1718 (CO); ^{1}H NMR ($CDCl_3$): δ 1.60–2.30 (6H, m, $(CH_2)_3$), 2.35 (3H, s, $COCH_3$), 3.90 (3H, s, OCH_3), 4.85 (1H, m, CH), 5.80 (1H, m, CH=), 6.00 (1H, m, CH=), 7.00 (1H, d, $J=9.00$ Hz, CH_{Ar}), 7.70 (1H, d, $J=2.00$ Hz, CH_{Ar}), 7.90 (1H, dd, $J=9.00$ Hz, $J=2.00$ Hz, CH_{Ar}).