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NOVEL SYNTHESIS OF MONOETHERS OF HYDROQUINONE AND RESORCINOL ON SOLUBLE POLYMER-SUPPORTS

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ABSTRACT

Monoethers of hydroquinone and resorcinol were easily prepared using PEG as soluble polymer-supports, monoprotection group and phase transfer catalyst with good yields and high selectivity of functionlization in homogenous solution.

Key Words: Synthesis; Monoethers; Hydroquinone; Resorcinol; Soluble polymer-supports

It is known those monoethers of hydroquinone or resorcinol are useful synthetic intermediates for the construction of various chemically and biologically significant molecules.[1] Therefore, a general method of the rapid synthesis of those molecules would be of great value and has been reported. Such as: reaction of mono or bis salts of hydroquinone with alkyl halide,[2] demethylation of the bis methyl ether of resorcinol,[3] reaction of trialkyl phosphites with hydroquinone,[4] reaction of hydroquinone with methanol using heteropolyacids or other acids as catalyst,[5] reaction of hydroquinone

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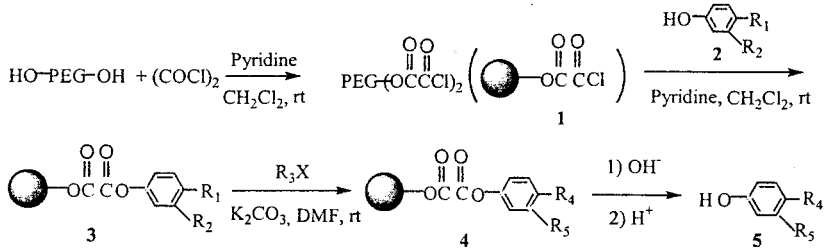
with alkyl halide using Al_2O_3-supported K_2CO_3 as a base reagent,[6] deprotection of benzyloxy using H_2/10% Pd-C after reaction of benzyloxy phenols with alkyl halide.[7] However each of the above methods suffered from a least one of the following drawbacks: (1) very low yields of monoether, (2) long reaction time, (3) necessary presence of a PTC, (4) expensive or not readily available reagents, (5) high reaction temperature, or (6) tedious work up procedures.

Functionalized insoluble polymers for use as protection groups have been received a great deal of attention in organic synthesis in recent years.[8] The reaction of hydroquinone or resorcinol on anion exchange resins with alkyl halide gave mixture of the monoether, diether and hydroquinone or resorcinol itself.[9] Leznoff reported the synthesis of monoether of symmetrical dihydroxy aromatic compounds using insoluble polymer as monoprotection group.[10] However there were drawbacks such as lower reactivity, extend reaction time and difficulty of monitoring the reaction progress and configuration of polymer-bound products.

Soluble polymers have been widely applied in organic synthesis, combines the strategical features of solution and solid-phase methods.[11,12] Poly(ethylene glycol) (PEG) are greatly used as soluble polymers-supports in organic synthesis, readily functionalized with different spacer and linker, soluble in many organic solvents and insoluble in poorly polar solvent. Thus one can carry out a reaction on a modified PEG immobilized compound in homogenous condition.

Having the above facts in mind and in continuation of our efforts to utilize soluble polymer-supported systems in organic synthesis.[13] We now first report in this article the synthesis of monoethers of hydroquinone and resorcinol using PEG as soluble polymer-supports, monoprotection group and phase transfer catalyst (Sch. 1).

Considering the balance between loading capacity and the solubility profile of the resulting polymer derivative, we choose PEG (MW 4000) as soluble polymer-supports, monoprotection group and phase transfer



Scheme 1.

catalyst in synthesis of a monoethers of hydroquinone and resorcinol. PEG reacted with excess of oxalyl chloride to give PEG-bound acid chloride **1** through ester linkage. The reaction proceed to completion as evidenced by disappearance of hydroxy, the appearance of ester group and acid chloride at 1737 and 1785 cm^{-1} in the IR spectrum. Without further purification, the PEG-bound acid chloride reacted with excess of **2** to give their respective PEG-bound phenolic ester **3**, in which one of the hydroxy groups was attached to the PEG through an ester linkage. **3** were easily isolated by precipitation with cold ether to remove excessive starting materials and by-products, reacted with R_3X in DMF in the presence of K_2CO_3 to give PEG-bound monoether **4**, meanwhile PEG can act as phase transfer catalyst.[14,15] Hydrolysis of **4** with 10% NaOH and acidification with 10% HCl until pH = 5 gave monoether **5** which were analyzed on thin-layer chromatography ($CHCl_3$/ethyl acetate = 4/1 as eluant) to show containing a little **2** and no diether. Selective functionlization yields have been improved. Table 1 includes representation examples.

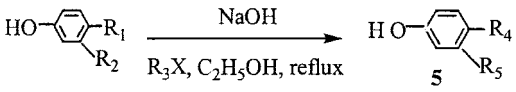
For comparison, we have also investigated the synthesis of monoethers of hydroquinone and resorcinol using conventional, non-polymeric reagents methods (Sch. 2).[16] Obtained products were a mixture containing unreacted starting materials, mono- and di-alkyl ethers, but monoether was less than 30%. This method proved lower selectivity of functionalization and difficult to work up (Table 2).

It is worthy of note that the reaction was easily carried out using PEG as soluble polymer-supports, monoprotection group and phase transfer catalyst in mild conditions with high selectivity of functionalization, the product was easily isolated and purified by simply precipitating the polymer by

Table 1. Preparation of Monoether of Hydroquinone and Resorcinol Using PEG as Soluble Polymer-Supports

5	R_1	R_2	R_3	R_4	R_5	Yield[a,b] (%)
a	OH	H	CH_3	OCH_3	H	50.6
b	OH	H	$CH_2CH{=}CH_2$	$OCH_2CH{=}CH_2$	H	53
c	OH	H	$PhCH_2$	$OPhCH_2$	H	65
d	OH	H	C_2H_5	OC_2H_5	H	33.7
e	H	OH	CH_3	H	OCH_3	51.7
f	H	OH	$CH_2CH{=}CH_2$	H	$OCH_2CH{=}CH_2$	50
g	H	OH	$PhCH_2$	H	$OPhCH_2$	56
h	H	OH	C_2H_5	H	OC_2H_5	30.5

[a]Isolated yields; [b]Products were characterised by comparison of their physical data, IR, ^1H NMR spectra with known samples.



Scheme 2.

Table 2. Preparation of Monoether of Hydroquinone and Resorcinol Using Conventional, Non-polymeric Reagents Methods

5	R_1	R_2	R_3	R_4	R_5	Yield[a] (%)
a	OH	H	CH_3	OCH_3	H	28.5
b	OH	H	$CH_2CH{=}CH_2$	$OCH_2CH{=}CH_2$	H	27.8
c	OH	H	$PhCH_2$	$OPhCH_2$	H	29.6
d	OH	H	C_2H_5	OC_2H_5	H	22.5
e	H	OH	CH_3	H	OCH_3	30.0
f	H	OH	$CH_2CH{=}CH_2$	H	$OCH_2CH{=}CH_2$	25.6
g	H	OH	$PhCH_2$	H	$OPhCH_2$	21.9
h	H	OH	C_2H_5	H	OC_2H_5	19.6

[a]Isolated yields.

addition of Et_2O and removing the unreacted materials and by-product by filtration, avoiding tedious work up procedures in contrast to using conventional, non-polymeric reagents methods. Isolation purity were easily followed by TLC analysis to observe disappearing of lower molecular reagent by precipitation and washed with cold Et_2O, the PEG-bound product configuration was readily analyzed by ^1H NMR and IR without detaching material from the polymer-supports in each step of the sequences in contrast to insoluble polymers for use as polymer-supports and protection groups.

In conclusion, we have developed the new liquid phase combinatorial synthesis of monoethers of hydroquinone and resorcinol with good yields and selectivity using modified PEG as soluble polymer-supports, mono-protection groups and phase transfer catalyst.

EXPERIMENTAL

All organic solvents were dried by standard methods. All PEG samples were melted at 80°C in vacuum for 30 min before use to remove traces of moisture. Melting points were determined on a Electrothermal melting point

apparatus and are uncorrected. IR spectra were recorded using KBr pellets on a IR-Spectrum One (PE). ^{1}H NMR spectra were recorded on Brucker Ac-80 instrument using $CDCl_3$ as solvents and TMS as internal standard.

Synthesis of Monoether of Hydroquinone and Resorcinol Using PEG as Soluble Polymer-Supports

Preparation of PEG-bound acid chloride **1** and general procedure for the preparation of PEG-bound monoesters **3**. To a ice-cold solution of oxalyl chloride (1.4 mL, 16 mmol) in CH_2Cl_2 (250 mL) was added the solution of PEG 4000 (28 g, 14 mmol-OH), pyridine (2.8 mL, 34 mmol) and CH_2Cl_2 (150 mL) with stirring. After 2 h, **2** (20 mmol) was added and the mixture was stirred 18 h at r.t. After precipitation with cold ether, washing with ether and recrystallization from absolute cold ethanol, white solid (97%) was obtained. TLC showed that the solid contained no **2** (acetone/petroleum ether = 1/3 as eluant), which could be illustrated by IR and ^{1}H NMR.

General procedure for the preparation of PEG-bound monoether 4: K_2CO_3 (0.8 g, 6 mmol) and alkyl halide (10 mmol) were added to a solution of **3** (6.0 g) in DMF (60 mL). The mixture was stirred for 18 h at r.t., filtered to remove K_2CO_3, concentrated the filter liquor under vacuum until slightly viscous, purification by precipitation in cold Et_2O to give **4**.

General procedure for the preparation of 5: 4 (5.6 g) was added to solution of 1 mol/L NaOH (30 mL). The mixture was stirred for 2 h at r.t., slowly dropwise added HCl (2 mol/L) until pH = 5, extracted with Et_2O and organic layer were washed with saturated brine and dried with dry $MgSO_4$, evaporated of the solvent under vacuum to give small volume residue, which was purified by flash chromatography ($CHCl_3$/ethyl acetate = 4/1 as eluant) to afford **5**.

General Procedure for the Preparation of 5 Using Conventional, Non-polymeric Reagents Methods

To a solution of **2** (20 mmol) and alkyl halide (20 mmol) in C_2H_5OH (25 mL), NaOH (20 mmol) in water (3 mL) was added dropwise under reflux within 60 min and the reaction mixture was further stirred for 7 h under reflux, evaporated to leave a residue that was dissolved in 30 mL H_2O and further neutralized with dilute aqueous solution of hydrochloric acid until pH = 5, extracted with Et_2O and organic layer were washed with saturated brine and dried with dry $MgSO_4$, evaporated of the solvent under vacuum to

give small volume residue, which was purified by flash chromatography ($CHCl_3$/ethyl acetate = 4/1 as eluant) to afford **5**.

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