Mitsunobu Reaction Using Triphenylphosphine Linked to Non-Cross-Linked Polystyrene

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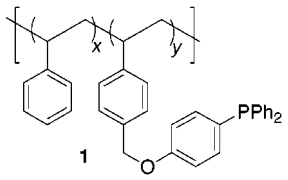
Received November 8, 2000

The Mitsunobu reaction of alcohols has been extensively used in organic synthesis for the preparation of esters, alcohols, aryl ethers, amine, and thioethers.[1] This reaction was found to be particularly effective to invert the configuration of chiral secondary alcohols since a clean S_N2 process is generally observed. Over the past decade, many efforts were directed toward replacing triphenylphosphine and diethyl or diisopropyl azodicarboxylate (which are respectively converted into triphenylphosphine oxide and the related dialkylhydrazino dicarboxylate) by other reagents to facilitate the isolation and purification of the desired product.[2] One alternative strategy that has been contemplated is to use solid-supported reagents[3,4] that could be simply filtered after the reaction. However, possible problems encountered with solid-supported reagents in Mitsunobu reactions include their lower reactivity due to the sterically less accessible reactive center. Furthermore, the slower reaction kinetics imparted by the biphasic system is generally circumvented by using a large excess of the reagent; such a solution is obviously not desirable and practical in Mitsunobu reactions. In this context, the Mitsunobu inversion reaction of secondary alcohols using a solid-supported triphenylphosphine has never been reported thus far.[5] In principle, the use of soluble polymer supports[6] could circumvent these problems if the reaction site is readily accessible and if the polymeric reagent retains the reactivity of free triphenylphosphine. We recently reported[7] the synthesis of triphenylphosphine linked to a non-cross-linked polystyrene[8] (**1**), and we have shown its effectiveness in the Staudinger−Aza−Wittig reaction. The polymer was easily prepared in three steps from commercially available non-cross-linked polystyrene, and it could be quantitatively recovered after the reaction. In this note, we show that this soluble polymer-bound phosphine is highly effective in the Mitsunobu reaction of secondary alcohols and in S_N2' nucleophilic substitution of Baylis−Hillman adducts.



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The Mitsunobu reaction on menthol was selected to optimize the efficiency of polymer **1** in these transformations and to monitor its sensitivity to steric hindrance of the starting alcohol. Interestingly, even though it is a fairly hindered secondary alcohol, menthol has been shown to react well with Ph_3P/DEAD/*p*-$NO_2C_6H_4COOH$[9] to produce the *p*-nitrobenzoate **2** in 83% yield.[10] The solvent optimization when polymer **1** was used as the triarylphosphine clearly indicated that either toluene or THF were suitable solvents (Table 1). Both were much superior to benzene which is often used in these reactions. The optimal concentrations were between 0.05 and 0.1 M but sometimes, stirring was easier under dilute conditions. Diisopropyl azodicarboxylate was also examined, and it gave a yield similar to that obtained with the diethyl derivative (75% conversion).

As expected, the use of tetramethylazodicarboxamide (TMAD)[11] did not lead to any significant amount of the desired product, and the starting material was recovered quantitatively.

Two other alcohols were tested, and the results were compared to those obtained with triphenylphosphine or triphenylphosphine bound to a cross-linked polystyrene (PPh_3−CLPS) (eqs 1 and 2). 2-(*S*)-Octanol could be converted into its benzoate antipode very effectively with the soluble phosphine polymer (eq 1). Conversely, the transformation was slightly less efficient if the analogous cross-linked phosphine was used. In a similar fashion, ethyl (*S*)-lactate could be transformed into the (*R*)-*p*-nitrobenzoate derivative in 71% yield (eq 2). In both cases, none of the starting alcohols were detected by ^1H NMR in the crude reaction mixture after extraction of the product out of the polymer. The isolation of the desired product required addition of methanol to precipitate the polymer.[12] The lower isolated yield could be a

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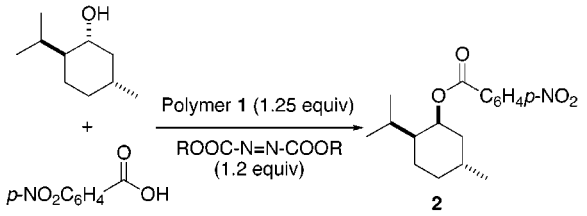
(12)) See Experimental Section for further details on the isolation.

10.1021/jo005727k CCC: $20.00
Published on Web 02/22/2001

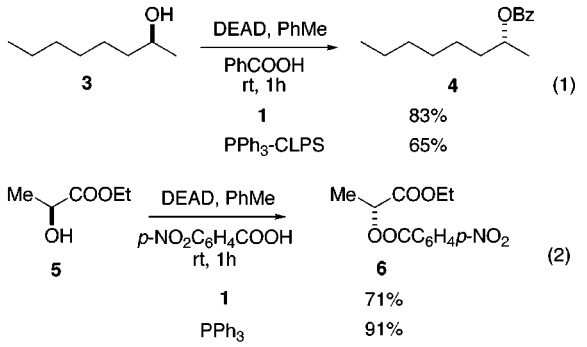
Table 1. Optimization of the Reaction Conditions for the Mitsunobu Reaction of Menthol[a]



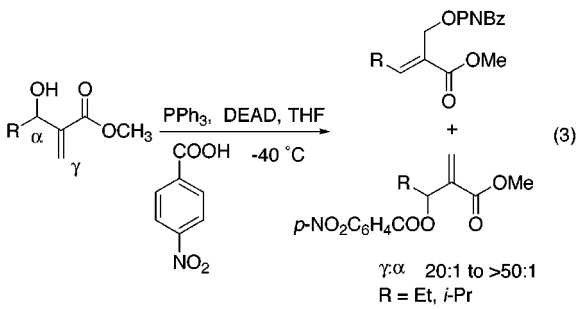
entry	solvent (concn)	R	conversion[b] (%)
1	PhH (0.1 M)	Et	50
2	PhH (0.1 M)	Et	38[c]
3	PhH (0.05 M)	Et	57
4	THF (0.05 M)	Et	70
5	toluene (0.1 M)	Et	72
6	toluene (0.05 M)	Et	75 (67)[d]
7	toluene (0.05 M)	*i*-Pr	75

[a] All the reactions were carried out as described in the general procedure. [b] Conversions were determined by ^{1}H NMR of the crude reaction product that was extracted out of the precipitated polymer. [c] In this entry 2.0 equiv of DEAD were used. [d] The yield in parentheses corresponds to the isolated yield of chromatographically pure ester.

consequence of the product being trapped in the polymer upon precipitation since the yield is highly dependent on the extraction procedure.

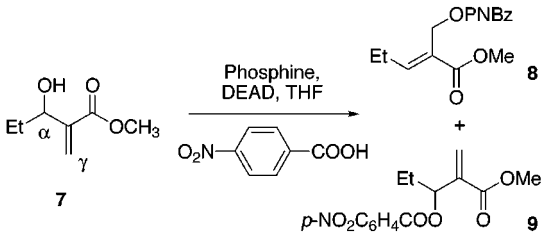


We next turned our attention on a reaction that could take advantage of the additional steric hindrance imparted by the polymeric backbone of phosphine **1**. We have previously developed a method that provides access to *E*-trisubstituted alkenes from Baylis−Hillman adducts (eq 3).[13] This process occurs via an highly regioselective S_N2' (γ-attack) Mitsunobu reaction. Since it is reasonable to assume that nucleophilic attack at the γ position should be more favored with bulkier phosphines, one may anticipate that better regioisomeric ratios will be observed if the soluble phosphine polymer is used in these reactions.



The results obtained for the Mitsunobu reaction on the Baylis−Hillman adduct **7** are summarized in Table 2. A

Table 2. Mitsunobu Reaction on Baylis−Hillman Adduct 7



entry	temp (°C)	ratio (**9**:**8**)[a]	phosphine	yield (%)[b]
1	rt	1:6	PPh_3	90
2	rt	1:20	**1**	88
3	0	1:10	PPh_3	86
4	0	1:>90	**1**	81
5	−40	1:25	PPh_3	85
6	−40	1:>90	**1**	65[c]

[a] The ratios were determined by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield of **8** + **9**. [c] In this case, the remaining was the starting alcohol **7**.

direct comparison between triphenylphosphine and polymer **1** is also provided. Two conclusions can be drawn from the data, the first being that the nucleophilic substitution reaction mediated by polymer **1** leads to a significantly more regioselective transformation. For example, when the reaction was done at room temperature, a 20:1 regioisomeric ratio of **8** and **9** (entry 2) was obtained when **1** was used compared to the 6:1 ratio observed with triphenylphosphine (entry 1). This trend was also observed at lower temperature. Another important feature of the reaction using the polymeric phosphine reagent is that higher selectivities are also observed at 0 °C. For example, the minor regioisomer could not be detected when the reaction was carried out at 0 °C. This contrasts with the 10:1 regioisomeric ratio obtained when the analogous reaction using triphenylphosphine was carried out at 0 °C or the 25:1 ratio at −40 °C. To our surprise, the polymer **1** was still soluble at −40 °C although the reaction mixture was quite viscous, and it still showed reactivity in the nucleophilic substitution reaction.

Experimental Section[14]

Typical Procedure for the Mitsunobu Reaction Using Polymer 1. (1*S*,2*S*,5*R*)-1-(4-Nitrobenzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol (2). To a solution of polymer **1** (333 mg, 0.32 mmol of phosphine) in PhMe (6 mL) were added *p*-nitrobenzoic acid (51 mg, 0.31 mmol) and menthol (40 mg, 0.26 mmol). To this clear solution was added DEAD (48 μL, 0.31 mmol) over 2 min. The reaction was then stirred at room temperature for 15 h. Volatiles were removed under reduced pressure, and the residue was suspended in MeOH (50 mL). The flask was equipped with a reflux condenser, and the suspension was heated under reflux for 4 h. The suspension was then filtered, and the polymer was redissolved in $CHCl_3$. The suspension/filtration cycle was repeated three times. The combined methanolic solutions were concentrated under reduced pressure, and the residue was purified by flash chromatography (10% EtOAc/hexane) to afford the pure nitrobenzoate ester as a white crystalline solid (79 mg, 67%): $[\alpha]^{25}_D = +18°$ (*c* 1, $CHCl_3$); lit.

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(14)) For the general experimental procedure, see ref 7.

$[\alpha]^{25}_D = +18°$ (*c* 1, $CHCl_3$).[15] The phosphine oxide was then quantitatively recovered and submitted to reducing conditions (*N*,*N*-dimethylaniline and trichlorosilane in *p*-dioxane at 100 °C) for its recycling according to our previously described procedure.[7]

(*R*)-1-Methylheptyl Benzoate (4). The title compound was obtained as a white solid on a 0.63 mmol scale (83%) according to the typical procedure: $[\alpha]^{25}_D = -38°$ (*c* 2, EtOH).[15]

Ethyl (*R*)-2-((4-Nitrobenzoyl)oxy)propionate (6). The title compound was obtained as a white solid on a 1.05 mmol scale (71%) according to the typical procedure described above: $[\alpha]^{25}_D = -13.1°$ (*c* 1, EtOH).[16]

Typical Procedure for the Mitsunobu Reaction on Baylis−Hillman Adducts. Methyl (*E*)-2-[[(4-Nitrobenzoyl)-oxy]methyl]-2-pentenoate (8). To a solution of polymer **1** (900 mg, 0.86 mmol of phosphine) in THF (34 mL) at 0 °C (bath temperature) were added *p*-nitrobenzoic acid (138 mg, 0.83 mmol) and the Baylis−Hillman adduct **7** (100 mg, 0.69 mmol). To this clear solution was added DEAD (130 μL, 0.83 mmol) over 2 min. The reaction was then stirred at 0 °C for 15 h. Volatiles were removed under reduced pressure, and the residue was suspended in Et_2O (50 mL). The flask was equipped with a reflux condenser, and the suspension was heated under reflux for 4 h. The suspension was then filtered, and the polymer was redissolved in Et_2O. The suspension/filtration cycle was repeated three times. The combined ether solutions were concentrated under reduced pressure, and the residue was purified by flash chromatography (10% EtOAc/hexane) to afford the nitrobenzoate ester **8** as a slightly yellow solid (164 mg, 81%). The characterization data were identical to those reported in the literature.[13a]

Acknowledgment. This work was supported by the FCAR Action Concertée program, Merck Frosst Canada, Boehringer Ingelheim (Canada) Ltd, AstraZeneca, Biochem Pharma Inc., and the Université de Montréal. A.A.B. is grateful to Boehringer Ingelheim (Canada) Ltd for a graduate fellowship.

JO005727K

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