Solid-Phase Enolate Chemistry Investigated Using HR-MAS NMR Spectroscopy

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Supported P4-*t*-Bu enolate chemistry of phenylacetyloxymethyl polystyrene (PS) resin was investigated using high-resolution magic angle spinning (HR-MAS) NMR spectroscopy. Direct analysis of the crude reaction suspensions through the use of a diffusion filter (DF) allowed a rapid selection of the optimal experimental conditions, but also the characterization of the enolate on the solid phase. Comparison with solution experiments and literature data allowed us to address partially the structure of the enolate. HR-MAS NMR spectra of the enolate revealed also a tight interaction of P4-*t*-Bu base with the polymer matrix.

Introduction

Although the concept of solid-phase organic synthesis is almost 40 years old, there has been rapid growth of this field in recent years due to the need for methodologies allowing the parallel synthesis of large numbers of compounds. In many cases, an organic reaction can be performed on the solid phase by using the experimental conditions available for solution chemistry. On the other hand, a supported reaction and its solution version may behave differently, especially when the immobilization can modify the structure and/or the reactivity of the intermediates or when the polymer can interact with the solutes.[1]

C−C bond-forming reactions[2] and, in particular, the reaction of enolates with carbon electrophiles represent an interesting entry to molecular diversity since many carbonyl derivatives are commercially available. Indeed, aldehydes, ketones, esters, or amides have been prepared on the solid phase by C-acylation or alkylation of enolates.[3] Enolates can exist as aggregates, tight ion pairs, solvent- or cryptand-separated ion pairs, and free ions. The *Z*/*E* configuration and the aggregated state (including the formation of mixed aggregates), and hence the reactivity of the enolate, is profoundly influenced by the concentration, the cation, the solvent, and the amount of base.

Factors affecting the formation and reactivity of enolates on the solid phase, and in particular of P4-*t*-Bu[4] enolates, have been scarcely studied. In the course of a study devoted to the synthesis of new anti-inflammatory[5] compounds and building blocks for the synthesis of chemical libraries, we have examined the influence of temperature, time of enolate formation, amount of base and loading on the yield of methylation of supported ester **1** (Scheme 1), by analysis of the crude reaction suspensions by DF HR-MAS NMR.[6] ^{1}H HR-MAS NMR is increasingly used for the quantification and step by step analysis of supported organic reactions,[7] provided that the resin is swollen in a deuterated solvent. The diffusion filter suppresses effectively all signals from molecules that retain their translational mobility (such as solvent

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(1) For example, immobilization of a compound on a solid support is a way to disfavor aggregation, as has been demonstrated for peptides by: (a) Warras, R.; Wieruszeski, J.-M.; Boutillon, C.; Lippens, G. *J. Am. Chem. Soc.* **2000**, *122*, 1789. For the effect of the polymer on supported reactions, see, for example: (b) Sauvagnat, B.; Lamaty, F.; Lazaro, R.; Martinez, J. R. *Acad. Sci. Paris Série IIc* **1998**, *1*, 777. (c) Varray, S.; Gauzy, C.; Lamaty, F.; Lazaro, R.; Martinez, J. *J. Org. Chem.* **2000**, *65*, 6787.

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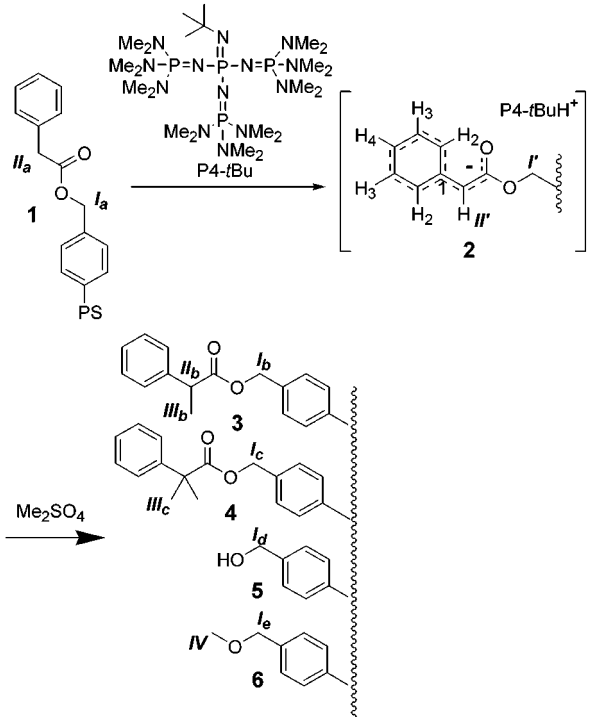
Scheme 1



and reagents) and, hence, allows the characterization of crude reaction suspensions. We further demonstrate that HR-MAS NMR can also detect sensitive intermediates, such as enolate **2**. The results are discussed in the light of the published data concerning the characterization of phenylacetate enolates in solution.[8] Finally, the DF HR-MAS NMR spectra of **2** in the crude reaction medium also permitted light to be shed on the behavior of the phosphazene base which was found to stick tightly to the solid support.

Results and Discussion

The Merrifield resin, being cheap, stable toward strong bases, and easy to dry, was chosen for our study, despite its inherently larger line widths in MAS NMR.[9] Phenylester **1** was obtained quantitatively by treating chloromethyl PS resin with anhydrous cesium phenylacetate in DMF. ^{1}H DF HR-MAS NMR analysis of **1** in THF-d_8 (Figure 1a) showed the absence of chloromethyl protons and two new signals at δ 5.01 and 3.60 ppm corresponding to the methylene protons of the benzyl (Ia) and phenylacetyl (IIa) moieties, respectively.[10]

To optimize rapidly the methylation of phenylester resin **1** and to evaluate the impact of the different parameters, the alkylations were performed in parallel. Following addition (hydrolysis) of acetic acid, the crude reaction suspensions were directly analyzed by DF HR-MAS NMR. Relative intensities in the diffusion filtered

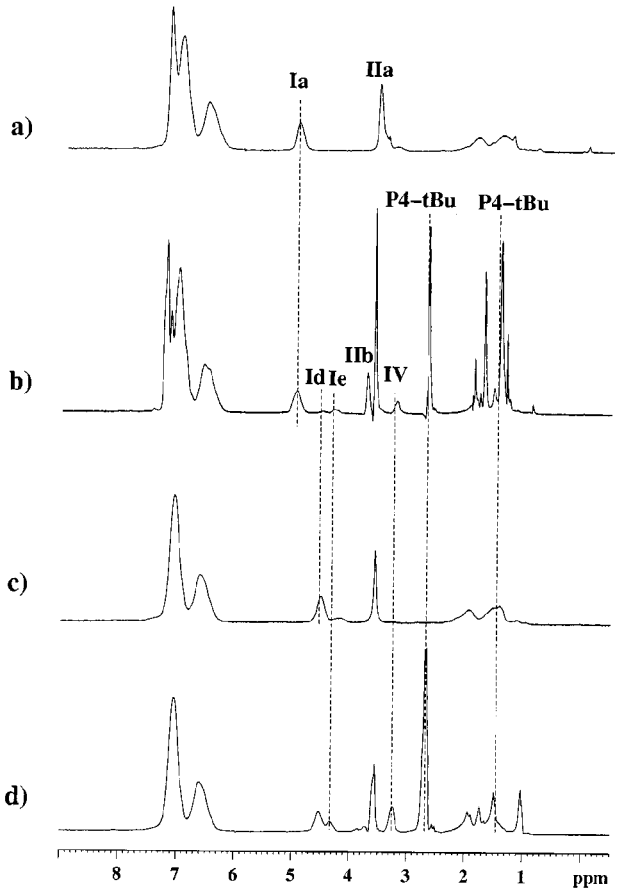


Figure 1. ^{1}H DF HR-MAS NMR spectra at 300 K of resins 1, 3, 5, and 6: (a) **1**, THF-d_8, 300 MHz; (b) **3**, THF-h_8, 600 MHz; (c) **5**, THF-d_8, 300 MHz; (d) **6**, THF-h_8, 300 MHz.

experiment of the different signals of methylated resin **3** were similar to those for the same resin analyzed in deuterated solvent.

Methylation of Resin 1 Using P4-Base and Dimethyl Sulfate. The phosphazene P4-*t*-Bu base (see Scheme 1), developed by Schwesinger, is an extremely strong (pK_{BH^+} (THF) 28.0), uncharged and metal-free base, which following addition of a proton has its positive charge delocalized over a volume of ca. 500 Å^3.[4c] The result of this charge delocalization is the ability to generate anionic species of extraordinary reactivity. In contrast to other Schwesinger phosphazene bases,[11] P4-*t*-Bu has been scarcely used in supported enolate chemistry,[12] and consequently, little data concerning the generation of supported P4-*t*-Bu enolates are available. To investigate the ease of enolate formation independently of the methylation step, the reactions were performed using a two-step procedure. Preliminary studies have shown that dimethyl sulfate was superior to methyliodide for the alkylation of supported phenylacetate enolate **2**, in accordance with previous reports.[13]

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(10) The loading of the starting Merrifield resin was 1.34 mmol/g. Thus, the ester loading of resin **1** was estimated to be 1.18 mmol/g.

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(13) P4-*t*-Bu undergoes methylation with MeI.

Scheme 2

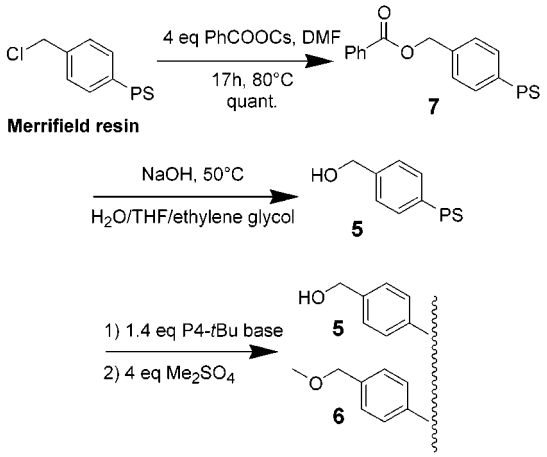


Table 1. Methylation of Resin 1: Effect of Temperature and Time of Enolate Formation[a]

entry	*T* (°C)	time of enolate formation (h)	supported monomethylation[b] (%)	hydrolysis[c] (%)	supported yield[d] (%)
1	−80	1	45	5	43
2	−80	1.5	58	7	54
3	−80	2	61	13	53
4	−50	1	46	7	42
5	−50	1.5	71	8	65
6	−50	2	100	14	86

[a] Reactions were performed using 1.4 equiv of P4-*t*-Bu base and 4 equiv of Me_2SO_4. [b] The percentage of supported monomethylation is the amount of **3** relative to the total amount of remaining supported phenylacetates **1**, **3**, and **4** [$2II_b/(I_a + I_b + I_c)$]. [c] The percentage of hydrolysis is the amount of **5** and **6** formed during the reaction [$(I_d + I_e)/\Sigma I_i$]. [d] The supported yield is the amount of monomethylated ester **2** relative to the initial phenylacetate loading [$I_b/\Sigma I_i$].

Thus, the former was used throughout this study. DF HR-MAS NMR analysis of methylated phenylacetate PS resins (Figure 1b) revealed two new peaks at 3.75 (IIb) and 1.46 (IIIb) ppm characteristic of ester **3**,[14] but also other minor signals at 4.52, 4.33, and 3.24 which were attributed to species **5** and **6** (Scheme 1, protons Id, Ie, and IV, respectively).

To confirm this assignment, benzyl alcohol resin **5** was synthesized as described in Scheme 2. As expected, the ^{1}H DF HR-MAS NMR spectrum of **5** displayed a signal at 4.52 ppm (Figure 1c). In addition, treatment of resin **5** with P4-*t*-Bu base and dimethyl sulfate resulted in the partial alkylation of the benzylic alcohol, as shown by the appearance of signals Ie and IV (Figure 1d).

Resin **1** was subjected to different methylation conditions, by varying reaction temperature, time of enolate formation, amount of P4-*t*-Bu base, and the loading in phenylacetate groups (Tables 1−3). Experiments were performed in duplicate on an 88 μmol scale. In a first series of experiments, the impact of temperature and time of enolate formation on the yield of monoalkylated ester **3** were examined (Table 1). At −80 °C, conversions were always incomplete, even after 2 h of enolate formation (Table 1, entries 1−3). On the other hand, working at −50 °C led to significant improvements, since 2 h of enolate formation resulted in the complete consumption of starting ester **1** (Table 1, entry 6).[15] According to the NMR peak area of proton IIb, ester **1** was essentially converted to the monomethylated derivative **3**. The absence of dimethylation was confirmed by analysis of the product obtained following saponification of ester **3**. Entries 4−6 of Table 1 highlight the importance of the time of enolate formation on both the level of supported monomethylation and hydrolysis. In a second series of experiments, the impact of the amount of base was examined, while the temperature (−50 °C) and the time of enolate formation (1 h) were kept constant. Increasing the amount of base led to better conversions, but also to high levels of hydrolysis. As a result, the supported yields of monomethylated ester **3** were not improved significantly (entries 2 and 3, Table 2). Thus, when compared to entries 4−6 of Table 1, these data demonstrate the importance of controling the reaction time rather than subjecting the solid support to an excess of base. In the rest of the study, the amount of P4-*t*-Bu base was maintained at 1.4 equiv. In the third set of experiments, the influence of the loading of ester **1** upon the methylation reaction was examined. For this study, the loading of the phenylacetate-PS resin **1** was

Table 2. Methylation of Resin 1. Effect of the Amount of Base[a]

entry	base (equiv)	supported monomethylation[b] (%)	hydrolysis[c] (%)	supported yield (%)[d]
1	1.4	46	7	43
2	1.8	61	8	55
3	2.2	70	20	57

[a] The base was reacted with supported ester **1** at −50 °C during 1 h. Methylation was performed using 4 equiv of Me_2SO_4. [b−d] See Table 1.

Table 3. Methylation of Resin 1. Effect of the Ester Loading and of the Time of Enolate Formation[a]

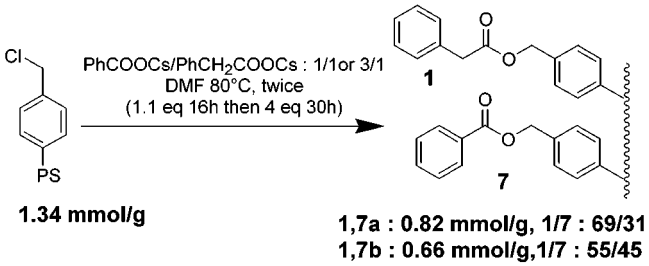
entry	resin loading (mmol/g)	time of enolate formation	supported monomethylation[b] (%)	total hydrolysis[c] (%)	supported yield[d] (%)
1	1.18	1	46	7	42
2	1.18	1.5	71	8	65
3	1.18	2	100	13	86
4	0.82	1	70	15	43
5	0.82	1.5	100	16	60
6	0.82	2	100	25	54
7	0.66	1	85	12	63
8	0.66	1.5	100	24	69
9	0.66	2	100	32	62

[a] The base was reacted with supported ester **1** at −50 °C. Methylation was performed using 1.4 equiv of P4-*t*-Bu and 4 equiv of Me_2SO_4. [b] See Table 1. [c] The percentage of total hydrolysis is the amount of **5** and **6** formed during the reaction by hydrolysis of both phenylacetate and benzoate groups. [d] See Table 1.

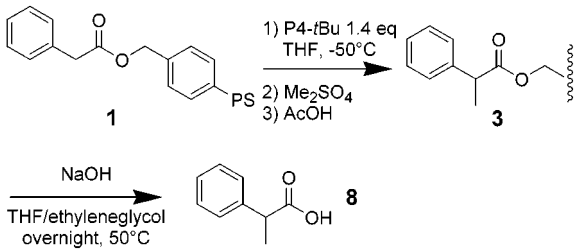
(14) These two signals were correlated to each other in the TOCSY HR-MAS NMR spectrum in THF-d_8 (see the Supporting Information).

(15) The kinetics of the ester deprotonation and methylation reactions are expected to be dependent upon temperature. However, the mobility of the polymer itself is known to have profound impact upon the micro-molecular diffusion. The glass transition temperature (T_g), the temperature at which substantial motion of the polymer chains begins, is one of the defining properties of a polymer. Since the rates of micromolecular diffusion are expected to decrease markedly upon cooling through T_g, it is best suited to work below T_g for a supported organic reaction. The value of T_g for 1% DVB PS vs weight fraction of THF has been studied: Gutierrez, M.; Ford, W. T. *J. Polymer Sci.: Part A* **1986**, *24*, 655. However, the value of T_g was determined experimentally only for low weight fractions of THF. In addition, these authors have shown that the Pochan equation, $\ln T_g = m_1 \ln T_{g1} + m_2 \ln T_{g2}$, where T_{gi} and m_i correspond to the glass transition temperatures and to the mass fractions of the pure solvent and polymer, cannot be used to approximate the T_g of 1% DVB−PS/THF mixture for high proportions of THF. In the absence of additional data, the mobility of the polymer at low temperature is difficult to evaluate.

Scheme 3



Scheme 4



lowered to 0.82 or 0.66 mmol/g by dilution of cesium phenylacetate with cesium benzoate as shown in Scheme 3. Quantitative substitution of the chlorobenzyl groups was verified by ^{1}H DF HR-MAS NMR, which allowed also the quantification of the loading in phenylacetate moieties.[16] The data collected in Table 3 (see entries 3, 5, 6, 8, and 9) indicate that the methylation conditions allowed the total conversion of enolate **2** into monomethyl derivative **3**. Thus, the percentage of supported monomethylation reflects the extent of enolate formation.

Comparison of entries 1, 4, and 7 highlights the importance of loading in phenylacetate groups upon the extent of enolate formation. At 1.18 mmol/g, 1.5 h of enolate formation led to 71% of supported monomethylation, whereas complete conversion of ester **1** into monomethyl derivative **3** was observed at 0.82 mmol/g using the same experimental conditions. For 1 h of reaction, the favorable impact of dilution upon enolate formation is also observed for the supported yields. This trend was not observed for longer reaction times, where hydrolysis of the ester groups was more pronounced.

Dilution of phenyl ester **1** (Scheme 1) on the solid phase should slow the kinetics of enolate formation. The opposite effect was observed in the present study. Owing to the small difference in the size of supported phenylacetate and benzoate esters, the observed effects cannot be ascribed to a decrease of the steric hindrance into the polymer. The favorable impact of dilution could be the consequence of a better diffusion of the base into the polymer matrix, due to the disruption of enolate aggregation.[17] However, in contrast to lithium enolates of phenylacetate esters, P4-*t*-Bu phenylacetate enolates were described to be monomeric in solution. As will be shown later, the "naked" character of supported P4-*t*-Bu enolate was demonstrated by HR-MAS NMR analysis of **2**. Thus, cross-linkage of the polymer backbone induced by aggregation of the formed enolates can be discarded. An explanation of these phenomena, which could be proposed at the light of HR-MAS NMR diffusion studies of diverse polystyrene-P4-*t*-Bu mixtures, is proposed at the end of this section.

To verify the efficacy of the optimization procedure, methylation of supported ester **1** was performed on a 0.6 mmol scale using the best experimental conditions (Table 1, entry 6, Scheme 4). Supported ester **3** was saponified using sodium hydroxide in a mixture of THF/H_2O/ethylene glycol. Ethylene glycol was used to obtain a homogeneous liquid phase compatible with the swelling of the polystyrene resin.[18] RP-HPLC analysis of the crude product revealed the absence of phenylacetic acid and one major peak corresponding to acid **8**, which was isolated with a 87% yield following purification. Dimethylphenylacetic acid was not detected. These data corroborates the DF HR-MAS NMR analysis of the supported ester **3**, which indicated the total consumption of the starting ester **1** and the probable absence of dialkylation.

HR-MAS NMR Analysis of Supported Enolate 2. The DF HR-MAS NMR analysis of supported P4-*t*-Bu enolate **2** was undertaken in order to gain further insight into its structure. Enolate **2** was prepared using the optimized experimental conditions (entry 3, Table 3). The reaction vessel was warmed to room temperature, and an aliquot of the suspension was transferred into the HR-MAS NMR rotor under argon. The ^{1}H DF HR-MAS NMR spectrum of enolate **2** is presented in Figure 2b. The airtightness of the rotor was found to be very high, since the ^{1}H NMR spectrum of **2** was not altered following 14 h of spinning at 6 kHz. This allowed the acquisition of an ^{1}H−^{13}C HSQC HR-MAS NMR spectrum, which is presented in Figure 2c.

Comparison of the ^{1}H spectra of resins **1** and **2** (Figure 2, parts a and b, respectively) revealed the appearance of three new peaks, two in the aromatic region at 6.68 and 6.01 ppm and one at 4.09 ppm near the THF signal. The signals at 6.68 and 6.01 ppm were correlated in the HSQC spectrum to carbons situated at 127.3 and 111.8 ppm and were attributed to protons H_3 and H_4 on the basis of solution NMR studies and literature data (Scheme 1).[19] Corset et al. have studied extensively by IR and ^{13}C NMR Na, Li, and K enolates of methyl and *t*-Bu phenylacetates.[7a] Charge delocalization of the enolate into the phenyl ring can be estimated by the $^{13}C_4$ negative shift, which reflects the state of aggregation of the enolate and its association with the cation.[20] K methyl phenylacetate enolate in THF or DMSO, and Li methyl phenylacetate enolate in DMSO or THF/HMPA are free ions or solvent-separated ion pairs. Consequently, the corresponding $^{13}C_4$ negative shift of about −15 ppm (C_4 at about 112 ppm) was found to be maximal. The $^{13}C_4$ negative shift found for supported P4-*t*-Bu enolate **2** is thus in agreement with a "naked" enolate. Interestingly, ^{1}H NMR and ^{1}H-^{13}C HSQC analysis of P4-*t*-Bu methyl phenylacetate enolate *at the same THF/hexane ratio* as

(16) The benzylic methylene groups of phenylacetate and benzoate groups were found at 5.01 and 5.24 ppm, respectively (HR-MAS NMR in CD_2Cl_2, TMS internal reference).

(17) Dilution of a compound on a solid support has been shown to disfavor noncovalent self-association processes or precipitation. Tjoeng, F. S.; Tam, J. P.; Merrifield, R. B. *Int. J. Pept. Protein Res.* **1979**, *14*, 262. See also ref 2a.

(18) Santini, R.; Griffith, M. C.; Qi, M. *Tetrahedron lett.* **1998**, *39*, 8951.

(19) The signal at 4.0 ppm could not be correlated due to a low signal-to-noise ratio.

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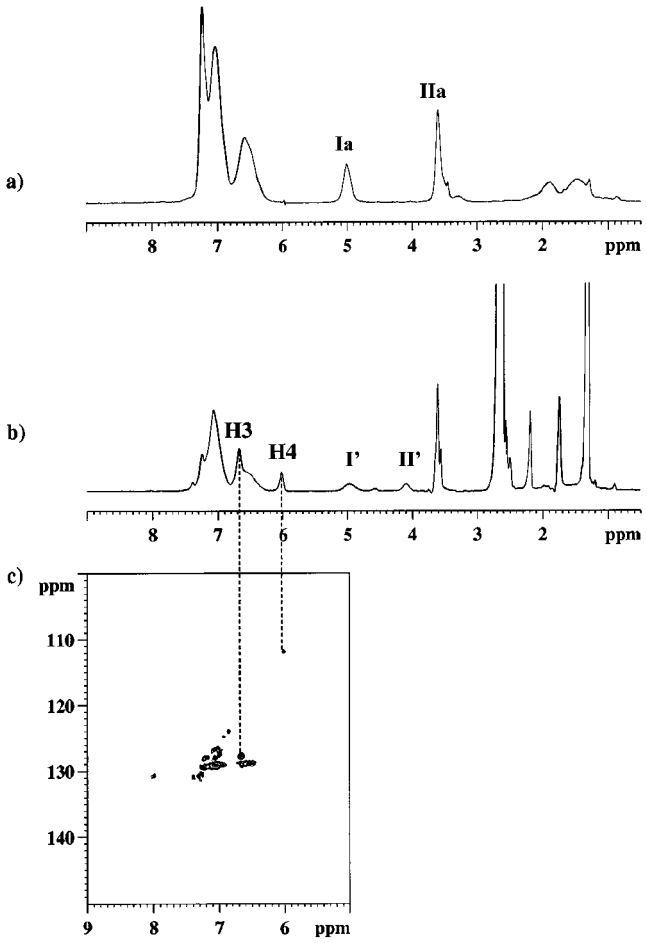
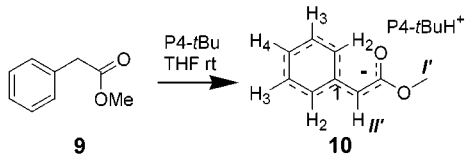


Figure 2. HR-MAS NMR spectra of resins 1 and 2 at 300 K: (a) **1**, ^{1}H DF, 300 MHz; (b) **2**, ^{1}H DF, (c) ^{1}H−^{13}C HSQC, 600 MHz.

Scheme 5



for supported experiments gave similar ^{1}H and ^{13}C chemicals shifts for C_4 and C_3 (5.90 ppm/111 and 6.57 ppm/127 ppm, respectively, Scheme 5).

The chemical shifts of the supported enolate are shifted downfield when compared to the solution experiments due to the high density of aromatic rings inside the beads, an observation which was also reported by Grice et al.[21] These data indicate that the interaction between the enolate and its P4-*t*-BuH^+ cation is not affected by the polymer. Importantly, working at a higher hexane concentration in solution resulted in a lower $^{13}C_4$ negative shift (−5 ppm) and to a lower dispersion of aromatic ^{1}H and ^{13}C chemical shifts (see the Supporting Information). This experiment suggests that at higher hexane/THF ratios the enolate interacts significantly with the P4-*t*-BuH^+ cation. The $^{13}C_4$ chemical shift is particularly high and close to those found for dimers of lithium methyl phenylacetate enolate in THF (120.1 ppm). This observation implies that the structure of the P4-*t*-Bu enolate, and probably its reactivity, may be influenced by the amount of base added to the reaction medium (P4-*t*-Bu is 1 M in hexane, see Table 2).

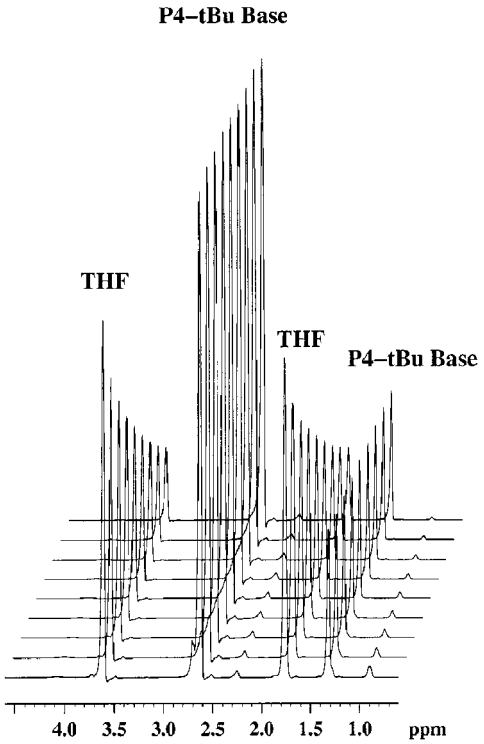


Figure 3. HR-MAS NMR diffusion study of supported enolate **2** (THF-h_8, 600 MHz, 300 K).

The II′ proton (see Scheme 5) of P4-*t*-Bu methyl phenylacetate enolate was found at 3.83 ppm and could be correlated in the ^{1}H−^{13}C HSQC NMR spectrum to carbon C_{II}′ situated at 67.4 ppm. The chemical shift of the corresponding carbon of lithium methyl phenylacetate enolate in DMSO/THF was reported to be at 66.9 ppm (free ion or solvent-separated ion pair). Thus, the signal at 4.09 ppm found in the ^{1}H HR-MAS NMR spectrum of enolate **2** was attributed to proton II′ (Scheme 1).[22] Finally, benzylic protons Ia of ester **1** (5.01 ppm) were shifted to 4.95 ppm in enolate **2**.

^{1}H HR-MAS NMR spectrum of enolate **2** (Figure 2b) displayed other interesting features. First, very strong signals due to P4-*t*-Bu base were observed at 2.62 (Me_2N) and 1.30 (*t*-Bu) ppm, despite the application of a diffusion filter which allows the attenuation of signals given by molecules diffusing freely in solution. Increasing the field gradient of the diffusion filter resulted as expected in the attenuation of the THF peaks at 3.60 and 1.70 ppm, but did not alter the intensity of P4-*t*-Bu peaks (Figure 3).

Obviously, some P4-*t*-Bu molecules have lost their translational mobility and behaved as if they were covalently anchored to the resin. P4-*t*-Bu sticks tighly to the solid support. Since supported P4-*t*-Bu enolate **2** is "naked", direct interaction of P4-*t*-Bu with the polystyrene backbone was supposed to occur. This hypothesis was verified by performing a diffusion study of resin **7** incubated with 1.4 equiv of P4-*t*-Bu (relative to resin loading), since the same strong and constant signals were

(21) Grice, P.; Leach, A. G.; Ley, S. V.; Massi, A.; Mynett, D. M. *J. Comb. Chem.* **2000**, *2*, 491.

(22) The corresponding ^{1}H−^{13}C correlation in the HSQC HR-MAS NMR spectrum was not detected, due probably to the broadening of the peak and to the noise induced by the proximity of THF-h_8 protons.

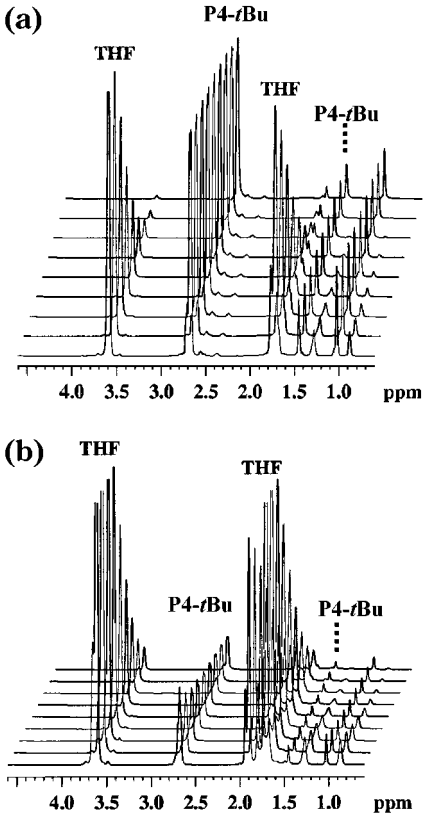


Figure 4. HR-MAS NMR diffusion studies at 300 K (600 MHz): (a) resin **7** incubated with P4-*t*-Bu; (b) resin **7** incubated with P4-*t*-Bu/AcOH 1/1.

observed (Figure 4a). Protonated P4-*t*-Bu (P4-*t*-Bu/AcOH: 1/1 mixture) was also found to stick to resin **7**, albeit to a lesser extent. Again, signals displayed by *t*-Bu and Me_2N groups were not affected by the diffusion study (Figure 4b). Interestingly, incubation of resin **7** with 1.4 equiv of P4-*t*-Bu resulted also in a significant broadening of aromatic and benzylic protons (compare Figure 5a and 5b). Addition of acetic acid (0.7 equiv, Figure 5c; 1.4 equiv, Figure 5d) led to a sharpening of these signals, but the ^{1}H NMR line width of resin **7** without base was not recovered (Figure 5a). Line broadening is also evident for the ^{1}H NMR spectrum of enolate **2** (compare parts a and b of Figure 2).[23] All these data suggest that the tight interaction of the base (protonated or not) with the polystyrene matrix results in the formation of polymer-base-polymer bridges, and thus to a partial loss of mobility of the polymer. Cross-linkage of the polymer as estimated by the line width of ^{1}H NMR spectra is more pronounced for the free base than for the protonated one, an observation which can be corroborated with the amount of free or protonated base immobilized on the polystyrene resin. The fact that interaction of the base with PS resin induces a rigidification of the polymer may be responsible for the effect of dilution of phenylacetate ester **1** on the kinetics of enolate **2** formation which was discussed previously. Indeed, since the amount of base was kept constant, dilution of ester **1** resulted in an increase of the PS−P4-*t*-Bu ratio and, thus, may result in a decrease of the base-induced cross-linking process and to a better diffusion of the reagents into the beads.

(23) This line broadening, in addition to the proximity of THF-h_8 protons for II′, precluded probably the observation of the corresponding ^{1}H−^{13}C correlations in the HSQC spectrum.

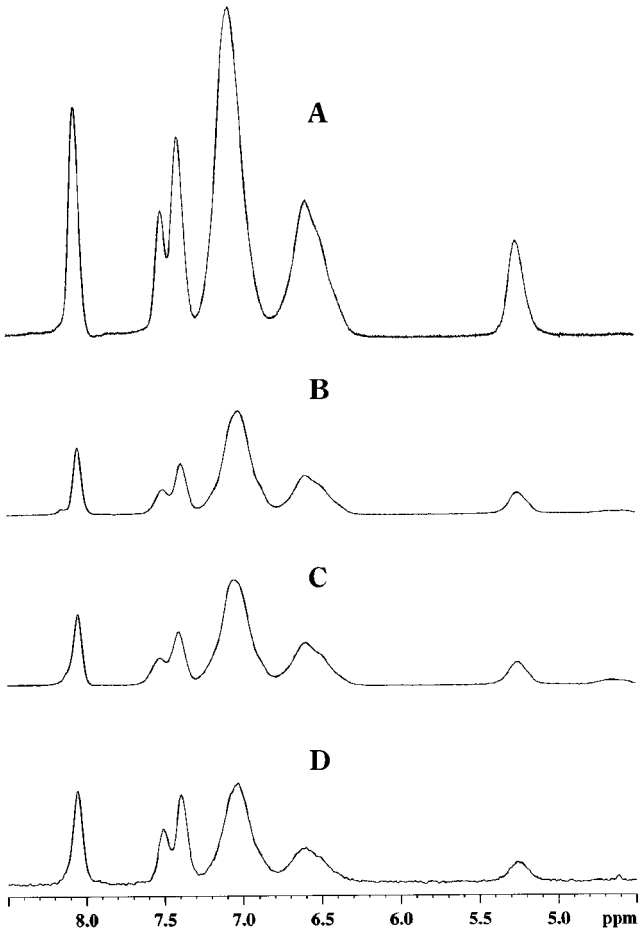


Figure 5. ^{1}H DF HR-MAS NMR (600 MHz) spectra of resin **7** at 300 K: (a) in THF-d_8 without P4-*t*-Bu; (b) in THF-h_8 with 1.4 equiv of P4-*t*-Bu; (c) in THF-h_8 with 1.4 of P4-*t*-Bu and 0.7 equiv of AcOH; (d) in THF-h_8 with 1.4 of P4-*t*-Bu and 1.4 equiv of AcOH.

Conclusion

Deprotonation of phenylacetate PS resin with P4-*t*-Bu base and methylation of the corresponding enolate was studied using DF HR-MAS NMR spectroscopy. First, analysis of the crude reaction suspensions following hydrolysis allowed the rapid optimization of enolate formation using nearly stoichiometric amounts of P4-*t*-Bu. The selected experimental conditions allowed the clean monomethylation of the supported ester. Dialkylation was not observed either by NMR or following separation of the product from the solid support. HR-MAS NMR spectroscopy proved also useful for the characterization of the immobilized enolate, which was found to be very similar to the species generated in solution. More generally, these experiments highlight the possibility to characterize sensitive supported intermediates, and to better understand the interactions between the polymer and the reagents, two important aspects for the development of supported organic chemistry.

Experimental Section

General Methods. THF was distilled over Na/benzophenone. DMF was distilled over CaH_2.

HR-MAS NMR Experiments. HR-MAS NMR experiments were performed using about 5 mg of resin swollen in deuterated solvent (CD_2Cl_2 or THF-d_8) or non deuterated solvent

(THF−hexane mixtures). The samples were introduced in a 4 mm rotor, together with 0.01% by volume of tetramethylsilane (TMS). For DF HR-MAS NMR spectra, 7.5 μL of THF-d_8 was added to the NMR sample. The sample corresponding to enolate **2** was prepared under argon atmosphere in a glovebox. NMR spectra were acquired at room temperature on a Bruker DRX 300 MHz (spinning: 3 kHz) or a Bruker DMX 600 MHz spectrometer (spinning: 6 kHz) with a 4 mm HR-MAS probe equipped with an uniaxial gradient. ^{1}H TOCSY spectrum of resin **3** was acquired with 8 scans per increment, 1024 × 400 complex points, and a mixing time of 80 ms. HSQC spectra were acquired with 80 scans per increments and 1024 × 256 complex points. DF HR-MAS NMR spectra were acquired at room temperature with 64 scans, with the LED impulsion sequence using a sinusoidal gradient of 45G.cm^{-1} for 5 ms and a diffusion delay of 30 ms. For diffusion studies, the gradient was decreased by increments of 5 G·cm^{-1} to obtain a series of nine spectra.

Liquid NMR Experiments. NMR spectra were acquired at 293 K on a Bruker DRX 300 MHz with a BBI 4 mm probe. For compound **8**, HSQC spectra were acquired with 80 scans per increments and 1024 × 256 complex points. Enolate **10** was prepared at room temperature directly in the NMR tube under argon. A 5.78 or 15.0 μL (40.2 or 104.3 μmol) portion was dissolved in 500 μL of THF-d_8. A 56.3 or 146 μL portion of P4-*t*-Bu 1 M in hexanes (Fluka) was added in one portion.

Synthesis of Resins 1 and 7. A 2.00 g (2.68 mmol) portion of Merrifield resin (1.34 mmol/g, Novabiochem) was suspended under argon in 6 mL of anhydrous DMF containing 4.00 g (14.9 mmol) of anhydrous cesium phenylacetate salt (or 3.76 g (14.8 mmol) of anhydrous cesium benzoate salt). The suspension was heated at 80 °C for 17 h. The beads were then washed with DMF (2 × 2 min), MeOH (2 × 2 min), and CH_2Cl_2 (4 × 2 min) and dried under vacuo. Resins **1** and **7** were characterized by HR-MAS NMR in CD_2Cl_2 containing 1% of TMS as the internal reference (δ in ppm). Resin **1**: 7.23 (Ar), 5.01 (ArCH_2O), 3.60 (CH_2CO). Resin **2**: 8.06−7.48−7.37 (Ar), 5.24 (ArCH_2O).

Dilution of Phenylacetate Resin 1 with Ester 7. Resins 1,7a and 1,7b. Dilution of phenylacetate moieties with benzoyl groups was performed by treating twice 2.0 g (2.68 mmol) of Merrifield resin (1.34 mmol/g) with a mixture of anhydrous cesium phenylacetate and cesium benzoate in DMF under argon and at 80 °C. Resin **1,7a**: $PhCH_2COOCs$/PhCOOCs: 374.4 mg/395.1 mg, 6 mL of DMF, 16 h at 80 °C, then $PhCH_2$-COOCs/PhCOOCs: 1.36 g/1.44 g, 10 mL of DMF, 30 h. Resin **1,7b**: $PhCH_2COOCs$/PhCOOCs: 197.5 mg/561.5 mg, 6 mL of DMF, 16 h at 80 °C, then $PhCH_2COOCs$/PhCOOCs: 718.4 mg/2.04 g, 10 mL of DMF, 30 h. The resins were analyzed by HR-MAS NMR (CD_2Cl_2, 1% TMS) to verify the complete substitution of the chloromethyl groups. The loading of resins **1,7a** (0.82 mmol/g) and **1,7b** (0.66 mmol/g) was determined by integration of CH_2OCO protons (phenylacetate 5.01 ppm, benzoate 5.24 ppm) in CD_2Cl_2 with 1% TMS by volume).

Methylation of Phenylacetate Resins. Typical Experimental Procedure. A 88.5 μmol portion of phenylacetate functions (75 mg of resin **1**, 107 mg of resin **1,7a** or 134.1 mg of resin **1,7b**) was suspended in 1.1 mL of dry THF under argon. The reaction flask was cooled to −50 °C. A 123.9 μL (123.9 μmol) portion of Schwesinger P4-*t*-Bu base 1 M in hexanes was added at once, and the beads were stirred for 2 h. A 33.5 μL (35.4 μmol) portion of Me_2SO_4 was then added to the reaction medium, and the beads were stirred 15 min at −50 °C. Hydrolysis was performed at −50 °C by addition of 9.2 μL (161 μmol) of acetic acid. The suspension was then warmed to room temperature, and an aliquot was transferred into the HR-MAS NMR rotor.

Synthesis of Acid 8. A 500 mg (0.6 mmol) portion of resin **1** was suspended in 7.4 mL of dry THF under argon. The reaction flask was cooled to −50 °C. An 826 μL (826 μmol) portion of Schwesinger P4-*t*-Bu base 1 M in hexanes was added at once, and the beads were stirred for 2 h. A 223.7 μL (2.4 mmol) portion of Me_2SO_4 was then added to the reaction medium, and the beads were stirred for 15 min at −50 °C. Hydrolysis was performed at −50 °C by addition of 61.3 μL (1.08 mmol) of glacial acetic acid. The suspension was warmed to room temperature. The beads were washed with THF (2 × 2 min) and CH_2Cl_2 (4 × 2 min) and dried in vacuo. Resin **3** was subsequently treated with 4 g (0.1 mol) of NaOH dissolved in 15 mL of a THF/H_2O/ethylene glycol: 1/1/0.25 by volume overnight at 50 °C. The beads were then filtered and washed with THF (2 × 10 mL). The pH of the combined filtrates was adjusted to 3.0 by addition of 2 N HCl. The aqueous phase was extracted with diethyl ether (3 × 60 mL). The combined organic phases were washed with saturated aqueous NaCl and evaporated under reduced pressure. The crude product (100.0 mg) was purified by RP-HPLC on a C18 Hyperprep (15 × 300 mm) column (eluent A, water containing 0.05% of TFA; eluent B, water/acetonitrile 1:4 containing 0.05% TFA, linear gradient 0−30% in 10 min and 30−60% in 50 min, detection at 215 nm, flow rate 3 mL/min). An 86.8 mg portion of compound **8** was obtained (87% yield, see the Supporting Information for the EI, RP-HPLC, ^{1}H and ^{13}C NMR characterizations). ^{1}H NMR (300 MHz, 300 K, CD_3OD): δ 1.48 ppm (d, J = 7.0 Hz, 3H, CH_3), 3.73 ppm (q, J = 6.0 Hz, 1H, CH), 7.36−7.23 (m, 5H, arom. CH); ^{13}C NMR (75 MHz): δ 177.7 ppm (C═O), 141.7 ppm (arom quart.), 128.5 ppm 127.5 ppm 126.9 ppm (arom CH), 45.9 ppm (CH), 18.11 ppm (CH_3).

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Supporting Information Available: NMR spectra (^{1}H or ^{1}H−^{13}C HSQC or TOCSY or diffusion studies) of resins **1**, **3**, **7**, **1**,**a**, **1**,**7b**, and **10**. RP-HPLC, mass and NMR (^{1}H and ^{13}C) spectra of monomethylated product **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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