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# New solid-supported phosphonate reagents for the synthesis of *Z*-α,β-unsaturated esters

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**Abstract**—Novel solid-supported phosphonate reagents have been prepared and evaluated for the synthesis of α,β-unsaturated esters with a preference for the *Z*-alkene. The optimal reagent was a hybrid of both Still–Gennari and Ando reagents, and showed good to high yields and fair to good *Z*-selectivity for the conversion of both aliphatic and aromatic aldehydes.

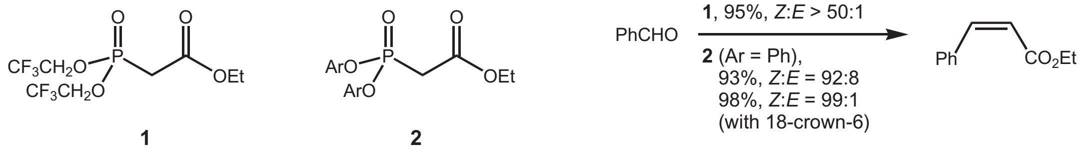
The use of polymer-supported reagents in organic synthesis is now well established.[1] In this context, the use of polymer-supported Wittig reagents[2] and Horner–Wadsworth–Emmons (HWE) reagents[3] have been reported, the latter methods leading predominantly to the formation of *E*-α,β-unsaturated esters and related compounds. This methodology is extremely useful in terms of facilitating the work-up process, particularly the removal of the phosphorus-containing by-products, and in the generation of libraries.

In 1983, Still and Gennari described the synthesis of α,β-unsaturated esters with high *Z*-stereoselectivity from a variety of aromatic, saturated and unsaturated aliphatic aldehydes using electrophilic bis(trifluoroethyl)phosphonoesters **1**.[4] A few years later, Ando reported the formation and the utilisation of new HWE reagents, ethyl (diarylphosphono)acetates **2**, which are also selective for the formation of a range of *Z*-α,β-unsaturated esters (Scheme 1).[5]

We now report the preparation and evaluation of new solid-supported HWE reagents related to **1** and **2** for the synthesis of *Z*-α,β-unsaturated esters.

The mixed solid-supported phosphonates used in the present study were readily prepared via ethyl(dichlorophosphonoacetate) (**4**), obtained from commercially available triethyl phosphonoacetate (**3**) and $PCl_5$.[5,6] The reaction of ethyl(dichlorophosphonoacetate) (**4**) with 1 equiv of a free alcohol in the presence of triethylamine, followed by 1 equiv of supported phenol **5** (polymer-bound phenol, product number: 56479-6 purchased from Aldrich) in the presence of triethylamine, enabled the preparation of a range of mixed solid-supported phosphonates **6**–**9** (Scheme 2).

Following this approach, we synthesised four different solid-supported phosphonates **6**–**9**. After filtration and thorough washing, the resulting resins were obtained and evidence of the coupling was determined by FT-IR



**Scheme 1.**

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*Keywords*: Solid supported; Ando; Still–Gennari; Horner–Wadsworth–Emmons.

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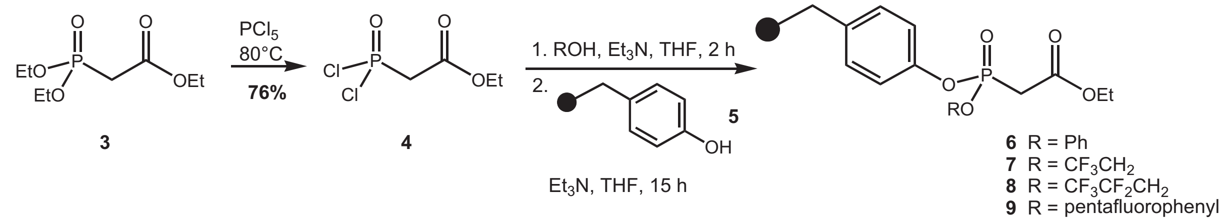


**Scheme 2.** General synthesis of solid-supported phosphonates.

(NaCl), showing typical carbonyl absorptions (1739–1741 $\text{cm}^{-1}$). The yields for the formation of resins **6**–**9** were estimated by weight to be ca. 70–80%, based on the initial loading of the polymer-bound phenol (1.7 mmol/g).

The reaction of THF swollen resins **6**–**9** with benzaldehyde and heptanal or octanal were carried out in the presence of sodium hydride at −78 °C. The results are summarised in Table 1.

Resin **6** (R = Ph), modelled on the well-known Ando phosphonate, gave poor *Z*-stereoselectivity (entry i, *E*-adduct predominated). Incorporation of trifluoroethanol and pentafluoropropanol (**7** and **8**, entries ii and iii), to mimic the Still–Gennari reagent, showed a clear improvement in *Z*-stereoselectivity, presumably due to acceleration of the elimination rate of the phosphonyl group. However, resin **9** substituted with a pentafluorophenol moiety again favoured the *E*-isomer (entry iv). This preliminary study indicated an enhancement of the *Z*-stereoselectivity using fluorinated alcohols. A similar result using methyl bis(2,4-difluorophenyl)phosphonoacetate has been observed in solution.[7]

In order to achieve higher *cis*-selectivity under convenient conditions, we therefore decided to complete the synthesis of the Merrifield-supported mixed phosphonate **14**, combining elements of both Still–Gennari and Ando reagents, which would be expected to be even more electrophilic at the phosphonate centre. The new resin **14** was prepared as described in Scheme 3. Reac-

**Table 1.** Reaction of resins **6**–**9** with aldehydes[a]

| Entry | Resin[b] | IR resin C=O stretch ($\text{cm}^{-1}$) | PhCHO yield[c] (*E*/*Z*)[d] | $C_6H_{13}CHO$ yield[c] (*E*/*Z*)[d] | $C_7H_{15}CHO$ yield[c] (*E*/*Z*)[d] |
|---|---|---|---|---|---|
| i | **6** | 1740 | 89% (71:29) | 67% (69:31) | — |
| ii | **7** | 1739 | 69% (52:48) | — | 67% (50:50) |
| iii | **8** | 1739 | 71%[e] (48:52) | — | 68%[e] (44:56) |
| iv | **9** | 1741 | 90% (70:30) | — | 95% (64:36) |

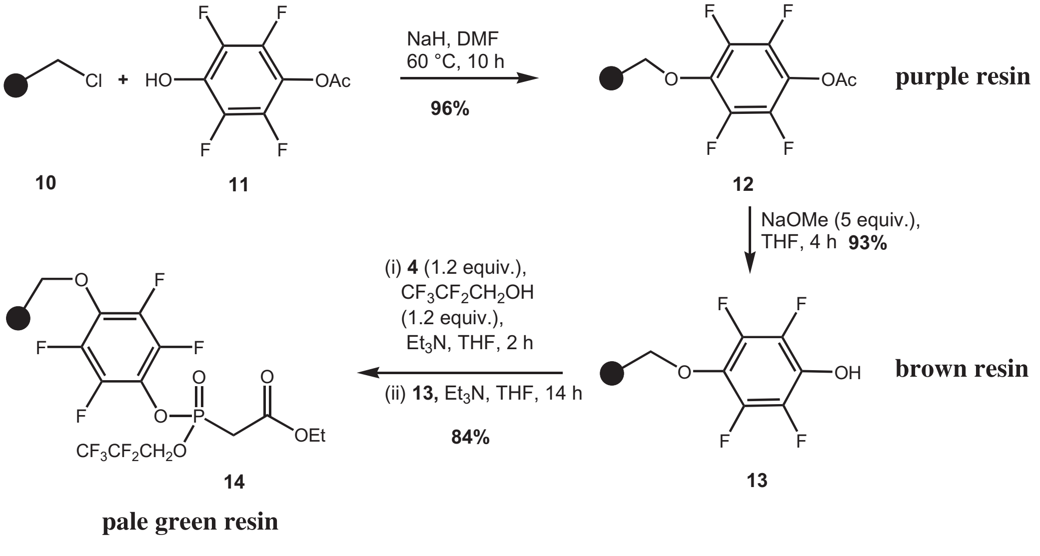
[a] Swelling of the resin (2 equiv) in THF at room temperature followed by addition of NaH (3 equiv) at 0 °C. After adding aldehyde (1 equiv) at −78 °C, the mixture was kept at −78 °C for 5 h and was warmed over 10 h to room temperature.

[b] Theoretical loading of resins **6**–**9**, based on the initial loading of the polymer-bound phenol (1.7 mmol/g) is, respectively, 1.23, 1.22, 1.15 and 1.11 mmol/g.

[c] Yields were determined after filtration of the crude reaction mixture through a pad of silica and concentration. Purity was determined to be >95% by $^1$H NMR spectroscopy.

[d] Ratio was determined by integration of the $^1$H NMR spectrum of the crude reaction mixture.

[e] Containing 10% of recovered aldehyde and determined by integration of the $^1$H NMR spectrum of the crude reaction mixture.



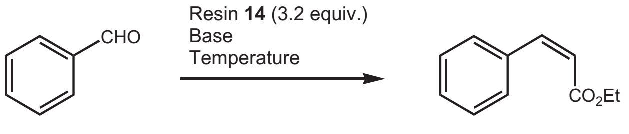
**Scheme 3.** Synthesis of the mixed resin **14**.

tion of DMF swollen Merrifield resin **10** (Merrifield resin 1%–divinylbenzene, catalogue number SC5004, purchased from Advanced ChemTech) with excess (2 equiv) of the sodium alkoxide of the mono-protected tetrafluorohydroquinone[8] **11** resulted in the formation of the resin **12**. Saponification of the latter with sodium methoxide in THF gave resin **13**. This was then submitted to the methodology described earlier, leading to the novel solid-supported phosphonate **14**. The progress of the reaction was easily monitored by the change of colour as well as by FT-IR spectroscopy. As a result of the coupling with the protected hydroquinone, the colour of resin **11** changed from white to purple, and a carbonyl band at 1789 $cm^{-1}$ appeared. After, the saponification step, the resin **13** was characterised by its brown colour and the disappearance of the carbonyl band. A pale green colour and a carbonyl band at 1741 $cm^{-1}$ characterised the supported phosphonate **14**. Yields were estimated by weight assuming an initial loading of 1.4 mmol/g for **10**.

With the new resin **14** in hand, we screened a range of conditions (bases, counterions and temperature) using benzaldehyde. The results are shown in Table 2.

Of the anionic bases used, potassium *tert*-butoxide offered a moderate stereoselectivity, but the presence of salts even after filtration was a problem (entry i). Potassium hexamethyldisilazide (KHMDS) gave decomposition of benzaldehyde (entry ii). However, we were delighted to find that NaH gave an excellent yield with 3:1 *Z*/*E* stereoselectivity. The addition of sodium iodide did not lead to an improvement in the *Z*-selectivity, as has been reported[9] in related solution state studies (compare entries iii and iv). Surprisingly at 25 °C using NaH, the selectivity was the same or slightly improved (compare entries iii and v).

**Table 2.** Bases and temperature screened for the conversion of benzaldehyde with resin **14**



**15**

| Entry | Conditions | Yield of **15**[a] (*E*/*Z*)[b] |
|---|---|---|
| i | *t*-BuOK (5 equiv), −78 °C, 6 h, then 10 h at 25 °C | Yield not determined (55:45) |
| ii | KHMDS (10 equiv), −78 °C, 5 h, then 10 h at 25 °C | No product |
| iii | NaH (10 equiv), −78 °C, 6 h, then 25 °C for 11 h | 83% (25:75) |
| iv | NaH (5 equiv), −78 °C, NaI (1 equiv), 6 h, then 25 °C for 4 h | 86% conversion (41:59) |
| v | NaH (10 equiv), 14 h, 25 °C | 96% (23:77) |

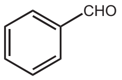
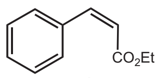
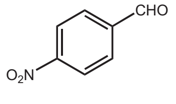
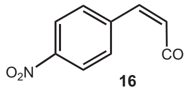
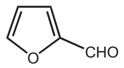
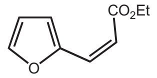
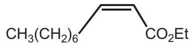
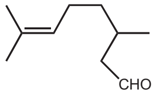
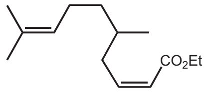
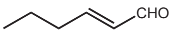
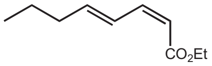
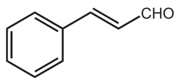
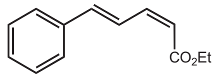
[a] Yields were determined after filtration of the crude reaction mixture through a short plug of silica and concentration. Purity determined to be >95% by $^1H$ NMR spectroscopy.

[b] Ratio was determined by integration of the $^1H$ NMR spectrum of the crude reaction mixture.

Using sodium hydride at room temperature offered a technically straightforward procedure for the utilisation of the resin **14**: after 14 h, the crude mixture is simply filtered through a short plug of silica, concentrated and dried. Using these conditions, a range of aldehydes was screened to determine the versatility of resin **14**. The results are summarised in Table 3.

As can be seen, phosphonate resin **14** provides a moderate to high degree of *Z*-selectivity under convenient reaction conditions with a range of aromatic and aliphatic aldehydes. Thus, in the aromatic examples (entries i–iii), benzaldehyde, *p*-nitrobenzaldehyde and

**Table 3.** *Z*-Selective HWE olefination with resin **14**[a] using NaH at room temperature[b]

| Entry | Aldehyde | Product | Yield[c] (*E*/*Z*)[d] |
|---|---|---|---|
| i |  |  **15** | 96% (23:77)[e] |
| ii |  |  **16** | 85%[10] (27:73) |
| iii |  |  | 91% (31:69) |
| iv | $CH_3(CH_2)_6CHO$ |  | 84% (31:69) |
| v |  |  | 46%[f] (37:63) |
| vi |  |  | 98% (40:60) |
| vii |  |  | 84% (33:67) |

[a] Loading of resin **14** determined to be 0.459 mmol/g by phosphorus elementary analysis based on the initial loading of the Merrifield resin of 1.4 mmol/g.

[b] To pre-swollen in THF resin **14** (3.2 equiv) at 0 °C was added NaH (10 equiv). After stirring at 25 °C for 1 h, the aldehyde (1 equiv) was added. After 14 h (2–4 h with *p*-nitrobenzaldehyde depending on the reaction temperature), the resin was filtered and the organic phase concentrated.

[c] Yields were determined after filtration of the crude reaction mixture through a pad of silica and concentration. Purity determined to be >95% by $^1H$ NMR spectroscopy.

[d] Ratio was determined by integration of the $^1H$ NMR spectrum of the crude reaction mixture.

[e] A control reaction has been carried out using resin **14** left for two weeks in air. Product **15** was obtained in 90% yield and 50:50 *E*/*Z* ratio.

[f] Reaction filtered after 22 h at 25 °C and yield obtained after column chromatography to remove a by-product.

2-furfural all gave good yields and *Z*-stereoselectivity. Octanal behaved similarly (entry iv) but the yield with citronellal was disappointing (entry v); an unidentified by-product was formed and column chromatography was required for the separation. *trans*-2-Hexenal and *trans*-cinnamaldehyde both underwent efficient conversion with reasonable stereoselectivity (entries vi and vii).

As the reaction with *p*-nitrobenzaldehyde proceeded so quickly, we undertook a brief optimisation study. We found that the scale of the reaction could be easily increased to 0.3 mmol in terms of the aldehyde. The amount of resin could be reduced to 2.5 equiv and the amount of NaH to 3 equiv.[10] We also established that resin **14** was still active after two weeks in the open air, although the stereoselectivity diminished (23:77% to 50:50).

In summary, we have demonstrated the synthesis and the use of a novel solid-supported fluorinated phosphonate, which in combination with NaH as base, allows the formation of *Z*-$\alpha,\beta$-unsaturated esters with good to high stereoselectivity without the need for chromatographic purification. The development of a range of improved high loading resins and a method to recycle the resins are under investigation.

## Acknowledgements

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10. Optimal conditions for the olefination of 4-nitrobenzaldehyde using resin **14**: To pre-swollen in THF (20 mL) resin **14** (1.669 g, 0.766 mmol) at 0 °C was added pre-washed NaH (22 mg, 0.917 mmol). The mixture was stirred gently (<200 rpm) for 45 min at 0 °C, then solid *p*-nitrobenzaldehyde (46 mg, 0.304 mmol) was added. The reaction mixture was stirred gently at 0 °C for 3 h, then 1 h at room temperature. The resin was filtered, washed with $Et_2O$ and the organic phase was concentrated in vacuo to afford **16** (57 mg, 85%, $E/Z = 27:73$) as a yellow oil. The data were consistent with those published.[11]
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