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Polymer-Assisted Horner–Emmons Olefination Using PASSflow Reactors: Pure Products Without Purification

Wladimir Solodenko,[a] Ulrich Kunz,[b] Gerhard Jas[c] and Andreas Kirschning[a,*]

[a]*Institut für Organische Chemie der Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany*
[b]*Institut für Chemische Verfahrenstechnik, TU Clausthal, Leibnizstr. 17, 38678 Clausthal-Zellerfeld, Germany*
[c]*CHELONA GmbH, Hermannswerder, Haus 17, 14473-Potsdam, Germany*

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Abstract—A PASSflow protocol for the Horner–Emmons olefination of aldehydes using polymer-bound hydroxide ions in flow-through reactors is presented which allows preparation of alkenes in very high yield with minimal purification.

Polymer-supported reagents have seen a dramatic renaissance lately,[1] because this hybrid solid/solution-phase technique allows simple purification and the possibility to use reagents in excess to drive reactions in solution to completion. The opportunity to employ this technique in conjunction with continuous flow processes is particularly appealing as this application would create an ideal almost workup-free technique for automated solution-phase synthesis.[2]

Recently, we reported on a new reactor system for polymer-assisted, solution-phase synthesis in the flow-through mode, which we termed the PASSflow technique.[3] A monolithic flowthrough microreactor, which is loaded with polymer-bound reagents or catalysts allowed to perform organic transformations in solution associated with low to moderate pressure drop. The monolithic block contains a novel, chemically functionalized highly porous polymer/glass composite. Polyvinylchlorobenzene (crosslinked with 2–20% of divinylbenzene) was prepared by precipitation polymerization in the pore volume of highly porous glass rods to yield a polymeric matrix inside the rod (Fig. 1).[4]

The polymeric structures obtained are small beads (1–5 μm diameter), and are crosslinked with polymeric bridges. This results in a monolithic polymeric phase with a high surface area which is wedged inside the microchannel pore system of the support. This composite material was embedded in a solvent-resistant tube which was followed by encapsulation with a pressure-resistant fiber-reinforced epoxy resin casing with two standard HPLC-fittings (Fig. 2). The polymer particles inside the pore volume can swell and shrink only in the pore volume, whereas the outer dimensions of the rod stay stable. Technical problems like bypassing or high pressure drop as observed in pure polymer packings are

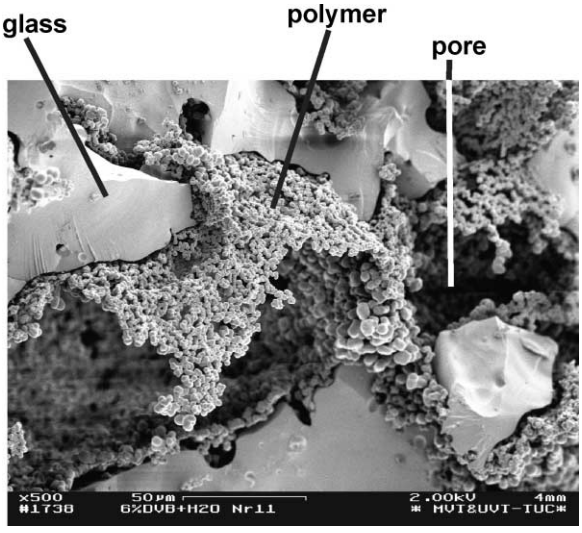

Figure 1. Scanning electron microscopic presentation of polystyrene/glass-composite. The scales are depicted close to the lower frame of the photograph.

*Corresponding author. Fax: +49-511-762-3011; e-mail: andreas.kirschning@oci.uni-hannover.de

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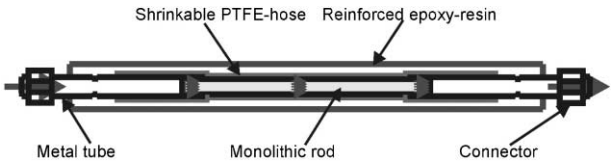
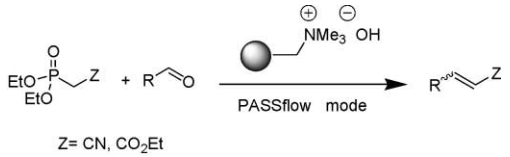


Figure 2. Cross sectional view through the PASSflow reactor (PTFE = polytetrafluoroethylene).



Scheme 1.

avoided. The benzylic chlorine was aminated using trimethyl amine in toluene to yield the corresponding polymer-anchored quarternary ammonium ion.

Combinatorial chemistry and automation of multistep syntheses require new strategies with minimal workup or ideally without purification protocols. In this context, polymer-assisted Wittig-type olefinations[5] including Horner–Emmons variants[6] are particularly appealing. Recently, an interesting protocol of the polymer-assisted Horner–Emmons olefination was reported by Barrett and co-workers. They performed a ring opening metathesis (ROMP) with 2-norbornenemethanol phosphonates; the polymerization afforded an immobilized phosphonate which in the presence of base and a carbonyl compound exclusively afforded (*E*)-configured α,β-unsaturated esters.[7]

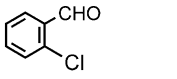
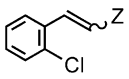
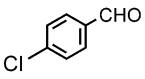
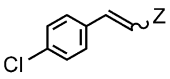
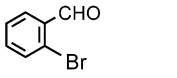
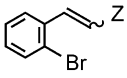
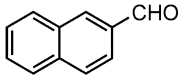
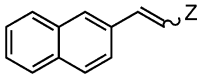
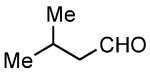
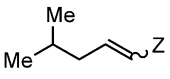
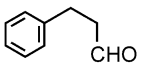
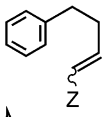
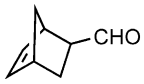
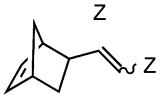
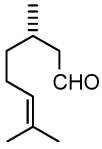
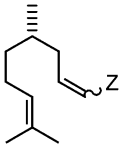
In this communication, we demonstrate that PASSflow reactors can ideally be employed for the efficient preparation of alkenes by applying of the Horner–Emmons olefination. Basically, workup like extraction, filtration and chromatographic purification is fully avoided.

We found that the reactor (hydroxide loaded) can successfully be employed for the Horner–Emmons olefination under the following conditions (Scheme 1 and Table 1). An equimolar mixture of diethyl phosphonoacetonitrile and aldehyde in acetonitrile circulates at room temperature through the reactor.[8] The reactor itself acts as a base thereby forming the intermediate phosphonate ion. This polymer-bound species reacts with the aldehyde to yield the alkene. Diethyl phosphate is a problematic byproduct of this reaction which in this case remains bound in the reactor. The desired alkene is formed in very high yield and in excellent purity after removal of the solvent.

When the less reactive triethyl phosphonoacetate was employed under the conditions described above formation of the α,β-unsaturated esters was also observed.[9] However, in this case the target α,β-unsaturated esters were partly hydrolyzed (up to 40%) also yielding the corresponding α,β-unsaturated carboxylic acids. This byproduct was trapped on the positively charged polymer. To overcome this complication the protocol was modified by drying the reactor in vacuo after it had been loaded with hydroxide ions. Instead of acetonitrile, anhydrous THF served as the solvent of choice. Under these conditions, the Horner–Emmons olefination was found to proceed smoothly, thus exclusively furnishing the pure α,β-unsaturated esters. Remarkably the olefinations proceeded rather rapidly and were completed within 30–120 min. Advantageously, the polymer does not need to be loaded with the phosphonate ion prior to olefination[6] but the anion is generated in situ. Indeed, we were unable to quantitatively load the reactor with these anions owing to solubility problems, which led to blocking of the PASSflow reactor. Finally, it needs to be pointed out that a single reactor was used for more than ten examples of Horner–Emmons olefination reactions.[11]

In essence, the polymer-assisted Horner–Emmons olefination method described in this communication has the

Table 1. Horner–Emmons olefination in the PASSflow mode

Aldehyde	Z	Alkene	% Yield[a] (*E*/*Z*-ratio)[b]
	CN CO_2Et		99 (1.4:1)[c] 93 (9:1)
	CN CO_2Et		97 (2.6:1)[d] 97 (only *E*-)
	CN CO_2Et		99 (1.6:1)[c] 96 (4:1)
	CN CO_2Et		99 (3:1)[d] 97 (only *E*-)
	CN		87 (2.3:1)
	CN		94 (2:1)
	CN CO_2Et		99[e] (2:1) 93[e] (only *E*-)
	CN CO_2Et		92 (2:1) 99 (only *E*-)

[a]Yields of isolated products (purity >95% according to ^1H NMR and GC). All compounds were characterized by ^1H NMR, IR, MS, and correlation with the reported data.
[b]Ratio determined by ^1H NMR spectroscopy.[10]
[c]Pure *E*- and *Z*-isomers were separated by flash column chromatography (silica gel; pentane/ether = 95:5.
[d]Pure *E*-isomer was obtained after crystallization from ethanol.
[e]Mixture of exo/*endo*-isomer.

following profound advantages[12] over alternate polymer-assisted Wittig-type olefinations:[5,6] (a) the flow-through reactors can repeatedly be regenerated and used; (b) various phosphonates can be used without the necessity of modifying the polymer; (c) none of the two reactants needs to be employed in excess; (d) the reaction times of these polymer-assisted olefinations are short (30–120 min versus 4–48 h of alternate polymer-assisted Wittig-type olefinations[7]); and (e) workup is extremely simple.

Acknowledgements

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References and Notes

1. Recent reviews: (a) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem.* **2001**, *113*, 670; *Angew. Chem. Int. Ed.* **2001**, *40*, 650. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Chem. Eur. J.* **2001**, *6*, 4445. (c) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815. (d) Drewry, D. H.; Coe, D. M.; Poon, S. *Med. Res. Rev.* **1999**, *19*, 97.

2. Taylor, R. T. In *Polymer Reagents and Catalysts*; Ford, W. T., Ed.; ACS Symposium Series 308; Washington, DC, 1986; p 132.

3. Kirschning, A.; Altwicker, C.; Dräger, G.; Harders, J.; Hoffmann, N.; Hoffmann, U.; Schönfeld, H.; Solodenko, W.; Kunz, U. *Angew. Chem. Int. Ed.* **2001**, *40*, 3995.

4. (a) Sundmacher, K.; Künne, H.; Kunz, U. *Chem. Ing. Tech.* **1998**, *70*, 267. (b) Altwicker, C. PhD thesis 2001, Technical University of Clausthal.

5. Cainelli, G.; Contento, M. F.; Manescalchi, F.; Regnoli, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2516.

6. (a) Bernhard, M.; Ford, W. T.; Nelson, E. C. *J. Org. Chem.* **1983**, *48*, 3164. (b) Clarke, S. D.; Harrison, C. R.; Hodge, P. *Tetrahedron Lett.* **1980**, *21*, 1375. (c) Castells, J.; Font, J.; Virgili, A. *J. Chem. Soc.* **1979**, 1.

7. Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. *J. Org. Lett.* **1999**, *1*, 579.

8. **Typical procedure for the Horner–Emmons olefination in the flowthrough mode using diethyl phosphonoacetonitrile (Z = CN)**: The microreactor (chloride loaded, 0.4 mequiv capacity) was flushed with 1 M sodium hydroxide solution (60 mL; until no chloride was detected using $AgNO_3$), followed by water (150 mL), methanol (30 mL), acetonitrile (30 mL), and finally dry acetonitrile (30 mL). Then, a solution of diethylphosphono acetonitrile (38.8 mg, 0.219 mmol) and 4-chlorobenzaldehyde (31.1 mg, 0.221 mmol) in anhydrous acetonitrile (3 mL) was pumped through the reactor (2.5 mL/min) at room temperature in a cyclic mode. After 1 h the reactor system was rinsed with acetonitrile (15 mL). The combined organic reaction mixtures were concentrated in vacuo to yield the target *p*-chlorocinnamonitrile (*E*/*Z** = 72:28; 35 mg, 0.213 mmol; 97%). IR: ν_{CN} 2216 cm^{-1}, $\nu_{C=C}$ 1665 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 5.34* (d, *J* = 12.1 Hz, = CH), 5.85 (d, *J* = 16.6 Hz, = CH), 6.95* (d, *J* = 12.1 Hz, = CH), 7.35 (d, *J* = 16.6 Hz, = CH), 7.05–7.70 (m, H_{ar}). MS: 163 (M^+, Cl^{35}), 165 (M^+, Cl^{37}). Crystallization from ethanol gave the pure (*E*)-isomer, mp 78–80 °C (mp 78 °C; Texier-Boullet, F.; Foucaud, A. *Synthesis* **1979**, 884).

9. **Typical procedure for the Horner–Emmons olefination in the flowthrough mode using triethyl phosphonoacetate (Z = CO_2Et)**: The reactor was loaded with hydroxide ions as described in ref 8 followed by successive washing with methanol (30 mL), and diethyl ether (30 mL). Finally the reactor was dried in vacuo at room temperature over P_2O_5 for 2–4 h. The reactor prepared in this way was washed with anhydrous THF (15 mL). After this procedure, a solution of 4-chlorobenzaldehyde (27.3 mg, 0.194 mmol) and triethyl phosphonoacetate (41.4 mg, 0.185 mmol) in anhydrous THF (3 mL) was allowed to circulate through the reactor (2.5 mL/min) at room temperature. After 2 h the reactor system was rinsed with anhydrous THF (15 mL). The combined reaction mixtures were concentrated in vacuo to yield target ethyl *p*-chlorocinnamate (only *E*-isomer; 38 mg, 0.18 mmol; 97%). IR: $\nu_{C=O}$ 1708 cm^{-1}, $\nu_{C=C}$ 1638 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.14 Hz, 3H, CH_3), 4.25 (q, *J* = 7.14 Hz, 2H, CH_2), 6.39 (d, *J* = 16.05 Hz, 1H, = C_αH), 7.31–7.42 (m, 4H, H_{ar}), 7.62 (d, *J* = 16.05 Hz, 1H, = C_βH). MS: 210 (M^+, Cl^{35}), 212 (M^+, Cl^{37}).

10. The *J*-values in the ^1H NMR spectra served as analytical data for determining the configuration of the olefinic double bonds (*trans*-isomers: 16.7–15.4 Hz and *cis*-isomer 12.2–10.7 Hz).

11. The by-product formed in course of the olefination can simply be removed from the reactor by washing with 1 M HCl. The reactor was regenerated by successively washing with methanol (10 mL), water (10 mL), 1 N NaOH (10 mL), water (10 mL), 2 M HCI (10 mL) and water (30 mL).

12. For automation common HPLC-equipment can be used (e.g., pumps, detectors, valves, dosing facilities).