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Horner–Emmons Synthesis with Minimal Purification Using ROMPGEL: A Novel High-Loading Matrix for Supported Reagents

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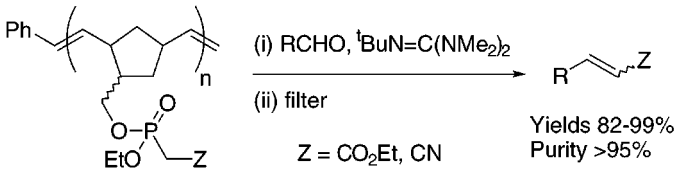
ABSTRACT



The synthesis and use of two novel high-loading Horner–Emmons ring-opening metathesis polymers are described. α,β-Unsaturated ethyl esters (*E*:*Z* > 99:1) and α,β-unsaturated nitriles (*E*:*Z* > 70:30) are obtained in excellent yields and purities from aldehydes with minimal purification.

Combinatorial chemistry has received much attention of late as an engine for the discovery of new pharmaceuticals, catalysts, and materials.[1] Library generation may be accomplished using solid phase organic synthesis or by using conventional solution phase chemistry. There is, however, an unending controversy as to which of the major synthetic strategies for library synthesis is superior. The primary advantage of solution phase chemistry is its familiarity to the synthetic chemist. Additionally, reactions are generally amenable to easy tracking and analysis. Nonetheless the complicated workup procedures usually associated with such reactions in solution have been a major hurdle to automation and the use of multistep sequences. Advances in automated chromatography (MPLC and HPLC) have gone some way toward addressing this problem, although each purification must still be monitored, since the polarities of compounds and impurities cannot be generalized across a library.[2] Acidic or basic aqueous extraction again relies on the requisite functionality on the impurities only.[3] Other strategies include the use of fluorous phase chemistry, although the lack of fluorinated reagents which often need to be prepared by highly specialized syntheses makes this method less attractive.[4]

A wide range of polymer-supported reagents have been developed, both for chemical transformations[5] and for

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(1) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor; S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. Boots, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132. Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144. Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 2289.

(2) Griffey, R. H.; An, H.; Cummins, L. L.; Gaus, H. J.; Haly, B.; Herrmann, R.; Cook, D. P. *Tetrahedron* **1998**, *54*, 4067.

(3) Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567. Kiankarimi, M.; Lowe, R.; McCarthy, J. R.; Whitten, J. P. *Tetrahedron Lett.* **1999**, *40*, 4497.

(4) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531. Curran, D. P.; Hadida, S. *J. Org. Chem.* **1996**, *61*, 6480. Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2292.

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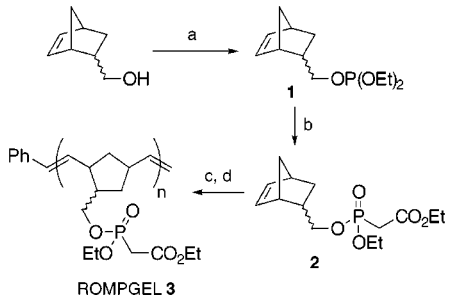
sequestering excesses of solution reactants[6] or chemically tagged reagents.[7] Simple filtration eliminates the need for any time-consuming chromatographic workup. Sequestering reagents can however suffer from slow rates of removal of contaminants and the complementarity of product and impurity functionality.

We have already reported a method of impurity annihilation of a solution-phase reaction by incorporation of excess reagents into an insoluble polymer, formed in situ.[8] We now report a chromatography-free Horner−Emmons reaction of aldehydes to α,β-unsaturated ethyl esters and nitriles.[9]

There is a clear need for maximizing the substrate loading of a polymer-supported reagent. In our approach, the reagent is also the monomer building block for the polymer.[10] As such, the polymer loading should ideally approach quantitative. Commercially available 2-norbornenemethanol (a mixture of *endo*- and *exo*-isomers) was converted to the phosphite[11] **1** followed by Arbusov[12] reaction to give the Horner−Emmons monomer **2**. Ring-opening metathesis polymerization[13] (ROMP**)** of the monomer was achieved in quantitative yield with Grubbs' catalyst[14] and terminated with ethyl vinyl ether (Scheme 1).[15] Since this new polymer is

Scheme 1



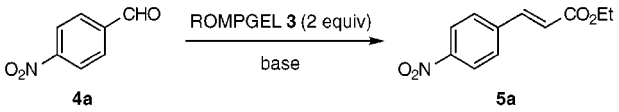
Reagents: (a) $(EtO)_2PCl$, NEt_3, hexane, 95%; (b) $BrCH_2CO_2Et$, heat, 100%; (c) $(PCy_3)_2Cl_2Ru{=}CHPh$ (1.5 mol%), CH_2Cl_2; (d) $EtOCH{=}CH_2$, 100%.

undiluted by cross-linking units or co-polymerization agents, the loading of the polymer should be identical to the molarity of the monomer, namely 3.3 mmol g^{-1}.[16]

The polymer thus formed was a solid when dry but demonstrated remarkable swelling properties in a range of organic solvents (MeCN, CH_2Cl_2, THF) and possessed a consistency similar to that of gelatin when solvated.[17] We term ROM polymers of this consistency as ROMPGELs. ROMPGEL **3** could be stored at room temperature and in the air over several weeks without any noticeable decomposition.

Horner−Emmons Reaction. A range of bases was screened for the ROMPGEL Horner−Emmons reaction using *p*-nitrobenzaldehyde. The results are shown in Table 1. Of

Table 1. Bases Screened for the Horner−Emmons Reaction



4a **5a**

run	base	*T*/h	convn to **5a**
1	K_2CO_3, toluene	24	no reaction
2	KHMDS, toluene	24	complex mixture
3	NaOEt, EtOH	4	complex mixture
4	NaOH, THF	4	20%[a]
5	LDA, THF	1	20%[a]
6	LDA, THF[b]	24	100%
7	LHMDS, THF[b]	16	100%
8	pyridine	24	no reaction
9	NEt_3	24	no reaction
10	DBU, LiCl, MeCN	48	50%
11	TMG,[c] MeCN	4	100%
12	Barton base,[d] MeCN	4	100%

[a] 4-NO_2-$C_6H_4CH_2OH$ isolated in 80% yield. [b] **3** pretreated with base (4 equiv, 2 h). Excess base removed by washing with dry THF prior to addition of aldehyde. [c] *N,N,N′,N′*-Tetramethylguanidine. [d] *N-tert*-Butyl-*N′,N′,N″,N″*-tetramethylguanidine.

the anionic bases used, solid potassium carbonate in toluene showed no detectable reaction after 24h (run 1). Both potassium hexamethyldisilazide (KHMDS, run 2) and sodium ethoxide (run 3) gave a complex mixture of products. Sodium hydroxide (run 4) and, unexpectedly though unsurprisingly, lithium diisopropylamide (LDA, run 5) both resulted in high

(5) Akelah, A.; Sherrington, D. C. *Chem. Rev.* **1981**, *81*, 557. Habermann, J.; Ley, S. V.; Schucht, O.; Thomas, A. W.; Murray, P. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1251 and references therein. Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253 and references therein.

(6) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. S. *J. Am. Chem. Soc.* **1997**, *119*, 4874. Parlow, J. J.; Mischke, D. A.; Woodard, S. S. *J. Org. Chem.* **1997**, *62*, 5908. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882. Armstrong, R. W.; Keating, T. A. *J. Am. Chem. Soc.* **1996**, *118*, 2574. Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hanh, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193. Janda, K. D. *J. Org. Chem.* **1998**, *63*, 889.

(7) Starkey, G. W.; Parlow, J. J.; Flynn, D. L. *Bioorg. Med. Chem. Lett.* **1998**, 2385.

(8) Barrett, A. G. M.; Smith, M. L.; Zecri, F. J. *Chem. Commun.* **1998**, 2317.

(9) Boutagy, J.; Thomas, R. *Chem. Rev.*, **1974**, *74*, 87. Wadsworth, W. S. *Org. React.* **1977**, *25*, 73. Maryanoff, B. E., Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(10) Ball, C. P.; Barrett, A. G. M.; Poitout, L. F.; Smith, M. L.; Thorn, Z. E. *Chem. Commun.* **1998**, 2453.

(11) Huyser, E. S.; Dieter, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 4205.

(12) Lombardo, L.; Taylor, R. J. K. *Synthesis* **1978**, 131. Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

(13) Gibson, V. C. *Adv. Mater.* **1994**, *6*, 37. Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 960. Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 7542. Schrock, R. H. *Acc. Chem. Res.* **1990**, *23*, 158. Breslow, D. S. *Prog. Polym. Sci.* **1993**, *18*, 1141.

(14) Bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride, commercially available from Fluka.

(15) ROM polymerization can easily be monitored by taking the ^1H NMR of aliquots in $CDCl_3$. The norbornene monomers have characteristic vinyl protons at 6−6.2 ppm. Releasing the ring strain shifts these signals to 5.2−5.5 ppm in the polymer.

(16) For a high-loading (2.6 mmol g^{-1}) ion-exchange Wadsworth−Emmons resin, see: Cainelli, G.; Contento, M.; Manescalchi, F.; Regnoli, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2516. For a moderate loading (0.6 mmol g^{-1}) polystyrene-derived Wadsworth−Emmons resin, see: Salvino, J. M.; Kresow, T. J.; Darnbrough, S.; Labaudiniere, R. *J. Comb. Chem.* **1999**, *1*, 134.

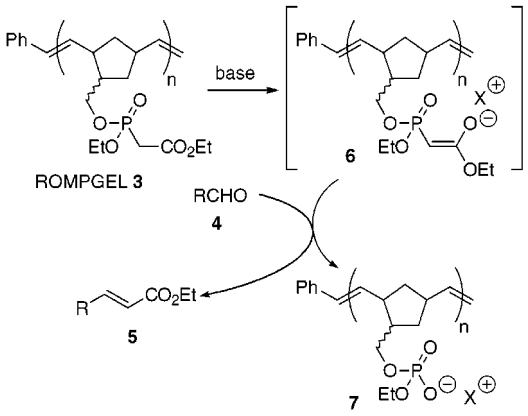
(17) Typically, 50 mg of dry ROMPGEL would swell to 5 mL when solvated in acetonitrile.

yields of *p*-nitrobenzyl alcohol, through Canizzarro and Meerwein−Pondorf−Verley reactions, respectively.[18] However, pretreating ROMPGEL **3** with excess LDA (4 equiv) for 2 h to generate the specific enolate, followed by removal the excess base and diisopropylamine by filtration and washing, before addition of the aldehyde gave the desired α,β-unsaturated ester in quantitative yield (run 6). Lithium hexamethyldisilazide (LHMDS, run 7) by the same procedure also gave a quantitative conversion.

Of the tertiary amine bases screened, the efficacy followed the increasing basicity. Neither pyridine nor triethylamine showed any reaction after 24 h (runs 8 and 9). Diazabicyclo-[4.3.0]undecane (DBU) with LiCl[19] (run 10) showed a slow rate of conversion whereas the guanidine bases tetramethylguanidine (TMG, run 11) and *tert*-butyltetramethylguanidine (Barton base,[20] run 12) both showed quantitative conversion after only 4 h.

Our purification-free strategy relies on the fact that after Horner−Emmons reaction the base will be trapped on the ROMPGEL (Scheme 2). Pretreatment of ROMPGEL **3** with

Scheme 2



LHMDS forms specific enolate **6** ($X^+ = Li^+$) (LHMDS and HMDS in solution are then removed by filtration). Both guanidine bases generate submolar concentrations of enolate **6** ($X^+ = RNH{=}C(NMe_2)_2^+$, R = H for TMG, ^{t}Bu for Barton base). The byproduct after Horner−Emmons reaction is the polymeric phosphate salt **7**, with X^+ as counterion. The ROMPGEL **3** is therefore limited to a single use per equivalent of aldehyde **4**.

All three bases, LHMDS, TMG, and the Barton base, were assayed in Horner−Emmons reaction on a range of aldehydes (Table 2).[21,22] Initial results showed that the reactions proceeded with excellent yields and purities of the α,β-unsaturated esters, with little difference between the three bases (runs 1−9); however the Barton base proved to be the most general and versatile. In all cases, the α,β-unsaturated esters obtained were of exclusively *trans* geometry.[9]

Table 2. ROMPGEL **3** Horner−Emmons Reaction. All Purities Were >95% As Measured by GCMS[22] (All Esters Were Exclusively Trans. Isolated Yields Are Given.)

run		aldehyde **4**	base	*T*/h	**5**	% yield
1	**4a**	4-O_2N-C_6H_4CHO	Barton[a]	4	**5a**	94
2			TMG[b]	4		95
3			LHMDS[c]	4		92
4	**4b**	2-F-C_6H_4CHO	Barton	4	**5b**	84
5			TMG	4		88
6			LHMDS	4		88
7	**4c**	3-Br-C_6H_4CHO	Barton	16	**5c**	88
8			TMG	16		92
9			LHMDS	24		60
10	**4d**	4-pyr-CHO	Barton	4	**5d**	96
11			TMG	4		53
12			LHMDS	4		97
13	**4e**	4-Ph-C_6H_4CHO	Barton	24	**5e**	85
14			LHMDS	24		98
15	**4f**	4-Me-C_6H_4CHO	Barton	48	**5f**	85
16			LHMDS	48		92
17	**4g**	$PhCH_2CH_2CHO$	Barton	16	**5g**	88
18			LHMDS	16		
19	**4h**	5-norbornene-2-CHO[d]	Barton	16	**5h**	82
20	**4i**	citronellal	Barton	16	**5i**	92

[a] 2.0 equiv. [b] 1.5 equiv. [c] ROMPGEL 3 pretreated with 4.0 equiv of base followed by filtration and washing. [d] *Exo*:*endo* mixture.

Reaction rates for LHMDS were generally slower (run 9). Also, we obtained a complex mixture of products when an aliphatic aldehyde was used (run 18), presumably due to aldehyde enolization.

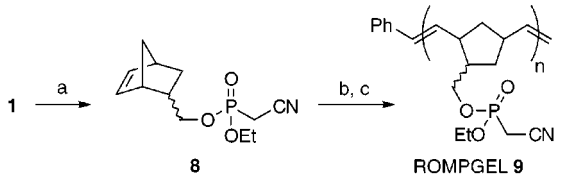
TMG performed well except when polar aldehydes were used. Filtration of the reaction mixture through a pad of silica removed the excess TMG but also trapped some of the product (run 10). Elution of the remaining product off the silica pad also carried through TMG which could not easily be removed by evaporation (bp 162 °C). Contaminant TMG could be removed in a second purification step, either with Dowex 50WX 8-400 strong acid resin (53% isolated yield of product, 95% purity), or Amberlite IRP 64 weak acid resin (95% yield, 95% purity). As well as being inconvenient, this was a nongeneral synthetic route, since purification conditions would depend on the structure of the aldehyde **4**.

The Barton base suffered none of the above problems. In the case of polar aldehydes (run 11), simple evaporation resulted in the removal of any contaminant base (bp 82 °C). Filtration through a plug of silica was necessary only to remove nonvolatile (presumably carbonate) salts of the Barton base. *We recommend the use of the Barton base in combinatorial chemistry as a strong, volatile, organic base, in the same way that trifluoroacetic acid is becoming universal.*

(18) Majewski, M. *Tetrahedron Lett.* **1988**, *29*, 4057.
(19) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(20) Commercially available from Fluka.
(21) In a typical procedure, the aldehyde **4** (0.045 mmol) and Barton base (0.09 mmol) were added to the ROMPGEL (0.09 mmol) in acetonitrile (1.5 mL). After stirring for the required time, the mixture was filtered through a 200 mg silica cartridge (Alltech Associates, cat. no. 209150), the silica was washed with EtOAc (10 mL), and the combined washings were evaporated in a stream of nitrogen.
(22) All compounds were characterized by ^{1}H and ^{13}C NMR, GC, and HRMS.

We have extended the methodology to another functionalized ROMPGEL. Thus phosphite **1** was condensed with bromoacetonitrile and the monomer **8** polymerized as before to give ROMPGEL **9** (Scheme 3). Again, in the loading of

Scheme 3



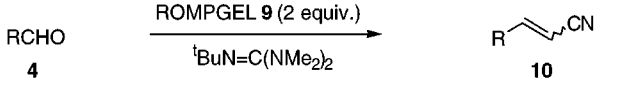
Reagents: (a) $BrCH_2CN$, heat, 86%; (c) $(PCy_3)_2Cl_2Ru{=}CHPh$ (1.5 mol%), CH_2Cl_2; (d) $EtOCH{=}CH_2$, 100%.

the polymer, the molarity of the polymer should be the same as the molarity of the monomer, namely 3.9 mmol g^{-1}.

Treatment of the same range of aldehydes **4** with ROMPGEL **9** (2 equiv) and Barton base (2 equiv) gave the α,β-unsaturated nitriles **10** in good to excellent yields and >95% purity after only filtration and evaporation. Generally, the rates of reaction of nitrile ROMPGEL **9** were faster than that of the ester ROMPGEL **3**, although now we obtained *E*:*Z* mixtures in most cases, as described in classical Horner−Emmons reactions (Table 3).

In summary, we have demonstrated the use of two novel high-loading polymer phosphonate resins which in combination with the Barton base allow a general purification-free Horner−Emmons synthesis of α,β-unsaturated esters and nitriles from both aromatic and aliphatic aldehydes. Further applications of ROMPGELs will be reported in due course.

Table 3. ROMPGEL **9** Horner−Emmons Reaction. All Purities Were >95% As Measured by GCMS.[22] All Yields Are Isolated Yields



run	aldehyde **4**	*T*/h	*E*:*Z* ratio[a]	**10**	% yield
1	**4a**	4	80:20	**10a**	95
2	**4b**	4	70:30	**10b**	94
3	**4c**	16	90:10	**10c**	90
4	**4d**	4	100:0	**10d**	86
5	**4e**	16	85:15	**10e**	91
6	**4f**	16	80:20	**10f**	98
7	**4g**	16	70:30	**10g**	93
8	**4h**	16	80:20	**10h**	86
9	**4i**	16	70:30	**10i**	85

[a] Ratio determined by ^1H NMR.

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Supporting Information Available: ^1H NMR spectra for compounds **1**, **2**, **3**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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