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Parallel Synthesis of Terminal Alkynes Using a ROMPgel-Supported Ethyl 1-Diazo-2-oxopropylphosphonate

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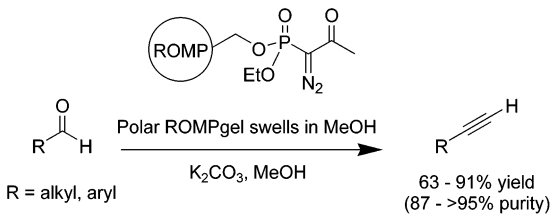
ABSTRACT



ROMPgel-supported ethyl 1-diazo-2-oxopropylphosphonate has been prepared, and the supported reagent has been effectively employed in the conversion of a variety of aldehydes into terminal alkynes under mild reaction conditions. The influence of cross-link structure, comonomers, and polymer structure on reaction efficiency has been examined.

In recent years, the subject of supported reagents has attracted considerable research interest. The synthesis of compound libraries is readily performed using supported reagents in a sequential and multistep fashion. The use of supported reagents in parallel synthesis simplifies purification, as only filtration and washing procedures are required to remove excess reagent and side products. They also allow straightforward reaction monitoring, applying classical solution-phase methods. Efforts to improve the loading and physical properties of supported reagents continue with many new and improved reagents reported.[1]

ROMPgel are a general class of high-loading polymer-supported reagents derived from the ring-opening metathesis polymerization (ROMPolymerization) of norbornene or 7-oxanorbornene monomers.[2] Readily available monomers can be easily functionalized in solution, in a small number of steps, purified and fully characterized prior to ROMPolymerization by ruthenium carbenes.[3] Living polymerization occurs since each chain generated by the alkylidene transition-metal catalyst does not facilitate chain transfer or chain termination, thus generating well-defined polymers with respect to molecular weight and polydispersity. In the presence of a cross-linker, a plethora of ROMPgel-supported reagents have been prepared in good yield and high purity and used in "purification free" parallel synthesis.[2]

Our recent interest has focused on the requirements for more functionalized building blocks and the rapid introduction of chemical diversity using readily available reagents. In particular, the synthesis of terminal alkynes has attracted our attention since further rapid increases in molecular complexity can be performed from these key intermediates. Only one supported reagent has been previously prepared for the synthesis of alkynes, and only two examples were reported.[4] Using a solid base, consisting of alumina coated with potassium fluoride (KF), ethynylbenzene (70% yield)

(1) (a) 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**, *23*, 3815−4195. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650−679.

(2) (a) Barrett, A. G. M.; Hopkins, B. T.; Köbberling, J. *Chem. Rev.* **2002**, *102*, 3301−3324. (b) Flynn, D. L.; Hanson, P. R.; Berk, S. C.; Makara, G. M. *Curr. Opin. Drug Discuss. Dev.* **2002**, *5*, 571−579.

(3) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565−1604.

(4) Yamawaki, J.; Kawate, T.; Ando, T.; Hanafusa, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1885−1886.

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and (phenylethynyl)benzene (89% yield) were synthesized through β-elimination from the corresponding vicinal dibromides. The need for both elevated temperatures and individually optimized reaction conditions reduces the general applicability of this reagent. The increased basicity of KF−alumina, compared to KF alone, may also prove incompatible with certain substrates.

The increasing use of phosphonate reagents in the synthesis of alkynes suggested milder reaction conditions could be developed for more readily available reaction precursors. Specifically, our attention was drawn to reagents containing a diazomethyl group. Both the dimethyl[5] and diethyl diazomethylphosphonates[6] and, more recently, dimethyl 1-diazo-2-oxopropylphosphonate[7] have attracted considerable interest. They have been used in the preparation of simple alkynes, in high yields and on large scale, or alternatively in the installation of a triple bond into more highly functionalized substrates, particularly in the latter stages of natural product syntheses.[8] The use of dimethyl 1-diazo-2-oxopropylphosphonate in basic methanol represents a significant improvement over the standard synthetic procedure for alkyne synthesis using dialkyl diazomethylphosphonates.[9] The reagent, under basic conditions, reacts with aldehydes and ketones by a Horner−Wadsworth−Emmons olefination reaction to generate an unstable diazoalkene, which may then thermally eliminate nitrogen. The resulting alkylidene carbene then rearranges smoothly to provide the alkyne.[8] By applying ROMPgel methodology, we investigated the preparation of a supported 1-diazo-2-oxopropylphosphonate reagent **8** (Scheme 1). The need to use methanol as solvent for the reaction[9] additionally provided the opportunity to explore the effect of polymer architecture on the swelling characteristics of the overall support (Table 1).

Scheme 1. Preparation of an Ethyl 1-Diazo-2-oxopropylphosphonate ROMPgel.

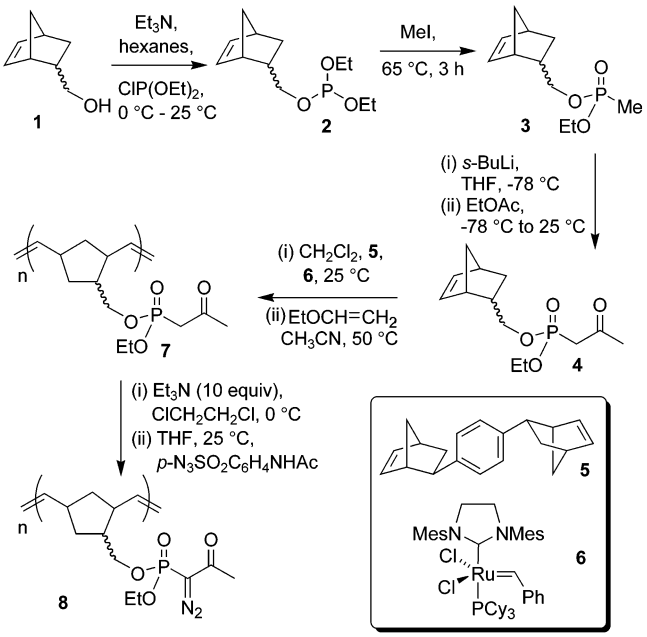
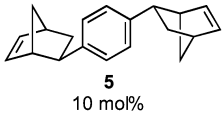
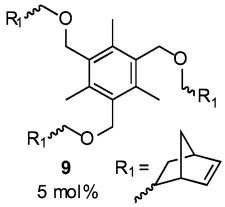
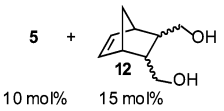
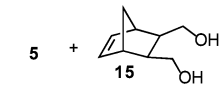


Table 1. Effect of Polymer Architecture on ROMPgel Swelling Properties in Methanol

monomer **4** + components	ROMPgel (% yield)	diazo-ROMPgel (% yield : % volume increase in MeOH)
 **5** 10 mol%	**7** (96)	**8** (92 : 183)
 **9** 5 mol%	**10** (98)	**11** (95 : 17)
 **5** + **12** 10 mol% 15 mol%	**13** (75)	**14** (94 : 300)
 **5** + **15** 10 mol% 15 mol%	**16** (100)	**17** (100 : 350)

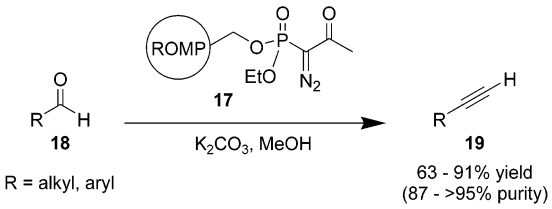
Bicyclo[2.2.1]hept-5-en-2-ylmethyl diethyl phosphite (**2**) was prepared from commercially available alcohol **1**, as previously reported.[10] Reaction of phosphite **2** with iodoacetone gave the desired Michaelis−Arbuzov product **4**, but in variable yield (23−46%). A higher overall yield of phosphonate **4** was obtained by reaction of phosphite **2** with iodomethane to give phosphonate **3** in 82% yield, followed by deprotonation with *sec*-butyllithium and subsequent addition of ethyl acetate (87% yield). Monomer **4** was readily polymerized in the presence of cross-linker **5** (10 mol %), using the second-generation Grubbs catalyst **6** to give ROMPgel **7** in 96% yield. Mild reaction conditions were developed for diazo-transfer to the ROMPgel **7** to give ROMPgel **8** in a loading of 2.86 mmol g^{-1}, and the route was found to be readily amenable to large-scale synthesis (38 mmol).

Applying the optimized reaction conditions previously reported for solution-phase chemistry[9] to ROMPgel **8** resulted in poor swelling of the polymer, inefficient conversion, and low yields for the transformation of aldehydes into alkynes. Consequently, two approaches were investigated to improve the ROMPgel swelling properties (Table 1). Replacement

(5) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379−1386.
(6) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869−874.
(7) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564. (b) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59−62.
(8) Eymery, F.; Iorga, B.; Savignac, P. *Synthesis* **2000**, *2*, 185−213.
(9) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *6*, 521−522.
(10) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **1999**, *1*, 579−582.

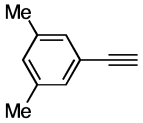
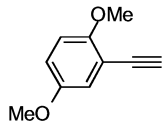
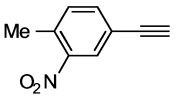
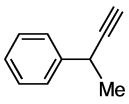
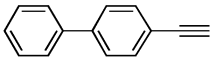
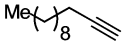
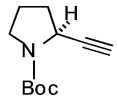
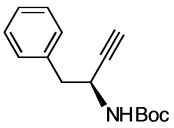
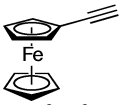
of cross-linker **5** with the more polar cross-linker **9** (5 mol %) gave ROMPgel **10** in 98% yield. Diazo-transfer to keto-phosphonate **10** proceeded to give ROMPgel **11**, which unfortunately failed to swell significantly in methanol and was much less effective than the previously prepared ROMPgel **8**. The second approach involved the preparation of a three-component ROMPgel **13** in 75% yield, containing monomer **4**, cross-linker **5**, and comonomer **12** (Table 1). Diazo-transfer to ROMPgel **13** gave reagent **14**, which demonstrated superior swelling properties to the previously prepared diazo-functionalized ROMPgels **8** and **11**. Unfortunately, copolymerization of **5** and **12** was incomplete and the comonomer **12** was consequently replaced by the pure *exo*-isomer **15**. With this modification, copolymerization proceeded in quantitative yield. The resultant polymer phosphonate was converted into the ROMPgel **17**, which was obtained with a loading of 2.70 mmol g^{-1} (Table 1). Similar observations of slower rates of ROMPolymerization of endo isomers, compared to the corresponding exo isomer, have been previously reported.[11] Reaction of ROMPgel **17** with a variety of aldehydes proceeded to give the corresponding terminal alkynes in good yield and high purity[12] (Scheme 2, Table 2). No racemization of compounds **19g** and **19h** was observed, by comparison of measured optical rotations against existing literature values,[13] which are in agreement with the earlier studies using diazophosphonate reagents.[14] The supported reagent **17** is stable at 0 °C with no significant loss in activity observed over a 3-week period of storage.

Scheme 2. Parallel Synthesis of Terminal Alkynes Using a ROMPgel-Supported Ethyl 1-Diazo-2-oxopropylphosphonate.



In conclusion, ROMPgel-supported ethyl 1-diazo-2-oxopropylphosphonate **17** has been prepared and the immobilized reagent used to convert a variety of aldehydes **18** into their corresponding terminal alkynes **19**. The ability to readily fine-tune the composition of the polymer support allowed high product yields to be obtained and thus provided further demonstration of the flexibility and compatibility of ROMPgels with conventional organic solvents.

Table 2. Yields and Purities of Terminal Alkynes **19**

	alkyne	time	% yield (% purity)[a]
19a		4 days	91 (>95)
19b		36 h	79 (90)
19c		36 h	83 (>95)
19d		5 days	81 (87)
19e		30 h	87 (>95)
19f		36 h	70 (>95)
19g		2 days	74 (>95)
19h		2 days	63 (>95)
19i		4 days	82 (92)

[a] Yields refer to isolated products. Purities as judged by ^{1}H and ^{13}C NMR spectra, GC−MS, and microanalysis.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Ivin, K. J. In *Olefin Metathesis*; Academic Press: London, 1983. (b) Dragutan, V.; Balaban, A. T.; Dimonie, M. In *Olefin Metathesis and Ring Opening Polymerization of Cyclo-Olefins*, 2nd ed.; Wiley-Interscience: New York, 1985. (c) Castner, K. F.; Calderon, N. *J. Mol. Catal.* **1982**, *15*, 47.

(12) In a typical experiment, degassed (N_2) MeOH (5 mL) was added to the aldehyde **18** (0.1 mL, 0.56 mmol), K_2CO_3 (0.38 g, 2.79 mmol), and polymer **17** (0.81 g, 2.19 mmol) under nitrogen, and the reaction mixture was shaken vigorously at 4 °C. When the transformation was complete (as monitored by TLC), MeOH was evaporated in vacuo, and the resulting residue was extracted with hexanes and filtered. The combined filtrates were concentrated in vacuo to leave the corresponding acetylene **19**.

(13) (a) Garvey, D. S.; Wasicak, J. T.; Elliott, R. L.; Lebold, S. A.; Hettinger, A.-M.; Carrera, G. M.; Lin, N.-H.; He, Y.; Holladay, M. W.; Anderson, D. J.; Cadman, E. D.; Raszkiewicz, J. L.; Sullivan, J. P.; Arneric, S. P. *J. Med. Chem.* **1994**, *37*, 4455−4463. (b) Hauske, J. R.; Dorff, P.; Julin, S.; Martinelli, G.; Bussolari, J. *Tetrehedron Lett.* **1992**, *33*, 3715−3716.

(14) (a) Reginato G.; Mordini A.; Messina F.; Degl'Innocenti A.; Poli G. *Tetrahedron* **1996**, *52*, 10985−10996 (b) see ref (9)