ORGANIC LETTERS

2001
Vol. 3, No. 2
271−273

Oxazole Synthesis with Minimal Purification: Synthesis and Application of a ROMPgel Tosmic Reagent†

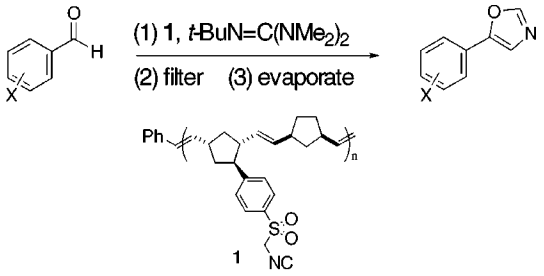
Anthony G. M. Barrett,*,‡ Susan M. Cramp,§ Alan J. Hennessy,‡ Panayiotis A. Procopiou,|| and Richard S. Roberts‡

Department of Chemistry, Imperial College of Science, Technology and Medicine, London, SW7 2AY, United Kingdom, Aventis CropScience, Fyfield Road, Ongar, Essex, CM5 0HW, United Kingdom, and Department of Medicinal Chemistry, Glaxo Wellcome Research and Development Ltd., Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, U.K.

agmb@ic.ac.uk

Received November 22, 2000

ABSTRACT



The synthesis of ring opening metathesis, polymer-supported Tosmic reagent 1 is described. This reagent was utilized in the conversion of aldehydes to oxazoles in good yields and purities.

The advent of combinatorial chemistry has allowed for the rapid, automated synthesis of libraries of compounds which together with high throughput screening have accelerated the discovery of active pharmaceutical compounds as well as catalysts, agrochemicals, and other fine chemicals.[1] Generation of these libraries of compounds has mainly been carried out by solid phase synthesis, but the use of efficient parallel solution phase chemistry is becoming an attractive alternative.[2] The familiarity of solution chemistry to the organic chemist and the ease of monitoring and analysis of reactions give the latter approach an advantage in many situations. However, parallel purification of products may be difficult despite recent advances in automatic chromatography (MPLC, HPLC), the use of fluorous phase chemistry,[3] and use of selective scavengers of impurities.[4]

The use of polymer-supported reagents allows for solution phase reactions to be driven to completion efficiently and also allows for the isolation of pure products by simple filtration and evaporation.[5] This method is also amenable to the parallel synthesis and purification of many compounds.

The majority of polymer-supported reagents have used cross-linked polystyrene as the insoluble support although

† Dedicated to Professor Jean Francois Normant on the occasion of his 65th birthday (January 29, 2001).

‡ Imperial College of Science.

§ Aventis CropScience.

|| Glaxo Wellcome Research and Development Ltd.

(1) (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. (b) Balkenhohl, F.; van dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 2289.

(2) (a) Bunin, B. A. *The Combinatorial Index*; Academic Press: San Diego, CA, 1998. (b) Booth, R. J.; Hodges, J. C. *Acc. Chem. Res.* **1999**, *32*, 18. (c) Baldino, C. M. *J. Comb. Chem.* **2000**, *2*, 89.

(3) (a) Curran, D. P.; *Angew. Chem., Int. Ed.* **1998**, *37*, 1174. (b) Linclau, B.; Sing, A. K.; Curran, D. P. *J. Org. Chem.* **1999**, *64*, 2835.

(4) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hanh, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193.

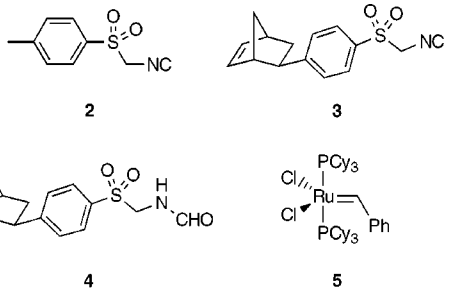
(5) (a) Caldarelli, M.; Habermann, J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 107.

10.1021/ol006912n CCC: $20.00
Published on Web 12/22/2000

recently we have reported that functionalized ring opening metathesis polymers (we have termed these ROMPgels) provide an effective alternative.[6] We have also reported the use of these ROMPgels in Horner−Emmons,[7] acyl transfer,[8] oxadiazole synthesis,[9] and amine-scavenging reactions.[10] We herein report the synthesis and application of a ROMPgel Tosmic reagent.

The Tosmic reagent **2**, introduced by van Leusen, facilitates a wide range of transformations. These include the synthesis of heterocycles such as oxazoles, pyrroles, imidazoles, and thiazoles.[11] Substituted Tosmic reagents have also found synthetic uses.[12] Purification of Tosmic reaction products have generally required chromatography, although Ganesan and co-workers have attempted to address this problem. They have used Ambersep 900 hydroxide resin as an ion-exchange base[13] and obtained a variety of aromatic oxazoles in good isolated yields (54−85%) but moderate crude purities (57−94%). They also used a Tentagel-supported Tosmic reagent[14] to prepare a variety of aromatic oxazoles in lower yields (25−50%), and chromatography was needed to obtain adequately pure compounds.

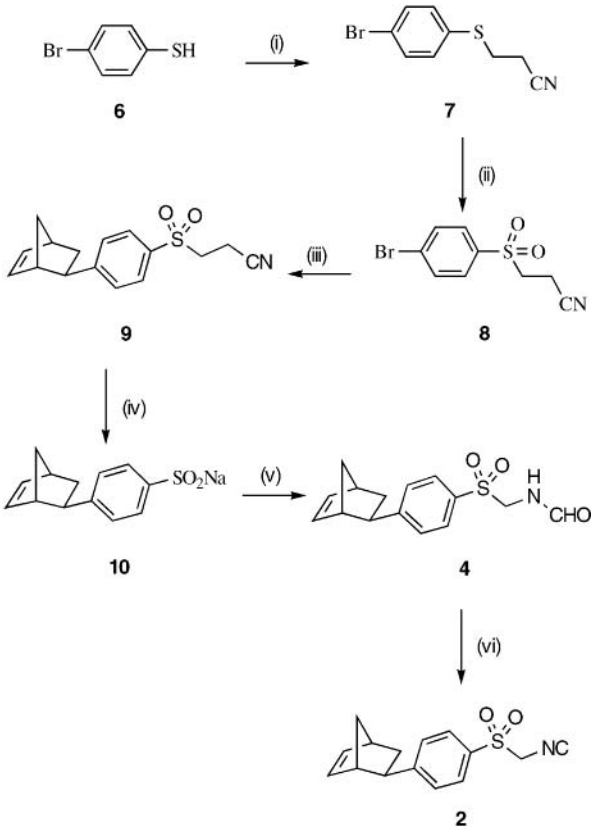
We envisaged that a ROMPgel Tosmic reagent should provide pure products when used in conjunction with a strong amine base such as *tert*-butyltetramethylguanidine.[15] Such a reagent should be available from the ring opening metathesis of isonitrile monomer **3** or the corresponding formamide **4** followed by dehydration.



2 **3** **4** **5**

Michael addition of 4-bromothiophenol to acrylonitrile under basic conditions gave sulfide **7** in 92% yield after recrystallization (Scheme 1). It was found necessary to oxidize the sulfide to the sulfone at this stage as epoxidation was found to be a side reaction once the norbornene moiety had been introduced. This oxidation was performed using

Scheme 1[a]



[a] Key: (i) acrylonitrile, Triton B, 92%; (ii) 3-$ClC_6H_4CO_3H$, CH_2Cl_2, 95%; (iii) $Pd(PPh_3)_2(OAc)_2$ (5 mol %), norbornadiene (5 equiv), piperidine (5 equiv), HCO_2H (3 equiv), DMF, 65%; (iv) NaOEt, EtOH, 100%; (v) paraformaldehyde (4 equiv), formamide (8 equiv), formic acid (4 equiv), 65 °C, 3 h, 71%; (vi) $^iPr_2NH$ (3 equiv), $POCl_3$ (1.1 equiv), CH_2Cl_2, 90% (crude yield).

m-chloroperbenzoic acid and proceeded in excellent yield to give **8**.

Palladium-catalyzed *exo*-hydroarylation of norbornadiene with **8** provided **9** in good yield.[16] Careful temperature control was required for optimum yields in this reaction due to competitive elimination at higher temperatures. Conversion to the sulfinate salt and its subsequent transformation to give formamide **4** proceeded in good yield.[17,18] All of these reactions proved amenable to multigram synthesis. Dehydration of formamide **4** using $POCl_3$ and $^iPr_2NH$ gave the desired isonitrile monomer **3**. While isonitrile **3** failed to undergo ROM polymerization presumably due to bonding to the coordinatively unsaturated ruthenium intermediate, formamide **4** was converted into the ROMP **11** in quantitative yield using 1.5 mol % of **5** under standard conditions.

Copolymerization of formamide **4** with norbornene gave a gellike polymer which underwent a facile dehydration to provide the target ROMP **1** in quantitative yield and 2.7 mmol/g loading. The dehydration step was carefully moni-

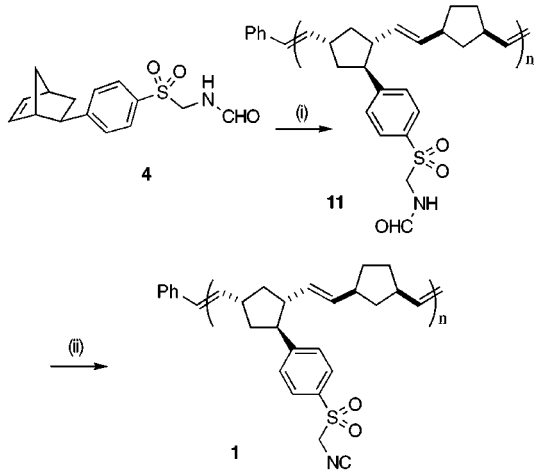
(6) The name originates from the swelling properties which these polymers exhibit when solvated.

(7) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **1999**, *1*, 579.
(8) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **2000**, *2*, 261.
(9) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Comb. Chem. High Throughput Screening* **2000**, *3*, 131.
(10) Arnauld, T.; Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **2000**, *2*, 2663.
(11) van Leusen, A. M.; van Leusen, D. *Encylopedia of reagents in organic synthesis*; Paquette, L. A., Ed.; J.; Wiley: New York, 1995; p 4973.
(12) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J. Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516.
(13) Kulkarni, B. A.; Ganesan, A. *Tetrahedron Lett.* **1999**, *40*, 5637.
(14) Kulkarni, B. A.; Ganesan, A. *Tetrahedron Lett.* **1999**, *40*, 5633.
(15) *tert*-Butyltetramethylguanidine or Barton base is commercially available from Fluka.

(16) Arcadi, A.; Marinelli, F.; Bernocchi, E.; Cacchi, S.; Ortar, G. *J. Organomet. Chem.* **1989**, *368*, 249.
(17) Truce, W. E. Roberts, F. E. *J. Org. Chem.* **1963**, *28*, 593.
(18) van Leusen, A. M.; Boerma, G. J. M.; Helmholdt, R. B.; Siderius, H.; Strating, J. *Tetrahedron Lett.* **1972**, *23*, 2367.

tored by IR to ensure complete conversion of formamide to isonitrile (Scheme 2).

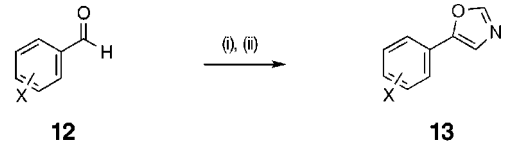
Scheme 2[a]



[a] Key: (i) **5** (1.5%), norbornene (1 equiv), CH_2Cl_2, 30 min, rt then ethyl vinyl ether, 100%; (ii) $^iPr_2NH$ (5 equiv), $POCl_3$ (2 equiv), THF, 100%.

ROMPgel **1** was found to be effective for the conversion of a range of aldehydes into oxazoles, which could be isolated without chromatography with high levels of purity (>95%). A typical procedure involved the reaction of aldehyde **12** with **1** (4 equiv) in acetonitrile (giving a 0.2 M solution) and *tert*-butyltetramethylguanidine (4 equiv) for 12 h at 65 °C (Scheme 3).

Scheme 3[a]



[a] Key: (i) **1** (4 equiv), *t*-BuN=C(NMe$_2$)$_2$ (4 equiv), MeCN, 70 °C, 12 h; (ii) filter, evaporate.

Parallel reaction in a small library gave oxazoles **13a**−**j** all in excellent purity (>95% as judged by GC and ^{1}H NMR) and in 68−90% isolated yield, Figure 1. The reaction is applicable to aldehydes substituted in the *ortho*, *meta*, or *para* positions and also works for heterocyclic aldehydes. The reaction was found to be tolerant of ester, nitrile, halo, and nitro functional groups. Purification was limited to filtration through a 1 cm plug of silica in a Pasteur pipet taking only one fraction followed by evaporation; therefore this process is amenable to automation. Use of more electron rich aldehydes decrease the rate of reaction, and therefore the reactions of benzaldehyde and anisaldehyde could only be driven to 90 and 66% conversion, respectively. Chromatography was therefore needed in order to obtain the pure oxazoles **k** and **l**. Longer reaction times, higher reaction temperatures, or the use of an aldehyde scavenger (polystyrene-supported arenesulfonyl-hydrazine)[19] gave lower product purities.

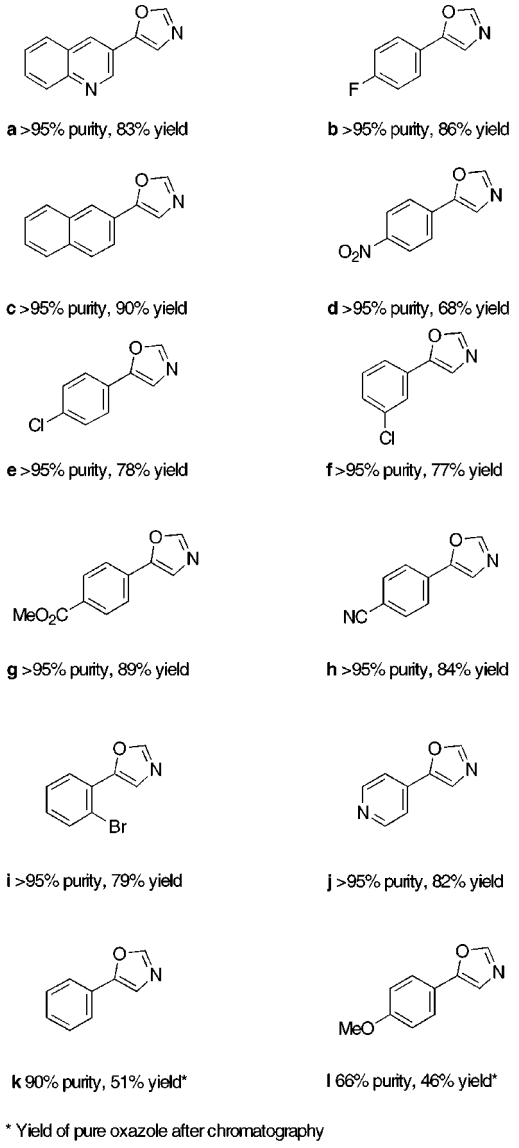


Figure 1.

In conclusion we have developed a ROMPgel Tosmic reagent and successfully applied it to the synthesis of a small library of oxazoles with minimal purification. This further demonstrates the utility of ROMPgels as polymer-supported reagents, and further work in this field from our laboratories will be reported in due course.

Acknowledgment. We thank Glaxo Wellcome Research for support of our research and for the generous endowment (to A.G.M.B.), Aventis CropScience for their generous support of this project (S.M.C.), the EPSRC, and the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College.
OL006912N

(19) Polystyrene-supported arenesulfonyl-hydrazine was obtained from Argonaut Technologies Inc.