ORGANIC LETTERS

2004
Vol. 6, No. 16
2657−2660

Development of High-Load, Soluble Oligomeric Sulfonate Esters via ROM Polymerization: Application to the Benzylation of Amines

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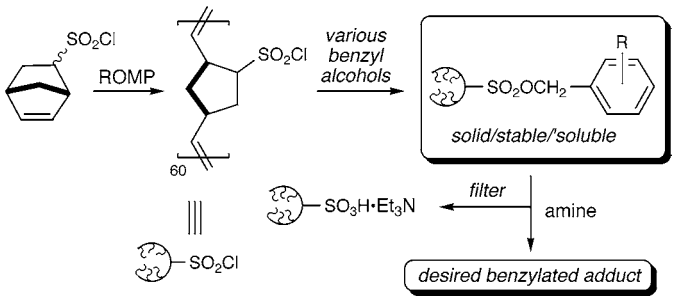
Received April 29, 2004

ABSTRACT



The development of high-load, soluble oligomeric sulfonate esters, generated via ROM polymerization, and their utility in the facile benzylation of an array of amines is reported. These polymeric sulfonate esters exist as free-flowing powders, are stable at refrigerated temperatures, and are readily dissolved in CH_2Cl_2. Following the benzylation event, purification is attained via simple filtration, followed by solvent removal to deliver the desired benzylated product in good to excellent yield and high purity.

The growing need for the rapid production of compounds for screening has necessitated the development of facilitated synthetic protocols whereby the science of synthesis and purification are integrated. In this context, an array of polymer-bound scavengers and reagents has appeared, effectively eliminating or circumventing the need for chromatographic purifications.[1] Recent successes in multistep total syntheses using almost exclusively immobilized reagents/scavengers[1e,2] are a testament to the power of this approach whereby filtration was the sole purification protocol employed. Despite huge advances in this area, the need for improvements in both resin-load capacity and reaction rates continues to warrant the development of new and improved immobilized reagents.

Soluble polymers,[3] with differential solubility profiles, have emerged as a means of exploiting solution-phase reaction kinetics with all the advantages of their solid-phase

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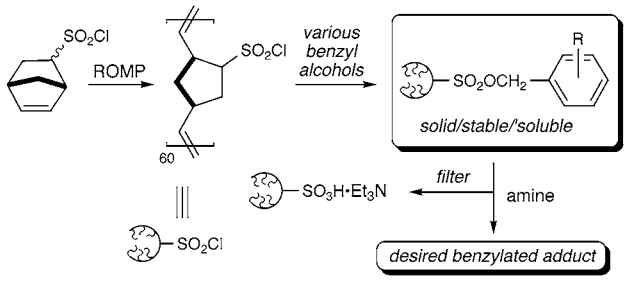
10.1021/ol049209y CCC: $27.50
Published on Web 07/07/2004

(1) (a) Regen, S. L.; Lee, D. P. *J. Org. Chem.* **1975**, *40*, 1669−1670. (b) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193−7196. (c) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217−1239. (d) Booth, R. J.; Hodges, J. C. *Acc. Chem. Res.* **1999**, *32*, 18−26. (e) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874−4881. (f) 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**, 3815−4195 (g) van Heerbeek, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.: Reek, J. N. H. *Chem. Rev.* **2002**, *102*, 3717−3756. (h) Yoshida, J.-I.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693−3716.

(2) (a) Baxendale, I. R.; Brusotti, G.; Matsuoka, M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 143−154. (b) Baxendale, I. R.; Ley, S. V.; Piutti, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2194−2197. (c) Storer, R. I.; Takemoto, T.; Jackson, P. S.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 2521−2525. (d) Parlow, J. J.; Flynn, D. L. *Tetrahedron* **1998**, *54*, 4013−4031.

counterparts. In addition, ring-opening metathesis polymerization (ROMP)[4] has surfaced as a means of facilitating synthesis via the generation of designer polymers with tunable properties and increased load levels when compared with traditional resins. Our interest in the development of facilitated synthetic protocols now leads us to report the synthesis and utility of an array of high-load, soluble oligomeric benzylating agents generated via ROM polymerization (Scheme 1).

Scheme 1

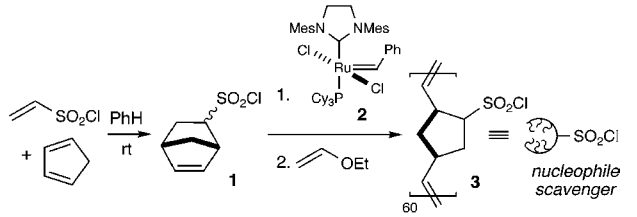


Benzylation continues to be one of the most commonly used alkylation reactions in organic chemistry.[5] Due to its ease of incorporation and removal, the benzyl group also serves as one of the most exploited protecting groups.[6] In addition, the hydrophobic, aromatic properties inherent to the benzyl group make it an ideal diversity element in combinatorial chemistry. When taken collectively, these attributes logically point toward the development of an immobilized benzylating agent. Surprisingly, to the best of our knowledge, the literature is void of examples demonstrating the use of immobilized benzylating agents.

The area of developing immobilized alkylating agents was first explored in 1996, when Roush and Hunt displaced a polymer-bound alkylsulfonate with NaI to derive the respective alkyl halide in good yield.[7] Reitz and co-workers subsequently reported the use of a polystyrene resin-bound sulfonyl chloride that was "activated" with a variety of alcohols and further reacted in situ with a panel of amines to achieve the desired alkylation in a process termed "catch and release".[8] In their protocol, arylsulfonyl chloride resins having load values in the 1.1−1.4 mmol/g range were reacted with a variety of alcohols to produce the desired insoluble polymeric alkylating agents.

A logical starting point for our development of a high-load, soluble benzylating agent was the oligomeric sulfonyl chloride (OSC, **3**) that we recently reported for homogeneous amine scavenging.[9] This OSC reagent is easily generated from the ROM polymerization of 2-chlorosulfonyl-5-norbornene (**1**) (derived from a simple Diels−Alder reaction) utilizing the second-generation Grubbs catalyst **2**. Following the quenching process with ethyl vinyl ether, the OSC reagent can be precipitated with ether to give a free-flowing powder in excellent yield (Scheme 2).[10]

Scheme 2



We initially investigated an in situ benzylation protocol that entailed reaction of the OSC reagent **3** with excess triethylamine, followed by treatment with benzyl alcohol. Subsequent addition of morpholine produced the benzylated product **6a** with high purity, albeit in low yield (30−35%). Repeated attempts with this in situ protocol have yet to improve the yield.

To circumvent this problem, we developed an improved procedure whereby the oligomeric benzyl sulfonate esters can be isolated and used in subsequent benzylation reactions. Thus, reverse addition of a solution of OSC in CH_2Cl_2 at 0 °C into a stirred solution of benzyl alcohol (1.50 equiv) and Et_3N (1.0 equiv) in CH_2Cl_2 produced a homogeneous mixture that was partitioned into diethyl ether to precipitate the oligomeric sulfonate esters **4a**−**j** as free-flowing powders in quantitative yields with theoretical load values of ∼3.5

(3) For reviews concerning soluble polymers, see: (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489−509. (b) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546−554. (c) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325−3344. (d) Haag, R. *Chem. Eur. J.* **2001**, *7*, 327−335. (e) Haag, R.; Sunder, A.; Hebel, A.; Roller, S. *J. Comb. Chem.* **2002**, *4*, 112−119. (f) Bergbreiter. D. E. *Chem. Rev.* **2002,** *102*, 3345−3384.

(4) For reviews concerning ROMP reagents, see: (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 Discov. Devel.* **2002**, *5*, 571−579. (c) Harned, A. M.; Probst, D. A.; Hanson, P. R. The Use of Olefin Metathesis in Combinatorial Chemistry: Supported and Chromatography-Free Syntheses. In *Handbook of Metathesis*; Grubbs, R. H., Ed.: Wiley-VCH: Weinheim, 2003; pp 361−402.

(5) Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*, 1st ed.; John Wiley and Sons: New York, 1995; pp 316−318. The most common reagents to achieve this process are the benzylic bromides, which present both safety and toxicity issues, most notably that they are severe lachrymators.

(6) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999; pp 76−86.

(7) Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc.* **1996**, *118*, 9998−9999.

(8) Recently, the development of versatile arylsulfonyl chloride resins as both scavenging resins and capture−release agents has been reported. (a) Rueter, J. K.; Nortey, S. O.; Baxter, E. W.; Leo, G. C.; Reitz, A. B. *Tetrahedron Lett.* **1998**, *39*, 975−978. (b) Baxter, E. W.; Rueter, J. K.; Nortey, S. O.; Reitz, A. B. *Tetrahedron Lett.* **1998**, *39*, 979−982. (c) Takahashi, T.; Ebata, S.; Doi, T. *Tetrahedron Lett.* **1998**, *39*, 1369−1372. (d) For a review on polymer-supported arylsulfonyl chloride resin, see: Huang, W.; He, B. *Chin. J. React. Polym. (Engl.)* **1992**, *1*, 61−70.

(9) (a) Moore, J. D.; Herpel, R. H.; Lichtsinn, J. R.; Flynn, D. L.; Hanson, P. R. *Org Lett.* **2003**, *5*, 105−107. For a related ROMP-derived bis-acid chloride oligomeric scavenger, see: (b) Moore, J. D.; Byrne, R. J.; Vedantham, P.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2003**, *5*, 4241−4244.

(10) We have previously found that there is good correlation between the mol % Grubbs catalyst added and the Gaussian distribution of oligomers formed, which we believe is the case with the OSC in Scheme 2. We have made this reagent several times (i.e., the preparation and reactivity is repeatable and consistently reliable). We normally obtain MALDI-TOF and/or GPC data on all oligomers formed; however, both methods have failed to give good results for this reactive oligomeric sulfonyl chloride (OSC).

mmol/g. These oligomers are extraordinarily stable for long periods of time and can thus be isolated and stored at refrigerated temperatures.[11] In addition, oligomers **4a**−**j** are readily dissolved in CH_2Cl_2 and can be added to a mixture of Et_3N and morpholine via cannulae, thus maintaining homogeneity for optimal reaction kinetics. Furthermore, the soluble aspects of this approach enable convenient dispensing that could ultimately provide an enormous advantage in parallel array synthetic protocols.

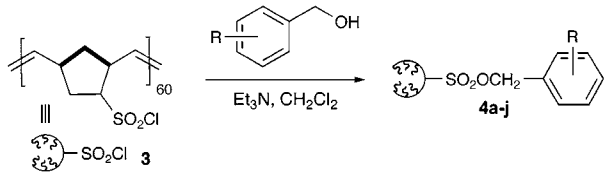
We began our investigation with the simple benzylation of morpholine (Table 1). Oligomers **4a**−**j** were easily dissolved in CH_2Cl_2 and added to a mixture of 5.0 equiv of Et_3N and 1.0 equiv of morpholine, thus maintaining the reaction kinetics of a homogeneous process.

Table 1. Benzylation of Morpholine Results

entry	starting material	R	product	yield (%)[a]	purity (%)[b]
1	**4a**	H	**6a**	98	95
2	**4b**	*o*-Me	**6b**	94	95
3	**4c**	*m*-Me	**6c**	87	93
4	**4d**	*p*-Me	**6d**	90	94
5	**4e**	*m*-Br	**6e**	84	>90
6	**4f**	*o*-NO_2	**6f**	87	92
7	**4g**	*p*-NO_2	**6g**	79	79[c]
8	**4h**	*p*-^{t}Bu	**6h**	86	85[c]
9	**4i**	*p*-Me, *m*-NO_2	**6i**	78	82[c]
10	**4j**	naph[d]	**6j**	93	76[c]

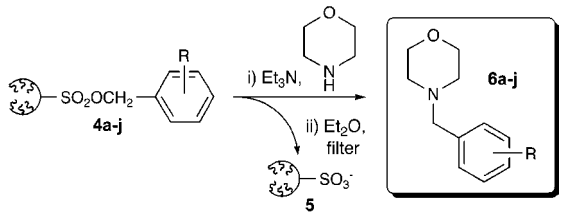
[a] Yield of crude after filtration. [b] Purities were determined by GC and confirmed by ^{1}H NMR. [c] Substantial contamination with the corresponding benzyl alcohol, as evident by ^{1}H NMR. [d] R = naph refers to a 1-naphthyl sulfonate ester, not a naphthyl R group.

Scheme 3



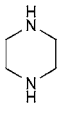
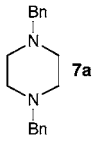
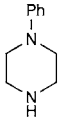
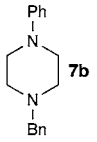
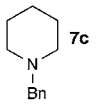
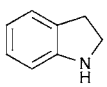
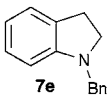
found to be slightly contaminated (<5%) with the corresponding benzyl alcohol, as evident by ^{1}H NMR, while entries 7−10 gave substantial amounts of the corresponding benzyl alcohol (15−20%). Presumably, these later entries resulted from substantial hydrolysis of the benzylating reagent during the reaction or the filtering process, thus warranting care to preserve an anhydrous environment.

Scheme 4



We next examined the benzylation of other secondary amines using the simple benzylating agent **4a**. Over the course of this study, it was found that cyclic secondary amines were the most successful in this process. The results of the benzylation of these scaffolds, using the identical procedure as above, led to the corresponding tertiary amines **7a**−**e** in good yields and purities as outlined below in Table 2. The benzylated products were found to be only slightly contaminated (<5%) with the benzyl alcohol, as evident by ^{1}H NMR analysis.

Table 2. Benzylation of Cyclic, Secondary Amines

entry	amine	pdt	yield (%)[a]	purity (%)[b]
1		 **7a**	68	>90
2		 **7b**	94	>90
3		 **7c**	87	>90
4		 **7d**	90	>90
5		 **7e**	92	>90

[a] Yield of crude after filtration. [b] Purities were determined by GC and confirmed by ^{1}H NMR. All of the benzylated products are slightly contaminated with benzyl alcohol, as evident by ^{1}H NMR.

Acyclic and aromatic amines were next investigated (Table 3), with benzylamine (entry 1) and anilines (entries 2 and 3) giving promising results. However, other acyclic amines

Table 3. Benzylation of Acyclic Amines and Other Nucleophiles Using Oligomeric Sulfonate Ester **4a**

entry	nucleophile (starting material)	expected product **8**	product distribution[a]
1	$BnNH_2$	Bn_2NH **8a** Bn_3N **8b**	87% (**8a**), 12% (**8b**)
2	PhNHMe	PhN(Me)Bn **8c**[b]	93% (**8c**), 6% (BnOH)
3	$PhNH_2$	PhNHBn **8d**	87% (**8d**), 4% ($PhNBn_2$)
4	Ph_2NH	Ph_2NBn **8e**	only starting material recovered
5	Et_2NH	Et_2NBn **8f**	no benzylation
6	Bn_2NH	Bn_3N **8b**	27% (**8b**), 71% (Bn_2NH), 2% (BnOH)
7	*p*-NO_2PhOH	*p*-NO_2PhOBn **8g**	only starting material recovered
8	$CH_3(CH_2)_{11}SH$	$CH_3(CH_2)_{11}SBn$ **8h**	only starting material recovered

[a] Determined by GC/MS. [b] Yield of crude after filtration was 81%. For ^1H NMR, ^{13}C NMR, and mass data of **8c**, see Table 1 in Supporting Information.

were more problematic (Table 3, entries 4−6) in producing the desired benzylated amines. In addition, other nucleophiles such as *p*-nitrophenol (entry 7) and 1-dodecanethiol (entry 8) also failed. We feel that nucleophilicity and/or steric effects are the primary factors in these benzylations. This fact is supported by the success of all cyclic amines (Tables 1 and 2) versus their acyclic secondary amino counterparts (Table 3, entries 1−6). Efforts are currently aimed at extending this protocol to additional nucleophiles.

In conclusion, we have demonstrated the first synthesis and utilization of a ROMP-derived oligomeric benzylating agent. These entities proved to be extremely efficient in the benzylation of cyclic, secondary amines and with limited success in the case of acyclic amines. Purification following the alkylation reaction was carried out via simple precipitation/filtration. Efforts to widen the scope of this reaction, as well as its extension into the arena of combinatorial chemistry, are underway. The results of these endeavors will be reported in due course.

Acknowledgment. This investigation was generously supported by partial funds provided by the National Science Foundation (NSF Career 9984926), the University of Kansas Research Development Fund, and the NIH Center of Excellence in Combinatorial Methodologies and Library Development (KU-CMLD, NIH 1P50 GM069663-01) with additional funds from the State of Kansas. The authors thank Neogenesis Pharmaceuticals, Inc., for providing generous postdoctoral support (M.Z.) and Materia, Inc., for supplying catalyst and helpful discussions.

Supporting Information Available: Detailed experimental procedures, tabulated ^1H NMR, ^{13}C NMR, and mass data, and ^1H NMR spectra of crude products obtained by the described successful benzylation method. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) We found that the stability of the oligomeric sulfonate esters is directly affected by the electronic influence of the aromatic substituent. For example, benzyl alcohols containing a methoxy group at either the ortho or para position generated unstable oligomers. This is attributed to the strong electron-donating ability of this substituent that could effectively displace the sulfonate and react immediately with adventitious water present.