2nd International Electronic Conference on Synthetic Organic Chemistry (ECSOC-2), http://www.mdpi.org/ecsoc/, September 1-30, 1998

[b0002]

Parallel Synthesis of 1,2,3-Thiadiazoles Employing a "Catch and Release" Strategy

Yonghan (Fred) Hu *, *Sylvie Baudart, Owen W. Gooding, Jeff W. Labadie, Wendy Miller, and John A. Porco, Jr.**
Argonaut Technologies, 887 Industrial Road, Suite G, San Carlos, CA 94070
Tel. (650) 598-1350, Fax (650) 598-1359

Abstract

1,2,3-thiadiazoles were synthesized in parallel using a polymer sulfonyl hydrazide resin (PS-TsNHNH$_2$) and employing a "catch and release" synthesis strategy. Resin capture of ketones synthesized from Weinreb amides and Grignard reagents afforded resin-bound sulfonylhydrazones. Cyclizative cleavage of support-bound sulfonylhydrazones with thionyl chloride afforded 1,2,3-thiadiazoles. Excess thionyl chloride was neutralized using liquid-liquid extraction cartridges.

Keywords

polystyrene sulfonylhydrazine resin, 1,2,3-thiadiazole, "catch and release", resin capture.

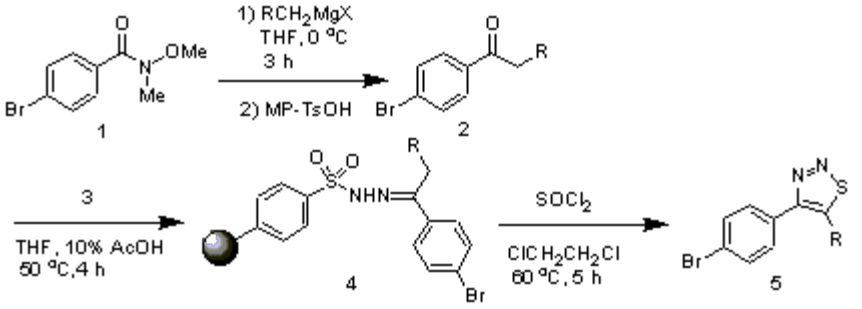
Introduction

Combinatorial solid-[1] and solution-phase [2] methods have been frequently employed in the synthesis of compound libraries of potential biological and therapeutic significance. Many novel methodologies have been developed, including "catch and release" and "resin capture" strategies for the expedited workup and purification of compounds synthesized in solution. [3,4] 1,2,3-Thiadiazoles are a class of important and biologically active compounds[5] as well as useful intermediates in organic synthesis.[6] For example, 4,5-bis-(4-methoxyphenyl)-1,2,3-thiadiazole was found to be an active inhibitor of collagen-induced platelet aggregation *in vitro*.[5a] Many methods have been developed for the synthesis of 1,2,3-thiadiazoles,[5d,5e] of which the Hurd-Mori cyclization of alpha-methylene ketones is the most convenient methodology.[7,8] Herein, we report a parallel synthesis of 1,2,3-thiadiazoles employing a "catch and release" strategy wherein ketones were prepared in solution and captured to the solid support *via* sulfonylhydrazone formation.

Results and Discussion

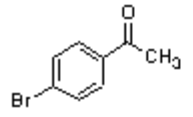
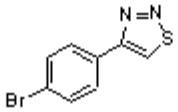
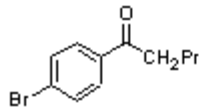
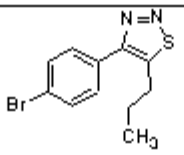
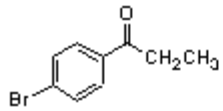
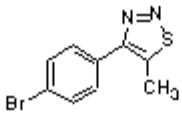
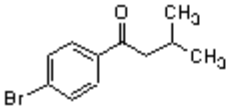
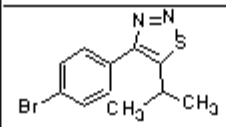
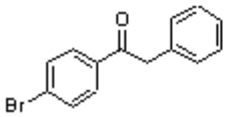
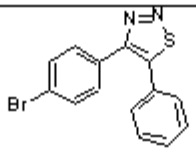
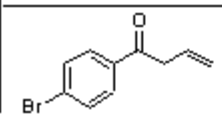
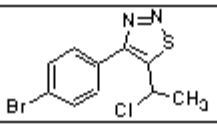
Recently we prepared a gel-type polystyrene-sulfonylhydrazide resin (PS-Ts-$NHNH_2$) for carbonyl scavenging applications. [9,10] We felt that the sulfonylhydrazide resin could also serve as a linker for carbonyl compounds in solid-phase synthesis. In our hands, sulfonylhydrazone formation was found to be complete in 2-4 h at 50 ^{o}C in the presence of acetic acid. The formation of support-bound sulfonyl hydrazones from *in situ* synthesized ketones may be facilitated by use of a "resin capture strategy"[4] (**Scheme 1, Table 1**). Six *p*-bromophenyl ketones were prepared in parallel on the Quest 210 Organic Synthesizer (Bank A) by reacting N-methoxy-N-methyl-*p*-bromobenzamide (**5**)[11] with a variety of Grignard reagents (THF, 0 ^{o}C). The reaction mixtures were quenched with a macroporous polystyrene-sulfonic acid resin (MP-TsOH) to decompose the tetrahedral intermediate.[12] Acetic acid (10% v/v) was added and the ketone solutions were directly transferred *via* cannula to reaction vessels or Quest 210 (Bank B) containing PS-$TsNHNH_2$ resin for sulfonylhydrazone formation. After thionyl chloride cleavage, purification of the cleavage solution was performed in parallel using saturated Na_2CO_3 preloaded onto liquid-liquid extraction cartridges.[13,14] A series of 1,2,3-thiadiazoles were prepared with various substituents at 5 position.[15] In the case of entry 6, the product from the further addition of HCl to the olefin was obtained. Compounds similar to those shown in entry 5 are of great interest since antithrombotic compounds have been found to bear aromatic substituents at both 4 and 5 positions of the 1,2,3-thiadiazole ring.[5a] Structurally similar compounds may, in principle, be generated by resin capture of ketones synthesized using other methods, *e.g*. aryl Grignard addition to N-methoxy-N-methyl-2-arylacetamides, or Friedel-Crafts reactions.[16]

Scheme 1. Thiadiazoles Prepared *via* "Resin capture" of Ketones



In summary, we have developed a very efficient hybrid solution/solid-phase sequence for the synthesis of 1,2,3-thiadiazoles employing "resin capture" of ketones without the need for chromatography. Cyclizative cleavage of resin-bound sulfonylhydrazones was accomplished using thionyl chloride to afford 1,2,3-thiadiazoles. Additional diversification reactions of resin-bound sulfonylhydrazones are possible, as well as alternative cleavage protocols (*e.g*. Shapiro olefin synthesis[17] , reductive cleavage[10c,18],) to form additional compound classes. Further studies along these lines are in progress and will be reported in due course.

Table 1. Thiadiazoles Prepared *via* "Resin Capture" of Ketones

Entry	Ketone 2	Thiadiazole 5	Yield (%)	GC Purity (%)
1			98	100
2			82	94
3			77	97
4			59	97
5			67	98
6			48	71

References

[1] (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem*. **1994**, *37*, 1233. For a recent review, see (b) Thompson, M. A.; Ellman, *J. A. Chem. Rev.* **1996**, *96*, 555.
[2] (a) Coffen, D. L. Ed. *Solution phase combinatorial chemistry; Tetrahedron*, **1998**; Vol. 54. (b) Kaldor, S.W.; Siegel, M.W. C*urr. Opin. Chem. Biol.* **1997**, *1*, 101.
[3] For "catch and release" of amines, see: (a) Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett*. **1997**, *38*, 3357. (b) Shuker, A. J.; Siegel, M. G.; Matthews, D. P.; Weigel, L. O. *Tetrahedron Lett*. **1997**, *38*, 6149. (c) Liu, Y.; Zhao, C.; Bergbreiter, D. E.; Romo, D. *J. Org. Chem.* **1998**, *63*, 3471.
[4] For examples of "resin capture", see: (a) Keating, T. A.; Armstrong, R. W. J*. Am. Chem. Soc.* **1996**, *118*, 2574. (b) Brown, A. D.; Armstrong, R. W. *J. Am. Chem. Soc*. **1996**, *118*, 6331. (c) Brown, S. D.; Armstrong, R. W. *J. Org. Chem*. **1997**, *62*, 7076. (c) Chen, C.; McDonald, I. A.; Munoz, B. *Tetrahedron Lett*. **1998**, *39*, 217.
[5] (a) Thomas, E. W.; Nishizawa, E. E.; Zimmermann, D. C., Williams, D. J. *J. Med. Chem*. **1985**, *28*, 442. (b) Lewis, G. S.; Nelson, P. H. *J. Med. Chem.* **1979**, *22*, 1214. (c) Britton, T. C.; Lobl, T. J.; Chidester, C. G., *J. Org. Chem*. **1984**, *49*, 4773. For reviews on the chemistry of 1,2,3-thiadiazoles, see: (d) Thomas, E. W. In "Comprehensive Heterocyclic Chemistry"; Potts, K. T., Vol Ed.; Katritzky, A. R., Rees, C. W., Series Eds.; Pergamon Press: London, 1984; Vol. 6, Part 4B, Chapter 4.24, p. 447. (e) Thomas, E. W. In "Comprehensive Heterocyclic Chemistry"; Storr, R. C., Vol Ed.; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Series Eds.; Pergamon Press: London, 1996; Vol. 4, Chapter 4.07, p. 289.
[6] Rovira, C.; Veciana, J.; Santalo, N.; Tarres, J.; Cirujeda, J.; Molins, E.; Llorca, J.; Espinosa, E. *J. Org. Chem*. **1994**, *59*, 3307.
[7] Hurd, C. D.; Mori, R. I. *J. Am. Chem. Soc.* **1955**, *77*, 5359.
[8] (a) Fujita, M.; Kobori, T.; Hiyama, T.; Kondo, K. *Heterocycles* **1993**, *36*, 33. (b) Stanetty, P.; Kremslehner, M.; Mullner, M. J. *Heterocyclic Chem*. **1996**, *33*, 1759.
[9] PS-TsNHNH$_2$ resin (1.8-2.5 mmol/g, 1% crosslinked polystyrene-co-divinylbenzene) is commercially

available from Argonaut Technologies.
[10] For reports on the preparation and use of sulfonylhydrazide resins, see: (a) Galioglu, O; Akar, A. Eur. Polym. J. 1989, 25, 313. (b) Emerson, D. W.; Emerson, R. R.; Joshi, S. C.; Sorensen, E. M.; Turek, J. M. *J. Org. Chem*. **1979**, *44*, 4634. (c) Kamogawa, H.; Kanzawa, A.; Kadoya, M.; Naito, T.; Nanasawa, M. Bull. *Chem. Soc. Jpn*. **1983**, *56*, 762.
[11] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
[12] MP-TsOH resin (1.1-1.6 mmol/g, macroporous polystyrene-co-divinylbenzene) is commercially available from Argonaut Technologies.
[13] Extube column: cartridges (Extube™ Extraction Columns preloaded with 3 mL saturated Na_2CO_3). Extube™ liquid-liquid extraction cartridges were purchased from Varian Sample Preparation Products, Harbor City, CA.
[14] For examples of parallel workups employing liquid-liquid extraction cartridges, see: (a) Johnson, C. R.; Zhang, B.; Fantauzzi, P.; Hocker, M.; Yager, K. M. *Tetrahedron* **1998**, *54*, 4097. (b) Breitenbucher, J. G.; Johnson, C. R.; Haight, M.; Phelan, J. C. *Tetrahedron Lett.* **1998**, *39*, 1295.
[15] Representative procedure for the preparation of 1,2,3-thiadiazoles (Table 1, entry 2): N-methoxy-N-methyl-p-bromobenzamide (0.215 mL, 1.25 mmol) in 3 mL anhydrous THF was added into a 5 mL reaction vessel on the Quest 210. Vessels were cooled to 0 ^oC using a recirculating chiller. To the reaction vessel was added n-butylmagnesium chloride (0.695 mL, 2.0 M, 1.38 mmol, 1.1 equiv.) via syringe. The reaction mixture was allowed to agitate at 0 ^oC for 3 h and quenched with 1 gram (1.45 mmol/g, 1.45 mmol) of MP-TsOH sulfonic acid resin. After agitation for 10 min at 0 ^oC followed by addition of 0.3 mL of AcOH, the solution was transferred to reaction vessel containing PS-$TsNHNH_2$ resin (200 mg, 2.4 mmol/g, 0.48 mmol). The reaction solution was then heated to 50 ^oC for 4 h. After returning to room temperature, the reaction was washed with THF (3 x), hexane (1 x), THF (1 x), and dichloromethane (2 x). Then 2.3 mL of dichloroethane and 0.7 mL of $SOCl_2$ (9.6 mmol, 20 equiv.) were added to the reaction vessel. After agitating for 5 h at 60^oC, the reaction mixture was filtered into a Varian Extube liquid-liquid extraction cartridge preloaded with 3 mL of saturated Na_2CO_3. The filtrate (and three dichloroethane washes) was filtered into a scintillation vial and the mixture was concentrated to afford 4-(4&#65533;-bromophenyl)-5-n-propyl-1,2,3-thiadiazole in 82% yield (94% GC purity).
[16] Olah, G. A. Friedel-Crafts and Related Reactions; Interscience Publishers: New York, 1963, Vol. 1.
[17] For a review, see: Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res*. **1983**, *16*, 55.
[18] Caglioti, L. *Org. Synth*. **1972**, *52*, 122.

For further information: please visit the homepage of the authors

---

Comments

During 1-30 September 1998, all comments on this poster should be sent by e-mail to ecsoc@listserv.arizona.edu with b0002 as the message subject of your e-mail. After the conference, please send all the comments and reprints requests to the author.
