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

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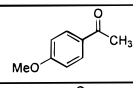
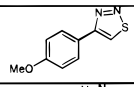
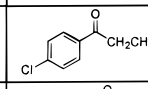
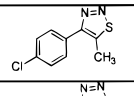
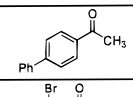
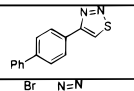
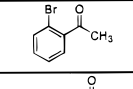
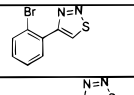
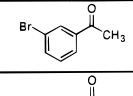
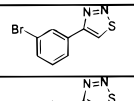
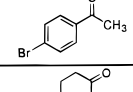
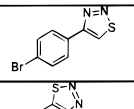
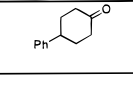
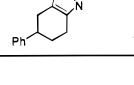
Combinatorial solid-[1] and solution-phase[2] methods have been frequently employed in the synthesis of compound libraries of potential biological and therapeutic significance. Many novel methodologies have been developed, including "catch and release" and "resin capture" strategies for the expedited workup and purification of compounds synthesized in solution.[3,4] In this paper, we report a parallel synthesis of 1,2,3-thiadiazoles employing a "catch and release" strategy wherein ketones may be prepared in solution and captured to the solid support via sulfonylhydrazone formation. 1,2,3-Thiadiazoles are an important class of 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,e] of which the Hurd−Mori cyclization of α-methylene ketones is the most convenient methodology.[7,8] Further transformation of support-bound sulfonylhydrazones (Stille coupling) before final cyclative release of 1,2,3-thiadiazoles from the resin is also described.

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 °C in the presence of acetic acid using 2.5 equiv of ketone. The large number of commercially available ketones provides access to a variety of support-bound sulfonylhydrazones which may be subject to cleavage using thionyl chloride (dichloroethane (DCE), 60 °C, 5 h) to afford 1,2,3-thiadiazoles. Seven ketones were selected and sulfonylhydrazone formation/Hurd−Mori cleavage conducted in parallel using the Quest 210 organic synthesizer. Although the regioselectivity of the Hurd−Mori reaction has been studied,[8a] only aromatic or symmetrical aliphatic ketones were employed herein to avoid the formation of regioisomeric products. Purification of the cleavage solution was performed in parallel using saturated Na_2CO_3 preloaded onto liquid−liquid extraction cartridges.[11] All thiadiazoles were obtained in high chemical yield and purity (Scheme 1, Table 1).

Table 1. Synthesis of 1,2,3-Thiadiazoles Using Commercially Available Ketones

Entry	Ketone	Thiadiazole	Yield (%)	GC Purity (Area %)
1		 **1**	100	99
2		 **2**	79	96
3		 **3**	95	97[a]
4		 **4**	100	98
5		 **5**	100	94
6		 **6**	96	100
7		 **7**	94	98

[a] Purity measured by HPLC (Area %).

The formation of support-bound sulfonylhydrazones from noncommercially available ketones may be facilitated by use of a "resin capture strategy"[4] (Scheme 2, Table 2). Six *p*-bromophenyl ketones were prepared in parallel on the Quest 210 organic synthesizer by reacting *N*-methoxy-*N*-methyl-*p*-bromobenzamide (**8**)[12] with a variety of Grignard reagents (THF, 0 °C). The reaction

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(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**, *54*. (b) Kaldor, S. W.; Siegel, M. W. *Curr. Opin. Chem. Biol.* **1997**, *1*, 101.

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(4) For examples of "resin capture", see: (a) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574. (b) Brown, S. 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.

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(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. Heterocycl. Chem.* **1996**, *33*, 1759.

(9) PS-$TsNHNH_2$ resin (1.8−2.5 mmol/g, 1% cross-linked 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) 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.

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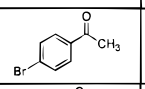
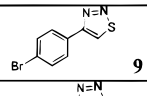
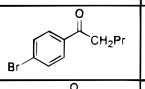
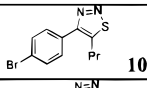
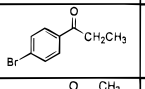
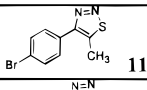
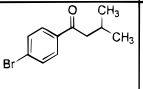
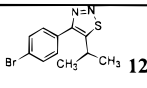
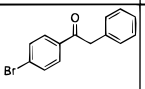
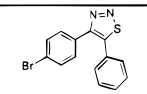
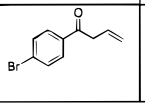
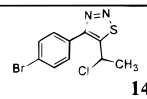
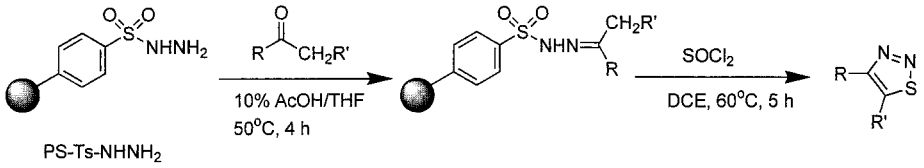
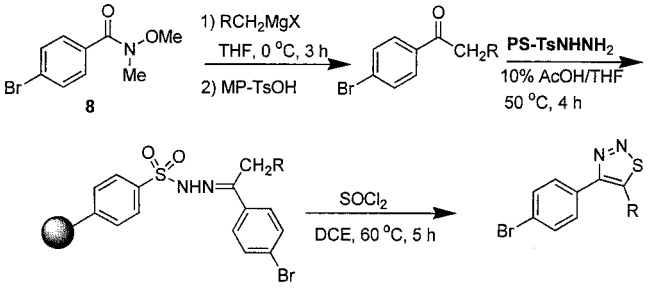
Table 2. 1,2,3-Thiadiazoles Prepared via "Resin Capture" of Ketones

Entry	RCH_2MgX	Ketone	Thiadiazole	Yield (%)	GC Purity (Area %)
1	MeMgCl		 **9**	98	100
2	*n*-BuMgCl		 **10**	82	94
3	EtMgBr		 **11**	77	97
4	*iso*-BuMgCl		 **12**	59	97
5	$PhCH_2MgCl$		 **13**	67	98
6	$CH_2=CHCH_2MgCl$		 **14**	48	71

Scheme 1. Synthesis of 1,2,3-Thiadiazoles Using Commercially Available Ketones



Scheme 2. 1,2,3-Thiadiazoles Prepared via "Resin Capture" of Ketones



mixtures were then quenched with a macroporous polystyrene−sulfonic acid resin (MP-TsOH) to decompose the tetrahedral intermediate.[13] Acetic acid (10% v/v) was added, and the ketone solutions were directly transferred via cannula to reaction vessels containing $PS\text{-}TsNHNH_2$ resin. After thionyl chloride cleavage and purification (vide supra), a series of 1,2,3-thiadiazoles were prepared with various substituents at 5 position. In the case of entry 6 of Table 2, compound **14**, resulting from the further addition of HCl (from $SOCl_2$) to the olefin, was obtained. Compounds similar to **13** 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.[14]

Support-bound sulfonylhydrazones with aryl halide substituents may be subjected to further transformations such as the Stille reaction[15,16] for the generation of more highly diverse thiadiazole structures. Thus, a support-bound sulfonylhydrazone generated from 4-bromoacetophenone (Scheme 3, R_1 = Br) was reacted with arylstannanes using either $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ as catalyst (10 mol % in DMF). The reactions were found to be complete in 24 h at 90 °C using either catalyst. After thionyl chloride cleavage and cartridge-based purification, the products were filtered through a small plug of silica gel to remove baseline impurities. Table 3 shows thiadiazole products generated from Stille coupling employing $Pd(PPh_3)_2Cl_2$ as catalyst (Scheme 3, Table 3). Entry 3 of Table 3 shows an example performed using "resin capture" of an aryl ketone prepared in situ from the Weinreb amide derivative.[12]

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. Cyclative cleavage of resin-bound sulfonylhydrazones was accomplished using thionyl chloride to afford 1,2,3-thiadiazoles. Stille coupling (C−C bond formation) of resin-bound intermediates was also demonstrated. Additional diversification reactions

(13) MP-TsOH resin (1.4 mmol/g, macroporous polystyrene-*co*-divinylbenzene) is commercially available from Argonaut Technologies.

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Scheme 3. 1,2,3-Thiadiazoles from Stille Coupling Using $Pd(PPh_3)_2Cl_2$ as Catalyst

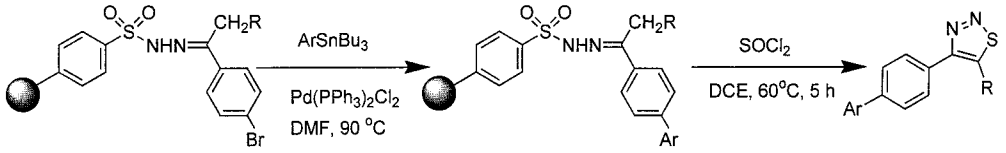
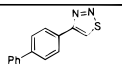
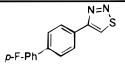
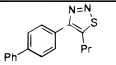


Table 3. 1,2,3-Thiadiazoles from Stille Coupling

Entry	Ketone	$ArSnBu_3$	Thiadiazole	Yield (%)	HPLC Purity (Area %)
1		$PhSnBu_3$	 **3**	80	87
2		*p*-F-$PhSnBu_3$	 **15**	76	93
3 [a]		$PhSnBu_3$	 **16**	71	85

[a] Aryl ketone synthesized from the reaction of *N*-methoxy-*N*-methyl-*p*-bromobenzamide (**5**) with *n*-BuMgCl.

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.

Experimental Section

General. Standard reagents were obtained from commercial suppliers and used without further purification. Polystyrene−sulfonylhydrazide resin (PS-Ts-$NHNH_2$) and macroporous polystyrene−sulfonic acid resin (MP-TsOH) were obtained from Argonaut Technologies (San Carlos, CA). *N*-Methoxy-*N*-methyl-*p*-bromobenzamide was prepared according to the literature procedure.[12] All parallel synthesis transformations were performed on the Quest 210 organic synthesizer (Argonaut Technologies, San Carlos, CA). Extube liquid−liquid extraction cartridges (Chem Elut, Part no. 1219-8003) were purchased from Varian Sample Preparation Products (Harbor City, CA). ^1H and ^{13}C NMR spectra were obtained on a Varian 300 MHz spectrometer in $CDCl_3$ and are reported in ppm. Mass spectroscopy was performed at SynPep Corp. (Dublin, CA). GC analysis was performed on a Hewlett-Packard 6890 GC with an HP-5 phenylmethylsilicone capillary column (30 m × 0.32 mm × 0.25 μm) (GC method 175 °C (3 min), ramp up to 300 °C (20 °C/min), 300 °C for 5 min). HPLC analysis was performed on a Hewlett-Packard 1050 HPLC with a Microsorb MV C18 column (HPLC method 2−95% acetonitrile/water (8 min), 95−2% acetonitrile/water (2 min)).

Experimental Procedure for the Synthesis of 1,2,3-Thiadiazoles via "Resin Capture" (Table 2, Entries 1−6). PS-Ts$NHNH_2$ resin (200 mg, 2.4 mmol/g, 0.48 mmol) was loaded into six 5-mL Teflon reaction vessels on bank A of the Quest 210 synthesizer. Reaction vessels containing resin were then purged with nitrogen for 2 min. On bank B of the Quest 210, *N*-methoxy-*N*-methyl-*p*-bromobenzamide[12] (215 μL, 1.25 mmol) was added into six 5-mL Teflon reaction vessels with 3 mL of dry THF, respectively. The reaction vessels were cooled to 0 °C using a Julabo recirculating chiller. To the reaction vessels were then added the appropriate Grignard reagents (1.38 mmol, 1.1 equiv: CH_3MgCl (3.0 M, 465 μL), *n*-BuMgCl (2.0 M, 695 μL), EtMgBr (3.14 M, 442 μL), *i*-BuMgCl (2.0 M, 695 μL), $PhCH_2$-MgCl (2.0 M, 695 μL), CH_2=$CHCH_2$ MgCl (2.0 M, 695 μL)) via syringe. The reaction mixtures were allowed to agitate at 0 °C for 3 h. To each reaction vessel was then added 1 g (1.45 mmol/g, 1.45 mmol) of MP-TsOH. After agitation for 10 min at 0 °C followed by addition of 0.3 mL of AcOH, the solutions were transferred using a transfer cannula to the corresponding reaction vessels containing PS-Ts$NHNH_2$ resin in bank A. The reaction vessels in bank A were agitated at 50 °C for 4 h. The reactions were cooled to room temperature, emptied, and washed with THF (3 × 4 mL), hexane (2 × 4 mL), and dichloroethane (3 × 4 mL). Then 2.3 mL dichloroethane and 700 μL of $SOCl_2$ (9.6 mmol, 20 equiv) were added to each reaction vessel. After agitating for 5 h at 60 °C, the reaction mixtures (and 3 × 4 mL dichloroethane washes) were filtered through liquid−liquid extraction cartridges (Extube Extraction Columns preloaded with 3 mL of saturated Na_2CO_3 for 10 min) into scintillation vials and concentrated to afford the 1,2,3-thiadiazole products.

1,2,3-Thiadiazole (9): ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1 H, =CH), 7.93 (d, 2 H, *J* = 8.7 Hz, Ar−H), 7.65 (d, 2 H, *J* = 8.7 Hz, Ar−H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 132.2, 130.0, 129.6, 128.7, 123.5 ppm.

1,2,3-Thiadiazole (10): ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 4 H, Ar−H), 3.02 (t, 2 H, *J* = 7.7 Hz, $-CH_2-$), 1.78 (m, 2 H, $-CH_2$-), 1.01 (t, 3 H, *J* = 7.4 Hz, $-CH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 153.1, 131.9, 130.3, 120.3, 123.0, 27.5, 25.0, 13.5 ppm; MS (APCI) calcd for $C_{11}H_{11}N_2SBr$ 282.1, found 283.0 $[M + 1]^+$.

1,2,3-Thiadiazole (11): ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H, Ar−H), 2.71 (s, 3 H, $-CH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 146.5, 132.8, 131.9, 130.1, 123.0, 10.1 ppm.

1,2,3-Thiadiazole (12): ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 2 H, *J* = 8.4 Hz, Ar−H), 7.56 (d, 2 H, *J* = 8.4 Hz, Ar−H), 3.51 (septet, 1 H, *J* = 6.6 Hz, −CH−), 1.39 (d, 6 H, *J* = 6.6 Hz, $-(CH_3)_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 157.7, 131.9, 130.5, 130.3, 123.1, 26.9, 25.6 ppm.

1,2,3-Thiadiazole (13): ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 5 H, Ph-H), 7.44−7.33 (m, 4 H, Ar−H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 151.1, 131.8, 131.6, 130.5, 129.8, 129.2, 129.1, 127.51, 123.2 ppm; MS (APCI) calcd for $C_{14}H_9N_2SBr$ 316.2, found 317.2 $[M + 1]^+$.

1,2,3-Thiadiazole (14): ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (m, 4 H, Ar−H), 5.39 (q, 1 H, *J* = 6.8 Hz, −CClH−), 1.97 (d, 3 H, *J* = 6.8 Hz, $-CH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 154.7, 132.3, 131.9, 130.4, 123.7, 48.0, 28.3 ppm; MS (EI) calcd for $C_{10}H_8N_2SBrCl$ 303.9, found 304 (M^+), 289, 276, 241, 236, 195 (base), 160, 149, 128, 116.

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Supporting Information Available: Experimental procedures and characterization data for thiadiazoles **1**−**7** and **15**−**16** and representative ^1H and ^{13}C NMR spectra for 1,2,3-thiadiazoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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