Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Traceless Solid-Phase Synthesis of 1,2,3-Thiadiazole Derivatives from Resin-Bound Acylhydrazine

Zhanxiang Liu [a], Yuanyuan Mu [a], Jie Lin [a] & Yiya Chen [a]

[a] Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou, China

Published online: 07 Nov 2008.

To cite this article: Zhanxiang Liu , Yuanyuan Mu , Jie Lin & Yiya Chen (2008): Traceless Solid-Phase Synthesis of 1,2,3-Thiadiazole Derivatives from Resin-Bound Acylhydrazine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:24, 4407-4414

To link to this article: http://dx.doi.org/10.1080/00397910802369521

Synthetic Communications®, 38: 4407–4414, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802369521

Taylor & Francis
Taylor & Francis Group

Traceless Solid-Phase Synthesis of 1,2,3-Thiadiazole Derivatives from Resin-Bound Acylhydrazine

Zhanxiang Liu, Yuanyuan Mu, Jie Lin, and Yiya Chen
Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou, China

Abstract: A novel synthesis of 1,2,3-thiadiazole derivatives using a traceless solid-phase approach is described, in which many kinds of 1,2,3-thiadiazole derivatives were efficiently obtained in good yields and high purities via traceless cyclization cleavage of resin-bound acylhydrazones with thionyl chloride.

Keywords: Resin-bound acylhydrazine, solid-phase synthesis, 1,2,3-thiadiazoles, traceless

Solid-phase organic synthesis (SPOS) has been developed into an important tool for the generation of libraries of potential biologically active and pharmacological molecules.[1] The advantages of this methodology have been well described in the recent literature: excess reagents can be used to drive reactions to completion, impurities and excess reagents can be removed by simple washing of the solid phase, and enormous numbers of compounds can be created using the mix and split technique. In addition, in some cases the most important point is that the regeneration and reuse of the recovered resin-bound reagents are possible, thus providing an environmentally benign system.

1,2,3-Thiadiazoles are heterocycles of great practical and theoretical interest.[2] 1,2,3-Thiadiazoles are an important class of biologically active

Received March 15, 2008.
Address correspondence to Zhanxiang Liu, Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou 310 028, China. E-mail: liuzhanx@zju.edu.cn

compounds. Many of thiadiazole derivatives exhibit antimicrobial, antipsychotic, antithrombotic and antitumor activities.[3] The 1,2,3-thiadiazole has also been explored as a heme ligand of cytochrome P450 inhibitors.[4]

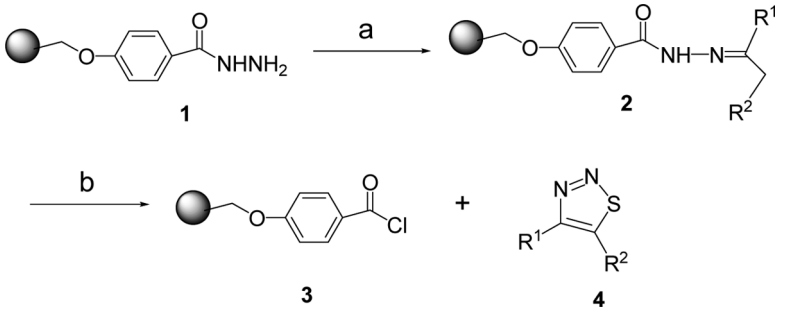
In addition, 1,2,3-thiadiazoles are valuable as key intermediates for substituted thioacetylenes, thioketenes, and substituted thioamides.[5] Also, 1,2,3-thiadiazoles would produce several active intermediates photochemically, such as thioketocarbene and thiocarbondiradical.[6] A lot of attention has been devoted to the thermal and photochemical decomposition reactions of the 1,2,3-thiadiazole ring because this system is the only thiadiazole isomer where loss of a nitrogen molecule can readily occur.

Consequently, methodologies for the preparation of 1,2,3-thiadiazoles have attracted much attention from both industry and academia, and numerous solution-phase syntheses of these compounds have been reported,[2] of which the Hurd–Mori cyclization of α-methylene ketones is by far the most widely used method.[7] However, a chromatographic separation is often necessary to remove the sulfonyl chloride or aromatic acid chloride formed in this reaction.

However, this class of reaction has received little attention in solid-support applications, with only one paper documenting the parallel synthesis of 1,2,3-thiadiazoles using support-bound sulfonylhydrazones.[8] In continuation of our ongoing interest in solid-phase synthesis, we have recently reported the easy method for preparation of polymer-supported acylhydrazine from Merrifield resin.[9] We have also reported the synthesis of 1,3,4-oxadiazoline-5-thione derivatives from resin-bound acylhydrazine. Its function as a linker for solid-phase synthesis has never been explored. To build on our research in this area, we describe here a convenient syntheses of 1,2,3-thiadiazole derivatives from acylhydrazine resin (Scheme 1).

We have prepared resin-bound acylhydrazine **1** from the Merrifield resin according to our method previously reported.[9] The acylhydrazine resin **1** was reacted with excess ketone using acetic acid as catalyst to give the corresponding resin-bound acylhydrazones **2**. After Hurd–Mori-type cleavage accomplished using thionyl chloride, a series of 1,2,3-thiadiazoles **4** were prepared with various substituents at 4 and 5 positions in good yields as well as excellent purities. Also the acylchloride resin **3** was released.

For each resin-bound intermediate, the structure was verified by Fourier transform infrared (FT-IR) spectra. The acylhydrazine resin **1** showed two strong signals of N–H at 3315 cm^{-1} and 3420 cm^{-1}. When the resin **1** was converted into resin **2**, the two peaks of N–H shifted to one signal with a new peak appearing at 1653 cm^{-1} for C=N of the

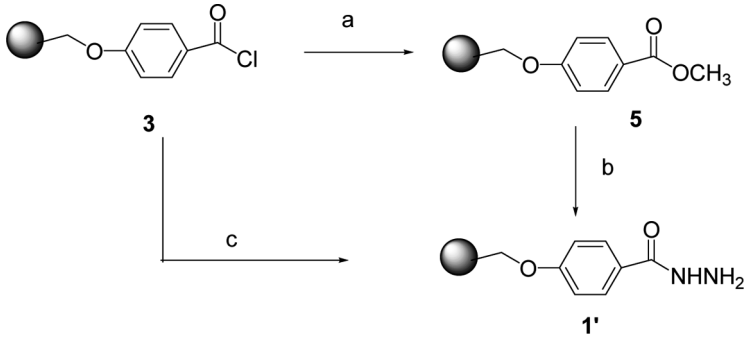


Scheme 1. Reagents and conditions: (a) $R^1COCH_2R^2$ (3 equiv.), AcOH, EtOH, reflux, 24 h; (b) $SOCl_2$, CH_2Cl_2, rt, 20 h.

acylhydrazones. After cleavage, the IR carbonyl peaks of released resin **3** shifted to 1789 cm^{-1} and 1737 cm^{-1}. Disappearance of the 1653 cm^{-1} peak indicated complete transformation of resin **1** into resin **3**.

Finally, we verified that the released resin **3** was reusable, which was treated with methanol to obtain the methyl ester resin **5** and further reacted with hydrazine hydrate to give the recovered acylhydrazines resin **1′**. Resin **3** was also directly transferred to the acylhydrazines resin **1′** by reacting with hydrazine hydrate (Scheme 2). The corresponding reactions were repeated by using the recovered resin **1′**, and after cleavage, 1,2,3-thiadiazole **4g** was given in nearly the same yield and purity as the first time. After reuse of resin **1′**, the released resin showed the same IR spectra as that of the resin **3**.

To demonstrate the usefulness of this approach, several 1,2,3-thiadiazoles were synthesized. The results are shown in Table 1. From Table 1,



Scheme 2. Reagents and conditions: (a) MeOH, reflux, 3 h; (b) $NH_2NH_2 \cdot H_2O$, HMPA, 90 °C; (c) $NH_2NH_2 \cdot H_2O$, HMPA, 90 °C, 10 h.

Table 1. Solid-phase synthesis of 1,2,3-thiadiazole derivatives **4**

Entry	Product	R^1	R^2	Yield (%)[a]	Purity (%)[b]
1	4a	CH_3	H	78	85
2	4b	n-C_3H_7	H	76	92
3	4c	C_2H_5	CH_3	82	90
4	4d	–$(CH_2)_4$–	–$(CH_2)_4$–		88
5	4e	Ph	H	89	92
6	4f	4-Cl–C_6H_4	H	88	92
7	4g	4-Br–C_6H_4	H	93	94
8	4h	4-CH_3O–C_6H_4	H	91	93
9	4i	CH_3	PhCO	81	90
10	4j	CH_3	COOEt	85	87
11	4g[c]	4-Br–C_6H_4	H	90	92

[a]Yield of crude product based on the loading of acylhydrazine resin **1**.
[b]Determined by HPLC analysis (area %).
[c]Using recovered resin **1′**.

we can find that the alkyl and aryl groups can be introduced in R^1 and R^2 with high purities and good yields, whereas compounds with functional groups such as ester and aryl ketone could be obtained (entry 9, 10). Also this method can be used to prepare the fused 1,2,3-thiadiazole (entry 4).

In conclusion, we have developed an efficient method for the solid-phase synthesis of diverse 1,2,3-thiadiazole derivatives in high yields and good purities by traceless cyclization cleavage of resin-bound acylhydrazones with thionyl chloride. The mild conditions were suitable for applications to the automated synthesis of diverse druglike molecules. The presented work substantially extends the chemical transformations to be carried out on solid supports to give the desired 1,2,3-thiadiazoles. Moreover, we have described a new traceless cleavage SPOS route and the polymer-supported acylhydrazine could be regenerated easily for reuse after cleavage. Further extension of this methodology to the synthesis of fused heterocyclic compounds is in progress.

EXPERIMENTAL

Starting materials were obtained from commercial suppliers and used without further purification. Solvents were distilled before use: CH_2Cl_2 was distilled from CaH_2 and $SOCl_2$ was distilled prior to use. Merrifield resin (100–200 mesh, cross-linked with 1% divinylbenzene, loading=1.95 mmol/g Cl) was purchased from commercial sources (Nankai University).

Acylhydrazine resin **1** was prepared from the Merrifield resin according to our method previously reported.[9] ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance (400-MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as internal standard. MS spectra (EI, 70 eV) were recorded on a HP5989B mass spectrometer. IR spectra were recorded on a Bruck Vector 22 spectrophotometer. Elemental analyses were performed on a Flash EA1112 instrument. High performance liquid chromatography (HPLC) was performed on an Agilent 1100 [column, Eclipse XDB-C18 5 μm, 4.6 × 150 mm; mobile phase, MeOH/H_2O, 80/20 (v/v); flow rate, 1.0 mL/min;detector, UV 254 nm]. The samples were further purified by thin-layer chromatography (TLC) for ^{13}C NMR and microanalyses.

General Procedure for Synthesis of 1,2,3-Thiadiazoles

To the mixture of the acylhydrazine resin **1** (0.5 g, loading = 1.59 mmol/g, based on N microanalysis) in absolute EtOH (5 mL), cyclohexone (0.235 g, 2.4 mmol) and 0.1 mL AcOH were added. Then the mixture was stirred and refluxed for 24 h. The resin was filtered and washed with EtOH (5 mL × 3) and CH_2Cl_2 (5 mL × 3) to remove contaminated species and then dried to afford the resin **2**. Resin **2** was well swollen in 10 mL dry CH_2Cl_2 for 10 min and 2 mL $SOCl_2$ was added. After stirring for 20 h at room temperature, the mixture was filtered and the resin was washed with CH_2Cl_2 (5 mL × 3). The filtrate was combined to afford the crude product by evaporation. The concentrate was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ solution and water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to obtained product 1,2,3-thiadiazoles **4d** as a pale yellow oil (98 mg, yield 88%).

All compounds gave satisfactory 400 M ^{1}H NMR, IR, and MS spectra. The new compounds gave satisfactory elemental analyses after purification.

Spectral Data of the Compounds

4-Methyl-1,2,3-thiadiazole (**4a**)

Yellow oil (lit.[10] oil). IR (KBr): 3075, 2930, 2870, 1579, 1511, 1477, 1337, 851, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.80$ (s, 3H), 8.23 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.1$, 132.2, 155.4. MS (EI, 70 eV): m/z (%) = 100 (M^+).

4-Propyl-1,2,3-thiadiazole (**4b**)

Yellow oil (lit.[11] bp 30–33 °C/0.4 mmHg) IR (KBr): 3074, 2959, 2870, 1450, 1235, 1100, 880, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.01$–1.05 (m, 3H), 1.84–1.90 (m, 2H), 3.13–3.17 (m, 2H), 8.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.8$, 26.8, 36.9, 132.2, 156.2. MS (EI, 70 eV): m/z (%) = 128 (M^+).

4-Ethyl-5-methyl-1,2,3-thiadiazole (**4c**)

Yellow oil (lit.[11] bp 34–36 °C/0.4 mmHg). IR (KBr): 2959, 2869, 1449, 1235, 1100, 878, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.33$–1.37 (t, 3H), 2.51 (s, 3H), 2.93–2.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.5$, 18.1, 25.3, 139.2, 155.2. MS (EI, 70 eV): m/z (%) = 128 (M^+).

4,5,6,7-Tetrahydrobenzo[d][1,2,3]thiadiazole (**4d**)

Pale yellow oil (lit.[7b] bp 51–52 °C/10^{-2} mmHg). IR (KBr): 2940, 2860, 1513, 1440, 1278, 1237, 909, 805 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.85$–1.93 (m, 4H), 2.95–2.97 (m, 2H), 3.12–3.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.3$, 26.8, 27.6, 139.2, 155.2. MS (EI, 70 eV): m/z (%) = 140 (M^+).

4-Phenyl-1,2,3-thiadiazole (**4e**)

White solid, mp 76–77 °C (lit.[12] 75–77 °C). IR (KBr): 3074, 1637, 1463, 1444, 1272, 1221, 936, 919, 766, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$–7.53 (m, 3H), 8.04–8.06 (m, 2H), 8.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 127.5$, 128.8, 129.6, 131.2, 133.1, 161.7. MS (EI, 70 eV): m/z (%) = 162 (M^+).

4-(4-Cholorophenyl)-1,2,3-thiadiazole (**4f**)

White solid, mp 136–138 °C (lit.[12] 136.0–137.5 °C). IR (KBr): 3085, 1597, 1509, 1455, 1406, 1264, 1225, 1091, 1011, 834, 808 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.47$–7.49 (d, 2H, $J = 8.8$ Hz), 7.98–8.00 (d, 2H, $J = 8.8$ Hz), 8.64 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 122.5$, 128.6, 129.4, 130.2, 133.2, 161.3. MS (EI, 70 eV): m/z (%) = 196 (M^+).

4-(4-Bromophenyl)-1,2,3-thiadiazole (**4g**)

White solid, mp 150–152 °C (lit.[12] 150–152 °C). IR (KBr): 3085, 1589, 1507, 1452, 1400, 1262, 1224, 1182, 1042, 1006, 931, 831, 805 cm^{-1}. ^1H NMR $\delta = 7.65–7.67$ (d, 2H, $J = 8.8$ Hz), 7.93–7.95 (d, 2H, $J = 8.8$ Hz), 8.66 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 123.4$, 128.8, 129.6, 130.2, 132.2, 161.6. MS (EI, 70 eV): m/z 240 (M^+, 25), 242 (M + 2, 25), 214 (100).

4-(4-Methoxylphenyl)-1,2,3-thiadiazole (**4h**)

White solid, mp 90–92 °C (lit.[12] 91–93.5 °C). IR (KBr): 3085, 1591, 1506, 1453, 1410, 1266, 1224, 1182, 1041, 1004, 931, 831, 806 cm^{-1}. ^1H NMR $\delta = 3.89$ (s, 3H), 7.03–7.05 (d, 2H, $J = 8.4$ Hz), 7.98–8.00 (d, 2H, $J = 8.4$ Hz), 8.53 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 123.4$, 128.8, 129.6, 130.2, 132.2, 161.6. MS (EI, 70 eV): m/z 192 (M^+, 25), 149 (100).

(4-Methyl-1,2,3-thiadiazol-5-yl)(phenyl)methanone (**4i**)

White solid, mp 51–52 °C (lit.[13] 51–52 °C). IR (KBr): 2925, 2850, 1683, 1597, 1509,1455, 1406, 1264, 1091, 808 cm^{-1}. ^1H NMR $\delta = 2.84$ (3H, s), 7.52–7.56 (2H, m), 7.67–7.70 (1H, m), 7.83–7.85 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.04$, 128.9, 129.2, 134.40, 137.86, 145.18, 160.76, 186.52. MS (EI, 70 eV): m/z 204 (M^+, 15), 105 (100). Anal. calcd. for $C_{10}H_8N_2OS$ C, 58.80; H, 3.95; N, 13.72; Found: C, 58.74; H, 4.12; N, 13.91.

Ethyl 4-Methyl-1,2,3-thiadiazole-5-carboxylate (**4j**)

Pale yellow oil (lit.[14], bp 76–78 °C/3 mmHg). IR (KBr): 2984, 2934, 1727, 1515, 1447, 1375, 1313, 1256, 1212, 1099, 1036, 763 cm^{-1}. ^1H NMR $\delta = 1.36–1.39$ (t, 3H), 2.94 (s, 3H), 4.35–4.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 16.54, 60.8, 145.18, 160.76, 166.52. MS (EI, 70 eV): m/z 172 (M^+).

ACKNOWLEDGMENTS

This work was supported by the Foundation of Education Deparment of Zhejiang Province (20070015) and Science and Technology Department of Zhejiang Province (2007C2116).

REFERENCES

1. (a) Czarnik, A. W. *Solid-Phase Organic Synthesis*; Wiley: New York, 2001; vol. 1; (b) Nicolaou, K. C.; Hanko, R.; Hartwig, W. *Handbook of Combinatorial Chemistry*; Wiley-VCH: Weinheim, Germany, 2002; (c) Dolle, R. E.; Bourdonnec, B. E.; Morales, G. A.; Moriarty, K. J.; Salvino, J. M. Comprehensive survey of combinatorial library synthesis: 2005. *J. Comb. Chem.* **2006**, *8*, 597–635.
2. Bakulev, V. A.; Dehaen, W. The chemistry of 1,2,3-thiadiazoles; In *The Chemistry of Heterocyclic Compounds*; E. C. Taylor, P. Wipf, A. Weissberger (Eds.); John Wiley & Sons: New York, 2004.
3. Katritzky, A. R.; Tymoshenko, D. O.; Nikonov, G. N. Novel nucleophilic 5-substitution route to 1,2,3-thiadiazoles. *J. Org. Chem.* **2001**, *66*, 4045–4046, and the references therein.
4. Babu, B. R.; Vaz, A. D. N. 1,2,3-Thiadiazole: A novel heterocyclic heme ligand for the design of cytochrome P450 inhibitors. *Biochemistry* **1997**, *36*, 7209–7216.
5. Thomas, E. W. In *Comprehensive Heterocyclic Chemistry II*; R. C. Storr, A. R. Katritzky, C. W. Rees, E. F. V. Sriven (Eds.); Pergamon: London, 1996; vol. 4, p. 289.
6. Thomas, E. W. In *Comprehensive Heterocyclic Chemistry II*; R. C. Storr, A. R. Katritzky, C. W. Rees, and E. F. V. Sriven, (Eds.); Pergamon: London, 1996; vol. 4, p. 447.
7. (a) Hurd, C. D.; Mori, R. I. On acylhydrazones and 1,2,3-Thiazoles. *J. Am. Chem. Soc.*, **1955**, *77*, 5359–5364; (b) Meier, H.; Trickes, G.; Laping, E.; Merkle, U. Umsetzung von substituierten Hydrazonen mit Thionylchlorid und Sulfurylchlorid. *Chem. Ber.* **1980**, *113*, 183; (c) Stanetty, P.; Kremslehner, M.; Mullner, M. Application of the Hurd–Mori reaction for the synthesis of tricyclic annelated 1,2,3-thiadiazoles. *J. Heterocycl. Chem.* **1996**, *33*, 1759–1763.
8. Hu, Y.; Baudart, S.; Porco, J. A. Parallel synthesis of 1,2,3-thiadiazoles employing a "catch and release" strategy. *J. Org. Chem.* **1999**, *64*, 1049–1051.
9. Liu, Z. X.; Zhao, J. L.; Huang, X. Solid-phase synthesis of 1,3,4-oxadiazoline-5-thione derivatives from resin-bound acylhydrazines. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1828–1830.
10. Sakai, K.; Hida, N.; Kondo, K. Reactions of polyhalo ketone tosylhydrazones with sulfide ion and primary amines: Cyclization to 1,2,3-thiadiazoles and 1,2,3-triazoles. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 179–183.
11. Zimmer, O.; Echter, T.; Merkle, U.; Meier, H. Bromination and dehydrobromination in the side chains of 1,2,3-thiadiazoles. *Liebigs. Ann. Chem.* **1982**, *4*, 683–698.
12. Thomas, E. W.; Nishizawa, E. E.; Zimmermann, D. C.; Williams, D. J. Synthesis and platelet aggregation inhibitory activity of 4,5-bis(substituted)-1,2,3-thiadiazoles. *J. Med. Chem.* **1985**, *28*, 442–446.
13. Shafiee, A. Synthesis of 1,2,3-thiadiazolo [4,5-d]pyridazines, a new heterocyclic ring system. *J. Heterocycl. Chem.* **1976**, *13*, 301–304.
14. Fan, Z. J.; Shi, Z. G.; Liu, X. F.; Fan, Z. Y.; Ai, Y. W. Synthesis and bioactivity of thiadiazole derivatives containing oxadiazole ring. PCT Int. Appl. CN 200610013185, 2006; *Chem. Abstr.* 2006, *145*, 293063.