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SCIENCE DIRECT
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 1828–1830

Solid-phase synthesis of 1,3,4-oxadiazoline-5-thione derivatives from resin-bound acylhydrazines

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Received 19 October 2005; revised 16 December 2005; accepted 5 January 2006
Available online 25 January 2006

Abstract—A new strategy for solid-phase synthesis of 2,5-disubstituted 1,3,4-oxadiazoles has been developed. The 1,3,4-oxadiazoline-5-thione derivatives were synthesized from resin-bound acylhydrazines in several steps providing 78–88% overall yields and excellent purity.

The high-throughput synthesis and screening of targeted and exploratory compound libraries has emerged as a key objective within the pharmaceutical industry as a means of identifying lead molecules with desirable biological activities.[1] Solid-phase synthesis has been recognized as a powerful and rapid method for the preparation of a large number of structurally distinct molecules.[2] A spin-off associated with 'rapid parallel synthesis' has been the construction of an impressive database of solid-supported organic reactions, with recent emphasis on the formation of small heterocyclic drug-like molecules on solid supports.[3]

The major advantages of solid-phase organic synthesis include simple separation and purification processes, which can be easily automated, since reagents can be used in excess, and impurities and by-products can be removed by simple filtration and washing procedures. Moreover, transferring traditional solution chemistry to the solid-phase or exploring new synthetic routes on solid support offers the opportunity for the development of novel methodologies for construction of libraries of small heterocyclic compounds.

Symmetrical and unsymmetrical 1,3,4-oxadiazoles have been reported to be biologically versatile compounds displaying a variety of biological effects, which include antiinflammatory,[4] antifungal,[5] antiparasitic,[6] and antimicrobial[7] activities. 2-Aryl-1,3,4-oxadiazoline-5-thiones possess sedative effects, antitubercular activity, and antiphlogistic properties,[8] also some derivatives showed benzodiazepine activity.[9] These have been of interest to the medicinal chemist for many years. Substituted 1,3,4-oxadiazoles have been successfully prepared by traditional synthesis via acylhydrazine.[10] Moreover, all intermediates and products were obtained in required purification by chromatography or recrystallization.

N-Acylhydrazines are a versatile class of nitrogen-substituted molecules with high degree of chemical reactivity, used as precursors and intermediates of many important organic molecules such as heterocycles, pharmaceuticals, polymers, dyestuffs, and photographic products.[11] Only few papers[12] describe to prepare combinatorial libraries of heterocyclic compounds on solid supports using this chemistry. To the best of our knowledge, solid-phase synthesis of 1,3,4-oxadiazoline-5-thione derivatives has not been reported up to now. Herein, we describe solid-phase synthesis of 1,3,4-oxadiazoles from resin-bound acylhydrazines. We planned to prepare polymer-supported hydrazide from the Merrifield resin (Scheme 1). The Merrifield resin **1** was first converted to the polymer-supported methyl ester resin **2** by reacting with excess methyl 4-hydroxy benzoate. The methyl ester resin **2** was treated with hydrazine hydrate in HMPA at 90 °C for several hours to give the corresponding hydrazide resin **3**. In this step, HMPA was essential to make the reaction finish completely. The resin **3** thus prepared was then reacted with CS_2/KOH at reflux to afford the 2-mercapto-1,3,4-oxadiazole resin **4**. Further reaction with NaOH and electrophilic reagents (RX) gave the corresponding resin **5**. Release of the final 1,3,4-oxadiazoles **6** was effected after

Keywords: Substituted 1,3,4-oxadiazoles; Solid-phase synthesis; Acylhydrazines.
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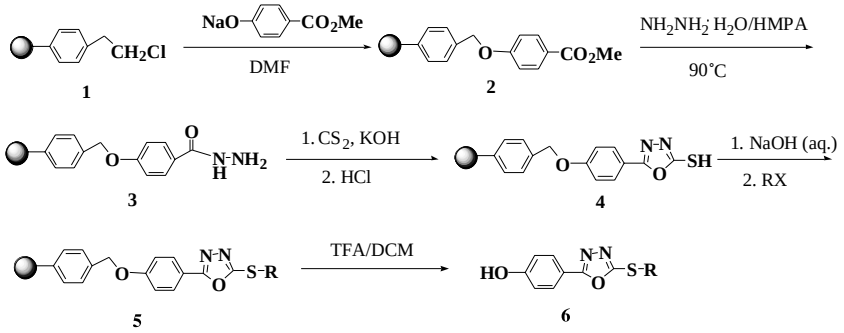
doi:10.1016/j.bmcl.2006.01.002



Scheme 1.

Table 1. Solid-phase synthesis of 1,3,4-oxadiazoline-5-thione derivatives

Entry	Product	R	X	Yield[a] (%)	Purity[b] (%)
1	**6a**	H	Cl	88	90
2	**6b**	CH_3	I	84	92
3	**6c**	Et	Br	82	81
4	**6d**	*n*-C_4H_9	Br	84	92
5	**6e**	Allyl	Br	81	86
6	**6f**	$PhCH_2$	Cl	88	92
7	**6g**	4-NO_2-$C_6H_4CH_2$	Cl	79	88
8	**6h**	$PhCOCH_2$	Br	84	94
9	**6i**	4-Me-$PhCOCH_2$	Br	76	90

[a] Yield of crude product based on the loading of acylhydrazine resin **3**.
[b] Determined by HPLC analysis.

cleavaged by treatment with 10% TFA in DCM. The compounds **6** were obtained after simple filtering and evaporating of the solvent. The products generally do not require further purification and show good purity by HPLC analysis.

Table 1 summarizes the yields and purities of a number of 1,3,4-oxadiazoline-5-thione derivatives that were prepared using this methodology.

The successful formation of resin **2** was supported by a comparative FTIR study of Merrifield resin **1** and a sample of resin **2** (KBr pellets). In the IR spectrum of resin **2**, several characteristic signals were present which confirmed the attachment of the methyl ester moiety to the resin. There was a strong band at 1714 cm^{-1}, typical for C=Os of the methyl esters. Also, the peak at 1260 cm^{-1} (CH_2-Cl) had disappeared. The formation of acylhydrazine resin **3** was shown by the disappeared strong carbonyl peak at 1714 cm^{-1}. There was also a weak peak at 1652 cm^{-1}. When the acylhydrazine resin was converted to the resin **4**, the IR peak shifted to 1612 cm^{-1}. When the resin **5** was cleavaged by TFA/DCM, the product **6** was obtained in good yield and high purity.[13,14] The resin **4** was treated with the base (NaOH) and then reacted with a variety of electrophilic reagents, such as alkyl halides, allyl bromide, benzyl halides, and phenylacyl bromide. All of these gave good results.[15]

In summary, we have studied and developed a new strategy for the preparation of 2,5-disubstituted 1,3,4-oxadiazoles on solid support. The use of resin-bound acylhydrazines in the reaction benefits the solid-phase synthetic route because it not only provides a short synthetic route to the desired products but its chemical versatility also adds to the diversity of the library. The 1,3,4-oxadiazoline-5-thione derivatives were synthesized in several steps providing 78–88% overall yields and excellent purity. The mild conditions were suitable for application to the automated synthesis of diverse drug-like molecules. Further work is in progress on the solid-phase synthesis of heterocyclic compounds via the resin-bound acylhydrazines.

Acknowledgment

We are grateful to the National Natural Science Foundation of China (Project Nos. 20472072, 20332060) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.01.002.

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13. Procedure for the preparation of the resin-bound acylhydride: To a stirred and cooled suspension of 50% NaH (0.48 g,10 mmol) in dry DMF (4 mL) was added dropwise a solution of methyl 4-hydroxy benzoate (10 mmol, 1.52 g) in 8 mL DMF under N_2 atmosphere. The mixture was allowed to stand for 30 min at room temperature. Then Merrifield resin (2 g, 1% cross-linked, 200–400 mesh, loading = 1.95 meq Cl/g) was added and the mixture was stirred at rt for 24 h. After being washed with H_2O, DMF, EtOH, and CH_2Cl_2, the methyl ester resin **2** was obtained. The methyl ester resin **2** (2 g) was added to the solution of hydrazine hydrate in HMPA (1:1, 6 mL). The mixture was stirred at 90 °C for 24 h. Filtered and washed with H_2O, DMF, H_2O, EtOH, and CH_2Cl_2, the acylhydrazine resin **3** (loading = 1.59 mmol/g, based on N microanalysis) was obtained (Caution! HMPA has relative toxicity).
14. General procedure for synthesis of 1,3,4-oxadiazoline-5-thiones: To the mixture of the acylhydrazine resin **3** (0.5 g, loading = 1.59 mmol/g), 5 mL of 2 M NaOH (aq), and 10 mL ethanol, CS_2 (0.86 g, 10 mmol) was added. Then the mixture was heated at reflux for 8 h. After cooling, the resin was filtered and 3 M HCl was added. The resin was then washed with EtOH, CH_2Cl_2 to remove contaminated species, and then dried to offer the resin **4**.
To a suspension of resin **4** in EtOH (15 mL), 1 mL of 10% NaOH was added. After being stirred for 30 min, RX (4 mmol) was added. The mixture was stirred for another 4 h at room temperature. The resin **5** was collected on a glass filter and washed completely with H_2O, EtOH, and CH_2Cl_2. Resin **5** was well swollen in 4 mL CH_2Cl_2, and 0.8 mL TFA was added. The mixture was stirred at room temperature for 1 h. The mixture was filtered and the resin was washed with EtOH and CH_2Cl_2. The washings were combined with the filtrate, concentrated to dryness to give the crude product **6**. Compound **6a**: mp 228–230 °C ^{1}H NMR (DMSO-d_6) δ 6.94 (d, 2H, J = 8 Hz), 7.86 (d, 2H, J = 8 Hz), 10.51 (s, 1H); ^{13}C NMR δ 113.63, 116.76, 129.28, 160.80, 161.90, 167.50, MS m/z (relative intensity) (EI 70ev) 194 (100), 134 (95), 119 (27), 107 (58), 79 (38) IR(KBr) υ_{max} (cm^{-1}) 3396, 3172, 1612, 1514, 1490, 1354, 1167, 968, 838. Calcd for $C_8H_6N_2O_2S$, C, 49.47; H, 3.11; N, 14.42; O, 16.48; S, 16.51. Found: C, 49.09; H, 3.26; N, 14.28.
15. The other analytical data of compounds **6b**–**6i** were listed in Supplementary material which is available online.