Solid-Phase Synthesis of 1,3,4-Oxadiazole and 1,3,4-Thiadiazole Derivatives via Selective, Reagent-Based Cyclization of Acyldithiocarbazate Resins

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Solid-Phase Synthesis of 1,3,4-Oxadiazole and 1,3,4-Thiadiazole Derivatives via Selective, Reagent-Based Cyclization of Acyldithiocarbazate Resins

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Solid-phase organic synthesis (SPOS) is now routinely used to prepare druglike, small organic molecules in medicinal chemistry programs. This procedure enables the generation of massive numbers of hit and lead compounds as part of high-throughput screening technologies.[1] Heterocyclic compounds are commonly used scaffolds on which pharmacophores are arranged to provide potent and selective drugs.[2] This is especially true for five-membered ring heterocyclic compounds, which serve as the core components of a large number of substances that possess a wide range of interesting biological activities. In this family, 1,3,4-oxadiazoles and 1,3,4-thiadiazoles have been used as "privileged" scaffolds to produce substances of interest in numerous therapeutic areas, such as antiinflammatory,[3] antimicrobial,[4] anticonvulsant,[5] and antihypertensive.[6] In addition, these heterocycles serve as intermediates in the preparation of various biologically important compounds.[7]

As a result of these applications, 1,3,4-oxadiazole[8,9] and 1,3,4-thiadiazole[9,10] derivatives have been targets of a number of solution- and solid-phase synthetic studies. However, preparative methods developed thus far lack diversity, since they employ different intermediates for the syntheses of the oxygen- and sulfur-containing compounds. As a part of a drug discovery effort that required a general method for facile and rapid solid-phase parallel synthesis of druglike five-membered heterocycles,[11] we developed a new procedure for the preparation of thiocarbamoylpyrazole and 1,2,4-triazole derivatives via a dithiocarbazate linker.[11d] In a recent investigation, described below, we expanded the utility of this technique by applying it to efficient solid-phase syntheses of 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives. The process employs an acyldithiocarbazate resin, from which the respective targets are generated by cyclodehydration or cyclodesulfurization reactions.[12] (Scheme 1)

The sequence used to prepare the acyldithiocarbazate resins **2** (Scheme 2) employs the Merrifield resin **1** as a polymer support. Treatment of **1** with carbon disulfide and various hydrazides in the presence of NaH at room temperature leads to production of the corresponding acyldithiocarbazate resins **2**.[13] The progress of these reactions was monitored by measuring (ATR-FTIR) the growth of typical acyldithiocarbazate infrared bands at 1665 and 1323 cm^{-1}. To investigate methods for reagent-based, skeletal, diversity-oriented synthesis of 1,3,4-oxadiazoles or 1,3,4-thiadiazoles, cyclization reactions of the acyldithiocarbazate resin **2a** were investigated by using various reagents, including EDC·HCl, DCC, TMSCl, *p*-TsCl, PPh_3, $SOCl_2$, PCl_5, and diphenyl chlorophosphate. The progress of these reactions was monitored by ATR-FTIR (at 1665 cm^{-1}). The desired products (**5a** or **8a**) are cleaved from the resins (**3a** or **6a**) by sequential treatment with *m*CPBA and NaOH in aqueous dioxane (producing the sulfone) and piperidine in 1,4-dioxane at 100 °C.

Scheme 1

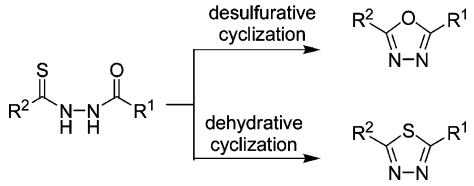
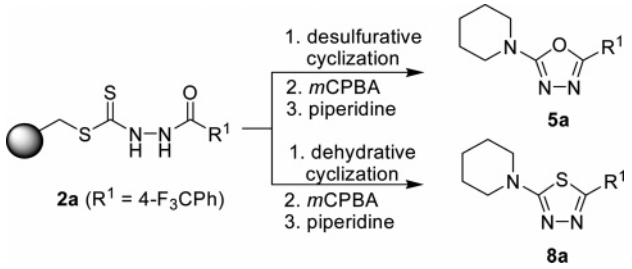


Table 1. Results of the Cyclization of the Acyldithiocarbazate Resin **2a**



entry	reagent	solvent	temp °C	time h	ratio (%)[a] **5a**	ratio (%)[a] **8a**	yield %[b]
1	EDC·HCl	DMSO	80	24	100	-	23
2	DCC	DMSO	80	24	98	2	19
3	$SOCl_2$	$CHCl_3$	80	12	99	1	28
4	*p*-TsCl/TEA	DCE	60	24	98	2	50
5	TMSCl	DCE	60	12	1	99	53
6	$(PhO)_2P(O)Cl$	DCE	60	12	2	98	51
7	PCl_5	$CHCl_3$	80	12	58	42	-
8	PPh_3	CCl_4	60	12	44	55	-

[a] Calculated by using LC/MS integrated peak areas of the crude product mixtures. [b] Four-step overall yields from the Merrifield resin **1** (loading capacity of the resin **1** is 0.94 mmol/g) of the major products after purification by short-pass chromatography.

The results of the cyclization reactions of **2a** are summarized in Table 1. Reactions of the acyldithiocarbazate resin with EDC·HCl and DCC both gave 1,3,4-oxadiazole **5a** as a major product but in low yield (entries 1 and 2, Table 1), whereas the use of $SOCl_2$ to promote this cyclization processleads to the 1,3,4-oxadiazole as a major product with high chemoselectivity (99:1) and a moderate yield

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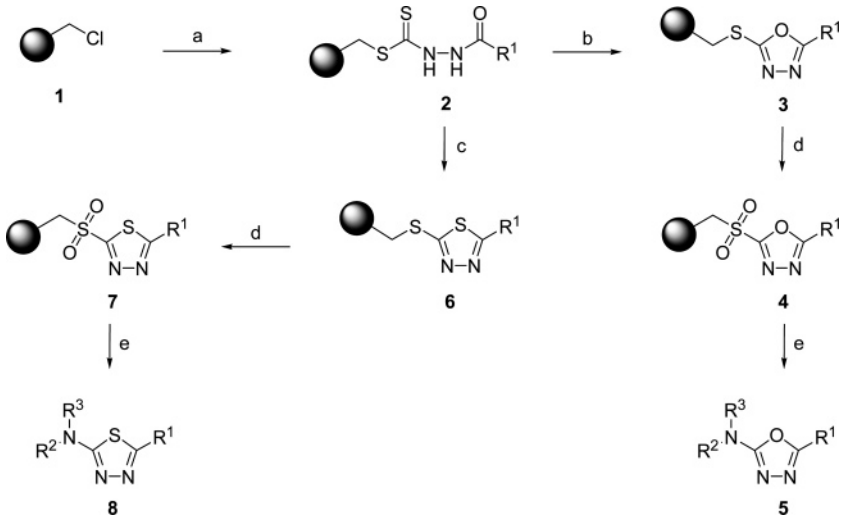
Scheme 2[a]



[a] Reagents and conditions: (a) hydrazides, CS_2, NaH, NMP, rt, 12 h; (b) desulfurative cyclization; (c) dehydrative cyclization; (d) *m*CPBA, 1 N aq NaOH, 1,4-dioxane, rt, 6 h; (e) R^2R^3NH, 1,4-dioxane, 100 °C, 24 h.

(28%) (entry 3, Table 1). Last, reaction of **2a**, promoted by *p*-TsCl in the presence of TEA in DCE at 60 °C, generates the 1,3,4-oxadiazole in high yield (50%) and high chemoselectivity (98:2) (entry 4, Table 1). The LC/MS spectrum of the crude product mixture containing the 1,3,4-oxadiazole formed in the *p*-TsCl-initiated process is shown in Figure 1a.

The 1,3,4-thiadiazole **8a** was produced in high yield (53%) and excellent chemoselectivity (99:1) by dehydrative cyclization upon treatment of **2a** with TMSCl in DCE at 60 °C (entry 5, Table 1; see Figure 1b LC/MS spectrum of the crude product). Similarly, reaction of **2a** with diphenyl chlorophosphate also gives **8a** in high yield (51%) and chemoselectivity (98:2) (entry 6). However, PCl_5 and PPh_3 treatment of **2a** produces **8a** but with low chemoselectivity (entries 7 and 8, Table 1).

To explore the diversity of this methodology, various amines were used to liberate the 1,3,4-oxadiazole and 1,3,4-thiadiazole (Tables 2 and 3, respectively) derivatives from functionalized sulfone-containing resin. Cleavage reactions with amines generally gave desired products in high yields. Exceptions to this trend are observed with the sterically hindered amines, such as dibenzylamine.

In summary, an efficient solid-phase method has been developed for the synthesis of 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives. The acyldithiocarbazate resins **2**,

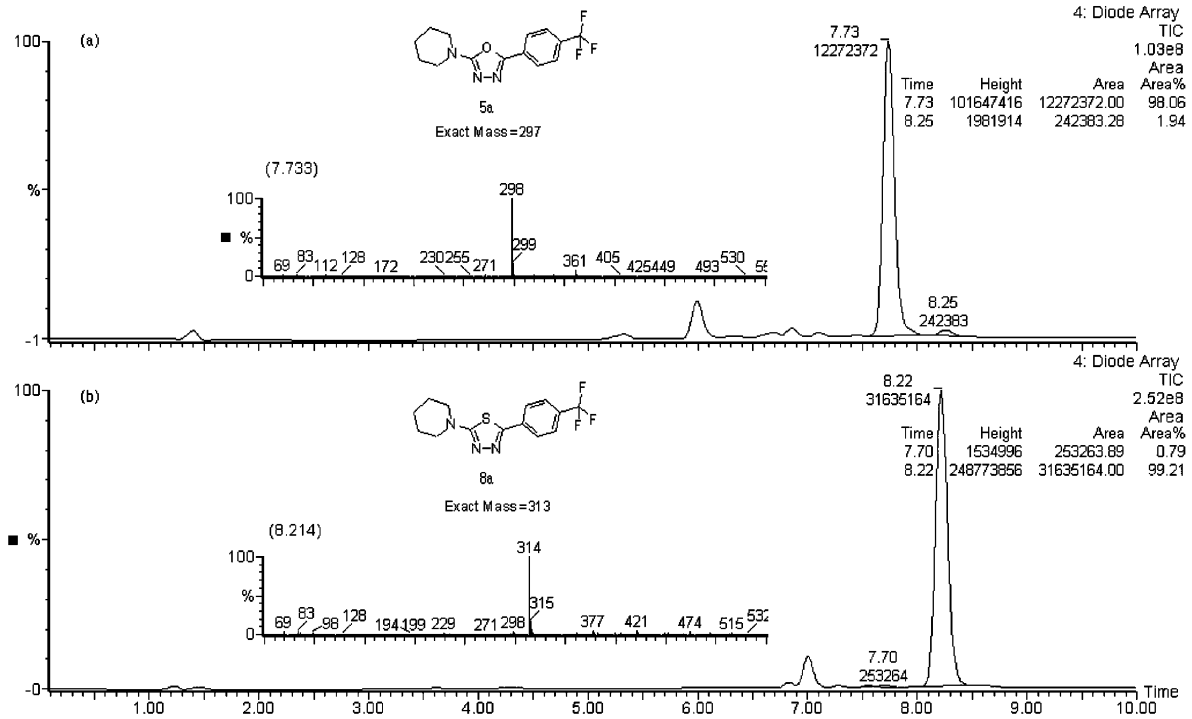
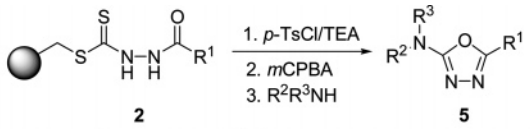
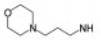
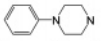


Figure 1. LC/MS spectra of the crude product mixtures, containing **5a** and **8a**, from cyclization reactions of **2a** promoted by *p*-TsCl and TMSCl, respectively.

Table 2. Synthesis of 1,3,4-Oxadiazoles from Resins **2**

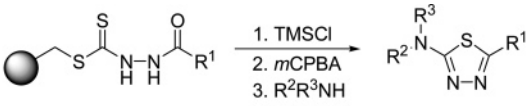


2 **5**

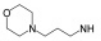
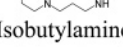
entry	R^1	R^2R^3NH	yield (%)[a]	purity (%)[b]
5a	4-F_3CPh	Piperidino	48	>99
5b	4-F_3CPh	Isobutylamino	34	93
5c	4-F_3CPh	4-MeOBnNH	37	92
5d	3-FPh	Morpholino	49	>99
5e	3-FPh	Piperidino	45	92
5f	Ph	Isobutylamino	45	>99
5g	Ph		72	>99
5h	4-MePh	Morpholino	54	>99
5i	4-*tert*-BuPh	4-ClBnNH	54	89
5j	4-*tert*-BuPh	3,5-Di-MeOPhNH	31	86
5k	4-*tert*-BuPh		54	99
5l	4-*tert*-BuPh	Dibenzylamino	trace	-

[a] Four-step overall yields (from Merrifield resin **1**, loading capacity of the resin **1** is 0.94 mmol/g) of the major products after purification by short-pass chromatography. [b] Purity was determined by LC/MS (UV peak integration at 200−600 nm) after short-pass silica gel column chromatography.

Table 3. Synthesis of 1,3,4-Thiadiazoles Form Resins **2**



2 **8**

entry	R^1	R^2R^3N	yield (%)[a]	purity (%)[b]
8a	4-F_3CPh	Piperidino	47	92
8b	4-F_3CPh	Isobutylamino	37	>99
8c	4-F_3CPh	Morpholino	43	99
8d	4-F_3CPh	4-MeOBnNH	49	97
8e	3-FPh		66	99
8f	3-FPh	Piperidino	30	91
8g	Ph	Piperidino	35	97
8h	Ph		46	99
8i	4-*tert*-BuPh	Isobutylamino	32	89
8j	4-*tert*-BuPh	Cyclohexylamino	34	90
8k	4-*tert*-BuPh	Piperidino	40	94
8l	4-*tert*-BuPh	Dibenzylamino	trace	-

[a] Four-step overall yields (from Merrifield resin **1**, loading capacity of the resin **1** is 0.94 mmol/g) of the major products after purification by short-pass chromatography. [b] Purity was determined by LC/MS (UV peak integration at 200−600 nm) after short-pass silica gel column chromatography.

which serve as key intermediates in this process, are generated by reaction of the Merrifield resin with hydrazides and CS_2. Cyclization reactions of the resulting resins, followed by oxidation and treatment with amines, give the oxadiazole and thiadiazole products, culminating reagent-based, skeletal diversity-oriented syntheses.

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Supporting Information Available. Experimental synthetic procedures and analytical data (ATR-FTIR, ^{1}H NMR, ^{13}C NMR, LC/MS, and HRMS) are given. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Hermakens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. (b) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Foder, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385.

(2) (a) Krchňák, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61. (b) Nfzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449. (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (d) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135.

(3) (a) Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1993**, *36*, 1090. (b) Song, Y.; Connor, D. T.; Sercel, A. D.; Sorenson, R. J.; Doubleday: R.; Unangst, P. C.; Roth, B. D.; Beylin, V. G.; Gilbertsen, R. B.; Chan, K.; Schrier, D. J.; Guglietta, A.; Bornemeier, D. A.; Dyer, R. D. *J. Med. Chem.* **1999**, *42*, 1161. (c) Labanauskas, L.; Kalcas, V.; Udrenaite, E.; Gaidelis, P.; Brukstus, A.; Dauksas, A. *Pharmazie* **2001**, *56*, 617. (d) Boschelli, D. H.; Connor, D. T.; Bornemeier, D. A.; Dyer, R. D.; Kennedy, J. A.; Kuipers, P. J.; Okonkwo, G. C.; Schrier, D. J.; Wright, C. D. *J. Med. Chem.* **1993**, *36*, 1802.

(4) (a) El-Emam, A. A.; Al-Deeb, O. A.; Al-Omar, M.; Lehmann, J. *Bioorg. Med. Chem.* **2004**, *12*, 5107. (b) Dogan, H. N.; Duran, A.; Rollas, S.; Sener, G.; Uysal, M. K.; Gülen, D. *Bioorg. Med. Chem.* **2002**, *10*, 2893. (c) Hollar, B. S.; Gonsalves, R.; Shenoy, S. *Eur. J. Med. Chem.* **2000**, *35*, 267.

(5) (a) Chapleo, C. B.; Myers, M.; Myers, P. L.; Saville, J. F.; Smith A. C. B.; Stillings, M. R.; Tulloch, I. F.; Walter, D. S.; Welbourn, A. P. *J. Med. Chem.* **1986**, *29*, 2273. (b) Chapleo, C. B.; Myers, P. L.; Smith, A. C.; Stillings, M. R.; Tulloch, I. F.; Walter, D. S. *J. Med. Chem.* **1988**, *31*, 7. (c) Akbarzadeh, T.; Tabatabai, S. A.; Khoshnoud, M. J.; Shafaghi, D.; Shafiee, A. *Bioorg. Med. Chem.* **2003**, *11*, 769. (d) Foroumadi, A.; Tabatabai, S. A.; Gitinezhad, G.; Zarrindast, M. R.; Shafiee, A. *Pharm. Pharmacol. Commun*. **2000**, *6*, 1.

(6) (a) Turner, S.; Myers, M.; Gadie, B.; Nelson, A. J.; Pape, R.; Saville, J. F.; Doxey, J. C.; Berridge, T. L. *J. Med. Chem.* **1988**, *31*, 902. (b) Turner, S.; Myers, M.; Gadie, B.; Hale, S. A.; Horsley, A.; Nelson, A. J.; Pape, R.; Saville, J. F.; Doxey, J. C.; Berridge, T. L. *J. Med. Chem.* **1988**, *31*, 907. (c) Tyagi, M.; Kumar, A. *Orient. J. Chem.* **2002**, *18*, 125.

(7) (a) Brown, P.; Best, D. J.; Broom, J. J. P.; Casels, R.; O'Hanlon, P. J.; Mitchell, T. J.; Osborne, N. F.; Wilson, J. M. *J. Med. Chem.* **1997**, *40*, 2563. (b) Chou, J. Y.; Lai, S. Y.; Pan, S. L.; Jow, G. M.; Cherm, J. W.; Guh, J. H. *Biochem. Pharmacol*. **2003**, *66*, 115.

(8) (a) Brown, B. J.; Clemens, I. R.; Neesom, J. K. *Synlett* **2000**, *1*, 131. (b) Kilburn, J. P.; Lau, J.; Jones, R. C. F. *Tetrahedron Lett.* **2001**, *42*, 2583. (c) Rostamizadeh, S.; Ghasem Housaini, S. A. *Tetrahedron Lett.* **2004**, *45*, 8753. (d) Coppo, F. T.; Evans, K. A.; Graybill, T. L.; Burton, G. *Tetrahedron Lett.* **2004**, *45*, 3257. (e) Brain, C. T.; Brunton, S. A. *Synlett* **2001**, *3*, 382. (f) Brain, C. T.; Paul, J. M.; Loong, Y.; Oakley, P. J. *Tetrahedron Lett.* **1999**, *40*, 3275.

(9) (a) Severinsen, R.; Kilburn, J. P.; Lau, J. F. *Tetrahedron* **2005**, *61*, 5565. (b) Baxendale, I. R.; Ley, S. V.; Martinelli, M. *Tetrahedron* **2005**, *61*, 5323.

(10) Kilburn, J. P.; Lau, J.; Jones, R. C. F. *Tetrahedron Lett.* **2003**, *44*, 7825. (b) Pernerstorfer, J.; Brands, M.; Schirok, H.; Stelte-Ludwig, B.; Woltering, E. *Tetrahedron* **2004**, *60*, 8627.
(11) (a) Yoo, S.-e.; Seo, J.-s.; Yi, K. Y.; Gong, Y.-D. *Tetrahedron Lett*. **1997**, *38*, 1203. (b) Yoo, S.-e.; Gong, Y.-D.; Seo, J.-s.; Sung, M.-M.; Lee, S.; Kim, Y. *J. Comb. Chem*. **1999**, *1*, 177. (c) Gong, Y.-D.; Yoo, S.-e. *Bull. Korean Chem. Soc*. **2001**, *21*, 941. (d) Hwang, J. Y.; Choi, H.-S.; Lee, D.-H.; Yoo. S.-e; Gong, Y.-D. *J. Comb. Chem*. **2005**, *7*, 136. (e) Hwang, J. Y.; Choi, H.-S.; Gong, Y.-D. *Tetrahedron Lett*. **2005**, *46*, 3107.
(12) Mansour, E. M. E.; Kassem, A. A.; El-Arabi, M. E.; Nasser, M. A.; El-Toukhy, A. A. *Pharmazie* **1990**, *45*, 435.
(13) Gomez, L.; Gellibert, F.; Wagner, A.; Mioskowski, C. *J. Comb. Chem*. **2000**, *2*, 75.

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