Tetrahedron Letters 49 (2008) 4746–4749

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Parallel solution phase synthesis of a library of amino acid derived 2-arylamino-[1,3,4]-oxadiazoles

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ARTICLE INFO

Article history:
Received 30 April 2008
Revised 22 May 2008
Accepted 23 May 2008
Available online 29 May 2008

ABSTRACT

A mild method for the synthesis of peptidomimetic 2-arylamino 5-substituted 1,3,4-oxadiazoles from Boc-protected α-amino acid derived hydrazides has been developed, and applied in a parallel solution-phase synthesis. The optimized reaction conditions involve a one-pot reaction of Boc-protected amino acid hydrazides with arylisothiocyanates in the presence of either Hg(II) chloride, Mukaiyama's reagent (2-chloro-*N*-methylpyridinium iodide) or polymer supported Mukaiyama's reagent, with triethylamine in dichloromethane at ambient temperature. The 1,3,4-oxadiazole products were obtained in good to excellent yields without any detectable epimerization. The reactions proceed via initial formation of thiosemicarbazides, followed by dehydrothiolative cyclization to the 1,3,4-oxadiazoles.

1,3,4-Oxadiazole derived compounds are known to display a wide range of biological activities including anti-inflammatory, analgesic, antibacterial, fungicidal, antimicrobial, hypoglycemic, antimalarial, antitubercular, antidepressant and other activities.[1] 1,3,4-Oxadiazoles can also serve as bioisosteric replacements of amide and ester functionalities,[2] and can participate in hydrogen bonding interactions as hydrogen bond acceptors. As such, their peptidomimetic ability has been explored[3] and reported in the development of Phe-Gly mimetics of dermorphin (Tyr-D-Ala-**Phe-Gly**-Tyr-Pro-Ser-NH_2) and Substance P (Arg-Pro-Lys-Pro-Gln-Gln-Phe-**Phe-Gly**-Leu-Met-NH_2).[4] In addition to their utility as bioactive molecules, 1,3,4-oxadiazoles are useful intermediates for organic synthesis,[5] particularly as electron-deficient azadienes in inverse electron demand Diels–Alder reactions.[6]

As part of our interest in the synthesis of peptidomimetic heterocycle-peptide hybrid molecules,[7] we now report an approach to the synthesis of amino acid derived 2-arylamino-[1,3,4]-oxadiazoles. Most of the synthetic methods available for the construction of 1,3,4-oxadiazoles involve rather forcing conditions and/or high temperatures that are unsuitable for use with amino acids or peptides.[8] Thus, we aimed to develop a reliable method, mild enough to avoid epimerization problems, and that would be compatible with orthogonal protecting groups. In addition, it was desirable that the approach be applicable to parallel solution-phase synthesis and, potentially suitable for combinatorial solid-phase library production. We envisaged that an approach based upon the dehydrothiolative cyclization of α-amino acid or peptide derived acylthiosemicarbazides would generate the corresponding 1,3,4-oxadiazoles. Although such a strategy has not been previously applied to amino acid derived 1,3,4-oxadiazoles, dehydrothiolation of simple acylthiosemicarbazides to give 1,3,4-oxadiazoles has been reported using a variety of reagents including lead oxide, mercury oxide, mercury acetate, copper sulfate, bromine, I_2/NaOH and DCC.[9] Moreover, the strategy we envisaged is similar to those we have previously employed for the synthesis of α-amino acid and peptide derived 5-aminotetrazoles and 2-iminohydantoins,[7,10] involving activation of thiourea intermediates.

Several Boc-protected amino acids (Phe, Leu, Ala) were first converted to the corresponding hydrazides **1** following a literature procedure using EDCI activation.[11] Reaction of the hydrazides **1** with arylisothiocyanates in CH_2Cl_2 for 20 min at room temperature provided the corresponding Boc-thiosemicarbazides **2a**–**h** quantitatively, without the need for chromatographic purification[12] (Table 1). Deprotection of **2** using 20% TFA/CH_2Cl_2 solution and treatment of the resulting thiosemicarbazides with $HgCl_2$ in the presence of triethylamine in acetonitrile for 12 h at room temperature gave the desired oxadiazole products **3a**–**h** in 78–85% isolated yields (Table 1).

The yields of the oxadiazoles were improved, and the purification protocol simplified, if the Boc group was not removed prior to the dehydrothiolative cyclization. Thus, reaction of Boc-protected hydrazides **1** with arylisothiocyanates gave the corresponding thiosemicarbazides **2**,[12] which on treatment with triethylamine and $HgCl_2$ led to the Boc-protected 1,3,4-oxadiazoles **4** (Table 2).[13,14] This method was suitable for parallel solution-phase synthesis, using semi-automated flash chromatographic purification. Twenty-four examples were prepared in parallel fashion starting from Boc-Ala-OH, Boc-Leu-OH and Boc-Phe-OH in combination with eight different arylisothiocyanates (Table 2). The products **4** were obtained in good to excellent yields, after reaction for 12 h at ambient temperature.

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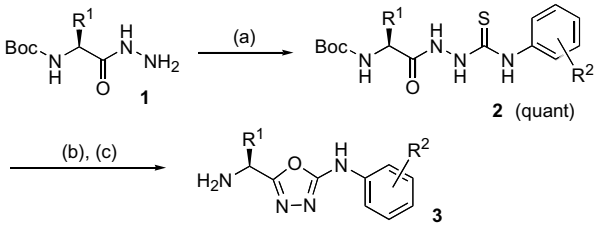
doi:10.1016/j.tetlet.2008.05.110

Table 1
Synthesis of amino acid derived acylthiosemicarbazides **2** and 5-substituted 2-arylamino 1,3,4-oxadiazoles **3**[a]



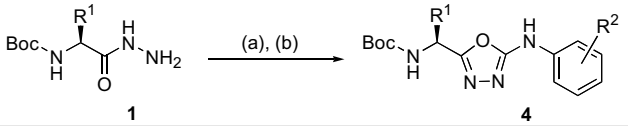
Entry	Products	R^1	R^2	Yield of **3**[b] %
1	**2/3a**	Me	H	80
2	**2/3b**	*i*-Pr	H	78
3	**2/3c**	Bn	H	85
4	**2/3d**	Bn	4-Me	80
5	**2/3e**	Bn	2-Br	79
6	**2/3f**	Bn	3-Br	78
7	**2/3g**	Bn	4-NO_2	80
8	**2/3h**	Bn	3,4,5-$(MeO)_3$	80

[a] Reagents: (a) ArNCS (1.0 equiv), CH_2Cl_2, rt, 20 min. (b) 20% TFA/CH_2Cl_2, rt, 1.5 h. (c) $HgCl_2$ (1.1 equiv), Et_3N (1.1 equiv), MeCN, rt, 12 h.
[b] Isolated yields obtained after column chromatographic purification (1% Et_3N in EtOAc:Hexanes 1:4).

The structure of the product oxadiazole **4Ce** was confirmed by X-ray crystallography (Fig. 1).[15] The solid-state conformation of **4Ce** revealed that the oxadiazole and bromophenyl rings were coplanar, maximizing conjugation of the anilino-N lone-pair.

A selection of eight of the *N*-Boc-protected compounds **4** were treated with 50% TFA/CH_2Cl_2 solution to give the deprotected

Table 2
Parallel synthesis of *N*-Boc-protected 5-substituted 2-arylamino 1,3,4-oxadiazoles **4** using $HgCl_2$ and Et_2N[a]



Entry	Product	R^1	R^2	Yield[b] %
1	**4Aa**	Me	H	85
2	**4Ab**	Me	2-Me	88
3	**4Ac**	Me	3-Me	86
4	**4Ad**	Me	4-Me	87
5	**4Ae**	Me	2-Br	97
6	**4Af**	Me	3-Br	99
7	**4Ag**	Me	4-NO_2	80
8	**4Ah**	Me	3,4,5-$(MeO)_3$	98
9	**4Ba**	*i*-Pr	H	92
10	**4Bb**	*i*-Pr	2-Me	88
11	**4Bc**	*i*-Pr	3-Me	80
12	**4Bd**	*i*-Pr	4-Me	89
13	**4Be**	*i*-Pr	2-Br	98
14	**4Bf**	*i*-Pr	3-Br	99
15	**4Bg**	*i*-Pr	4-NO_2	85
16	**4Bh**	*i*-Pr	3,4,5-$(MeO)_3$	96
17	**4Ca**	Bn	H	89
18	**4Cb**	Bn	2-Me	89
19	**4Cc**	Bn	3-Me	80
20	**4Cd**	Bn	4-Me	87
21	**4Ce**	Bn	2-Br	99
22	**4Cf**	Bn	3-Br	99
23	**4Cg**	Bn	4-NO_2	75
24	**4Ch**	Bn	3,4,5-$(MeO)_3$	97

[a] Reagents: (a) ArNCS (1.0 equiv), CH_2Cl_2, rt, 20 min. (b) $HgCl_2$ (1.1 equiv), Et_3N (1.1 equiv), MeCN, rt, 12 h.
[b] Isolated yields obtained after column chromatographic purification (EtOAc:Hexanes 1:4).

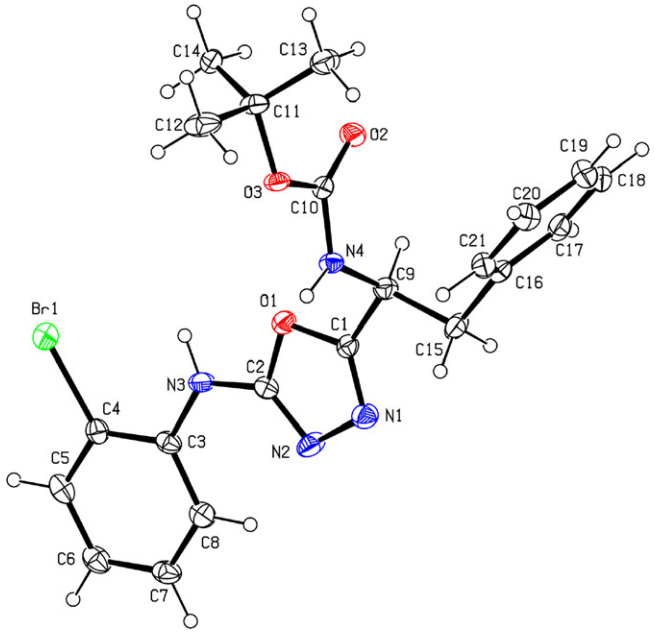
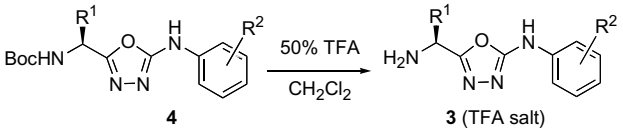


Figure 1. X-ray crystal structure of the 1,3,4-oxadiazole **4Ce**. Thermal ellipsoids are shown at 30% probability.

compounds **3** as their TFA salts. The products were obtained in excellent yields and high purities without the need for chromatographic separation (Table 3). The yields and purities of the compounds **3a**–**f**,**h** obtained in this manner (i.e., synthesized via **4**) were comparable to the results for the syntheses of these compounds where *N*-Boc deprotection preceded oxadiazole formation (i.e., Table 1). In general, however, synthesis and storage via the *N*-Boc-protected compounds **4** is preferable due to the greater long-term stability of **4** and the TFA salt of **3**, compared to the free-base form of **3**.

Proline derived 1,3,4-oxadiazoles **6** can also be synthesized using these two approaches (Table 4). In the first approach, initial formation of the Pro-derived thiosemicarbazide was followed by Boc-deprotection using 20% TFA/CH_2Cl_2, and then immediate cyclization to give **6a**–**h**. This approach had the advantage of not requiring isolation of any of the intermediates. However, the crude products **6a**–**h** were obtained with only 80–87% purity,[16] necessitating flash chromatographic purification of **6**. In the second approach, the intermediate thiosemicarbazides were first cyclized to give **5a**–**h**, and subsequently deprotected using 50% TFA/CH_2Cl_2

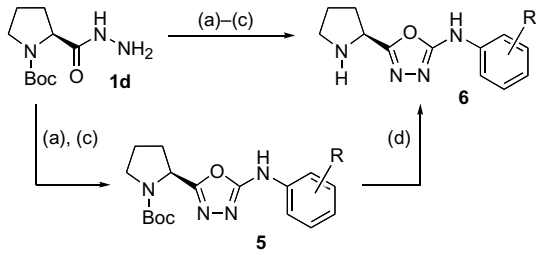
Table 3
Boc group deprotection of **4** into **3**



Entry	Product	R^1	R^2	Yield,[a] % (Purity[b] %)
1	**3a**	Me	H	99 (94)
2	**3b**	*i*-Pr	H	98 (97)
3	**3c**	Bn	H	99 (95)
4	**3d**	Bn	4-Me	99 (91)
5	**3e**	Bn	2-Br	97 (92)
6	**3f**	Bn	3-Br	98 (95)
7	**3h**	Bn	3,4,5-$(MeO)_3$	98 (97)
8	**3i**	Bn	3-Me	99 (93)

[a] Yield of the unchromatographed product.
[b] Determined by HPLC/LCMS with the UV absorption measured at 254 nm.

Table 4
Synthesis of proline derived 1,3,4-oxadiazoles **5** and **6**[a]



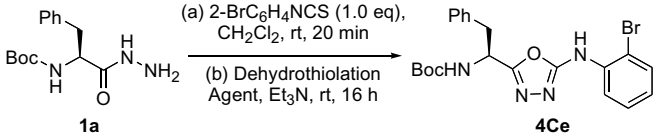
Entry	R	Products	Yield of **6**[b,c] (%)	Yield of **5**[b,d] (%)
1	H	**5/6a**	78	87
2	2-Me	**5/6b**	75	88
3	3-Me	**5/6c**	75	84
4	4-Me	**5/6d**	77	84
5	2-Br	**5/6e**	84	96
6	3-Br	**5/6f**	86	95
7	4-NO_2	**5/6g**	73	86
8	3,4,5-$(MeO)_3$	**5/6h**	82	98

[a] Reagents: (a) ArNCS (1.0 equiv), CH_2Cl_2, rt, 20 min, (b) 20% TFA/CH_2Cl_2, rt, 1.5 h, (c) $HgCl_2$ (1.1 equiv), Et_3N (1.1 equiv), MeCN, rt, 12 h, (d) 50% TFA/CH_2Cl_2, rt, 30 min.
[b] Isolated yields obtained after column chromatographic purification based on the starting Boc-protected hydrazide **1d**.
[c] Isolated yields of **6** produced using (a)–(c).
[d] Isolated yields of **6** prepared by deprotection of **5** were quantitative.

to give **6a–h**. The initial Boc-protected products **5** were isolated in good yields. Again, column chromatographic purification following the cyclization step was required, since the crude products **5** had 85–93% purity.[16] Deprotection of **5a–h** occurred in quantitative yields to give **6a–h** as the TFA salts in excellent purities ($\geqslant$98%, as confirmed by ^{1}H NMR analysis) without the need for chromatographic purification. Overall, although both approaches required a single chromatographic purification, purification of **5** was more straightforward than for **6**, and the overall yields of **6** were higher via **5**. In addition, the Boc-protected compounds **5** were suitable for long-term storage.

We were also interested in developing conditions using alternative dehydrothiolating agents for the reaction, to avoid the use of $HgCl_2$. As a first step, the formation of 1,3,4-oxadiazole **4Ce** from **1a** was compared using three different dehydrothiolating agents: $HgCl_2$, Mukaiyama's reagent (2-chloro-*N*-methylpyridinium iodide, **7**[17]), and its polymer-supported equivalent **8**[17,18] (Table 5). Each experiment was conducted at ambient temperature for 16 h, affording **4Ce** in excellent yields (92–95%) with excellent purities (98–99%). For compound **4Ce**, synthesized using either $HgCl_2$ or Mukaiyama's reagent, purification by column chromatography was required. For compound **4Ce** synthesized by the $HgCl_2$ protocol, NMR analysis of the crude sample showed excellent purity. However, ICP AES analysis revealed the presence of ~200 ppm of Hg in the crude solid sample after aqueous work-up, while the Hg level of the same sample after flash chromatography was not detectable by ICP AES. The use of Mukaiyama's reagent is of course advantageous due to its lower toxicity; however, the products obtained using this method must also be purified by column chromatography to remove the organic by-products. The use of the polymer-supported CMPI equivalent **8** avoids the toxicity/environmental problems associated with the use of mercury salts, while requiring only a simple filtration upon completion of the reaction. Thus, in the case of the compound **4Ce** prepared using solid supported reagent **8**, NMR analysis of the crude sample showed excellent purity, and column chromatographic purification was not required. Another operational simplification permitted by the use of the polymer-supported reagent **8** is that all of the reagents can be added at the same time (i.e., without the pre-treatment of the hydrazide with the arylisothiocyanate). Thus, stirring of **1a**, 2-bromophenyl isothiocyanate (1 equiv), **7** (5 equiv) and triethylamine (5 equiv) for 16 h gave **4Ce** in 94% yield, compared to a 95% yield (Table 5) obtained for the two-stage addition. Finally, a possible concern for α-amino acid derived compounds is whether stereochemical integrity is retained in the products. Chiral HPLC determination (Chiralcel OD column) of independently synthesized (*R*)-**4Ce** and (*S*)-**4Ce** verified that epimerization was not observed ($\leqslant$0.01%) under the reaction conditions.

Table 5
Comparative study of dehydrothiolating agents used for the formation of **4Ce**



Entry	Reaction conditions	Yield (%)
1	$HgCl_2$ (1.1 equiv), Et_3N (3.0 equiv), MeCN, 16 h	92[a]
2	CMPI **7** (5.0 equiv), Et_3N (5.0 equiv), MeCN, 16 h	94[a]
3	Polymer-supported CMPI **8** (5.0 equiv), Et_3N (5.0 equiv), MeCN:CH_2Cl_2 (1:1), 16 h	95

[a] Isolated yield after column chromatography.

In conclusion, a convenient method for the synthesis of 2-arylamino 5-substituted 1,3,4-oxadiazoles from Boc-protected amino acid derived hydrazides has been developed. Further studies on the synthesis and applications of 1,3,4-oxadiazoles as peptidomimetic building blocks will be reported in due course.

Acknowledgements

We thank Dr. Ghotas Evindar for preliminary experiments, Dr. Alex Young for MS analyses, and Dan Mathers for ICP AES analyses. The Natural Science and Engineering Research Council of Canada (NSERC) and the Ontario Research and Development Fund (ORDCF) supported this work. J.I.G. is grateful to the University of Toronto for fellowship support.

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Pergamon: Oxford, 1996; pp 267–287; (f) Hetzheim, A. In *Houben-Weyl Methoden der Organischen Chemie*; Schaumann, E., Ed.; Thieme: Stuttgart, 1994; Vol. E8c, pp 526–647; (g) Weaver, G. W. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Storr, R. C., Gilchrist, T. L., Eds.; Thieme: Stuttgart, 2003; Vol. 13, pp 219–251.

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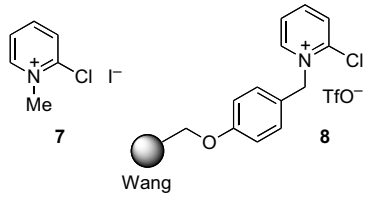
12. The Boc-thiosemicarbazides **2** did not require purification for use in the next step.
13. Hydrazide **1** (7.20 mmol) and arylisothiocyanate (7.20 mmol, 1.0 equiv) in CH_2Cl_2 (5 ml) were stirred for 20 min at room temperature. The solvent was removed in vacuo to give **2** which was immediately used in the next step. To a solution of **2** (0.36 mmol) in CH_3CN (3 ml) was added $HgCl_2$ (108.6 mg, 0.4 mmol) and triethylamine (0.088 ml, 1.10 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction slurry was filtered through a short plug of Celite and the solvent was removed in vacuo. The crude products were purified using semi-automated flash chromatography (silica gel, EtOAc/hexanes 1:4) on a Biotage SP1 instrument.
14. Representative chararacterization data. (*S*) Isomer: {1-[5-(2-Bromophenylamino)-[1,3,4]oxadiazol-2-yl]-2-phenylethyl}-carbamic acid *tert*-butyl ester **4Ce**: white solid; mp = 147–148 °C; $[\alpha]_D^{26}$ −53.0 (MeOH, *c 0.99);* R_f = 0.27 (EtOAc–hexanes; 1:4); IR (thin film) ν 3350, 2949, 1700, 1696, 1590, 1521, 1450, 1376, 1308, 1276, 1206, 1009, 878, 720, 670 cm^{-1}; ^1H NMR (300 MHz, CD_3OD–CD_2Cl_2 3:1) δ 8.00 (1H, dd, *J* = 8.0, 1.0 Hz), 7.60 (1H, dd, *J* = 8.0, 1.0 Hz), 7.36 (1H, ddd, *J* = 8.0, 8.0, 1.2 Hz), 7.22–7.31 (5H, m), 7.02 (1H, ddd, *J* = 8.0, 8.0, 1.0 Hz), 5.02–5.09 (1H, m), 3.28 (1H, dd, *J* = 13.5, 6.5 Hz), 3.13 (1H, dd, *J* = 13.5, 9.0 Hz), 1.36 (9H, br s); ^{13}C NMR (100 MHz, CD_3OD:CD_2Cl_2 3:1) δ 161.6, 159.4, 155.2, 135.4, 133.4, 132.6, 128.9, 128.3, 127.1, 124.0, 120.9, 118.7, 111.6, 80.5, 42.6, 28.5, 22.8; HRMS (ESI) *m/e* ($[M+1]^+$) calcd for $C_{21}H_{24}N_4O_3Br$ 459.1024, found 459.1026.
15. Crystallographic data (excluding structure factors) for the structure of compound **4Ce** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 683066.
16. Purities of **5** and **6** were determined by HPLC/LCMS with the UV absorption measured at 254 nm.
17. 

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18. Polymer-supported CMPI equivalent **8** is prepared by treatment of Wang resin with excess of 2-chloropyridine and triflic anhydride, see: (a) Crosignani, S.; Gonzalez, J.; Swinnen, D. *Org. Lett.* **2004**, *6*, 4579–4582; (b) Crosignani, S.; Swinnen, D. *J. Comb. Chem.* **2005**, *7*, 688–696.