An effective conversion of *N'*-ethoxymethylene-2-(*N*-Boc-amino)propionohydrazides into 2-(1-aminoethyl)-1,3,4-oxadiazoles

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Abstract
A series of *N'*-ethoxymethylene-2-(*N*-Boc-amino)propionohydrazide derivatives was obtained from the reactions of *N*-Boc-protected alanine hydrazide and triethyl orthoesters. They underwent cyclization to the corresponding 2-(1-*N*-Boc-aminoethyl)-1,3,4-oxadiazoles in glacial acetic acid.

Keywords: *N'*-Ethoxymethylene-2-(*N*-Boc-amino)propionohydrazide, 1,3,4-oxadiazole, cyclization, *syn* and *anti* isomerism, Boc protecting group

Introduction

1,3,4-Oxadiazoles belong to a group of heterocyclic compounds that exhibit a wide range of biological activities.[1] A lot of compounds containing such an arrangement demonstrate strong antibacterial, anticonvulsant and anticancer activities; some of them are even used to fight infections involving AIDS.[2-4] They also have some industrial applications in agriculture as pesticides, acaricides and nematocides[5,6] or in material science because of their precious electrochemical properties.[7,8]

The most popular method to synthesize 1,3,4-oxadiazoles uses acid hydrazides as substrates that undergo reaction with aromatic aldehydes,[9] carboxylic acids[4] and orthoesters.[10] Another comprises the reactions of diacylhydrazines with a range of cyclodehydrating agents, for example: polyphosphoric acid,[11] phosphorus oxychloride,[12] thionyl chloride,[13] or boron trifluoride diethyl etherate[14].

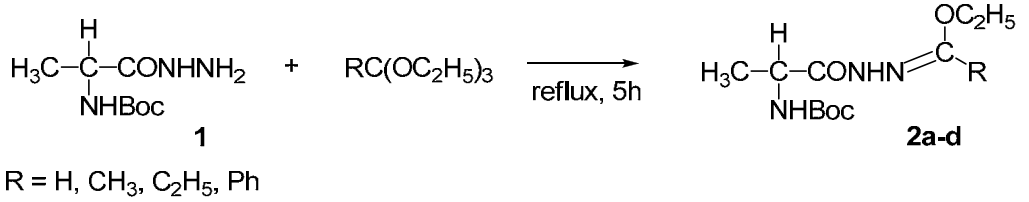
Our earlier research on the reactions of α-hydroxyacid hydrazides with triethyl orthoesters in the presence of glacial acetic acid led us to a mixture of two heterocyclic compounds: the derivatives of 1,3,4-oxadiazole and 1,3,4-oxadiazin-5(*6H*)-one.[15] The formation of the latter six-membered compounds was the result of the presence of a highly reactive hydroxy group in the molecule of hydrazide. The hydrazides of other acids, α-aminocarboxylic ones, possessing the

more reactive group at the α position, undergo the reaction with triethyl orthoesters yielding mainly the six-membered derivatives of 1,2,4-triazine-6(5*H*)-one.[16] However, the protection of such a group in the α-amino substrate prevents the formation of the latter compounds and the five-membered 2-aminomethyl-1,3,4-oxadiazoles are the only products of the reaction.[17] Such compounds are of the great importance because they could be used as building blocks for macrocyclic systems.

Herein, we describe an easy procedure for the synthesis of *N'*-ethoxymethylene-2-(*N*-Boc-amino)propionohydrazides and its application to the formation of 2-aminoethyl-1,3,4-oxadiazole derivatives.

Results and Discussion

The starting material was the racemic *DL*-alanine hydrazide protected at the α-amino group with *tert*-butoxycarbonyl. It was obtained in a few-step procedure according to well-known protocols. At first, the racemic *DL*-alanine was treated with methanol and thionyl chloride yielding *DL*-alanine methyl ester hydrochloride. The ester, which was produced in satisfactory yields, was protected by Boc_2O in the presence of triethylamine and then transformed into the desired hydrazide **1** by the reaction with hydrazine hydrate. Heating *N*-Boc-*DL*-alanine hydrazide **1** with the excess of triethyl orthoester (R = H, Me, Et, Ph, Scheme 1) we obtained the four acyclic derivatives of *N'*-ethoxymethylene-2-(*N*-Boc-amino)propionohydrazide **2** as stable solids.



Scheme 1

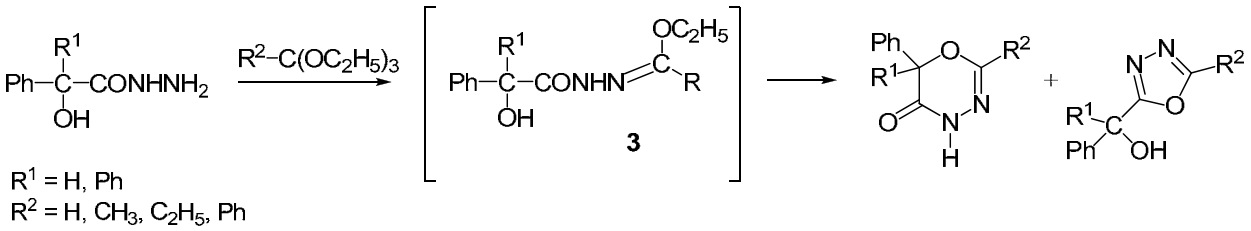
The yields of products are high (80-83%), except for the reaction with triethyl orthoformate (52%). The new compounds were characterized by elemental analysis and typical spectroscopic methods.

Table 1. Products of reactions of *N*-Boc-*DL*-alanine hydrazide **1** with triethyl orthoesters

Entry	Product	R	Yield, %
1	**2a**	H	52
2	**2b**	CH_3	80
3	**2c**	C_2H_5	82
4	**2d**	Ph	83

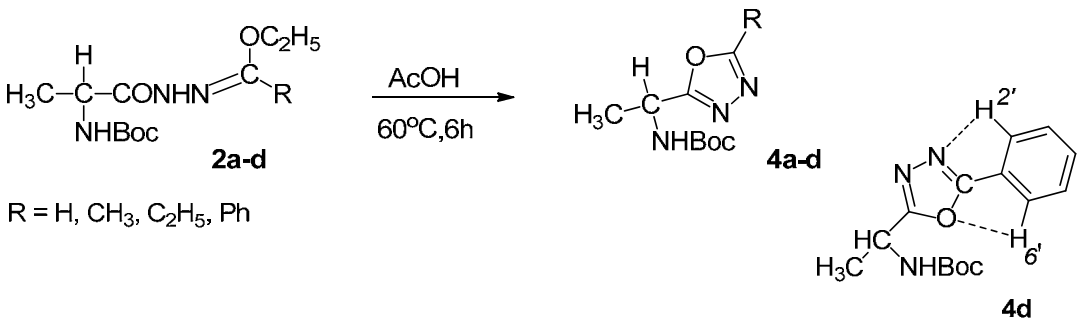
Both ^{1}H and ^{13}C-NMR spectra show all the expected signals. Analyzing ^{1}H-NMR spectra of **2a-d** in DMSO we found that they show a double number of peaks due to *syn* and *anti* geometric isomerism. The signals coalesced upon heating the solution to 100°C. The most characteristic peaks in the ^{1}H-NMR spectra come from protons of the ethoxy group, which was introduced to the molecule of **2** by orthoester and appears as triplet (-CH_3) at ca. 1.40 ppm and quartet (-CH_2-) ranging from 3.60 to 4.30 ppm. In the ^{13}C-NMR spectra, the characteristic methylene carbon atom comes at ca.165 ppm. Two other typical signals of the ethoxy group which was introduced to *N'*-ethoxymethylene-2-(*N*-Boc-amino)propionohydrazide moiety, appear at 15 ppm (-CH_3) and 61-68 ppm (-OCH_2-).

Working earlier on the synthesis making use of α-hydroxycarboxylic acid hydrazides[15] we came to the conclusion that the acyclic compound **3**, belonging to the same class of iminoesters, should play the essential role in the formation of both heterocyclic 1,3,4-oxadiazole and 1,3,4-oxadiazin-5(*6H*)-one systems (Scheme 2).



Scheme 2

Thus, the synthesized iminoesters **2a-d** were subjected to heating in acidic media in order to obtain the desired five-membered 1,3,4-oxadiazoles **4** (Scheme 3).



R = H, CH_3, C_2H_5, Ph

Scheme 3

The cyclization occurred in glacial acetic acid at elevated temperature to give the appropriate 5-substituted 2-aminoethyl-1,3,4-oxadiazoles **4a-d**. The yields of products **4a-d** are very high (Table 2), almost quantitative.

Table 2. The synthesis of 2-(1-*N*-Boc-aminoethyl)-1,3,4-oxadiazoles **4** from *N*'-ethoxymethylene-2-(*N*-Boc-amino)propionohydrazide **2**

Entry	Product	R	Yield, %
1	**4a**	H	95
2	**4b**	CH_3	97
3	**4c**	C_2H_5	98
4	**4d**	Ph	98

The structures of new products were confirmed by elemental analysis and typical spectroscopic methods. The ^{1}H-NMR spectra show the disappearance of both the ethoxy group and the proton adjacent to hydrazide nitrogen atom, indicating the loss of ethanol during the reaction course. In the ^{13}C-NMR spectra, the characteristic ring carbon atom C-2 is seen at ca.167 ppm. The location of the second carbon atom C-5 depends on the type of substituent attached to this position. For the unsubstituted compound **4a** it appears at 154 ppm while for the rest of 1,3,4-oxadiazoles **4b-d** at ca. 164 ppm.

Analyzing the ^{1}H-NMR spectra of 2-(1-aminoethyl)-5-phenyl-1,3,4-oxadiazole **4d** (Scheme 3), we found that the two protons H-2' and H-6' of the phenyl group substituted at position five of the 1,3,4-oxadiazole ring are shifted to low fields and appear as doublet at 7.95 ppm. Similar observations were made for other 1,3,4-oxadiazoles possesing the benzene ring in the mentioned position.[17] Such significant change in the chemical shift could result from the proximity of H-2' and H-6' protons to the ring's nitrogen and oxygen atoms or from the presence of hydrogen bonds linking heteroatoms and the indicated protons. Thus, both 1,3,4-oxadiazole and the phenyl rings lie untwisted in the same plane and are conjugated.

Conclusions

In conclusion, we have presented a two-step procedure for the preparation of 2-(1-*N*-Boc-aminoethyl)-1,3,4-oxadiazoles from the racemic *DL*-alanine hydrazide and triethyl orthoesters *via* stable intermediates, the derivatives of *N'*-ethoxymethylene-2-(*N*-Boc-amino) propionohydrazide. This easy and efficient procedure may be applied to the synthesis of macrocyclic systems based on the easy-to-bind 2-(1-aminoethyl)-1,3,4-oxadiazole moiety.

Experimental Section

General. Melting points were measured using an APA II melting point apparatus and are uncorrected. UV spectra were recorded on a Shimadzu UV-2102 spectrophotometer. Elemental analyses were performed with a VarioEL analyzer. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Inova 300 spectrometer in DMSO solution using TMS as the internal standard. Thin-layer chromatography was performed on silica gel 60 F_{254} (Merck) thin layer chromatography plates using benzene-ethyl acetate (1:5 v/v) as the mobile phase.

Procedure for the synthesis of *N'*-ethoxymethylene-2-(*N*-Boc-amino)-propionohydrazides 2 The starting *N*-Boc protected *DL*-alanine hydrazide **1** (0.01 mol, 3.00 g) was added to a mixture of the appropriate triethyl orthoester (0.05 mol) and kept under reflux for about 5 h. After cooling the excessive orthoester was evaporated under reduced pressure. The crude oils were triturated with diethyl ether and then purified by crystallization from benzene-hexane mixtures.

***N'*-Ethoxymethylene-2-(*N*-Boc-amino)propionohydrazide 2a.** Yield 52%; white crystals; mp 121-123 ^{o}C; *Rf* 0.35. UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH 230.60 (10.67). ^{1}H-NMR (300 MHz, $CDCl_3$-d_1, Me_4Si): δ = 1.18-1.42 (m, 15H, OCH_2CH_3, CH_3-BOC, CH_3-*Ala*), 3.64 (q, 2H, OCH_2CH_3), 4.02-4.22 (m, 3H, OCH_2CH_3, CH-*Ala*), 4.98 (m, 1H, CH-*Ala*), 5.23 (s, 1H, H-R), 5.36 (s, 1H, H-R), 6.43 (s, 1H, NH-*Ala*), 6.65 (s, 1H, NH-*Ala*), 8.63 (s, 1H, NH), 9.42 (s, 1H, NH); ^{13}C-NMR (75 MHz, $CDCl_3$-d_1, Me_4Si): δ =15.34 (OCH_2CH_3), 18.53 (CH_3-*Ala*), 28.27 (CH_3-BOC), 48.84 (CH), 62.12 (OCH_2CH_3), 77.43 (C-BOC), 155.10 (C=O-BOC), 165.16 (C=N), 168.76 (C=O-*Ala*). Anal. Calcd. for $C_{11}H_{21}N_3O_4$: C, 51.04; H, 8.20; N, 16.16. Found: C, 51.00; H, 8.15; N, 16.20.

***N'*-(1-Ethoxyethylene)-2-(*N*-Boc-amino)propionohydrazide 2b.** Yield 80%; white crystals; mp 105-108 ^{o}C; *Rf* 0.36. UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH 230.00 (7.34). ^{1}H-NMR (300 MHz, DMSO-d_6, Me_4Si): δ = 1.12-1.25 (m, 6H, OCH_2CH_3, CH_3- *Ala*), 1.36 (s, 9H, CH_3-BOC), 1.84 (s, 3H, CH_3-R), 1.92 (s, 3H, CH_3-R), 3.92-4.16 (m, 3H, OCH_2CH_3, CH-*Ala*), 4.61 (m, 1H, CH-*Ala*), 6.78 (d, *J* = 7.2 Hz, 1H, NH-*Ala*), 6.96 (d, *J* = 7.2 Hz, 1H, NH-*Ala*), 9.80 (s, 1H, NH), 9.92 (s, 1H, NH); ^{13}C-NMR (75 MHz, DMSO-d_6, Me_4Si): δ = 14.66 (CH_3-R), 15.73 (OCH_2CH_3), 18.65 (CH_3-*Ala*), 28.72 (CH_3-BOC), 49.25 (CH), 62.28 (OCH_2CH_3), 78.44 (C-BOC), 155.62 (C=O-BOC), 165.63

(C=N), 168.76 (C=O-*Ala*). Anal. Calcd.for $C_{12}H_{23}N_3O_4$: C, 52.94; H, 8.42; N, 15.35. Found: C, 52.80; H, 8.40; N, 15.40.

***N'*-(1-Ethoxypropylene)-2-(*N*-Boc-amino)propionohydrazide 2c.** Yield 82%; white crystals; mp 98-99 °C; *Rf* 0.32. UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH 230.60 (9.62). ^{1}H-NMR (300 MHz, DMSO-d_6, Me_4Si): δ = 0.92 (t, *J* = 7.5 Hz, 3H, CH_3CH_2-R), 1.04 (t, *J* = 7.5 Hz, 3H, CH_3CH_2-R), 1.12-1.24 (m, 6H, OCH_2CH_3, CH_3-*Ala*), 1.35 (s, 9H, CH_3-BOC), 2.24 (q, *J* = 7.5 Hz, 2H, CH_3CH_2-R), 2.40 (q, *J* = 7.5 Hz 2H, CH_3CH_2-R), 3.85-4.14 (m, 3H, OCH_2CH_3, CH-*Ala*), 4.58 (m, 1H, CH-*Ala*), 6.78 (br s, 1H, NH-*Ala*), 6.96 (br s, 1H, NH-*Ala*), 9.82 (s, 1H, NH), 9.94 (s, 1H, NH); ^{13}C-NMR (75 MHz, DMSO-d_6, Me_4Si): δ = 9.58 (CH_3CH_2-R), 14.13 (OCH_2CH_3), 18.10 (CH_3-*Ala*), 21.56 (CH_3CH_2-R), 28.20 (CH_3-BOC), 48.73 (CH), 61.73 (OCH_2CH_3), 77.96 (C-BOC), 156.80 (C=O-BOC), 166.58 (C=N), 168.38 (C=O-*Ala*). Anal. Calcd. for $C_{13}H_{25}N_3O_4$: C, 54.39; H, 8.78; N, 14.48. Found: C, 54.45; H, 8.70; N, 14.60.

***N'*-(1-Ethoxybenzylidene)-2-(*N*-Boc-amino)propionohydrazide 2d.** Yield 83%; white crystals; mp 96-97 °C; *Rf* 0.49. UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH 266.00 (17.14), 203.60 (15.77). ^{1}H-NMR (300 MHz, DMSO-d_6, Me_4Si): δ = 1.16-1.42 (m, 15H, OCH_2CH_3, CH_3-BOC, CH_3-*Ala*), 3.95-4.32 (m, 3H, OCH_2CH_3, CH-*Ala*), 4.82 (m, 1H, CH-*Ala*), 6.95(d, *J* = 7.5 Hz, 1H, NH-*Ala*), 7.25 (d, *J* = 7.5 Hz, 1H, NH-*Ala*), 7.50-7.64 (m, 5H, Ph-R), 9.86 (s, 1H, NH), 10.43 (s, 1H, NH); ^{13}C-NMR (75 MHz, DMSO-d_6, Me_4Si): δ = 15.12 (OCH_2CH_3), 17.59 (CH_3-*Ala*), 28.20 (CH_3-BOC), 48.81 (CH), 66.63 (OCH_2CH_3), 78.30 (C-BOC), 127.23, 127.90, 128.79, 130.50 (C_6H_5), 155.38 (C=O-BOC), 166.60 (C=N), 169.02 (C=O-*Ala*). Anal. Calcd. for $C_{17}H_{25}N_3O_4$: C, 60.90; H, 7.46; N, 12.54. Found: C, 60.79; H, 7.50; N, 12.63.

Procedure for the preparation of *N*-Boc protected 2-(1-aminoethyl)-1,3,4-oxadiazoles 4

The appropriate *N'*-ethoxymethylene-2-(*N*-Boc-amino)propionohydrazides **2** (5 mmol) was dissolved in 10 mL of glacial AcOH. The mixture was kept on a water bath at 60°C for about 6 hours (TLC). Then the solution was concentrated on a rotary evaporator. The crude products **4a-d** were subjected to the column chromatography (silica gel, eluent: benzene-AcOEt, 1:5 mixture) or were crystallized from benzene-hexane mixtures.

2-(1-*N*-Boc-aminoethyl)-1,3,4-oxadiazole 4a. Yield 95%; white crystals; mp 81-83 °C; (lit[18] 80-82 °C); *Rf* 0.45. UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH 203.20 (1.52). ^{1}H-NMR (300 MHz, DMSO-d_6, Me_4Si): δ = 1.37 (s, 9H, CH_3-BOC), 1.43 (d, *J* = 7.2 Hz, 3H, CH_3-*Ala*), 4.89 (qui, *J* = 7.2 Hz, 1H, CH-*Ala*), 7.62 (d, *J* = 7.2 Hz, 1H, NH-*Ala*), 9.14 (s, 1H, H-R); ^{13}C-NMR (75 MHz, DMSO-d_6, Me_4Si): δ = 18.34 (CH_3-*Ala*), 28.19 (CH_3-BOC), 42.36 (CH), 78.61 (C-BOC), 154.47 (C-5), 154.96 (C=O-BOC), 167.36 (C-2). Anal. Calcd. for $C_9H_{15}N_3O_3$: C, 50.70; H, 7.04; N, 19.72. Found: C, 50.57; H, 7.25; N, 19.62.

5-methyl-2-(1-*N*-Boc-aminoethyl)-1,3,4-oxadiazole 4b. Yield 97%; white crystals; mp 79-80 °C; *Rf* 0.44. UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH 202.80 (1.94). ^{1}H-NMR (300 MHz, DMSO-d_6, Me_4Si): δ = 1.37 (s, 9H, CH_3-BOC), 1.40 (d, *J* = 6.9 Hz, 3H, CH_3-*Ala*), 2.45 (s, 3H, CH_3-R), 4.80 (quin, *J* = 6.9 Hz, 1H, CH-*Ala*), 7.57 (d, *J* = 6.9 Hz, 1H, NH-*Ala*); ^{13}C-NMR (75 MHz, DMSO-d_6, Me_4Si): δ = 10.43 (CH_3-R), 18.34 (CH_3-*Ala*), 28.12 (CH_3-BOC), 42.26 (CH), 78.46 (C-BOC), 154.83

(C=O-BOC), 163.63 (C-5), 167.37 (C-2). Anal. Calcd. for $C_{10}H_{17}N_3O_3$: C, 52.86; H, 7.49; N, 18.50. Found: C, 53.01; H, 7.59; N, 18.35.

5-ethyl 2-(1-*N*-Boc-aminoethyl)-1,3,4-oxadiazole 4c. Yield 98%; white crystals; mp 48-49 ^oC; *Rf* 0.46. UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH 204.80 (6.97). ^{1}H-NMR (300 MHz, DMSO-d_6, Me_4Si): δ = 1.22 (t, *J* = 7.5 Hz, 3H, CH_3CH_2-R), 1.37 (s, 9H, CH_3-BOC), 1.41 (d, *J* = 6.9 Hz, 3H, CH_3-Ala), 2.81 (quin, *J* = 7.5 Hz, 2H, CH_3CH_2-R), 4.81 (quin, *J* = 6.9 Hz, 1H, CH-*Ala*), 7.58 (d, *J* = 6.9 Hz, 1H, NH-*Ala*); ^{13}C-NMR (75 MHz, DMSO-d_6, Me_4Si): δ = 10.44 (CH_3CH_2-R), 18.27 (CH_3CH_2-R), 18.31 (CH_3-*Ala*), 28.12 (CH_3-BOC), 42.34 (CH), 78.45 (C-BOC), 154.85 (C=O-BOC), 163.72 (C-5), 167.48 (C-2). Anal. Calcd. for $C_{11}H_{19}N_3O_3$: C, 54.77; H, 7.88; N, 17.43. Found: C, 54.76; H, 7.98; N, 17.33.

5-phenyl-2-(1-*N*-Boc-aminoethyl)-1,3,4-oxadiazole 4d. Yield 98%; white crystals; mp 143-145 ^oC; *Rf* 0.59. UV: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH 250.40 (19.34), 204.80 (18.78). ^{1}H-NMR (300 MHz, DMSO-d_6, Me_4Si): δ = 1.39 (s, 9H, CH_3-BOC), 1.50 (d, *J* = 6.9 Hz, 3H, CH_3-*Ala*), 4.95 (quin, *J* = 6.9 Hz, 1H, CH), 7.58-7.62 (m, 3H, Ph-R: H-C-3', H-4', H-5'), 7.69 (d, *J* = 6.9 Hz, 1H, NH-*Ala*), 7.95 (d, *J* = 7.2 Hz, 2H, Ph-R: H-2', H-6'); ^{13}C-NMR (75 MHz, DMSO-d_6, Me_4Si): δ =18.27 (CH_3-*Ala*), 28.10 (CH_3-BOC), 42.54 (CH), 78.57 (C-BOC), 123.36, 126.35, 129.44, 131.94 (C_6H_5), 154.95 (C=O-BOC), 163.94 (C-5), 167.69 (C-2). Anal. Calcd. for $C_{15}H_{19}N_3O_3$: C, 62.28; H, 6.58; N, 14.53. Found: C, 62.19; H, 6.65; N, 14.47.

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