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 $\alpha$-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, $\alpha$-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(5H)-one. 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. Such compounds are of 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 Boc₂O 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](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>H</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>CH₃</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>C₂H₅</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>Ph</td>
<td>83</td>
</tr>
</tbody>
</table>

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](image)

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).
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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>H</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>CH₃</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>C₂H₅</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>Ph</td>
<td>98</td>
</tr>
</tbody>
</table>

The structures of new products were confirmed by elemental analysis and typical spectroscopic methods. The ¹H-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 ¹³C-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 ¹H-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 possessing the benzene ring in the mentioned position. 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’-(1-Ethoxyethylene)-2-(N-Boc-amino)propionohydrazide 2a. Yield 52%; white crystals; mp 121-123 °C; Rf 0.35. UV: $\lambda_{\text{max}}$ (ε $\times 10^{-3}$) MeOH 230.60 (10.67). $^1$H-NMR (300 MHz, CDCl$_3$-d$_1$, Me$_4$Si): δ = 1.18-1.42 (m, 15H, OCH$_2$CH$_3$, CH$_3$-BOC, CH$_3$-Ala), 3.64 (q, 2H, OCH$_2$CH$_3$), 4.02-4.22 (m, 3H, OCH$_2$CH$_3$, 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$_4$Si): δ = 15.34 (OCH$_2$CH$_3$), 18.53 (CH$_3$-Ala), 28.27 (CH$_3$-BOC), 48.84 (CH), 62.12 (OCH$_2$CH$_3$), 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$_3$O$_4$: 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 °C; Rf 0.36. UV: $\lambda_{\text{max}}$ (ε $\times 10^{-3}$) MeOH 230.00 (7.34). $^1$H-NMR (300 MHz, DMSO-d$_6$, Me$_4$Si): δ = 1.12-1.25 (m, 6H, OCH$_2$CH$_3$, 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$_2$CH$_3$, 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$_4$Si): δ = 14.66 (CH$_3$-R), 15.73 (OCH$_2$CH$_3$), 18.65 (CH$_3$-Ala), 28.72 (CH$_3$-BOC), 49.25 (CH), 62.28 (OCH$_2$CH$_3$), 78.44 (C-BOC), 155.62 (C=O-BOC), 165.63
(C=N), 168.76 (C=O-Ala). Anal. Calcd. for $C_{12}H_{23}N_{3}O_4$: 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; $R_f$ 0.32. UV: $\lambda_{\text{max}}$ (e-$10^3$) MeOH 230.60 (9.62). $^1H$-NMR (300 MHz, DMSO-$d_6$, Me$_4$Si): $\delta$ = 0.92 (t, $J = 7.5$ Hz, 3H, CH$_3$-CH$_2$-R), 1.04 (t, $J = 7.5$ Hz, 3H, CH$_3$-CH$_2$-R), 1.12-1.24 (m, 6H, OCH$_2$CH$_3$, CH$_3$-Ala), 1.35 (s, 9H, CH$_3$-BOC), 2.24 (q, $J = 7.5$ Hz, 2H, CH$_3$-CH$_2$-R), 2.40 (q, $J = 7.5$ Hz 2H, CH$_3$-CH$_2$-R), 3.85-4.14 (m, 3H, OCH$_2$CH$_3$, 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$_4$Si): $\delta$ = 9.58 (CH$_3$-CH$_2$-R), 14.13 (OCH$_2$CH$_3$), 18.10 (CH$_3$-Ala), 21.56 (CH$_3$-CH$_2$-R), 28.20 (CH$_3$-BOC), 48.73 (CH), 61.73 (OCH$_2$CH$_3$), 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; $R_f$ 0.49. UV: $\lambda_{\text{max}}$ (e-$10^3$) MeOH 266.00 (17.14), 203.60 (15.77). $^1H$-NMR (300 MHz, DMSO-$d_6$, Me$_4$Si): $\delta$ = 1.16-1.42 (m, 15H, OCH$_2$CH$_3$, CH$_3$-BOC, CH$_3$-Ala), 3.95-4.32 (m, 3H, OCH$_2$CH$_3$, 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-H), 9.86 (s, 1H, NH), 10.43 (s, 1H, NH); $^{13}$C-NMR (75 MHz, DMSO-$d_6$, Me$_4$Si): $\delta$ = 15.12 (OCH$_2$CH$_3$), 17.59 (CH$_3$-Ala), 28.20 (CH$_3$-BOC), 48.81 (CH), 66.63 (OCH$_2$CH$_3$), 78.30 (C-BOC), 127.23, 127.90, 128.79, 130.50 (C$_6$H$_5$), 155.38 (C=O-BOC), 166.60 (C=N), 169.02 (C=O-Ala). Anal. Calcd. for $C_{17}H_{28}N_3O_4$: 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); $R_f$ 0.45. UV: $\lambda_{\text{max}}$ (e-$10^3$) MeOH 203.20 (1.52). $^1H$-NMR (300 MHz, DMSO-$d_6$, Me$_4$Si): $\delta$ = 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$_4$Si): $\delta$ = 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 $C_9H_{15}N_3O_2$: 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; $R_f$ 0.44. UV: $\lambda_{\text{max}}$ (e-$10^3$) MeOH 202.80 (1.94). $^1H$-NMR (300 MHz, DMSO-$d_6$, Me$_4$Si): $\delta$ = 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$_4$Si): $\delta$ = 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_{3}O_{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 °C; Rf 0.46. UV: λ_{max} (ε⋅10^{-3}) MeOH 204.80 (6.97). ¹H-NMR (300 MHz, DMSO-d₆, Me₄Si): δ = 1.22 (t, J = 7.5 Hz, 3H, CH₃CH₂-R), 1.37 (s, 9H, CH₃-BOC), 1.41 (d, J = 6.9 Hz, 3H, CH₃-Ala), 2.81 (quin, J = 7.5 Hz, 2H, CH₂CH₂-R), 4.81 (quin, J = 6.9 Hz, 1H, CH-Ala), 7.58 (d, J = 6.9 Hz, 1H, NH-Ala); ¹³C-NMR (75 MHz, DMSO-d₆, Me₄Si): δ = 10.44 (CH₃CH₂-R), 18.27 (CH₃CH₂-R), 18.31 (CH₃-Ala), 28.12 (CH₃-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_{3}O_{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 °C; Rf 0.59. UV: λ_{max} (ε⋅10^{-3}) MeOH 250.40 (19.34), 204.80 (18.78). ¹H-NMR (300 MHz, DMSO-d₆, Me₄Si): δ = 1.39 (s, 9H, CH₃-BOC), 1.50 (d, J = 6.9 Hz, 3H, CH₃-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’); ¹³C-NMR (75 MHz, DMSO-d₆, Me₄Si): δ = 18.27 (CH₃-Ala), 28.10 (CH₃-BOC), 42.54 (CH), 78.57 (C-BOC), 131.94 (C₆H₅), 154.95 (C=O-BOC), 163.94 (C-5), 167.69 (C-2). Anal. Calcd. for C_{15}H_{19}N_{3}O_{3}: C, 62.28; H, 6.58; N, 14.53. Found: C, 62.19; H, 6.65; N, 14.47.

References