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Article

Synthesis of Some 3-Aryl-1,2,4-oxadiazoles Carrying a Protected L-Alanine Side Chain

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A síntese de alguns derivados dos 1,2,4-oxadiazóis (**4a-d**) partindo das arilamidoximas apropriadas (**1a-d**) e do ácido *N*-*t*-butoxycarbonil-*O*-benzil-L-aspártico é descrita. As estruturas destes novos compostos foram determinadas por meios espectroscópicos.

The synthesis of some 1,2,4-oxadiazole derivatives (**4a-d**) starting from arylamidoximes **1a-d** and *N*-*t*-butoxycarbonyl-*O*-benzyl-L-aspartic acid is described. The structures of these new products have been determined by spectroscopic methods.

Keywords: *arylamidoximes, L-aspartic acid, 1,2,4-oxadiazoles, L-alanine derivatives*

Introduction

1,2,4-Oxadiazoles are an important class of compounds[1]. Many of them have been found to possess biological activity. For example, some are analgesics, anti-inflammatory agents[2,3], antimicrobials[3], antivirals[4,5], pesticides and insecticides[6,7]. Some have pronounced β-adrenoreceptor blocking activity combined with moderate α-adrenoreceptor blocking properties[8] among others[1].

Recently, emphasis has been given to synthesize oxadiazoles having novel functional groups attached either to C-3 or C-5 of the 1,2,4-oxadiazole ring. Sokolov *et al.*[9] prepared 1,2,4-oxadiazoles by the reaction of lactone 1,4-benzodioxin-2(3H)-one with amidoximes in an aprotic polar solvent such as DMSO or dioxane at 90-140 °C esp. 100-105 °C. A generalized and efficient synthesis of 1,2,4-oxadiazoles from 1,2,5 oxadiazoles has also been described by Buscemi and collaborators[10]. Synthesis and reaction of lithiated oxadiazoles have been reviewed by Grimmet and Iddon[11]. Improved synthesis of oxadiazoles under microwave irradiation conditions was also studied by Oussaid *et al.*[12a] and Srivastava and colaborators[12b,c].

In our continuing program to discover more biologically potent 1,2,4-oxadiazoles[12b,c], we attempted to synthesize oxadiazoles having an amino acid function attached at C-5 from benzamidoximes **1a-d** with *N*- and *O*- protected aspartic acid having a terminal carboxyl function free (**2**). These products might be potential compounds for biological activity tests. A literature search revealed that no such oxadiazoles have yet been prepared. This paper therefore describes the synthesis of four oxadiazoles **4a-d** having an alanine moiety attached to C-5 of the heterocyclic ring.

Results and Discussion

When amidoximes **1a-d** were reacted with *N*- and *O*-protected aspartic acid **2** in the presence of dicyclohexylcarbodiimide (DCC) in dichloromethane at room temperature, the starting amidoxime was consumed in a short time as evidenced by thin-layer chromatography.

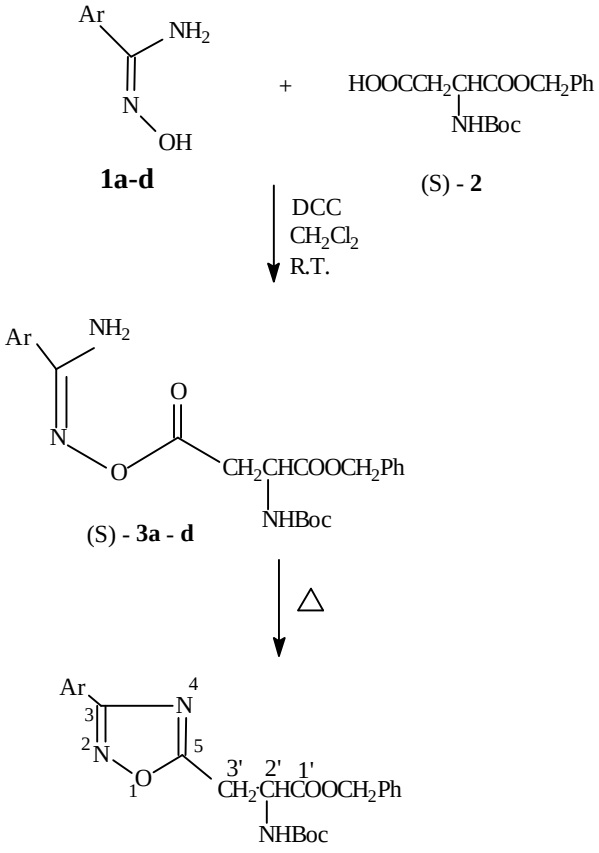
Purification by liquid chromatography on a silica gel column using n-hexane-ethyl acetate (9:1) as eluent provided the products presumably **3a-d** with have R_f values (≤ 0.6), slightly higher than benzamidoximes ($R_f \leq 0.4$). Compounds **3a-d** were obtained as solids. However, no effort was made to identify them with precision. It is common that an amidoxime forms an *O*-acyl product when allowed to react with a carboxylic acid[13]. Therefore, it is safe to assume that the structures of **3a-d** are the ones as shown in the Scheme 1.

When **3a-d** were heated (100-110 °C) separately for 5 to 15 h, they lost water and formed oxadiazoles **4a-d**.

The IR spectra of compounds **4a-d** showed the following absorptions: 1733 (-COO-), 1685 (-NHCOO-), 3354.5 (NH), 1594.7 cm^{-1} (C=N of the five membred ring)[3].

An examination of the ^{1}H-NMR spectrum of compound **4a** showed the following signals: H-2' at δ 5.42 as a broad multiplet. This is due to the coupling with two protons attached on C-3' and the NH proton. The benzylic protons appeared at δ 5.12 as a singlet. The protons on C-3' are not equivalent and provided two sets of signals - one at δ 3.29 (ddd, 1H, J ≈ 17.00 Hz, J ≈ 3.00 Hz and J ≤ l.00 Hz) and the other at δ 3.12 (dd, 1H, J = 17.00 Hz, J = 5.04 Hz). The NH proton gave a broad unresolved doublet at δ 5.75 indicating its coupling with H-2'. Addition of D_2O caused the disappearance of this signal thus confirming its identity. ^{1}H-NMR chemical shifts of compounds **4a-d** are given in Table 1.

It is necessary to comment about compounds **4a-d**. All four compounds gave negative specific rotations (Table 2). Three of them, **4a-c**, have rotations between -17.0° to - 21.5°, but **4d** showed $[\alpha]_D^{25}$ equal to -6.4°. Since the intermediates **3a-d** were heated at an elevated temperature for cyclization, there existed the posibility of either partial or total racemization of **4a-d**. In order to clarify this point, we carried out the experiment by adding the chiral shift reagent, tris[3-(trifluoromethylhydroxymethylene(+)camphorato]$_3$ europium derivatiave, directly in the NMR tube and obtained the spectrum each time after adding the shift



Ar

a : Ph
b: *m* - CH_3Ph
c: *p* - CH_3Ph
d: *p* - ClPh

Scheme 1.

Table 1. 300 MHz ^{1}H-NMR chemical shifts (in ppm) of compounds **4a-d** in $CDCl_3$.

Compounds	CH	-CH_2	Ar-CH_2	(CH_3)$_3$	NH	Ph	Ar
4a	5.42(m)	3.29(ddd) 3.12(dd)	5.12(s)	1.43(9H,s)	5.75(d)	7.31(s)	7.43-7.54 (3H, m, meta and para protons) 8.02-8.08 (2H, m, ortho protons)
4b*	5.41(m)	3.29(ddd) 3.12(dd)	5.16(s)	1.42(9H,s)	5.79(d)	7.30(s)	7.74-7.90 (2H, m, ortho protons) 7.26-7.40 (2H,m, meta and para protons)
4c*	5.41(m)	3.29(ddd) 3.11(dd)	5.12(s)	1.43(9H,s)	5.79(d)	7.27(s)	7.61(AA'BB" system, J = 8.24 Hz)
4d	5.40(m)	3.24(ddd)	5.12(s)	1.43(9h,S)	5.79(d)	7.29(s)	7.69(AA"BB" system, J = 8,70 Hz)

+ Chemical shift at mid-point.

$ArCH_3$ appeared at δ 2.42 ppm.

Table 2. Some physical data of compounds **4a-d**.

Compounds	m.p. (°C)	(Solv.)	yield[+] %	Elemental Analysis		
				Calculated (%)	Found(%)	$[\alpha]_D^{25}$
4a	60	(n-Hexane)	54	C, 65.24; H, 5.95; N, 9.92	C, 65.23; H, 6.33; N, 9.62	-17.0 ($CHCl_3$, C = 1.54)
4b	55	(Benzene- -n-Hexane)	60	C, 65.89; H, 6.22; N, 9.60	C, 65.68; H, 6.52; N, 9.83	-20.0 ($CHCl_3$, C = 0.78)
4c	88	(Benzene--n-Hexane)	60	C, 65.89; H, 6.22; N, 9.60	C, 66.23; H, 6.26; N, 9.15	-21.5 ($CHCl_3$, C = 0.59)
4d	90-91	n-Hexane	66	C, 60.33; H, 5.28; N, 9.17	C, 60.50; H, 5.56; N, 8.97	-6.4 ($CHCl_3$, C = 0.45)

[+]The yields are based ou the conversion of compouds **3a-d** to **4a-d**.

reagent. The object was to see if H-2 gives two signals after the complexation occurs. The H-2' signal of compound **4a** moved 45.0Hz downfield after two such additions. The NH proton also moved to lower field by 21.0 Hz. At each small addition of the shift reagent, we tried to amplify the region between δ 5.6-5.0 ppm. However, no separation of the H-2' signal was observed. Compound **4d** showed similar downfield shift without any separation of the H-2' signal. With this observation, we feel that there was no racemization of compounds **4a-d**.

Experimental

Melting points were determined with a Thomas Hoover apparatus and are uncorrected. Elemental analyses of compounds **4a**,**b**,**d** were performed in the Laboratoire de Spectrométrie de masse de 1' Université de Montpellier II, France, and **4c** was done by Luzia Narimatsu of Instituto de Química da Universidade de São Paulo, SP. Infrared spectra were recorded on a Bruker spectrophotometer Model IFS66. 300 MHz ^{1}H-NMR spectra were recorded on a Varian Unity plus instrument, using $CDCl_3$ as solvent and TMS as internal reference. Thin-layer chromatography (tlc) was done on plates coated with silica gel having flluorescent indicator (Merck) and the spots were detected under ultraviolet light. Specific rotations were measured on JASCO polarimeter Model DIP-370.

Arylamidoximes

These compounds were obtained by the method reported in the literature[14].

*O-(N-t-Butyloxycarbonyl-O-benzyl-L-alanylcarbonyl) arylamidoximes (**3a-d**)*

The appropriate arylamidoxime (2.13 mmol) in dry dichloromethane (10 mL) was allowed to react with *N*-butoxycarbonyl-*O*-benzyl-L-aspartic acid[15] (2.13 mmol), in the presence of dicyclohexylcarbodiimide (2.35 mmol) for l h at room temperature. The product obtained was chromatographed on a silica gel column using hexane-ethyl acetate (6:4) as eluent. The fractions having the desired product were combined and the solvent removed under reduced pressure. The yields were approximately 80%.

*N-t-Butoxycarbonyl-O-benzyl-3-[3-(aryl)-1,2,4-oxadiazol-5-yl]L-alanine (**4a-d**)*

The compounds **3a-c** were heated individually at 100-110 °C for 5 h. Tlc showed the disappearance of the starting compound. The products obtained were chromatographed on a silica gel column using hexane-ethyl acetate (9:1) and were purified by crystallization (see Table 2). Compound **3d** required heating for 15 h to complete cyclization. The physical properties and elemental analyses of all compounds are given in Table 2.

Conclusions

We have been able to show that *O*- and *N*-protected aspartic acid having a free terminal carboxyl function reacts with arylamidoximes at room temperature to give the intermediates **3a-d**. These intermediates are easily transformed to **4a-d** by heating at 100-110 °C. It is also concluded that the heating conditions which we employed did not cause any noticiable racemization.

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15. One of us (A.D.S.) prepared *N*- and *O*- protected L-aspartic acid in the laboratory of Chimie-Therapeutique de l'Université de Montpellier I, where it is prepared routinely; crystallized from benzene-hexane, m.p. 98-99 °C. $[\alpha]_D^{25}$ + 16.33 ($CHCl_3$, c = 4.5%). The compound appears to be one enantiomer as shown by the ^{1}H-NMR experiment using tris[3- trifluoromethylhydroxymethylene(+)camphorato]$_3$ europium derivative as a shift reagent.