On the Synthesis of Geminally Functionalized Heterocyclic Aminocarboxylic Acid Esters

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The title compounds **5** can be easily obtained by two alternative procedures: 1,3-dipolar cycloaddition to benzamidocinnamates **3** prepared by methanolysis of the corresponding oxazolones **1** or methanolysis of the spirooxazolones **4** synthesized by 1,3-dipolar cycloaddition to oxazolones **1**. Both reaction sequences show the same stereo and regioselectivity.

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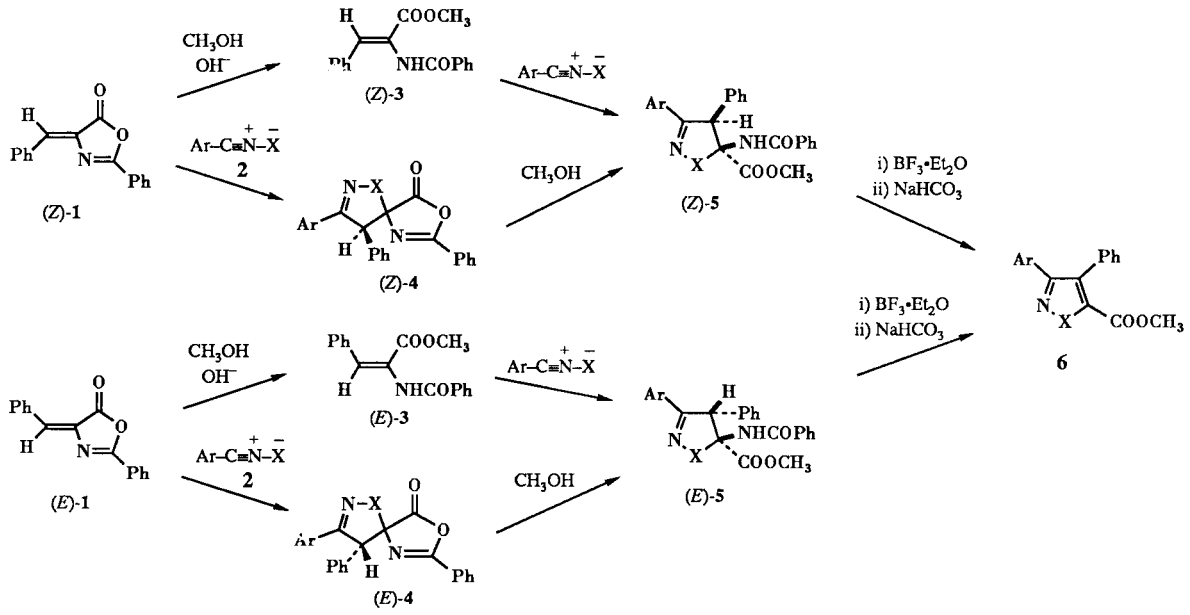
In connection with our previous studies on 1,3-dipolar cycloaddition reactions of nitrile oxides and nitrile imines with 4-arylidene-5(4*H*)-oxazolones and their thia and aza analogues, as a possible route for the synthesis of heterocyclic aminoacid derivatives [2,3,4,5], we examine in this paper the analogous reactions with methyl 2-benzamidocinnamates, the esters of the corresponding didehydroaminoacids. Didehydroaminoacid derivatives are of considerable interest in both organic synthesis and biological transformations [6]. Diels-Alder reactions and 1,3-dipolar cycloadditions to *N*-acyl-α,β-dehydroalaninates have been reported to give geminally functionalized cycloaliphatic and heterocyclic aminocarboxylic acid derivatives [7,8]. The action of diazomethane on acetamido and benzamidocinnamates has been also studied [9,10]. Depending on the configuration of the starting materials and the reaction conditions the initially formed pyrazolines give different products.

(*Z*)- and (*E*)-2-benzamidocinnamates **3**, prepared from the (*Z*)- and (*E*)-oxazolones **1**, reacted with nitrile oxides and nitrile imines to afford the corresponding isoxazoline and pyrazoline derivatives **5**. Reactions with the stable nitrile oxides **2a,b** were carried out by refluxing equimolar amounts of the reactants in chloroform solution for 35-75 hours. The unstable nitrile imines were prepared *in situ* from the corresponding hydrazonoyl chlorides and the reactions were carried out by refluxing in chloroform equimolar amounts of **3** and hydrazonoyl chloride in the presence of triethylamine for 19-50 hours. The yields of **5** isolated by column chromatography were 70-85%. (*E*)-isomer

Scheme 1



2a, (*Z*)-**4a**, (*E*)-**4a**, (*Z*)-**5a**, (*E*)-**5a,6a**	Ar = 2,4,6-$(CH_3)_3C_6H_2$ = Mes	X = O
2b, (*Z*)-**4b**, (*E*)-**4b**, (*Z*)-**5b**, (*E*)-**5b,6b**	Ar = 2,6-$Cl_2C_6H_3$	X = O
2c, (*Z*)-**4c**, (*E*)-**4c**, (*Z*)-**5c**, (*E*)-**5c,6c**	Ar = Ph	X = N–Ph
2d, (*Z*)-**4d**, (*Z*)-**5d**,	Ar = 4-$CH_3C_6H_4$	X = N–Ph
2e, (*Z*)-**4e**, (*Z*)-**5e**,	Ar = 4-ClC_6H_4	X = N–Ph

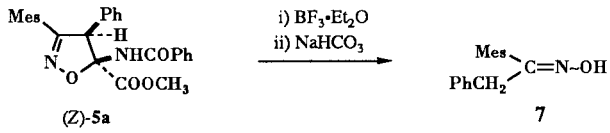
3 was more reactive than (*Z*)-isomer and shorter reaction times were required for both reactions with nitrile oxides and nitrile imines.

All the reactions were regioselective and stereoselective. Thus, in all cases only one cycloadduct was isolated which was the same to that obtained by methanolysis of the corresponding spirocycloadducts **4**, synthesized by cycloaddition of **2** to 2-phenyl-4-benzylidene-5(4*H*)-oxazolone **1** [2,3]. The regioisomeric structure of the cycloadducts **5** was previously confirmed *via* their transformation to isoxazole and pyrazole-5-carboxylic acids [3]. Considering the stereochemistry of the obtained compounds it is accepted that it is the same as the starting dipolarophiles, since all the steps involved in both reaction sequences are stereoselective. It is worth to mention that even reaction of (*E*)-isomer **3** with nitrile imine **2c** gave only (*E*)-isomer **5**, although from a blank experiment it was found (*E*)-**3** is isomerized to (*Z*)-**3** after 15 hours reflux in chloroform containing catalytic amounts of triethylamine. Because of the analogous isomerization of the oxazolone (*E*)-**1** to (*Z*)-**1** reaction of (*E*)-**1** with **2c** has resulted in mixtures of (*E*)- and (*Z*)-**4** [3]. Obviously in the case of the ester (*E*)-**3** cycloaddition is faster than isomerization.

Analytical and spectral data (^{1}H nmr, ir, ms) are in accordance with the proposed structures. In the ^{1}H nmr spectra the carbomethoxy group of (*E*)-isomers appears upfield to that of (*Z*)-isomers ($\Delta\delta$ = 0.46-0.61 ppm). This upfield shift of the carbomethoxy group protons, when they are syn to an aromatic substituent is observed in analogous derivatives of geminally functionalized aminocarboxylic acids and it is indicative of the *E* configuration [11,12]. Also the amidic proton gives rise to an upfield signal in the (*Z*)-isomers (6.58-6.89 ppm) compared to that of (*E*)-isomers which falls in the aromatic region (7.10-8.10 ppm). This difference has been also used to decide between the two stereoisomeric structures [13]. Considering the heterocyclic ring proton chemical shifts no analogous regularities are observed. Probably this chemical shift is mainly influenced by the relative spatial arrangement of both 3- and 4-aryl groups.

Both (*Z*)- and (*E*)-pyrazolines **5c**, as well as (*E*)-isoxazolines **5a** and **5b** are readily aromatized to the corresponding isoxazoles and pyrazoles by treatment with boron trifluoride etherate in accordance to the same aromatization reaction of the diazomethane cycloadducts to **3** [14]. However, (*Z*)-isoxazolines **5a** and **5b** react only if a large excess of boron trifluoride etherate is used and after prolonged heating. Under these conditions in the case of isoxazoline (*Z*)-**5a** instead of the expected isoxazole **6a**, the oxime **7** was obtained after the work up of the reaction mixture. Oxime **7** is probably formed *via* cleavage of the N-O bond and further hydrolysis and degradation of the ester moiety. The N-O cleavage must happen prior to the abstraction of benzamide since compound **6a** does not give **7** under further treatment with boron trifluoride etherate.

Scheme 2



(*Z*)-5a 7

In summary, the esters **5** of geminally functionalized heterocyclic aminocarboxylic acids can be obtained from both reaction sequences (Scheme 1) in satisfactory yields. Although former cycloaddition to **1** and subsequent nucleophilic ring opening of **4** can be used for the synthesis of a variety of aminocarboxylic acid derivatives [2,3], since the ring opening of a saturated oxazolone requires smoother reaction conditions than that of an unsaturated oxazolone, especially for the synthesis of methyl esters **5**, former methanolysis of **1** and subsequent cycloaddition offers the advantage that the intermediate spiro cycloadducts **4**, a rather sensitive and difficult to be handled class of compounds, can be avoided.

EXPERIMENTAL

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. The ir spectra were taken in Nujol with a Perkin-Elmer 297 spectrometer. The ^{1}H nmr spectra were recorded with a Bruker AW 80 (80 MHz) spectrometer (chemical shifts in δ units with tetramethyl silane as internal standard). The mass spectra were measured with a Hitachi-Perkin-Elmer RMU-6L spectrometer with an ionization energy of 70 eV. Elemental analyses were performed with a Perkin-Elmer Model 240B CHN Analyser.

Preparation of Starting Materials.

Oxazolone (*Z*)-**1** was prepared by a Perkin-Erlemeyer reaction [15]. Oxazolone (*E*)-**1** was prepared by isomerization of the (*Z*)-isomer in saturated hydrobromic acid [16]. Methyl (*Z*)- and (*E*)-2-benzamidocinnamates **3** were perpared by basic methanolysis of the corresponding oxazolones [17]. Mesitonitrile oxide **2a** and 2,6-dichlorobenzonitrile oxide **2b** were prepared by reaction of the corresponding aldoximes with *N*-bromosuccinimide and triethylamine [18]. Diarylnitrile imines **2c-e** were prepared *in situ* by the action of triethylamine on the corresponding *N*-phenylarylhydrazonoyl chlorides [19]. The melting points of the prepared starting compounds, which were known compounds, were in accordance with those given in the literature.

Reactions of (*Z*) and (*E*)-2-Benzamidocinnamates **3** with Nitrile Oxides **2a,b**.

A solution of the ester **3**, (1 mmole) and nitrile oxide **2a,b** (1 mmole) in dichloromethane was heated at reflux for 35 hours in the reactions with (*E*)-**3** and for 75 hours in the reactions with (*Z*)-**3**. The reactions were monitored by tlc until the disappearance of the starting nitrile oxide. Then the solvent was evaporated and the residue was treated by column chromatography

(silica gel, hexane/ethyl acetate, 5:1) to give the methyl 3-aryl-4-phenyl-5-benzoylamino-2-isoxazoline-5-carboxylates **5** as colorless solids, which were recrystallized from dichloromethane/hexane mixtures.

Compound (*Z*)-**5a**.

This compound was obtained from **3** and **2a** in 75% yield and it was identified with that previously reported [3].

Compound (*Z*)-**5b**.

This compound was obtained from **3** and **2b** in 70% yield, mp 186-189°; ir (Nujol): 3350 (NH), 1750, 1660 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.92 (s, 3H), 5.80 (s, 1H), 6.58 (br s, 1H), 7.10-7.60 (m, 13H); ms: m/z 412/410/408 (11, M^+-$HCOOCH_3$), 351/349/347 (6), 292/290/288 (34), 281 (3), 264/262/260 (15), 175/173/171 (9), 105 (100).

Anal. Calcd. for $C_{24}H_{18}Cl_2N_2O_4$: C, 61.40; H, 3.84; N, 5.97. Found: C, 61.31; H, 3.70; N, 5.78.

Compound (*E*)-**5a**.

This compound was obtained from (*E*)-**3** and **2a** in 70% yield, mp 105-107°; ir (Nujol): 3270 (NH), 1750, 1640 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.22 (s, 3H), 2.44 (s, 6H), 3.42 (s, 3H), 6.18 (s, 1H), 6.82 (s, 2H), 7.08-8.00 (m, 11H); ms: m/z 442 (<1, M^+), 321 (17), 262 (33), 234 (28), 161 (11), 105 (100).

Anal. Calcd. for $C_{27}H_{26}N_2O_4$: C, 73.28; H, 5.92; N, 6.33. Found: C, 73.18; H, 5.99; N, 6.16.

Compound (*E*)-**5b**.

This compound was obtained from (*E*)-**3** and **2b** in 80% yield, mp 184-186°; ir (Nujol): 3270 (NH), 1755, 1640 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.46 (s, 3H), 5.68 (s, 1H), 7.21-7.90 (m, 14H); ms: m/z 472/470/468 (2, M^+) 412/410/408 (9), 351/349/347 (53), 292/290/288 (100), 281 (11), 264/262/260 (26), 175/173/171 (20), 105 (90).

Anal. Calcd. for $C_{24}H_{18}Cl_2N_2O_4$: C, 61.40; H, 3.84; N, 5.97. Found: C, 61.35; H, 3.70; N, 5.92.

Reactions of 2-Benzamidocinnamates **3** with Nitrile Imines **2c-e**.

A solution of the ester **3** (1 mmole) and *N*-phenylarylhydrazonoyl chloride (1 mmole) in chloroform was treated with triethylamine (1.2 mmoles) and was heated at reflux for 12 hours in the reactions with (*E*)-**3** and for 50 hours in the reactions with (*Z*)-**3**. Then the reaction solution was extracted with water to remove triethylamine hydrochloride and was concentrated. Column chromatography of the residue gave methyl 1,4-diphenyl-3-aryl-5-benzoylamino-2-pyrazoline-5-carboxylates (*Z*)-**5c-e** and (*E*)-**5c** as colorless solids, which were recrystallized from dichloromethane/hexane mixtures.

Compound (*Z*)-**5c**.

This compound was obtained from (*Z*)-**3** and **2c** in 70% yield and it was identified with that previously reported [3].

Compound (*Z*)-**5d**.

This compound was obtained from (*Z*)-**3** and **2d** in 80% yield, mp 87-89°; ir (Nujol): 3420 (NH), 1725, 1680 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.25 (s, 3H), 3.71 (s, 3H), 5.58 (s, 1H), 6.60 (br s, 1H), 6.75-7.85 (m, 19H); ms: m/z 489 (4, M^+), 429 (15), 368 (3), 105 (45), 77 (100).

Anal. Calcd. for $C_{31}H_{27}N_3O_3$: C, 76.05; H, 5.56; N, 8.58. Found: C, 76.17; H, 5.38; N, 8.50.

Compound (*Z*)-**5e**.

This compound was obtained from (*Z*)-**3** and **2e** in 85% yield, mp 130-132°; ir (Nujol): 3400 (NH), 1720, 1685 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.73 (s, 3H), 5.52 (s, 1H), 6.70 (br s, 1H), 6.90-7.70 (m, 19H), ms: m/z 511/509 (9, M^+), 451/449 (22), 390/388 (7), 105 (100), 77 (80).

Anal. Calcd. for $C_{30}H_{24}ClN_3O_3$: C, 70.66; H, 4.71; N, 8.24. Found: C, 70.79; H, 4.52; N, 8.23.

Compound (*E*)-**5c**.

This compound was obtained from (**E**)-**3** and **2c** in 90% yield, mp 166-168°; ir (Nujol): 3360 (NH), 1730, 1680 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.09 (s, 3H), 5.70 (s, 1H), 6.69-7.89 (m, 20H), 8.08 (br s, 1H); ms: m/z 475 (2, M^+), 415 (5), 354 (69), 105 (60), 77 (100).

Anal. Calcd. for $C_{30}H_{25}N_3O_3$: C, 75.77; H, 5.30; N, 8.84. Found: C, 75.60; H, 5.35; N, 8.64.

Methanolysis of Spiro Compounds **4**.

Methanolysis of spiro compounds **4** was carried out by heating at reflux a methanolic solution of the corresponding compound (3 hours for isoxazolines (*Z*)-**4a**, (*Z*)-**4b**, (*E*)-**4a**, (*E*)-**4b**; 15 hours for pyrazoline (*Z*)-**4c**; 25 hours for pyrazoline (*E*)-**4c**). After evaporation of the solvent the residue solid was recrystallized from dichloromethane/hexane mixtures to give the corresponding esters **5** in 80-90% yields, or in the reaction of (*Z*)-**4c** it was chromatographed (silica gel, hexane/ethyl acetate 4:1) to give the ester (*Z*)-**5c** in 65% yield along with some 1,3,4-triphenylpyrazole-5-carboxylic acid [3].

Reaction of Compounds **5** with Boron Trifluoride Etherate.

The aromatization of compounds **5** was carried out according to the procedure previously described by Cativiela [10]. Thus, a solution of **5** (1 mmole) was treated with boron trifluoride etherate (3 mmoles for (*E*)-**5a**, (*E*)-**5b**, (*Z*)-**5c**, (*E*)-**5c**; 6 mmoles for (*Z*)-**5a**; 12 mmoles for (*Z*)-**5b**) and it was heated at reflux (20-40 minutes for (*E*)-**5a**, (*E*)-**5b**, (*Z*)-**5c**, (*E*)-**5c**; 4 hours for (*Z*)-**5a**, (*Z*)-**5b**). Then the solvent was evaporated, the residue was heated at reflux with a saturated solution of sodium bicarbonate (20 ml) and the resultant solid was filtered and dried to give the corresponding 3-aryl-5-carbomethoxyheterocycles **6** or the oxime **7** in the case of the reaction of (*Z*)-**5a**.

Compound **6a**.

This compound was obtained from (*E*)-**5a** in 92% yield identified as previously described [2].

Compound **6b**.

This compound was obtained from (*E*)-**5b** and (*Z*)-**5b** in 75% and 60% yields respectively, mp 120-122°; ir (Nujol): 1730 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.92 (s, 3H), 7.19-7.33 (m, 8H); ms: m/z 351/349/347 (13, M^+), 292/290/288 (18), 264/262/260 (5), 59 (100).

Anal. Calcd. for $C_{17}H_{11}Cl_2NO_3$: C, 58.64; H, 3.18; N, 4.02. Found: C, 58.91; H, 3.30; N, 4.05.

Compound **6c**.

This compound was obtained from (*Z*)-**5c** and (*E*)-**5c** in 97% and 92% yields respectively, mp 107-109°; ir (Nujol): 1730 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.55 (s, 3H),

7.02-7.52 (m, 15H); ms: m/z 354 (100, M^+), 323 (11), 295 (11).

Anal. Calcd. for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.91. Found: C, 77.81; H, 5.08; N, 7.85.

Compound **7**.

This compound was obtained from (*Z*)-**5a** in 80% yield, mp 147-150°; ir (Nujol): 3250 (OH), 1650 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.03 (s, 3H), 2.21 (s, 3H), 3.71 (s, 2H), 6.54 (br s, 1H), 6.82 (s, 2H), 7.30 (s, 5H); ms: m/z 253 (24, M^+), 162 (28), 161 (29), 135 (100).

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.51; H, 7.50; N, 5.48.

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