Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8489–8496

Synthesis and reactivity of a 1,4-dihydropyrazine derivative

Anabela Rodrigues, Paula M. T. Ferreira and Luís S. Monteiro*

Departamento de Química, Universidade do Minho, Gualtar, 4710-057 Braga, Portugal

Received 2 April 2004; revised 11 June 2004; accepted 30 June 2004

Available online 31 July 2004

Abstract—*N*,*N*-Bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine can be obtained in high yield by treatment of the methyl ester of *N*-(4-toluenesulfonyl)-*N*-(*tert*-butoxycarbonyl)-α,β-didehydroalanine with dimethylaminopyridine and potassium carbonate. This compound was used as substrate in Michael addition reactions with several types of nucleophiles. The electrochemical behaviour of this pyrazine derivative was also studied by cyclic voltammetry and by controlled potential electrolysis.

1. Introduction

Diazines constitute an important class of heterocyclic compounds present in several natural occurring compounds. Pyrazines are found in the luminescent chromophores of certain marine organisms,[1] in cephalostatins isolated from *Cephalodiscus Gilchrist* which are powerful anticancer agents,[2] in the fungal metabolite aspergillic acid[3] and in foods as potent flavour components.[4] 1,4-Dihydropyrazine is an important structural unit of certain redox-active biological molecules such as flavin coenzymes and several marine luciferines.[5] 1,4-Dihydropyrazine derivatives also constitute interesting electron donors in conducting charge transfer complexes and magnetic materials. The properties of 1,4-dihydropyrazines depend on the nature of the substituents and on the planarity of the ring. When planar, these ring systems can be considered 'anti-aromatic' due to cyclic 8π-electron conjugation.[5]

Recently, we have demonstrated the versatility of the methyl ester of *N*-(4-toluenesulfonyl)-*N*-(*tert*-butoxycarbonyl)-α,β-didehydroalanine [Tos-ΔAla(*N*-Boc)-OMe][6] as a substrate in Michael addition reactions. This compound is easily prepared in high yield from Tos-Ser-OMe by a di-*tert*-butylpyrocarbonate/dimethylaminopyridine [$(Boc)_2O$/DMAP] mediated dehydration.[6] Depending on the structure of the nucleophile, several types of compounds can be synthesized from Tos-ΔAla(*N*-Boc)-OMe, namely β-substituted alanine and dehydroalanine derivatives,[7] furanic amino acids, which by treatment with TFA yield dehydroproline derivatives[8] and α,-substituted β-sufinylamino acids.[8] It was also found that Tos-ΔAla(*N*-Boc)-OMe in the presence of DMAP undergoes a rearrangement to give the *E* isomer of the methyl ester of *N*-(*tert*-butoxycarbonyl)-*O*-(4-toluenesulfonyl)-α,β-didehydroserine.[7] Here in, we describe the synthesis and discuss the reactivity of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine obtained from Tos-ΔAla(*N*-Boc)-OMe.

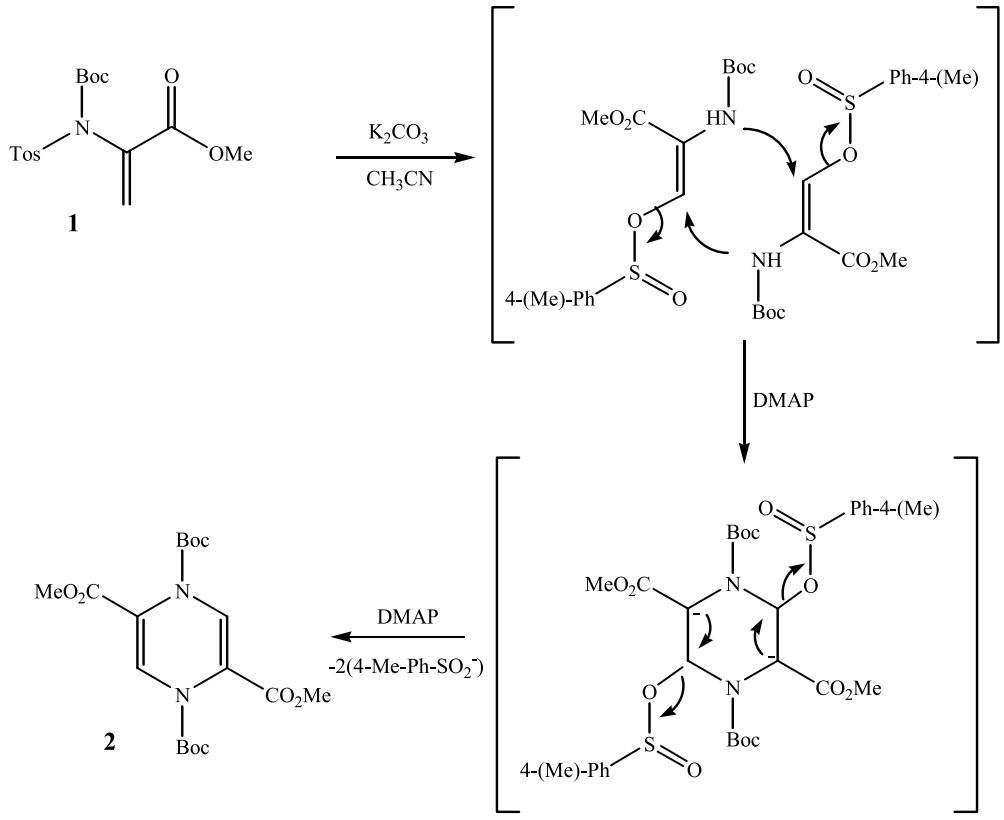
2. Results and discussion

When Tos-ΔAla(*N*-Boc)-OMe (compound **1**) was reacted with DMAP in acetonitrile in the presence of an excess of potassium carbonate the product obtained was *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine in 89% yield (compound **2**, Scheme 1). By sampling the reaction mixture and carrying out ^{1}H NMR analysis, it was found that the reaction proceeds via the formation of the methyl ester of *N*-(*tert*-butoxycarbonyl)-*O*-(4-toluenesulfinyl)-α,β-didehydroserine. Alternatively, compound **2** can be prepared in a one pot procedure from Tos-Ser-OMe by reacting with $(Boc)_2O$ and DMAP (0.1 equiv) in dry acetonitrile for 30 min and then adding K_2CO_3 (6 equiv) and more DMAP (1 equiv) (78% yield).

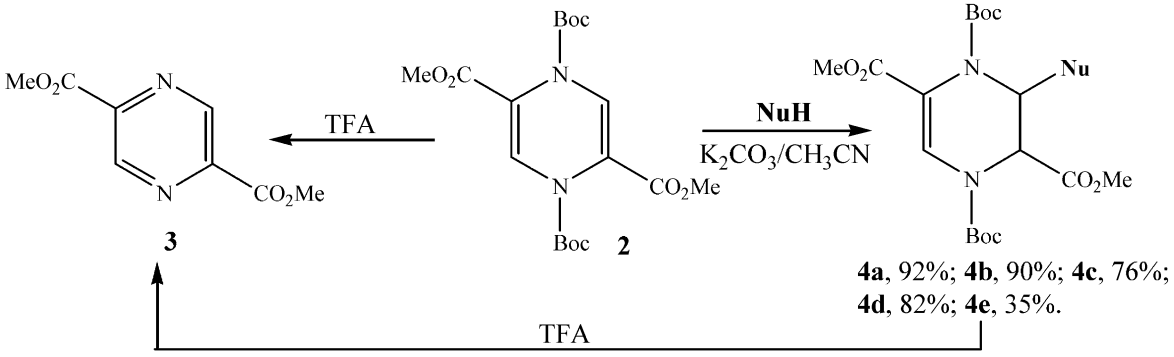
The presence of electron withdrawing substituents on 1,4-dihydropyrazine systems has a stabilizing effect thus allowing the preparation and isolation of such compounds.[5b] In the case of compound **2** the stabilizing effect of the ester groups is reinforced by the presence of the Boc groups on the nitrogen atoms. These groups are essential for stabilization of this 1,4-dihydropyrazine system since treatment of compound **2** with TFA gave 2,5-bis-methoxycarbonylpyrazine in 71% yield (compound **3**, Scheme 2). The methoxycarbonyl substituents in compound **3** cause the

Keywords: Dehydroalanines; 1,4-Dihydropyrazine; Pyrazine; Michael adddition; Electrolysis.
* Corresponding author. Tel.: +351253604374; fax: +351253678983; e-mail: monteiro@quimica.uminho.pt

0040–4020/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tet.2004.06.127



Scheme 1.



NuH: 1,2,4-triazole, **a**; 3-formylindole, **b**; 4-bromothiophenol, **c**; benzylamine, **d**; sodium methoxide, **e**.

Scheme 2.

aromatic protons to show a downfield shift in the ^{1}HNMR spectrum (9.42 ppm in $CDCl_3$) when compared with those of unsubstituted pyrazine (8.60 ppm in $CDCl_3$).[9]

The four electron-withdrawing groups of compound **2** made it possible to use this compound as an electrophile in Michael addition reactions. Thus, compound **2** was treated with several types of nucleophiles namely: 1,2,4-triazole, 3-formylindole, benzylamine, 4-bromothiophenol and sodium methoxide to give one of the diasteriomers of the corresponding 3-substituted-2,5-bis-methoxycarbonyl-1,2,3,4-tetrahydropyrazine derivatives in good to high yields (compounds **4a**-**e**, Scheme 2). ^{1}H NMR spectra of these addition products at 25 °C in $CDCl_3$ showed **4a**-**e** to be rotameric mixtures with no coupling between the 2-H and 3-H protons which indicate that the diastereomer obtained corresponds to the *trans* isomer. ^{1}H NMR analysis of the Michael adducts show that the remaining vinylic proton suffers from a downfield shift (from 7.09 ppm to values ranging from 7.24 to 7.78 ppm). This has been found in other cases in which cyclic 8π-electron conjugated systems are reduced to non-aromatic compounds.[5b,10] Treatment of compounds **4c** and **4d** with TFA resulted in cleavage of the Boc groups and elimination of the nucleophile giving the pyrazine derivative **3** (76 and 74%, respectively). This indicates that the presence of electron withdrawing

substituents on the nitrogen atoms is also essential for stabilization of these non-aromatic tetrahydropyrazine systems.

The UV spectrum of compound **2** shows two absorption bands at 225 and 276 nm (extinction coefficients of 43,265 and 31,720 $M^{-1}\,cm^{-1}$) and is similar to the UV spectrum of compound **3** which shows absorption bands at the same wavelengths (extinction coefficients of 34,615 and 23,330 $M^{-1}\,cm^{-1}$) (Fig. 1).

Cyclic voltammetry of compound **2** between −1.0 and

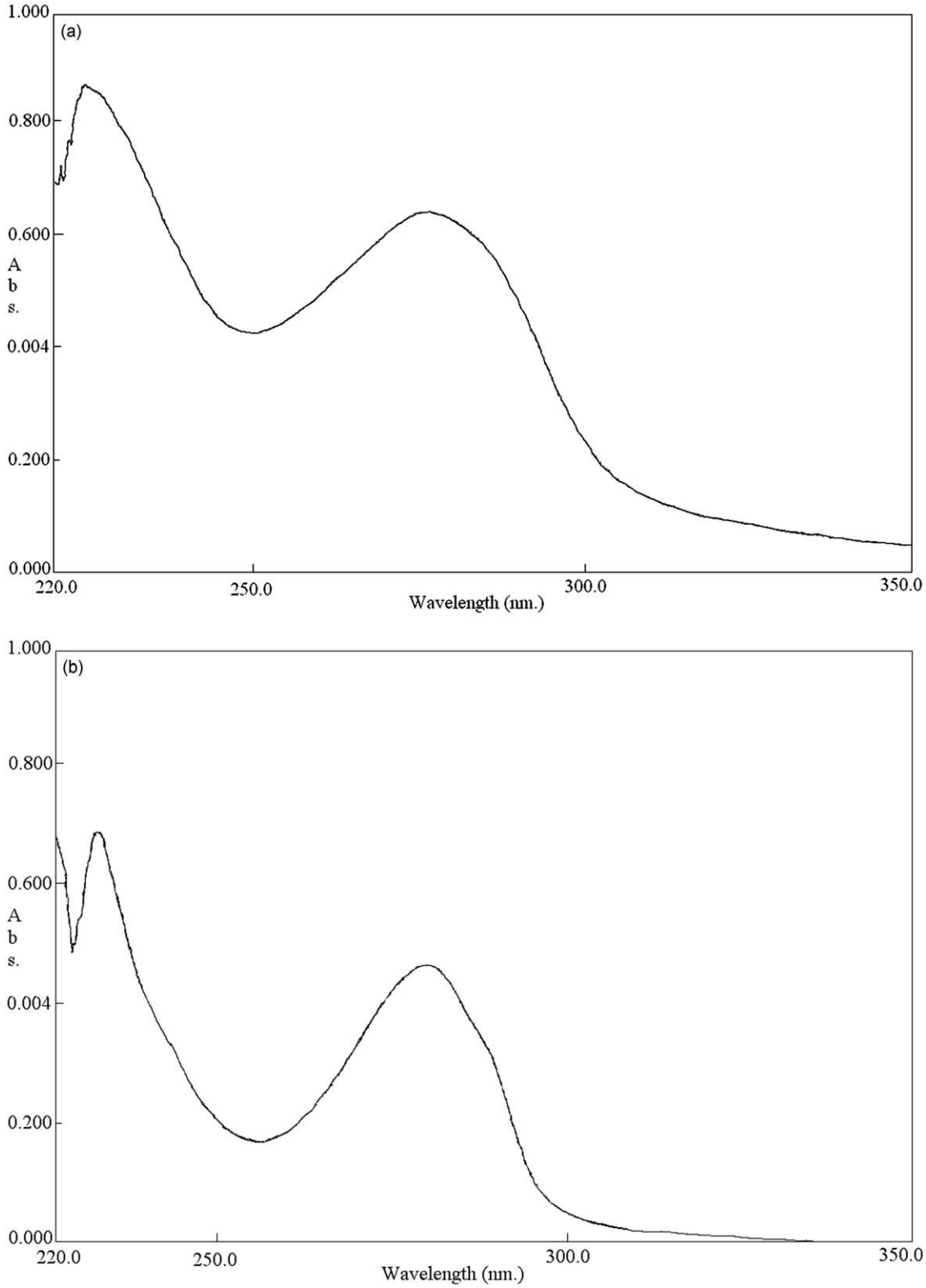


Figure 1. UV spectra of compounds **2** and **3** in dichloromethane.

1.8 V showed a single oxidation peak at 1.20 V versus SCE (Fig. 2). The oxidation potential described for *N*-ethyl-1,4-dihydropyrazine is −0.67 V versus SCE.[11] Thus, the high potentials for oxidation of compound **2** can be assigned to the electron-withdrawing effect of the substituents which makes the loss of electrons more difficult. A potential sweep from 0 to −2.8 V showed a reduction peak at −2.14 V versus SCE (Fig. 2).

The pyrazine derivative (compound **3**) shows no oxidation peak in the range between −1.0 and 1.8 V. A potential sweep from 0 to −2.8 V showed two reduction peaks at

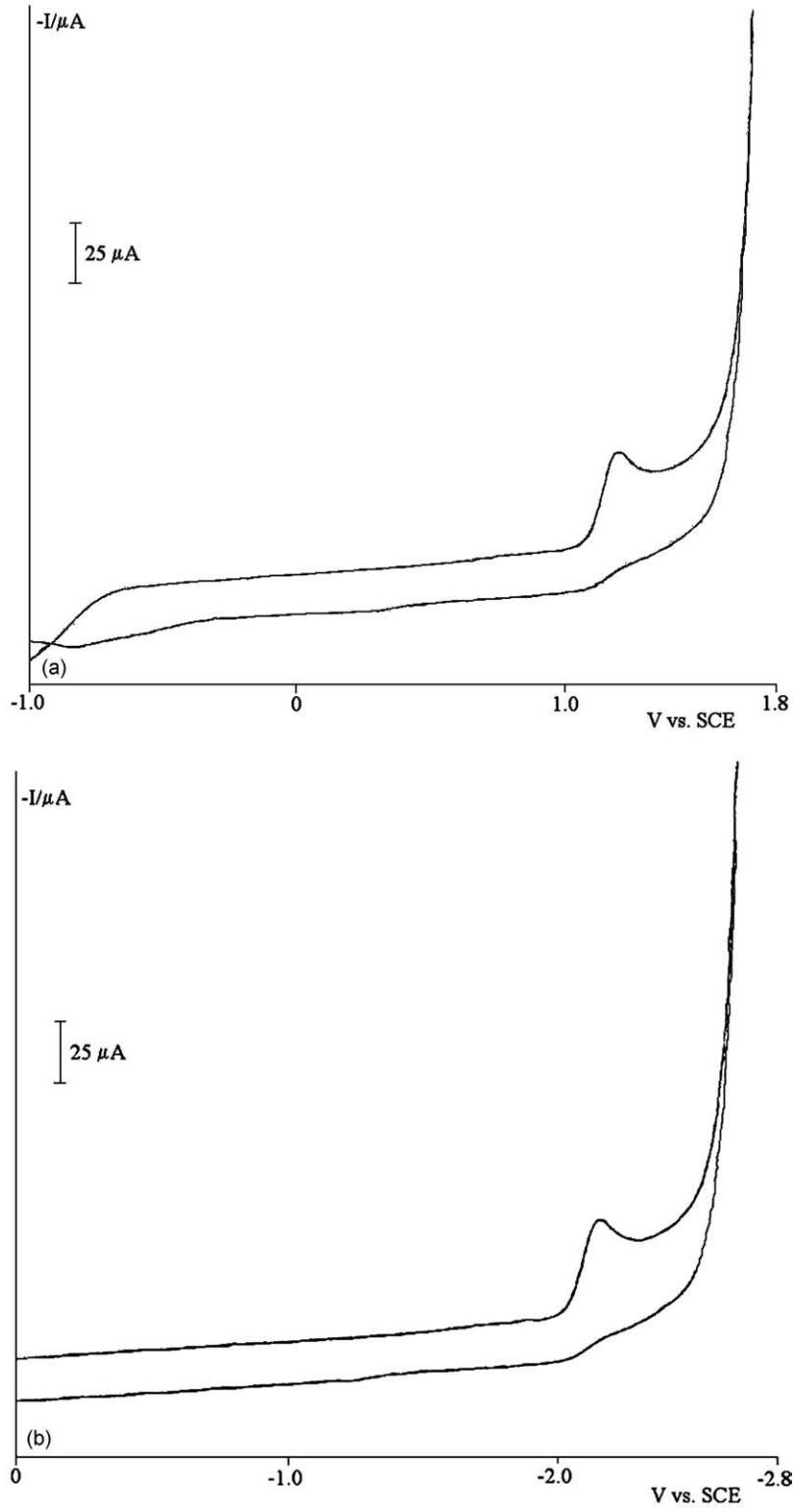


Figure 2. Cyclic voltammograms at a vitreous carbon electrode of a 0.005 mol dm^{-3} solution of compound **2** in DMF with 0.1 mol dm^{-3} Bu_4NBF_4 as supporting electrolyte at a sweep rate of 100 mV s^{-1} (SCE=standard calomel electrode).

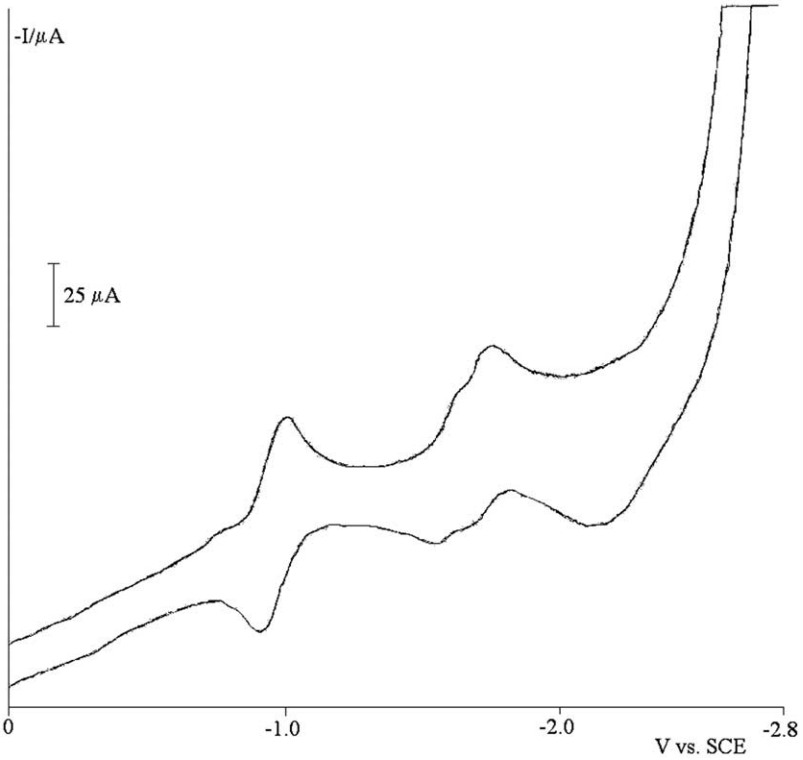


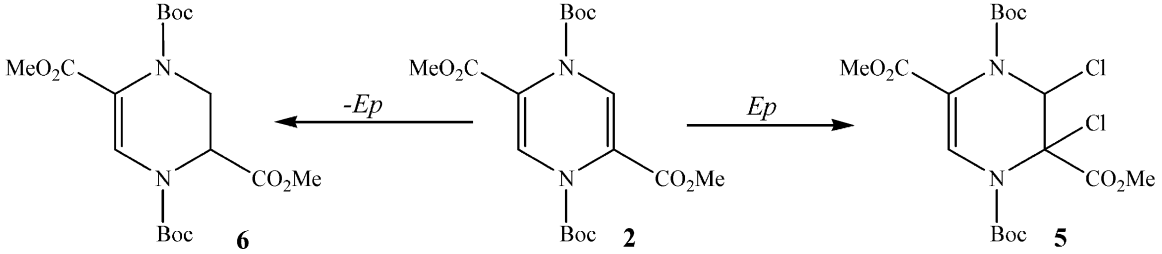
Figure 3. Cyclic voltammogram at a vitreous carbon electrode of a 0.005 mol dm^{-3} solution of compound **3** in DMF with 0.1 mol dm^{-3} Bu_4NBF_4 as supporting electrolyte at a sweep rate of 100 mV^{-1} (SCE=standard calomel electrode).

−1.00 and −1.82 V versus SCE (Fig. 3). Considering the electron-withdrawing effect of the substituents, the first reduction potential for 2,5-bis-methoxycarbonylpyrazine is in agreement with that found for: unsubstituted pyrazine (−2.16 versus SCE);[12] 2-carboxamide pyrazine (−1.75 V versus SCE);[13] and with the first reduction peak of chloropyrazine (−1.78 V versus SCE).[12]

In view of the cyclic voltammetry data obtained, controlled potential electrolysis of compound **2** at the oxidation and reduction peak potentials were carried out. In these reactions tetraethylammonium chloride was used as supporting electrolyte and triethylammonium chloride as electron donor. Oxidation of compound **2** gave one of the diastereomers of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,3-dichloro-2,5-bis-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (compound **5**) in 91% yield (Scheme 3). The formation of this compound can be due to oxidation to give a radical cation which reacts with the chloride ions present in solution. Reduction of compound **2** gave as expected *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (compound **6**) in 55% yield (Scheme 3).

3. Conclusion

The common method for the synthesis of pyrazines involves the cyclocondensation of nitrogen nucleophiles onto α-dicarbonyl systems. We developed a new high yielding method for the synthesis of a 1,4-dihydropyrazine derivative from the methyl ester of *N*-(4-toluenesulfonyl)-*N*-(*tert*-butoxycarbonyl)-α,β-didehydroalanine by treatment with DMAP and K_2CO_3. This compound was easily converted into 2,5-bis-carboxymethylpyrazine by treatment with TFA. The 1,4-dihydropyrazine derivative is also a good substrate for the diastereoselective synthesis of several tetrahydropyrazines, in good to high yields, either by Michael addition reactions or by controlled potential electrolysis. Several of these diazine derivatives can have biological activity since pyrazinamide is one of the front line agents against *M. Tuberculosis*,[14] some dihydropyrazines such as



Scheme 3.

2,3-dihydro-5,6-dimethylpyrazine showed DNA strand-breaking activity in plasmid[15] and tetrahydropyrazines have been used in the synthesis of a HIV protease inhibitor.[16]

4. Experimental

4.1. Materials and methods

Melting points were determined in a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus at 300 and 75.4 MHz, respectively. ^{1}H–^{1}H spin–spin decoupling and DEPT θ 45° were used. Chemical shifts are given in ppm and coupling constants in Hz. MS and HRMS data were recorded by the mass spectrometry service of the University of Vigo, Spain. Elemental analysis was performed on a LECO CHNS 932 elemental analyser.

The reactions were monitored by thin layer chromatography (TLC). Column chromatography was performed on Macherey–Nagel silica gel 230–400 mesh. Petroleum ether refers to the boiling range 40–60 °C.

4.1.1. Synthesis of Tos-ΔAla(*N*-Boc)-OMe. The synthesis of these compounds was described in Ref. 6.

4.1.2. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine (2) from Tos-ΔAla(*N*-Boc)-OMe. To a solution of Tos-ΔAla(*N*-Boc)-OMe in acetonitrile (0.1 mol dm^{-3}), K_2CO_3 (6 equiv) was added, followed by 1 equiv of DMAP, with fast stirring at room temperature. The reaction was monitored by TLC, (diethyl ether/*n*-hexane, 1:1) and when no starting material nor Boc-ΔSer(*O*-toluenesulfinyl)-OMe was detected ($\approx$72 h), the solution was filtered and evaporated at reduced pressure (the same procedure but heating the reaction mixture under reflux allowed the reaction to be complete in 12 h). The residue obtained was partitioned between 200 cm^3 of diethyl ether and 100 cm^3 of $KHSO_4$ (1 mol dm^{-3}). The organic phase was thoroughly washed with $KHSO_4$ (1 mol dm^{-3}), $NaHCO_3$ (1 mol dm^{-3}) and brine (3$\times$50 cm^3 each), and dried over $MgSO_4$. Removal of the solvent afforded pure compound **2** (89%), mp 155.0–156.0 °C (from diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$): 1.50 (18H, s, CH_3 2Boc), 3.80 (6H, s, 2CH_3 OMe), 7.09 (2H, s, 3-H+6-H); ^{13}C NMR ($CDCl_3$): 27.88, 52.27, 83.65, 119.82, 127.68, 148.82, 162.58; MS: *m*/*z* (%)=399 (14) [M$^+$+1], 398 (20) [M$^+$], 343 (36) [M$^+$−CO_2Me], 298 (6) [M$^+$−Boc], 198 (100) [M$^+$−2Boc]. Anal. Calcd for $C_{18}H_{26}N_2O_8$ (398.41): C 54.27; H 6.58; N 7.03; found C 54.42; H 6.72; N 6.94.

4.1.3. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine (2) from Tos-Ser-OMe. To a solution of Tos-Ser-OMe in dry acetonitrile (0.1 mol dm^{-3}), 0.1 equiv of DMAP were added, followed by Boc_2O (2.2 equiv) with fast stirring at room temperature. After reacting for 30 min more DMAP (1 equiv) was added and also K_2CO_3 (6 equiv). After reacting for approximately 3 days the same work-up as described above was carried out to give compound **2** (78% yield).

4.1.4. Synthesis of 2,5-bis-methoxycarbonylpyrazine (3). To a solution of compound **2** in dichloromethane (0.02 mol dm^{-3}), 10% trifluoroacetic acid was added with fast stirring at room temperature. The reaction was monitored by TLC, (diethyl ether/*n*-hexane, 1:1) and when no starting material was detected removal of the solvent afforded pure compound **3** (71%), mp 145.5–147.0 °C (from diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$): 4.10 (6H, s, 2CH_3 OMe), 9.42 (2H, s, 3-H+6-H); ^{13}C NMR ($CDCl_3$): 53.55, 145.18, 145.52, 163.52. Anal. Calcd for $C_8H_8N_2O_4$ (196.16): C 48.98; H 4.11; N 14.28; found C 49.06; H 4.10; N 14.00.

4.1.5. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-3-(triazol-1-yl)-1,2,3,4-tetrahydropyrazine (4a). To a solution of compound **2** in acetonitrile (0.1 mol dm^{-3}), K_2CO_3 (6 equiv) was added, followed by 1 equiv of 1,2,4-triazole, with fast stirring at room temperature. The reaction was monitored by TLC, (diethyl ether/*n*-hexane, 1:1) and when no starting material was detected ($\approx$16 h), the solution was filtered and evaporated under reduced pressure. The residue obtained was partitioned between 100 cm^3 of diethyl ether and 30 cm^3 of $NaHCO_3$ (1 mol dm^{-3}). The organic phase was washed with $NaHCO_3$ (1 mol dm^{-3}) and brine (2$\times$30 cm^3 each), and dried over $MgSO_4$. Removal of the solvent afforded compound **4a** as an enantiomeric mixture of the *trans* diastereomer (92%); oil; ^{1}H NMR ($CDCl_3$) (2 rotamers): 1.48, 1.50 (36H, 2s, CH_3 Boc), 3.79, 3.81 (12H, 2s, CH_3 OMe), 5.93, 6.03, 6.93, 6.99 (4H, 4s, 2-H+3-H pyr.), 7.36, 7.57 (2H, 2s, 6-H pyr.), 7.92 (2H, s, 3-*H* or 5-*H* triaz.), 8.32 (2H, s, 3-*H* or 5-*H* triaz.); ^{13}C NMR ($CDCl_3$): 27.69, 27.83, 52.15, 53.12, 56.26, 57.40, 63.20, 83.79, 84.37, 122.46, 127.64, 148.50, 150.04, 152.26, 166.72; MS: *m*/*z* (%)=467 (7) [M$^+$], 367 (3) [M$^+$−Boc], 267 (24) [M$^+$−2Boc], 198 (100) [M$^+$−2Boc-triaz.]; HRMS found 467.2016, Calcd for $C_{20}H_{29}N_5O_8$ 467.2016.

4.1.6. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-3-(3-formylindol-1-yl)-1,2,3,4-tetrahydropyrazine (4b). The same procedure described for the synthesis of compound **4a** was applied substituting 3-formylindole for 1,2,4-triazole. Removal of the solvent afforded compound **4b** as an enantiomeric mixture of the *trans* diastereomer (90%), mp 156.0–157.0 °C (from ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$) (2 rotamers): 1.48, 1.54 (36H, 2s, CH_3 Boc), 3.75, 3.84 (12H, 2s, CH_3 OMe), 5.40, 5.56 (2H, 2s, 2-H or 3-H pyr.), 7.23–7.58 (10H, m, 2-H or 3-H+6-H pyr.+2-H+5-H+6-H ind.), 7.73 (2H, d, *J*=7.5 Hz, 7-H ind.), 8.31 (2H, d, *J*=7.8 Hz, 4-H ind.), 9.95 (2H, s, C*H*O); ^{13}C NMR ($CDCl_3$): 27.73, 27.92, 52.12, 53.39, 57.01, 59.95, 83.76, 85.32, 110.33, 110.65, 119.27, 121.69, 122.13, 123.67, 124.84, 125.13, 134.17, 136.60, 150.41, 151.83, 163.91, 166.70, 184.94. Anal. Calcd for $C_{27}H_{33}N_3O_9$ (543.57): C 59.66; H 6.12; N 7.73; found C 59.87; H 6.18; N 7.78.

4.1.7. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-3-(4-bromophenylsulfanyl)-1,2,3,4-tetrahydropyrazine (4c). The same procedure described for the synthesis of compound **4a** was applied substituting 4-bromothiophenol for 1,2,4-triazole. Removal of the solvent afforded compound **4c** as an enantiomeric mixture

of the *trans* diastereomer (76%), mp 137.0–138.5 °C (from diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$) (2 rotamers): 1.34, 1.49, 1.57 (36H, 3s, C*H*$_3$ Boc), 3.69, 3.78 (12H, 2s, C*H*$_3$ OMe), 4.89, 5.08 (2H, 2s, 2-H or 3-H), 6.15, 6.21 (2H, 2s, 2-H or 3-H), 7.48 (8H, broad s, ArH), 7.56, 7.78 (2H, 2s, 6-H); ^{13}C NMR ($CDCl_3$): 27.66, 28.00, 51.83, 52.87, 57.30, 57.60, 58.23, 59.77, 82.41, 84.29, 108,52, 122.44, 130.50, 132.04, 135.32, 150.67, 151.22, 164.26, 167.27. Anal. Calcd for $C_{24}H_{31}N_2O_8SBr$ (587.48): C 49.07; H 5.32; N 4.77; S 5.46; found C 49.40; H 5.52; N 4.81; S 5.40.

4.1.8. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-3-(benzylamino)-1,2,3,4-tetrahydropyrazine (4d). The same procedure described for the synthesis of compound **4a** was applied substituting benzylamine for 1,2,4-triazole. Removal of the solvent afforded compound **4d** as an enantiomeric mixture of the *trans* diastereomer (82%), mp 106.5–107.5 °C (from diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$) (2 rotamers): 1.42, 1.45, 1.52 (36H, 3s, C*H*$_3$ Boc), 3.70 (6H, s, C*H*$_3$ OMe), 3.80–3.92 (10H, m, C*H*$_3$ OMe + C*H*$_2$ Bn), 4.82, 4.97 (2H, 2s, 2-H or 3-H), 5.60, 5.65 (2H, 2s, 2-H or 3-H), 7.28–7.36 (10H, m, ArH), 7.50, 7.71 (2H, 2s, 6-H); ^{13}C NMR ($CDCl_3$): 27.87, 27.97, 49.47, 51.77, 52.57, 59.27, 60.55, 62.41, 81.58, 84.02, 121.51, 127.25, 128.43, 128.56, 139.17, 150.69, 152.75, 164.99, 167.85, 168.07. Anal. Calcd for $C_{25}H_{35}N_3O_8$ (505.56): C 59.39; H 6.98; N 8.31; found C 59.43; H 7.21; N 8.05.

4.1.9. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-3-methoxy-1,2,3,4-tetrahydropyrazine (4e). The same procedure described for the synthesis of compound **4a** was applied substituting sodium methoxide for 1,2,4-triazole. Removal of the solvent afforded compound **4e** as an enantiomeric mixture of the *trans* diastereomer (35%); oil; ^{1}H NMR ($CDCl_3$) (2 rotamers): 1.43, 1.47, 1.53 (36H, 3s, C*H*$_3$ Boc), 3.40 (6H, s, C*H*$_3$ COMe), 3.70, 3.79 (12H, 2s, C*H*$_3$ COOMe), 4.89, 5.05 (2H, 2s, 2-H or 3-H), 5.79, 5.84 (2H, 2s, 2-H or 3-H), 7.51, 7.72 (2H, 2s, 6-H), ^{13}C NMR ($CDCl_3$): 27.85, 28.01, 51.77, 52.70, 55.26, 58.78, 60.18, 77.96, 82.02, 83.56, 83.91, 107.85, 122.47, 150.81, 167.37; MS: *m*/*z* (%)=430 (8) [M^+], 230 (100) [M^+-2Boc], 199 (21) [M^+-2Boc-OMe]; HRMS found 430.1947, Calcd for $C_{19}H_{30}N_2O_9$ 430.1951.

4.1.10. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,3-dichloro-2,5-bis-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (5). A solution of Et_4NCl (0.1 mol dm^{-3}; supporting electrolyte) and Et_3NHCl (0.04 mol dm^{-3}; proton donor) in MeCN was added to a two compartment, three-electrode cell. Compound **2** (99.5 mg, 0.25 mmol) was added to the anodic compartment and a cyclic voltammogram recorded. The potential was adjusted to a value 50 mV more positive than that corresponding to the CV peak and the electrolysis started, the reaction being monitored by HPLC. When all starting material had disappeared, the content of the anodic compartment was concentrated under reduced pressure and the residue partitioned between 100 cm^3 of ethyl acetate and 50 cm^3 of water. The organic phase was then washed with water and brine (3×30 cm^3 each) and dried over $MgSO_4$. The solution was filtered and the solvent removed to give a residue which was submitted to column chromatography using diethyl ether/*n*-hexane (1:2) as eluent to give compound **5** (106.8 mg, 91%), mp 119.5–121.0 °C (from diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$): 1.49, 1.53 (18H, 2s, C*H*$_3$ Boc), 3.82, 3.88 (6H, 2s, C*H*$_3$ OMe), 6.61 (1H, s, 3-H), 7.56 (1H, s, 6-H); ^{13}C NMR ($CDCl_3$): 27.70, 27.76, 52.24, 54.24, 68,71, 83.93, 85.91, 109.74, 122.00, 126.15, 148.79, 149.05, 163.20, 163.68; MS: *m*/*z* (%)=470 (1) [M^++2], 468 (1.3) [M^+], 368 (2) [M^+-Boc], 268 (57) [M^+-2Boc], 233 (63) [M^+-2Boc-Cl], 197 (100) [M^+-2Boc-2Cl]. HRMS found 468.1082, Calcd for $C_{18}H_{26}N_2O_8Cl_2$ 468.1066.

4.1.11. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (6). The same procedure as described above was followed but adding compound **2** (99.5 mg, 0.25 mmol) to the cathodic compartment to give compound **6** (55.2 mg, 55.2%). ^{1}H NMR ($CDCl_3$): 1.41, 1.52 (18H, 2s, C*H*$_3$ Boc), 2.96–3.08 (1H, m, 3-H), 3.71, 3.78 (6H, s, 2C*H*$_3$ OMe), 4.68–4.90 (2H, m, 2-H + 3-H), 7.53 (1H, s, 6-H); ^{13}C NMR ($CDCl_3$): 27.82, 27.88, 42.27, 51.75, 52.62, 54.70, 55.98, 81.69, 83.58, 83.90, 109.60, 123.01, 150.52, 150.64, 169.00, 169.35; MS: *m*/*z* (%)=400 (4) [M^+], 200 (100) [M^+-2Boc], 167 (11) [M^+-2Boc-OMe], 141 (13) [M^+-2Boc-CO_2Me]; HRMS found 400.1857, Calcd for $C_{18}H_{28}N_2O_8$ 400.1846.

Acknowledgements

We wish to thank the Fundação para a Ciência e a Tecnologia for financial support (project no. POCTI/1999/QUI/32689).

References

1. (a) Jones, K.; Keenan, M.; Hibbert, F. *Synlett* **1996**, 509–510. (b) Cavalier, J.; Marchand, C.; Rees, J.; Marchand-Brynaert, J. *Synthesis* **2001**, 768–772.
2. Lotowski, Z.; Gryszkiewiez, A.; Borowiecka, J. B.; Nikitiuk, A.; Morzycki, J. W. *J. Chem. Res., (S)* **1999**, 662–663.
3. Vazquez, J.; González, J. J. L.; Márquez, F.; Pongor, G.; Boogs, J. E. *J. Phys. Chem., A* **2000**, *104*, 2599–2612.
4. (a) Fourrey, J. L.; Beauhaire, J.; Yuan, C. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1841–1843. (b) Shu, C. *J. Agric. Food Chem.* **1999**, *47*, 4332–4335.
5. (a) Brook, D. J. R.; Haltiwanger, R. C.; Koch, T. H. *J. Am. Chem. Soc.* **1992**, *6017*, 6023. (b) Brook, D. J. R.; Noll, B. C.; Koch, T. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 289–292.
6. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett.* **1998**, *39*, 9575–9578.
7. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3167–3173.
8. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Eur. J. Org. Chem.* **2003**, *14*, 2635–2644.
9. Abraham, R. J.; Reid, M. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1081–1091.
10. Kain, W. *J. Am. Chem. Soc.* **1983**, *105*, 707–713.

11. Baumgarten, J.; Bessenbacher, C.; Kaim, W.; Stahl, T. *J. Am. Chem. Soc.* **1989**, *111*, 2126–2131.
12. Mubarak, M. S.; Peters, D. G. *J. Electroanal. Chem.* **2001**, *507*, 110–117.
13. Ragnarsson, U.; Grehn, L.; Maia, H. L. S.; Monteiro, L. S. *Org. Lett.* **2001**, *3*, 2021–2023.
14. Seitz, L. E.; Sulling, W. J.; Reynolds, R. C. *J. Med. Chem.* **2002**, *45*, 5604–5606.
15. Yamaguchi, T.; Eto, M.; Harano, K.; Kashibe, N.; Watanabe, K.; Ito, S. *Tetrahedron* **1999**, *55*, 675–686.
16. (a) Rossen, K.; Pye, P. J.; DiMichele, L. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 6823–6826. (b) Rossen, K.; Weissman, S. A.; Sager, J.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 6419–6422.