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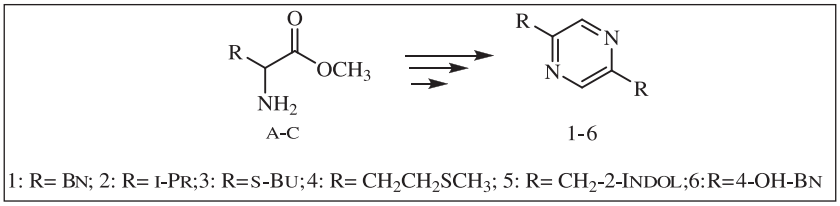

Through the self-condensation of α-amino aldehydes, the synthesis of symmetrical disubstituted pyrazines was achieved in a three-step one-pot reaction. The α-amino aldehydes were easily obtained by treating methyl esters of natural α-amino acids with diisobutylaluminium hydride.

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INTRODUCTION

Pyrazines are essential components for the flavor and odor of foods and some wines such as Cabernet Sauvignon [1–3] as well as the pheromones of some insect species [4]. In medicinal chemistry, pyrazines are important intermediates [5].

In nature, pyrazines are enzymatically produced through amino acids, and they are common units of a great variety of natural marine products with cytotoxic and antitumor properties [6–8]. In the production of potassium Clavulanate, an important β-lactamases inhibitor is necessary to account for standards of some pyrazines to determine and prove the purity level of the pharmaceutical drug; as a consequence, the synthesis of these heterocycles, therefore, is required [9].

There are several methods for the synthesis of pyrazines in the laboratory, such as the condensation of 1,2-diamines with vicinal dicarbonyl compounds followed by oxidation [10,11a,b] and the condensation of α-amino carbonyls [12,13]. The main problem with those methods consists in the necessary chemical steps to obtain the starting materials and mainly α-amino aldehydes [14].

It is well known that the diisobutylaluminium hydride (DIBAL-H) is a very good reducing agent to transform all kinds of carbonyl groups to the corresponding alcohol, but at low temperatures, however, esters are cleanly reduced to the corresponding aldehydes used for our transformation [15].

RESULTS AND DISCUSSION

Herein, we are reporting a straightforward method to obtain α-amino aldehydes by the DIBAL-H reduction of α-amino methyl esters from natural α-amino acids [16]. The reduction occurred very rapidly, and several products were observed by TLC. Because the formation of pyrazines was our goal, the reaction mixture was worked-up as indicated in the experimental; however, when an oxidation agent as oxone was added, the reaction mixture was cleaner and easier to work up to produce pyrazines [15b] (Scheme 1).

Although we attempted to isolate the formed α-amino aldehyde precursors, the auto condensation occurs spontaneously, leading to dehydropyrazines undergoing consequent oxidation to the corresponding pyrazines **1–6** (Fig. 1).

The three-step one-pot reaction yielded about 50% overall yield. In Table 1, we present the yield and the physical properties.

The structures were easily characterized by ^{1}H NMR, ^{13}C NMR, as well as mass spectrometry. As an example, the 2,5-dibenzylpyrazine **1** shows the signal for the aromatic protons of the heterocycle in ^{1}H NMR at 8.38 ppm and the signals for carbons 3,6 and carbons 2,5 in ^{13}C NMR at 142.8 and 153.6 ppm, respectively. All other pyrazines give very similar spectra as shown in Table 2.

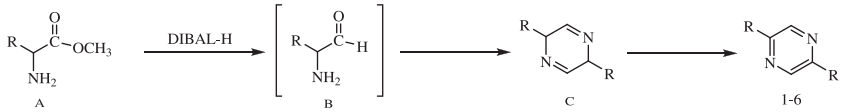
CONCLUSIONS

We are presenting a short and easy method for the synthesis of symmetrical disubstituted pyrazines. The three-step one-pot reaction gave more than 50% overall yield, which represents an average of 80% yield for each step. This method can be applied to almost any α-amino ester.

EXPERIMENTAL

General. All reagents were obtained from commercial sources. Silica gel plates (0.25 mm, $60F_{254}$) were used for analytical TLC. Chromatographic purifications were performed using silica gel (60 μm, 40–63 mesh) according to the method of Still [17]. Yields are reported for isolated compounds. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Varian UNITY

Scheme 1



1: R= Bn; 2: R= i-Pr; 3: R=s-Bu; 4: R= $CH_2CH_2SCH_3$; 5: R= CH_2-2-Indol; 6: R= 4-OH-Bn

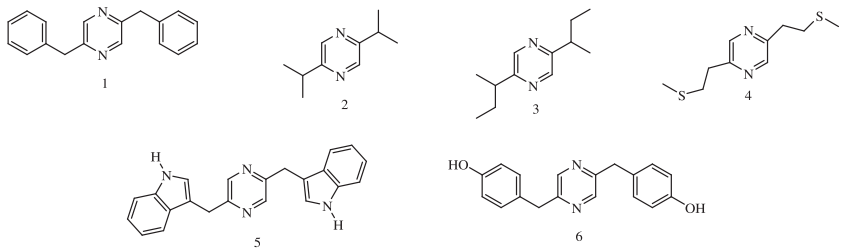


Figure 1. Chemical structures of pyrazines.

Table 1

Synthesis of symmetrical disubstituted pyrazines (Scheme 1).

Compound	Yield (%)	Features
2,5-Dibenzylpyrazine **1**	53	Colorleess solid mp 51–52°C
2,5-Diisopropylpyrazine **2**	52	Yellow oil
2,5-Di-sec-butylpyrazine **3**	53	Yellow oil
2,5-Bis(2-(methylthio)ethyl) pyrazine **4**	50	Yellow oil
2,5-Bis((1*H*-indol-3-yl)methyl) pyrazine **5**	50	Reddish solid mp 160–162°C
2,5-Bis(4-hydroxybenzyl)pyrazine **6**	49	White solid mp 210–212°C

Table 2

^{1}H NMR and ^{13}C NMR data for pyrazines (ppm).

Compound	^{1}H NMR CH	^{13}C NMR CH	^{13}C NMR quaternary
2,5-Dibenzylpyrazine **1**	8.38	142.8	153.6
2,5-Diisopropylpyrazine **2**	8.39	141.8	159.3
2,5-Di-sec-butylpyrazine **3**	8.37	142.8	158.6
2,5-Bis(2-(methylthio) ethyl)pyrazine **4**	8.42	144.0	153.3
2,5-Bis((1*H*-indol-3-yl) methyl)pyrazine **5**	8.45	143.0	153.8
2,5-Bis(4-hydroxybenzyl) pyrazine **6**	8.36	143.3	154.0

INOVA 300 MHz spectrometer in a solution of $CDCl_3$, DMSO-d_6, and CD_3OD. Chemical shifts are reported in parts per million (ppm δ), relative internal Me_4Si (δ 0.00) for ^{1}H, and internal chloroform (δ 77.0) and DMSO (δ 39.5) for ^{13}C; coupling constants are reported in Hertz (Hz). Mass spectra were obtained on a Thermo-Electron spectrometer. Elemental analysis was obtained on a Perkin Elmer PE2400 instrument.

General procedure for the synthesis of 2,5-bis disubstituted pyrazines (1–6). The α-amino acid methyl ester (0.1 g, 0.6 mmol) and toluene (10 mL) were added to a three-neck flask under nitrogen atmosphere and a magnetic stirring bar. The solution was cooled to −78°C, and then, a 1.5 M solution of DIBAL-H in toluene (6 mmol) was added. When the reaction was completed (2 h), the reaction mixture was treated with a mixture of AcOEt/H_2O (9:1) 10 mL and stirred for an additional 1 h at room temperature. The suspension was filtered through celite, and the solution was washed with a saturated aqueous solution of NaCl (2 × 5 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography.

2,5-Dibenzylpyrazine (1). This compound was obtained from phenylalanine methyl ester as a colorless solid; 0.038 g (53%), mp 51–52°C; ^{1}H NMR (deuteriochloroform): δ 4.12 (s, 4H, CH_2), 7.21–7.33 (m, 10H, phenyl), 8.38 (s, 2H pyrazine); ^{13}C NMR (deuteriochloroform): 41.5 (CH_2), 126.7, 128.7, 129.0, 138.3 (CH and C phenyl), 143.7 (CH, pyrazine), 153.6 (C, pyrazine); ms: *m/z* 260 (55), 259 (100), 115 (35), 91 (23), 65 (8). *Anal*. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 82.87; H, 6.16; N, 10.80.

2,5-Diisopropylpyrazine (2). This compound was obtained from valine methyl ester as an oil; 0.032 g (52%),^{1}H NMR (deuteriochloroform): δ 1.32 (d, 12H, CH_3, J = 6 Hz), 3.08 (sep, 2H, CH, J = 6.9 Hz), 8.39 (s, 2H, pyrazine); ^{13}C NMR (deuteriochloroform): 22.2 (CH_3), 33.5 (CH), 141.8 (CH, pyrazine), 159.3 (C, pyrazine); ms: *m/z* 164 (30), 149 (100), 136 (35).

2,5-Di-sec-butylpyrazine (3). This compound was obtained from isoleucine methyl ester as an oil; 0.035 g (50%),^{1}H NMR (deuteriochloroform): δ 0.85 (t, 6H, CH_3, J = 7.4 Hz), 1.31 (d, 6H, CH_3, J = 6.9 Hz), 1.82 and 1.61 (m, 4H, CH_2), 2.8 (sex, 2H, CH, J = 6.9 Hz), 8.37 (s, 2H, pyrazine); ^{13}C NMR (deuteriochloroform): 12.1 (CH3), 20.0 (CH_3), 29.7 (CH_2), 40.7 (CH), 142.8 (CH, pyrazine), 158.6 (C, pyrazine); HRMS (esi: *m/z*) Calcd for $C_{12}H_{20}N_2$ 192.1621. Found: 192.1526.

2,5-Bis(2-(methylthio)ethyl))pyrazine (4). This compound was obtained from methionine methyl ester as an oil; 0.035 g (50%),^{1}H NMR (deuteriochloroform): δ 2.13 (s, 6H, CH_3), 2.91

(t, 4H, CH_2, $J = 6.0$ Hz), 3.08 (t, 4H, CH_2, $J = 6.0$ Hz), 8.42 (s, 2H, pyrazine); ^{13}C NMR (deuteriochloroform): 15.7 (CH_3), 33.6 (CH_2), 34.9 (CH_2), 144.0 (CH, pyrazine), 153.3 (C, pyrazine). HRMS (esi: *m*/*z*) Calcd for $C_{10}H_{16}N_2S_2$ 228.0749. Found: 228.0735.

***2,5-Bis((1H*-indol-3-yl)methyl)pyrazine (5**). This compound was obtained from tryptophan methyl ester as a reddish solid; 0.038 g (50%), mp 160–162°C; ^1H NMR (DMSO-d_6) 4.16 (s, 4H, CH_2), 7.46–6.89 (m, 10H, indole), 8.45 (s, 2H, pyrazine), 10.90 (s, 4H, NH-indole); ^{13}C NMR (DMSO-d_6) 30.9 (CH_2), 136.3–111.5 (indole), 143.0 (CH, pyrazine), 153.8 (C, pyrazine); HRMS (esi: *m*/*z*) Calcd for $C_{22}H_{18}N_4$ 338.1526. Found: 338.1512.

2,5-Bis(4-hydroxybenzyl)pyrazine (6). This compound was obtained from tyrosine methyl ester as a white solid; 0.036 g (49%), mp 210–210°C; ^1H NMR (CD_3OD): δ 4.03 (s, 4H, CH_2), 7.06 (d, 4H, phenyl, $J = 8.7$ Hz), 6.71 (d, 4H, phenyl, $J = 8.7$), 8.36 (s, 2H, pyrazine); ^{13}C NMR (DMSO-d_6) 39.6 (CH_2), 129.9, 115.4 (CH, phenyl), 129.2 (C, phenyl), 143.3 (CH, pyrazine), 154.0 (C, pyrazine), 155.9 (C, phenyl); ms: *m*/*z* 292 (100), 294 (2), 293 (20), 291 (95), 131 (12), 107 (29), 77 (2); HRMS (esi: *m*/*z*) Calcd for $C_{18}H_{16}O_2N_2$ 292.1206. Found: 292.1198.

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