Synthesis of *Meso*-tetra Acid and Ester Functionalized Calix[4]pyrroles

Ahmet Akar* and Abdullah Aydogan

Istanbul Technical University
Faculty of Science and Letters, Chemistry Department
Maslak 34469, Istanbul-Turkey
akara@itu.edu.tr

Received May 20, 2004

Novel *meso*-tetracarboxylic acid and *meso*-tetraester functionalized calix[4]pyrroles were synthesized by condensation of pyrrole with levulinic acid and ethyl pyruvate in sufficient yields. In addition, mixed condensation products can also be synthesized using this method . These new compounds may be useful as molecular receptors and polyfunctional starting materials for further derivatization.

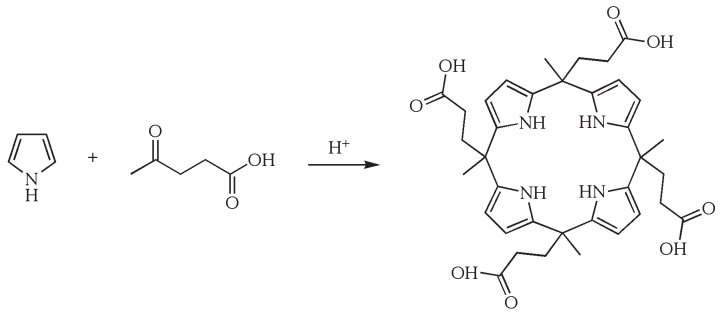
J. Heterocyclic Chem., **42**, 931 (2005).

Introduction.

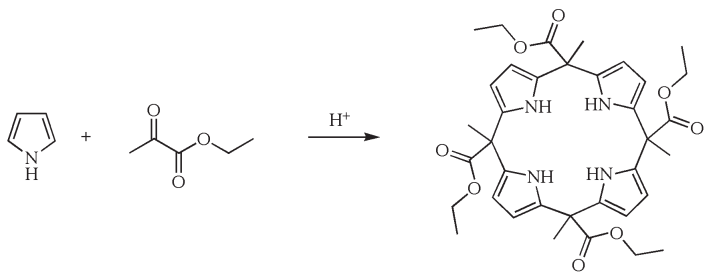
Calix[4]pyrroles are macrocyclic species that are composed of four pyrrole rings linked in the α-positions *via* sp^3-hybridized carbon atoms. These molecules were first synthesized by Baeyer in 1886 [1] and have recently gained much atttention. Several synthetic methodologies have been developed by a number of research groups [2a-d]. Single crystal studies of calix[4]pyrrole have been carried out [3a-b,4] in order to elucidate their molecular composition. As a result of these studies calix[4]pyrroles were found to adopt a 1,3-alternate conformation in the solid state and changes to a cone conformation on binding to an anion. Sessler and co-workers [4] has extensively studied the anion binding property of *meso*-octamethylcalix[4]pyrrole in solution and in the solid state. Calix[4]pyrrole chemistry has now emerged as one of the key areas in the field of molecular recognition as a result of this potential applications [5].

Several types of substituted calix[4]pyrroles have been synthesized to improve their anion binding properties [3c,5,6,7]. In this junction, calix[4]pyrrole based optical sensors [8], solid-phase HPLC supports for the seperation of anions [9] were produced. Modified calix[4]pyrroles [10] were also synthesized and their anion binding properties studied.

Scheme 1



(**1**)



(**2**)

Therefore, the synthesis of functionalized calix[4]-pyrroles is very important in order to develop new anion receptors and selective sensors. With this aim, we studied the reaction of pyrrole with levulinic acid and ethyl pyruvate to obtain carboxylic acid and ester functionalized calix[4]pyrroles. Mixed condensation reactions of pyrrole and acetone with levulinic acid and ethyl pyruvate were also studied.

Results and Discussion.

Meso-tetra carboxylic acid and ester functionalized calix[4]pyrrole compounds (**1** and **2**) were synthesized in sufficient yield during the condensation reactions. The structure of compound **1** and **2** were confirmed from their FTIR, NMR and Mass spectra .

The FTIR spectrum of the compound **1** showed a broad peak at about 2667 cm^{-1} and a sharp peak at 1707 cm^{-1} due to carboxylic acid groups and at 3371 cm^{-1} due to N-H groups. The ^{1}H-NMR spectrum of compound **1** showed a broad singlet of N-H protons at δ=8.81 ppm and a singlet C-H protons of pyrrole rings at δ=5.69 ppm . The COOH protons at δ=11.21 ppm, The CH_2 protons at δ=2.72 and 2.49 ppm are observed as triplets and the CH_3 protons at δ=1.51 ppm as a broad peak. The FAB-MS spectrum of compound **1** showed an ion of *m/z* 660 corresponding to the M^+.

The FTIR spectrum of compound **2** showed a peak at 1724 cm^{-1} due to the ester groups and at 3439 cm^{-1} due to N-H groups. In the ^{1}H-NMR spectrum of the compound **2** a broad peak corresponding to the N-H protons at δ=8.72 ppm and a singlet at δ=5.82 ppm due to the C-H protons of the pyrrole rings are observed. Protons of ethyl groups appeared as a quartet at δ=4.12 ppm due to CH_2 protons and as a triplet at δ=1.18 ppm due to CH_3 protons. A singlet at δ=1.80 ppm is due to CH_3 protons. The FAB-MS spectrum of compound **2** showed an ion of *m/z* 661 corresponding to MH^+. The structure of **2** is also supported by an Hetcor NMR spectrum (Figure 1).

The mixture of levulinic acid and acetone with the ratio of 1:1 is used for the mixed condenzation rection in which compound **3** is produced. In the NMR spectrum of the compound **3**, a broad peak corresponding to the N-H protons at δ= 7.88 ppm and C-H protons corresponding to the pyrrole rings at δ=5.85 ppm are observed. Similar to the structure of **1**, carboxyl protons are observed at δ=11.17 ppm, CH_2 protons at δ=2.78 ppm and 2.54 ppm as triplets and a broad resonance corresponding to the CH_3 protons at δ=1.51 ppm. These peaks show the 1,3-fuctionalized structure of the compound **3**.

When an ethyl pyruvate and acetone mixture with 1:1 ratio is used for the mixed condenzation reaction, the compound containing 1:1 ethyl pyruvate and acetone moieties **4** was produced. In the NMR spectrum of compound **4**, a broad singlet corresponding to the N-H protons at δ=7.49 ppm and C-H protons of pyrrole rings at δ=5.90 ppm is observed. Triplet CH_3 resonances at δ=1.25 ppm and quartet CH_2 resonances at δ=4.18 showed the ester moieties. The proton ratios are appopriate for the 1,3-functionalized calix[4]pyrrole system of compounds **3** and **4**

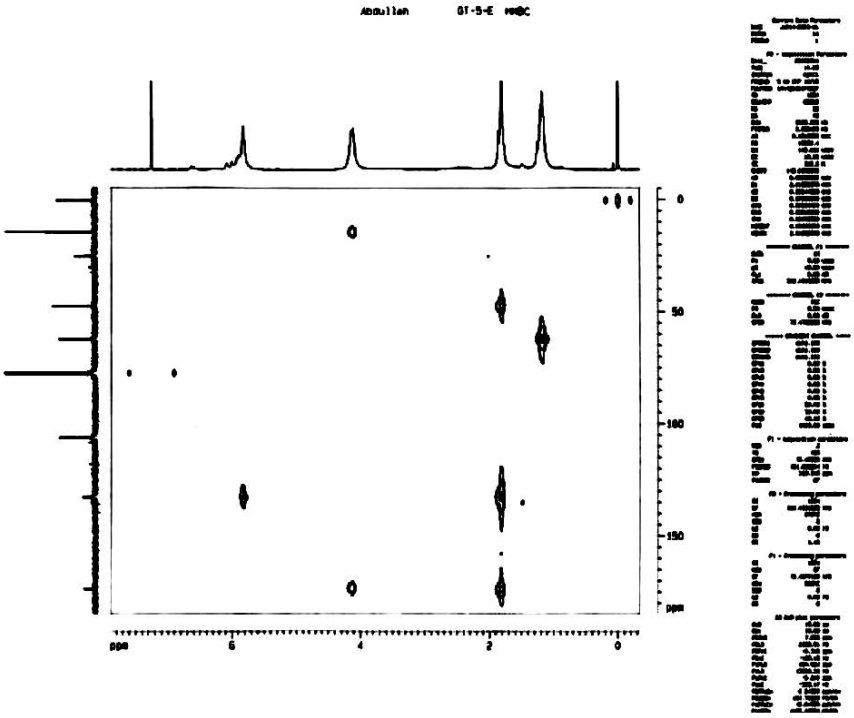
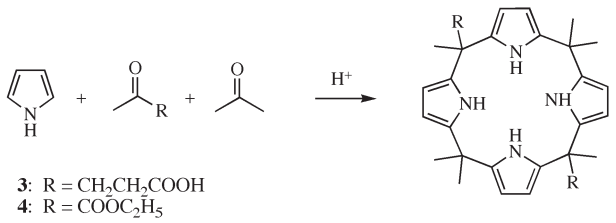


Figure 1. Hetcor NMR spectrum of the compound **2**.

Scheme 2



3: R = CH_2CH_2COOH
4: R = $COOC_2H_5$

EXPERIMENTAL

General.

FTIR spectra were recorded on a Jasco FT-IR-5300 FT-IR spectrometer (KBr). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 250 MHz AC-3000 spectrometer using TMS as an internal standard. FAB-MS were recorded on VG Zabsec MS instrument, HRMS were recorded on ZAB-E4F MS instrument. Pyrrole and solvents were purified by distillation according to literature prior to use, other reagents were used without purification as purchased. Yields refer to isolated pure products.

Synthesis of the compound (**1**).

Levulinic acid (1.68 g, 14.5 mmol) and pyrrole (0.97 g, 14.5 mmol) were dissolved in dry CH_2Cl_2 (25 ml), and cooled to 0 °C. The mixture bubbled with N_2 for 10 min, HCl (37%, 0.2 ml) was added dropwise over the mixture in ten minutes under nitrogen atmosphere. The mixture was stirred at 0 °C for 2 h and then room temperature overnight. After overnight, the solvent was removed and the crude product, which was dissolved in ethyl acetate, was washed with water (100 ml) three times and dried with Na_2SO_4. After removing the solvent FAB mass spectra showed the presence of compound **1**. Chromatographic purification (silica gel, chloroform/methanol: 1/1) yielded **1** as a yellow solid (1.44 g, 60%). Mp: Decomposes over 200 °C. IR (KBr disc): ν 3371, 3105, 2974, 2667, 1707, 1577, 1367, 1035. ^{1}H-NMR (250 MHz, Acetone-d_6): δ 11.21(br, 4H, COOH), 8.81 (br, 4H, NH), 5.69 (br, 8H, pyrrole CH), 2.72 (t, J=6 Hz, 8H, CH_2), 2.49 (t, J=6 Hz, 8H, CH_2), 1.51 (br, 12H, CH_3). ^{13}C-NMR (250 MHz, Acetone-d_6): δ 18.25, 30.22, 30.69, 51.46, 95.6, 128.7, 166.11. FAB MS (m/z): 660 (M^+). HRMS (m/z): calculated for $C_{36}H_{44}N_4O_8$: 660.3159; found 660.3120.

Anal. Calcd. for $C_{36}H_{44}N_4O_8$: C 65.44, H 6.71, N 8.48. Found: C 64.98, H 6.65, N 8.27.

Synthesis of the Compound (**2**).

A mixture of pyrrole (0.97 g, 14.5 mmol) and ethyl pyruvate (1.68 g, 14.5 mmol) were dissolved in dry CH_2Cl_2 (25 ml) and cooled to 0 °C. The mixture bubbled with N_2 for 10 min, HCl (37%, 0.2 ml) was added dropwise over the mixture in ten minutes under nitrogen atmosphere. After adding the catalyst, the reaction mixture was stirred at 0 °C for 2 h and then room temperature overnight. After the reaction, the mixture was washed with water (100 ml) three times and dried with Na_2SO_4. After removing the solvent FAB mass spectra showed the presence of the tetra cyclic product (**2**) of the condensation reaction. Chromatographic purification (Ethyl alcohol/hexane: 1.5/1) yielded (1.92 g, 80%) **2** as a yellow solid powder crystals. Mp: Decomposes over 196°C. IR (KBr disc): ν 3439, 3108, 2984, 1724, 1570, 1375, 1197. ^{1}H-NMR (250 MHz, Chloroform-d): δ 8.72 (br, s, 4H, NH), 5.82 (br, s, 8H, pyrrole CH), 4.12 (q, J=7 Hz, 8H, ester CH_2), 1.80 (br, s, 12H, CH_3), 1.18 (t, J=7 Hz, 12H, ester CH_3). ^{13}C-NMR (250 MHz, Chloroform-d) δ 13.96, 24.8, 47.1, 61.8, 105.9, 132.3, 173.4, FAB MS (m/z): 661 (MH^+). HRMS (m/z): calculated for $C_{36}H_{44}N_4O_8$: 660.3159; found 660.3165.

Anal. Calcd. for $C_{36}H_{44}N_4O_8$: C 65.44, H 6.71, N 8.48. Found: C 65.15, H 6.78, N 8.18.

Synthesis of Mixed Condensation Products (**3** and **4**).

General procedure for synthesis of the mixed condensation products is: A mixture of pyrrole (0.97 g, 14.5 mmol), levulinic acid (for **3**) or ethyl pyruvate (for **4**) (0.84 g, 7.25 mmol) and acetone (0.42 g, 7.25 mmol) were dissolved in an appropriate dry solvent [11] then the solution bubbled for 10 min with N_2 and cooled to 0 °C. HCl (37%, 0.2 ml) was added dropwise over the mixture in ten minutes under nitrogen atmosphere. After overnight, precipitates [12] were filtered and then solvent was removed. Crude product was dissolved in EtOAc, washed with water (100 ml) three times, dried with Na_2SO_4 and purified with column chromatography [13].

Compound (**3**).

This compound was obtained as a yellow powder with yield 0.95 g (48%). Mp: decomposes over 215 °C; IR (KBr disc): ν 3109, 2978,1706, 1570, 1380, 1032; ^{1}H-NMR (250 MHz, Chloroform-d): δ 11.17(br, 2H, acid -OH), 7.88 (br, s, 4H, NH), 5.85 (br, m, 8H, pyrrole CH), 2.78 (t, J=6 Hz, 4H, acid CH_2), 2.54 (t, J=6 Hz, 4H, acid CH_2),1.82 (6H, CH_3), 1.54 (br, 12H, CH_3); ^{13}C-NMR (250 MHz, Chloroform-d): δ 29.28, 30.11, 31,42, 42.7, 46.03, 46.12, 104.76, 106.23, 130.20, 133,17, 176.48; FAB MS (m/z): 544 (M^+); HRMS (m/z): calculated for $C_{32}H_{40}N_4O_4$: 544.3049, found 544.3075.

Anal. Calcd. for $C_{32}H_{40}N_4O_4$: C 70.56, H 7.40, N 10.29. Found: C 70.68, H 7.30, N 10.38.

The Compound (**4**).

This compound was obtained as a white powder with yield 1.08 g (55%). Mp: 183-184°C; IR (KBr disc): ν 3443, 2972,1725, 1577, 1413, 1232; ^{1}H-NMR (250 MHz, Chloroform-d): δ 7.49 (br, s, 4H, NH), 5.90 (m, 8H, pyrrole CH), 4.18 (q, J=7 Hz, 4H, ester CH_2), 1.74 (s, 6H, CH_3), 1.49 (s, 12H, CH_3), 1.25 (t, J=7, 6H, ester CH_3), ^{13}C-NMR (250 MHz, Chloroform-d): δ 14.09, 24.31, 29.21, 35.33, 47.28, 61.57, 103.27, 150.4, 131.92, 139.01, 172.94; FAB MS (m/z): 544 (M^+), HRMS (m/z): calculated for $C_{32}H_{40}N_4O_4$: 544.3049, found 544.3017.

Anal. Calcd. for $C_{32}H_{40}N_4O_4$: C 70.56, H 7.40, N 10.29. Found: C 70.38, H 7.55, N 10.02.

Acknowledgement.

We thank Prof. Dr. E. Kleinpeter (Universität Potsdam, Germany) for recording Cosy and Hetcor NMRs.

REFERENCES AND NOTES

[1] A. Baeyer, *Ber. Dtsch. Chem. Ges.*, **19**, 2184 (1886).

[2a] P. Rothemund and J. L. Gage, *J. Am. Chem. Soc.*, **77**, 3340-3342 (1955); [b] M. Dennstedt, *Ber. Dtsch. Chem. Ges*., **23**, 1370 (1890);

[c] M. Dennstedt, Zimmermann, *J. Chem. Ber.*, **20**, 850 (1887); [d] W. H. Brown, B. J. Hutchinson and M. H. MacKinnon, *Can. J. Chem.*, **49**, 4017 (1971).

[3a] D. Jacoby, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Chem. Soc., Chem. Commun.*, 790 (1991); [b] P. A. Gale, J. L. Sessler and V. Král, *Chem. Commun.*, 1 (1998).

[4] P. A. Gale, J. L. Sessler, V. Král and V. Lynch, *J. Am. Chem. Soc.*, **118**, 5140 (1996).

[5] C. J. Woods, S. Camiolo,M. E. Light, S. J. Coles, M. B. Hursthouse, M. A. King, P. A. Gale and J. W. Essex, *J. Am. Chem. Soc*., **124**, 8644 (2002).

[6] D. Yoon, H. Hwang and C. Lee, *Angew. Chem. Int. Ed*., **41**, 1757 (2002).

[7] P. A. Gale, P. Anzenbacher and J. L. Sessler, *Coordination Chem. Rev*., 57 (2001).

[8] H. Miyaji, P. Anzenbacher, J. L. Sessler, E. R. Bleasdale and P. A. Gale, *Chem. Commun*., 1723 (1999).

[9] J. L. Sessler, P. A. Gale and J. W. Genge, *Chem. Eur. J.*, **4**, 1095 (1998).

[10] J. L. Sessler, P. Anzenbacher, H. Miyaji, K. Jursíková, E. R. Bleasdale and P. A. Gale, *Ind. Eng. Chem. Res.*, **39**, 3471 (2002).

[11] CH_2Cl_2, CCl_4 for levulinic acid, MeOH for ethyl pyruvate.

[12] In the reaction with levulinic acid: there is no precipitate with CH_2Cl_2 and CCl_4, with ethyl pyruvate: precipitate is the desired product.

[13] Eluent with levulinic acid: $CHCl_3$/MeOH (1/1).