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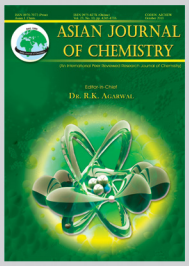

NOTE

Synthesis of L-Phenylalanine Ester Derivatives of *p-tert*-butylcalix[8]arene

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Synthetic routes were developed to link L-phenylalanine ester at the lower rim of *p-tert*-butylcalix[8]arene. Amide-type halides (**2a-c**) were synthesized by chloroacetic chloride and L-phenylalanine ester hydrochloride (**1a-c**), then reacted with *p-tert*-butylcalix[8]arene to produce L-phenylalanine ester derivatives of *p-tert*-butylcalix[8]arene (**4a-c**). The structure of the new compouds were characterized by IR and ^{1}H NMR spectra.

Key Words: L-phenylalanine ester derivatives of *p-tert*-butylcalix[8]arene, Synthesize, Characterization.

Calix[n]arenes were known as the third generation of supramolecular host compounds after cyclodextrins and crown ethers, which can be modified by introducing many kinds of functional groups at the lower rim or the upper rim. Along with the rapid development of chirality science, the preparation of optically active chiral calixarene is becoming increasingly important for research in chemistry and biochemistry. Calixarene have no chirality, some optical activity groups can be introduced into the lower rim or the upper rim of calixarene to get chirality. The chiral calix[4]arenes have attracted the attention of several research groups[1-5].

Interests for these macrocycles like chiral calix[6]arene have been studied[6,7], but relatively little attention has been paid to the synthesis of chiral calix[8]arene. It is still a primary task for chemists to enlarge the family member of chiral calix[8]arene derivatives with functional varieties.

The present work shows our efforts on optically active chiral calix[8]arene, synthetic routes were developed to link L-phenylalanine ester at the lower rim of *p-tert*-butylcalix-[8]arene to produce L-phenylalanine ester derivatives of *p-tert*-butylcalix[8]arene (**Scheme-II**). The structure of the new compouds were characterized by IR, ^{1}H NMR spectra.

All the chemical reagents used are of analytical pure grade,and methanol, ethanol, propanol were deal with anhydrous operation. *p-tert*-Butylcalix[8]arene was synthesized to the procedure described in the previous study[8]. **1a-c** were synthesized according to the literature procedures[9].

Melting points were recorded on a digital microscope and are uncorrected. IR (KBr) spectra (V cm^{-1}) were obtained on Nicolet AVATAR 370 spectrometer, ^{1}H NMR spectra were taken in DMSO-d_6 on a Varian INOVA-300 NMR spectrometer, using TMS as internal standard. The specific rotations were measured on an Optical Instrument Ltd. WZZ-ZS polarimeter made in Shanghai Jinke.

General procedure

Preparation of intermediates 2a-c: 20 mmol of L-phenylalanine ester hydrochlorides **1a-c** was dissolved by distilled water and adjusted to pH 10 with K_2CO_3, then extracted by CH_2Cl_2. The extract after drying and K_2CO_3 was put into 3 mouth flask, Then 7 mL of CH_2Cl_2 of 2.53 mL (20 mmol) $ClCH_2COCl$ was added by using constant pressure funnel. The mixture was refluxed for 1 h. The mixture after reaction was washed by water and dried over Na_2SO_4 and the residue was purified by silica gel chromatography (EtOAc/petroleum ether) to afford *N*-chloroacetyl phenylalanine ester derivatives **2a-c**.

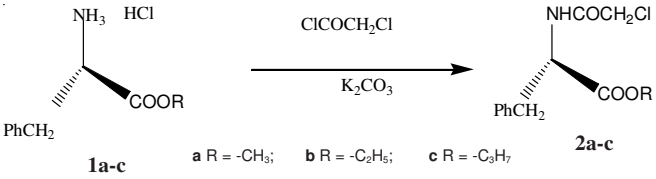
Preparation of intermediates 4a-c: 1 mmol of **3**, 1.25 mmol **2a-c**, 1 mmol of anhydrous K_2CO_3 and 2 mmol of KI in a mixture of 25 mL of anhydrous acetone and 10 mL of toluene were refluxed under the protection of N_2 for 48 h. After removal of solvent, 60 mL chloromform was added to the residue to wash three times, then dried over Na_2SO_4. After remove of chloroform, the crude product was purified by silica gel chromatography (EtOAc/chloromform) to afford the L-phenylalanine ester derivatives of *p-tert*-butylcalix[8]arene **4a-c** (Table-1).

The reaction of L-phenylalanine ester hydrochloride with chloroacetic chloride afforded the useful intermediates **2a-c** (**Scheme-I**) and the reaction was carried out under the system without any water.

TABLE-1
MELTING POINTS AND α OF **2a-c, 4a-c**

Compd.	m.p. [a] /(ºC)	$[\alpha]_D^{20}$
2a	70-72	+ 27.8 (1.87, $CHCl_3$)
2b	67-69	+ 28.4 (1.02, $CHCl_3$)
2c	61-63	+ 29.5 (0.82, $CHCl_3$)
4c	210-212	+ 31.4 (0.51, $CHCl_3$)
4d	204-206	+ 34.8 (0.48, $CHCl_3$)
4e	295-197	+ 37.4 (0.32, $CHCl_3$)

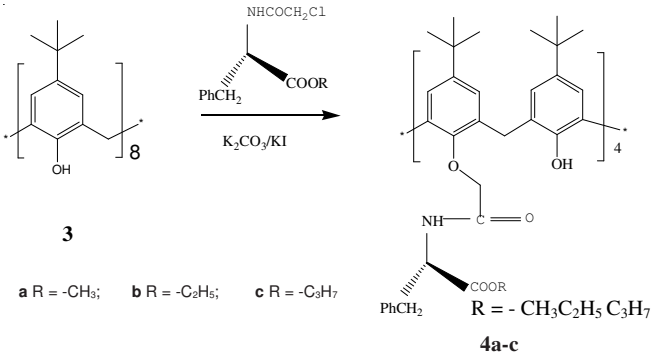
[a] Melting points were recorded on a digital microscope and are uncorrected.



Scheme-I

Preparation of intermediates 4a-c: Intermediates **2a-c** were connected to the lower rim of *p-tert*-butylcalix[8]arene by the reaction of compound **3** with **2a-c** in the presence of anhydrous K_2CO_3 in a mixture of anhydrous acetone and toluene to give the expected products **4a-c** in moderate yields (**Scheme-II**). The presence of KI can accelerate reaction. The reaction was carried out under the protection of N_2, which protect hydroxyl group from oxidation.

The IR spectra of compounds **4a-c** showed absroption at 3430 cm^{-1} (O-H), 3312 cm^{-1} (N-H), 1740 cm^{-1} (C=O in ester), 1672 cm^{-1} (C=O in amide), ^{1}H NMR compounds **4a-c** showed singlets for the methylene resonances (Table-2), but *p-tert*-butylcalix[8]arene **3** showed double peak for the methylene resonances[8], which may mean the conformational inversion after etheration and the systematically studies utilizing these derivatives for the application is conducting.



Scheme-II

Conclusion

The useful intermediate **2a-c** can be easily prepared by the reaction of L-phenylalanine ester hydrochloride with chloroacetic chloride. And attaching of these chiral fragments to the platforms of the lower rim of *p-tert*-butylcalix[8]arene affords a new kind of chiral calix[8]arene dedrivatives. All the structures of the new compouds were characterized by IR and ^{1}H NMR spectra.

TABLE-2
^{1}H NMR SPECTRA OF COMPOUNDS **2a-c, 4a-c**

Compd.	^{1}H NMR, δ, ppm
2a	7.92 (d, *J* = 7.6 Hz 1H, NH), 7.08, 7.11, 7.23 (m, 5H, ArH) 4.71 - 4.82 (m, 1H, CH), 4.17 (s, 2H, CH_2Cl), 3.67 (s, 3H, $COOCH_3$), 3.26 (d, *J* = 12.2 Hz, 2H, CH_2Ar)
2b	7.96 (d, *J* = 7.9 Hz, 1H, NH), 7.08, 7.11, 7.23 (m, 5H, ArH), 4.71 - 4.82 (m, 1H, CH), 4.10 - 4.16 (m, 2H, $COOCH_2CH_3$), 4.18 (s, 2H, CH_2Cl), 3.24 (d, *J* = 11.6 Hz, 2H, CH_2Ar), 1.30 (t, *J* = 14.7 Hz, 3H, $COOCH_2CH_3$)
2c	7.93 (d, *J* = 7.3Hz, 1H, NH), 7.08, 7.11, 7.23 (m, 5H, ArH) 4.71 - 4.82 (m, 1H, CH), 4.18 (s, 2H, CH_2Cl), 4.02 (t, *J* = 7.6 Hz, 2H, $COOCH_2CH_2$), 3.25 (d, *J* = 10.7 Hz, 2H, CH_2Ar), 1.60 (m, 2H, $COOCH_2CH_2$), 0.96 (t, *J* = 13.2 Hz, 3H, $COOCH_2$ CH_2CH_3)
4a	9.04 (d, *J* = 12.3 Hz, 4H, NH), 7.52 (s, 4H, OH), 7.08, 7.11, 7.23 (m, 20H, ArH), 6.84 - 7.05 (m, 16H, ArH), 4.90 (m, 4H, CHMeAr), 4.04 - 4.28 (m, 24H, OCH_2, $ArCH_2Ar$), 3.18 (d, *J* = 13.8 Hz, 8H, CH_2Ar), 3.58 (s, 12H, $COOCH_3$)), 1.09 [s, 72H, $C(CH_3)_3$]
4b	9.04 (d, *J* = 12.3 Hz, 4H, NH), 7.52 (s, 4H, OH), 7.08, 7.11, 7.23 (m, 20H, ArH), 6.84 - 7.05 (m, 16H, ArH), 4.90 (m, 4H, CHMeAr), 4.01 - 4.24 (m, 32H, OCH_2, $ArCH_2Ar$, $COOCH_2CH_3$), 3.17 (d, *J* = 11.6 Hz, 8H, CH_2Ar), 1.24 (t, *J* = 13.9 Hz, 24H, $COOCH_2CH_3$), 1.08 [s, 72H, $C(CH_3)_3$]
4c	9.04 (d, *J* = 12.3 Hz, 4H, NH), 7.52 (s, 4H, OH), 7.08, 7.11, 7.23 (m, 20H, ArH), 6.84 - 7.05 (m, 16H, ArH), 4.90 (m, 4H, CHMeAr), 4.06 - 4.27 (m, 32H, OCH_2, $ArCH_2Ar$, $COOCH_2CH_2$), 3.16 (d, *J* = 10.8 Hz, 8H, CH_2Ar), 1.54 (m, 16H, $COOCH_2CH_2$), 1.07 [s, 72H, $C(CH_3)_3$], 0.95 (t, *J* = 13.2 Hz, 3H, $COOCH_2CH_2CH_3$)

[1] ^{1}H NMR spectra were taken in DMSO-d6, using TMS as internal standard.

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