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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 9077–9081

$Mo(CO)_6$-mediated synthesis of calix[4]arenes carrying β-hydroxy ketones or α,β-unsaturated-β-amino ketones

Annamalai Senthilvelan, Ming-Tsung Tsai, Kai-Chi Chang and Wen-Sheng Chung*

Department of Applied Chemistry, National Chiao-Tung University, Hsinchu 30050, Taiwan, ROC

Received 31 August 2006; revised 6 October 2006; accepted 17 October 2006
Available online 7 November 2006

Abstract—$Mo(CO)_6$-mediated ring opening reactions of calix[4]arene isoxazolines/isoxazoles provide a new synthetic methodology for calix[4]arenes carrying bifunctional β-hydroxy ketones or α,β-unsaturated-β-amino ketones. $Mo(CO)_6$ is a highly selective and convenient reagent for the ring opening process of these supramolecular isoxazolines/isoxazoles.

The interest in calix[4]arene chemistry is rapidly increasing because its derivatives can form inclusion complexes with cations or neutral molecules.[1] The introduction of esters, ketones, amides or β-ketoimine groups to the lower rim of calix[4]arenes have been known and they act as efficient ligands[2] for cationic bindings. In the quest for new fluorogenic sensors for metal ions, we have devised a strategy for attaching isoxazoline or isoxazole units onto the upper or lower rims of calix[4]-arenes[3] using 1,3-dipolar cycloadditions. Such a strategy would provide arrays of calix[4]arenes possessing various bifunctional groups if ring opening reactions on the attached isoxazolines or isoxazoles could be executed successfully. Traditionally, ring opening reactions of such heterocycles have been performed using either metal reducing agents[4,5] or photochemical methods.[6]

In an earlier publication,[7] we reported the Raney Ni-mediated ring opening reaction of a calix[4]arene isoxazoline. Even though the reaction proceeded well, we could not isolate the ring-opened product because it formed a very strong complex with the Ni^{2+} ion, as confirmed by mass spectrometric and IR spectroscopic data.

In continuation of our interest on the $Mo(CO)_6$-mediated ring opening reactions of isoxazolines,[8] we report here the synthesis of calix[4]arenes carrying β-hydroxy ketones or α,β-unsaturated-β-amino ketones by the ring opening reactions of calix[4]arene isoxazolines and isoxazoles. There are several methods known for achieving N–O bond cleavage in an isoxazoline/isoxazole ring, namely, reduction with Raney Ni,[5,9] $LiAlH_4$,[10] H_2/Pd–C,[11] $TiCl_3$,[12] SmI_2,[13] and $Mo(CO)_6$.[14] Among these methods, the $Mo(CO)_6$-mediated ring opening of isoxazolines/isoxazoles appears to be the most efficient one. To the best of our knowledge, the $Mo(CO)_6$-mediated ring opening reactions of calix[4]arene isoxazolines/isoxazoles have not yet been reported previously.

Firstly, we studied the ring opening reactions of lower rim calix[4]arene isoxazolines **1a**–**c**, which were obtained through 1,3-dipolar cycloaddition[7] reaction of 25-allyloxy-26,27,28-trihydroxycalix[4]arene[15] with aryl hydroximoyl chloride in THF using Et_3N as a base. The structures of **1a**–**c** were confirmed spectroscopically. The ^{13}C NMR of **1a**–**c** showing methylene bridge carbons between δ 30 and 32 confirmed that calix[4]arenes **1a**–**c** were in cone conformation. After refluxing a mixture of **1a** with $Mo(CO)_6$ (4 mol equiv) in wet acetonitrile for 48 h, we obtained the expected β-hydroxy ketone **2a** in a 38% yield. In addition to recovered **1a**,[16] we also obtained the cleaved product **3** in a 32% yield. Likewise, $Mo(CO)_6$-mediated ring opening reactions of calix[4]arene isoxazolines **1b**,**c** (Table 1) were successfully carried out to the corresponding β-hydroxy ketones **2b**,**c**.

The structures of compounds **2a**–**c** and **3** were confirmed spectroscopically[17] and compound **3** was compared with the authentic sample. The cone conformation of

Keywords: Calix[4]arene isoxazolines/isoxazoles; Molybdenum hexacarbonyl; β-Hydroxy ketones; α,β-Unsaturated-β-amino ketones.
* Corresponding author. Tel.: +886 35131517; fax: +886 35723764; e-mail: wschung@cc.nctu.edu.tw

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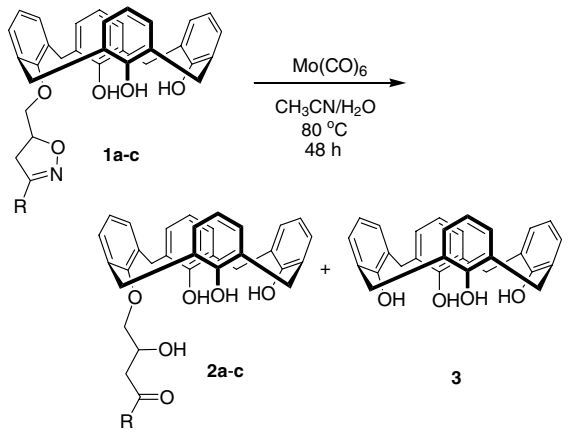
doi:10.1016/j.tetlet.2006.10.082

Table 1. Ring opening reactions of lower rim calix[4]arene isoxazolines **1a–c**



Compound	R	**2** Yield[a] (%)	**3** Yield[a] (%)
1a	5-Methylthien-2-yl	38	32
1b	5-Chlorothien-2-yl	31	17
1c	5-Chlorofuran-2-yl	55	15

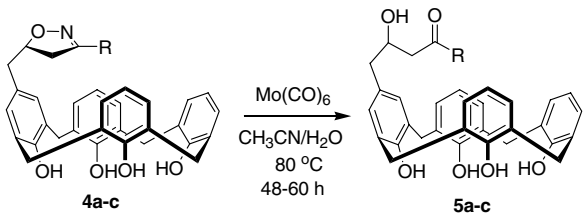
[a] Isolated yields based on recovered starting material.

calix[4]arenes **2a–c** were confirmed by observing the methylene bridge carbons between δ 31 and 32 in ^{13}C NMR spectra. We also confirmed that the calix[4]arene **3** came from the direct cleavage of **1** but not from **2** because the reaction of isolated **2a** with $Mo(CO)_6$ under the same reaction conditions did not lead to the formation of **3**.

Next, we studied the ring opening reactions of upper rim calix[4]arene isoxazolines **4a–c**. Isoxazolines **4a–c** were synthesized by 1,3-dipolar cycloaddition reaction of 5-allylcalix[4]arene[15] with the aryl substituted hydroximoyl chloride in THF by the known method.[7]

The structures of compounds **4a–c** have been confirmed by spectral data, where compound **4a** has already been reported previously.[7] Table 2 summaries the results of ring opening reactions of isoxazolines **4a–c** in the presence of $Mo(CO)_6$ (4 mol equiv) using CH_3CN/H_2O at 80 °C. The expected β-hydroxy ketones **5a–c**, were obtained in modest yields after 48–60 h of reaction. The structures of compounds **5a–c** were confirmed spectroscopically.[18] The appearance of methylene bridge carbons at around δ 31 in the ^{13}C NMR spectra, confirmed that structures of calix[4]arenes **4** and **5** were in cone conformation.

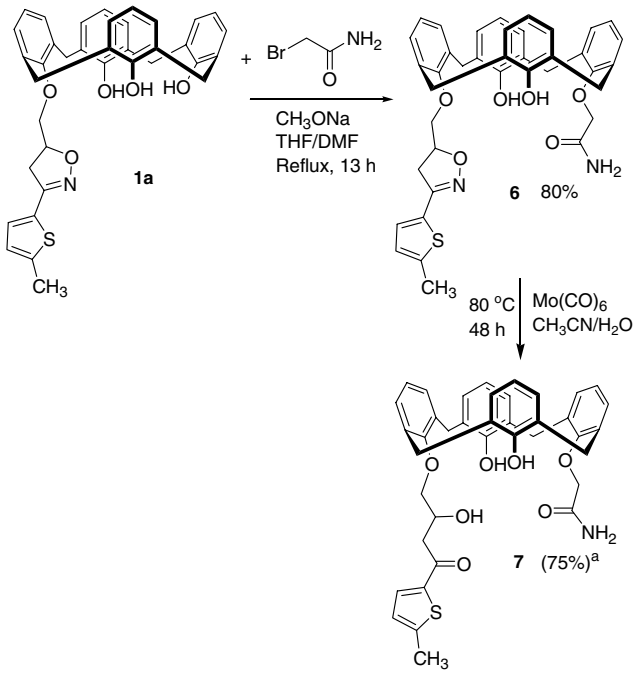
Table 2. Ring opening reactions of upper rim calix[4]arene isoxazolines **4a–c**



Compound	R	**5** Yield (%)
4a	Phenyl	30[a]
4b	5-Methylthien-2-yl	49
4c	5-Chlorofuran-2-yl	32

[a] Isolated yield based on recovered starting material.

Since, the ring opening reactions were successfully carried out at lower and upper rim calix[4]arene isoxazolines, we wondered whether the ring opening reaction of the calix[4]arene isoxazolines would still work in the presence of other functional groups at the lower rim. Hence, we studied the ring opening reaction of amide-substituted calix[4]arene isoxazoline **6**, which was synthesized by the reaction of **1a** with bromoacetamide in the presence of sodium methoxide (or K_2CO_3) using THF/DMF as a solvent (Scheme 1). The structure of compound **6** was confirmed by spectral data (see Supplementary data). The cone conformation of calix[4]arene **6** was confirmed by ^{13}C NMR spectrum, showing the methylene bridge carbons at δ 31.0, 31.4, and 31.7. The reaction of **6** with $Mo(CO)_6$ (3 mol equiv) in a wet acetonitrile at 80 °C for 48 h, gave the expected β-hydroxy ketone **7** (75%) and the recovered **6** (15%). Under the reaction conditions, neither the amide linkage nor the thienoisoxazoline group was cleaved (Scheme 1). The structure of compound **7** was confirmed by spectral data. The ^{13}C NMR spectrum of **7** showing methylene bridge carbons at δ 31.0, 31.3, and 31.6, confirmed that compound **7** was in cone conformation. The amide and the β-hydroxy ketone carbonyls appeared at δ 170.9 and 191.4, respectively (see Supplementary data). It is worth noting that in the ring opening reactions of lower and upper rim calix[4]arene isoxazolines, we did not observe even a trace amount of metal complexation in the ring opened products. This warrants that $Mo(CO)_6$ is a suitable and selective reagent for the ring opening reactions of calix[4]arene isoxazolines.[19]



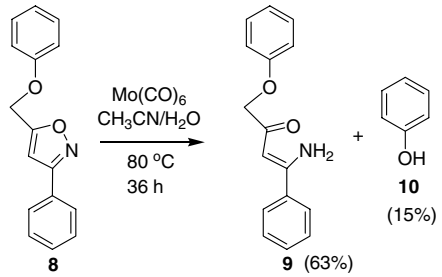
Scheme 1. Ring opening reaction of lower rim amide substituted calix[4]arene isoxazoline **6**. (a) Isolated yield based on recovered starting material.

After successfully performing the ring opening reactions on calix[4]arene isoxazolines, we extended this methodology to calix[4]arene isoxazoles. First, we optimized the ring opening reaction condition for calix[4]arene isoxazoles, by studying the ring opening reaction of isoxazole **8**, obtained by the 1,3-dipolar cycloaddition of propargyloxy benzene with phenyl nitrile oxide, using the reported method.[7] The reaction of isoxazole **8** with $Mo(CO)_6$ (3 mol equiv) in CH_3CN/H_2O for 36 h gave the expected ring opened α,β-unsaturated-β-amino-ketone **9** in a 63% yield (Scheme 2), in addition to cleaved phenol **10** (15% yield). The structure of compounds **8**–**10** were confirmed by spectral data (see Supplementary data). Furthermore, compound **10** was compared with the authentic sample.

Next, we studied the ring opening reaction of calix[4]-arene isoxazoles, using the optimized reaction condition mentioned above. Calix[4]arene isoxazoles **12a**,**b** were synthesized by 1,3-dipolar cycloaddition reaction of 25-propargyloxy-26,27,28-trihydroxycalix[4]arene **11**[20] with the aryl substituted hydroximoyl chloride in toluene using Et_3N as a base (Table 3). The structures of compounds **12a**,**b** were consistent with the spectroscopic data (see Supplementary data). Heating a solution of **12a** with $Mo(CO)_6$ (3 mol equiv) in wet acetonitrile at 80 °C for 36 h furnished the expected isoxazole ring-opened β-amino-α,β-unsaturated ketone **13a** in a 53% yield. Likewise, calix[4]arene isoxazole **12b** with $Mo(CO)_6$ under a similar reaction condition gave the expected β-amino ketone **13b** in a 58% yield (Table 3).[19] In both cases calix[4]arene **3** was also observed, which was confirmed by the authentic sample.

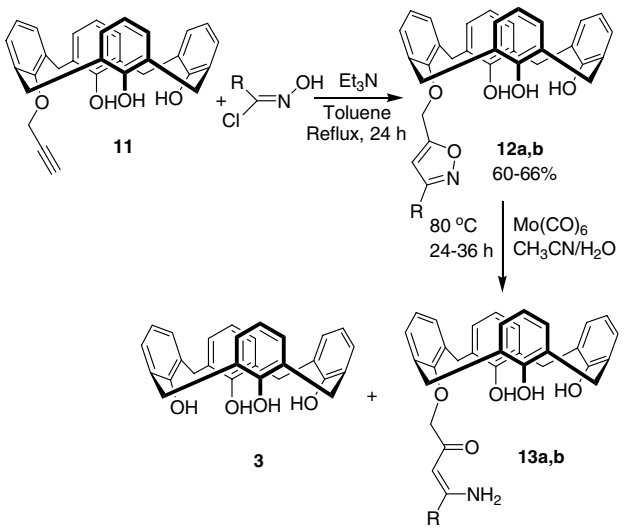
The structures of **13a**,**b** were confirmed by spectral data.[21] The ^1H NMR spectra of compounds **12** and **13** showing AB quartets for methylene bridge protons with coupling constant 13 Hz and the signals between δ 31 and 32 in the ^{13}C spectra were assigned to the methylene bridge carbons, which confirmed the cone conformation of calix[4]arenes **12a**,**b** and **13a**,**b**.

In the ring opening reaction of calix[4]arene isoxazolines or isoxazoles, molybdenum hexacarbonyl selectively assisted the N–O bond cleavage to form a nitrene complex, which underwent hydrolysis in the presence of water to give β-hydroxy ketones or α,β-unsaturated-β-amino ketones, respectively. The formation of nitrene complex in the ring opening reactions of isoxazolines[8,22] or isoxazoles[23] has been already reported.



Scheme 2. Ring opening reaction of 5-(phenoxy methyl)-3-phenyl isoxazole **8**.

Table 3. Ring opening reactions of calix[4]arene isoxazoles **12a**,**b**



Compound	R	**13** Yield (%)	**3** Yield (%)
12a	5-Chlorothien-2-yl	53	16
12b	5-Chlorofuran-2-yl	58	18

In summary, we have reported here a selective and convenient method for the ring opening reactions of calix[4]arene isoxazolines and isoxazoles. We have also successfully demonstrated that the ring opening reaction of calix[4]arene isoxazoline with amide substituent was feasible. This 1,3-dipolar cycloaddition and ring opening protocol provides an efficient method in attaching bifunctional ligands onto the upper and/or lower rims of calix[4]arenes. Further investigations on the ring opening reactions of calix[4]arene bis-isoxazoles and host–guest studies of the multifunctional calix[4]arenes are ongoing in our laboratory.

Acknowledgements

We thank the National Science Council (NSC) and MOE ATU program of the Ministry of Education of Taiwan, ROC for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.082.

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16. The recovery of starting material is commonly observed in the ring-opening reaction of isoxazolines using $Mo(CO)_6$, see: (a) Guarna, A.; Guidi, A.; Goti, A.; Brandi, A.; De Sarlo, F. *Synthesis* **1989**, 175–178; (b) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410–6424.
17. *Procedure for the ring opening reaction of lower rim calix[4]arene isoxazoline* **1a**: An acetonitrile (18 mL) solution of **1a** (0.247 mmol) and molybdenum hexacarbonyl (0.988 mmol) containing water (three drops) was refluxed at 80 °C for 48 h. The solvent was removed under reduced pressure and the residue was purified over silica gel column to give **2a** (38%), **3** (32%) and recovered **1a** (9%).
Spectral data of **1a**: Yellow solid; mp 154–156 °C; $R_f = 0.47$ (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.49 (s, 3H, CH_3), 3.36–3.70 (m, 5H), 4.06–4.46 (m, 7H), 5.27–5.31 (m, 1H), 6.60–7.07 (m, 13H), 7.19 (d, $J = 3.5$ Hz, 1H), 8.68 (s, 1H), 9.03 (s, 1H), 9.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 15.5 (CH_3), 31.0 (CH_2), 31.6 (CH_2), 31.7 (CH_2), 37.3 (CH_2), 76.9 (CH_2), 79.0 (CH), 120.4 (CH), 120.8 (CH), 121.7 (CH), 125.6 (CH), 126.3 (CH), 127.6 (Cq), 127.9 (Cq), 128.0 (Cq), 128.2 (CH), 128.2 (Cq), 128.3 (Cq), 128.3 (CH), 128.6 (CH), 128.6 (Cq), 128.7 (CH), 128.8 (CH), 129.0 (Cq), 129.3 (CH), 129.5 (CH), 129.6 (CH), 133.6 (Cq), 134.1 (Cq), 143.8 (Cq), 148.9 (Cq), 150.5 (Cq), 150.6 (Cq), 151.1 (Cq), 152.7 (Cq); MS (EI) *m*/*z* 603 (M^+, 48), 604 (M^++1, 10), 605 (M^++2, 3), 424 (100), 166 (90); HR MS (FAB) calcd for $C_{37}H_{33}NO_5S$ 603.2079. Found 603.2075.
Spectral data of **2a**: Yellow solid; mp 140–142 °C; $R_f = 0.4$ (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.54 (s, 3H, CH_3), 3.44–3.62 (m, 6H), 4.11–4.53 (m, 6H), 4.85–4.87 (m, 1H), 5.02 (br s, 1H), 6.65–6.72 (m, 3H), 6.84–7.12 (m, 10H), 7.75 (d, $J = 3.7$ Hz, 1H), 9.47 (s, 1H), 9.50 (s, 1H), 9.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 16.1 (CH_3), 31.1 (CH_2), 31.5 (CH_2), 31.8 (CH_2), 31.9 (CH_2), 41.8 (CH_2), 67.4 (CH), 80.5 (CH_2), 121.1 (CH), 121.4 (CH), 122.0 (CH), 126.5 (CH), 127.1 (CH), 127.7 (Cq), 128.2 (Cq), 128.4 (Cq), 128.4 (Cq), 128.5 (CH), 128.6 (CH), 128.8 (CH), 128.9 (Cq), 129.0 (CH), 129.2 (CH), 129.7 (CH), 133.7 (CH), 133.8 (Cq), 134.5 (Cq), 141.8 (Cq), 148.9 (Cq), 150.0 (Cq), 150.5 (Cq), 150.7 (Cq), 150.9 (Cq), 191.0 (Cq); MS (EI) *m*/*z* 588 ($M^+ - H_2O$, 6), 424 (100), 197 (40); HR MS (FAB) calcd for [$M^+ - H_2O$] $C_{37}H_{32}O_5S$ 588.1970; found 588.1993.
18. *Procedure for the ring opening reaction of upper rim calix[4]arene isoxazoline* **4b**: A mixture of **4b** (0.20 mmol) and molybdenum hexacarbonyl (0.802 mmol) in acetonitrile (18 mL) containing water (three drops) was refluxed at 80 °C for 48 h. After removing the solvent, the residue was purified over silica gel column to give the expected β-hydroxy ketone **5b** (49%).
Spectral data of **4b**: Yellow solid, mp 148–150 °C; $R_f = 0.2$ (hexane/EtOAc = 5/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.50 (s, 3H, CH_3), 2.63–2.70 (m, 1H), 2.91–3.01 (m, 2H), 3.19–3.28 (m, 1H), 3.57 (br s, 4H), 4.27 (br s, 4H), 4.82–4.88 (m, 1H), 6.70–6.79 (m, 4H, ArH), 6.93–6.96 (m, 3H, ArH), 7.07–7.10 (m, 6H, ArH), 10.2 (s, 4H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.4 (CH_3), 31.6 (CH_2), 39.9 (CH_2), 40.0 (CH_2), 81.8 (CH), 122.1 (CH), 122.2 (CH), 125.4 (CH), 128.1 (CH), 128.2 (Cq), 128.3 (Cq), 128.5 (Cq), 128.9 (CH), 128.9 (CH), 129.7 (CH), 129.8 (Cq), 130.5 (Cq), 143.3 (Cq), 147.5 (Cq), 148.7 (Cq), 148.7 (Cq), 152.3 (Cq); MS (EI) *m*/*z* (%): 604 (M^++1, 10), 603 (M^+, 40), 466 (45), 437 (100), 124 (50), 91 (50); HR MS (FAB) *m*/*z*: calcd for [$M+H^+$] $C_{37}H_{34}NO_5S$ 604.2157; found 604.2162.
Spectral data of **5b**: Brownish yellow solid, mp 160–162 °C; $R_f = 0.22$ (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.54 (s, 3H, CH_3), 2.61–2.76 (m, 2H), 2.95–3.04 (m, 2H), 3.16 (br s, 1H, OH), 3.48–3.72 (br m, 4H), 4.25–4.32 (br m, 5H), 6.72–6.82 (m, 4H, ArH), 6.95 (s, 2H, ArH), 7.06–7.14 (m, 6H, ArH), 7.47 (d, $J = 3.7$ Hz, 1H, ArH), 10.21 (s, 4H, OH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 16.1 (CH_3), 31.6 (CH_2), 31.7 (CH_2), 42.2 (CH_2), 44.1 (CH_2), 69.1 (CH), 122.3 (CH), 126.8 (CH), 128.2 (Cq), 128.2 (Cq), 128.3 (Cq), 128.9 (CH), 129.9 (CH), 131.5 (Cq), 133.2 (CH), 141.8 (Cq), 147.4 (Cq), 148.8 (Cq), 148.8 (Cq), 150.5 (Cq), 192.7 (Cq); MS (EI) *m*/*z* (%): 589 ($M^+ - 17$, 5), 588 (8), 466 (100), 125 (90), 91 (40); HR MS (FAB) *m*/*z*: calcd for [$M+H^+$] $C_{37}H_{35}O_6S$ 607.2154; found 607.2127.
19. In addition to $Mo(CO)_6$-mediated ring-cleavage, we also attempted to cleave cycloadducts **1a** and **12a** using H_2/Pd–C. No reaction was observed in isoxazoline **1a**. Whereas, only complex mixtures of products were observed without any major product in the ring opening reaction of isoxazole **12a**.
20. Compound **11** was synthesized by refluxing the mixture of calix[4]arene (5 mmol), propargyl bromide (11.2 mmol) and sodium methoxide (5.9 mmol) in acetonitrile (120 mL) for 8 h. After completion of reaction, the solvent was removed under reduced pressure and the residue was purified by silica gel column to get **11** (60%). For the synthesis of a similar *p-tert*-butylcalix[4]arene with propargyloxyl group please see: Santoyo-González, F.; Torres-

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21. *Procedure for the ring opening reaction of calix[4]arene isoxazole* **12a**: A mixture of **12a** (0.169 mmol) and molybdenum hexacarbonyl (0.507 mmol) in acetonitrile 18 mL containing water (three drops) was heated at 80 °C for 36 h. After completion of reaction, the expected α,β-unsaturated-β-amino ketone **13a** was obtained in a 53% yield after column chromatography on silica gel.
Spectral data of **13a**: Brown solid; mp 228–230 °C; $R_f = 0.4$ (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.44 and 4.52 (ABq, $J = 13.0$ Hz, 4H), 3.46 and 4.31 (ABq, $J = 13.7$ Hz, 4H), 4.85 (s, 2H), 5.91 (s, 1H), 6.64–6.71 (m, 3H), 6.86 (t, $J = 7.5$ Hz, 1H), 6.96 (d, $J = 4$ Hz, 1H), 7.00–7.09 (m, 8H), 7.36 (d, $J = 4$ Hz, 1H), 9.40 (br s, 2H), 9.82 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 31.5 (CH_2), 31.9 (CH_2), 78.9 (CH_2), 89.8 (CH), 120.9 (CH), 121.6 (CH), 125.9 (CH), 126.6 (CH), 127.4 (CH), 128.3 (Cq), 128.4 (CH), 128.4 (Cq), 128.6 (Cq), 128.7 (CH), 129.3 (CH), 133.9 (Cq), 134.2 (Cq), 137.1 (Cq), 149.6 (Cq), 150.6 (Cq), 152.6 (Cq), 154.5 (Cq), 193.2 (Cq); MS (EI) m/z 623 (M^+, 5), 625 (M^++2, 2), 607 (90), 424 (50), 150 (100); HRMS (FAB) calcd for $C_{36}H_{30}{}^{37}ClNO_5S$ 625.1504; found 625.1505.

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