A facile electrochemical approach for the synthesis of macrocyclic alkanones

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The synthesis of macrocyclic alkanones, viz. cyclotetradecanone 4a, cyclohexadecanone 4b, cyclooctadecanone 4c, cyclopentadecanone 4d and cycloheptadecanone 4e have been carried out by using Kolbe symmetrical/unsymmetrical dimerisation followed by cyclization in Na-xylene and subsequent reduction with Zn-HCl in 70-80% yield. The products of anodic cross coupling have been separated by column chromatography over silica gel (60-120 mesh) by eluting with benzene-methanol (95:5). An effort has been made to optimize the electrochemical step by investigating the effect of different parameters, viz. degree of partial neutralization, current density and electrode material. The products have been characterised by elemental analyses and IR and $^1$H NMR spectral data.

Large ring cyclic ketones, e.g. 3-methylcyclopentadecanone (muscone), cyclopentadecanone (exaltone), cyclopentadecene-9-ones, cycloheptadecanone (dihydrocivetone), etc. have been found to be important musk components. Some cyclic ketones, particularly C$_{13}$-C$_{17}$ were also reported to be useful repellents for dogs, cats, pigeons and rodents, etc. Hasegawa has found that macrocyclic ketones along with terpenes, e.g. cyclododecanone and limonene were notable effective deodorant in ignition and fire extinguishing of fuel oils. Other notable applications cited in the literature are, e.g. the role of cyclododecanone and limonene in the preparation of protein non-adsorptive microporous polysulfone membranes with high strength and flux, used in biotechnology, as additives of electrophotographic developing sheets, etc.

Electrolysis. The electrolysis was carried out as under: The partially neutralized solution of $\text{NaOH}$, $\text{50 mL}$, beaker. A magnetic needle was put in the cell. Pt-foil/Ti-foil/graphite sheet (area 9 cm$^2$) was used as anode. Two graphite sheets, facing both sides of anode were used as auxiliary electrodes. The solution was stirred magnetically. The cell was divided. A constant current of 1 F/mole charge transfer. The temperature of the cell was maintained 28 $\pm$ 2°C with the help of ice cold water bath. At the completion of the reaction, the solution became alkaline (pH 8.5-10).

Work up. After completion of the electrolysis, the solution was filtered. The filtrate was then neutralised with acetic acid and methanol was removed by distillation. The residue was diluted with water and the organic material was extracted with ether (3 x 50 mL). The ether layer was extracted with 5% aq. NaOH, which removed the starting material(s). The

Note

A facile electrochemical approach for the synthesis of macrocyclic alkanones has been well documented. Our interest in anodic coupling and wide applicability of macrocyclic alkanones has prompted us to explore a convenient and easier methodology by anodic oxidative route followed by a few chemical steps.

Experimental Section

General. Melting points of the compounds were determined in soft glass capillaries in an electrothermal apparatus. IR spectra were recorded on Nicolet Megna FT-IR 550 spectrometer using KBr pellets/Neat. $^1$H NMR spectra were run on FX 90 Q Jeol spectrometer (90 MHz) using TMS as an internal standard.

Materials. Octaneoic acid (Aldrich), nonanedioic acid (Merck) and decanedioic acid (SD Fine) were used without further purification. Their monoethyl esters were prepared by reported synthetic method.

Cell assembly. The cell consisted of a 250 mL beaker with a provision to hold electrodes and thermometer. A magnetic needle was put in the cell. Pt-foil/Ti-foil/graphite sheet (area 9 cm$^2$) was used as anode. Two graphite sheets, facing both sides of anode were used as auxiliary electrodes. The solution was stirred magnetically. The cell was divided. A constant current was passed from a current regulated power supply (0-10A / 0-100V), fabricated by University Science Instrumentation Centre, University of Rajasthan, Jaipur. The instrument was calibrated before use.

Electrolysis. The electrolysis was carried out as under: The partially neutralized solution of 0.03 m monoethyl esters of dioic acids 1a-e or 1a / 1c and 1b by calculated sodium methoxide in methanol was anodically oxidized corresponding to 1 F/mole charge transfer. The temperature of the cell was maintained 28 $\pm$ 2°C with the help of ice cold water bath. At the completion of the reaction, the solution became alkaline (pH 8.5-10).

Work up. After completion of the electrolysis, the solution was filtered. The filtrate was then neutralised with acetic acid and methanol was removed by distillation. The residue was diluted with water and the organic material was extracted with ether (3 x 50 mL). The ether layer was extracted with 5% aq. NaOH, which removed the starting material(s). The
ether layer was dried over anhyd. sodium sulfate, filtered and ether was distilled to give a mixture of neutral products. This organic mixture was chromatographed over silica gel column (60-120 mesh) and eluted with benzene-methanol (95:5) to afford dimerized product(s).

Preparation of 2-hydroxycycloalkanones 3a-e.

Diethyl alkanedioate 2a-e (0.05 mole) in xylene (20 mL) was added to a stirred boiling suspension of pulverized sodium (5 g) in xylene (620 mL), under nitrogen in 2 hr. Stirring was done further for half an hour and then the mixture was cooled to room temperature followed with treatment with ethyl alcohol (60 mL) under the current of nitrogen. The xylene layer was washed with water to make it free from alkali and distilled out. The title compound was obtained in 64-70% yield. The b.p. and elemental analyses of 3a-e were found as under.

3a: 130-31° C/0.1 mm. Anal. Found: C, 74.39; H, 11.54. Calcd for C14H26O2: C, 74.33; H, 11.50%.

3b: 143° C/0.1 mm. Anal. Found: C, 75.62; H, 11.82. Calcd for C15H28O2: C, 75.59; H, 11.81%.

3c: 172-4° C/0.1 mm. Anal. Found: C, 76.66; H, 12.08. Calcd for C16H30O2: C, 76.59; H, 12.05%.

3d: 140°C/0.1 mm. (138°C/0.1 mm)17 Anal. Found: C, 75.04; H, 11.69. Calcd for C17H32O2: C, 75.00; H, 11.66%.

3e: 162° C/0.1 mm. (150-50/0.05-0.08 mm)12 Anal. Found: C, 76.13; H, 12.00. Calcd for C18H34O2: C, 76.11; H, 11.94%.

The IR and 1H NMR spectra of 3a-e were consistent with their proposed structures.

Synthesis of cycloalkanones 4a-e. 3a-e (0.037 mole) in dioxane (200 mL) containing zinc wool (15 g) was heated in an oil bath (95-100°C). Hydrogen chloride gas was passed for 5 hr. Water (1 mL) was added and the gas was passed further for 5 hr to dissolve the crystals of zinc chloride formed during the reaction. Fresh zinc wool (5 g) was further added and HCl gas was further passed slowly for 7 hr more. Dioxane was removed by distillation and the residue was diluted with water. The organic compound was extracted with pet. ether. The pet. ether layer was washed with water, dried over anhyd Na2SO4 and the solvent was removed by distillation. The product obtained was recrystallized with methanol. The products 4a-e were obtained in 73-80% yield. Their physicochemical data, elemental analyses and spectroscopic data are presented in Table I.

Results and Discussion

The main strategy employed for the synthesis of macrocyclic alkanones is to synthesize terminal alkanedioate (C14,15) by utilizing anodic coupling of

| Table I—Characterization data and IR and 1H NMR spectroscopic data of compounds 4a-e |
|-----------------|-----------------|-----------------|
| Compd | m.p.(°C) (Reported) | Found (Calcd) % | IR νmax in cm⁻¹ | 1H NMR |
| | | | | (δ, ppm) TMS (CDCl₃) |
| 4a | 52.4 (52)²⁶ | 80.09 (80.00) | 12.39 (12.38) | 3400(C=O overtone); 1708 (C=Ost); 720 & 710 [(CH₃)₂(bend)]; 2CH₂(CH₂CH₂-CO) ; 2.40, t, 4H, CH₂(CHrCHrCO) | 1.33, s, 22H, 11CH₂; 1.63, m, 2CH₂(CH₂-CO) : 2.40, t, 4H, CH₂(CHrCHrCO) |
| 4b | 57 (56)²⁶ | 80.70 (80.67) | 12.65 (12.60) | 3405(C=O overtone); 1707 (C=Ost); 722 & 710 [(CH₃)₂(bend)]; 2CH₂(CH₂CH₂-CO) ; 2.45, t, 4H, CH₂(CHrCHrCO) | 1.33, s, 22H, 11CH₂; 1.66, m, 2CH₂(CH₂-CO) : 2.45, t, 4H, CH₂(CHrCHrCO) |
| 4c | 72.5 (71)²⁶ | 81.30 (81.20) | 12.81 (12.78) | 3404(C=O overtone); 1705 (C=Ost); 725 & 712 [(CH₃)₂(bend)]; 2CH₂(CH₂CH₂-CO) ; 2.46, t, 4H, CH₂(CHrCHrCO) | 1.32, s, 26H, 13CH₂; 1.66, m, 2CH₂(CH₂-CO) : 2.45, t, 4H, CH₂(CHrCHrCO) |
| 4d | 64.5 (63)²⁶ | 80.41 (80.35) | 13.01 (12.50) | 3400(C=O overtone); 1705 (C=Ost); 720 & 705 [(CH₃)₂(bend)]; 2CH₂(CH₂CH₂-CO) ; 1.34, s, 20H, 10CH₂; 1.65, m, 2CH₂(CH₂-CO) : 2.45, t, 4H, CH₂(CHrCHrCO) |
| 4e | 64.5 (63)²⁶ | 81.01 (80.95) | 12.69 (12.69) | 3403(C=O overtone); 1705 (C=Ost); 720 & 707 [(CH₃)₂(bend)]; 2CH₂(CH₂CH₂-CO) ; 2.46, t, 4H, CH₂(CHrCHrCO) | 1.32, s, 24H, 12CH₂; 1.67, m, 2CH₂(CH₂-CO) : 2.45, t, 4H, CH₂(CHrCHrCO) |
suitable half-esters. In our case, the partially neutralized half-esters of octanedioic acid 1a, nonanedioic acid 1b and decanedioic acid 1c were anodically oxidized for charge corresponding to 1 F/mole, at Pt/Ti/Cn methanol to yield dimeric half-esters, viz diethyl etradecanedioate 2a, diethyl hexadecanedioate 2b and diethyl octadecanedioate 2c respectively by anodic coupling.

\[
\text{EtOOC(CH}_2\text{n)COOH} \rightarrow \cancel{2e} \rightarrow \text{EtOOC(CH}_2\text{)}_2\text{COOEt}
\]

\( n=6,7,8 \) for 1a, 1b & 1c

The diesters, viz. diethylpentadecanedioate 2d and diethyl heptadecanedioate 2e were synthesized by anodic cross coupling (at Pt/Ti/C) of the half-esters, viz. 1b and 1a / 1c.

\[
\text{EtOOC(CH}_2\text{n)COOH + EtOOC(CH}_2\text{)}_2\text{COOH} \rightarrow \cancel{2e} \rightarrow \text{EtOOC(CH}_2\text{n+7)COOEt + 2a/c + 2b}
\]

The dimeric products 2a-e on refluxing with Na-xylene afforded corresponding 2-hydroxy-cycloalkanone C_{14-18}3a-e which on reduction with Zn-HCl gave the final product, viz. cycloalkanones C_{14-18}4a-e in 70-80% yield.

The success of this methodology was dependent on the efficiency of the anodic dimerization and thus it was thought worthwhile to optimize anodic dimerization by investigating the radical coupling process by varying parameters as shown below:

**Degree of neutralization:** The results of anodic dimerization at varying degree of neutralization 10%-25% for the compounds 2a-e are summarized in Table II.

The data presented in Table II suggest that maximum yield (67-81%) of desired products 2a-e was obtained at 15% neutralization. This is in agreement of the earlier observations\(^{19}\) that pH greater than 8 is not favourable for radical coupling.

**Current density:** The results of varying current density are presented in Table III.

The results from Table III suggest that current density 0.11 A cm\(^{-2}\) was most suitable for radical coupling step.

**Anode material:** The radical coupling process has been investigated on different anodes and the results are grouped in Table IV.

The yield of diesters 2a-e at graphite anode were lowest. This was due to the adsorption of radical and then its discharge as corresponding carbonium ion. These observations are in consonance with the earlier report\(^{20}\) that the graphite contains the paramagnetic centers, which bind the free radicals formed and then discharge them as carbonium ion in second electron transfer step. The yield of 2a-e were good at platinum and titanium, although platinum was superior.

**Table II—Anodic oxidation of methanolic solution of half-ester(s) at different neutralizations. Anode platinum foil, cathode graphite sheet, current 1.0 A. (c.d. 0.11 A cm\(^{-2}\)), electrolyte methanol and temperature 28±2°C.**

<table>
<thead>
<tr>
<th>Neutralization degree (%)</th>
<th>Product</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yield (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>67</td>
<td>80</td>
<td>66</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>68</td>
<td>81</td>
<td>64</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>65</td>
<td>78</td>
<td>59</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>2d*</td>
<td>56</td>
<td>69</td>
<td>52</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>2e*</td>
<td>50</td>
<td>67</td>
<td>48</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

* Molar ratio of half-esters 1:1

**Table III—Kolbe electrolysis of half-esters in methanol, degree of neutralization 15%, anode platinum, cathode graphite at varying current densities. Temperature 28±2°C.**

<table>
<thead>
<tr>
<th>Current</th>
<th>Yield (%) of products</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>61 64 60 56 53</td>
</tr>
<tr>
<td>1.0</td>
<td>60 81 78 69 67</td>
</tr>
<tr>
<td>1.5</td>
<td>57 69 62 52 54</td>
</tr>
</tbody>
</table>

* Molar ratio of half-esters 1:1

**Table IV—Anodic oxidation of partially neutralized (15%) methanolic solution of half-ester(s) at different anode materials. Cathode graphite, current 1.0 A. (c.d. 0.11 A cm\(^{-2}\)) and temperature 28±2°C.**

<table>
<thead>
<tr>
<th>Anode-Cathode</th>
<th>Yield (%) of products</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>80 81 78 69 67</td>
</tr>
<tr>
<td>2b</td>
<td>72 74 69 61 59</td>
</tr>
<tr>
<td>2c</td>
<td>23 22 20 15 17</td>
</tr>
</tbody>
</table>

* Molar ratio of half-esters 1:1
Conclusion
Under optimum conditions 2a-e were obtained in 80, 81, 78, 69 and 67% yield respectively and their corresponding cyclic ketones were obtained in 75, 73, 70, 77 and 80% respectively.

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References