Direct chemo, regio & diastereoselective synthesis of \(\beta\)-keto ethers from acrylonitrile by cascade-aldol/ oxo-Michael reaction in cyclododecanone

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Experimental part
General information

All Chemicals were purchased from commercial sources and they were used without further purification unless otherwise specified. TLC - Thin layer chromatography was performed on pre-coated silica gel on alumina plates using UV light to visualize the course of reaction. Purification of reaction mixture was carried out by simple workup and isolated yields after the recrystallization are reported. Melting points were using microprocessor digital melting point apparatus and are uncorrected. IR spectra were recorded in the range 4000-400 cm⁻¹ using KBr pellet technique. ¹H NMR and ¹³C NMR spectra were recorded at room temperature on a 400 MHz using CDCl₃ as the solvent with TMS as an internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p= pentet, multiplet, br = broad. HRMS analysis was obtained from double focusing electron impact method.

General reaction procedure for the synthesis β-keto ethers

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\begin{align*}
&1 \quad \text{equiv} \quad 2 \quad \text{equiv} \quad 3 \quad \text{equiv} \\
&\text{NaOH/H}_2\text{O (1 mol%)} \\
&\text{Solvent-free, stirring, r.t.} \\
\end{align*}
\]

In a dry conical flask with stopcock equipped with mechanical stirrer, 5 mmol of cyclododecanone (CDD), 5 mmol of various benzaldehydes (2), 15 mmol of acrylonitrile (3) and 1 mol % of NaOH were added. This reaction mixture was stirred at room temperature this process was monitored by TLC. The reaction mixture was neutralized by 0.1 HCl solution and extracted with CHCl₃ (2 X 15) followed by the drying of organic layer over anhydrous Na₂SO₄. The solvent was removed under vacuum to give the crude product, which was finally subjected to recrystallization using mixture of solvents. This produced the expected product in moderate to good yield, as indicated in Table 2.
The NMR results showed that the extension of C-C bond was formed from the acrylonitrile position. As a result, in $^1$H spectrum, the methylene protons of $\beta$-OCH$_2$ appeared at around 3.24-3.31 ppm as a triplet and other methylene protons of CH$_2$-CN were obtained in the region of ~2.39-2.38 as a triplet. This has been held to be true in $^{13}$H and DEPT 135 spectrum also; the peak at around 63 ppm indentified as a $\beta$-OCH$_2$ group in negative sign and other CH$_2$-CN peak appeared at around 18 ppm in the same sign, as shown in Fig.1. Hence, the title compounds were obtained via the cascade-aldol/Michael reaction without any doubt.

3-((2-oxocyclododecyl)(phenyl)methoxy)propanenitrile (5a)
The white crude solid was recrystallized by CHCl$_3$ and EtOH (1:1 ratio) to afford *Anti*-\(\beta\)-keto ether (1.35g, 79%, $dr = 98/2$); $R_f$ 0.5 (4:1 hexane:EtOAc); m.p: 89-91°C. FT-IR (KBr) $\nu$ = 3025, 2927, 2250, 1701 (C=O), 1620, 1105 (O ether). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.35 (d, $J = 8$Hz, 2H, Ar-CH), 7.26 (d, $J = 8$Hz, 3H, Ar-CH), 4.36 (d, $J = 8$Hz, 1H, $\beta$-CH*), 3.71-3.36 (m, 2H, $\beta$-CH*-$\beta$-CH$_2$), 2.91 (t, $J = 20$Hz, 1H, $\alpha$-CH*), 2.83-2.77 (m, 1H, CH$_2$-CN), 2.62-2.50 (m, 1H, CH$_2$-CN), 2.49-2.40 (m, 2H, $\alpha'$-CH$_2$), 2.16 (s, 1H, $\beta$-CH$_2$), 1.83 (s, 1H, $\beta$-CH$_2$), 1.67 (s, 1H, CH$_{2ali}$), 1.43-1.23 (m, 13H, CH$_{2ali}$), 1.05 (s, 2H, CH$_{2ali}$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 213.0 (C=O), 137.5 (Ar-C), 134.5, 129.1, 129.0, 117.7 (CN), 83.5 (C=CH*), 63.3 (-OCH$_2$), 57.9 (C=CH*), 40.4 (C=CH$_{2ali}$-ring), 31.0, 26.9, 26.4, 26.1, 24.3, 24.2,
3-((2-oxocyclododecyl)(toluyl)methoxy)propanenitrile (5b)
The white crude solid was recrystallized by CHCl₃ and EtOH (1:1 ratio) to afford *Anti-β*-keto ether (1.53g, 86%, *dr* = 87/13); *R*₂ 0.55 (4:1 hexane:EtOAc); m.p: 115-117°C. **FT-IR** (*KBr*): *ν* = 3028, 2927, 2249, 1702 (C=O), 1621, 1104 (C-O ether). ¹H NMR (400 MHz, CDCl₃): *δ* = 7.69 (d, *J* = 4Hz, 2H, Ar-CH), 7.23-7.11 (m, 2H, Ar-CH), 4.30 (t, *J* = 16Hz, 1H, β-CH*), 3.73 (t, *J* = 12Hz, 1H, β-CH*-O-CH₂), 3.34 (d, *J* = 4Hz, 1H, β-CH*-O-CH₂), 2.98 (d, *J* = 8Hz, 1H, α-CH'), 2.71-2.67 (m, 1H, CH₂-CN), 2.64-2.62 (m, 1H, CH₂-CN), 2.41-2.34 (m, 5H, Ar-CH₃ and α'-CH₂ali protons were merged), 1.75 (bs, 4H), 1.45-1.04 (m, 14H, CH₂ali). ¹³C NMR (100 MHz, CDCl₃): *δ* = 213.6 (C=O), 138.4 (Ar-C), 135.7 (C-CH₃), 129.7, 129.4, 129.2, 127.6, 117.8 (CN), 84.1 (*β*-CH*), 72.5, 65.9, 65.2, 63.0 (-OCH₂), 58.2 (α'-CH*), 39.8 (α'-CH₂ali-ring), 26.9, 26.3, 26.0, 24.3, 24.2, 23.0, 22.3, 21.8, 21.6, 21.2 (*β'-CH₂ali-ring), 18.9, 18.8 (CH₂-CN). **HRMS (EI) m/z:** Calc. for C₂₃H₃₁NO₂, 341.2355 [M⁺]; Found 341.2349.

3-((2-oxocyclododecyl)(4-Methoxyphenyl)methoxy)propanenitrile (5c)
The white crude solid was recrystallized by CHCl₃ and EtOH (1:1 ratio) to afford *Anti-β*-keto ether (1.52g, 82%, *dr* = 98/2); *R*₂ 0.52 (4:1 hexane:EtOAc); m.p: 108-110°C. **FT-IR** (*KBr*): *ν* = 3024, 2923, 2242 (CN₃), 1702 (C=O), 1618, 1103 (C-O ether). ¹H NMR (400 MHz, CDCl₃): *δ* = 7.28 (d, *J* = 8Hz, 2H, Ar-CH), 6.93 (d, *J* = 8Hz, 2H, Ar-CH), 4.35 (d, *J* = 8Hz, 1H, β-CH'), 3.85 (s, 3H, Ar-OCH₃), 3.39 (bs, 1H, β-CH'⁻O-CH₂), 2.96 (t, *J* = 20Hz, 1H, α-CH'), 2.82 (t, *J* = 20Hz, 1H, CH₂-CN), 2.65 (t, *J* = 20Hz, 1H, CH₂-CN), 2.46 (bs, 2H, α'-CH₂), 2.20 (s, 1H, CH₂ali), 1.80 (bs, 2H, CH₂ali), 1.66 (s, 1H, CH₂ali), 1.47-1.27 (m, 12H, CH₂ali), 1.09 (bs, 3H, CH₂ali). ¹³C NMR (100 MHz, CDCl₃): *δ* = 213.6 (C=O), 159.8 (Ar-OCH₃), 130.8 (Ar-C), 128.9, 128.9, 117.9 (CN), 114.2, 83.9 (*β*-CH*), 63.0 (-OCH₂), 58.2 (α'-CH*), 55.2 (OCH₃), 38.2 (α'-CH₂ali-ring), 26.4, 26.1, 24.4, 24.3, 23.1, 22.4, 21.9 (*β'-CH₂ali-ring), 18.8 (CH₂-CN). **HRMS (EI) m/z:** Calc. for C₂₃H₂₃NO₂, 371.2465 [M⁺]; Found 371.2465.

3-((2-oxocyclododecyl)(4-Ethylphenyl)methoxy)propanenitrile (5d)
The white crude solid was recrystallized by CHCl₃ and EtOH (1:1 ratio) to afford *Anti-β*-keto ether (1.44 g, 78%, *dr* = 98/2); *R*₂ 0.6 (4:1 hexane:EtOAc); m.p: 89-91°C. **FT-IR** (*KBr*): *ν* = 3029, 2928, 2250 (CN₃), 1703 (C=O), 1621, 1108 (C-O ether). ¹H NMR (400 MHz, CDCl₃): *δ* = 7.75-7.73 (d, *J* = 8Hz, 1H, Ar-CH), 7.29-7.27 (t, *J* = 8Hz, 1H, Ar-CH), 7.25-7.19 (m, 2H, Ar-CH), 4.36-4.32 (m, 1H, β-CH'), 3.81-3.74 (m, 1H, β-CH'⁻O-CH₂), 3.41-3.35 (m, 1H, β-CH'⁻O-CH₂), 2.99-2.93 (dd, *J* = 18.4, 8, 4Hz, 1H, α-CH'), 2.70-2.65 (m, 4H, CH₂-CN & α'-CH₂ring), 2.46-2.43 (q, *J* = 8.4, 6.4Hz, 2H, ethyl group of CH₂), 1.80-1.72 (m, 3H, CH₂ali), 1.33-1.24 (m, 15H, CH₂ali), 1.10-1.08 (m, 3H, CH₂ali). ¹³C NMR (100 MHz, CDCl₃): *δ* = 213.5 (C=O), 145.7, 144.6, 135.9, 129.2, 128.5, 128.1, 127.6, 117.8 (CN), 84.1 (*β*-CH*), 65.9 (-OCH₂), 58.1 (α'-CH*), 40.4 2 (α'-CH₂ali-ring), 28.5, 26.9, 26.3, 26.0, 24.3, 24.1, 23.0, 22.3, 21.8 (*β'-CH₂ali-ring), 18.8, 18.7 **HRMS (EI) m/z:** Calc. for C₂₄H₃₅NO₂, 369.2668 [M⁺]; Found 369.2673.

3-((2-oxocyclododecyl)(4-Chlorophenyl)methoxy)propanenitrile (5e)
The white crude solid was recrystallized by CHCl₃ and EtOH (1:1 ratio) to afford *Anti-β*-keto ether (1.625g, 87%, *dr* = 91/9); *R*₂ 0.6 (4:1 hexane:EtOAc); m.p: 141-143°C. **FT-IR** (*KBr*): *ν* = 3027, 2926, 2248 (CN₃), 1701 (C=O), 1619, 1105 (C-O ether), 731 (C-Cl). ¹H NMR (400 MHz, CDCl₃): *δ* = 7.42-7.21 (m, 4H, Ar-CH), 4.34 (d, *J* = 12Hz, 0.90H, β-CH'), 3.77-3.73 (dd, *J* = 8, 4Hz, 0.1H β-CH'), 3.42-3.35 (m, 2H, β-CH'⁻O-CH₂), 2.95 (t, *J* = 20Hz, 1H, α-CH*), 2.81-2.75 (dd, *J* = 16, 8.4Hz, 1H, CH₂-CN), 2.75-2.67 (m, 4H, CH₂-CN).
The white crude solid was recrystallized by CHCl₃ and EtOH (1:1 ratio) to afford Anti-β-keto ether (1.71 g, 81%, dr = 98/2); Rf 0.6 (4:1 hexane:EtOAc); m.p: 144-146°C. FT-IR (KBr) ν = 3026, 2928, 2250 (CN, st.), 1702 (C=O), 1620, 1106 (C=O ether), 731 (C-Br). ^1H NMR (400 MHz, CDCl₃): δ = 7.50 (d, J = 12Hz, 2H, Ar-CH), 7.20 (d, J = 12Hz, 2H, Ar-CH), 4.34 (d, J = 12Hz, 1H, β-CH^1), 3.36 (t, J = 12Hz, 2H β-CH^2-O-CH₂), 2.94-2.88 (td, J = 4, 12, 16Hz, 1H, α-CH*), 2.81-2.76 (m, 1H, CH₂-CN), 2.62-2.59 (m, 2H, CH₂-CN & β-CH), 2.46-2.42 (m, 2H, CH₂-aril), 1.86-1.81 (m, 1H, CH₂-aril), 1.71-1.67 (m, 1H, CH₂-aril), 1.43-1.18 (m, 13H, CH₂-aril), 1.08-1.05 (m, 2H, CH₂-aril). ^13C NMR (100 MHz, CDCl₃): δ = 212.9 (C=O), 138.0 (β-CH^2-Ar-C), 132.0, 131.7, 129.3, 122.6 (Ar-C-Br), 117.7 (CN), 83.5 (β-CH^2), 63.3 (α-CH*-O-CH₂), 57.9 (α-CH^2), 53.5, 40.4(α′-CH₂2ring), 31.0, 26.8, 26.3, 26.0, 24.3, 22.9, 22.3, 18.7 (CH₂-CN). HRMS (EI) m/z: Calc. for C₂₂H₃₅BrNO₂, 359.1965 [M]^+; Found 359.1969.

3-((2-oxytocyclododecyl)(4-Bromophenyl)methoxy)propanenitrile (5f)

The white crude solid was recrystallized by CHCl₃ and EtOH (1:1 ratio) to afford Anti-β-keto ether (1.71 g, 81%, dr = 98/2); Rf 0.6 (4:1 hexane:EtOAc); m.p: 144-146°C. FT-IR (KBr) ν = 3026, 2928, 2250 (CN, st.), 1702 (C=O), 1620, 1106 (C=O ether), 731 (C-Br). ^1H NMR (400 MHz, CDCl₃): δ = 7.46-7.427 (m, 1H, Ar-CH), 7.37-7.28 (m, 1H, Ar-CH), 7.25-7.21 (m, 1H, Ar-CH), 7.11-7.06 (m, 1H, Ar-CH), 4.87 (d, J = 12Hz, 1H, β-CH^1), 3.49-3.96 (m, 2H, CH₂-aril), 3.08-3.02 (td, J =4, 8, 12Hz, 1H, CH₂-aril), 2.83-2.76 (m, 1H, CH₂-aril), 2.70-2.62 (m, 1H, CH₂-aril), 2.50-2.47 (m, 1H, CH₂-aril), 1.84-1.76 (m, 1H, CH₂-aril), 1.67 (bs, 1H CH₂-aril), 1.580-1.532 (m, 1H, CH₂-aril), 1.34-1.12 (m, 15H, CH₂-aril); ^13C NMR (100 MHz, CDCl₃): δ = 212.6(C=O), 162.4, 160.0(CH-F), 130.1(β-CH-Ar), 130.0, 128.5, 125.9, 128.8, 124.9, 124.8, 117.5 (CN), 115.6, 115.4, 76.7 (β-CH^1), 63.4 (β-CH^2-O-C₂H₂ether), 57.5 (α-CH^2), 39.8, (β′-CH₂2ring), 26.4 (β-CH₂2ring), 26.3, 26.0, 24.2, 24.1, 24.0, 22.8, 22.2, 21.7 (CH₂-CN), 18.6 CH₂-CN); HRMS (EI) m/z: Calc. for C₂₂H₃₅BrNO₂, 359.1965 [M]^+; Found 359.1969.
The white crude solid was recrystallized by CHCl₃ and EtOH (1:1 ratio) to afford Anti-β-keto ether (1.135 g, 61%, dr = 92/8); Rₓ 0.6 (4:1 hexane:EtOAc); m.p: 103-106°C. FT-IR (KBr) v = 3027, 2921, 2247 (CN st.), 1701 (C=O), 1617, 1106 (C-O ether). ¹H NMR (400 MHz, CDCl₃): δ = 7.43-7.18 (m, 2H, Ar-CH), 6.97-6.85 (m, 2H, Ar-CH), 4.37-4.29 (m, 1H, β-CHβ′), 3.81 (bs, 3H, Ar-OCH₃), 3.78-3.67 (m, 2H, β-CHβ′-O-CH₂), 3.37 (t, J = 8Hz, 1H, α-CH′), 2.92 (t, J = 20Hz, 1H), 2.794-2.74 (m, 2H, CH₂al), 2.69-2.66 (m, 2H, CH₂al), 2.45-2.43 (m, 1H, CH₂al), 1.76 (bs, 2H, CH₂al), 1.45-1.19 (m, 12H, CH₂al), 1.06 (bs, 2H, CH₂al). ¹³C NMR (100 MHz, CDCl₃): δ = 213.3 (C=O), 159.9 (Ar-C-CH₂), 145.4, 143.0, 140.4, 133.9, 129.9, 129.6, 121.9, 120.1, 117.8, 117.2 (CN), 114.1, 113.4, 112.6, 107.3, 84.1 (β-CH*), 72.2, 65.2, 63.1 (β'-CH*-OCH₂), 58.2, 55.3, 55.2 (α-CH*), 39.7 (α'-CH₂al- ring), 26.8, 26.3, 26.0, 24.2, 24.2, 24.1, 23.0, 22.3, 21.7, 18.8, 18.7, 18.3 (CH₂-CN). HRMS (EI) m/z: Calc. for C₂₂H₂₃NO₃, 371.2460 [M]+; Found 371.2469.

3-(2-oxocyclooctadecyl)(2-Chlorophenyl)methoxy)propanenitrile (5j)
The white crude solid was recrystallized by CHCl₃ and EtOH (1:1 ratio) to afford Anti-β-keto ether (1.375 g, 73%, dr = 87/13); Rₓ 0.6 (4:1 hexane:EtOAc); m.p: 114-116°C. FT-IR (KBr) v = 3027, 2926, 2250 (CN st.), 1700 (C=O), 1620, 1104 (C-O ether), 732 (C-Cl). ¹H NMR (400 MHz, CDCl₃): δ = 7.49 (d, J = 8Hz, 0.85H, Ar-CH), 7.45 (dd, J = 8Hz, 0.15H, Ar-CH), 7.39-7.30 (m, 2H, Ar-CH), 7.29-7.22 (m, 2H, Ar-CH), 3.29-3.19 (m, 2H, β-CHβ′-O-CH₂), 3.01 (t, J = 12Hz, 0.85H, β-CHβ′) 2.86 (t, J = 12Hz, 0.15H, β-CH′), 2.77-2.67 (m, 2H CH₂al), 2.64 (t, J = 16Hz, 1H, CH₂al), 2.58-2.42 (m, 2H CH₂al), 1.80-1.60 (m, 2H CH₂al), 1.33-1.08 (m, 15H CH₂al); ¹³C NMR (100 MHz, CDCl₃): δ = 211.8 (C=O), 211.5, 136.7 (Ar-C), 134.6 (Ar-C-CH₂), 129.7, 129.6, 128.6, 127.8, 117.7 (CN), 79.31 (β-CH*), 66.0, 63.6 (-OCH₂), 63.4 (α-CH*), 58.6, 39.5 (α'-CH₂al- ring), 26.4, 26.3, 26.0, 24.4, 23.2, 23.4, 22.4, 21.8 (β'-CH₂al- ring), 19.0, 18.9, 18.8 (CH₂-CN). HRMS (EI) m/z: Calc. for C₂₂H₂₃ClNO₂, 375.1965 [M]+; Found 375.1970.

3-(2-oxocyclooctadecyl)(2-Bromophenyl)methoxy)propanenitrile (5k)
The white crude solid was recrystallized by CHCl₃ and EtOH (1:1 ratio) to afford Anti-β-keto ether (1.595 g, 76%, dr = 98/2); Rₓ 0.6 (4:1 hexane:EtOAc); m.p: 125-127°C. FT-IR (KBr) v = 3027, 2929, 2245, 1702 (C=O), 1619, 1104 (C-O ether), 735 (C-Br). ¹H NMR (400 MHz, CDCl₃): δ = 7.56 (d, J = 8Hz, 1H ArCH), 7.46 (d, J = 8Hz, 1H ArCH), 7.38 (t, J = 12Hz, 1H ArCH), 7.19 (t, J = 16Hz, 1H ArCH) 5.05 (d, J = 8Hz, 1H, β-CH′), 3.47-3.41 (m, 1H, β-CHβ′-O-CH₂), 3.38-3.33 (m, 1H-CH′) 2.99 (bs, 1H CH₂al), 2.71 (t, J = 12Hz, 1H CH₂al), 2.52-2.41 (m, 2H, CH₂al), 1.80-1.62 (m, 2H, CH₂al), 1.32-1.20 (m, 15H, CH₂al), 1.08-1.07 (m, 2H, CH₂al); ¹³C NMR (100 MHz, CDCl₃): δ = 212.6 (C=O), 138.2 (Ar-C), 132.8, 129.9, 128.8, 128.4, 124.9 (C-Br), 117.5 (CN), 81.6 (β-CH*), 63.2 (-OCH₂), 58.5 (α-CH*), 39.4 (α'-CH₂al- ring), 26.3, 25.9, 24.3, 24.2, 24.1, 23.4, 22.3 (β'-CH₂al- ring), 21.7, 18.7 (CH₂-CN). HRMS (EI) m/z: Calc. for C₂₂H₂₃BrNO₂, 419.1460 [M]+; Found 419.1466.

3-(2-oxocyclooctadecyl)(2-Bromophenyl)methoxy)propanenitrile (5l)
The white crude solid was recrystallized by CHCl₃ and EtOH (1:1 ratio) to afford Anti-β-keto ether product (1.26 g, 70%, dr = 79/21); Rₓ 0.55 (4:1 hexane:EtOAc); m.p: 87-89°C. FT-IR (KBr) v = 3029, 2922, 2248, 1701 (C=O), 1620, 1107 (C-O ether), 746 (C-F). ¹H NMR (400 MHz, CDCl₃): δ = 7.43-7.39 (td, J = 4, 6, 16Hz, 1H, Ar-CH), 7.34-7.28 (m, 1H, Ar-CH), 7.20 (t, J = 16Hz, 1H, Ar-CH), 7.05 (t, J = 20Hz, 1H, Ar-CH), 4.85 (d, J = 20Hz, 1H, β-CHβ′), 3.46-3.36 (m, 2H, β-CHβ′-O-CH₂), 3.05-2.99 (td, J = 4, 10, 20Hz, 1H, α-CH′), 2.75-2.64 (m, 2H, CH₂-CN), 2.48-2.44 (m, 2H, CH₂-CN), 1.81-1.69 (m, 2H, α'-CH₂), 1.55-1.50 (m, 1H, CH₂al), 1.31-1.09 (m, 16H, CH₂al); ¹³C NMR (100 MHz, CDCl₃): δ = 212.7 (C=O), 162.5 (C-F), 160.0, 130.2, 130.1, 128.6, 128.5, 126.0, 125.8, 125.0, 124.9 (Ar-C), 117.6 (CN), 115.7, 115.4, 76.6 (β-CH* merged with CDCl₃), 63.5 (-OCH₂), 57.6 (α-CH*), 39.8 (α'-CH₂al- ring), 26.4,

3-((2-oxocyclododecyl)(2,4-Chlorophenyl)methoxy)propanenitrile (5m)
The white crude solid was recrystallized by CHCl₃ and EtOH (1:1 ratio) to afford Anti-β-keto ether product (1.55 g, 76%, dr = 79/21); Rf 0.65 (4:1 hexane:EtOAc); m.p: 107-109°C. **FT-IR (KBr) ν:** 3027, 2928, 2249, 1703 (C=O), 1620, 1105 (C-O ether), 746 (C-Cl). **¹H NMR (400 MHz, CDCl₃):** δ = 7.42-7 (d, J = 8Hz, 1H, Ar-CH), 7.39 (s, 1H, Ar-CH), 7.32 (d, J = 8Hz, 1H, Ar-CH), 5.00 (d, J = 8Hz, 1H, β-CH*), 3.44-3.39 (m, 1H β-CH*-O-CH₂), 3.36-3.30 (m, 1H, β-CH*-O-CH₂), 2.95 (t, J = 16Hz, 1H α-CH*), 2.75-2.62 (m, 2H CH₂-CN), 2.50-2.40 (m, 2H, CH₂-CN & α'-CH₂ring), 1.76-1.78 (m, 2H, CH₂ali), 1.61-1.55 (m, 1H, CH₂ali), 1.30-1.18 (m, 13H, CH₂ali), 1.09-1.06 (m, 2H, CH₂ali). **¹³C NMR (100 MHz, CDCl₃):** δ = 212.3 (C=O), 135.4, 135.1 (β-CH*-Ar-C), 134.8 (Ar-2Cl), 129.6, 129.6, 129.3, 128.3, 117.5 (CN), 78.8 (β-CH*), 65.9 (β-CH*-O-CH₂), 63.47 (α-CH*), 58.4, 39.9 (α'-CH₂ring), 30.9, 26.3, 26.3, 26.0, 24.3, 24.1, 23.3, 22.3, 21.8, 18.9 (CH₂-CN). **HRMS (EI) m/z:** Calc. for C₂₂H₂₉Cl₂NO₂, 409.1575 [M⁺]; Found 409.1579.
$^1$H NMR Spectra of 3-((2-oxocyclododecyl)(phenyl)methoxy)propanenitrile (5a)

$^{13}$C NMR Spectra of 3-((2-oxocyclododecyl)(phenyl)methoxy)propanenitrile (5a)
$^1$H NMR Spectra of 3-((2-oxocyclododecyl)(4-tolyl)methoxy)propanenitrile (5b)

$^{13}$C NMR Spectra of 3-((2-oxocyclododecyl)(4-tolyl)methoxy)propanenitrile (5b)
$^1$H NMR Spectra of 3-((2-oxocyclododecyl)(4-methoxyphenyl)methoxy)propanenitrile (5c)

$^{13}$C NMR Spectra of 3-((2-oxocyclododecyl)(4-methoxyphenyl)methoxy)propanenitrile (5c)
$^1$H NMR Spectra of 3-((2-oxocyclododecyl)(4-Chlorophenyl)methoxy)propanenitrile (5e)

$^{13}$C NMR Spectra of 3-((2-oxocyclododecyl)(4-Chlorophenyl)methoxy)propanenitrile (5e)
$^1$H NMR Spectra of 3-((2-oxocyclododecyl)(4-Bromophenyl)methoxy)propanenitrile (5f)

$^{13}$C NMR Spectra of 3-((2-oxocyclododecyl)(4-Bromophenyl)methoxy)propanenitrile (5f)
DEPT 135 NMR Spectra of 3-((2-oxocyclododecyl)(4-Bromophenyl)methoxy)propanenitrile (5f)

\[ ^1H \text{ NMR Spectra of 3-((2-oxocyclododecyl)(4-Fluorophenyl)methoxy)propanenitrile (5g)} \]
$^{13}$C NMR Spectra of 3-((2-oxocyclododecyl)(4-Fluorophenyl)methoxy)propanenitrile (5g)

DEPT 135 Spectra of 3-((2-oxocyclododecyl)(4-Fluorophenyl)methoxy)propanenitrile (5g)
$^1$H NMR Spectra of 3-((2-oxocyclododecyl)(3-Fluorophenyl)methoxy)propanenitrile (5h)

$^{13}$C NMR Spectra of 3-((2-oxocyclododecyl)(3-Fluorophenyl)methoxy)propanenitrile (5h)
DEPT 135 NMR Spectra of 3-((2-oxocyclododecyl)(3-Fluorophenyl)methoxy)propanenitrile (5h)

$^1$H NMR Spectra of 3-((2-oxocyclododecyl)(3-Methoxyphenyl)methoxy)propanenitrile (5i)
$^{13}$C NMR Spectra of 3-((2-oxocyclododecyl)(3-Methoxyphenyl)methoxy)propanenitrile (5i)

$^1$H NMR Spectra of 3-((2-oxocyclododecyl)(2-Chlorophenyl)methoxy)propanenitrile (5j)
$^{13}$C NMR Spectra of 3-((2-oxocyclododecyl)(2-Chlorophenyl)methoxy)propanenitrile (5j)

DEPT135-NMR Spectra of 3-((2-oxocyclododecyl)(2-Chlorophenyl)methoxy)propanenitrile (5j)
$^1$H NMR Spectra of 3-((2-oxocyclododecyl)(2-Bromophenyl)methoxy)propanitrile (5k)

$^{13}$C NMR Spectra of 3-((2-oxocyclododecyl)(2-Bromophenyl)methoxy)propanitrile (5k)
DEPT135NMR Spectra of 3-((2-oxocyclododecyl)(2-Bromophenyl)methoxy)propanenitrile (5k)

\[ \text{^1H NMR Spectra of 3-((2-oxocyclododecyl)(2-Fluoroophenyl)methoxy)propanenitrile (5l)} \]
$^{13}$C NMR Spectra of 3-((2-oxocyclododecyl)(2-Fluorophenyl)methoxy)propanenitrile (5l)

DEPT 135 NMR Spectra of 3-((2-oxocyclododecyl)(2-Fluorophenyl)methoxy)propanenitrile (5l)
$^1$H NMR Spectra of 3-((2-oxocyclododecyl)(2,4-Chlorophenyl)methoxy)propanenitrile (5m)

$^{13}$C NMR Spectra of 3-((2-oxocyclododecyl)(2,4-Chlorophenyl)methoxy)propanenitrile (5m)
DEPT 135 NMR Spectra of 3-((2-oxocyclododecyl)(2,4-Chlorophenyl)methoxy)propanenitrile (5m)