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NOVEL APPLICATION OF ELECTROOXIDATIVE METHOD FOR THE CYCLIZATION OF *N*-BENZYL-2-(HYDROXYMETHYL)- AND *N*-BENZYL-2-(2-HYDROXYETHYL)PIPERIDINES

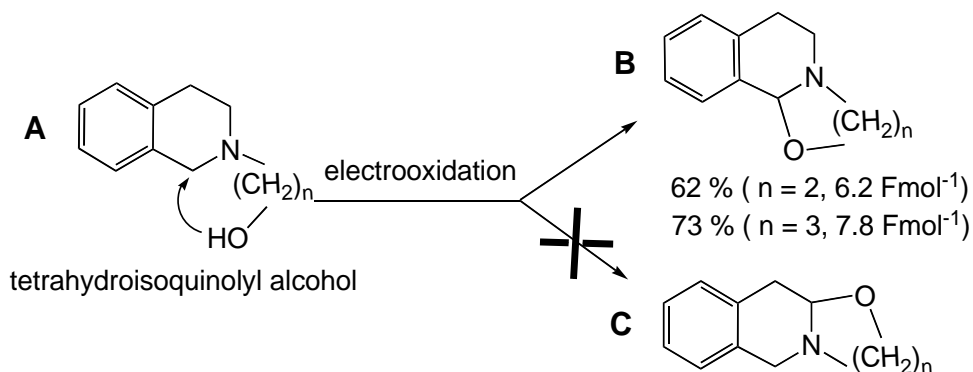
Mitsuhiro Okimoto,* Takashi Yoshida, Masayuki Hoshi, and Kousuke Ohashi

Department of Biotechnology and Environmental Chemistry, Kitami Institute of Technology, Koen-cho 165, Kitami, Hokkaido 090-8507, Japan
e-mail: okimotmt@mail.kitami-it.ac.jp

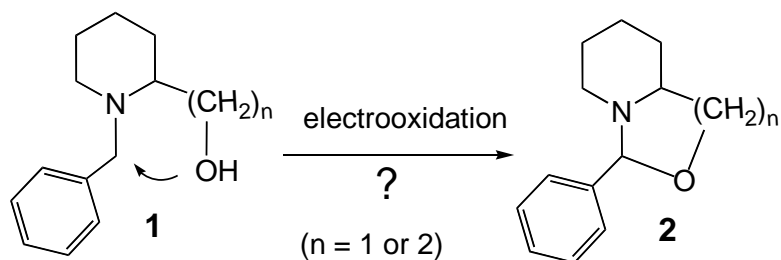
Abstract – Several novel 1,3-oxazinane and oxazolidine derivatives were obtained from the corresponding *N*-benzyl-2-(2-hydroxyethyl)- and *N*-benzyl-2-(hydroxymethyl)piperidines via electrochemical oxidation. The reactions were carried out in methanol under basic conditions. The yields of the cyclic products were significantly improved using catalytic amounts of iodide ions, which presumably act as effective electron carriers in the two-electron oxidation process.

It is well known that electrooxidation provides a useful and an attractive methodology for the transformation of a variety of organic compounds into their oxidative forms.¹ Such electrooxidation reactions are carried out under very mild reaction conditions without the use of hazardous oxidants. Although the oxidative strength of such reactions is relatively weaker than that of metal oxidants, the electrooxidative method often provides specific and/or unique reaction products that are difficult to obtain using typical chemical reagents.² Previously we reported the electrooxidation of tetrahydroisoquinolyl alcohols **A** in the presence of KI in methanol under basic conditions (Scheme 1), in which, the hydroxy group attacked only the benzylic carbon to yield cyclic compound **B**, without any formation of cyclic compound **C**.³ Based upon the results, we reasoned that *N*-benzylpiperidines, which possess a hydroxy alkyl group (**1**), would undergo electrooxidative cyclization to afford the corresponding phenyloxazolidine (**2**, *n* = 1) or phenyl-1, 3-oxazinane (**2**, *n* = 2) derivatives (Scheme 2). In this study, we report the successful formation of cyclic compounds **2** (*n* = 1, 2) via electrochemical oxidation using **1** (*n* = 1, 2) as the starting substrates. Although there are some reports describing their syntheses and/or

conformational analyses,⁴ the preparation of these compounds via electrooxidation has not been reported

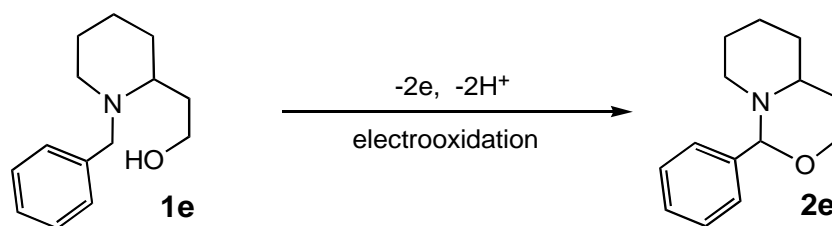


Scheme 1. Electrooxidative cyclization of tetrahydroisoquinolyl alcohols



Scheme 2. Electrooxidative cyclization of *N*-benzyl-2-(hydroxyalkyl)piperidine

to the best of our knowledge. Initially, the optimal reaction conditions for the electrooxidation were determined using *N*-benzyl-2-(2-hydroxyethyl)piperidine (**1e**) as the model substrate. The various combinations of the supporting electrolytes (mediators and bases), along with the corresponding yields of the resulting cyclized compounds **2e**, are listed in Table 1. When NaOMe or KI was used alone, the yield of **2e** was merely 35% (entry 1) and 40% (entry 2), respectively. Remarkably, the combination of KI (0.25 equivalents) and NaOMe (0.63 equivalents) increased the yield of **2e** to 57% (entry 3) – furthermore, increasing the amount of NaOMe to 1.25 equivalents (entry 4) improved the yield to nearly 70%. The use of a strong base such as *t*-BuOK also resulted in a comparable yield of 68% (entry 9). In contrast, replacing NaOMe with a weaker base such as NaOH (entry 7) or NaOAc (entry 8) decreased the yields of **2e**. Substitution of KI (entry 4) with KBr (entry 10) or KCl (entry 11) resulted in lower yields of **2e** (37% and 31%, respectively). These results indicate that the yield of **2e** is strongly affected by not only the catalytic amounts of KI, but by the nature of the base and the mediators. During the initial stages of the electrooxidation reaction, the yield of **2e** was proportional to the amount of current passed – specifically, 34% after 3.0 Fmol⁻¹, then 67% after 6.0 Fmol⁻¹. However, as the reaction progressed, the efficiency of the reaction gradually decreased to 66% after 8.0 Fmol⁻¹.

Table 1. Effect of mediator and base on the yield of cyclized product **2e**^a

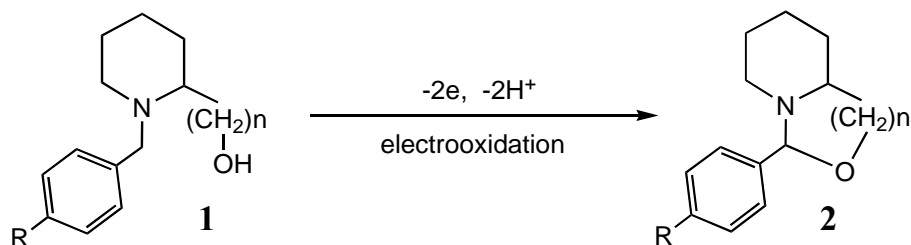
Entry	Mediator (mmol)		Base (mmol)		Yield (%) ^b	
					2e	1e
1	None		NaOMe	5	35	3
2	KI	2	None		40	trace
3	KI	2	NaOMe	5	57	trace
4	KI	2	NaOMe	10	69	trace
5	KI	2	NaOMe	40	55	10
6	KI	8	NaOMe	5	42	8
7	KI	2	NaOH	10	62	2
8	KI	2	NaOAc	5	37	0
9	KI	2	<i>t</i> -BuOK	10	68	trace
10	KBr	2	NaOMe	10	37	4
11	KCl	2	NaOMe	10	31	4

^a**1e**: 8 mmol, MeOH: 40 mL, Constant current: 0.3 A, Current passed: 6.2 Fmol⁻¹, Anode: Pt, Cathode: Ni, Reaction temp.: *ca.* 5 °C. ^b Yields of **2e** and unreacted **1e** were determined by GC analysis.

Accordingly, the consumption of **1e** required significant amounts of electrical current. Subsequently, we applied our electrooxidation procedure using substituted *N*-benzyl-2-(2-hydroxyethyl)piperidines **1f-1h** and *N*-benzyl-2-(hydroxymethyl)piperidines **1a-1d** to afford 1,3-oxazinan-2-ylidene **2f-2h** and oxazolidin-2-ylidene **2a-2d**, respectively (Table 2).⁵ During the reaction, the composition of the anolyte was monitored using GC analysis. Although the consumption of methanol derivatives **1a-1d** were faster than that of ethanol derivatives **1e-1h**, the yields of the corresponding products **2a-2d** were lower than that of **2e-2h**, which can be attributed to the difference in the structural strain between the five- and six-membered ring of the cyclized products. In both cases, substituent effects of the benzene ring, specifically in the *para*-position, were not observed, in terms of the yields of **2**. For the low-yielding reactions, considerable amount of a tar-like material remained in the distillation flask and/or on the top of the column during chromatography

purifications. Although the details of the reaction mechanism remain unclear, a proposed reaction pathway is illustrated in Scheme 3. At the beginning of the reaction, the iodide ion (I^-) readily

Table 2. Anodic cyclization of *N*-benzyl-2-(2-hydroxyethyl)- and *N*-benzyl-2-(hydroxymethyl)piperidines^a

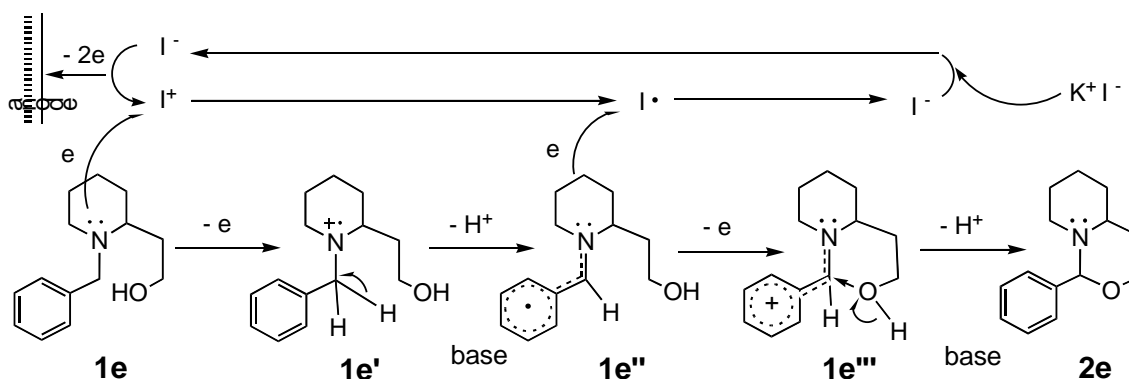


Substrate	1 a-h		Current passed (Fmol ⁻¹)	Isolated yield of 2 a-h (%)
	R	n		
1a	H	1	3.8	60
1b	Me	1	3.9	62
1c	MeO	1	3.7	61
1d	Cl	1	3.7	59
1e	H	2	6.2	65
1f	Me	2	5.3	66
1g	MeO	2	4.9	63
1h	Cl	2	5.4	67

^a**1**: 8 mmol, KI: 2 mmol, NaOMe: 10 mmol, MeOH: 40 mL, Constant current: 0.3A, Anode: Pt, Cathode: Ni, Reaction temp.: ca. 5 °C.

undergoes a two-electron oxidation step on the anode to form an iodonium ion (I^+), which would abstract one electron from the nitrogen atom of the substrate followed by deprotonation resulting in a stable benzylic radical **1e''**. Radical **1e''** would immediately lose an electron to form cation **1e'''**, which would undergo an intramolecular nucleophilic attack by the oxygen atom of the hydroxy group to give the cyclic product. Accordingly, the presence of a strong base such as NaOMe would aid the deprotonation step during the course of the reaction. In a separate study, *N*-(2-phenyl)ethyl-2-(2-hydroxyethyl)piperidine was subjected to electrooxidation under similar conditions – unfortunately, the reaction was not specific and afforded multiple products, as shown by GC analysis. In this case, the substrate lacked a benzylic carbon that is directly adjacent to the nitrogen atom for the formation of a conjugate system. In conclusion, we have successfully carried out the electrochemical oxidations of *N*-benzyl-2-

(2-hydroxyethyl)- and *N*-benzyl-2-(hydroxymethyl)piperidines. Although the yields were moderate, the reactions afforded novel products, and provided new insight into the peculiar electrooxidative behavior of *N*-benzyl-2-(hydroxyalkyl)piperidines. Moreover, the electrooxidation reactions could be carried out under very mild reaction conditions without the use of hazardous oxidants. Further investigations into the stereo-specificity of the reactions are currently underway in our laboratories.



Scheme 3. Proposed scheme of the electrooxidative cyclization

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5. EXPERIMENTAL: *N*-Benzyl-2-(2-hydroxyethyl)- and *N*-benzyl-2-(hydroxymethyl)piperidines were prepared by typical benzylation of 2-(hydroxymethyl)- or 2-(2-hydroxyethyl)piperidine, respectively, using benzyl chloride by refluxing in EtOH for 3h (83 - 93%). Preparative-scale electrooxidations were carried out in a tall 50 mL beaker equipped with a fine frit cup as the cathode compartment with a nickel coil cathode, along with a cylindrical platinum net anode (50 mesh). Typical procedures: a solution of *N*-benzyl-2-(2-hydroxyethyl)piperidine (8 mmol) in MeOH (40 mL) containing KI (2 mmol) and NaOMe (10 mmol) was electro-oxidized under a constant current (0.3 A) with magnetically stirring at *ca.* 5 °C. While monitoring the reaction using GC analysis, electric current was passed until almost all of the substrate was consumed. Upon passage of the electrolytic current (6.2 F mol⁻¹), the reaction mixture was concentrated *in vacuo* (*ca.* 10 mL) at approximately 50 °C. The resulting residue was extracted using Et₂O (3 × 40 mL), in the absence of water. The resulting cloudy ether solution was dried over sodium sulfate overnight, filtered, then concentrated *in vacuo* to afford the crude product. The cyclized products were purified by distillation under reduced pressure and/or by silica gel column chromatography using Et₂O/*n*-hexane as the eluent. The boiling and/or melting points, IR, NMR, and MS data of the products are listed below.

2a bp 151-153 °C/15 mmHg. Silica gel TLC: *R_f* = 0.68 (Et₂O : *n*-hexane = 1:1). IR (neat): 2937, 2871, 1456, 1377, 1099, 1078, 1024, 755, 699 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.18-1.14 (m, 1H), 1.44-1.66 (m, 3H), 1.72-1.86 (m, 2H), 1.98-2.06 (m, 1H), 2.44-2.54 (m, 1H), 2.64-2.74 (m, 1H), 3.60-3.74 (m, 1H), 4.04-4.16 (m, 1H), 4.59 (s, 1H), 7.18-7.38 (m, 3H, Arom), 7.38-7.48 (m, 2H, Arom). ¹³C NMR (CDCl₃): δ = 23.52 (CH₂), 24.75 (CH₂), 26.59 (CH₂), 47.14 (CH₂), 62.77 (CH), 71.23 (CH₂), 96.62 (CH), 128.00 (CH), 128.18 (CH), 128.84 (CH), 139.18 (C). MS *m/z* (%): 203(36) [M⁺], 202(73), 173(34), 172(60), 126(100) [M⁺-C₆H₅], 105(39), 98(24), 91(51), 77(29), 65(13). HRMS: *m/z* calcd. for C₁₃H₁₇NO: 203.1310; found: 203.1324 [M⁺].

2b mp 48-49 °C. Silica gel TLC: *R_f* = 0.67 (Et₂O : *n*-hexane = 1:1). IR (KBr): 2944, 1326, 1196, 1149, 1124, 1090 (s), 1017, 935, 821, 804 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.18-1.42 (m, 2H), 1.45-1.46 (m, 1H), 1.57-1.65 (m, 1H), 1.78-1.86 (m, 2H), 1.96-2.06 (m, 1H), 2.34 (s, 3H, CH₃), 2.43-2.52 (m, 1H), 2.66-2.73 (m, 1H), 3.62-6.68 (m, 1H), 4.01-4.07 (m, 1H), 4.56 (s, 1H), 7.15 (d, *J* = 8Hz, 2H, Arom), 7.34 (d, *J* = 8Hz, 2H, Arom). ¹³C NMR (CDCl₃): δ = 21.26 (CH₃), 23.56 (CH₂), 24.78 (CH₂), 26.99 (CH₂), 41.18 (CH₂), 62.79 (CH), 71.17 (CH₂), 96.54 (CH), 127.94 (CH), 128.91 (CH), 136.23 (C), 138.58 (C). MS *m/z* (%): 217(49) [M⁺], 216(99), 187(34), 186(63), 127(26), 126(100) [M⁺-C₆H₄CH₃], 119(34), 98(25), 91(37), 41(28). HRMS: *m/z* calcd. for C₁₄H₁₉NO: 217.1467; found: 217.1457 [M⁺].

2c mp 30-31 °C. Silica gel TLC: R_f = 0.54 (Et₂O : *n*-hexane = 1:1). IR (KBr): 2943 (s), 1613, 1515, 1300, 1248 (s), 1169, 1092, 1026 (s), 825, 807 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.22-1.42 (m, 2H), 1.44-1.56 (m, 1H), 1.58-1.65 (m, 1H), 1.78-1.87 (m, 2H), 1.95-2.05 (m, 1H), 2.43-2.51 (m, 1H), 2.64-2.72 (m, 1H), 3.61-3.67 (m, 1H), 3.79 (s, 3H, CH₃O), 4.00-4.06 (m, 1H), 4.55 (s, 1H), 6.88 (d, J = 8Hz, 2H, Arom), 7.38 (d, J = 8Hz, 2H, Arom). ¹³C NMR (CDCl₃): δ = 23.57 (CH₂), 24.80 (CH₂), 27.03 (CH₂), 47.17 (CH₂), 55.23 (CH₃O), 67.75 (CH), 71.08 (CH₂), 96.34 (CH), 113.61 (CH), 129.25 (CH), 131.30 (C), 160.12 (C). MS m/z (%): 233(26) [M⁺], 232(100), 203(14), 202(32), 135(28), 126(56) [M⁺-C₆H₄OCH₃], 121(15), 119(5), 96(5), 79(9), 41(7). HRMS: m/z calcd. for C₁₄H₁₉NO₂: 233.1416; found : 233.1421 [M⁺].

2d mp 36-37 °C. Silica gel TLC: R_f = 0.66 (Et₂O : *n*-hexane = 1:1). IR (KBr): 2939 (s), 2804, 1492, 1363, 1089 (s), 1023, 1015, 841, 823, 807 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.18-1.40 (m, 2H), 1.42-1.55 (m, 1H), 1.58-1.72 (m, 1H), 1.75-1.91 (m, 2H), 1.97-2.08 (m, 1H), 2.42-2.54 (m, 1H), 2.62-2.70 (m, 1H), 3.62-3.70 (m, 1H), 4.02-4.08 (m, 1H), 4.56 (s, 1H), 7.32 (d, J = 8Hz, 2H, Arom), 7.39 (d, J = 8Hz, 2H, Arom). ¹³C NMR (CDCl₃): δ = 23.49 (CH₂), 24.74 (CH₂), 26.96 (CH₂), 47.09 (CH₂), 62.74 (CH), 71.33 (CH₂), 95.82 (CH), 128.43 (CH), 129.44 (CH), 134.59 (C), 137.87 (C). MS m/z (%): 239(20) [M⁺, ³⁷C], 238(46), 237(56) [M⁺, ³⁵C], 236(85), 208(43), 207(46), 206(61), 139(43), 127(43), 126(100) [M⁺-C₆H₄Cl], 41(38). HRMS: m/z calcd. for C₁₃H₁₆NOCl: 237.0920; found: 237.0952 [M⁺].

2e bp 113-115 °C/2 mmHg, mp 53-55 °C. Silica gel TLC: R_f = 0.53 (Et₂O : *n*-hexane = 1:1). IR (KBr): 2934, 2844, 1453, 1369, 1130, 1118, 1083, 755, 670 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.22-1.34 (m, 1H), 1.38-1.52 (m, 4H), 1.58-1.76 (m, 3H), 1.82-1.96 (m, 1H), 2.20-2.30 (m, 1H), 2.34-2.44 (m, 1H), 3.60-3.74 (m, 1H), 4.06-4.16 (m, 1H), 4.34 (s, 1H), 7.22-7.38 (m, 3H, Arom), 7.39-7.52 (m, 2H, Arom). ¹³C NMR (CDCl₃): δ = 24.10 (CH₂), 25.53 (CH₂), 32.42 (CH₂), 32.74 (CH₂), 49.03 (CH₂), 61.41 (CH), 67.82 (CH₂), 97.39 (CH), 127.88 (CH), 128.25 (CH), 128.52 (CH), 139.86 (C). MS m/z (%): 217(4) [M⁺], 173(83), 172(43), 140(42) [M⁺-C₆H₅], 105(15), 96(20), 92(28), 91(100), 82(18), 77(13), 65(20). HRMS: m/z calcd. for C₁₄H₁₉NO: 217.1467; found: 217.1446 [M⁺].

2f mp 66-67 °C. Silica gel TLC: R_f = 0.49 (Et₂O : *n*-hexane = 1:1). IR (KBr): 2934 (s), 2922, 1368, 1255, 1118 (s), 1096, 1081, 1043, 817 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.21-1.34 (m, 1H), 1.35-1.54 (m, 4H), 1.56-1.75 (m, 3H), 1.82-1.95 (m, 1H), 2.18-2.28 (m, 1H), 2.33 (s, 3H, CH₃), 2.80-3.45 (m, 1H), 3.65-3.74 (m, 1H), 4.07-4.12 (m, 1H), 4.30 (s, 1H), 7.14 (d, J = 8Hz, 2H, Arom), 7.34 (d, J = 8Hz, 2H, Arom). ¹³C NMR (CDCl₃): δ = 21.23 (CH₃), 24.14 (CH₂), 25.55 (CH₂), 32.48 (CH₂), 32.76 (CH₂), 49.12 (CH₂), 61.54 (CH), 67.83 (CH₂), 97.33 (CH), 127.77 (CH), 128.96 (CH), 136.94 (C), 138.22 (C). MS m/z (%): 231(23) [M⁺], 230(32), 187(64), 140(79) [M⁺-C₆H₄CH₃],

120(42), 112(35), 105(100), 91(31), 83(34), 55(35). HRMS: m/z calcd. for $C_{15}H_{21}NO$: 231.1623; found: 231.1657 [M^+].

2g mp 88-89 °C. Silica gel TLC: $R_f = 0.30$ ($Et_2O : n\text{-hexane} = 1:1$). IR (KBr): 2921 (s), 1615, 1517, 1245 (s), 1175, 1115, 1079 (s), 1030, 831, 821 cm^{-1} . 1H NMR ($CDCl_3$): $\delta = 1.18\text{-}1.33$ (m, 1H), 1.37-1.52 (m, 4H), 1.58-1.76 (m, 4H), 1.80-1.95 (m, 1H), 2.17-2.27 (m, 1H), 2.37-2.44 (m, 1H), 3.65-3.74 (m, 1H), 3.78 (s, 3H, CH_3O), 4.28 (s, 1H), 6.86 (d, $J = 8Hz$, 2H, Arom), 7.37 (d, $J = 8Hz$, 2H, Arom). ^{13}C NMR ($CDCl_3$): $\delta = 24.18$ (CH_2), 25.59 (CH_2), 32.57 (CH_2), 32.80 (CH_2), 49.18 (CH_2), 55.23 (CH_3O), 61.58 (CH), 67.80 (CH_2), 97.02 (CH), 113.63 (CH), 129.00 (CH), 132.25 (C), 159.74 (C). MS m/z (%): 247(2) [M^+], 246(3), 203(18), 140(7) [$M^+ - C_6H_4OCH_3$], 136(9), 135(6), 122(10), 121(100), 92(4), 77(5), 76(6). HRMS: m/z calcd. for $C_{15}H_{21}NO_2$: 247.1572; found: 247.1580 [M^+].

2h mp 70-71 °C. Silica gel TLC: $R_f = 0.54$ ($Et_2O : n\text{-hexane} = 1:1$). IR (KBr): 2924 (s), 2847, 2788, 1367, 1226, 1119, 1083 (s), 1043, 1011, 820 cm^{-1} . 1H NMR ($CDCl_3$): $\delta = 1.18\text{-}1.32$ (m, 1H), 1.33-1.53 (m, 4H), 1.56-1.76 (m, 3H), 1.80-1.94 (m, 1H), 2.20-2.30 (m, 1H), 2.32-2.40 (m, 1H), 3.64-3.74 (m, 1H), 4.06-4.13 (m, 1H), 4.32 (s, 1H), 7.31 (d, $J = 8Hz$, 2H, Arom), 7.40 (d, $J = 8Hz$, 2H, Arom). ^{13}C NMR ($CDCl_3$): $\delta = 24.00$ (CH_2), 25.49 (CH_2), 32.23 (CH_2), 32.69 (CH_2), 48.89 (CH_2), 61.26 (CH), 67.81 (CH_2), 96.42 (CH), 128.45 (CH), 129.30 (CH), 134.17 (C), 138.49 (C). MS m/z (%): 253(7) [M^+ , ^{37}C], 251(20) [M^+ , ^{35}C], 250(25), 207(44), 141(42), 140(100) [$M^+ - C_6H_4Cl$], 127(36), 125(66), 112(38), 83(36), 55(37). HRMS: m/z calcd. for $C_{14}H_{18}NOCl$: 251.1077; found: 251.1102 [M^+].