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Short Report

A Mild Procedure for α,α-Dichlorination of Cyclic Aryl Ketones using Commercial Bleach

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Aril cetonas cíclicas α,α-dicloradas foram obtidas pelo tratamento de uma solução metanólica da correspondente cetona com cândida comercial em condições ambiente com rendimentos que variaram de 61 a 92%. A reação ocorre em cetonas contendo tanto grupos doadores quanto retiradores de elétrons, mas parece ser sensível a efeitos estéricos. Além disso, aril-cicloalcanonas com anéis de cinco, seis e sete membros podem ser utilizadas como substrato.

α,α-Dichloro-cyclic aryl ketones were obtained treating a methanolic solution of the corresponding ketone with commercial bleach at ambient conditions in yields varying from 61 to 92%. Electron-donating and -withdrawing groups in the starting ketone are tolerated but the reaction appears to be sensitive to steric effects. Moreover, five-, six-, and seven-membered aryl-cycloalkanones can be used as substrate.

Keywords: bleach, tetralones, ketones, chlorination

Introduction

Over the last decades, α,α-dichloroketones have been used as substrate in several reactions in synthetic organic chemistry, including important steps in the synthesis of natural products.[1] Thus, several methods have been developed for the preparation of α,α-dichloroketones, where the most used is the direct dichlorination of the corresponding ketone. This transformation has been performed with cyclic aryl ketones in a variety of different forms, using: *i*) Cl_2 in CH_2Cl_2[2] or in DMF;[3] *ii*) thionyl chloride in CCl_4;[4] *iii*) thionyl chloride followed treatment with H_2O_2;[5] *iv*) sulfuryl chloride;[6] *v*) 2-chloropyridazin-3(2*H*)-one in CH_2Cl_2 in the presence of H_2SO_4;[7] *vi*) manganese(III) acetate in boiling AcOH in the presence of LiCl;[8] *vii*) $FeCl_3$ in a mixture of AcOH/H_2O;[9] and *viii*) copper(II) chloride in DMF[10] or in acetonitrile.[11] In this scenario, we herein present a simple and mild procedure to obtain several α,α-dichloro cyclic aryl ketones using commercial bleach, at room temperature and without the control of the pH, showing the influence of alkyl, electron donating- and electron-withdrawing groups, as well as the ring size of the substrate. Bleach is an inexpensive and environmentally friendly reagent that has a number of applications, including the chlorolactonization of β- and γ-unsaturated carboxylic acids,[12] the oxidation of alcohols,[13] as co-oxidant in TEMPO-catalyzed oxidations,[14] and the dichlorination of dicarbonylic compounds in AcOH/Me_2CO at 0 °C.[15] During the development of this work, a patent by Kumamoto *et al.*,[16] reported the use of bleach for the α,α-dichlorination of a single ketone, namely 5-nitro-1-tetralone, at 50 °C and keeping the pH of the solution around 10.

Results and Discussion

When bleach was added to a methanolic solution of 1-tetralone (**1**) at room temperature, 2,2-dichloro-1-tetralone was obtained in 90% yield (Table 1, entry 1). The reaction is very clean, with no side reactions. Indeed, the NMR of the crude product does not show the presence of any impurity. Furthermore, the haloform reaction, that could be a side reaction,[17] was not observed. Presumably, this transformation occurs by the reaction of the enolate of the ketone with a chloro-containing species in solution, such as chlorine or ClOH. Next, the same protocol was applied to other ketones. Treating tetralones containing an electron-donating substituent in the aromatic ring, such as **2-4** with bleach gave, respectively, the corresponding α,α-dichlorinated products **9-11,** in high yields (entries 2-4). The reaction of 7-nitro-1-tetralone (**5**) led also to the desired product, although in lower yield than the other tetralones (compare entry 5 with entries 1-4). Thus, the presence of an electron-withdrawing group has some

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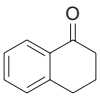
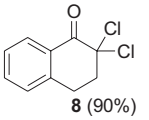
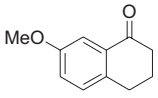
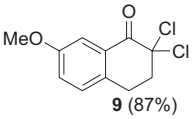
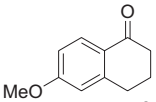
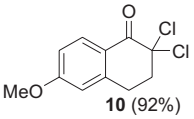
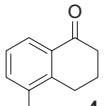
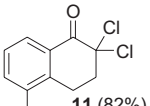
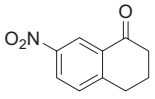
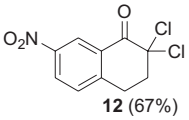
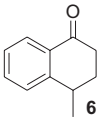
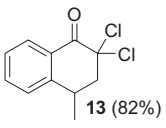
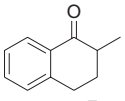
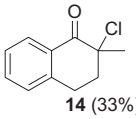
influence in the reactivity, which agrees with the result of Kumamoto *et al.*[16] that performed the chlorination of a similar ketone at 50 °C. The influence of alkyl groups was then investigated. The reaction of 4-methyl-1-tetralone (**6**) with bleach afforded the dichlorinated product in good yield (entry 6). However, when 2-methyl-1-tetralone (**7**) was treated with bleach only 33% of the starting material was converted to the product even after 4 days of reaction time (entry 7). In summary, tetralones can be dichlorinated in an efficient manner. Electron-donating and withdrawing groups are tolerated but the reaction appears to be sensitive to steric effects.

Table 1. Reaction of 1-Tetralones with Bleach in MeOH

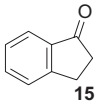
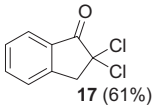
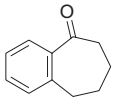
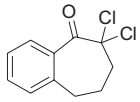
Entry	Substrate	Product (Yield)
1	 **1**	 **8** (90%)
2	 **2**	 **9** (87%)
3	 **3**	 **10** (92%)
4	 **4**	 **11** (82%)
5	 **5**	 **12** (67%)
6	 **6**	 **13** (82%)
7	 **7**	 **14** (33%)*

*Conversion estimated by GC analysis.

The reactivity of a cyclohexanone was also investigated. When 4-*t*-butylcyclohexanone was treated with bleach in conditions similar to that presented above, no reaction was observed. The different behavior between the alkyl and the aryl ketones may be explained by the difference of the acidity of the α-hydrogen, where the pKa value of aryl ketones (pK_a of 1-tetralone in DMSO: 24.7[18]) is nearly two units lower than that of the corresponding alkyl ketone (pK_a of cyclohexanone in DMSO: 26.4[19]).

The effect of the ring size was examined for ketones with a five- and a seven-membered ring. The reaction of 1-indanone and of 1-benzosuberone (**15** and **16**, respectively) with bleach gave the expected dichloro ketones in 61 and 64% yield, respectively (Table 2). Although still good, these yields are clearly lower than that obtained for the six-membered ring ketone **1**.

Table 2. Reaction of Cyclic Ketones with Bleach in MeOH

Entry	Substrate	Product (Yield)
1	 **15**	 **17** (61%)
2	 **16**	 **18** (64%)

Conclusions

In conclusion, a simple, cheap and efficient method for the preparation of α,α-dichlorinated ketones from readily available cyclic aryl ketones and commercial bleach was developed. This protocol avoids the use of hazardous material and/or difficult procedures.

Experimental

The reactions were carried out using Daclor® commercial bleach (pH 12, 2.0-2.2% of chlorine). The aryl ketones, besides 7-nitro-1-tetralone,[20] are commercially available. Melting points were determined on a Büchi Melting Point B-545 and are uncorrected. Shimadzu GC-2010 was used to monitor the progress of the reactions. ^1H and ^{13}C NMR spectra were recorded on Bruker spectrometers. IR spectra were measured on a Perkin-Elmer 1750 FT. High resolution mass spectra were performed on a VG Autospec/Fission Instrument and MicroTOF LC from Bruker Daltonics. Although the crude products were often obtained quite pure, analytical pure substances could be obtained by flash chromatography using silica-gel Acros 200-400 Mesh (30% AcOEt in hexanes).

*2,2-Dichloro-1-tetralone (**8**). General procedure for the preparation of the dichlorinated ketones*

To a stirred solution of **1** (0.045 g, 0.31 mmol) in MeOH (0.8 mL) at rt was added commercial household bleach portionwise (4.5 mL). The solution turned white. After 6 h, H_2O was added and the aqueous mixture was extracted 3 times with Et_2O (30 mL). The combined organic phase was washed with brine, dried over anhyd $MgSO_4$ and the solvent was removed under reduced pressure affording **2** (0.059 g, 0.28 mmol, 90%), as a white powder (mp 76.2-77.0 °C; lit.:[21] 76 °C).

*2,2-Dichloro-7-methoxy-1-tetralone (**9**)*

The preparation was performed as above but using **2** (0.036 g, 0.20 mmol), MeOH (0.4 mL) and bleach (2.5 mL) giving **9** (0.045 g, 0.18 mmol, 92%) as a white powder; mp 92.7-94.1 °C; IR (KBr) ν_{max}/cm^{-1}: 1702, 1025, 709; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.93 (t, *J* 5.7 Hz, 2H), 3.13 (t, *J* 5.7 Hz, 2H), 3.84 (s, 3H), 7.14-7.17 (m, 2H), 7.58 (d, *J* 2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.6, 43.4, 55.5, 86.3, 111.2, 123.2, 129.0, 129.9, 134.8, 158.8, 183.9; LRMS (EI) *m/z* (rel. int.) 244 (M^+, 25%), 209 (24), 120 (100); Anal. calc. for $C_{11}H_{10}Cl_2O_2$: C, 53.90; H, 4.11. Found: C, 54.33; H,4.07.

*2,2-Dichloro-6-methoxy-1-tetralone (**10**)*

The preparation was performed as above but using **3** (0.036 g, 0.20 mmol), MeOH (0.4 mL) and bleach (2.5 mL) giving **10** (0.045 g, 0.18 mmol, 92%) as a white powder (mp 84.4-86.2 °C; lit.:[4] 85-87 °C).

*2,2-Dichloro-5-methoxy-1-tetralone (**11**)*

The preparation was performed as above but using **4** (0.051 g, 0.29 mmol), MeOH (0.5 mL) and bleach (2.9 mL) giving **11** (0.058 g, 0.24 mmol, 82%) as a pale yellow oil.[6]

*2,2-Dichloro-7-nitro-1-tetralone (**12**)*

The preparation was performed as above but using **5** (0.115 g, 0.60 mmol), MeOH (1.2 mL) and bleach (7.2 mL) giving **12** (0.104 g, 0.40 mmol, 67%) as a pale yellow solid (mp 118.6.-120.2 ºC); IR (KBr) ν_{max}/cm^{-1}: 1711, 1526, 635; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.05 (t, *J* 6.1 Hz, 2H), 3.38 (t, *J* 6.1 Hz), 7.57 (d, *J* 8.8 Hz, 1H), 8.39 (dd, *J* 8.3 and 2.6 Hz, 1H), 8.93 (d, *J* 2.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.5, 42.1, 85.0, 124.8, 128.2, 129.3, 130.5, 147.3, 148.5, 182.2; LRMS: *m/z* (rel. int.) 259 (M^+, 5%), 163 (100), 115 (20); Anal. calc. for $C_{10}H_7Cl_2NO_3$: C, 46.18; H, 2.71; N, 5.39. Found: C, 46.43; H, 2.89; N, 5.09.

*2,2-Dichloro-4-methyl-1-tetralone (**13**)*

The preparation was performed as above but using **6** (0.086 g, 0.54 mmol), MeOH (1.0 mL) and bleach (5.0 mL) giving **13** (0.101 g, 0.44 mmol, 82%), as a colorless oil; IR (film) ν_{max}/cm^{-1}: 1709, 1216, 822; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 (d, *J* 7.0, 3H), 2.60 (dd, *J* 14.5 and 11.0 Hz, 1H), 3.45 (m, 1H), 6.07 (dd, *J* 14.5 and 4.4 Hz, 1H), 7.42 (d, *J* 9.6 Hz, 2H), 7.62 (td, *J* 7.7 and 1.3 Hz, 1H), 8.15 (dd, *J* 8.3 and 1.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.1, 31.0, 51.2, 85.6, 126.6, 127.3, 127.7, 129.7, 134.8, 146.6, 184.2; LRMS *m/z* (rel. int.) 228 (M^+, 7%), 192 (4), 132 (100); HRMS [ESI(+)] calc. for $[C_{11}H_{10}Cl_2ONa]^+$: 251.0006. Found: 250.9997.

*Reaction of **7** with bleach in MeOH*

The reaction was performed as above but using **7** (0.073 g, 0.46 mmol), MeOH (0.9 mL) and bleach (4.6 mL) giving after 4 days a conversion of 33% to **14** determined by GC analysis. A 2,3:1 mixture of **7**:**14** was obtained (0.065 g), as a colorless oil; ^{1}H RMN (300 MHz, $CDCl_3$) δ 1.82 (s, 3H), 2.37-2.28 (m, 1H), 3.37 (ddd, *J* 17.0, 11.2 and 4.7 Hz, 1H), 8.09 (dd, *J* 1.2 Hz, 1H), other signals overlap with **7**.

*2,2-Dichloro-1-indanone (**17**)*

The preparation was performed as above but using **15** (0.115 g, 0.60 mmol), MeOH (1.2 mL) and bleach (7.2 mL) giving **17** (0.104 g, 0.40 mmol, 67%) as a white solid (mp 73.5-75.3 °C; lit.:[7] 74-75 °C).

*2,2-Dichloro-1-benzosuberone (**18**)*

The preparation was performed as above but using **16** (0.115 g, 0.60 mmol), MeOH (1.2 mL) and bleach (7.2 mL) giving **18** (0.104 g, 0.40 mmol, 64%) as a colorless oil; IR (film) ν_{max}/cm^{-1}: 1713, 1245, 953; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.08 (dddd, *J* 7.0, 6.6, 6.2 and 5.7 Hz, 2H), 2.68 (dd, *J* 6.6 and 5.7 Hz, 2H), 2.85 (dd, *J* 7.0 and 6.3 Hz, 2H), 7.17 (d, *J* 7.5 Hz, 1H), 7.34 (dd, *J* 7.5 and 0.9 Hz, 1H), 7.43 (dd, *J* 7.5 and 1.8 Hz, 1H), 7.49 (dd, *J* 7.5 and 1.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.8, 32.3, 44.0, 89.4, 127.0, 129.0, 129.3, 132.3, 136.6, 137.0, 195.8; LRMS *m/z* (rel. int.) 228 (M^+, 13%), 165 (54), 131 (100); HRMS [ESI(+)] calc. for $[C_{11}H_{10}Cl_2ONa]^+$: 251.0006. Found: 250.9999.

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Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br, as PDF file.

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A Mild Procedure for the α,α-Dichlorination of Cyclic Aryl Ketones using Commercial Bleach

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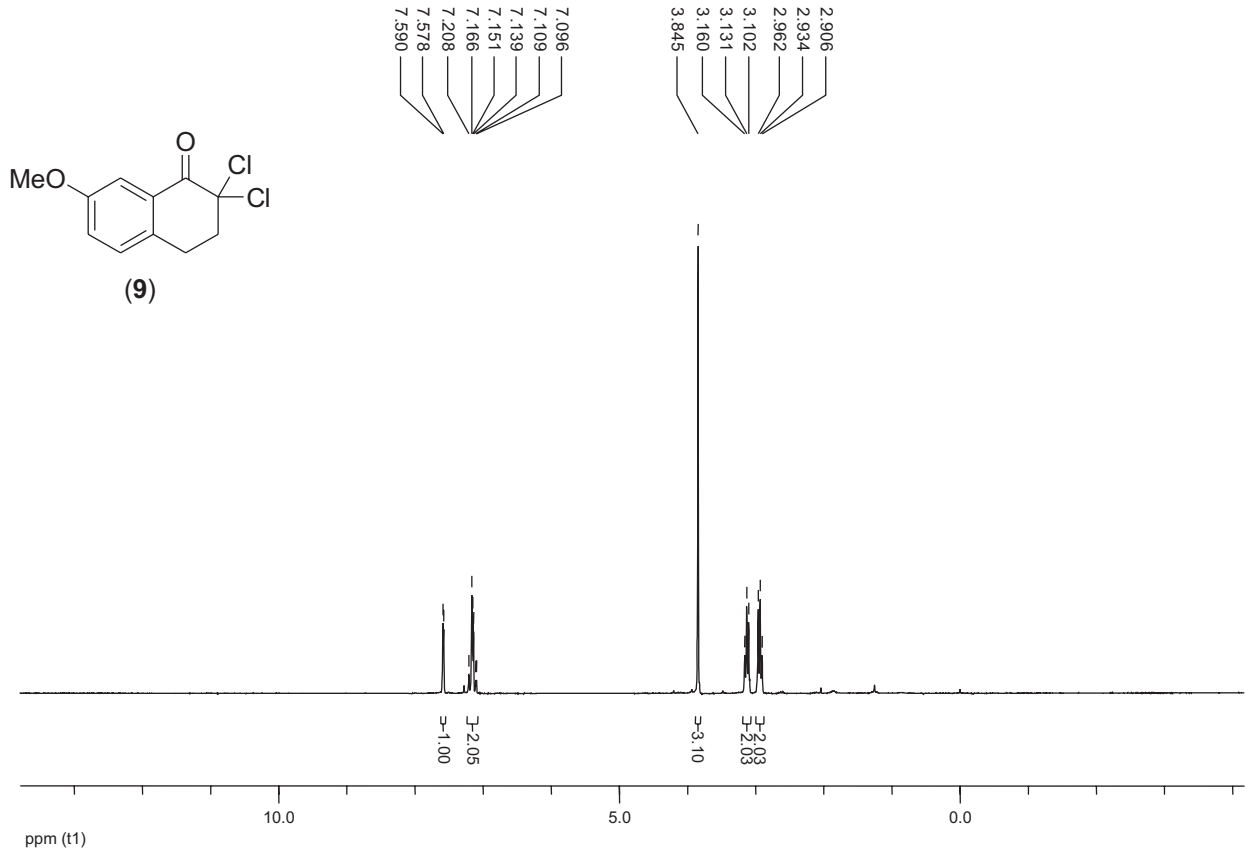

Figure S1. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **9**.

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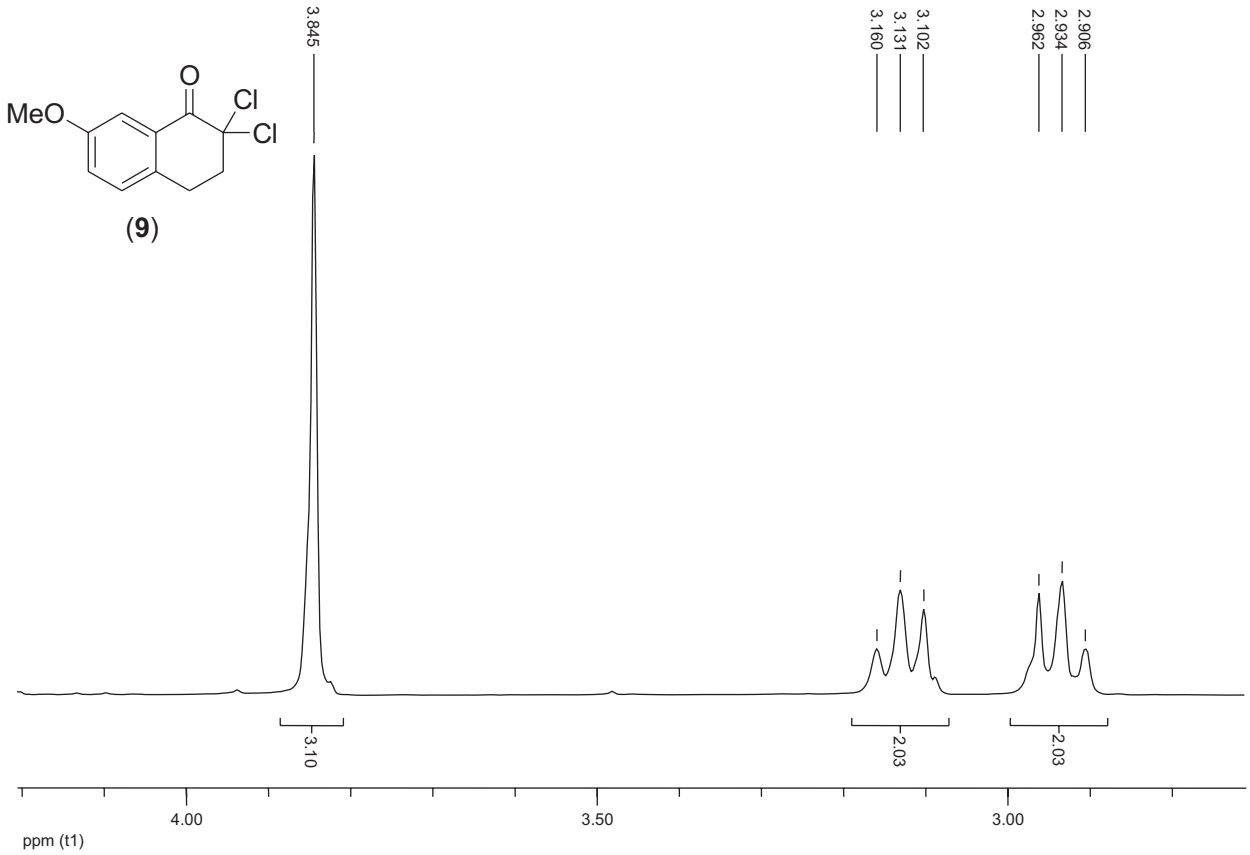

Figure S2. Detail of the ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **9**.

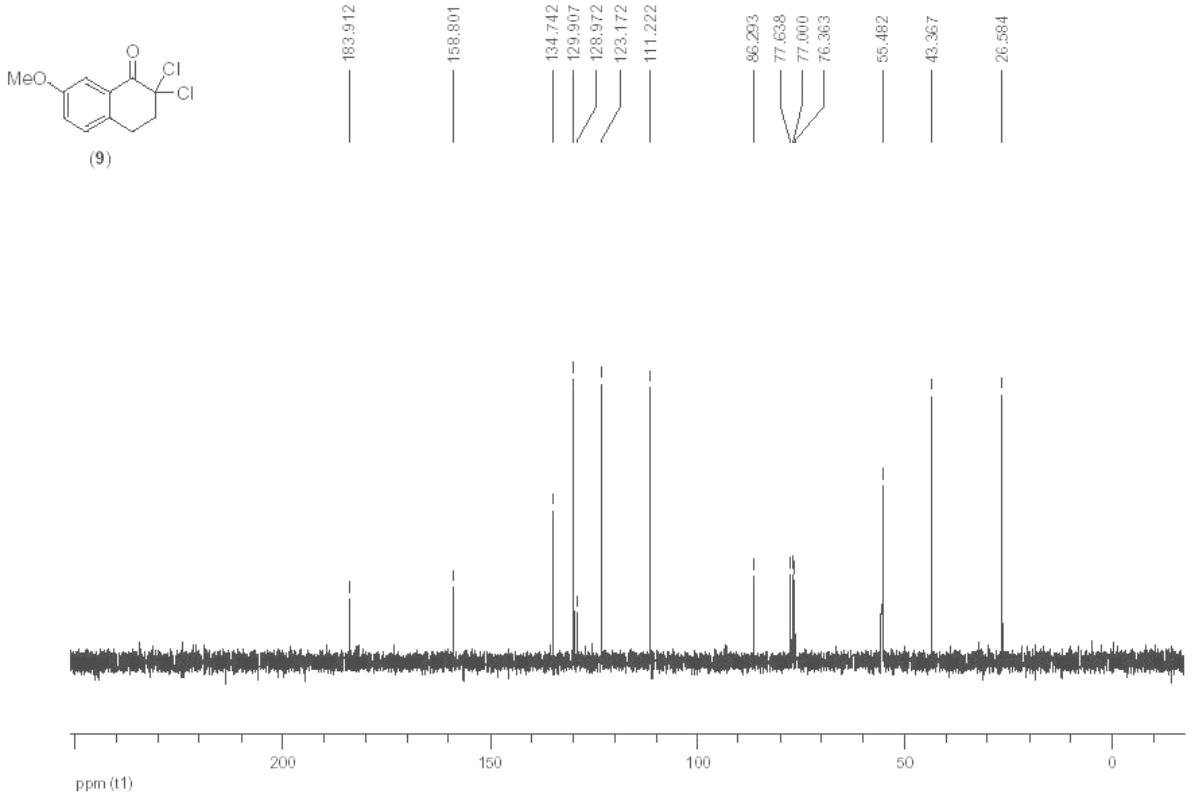

Figure S3. ^{13}C NMR spectrum (50 MHz, $CDCl_3$) of compound **9**.

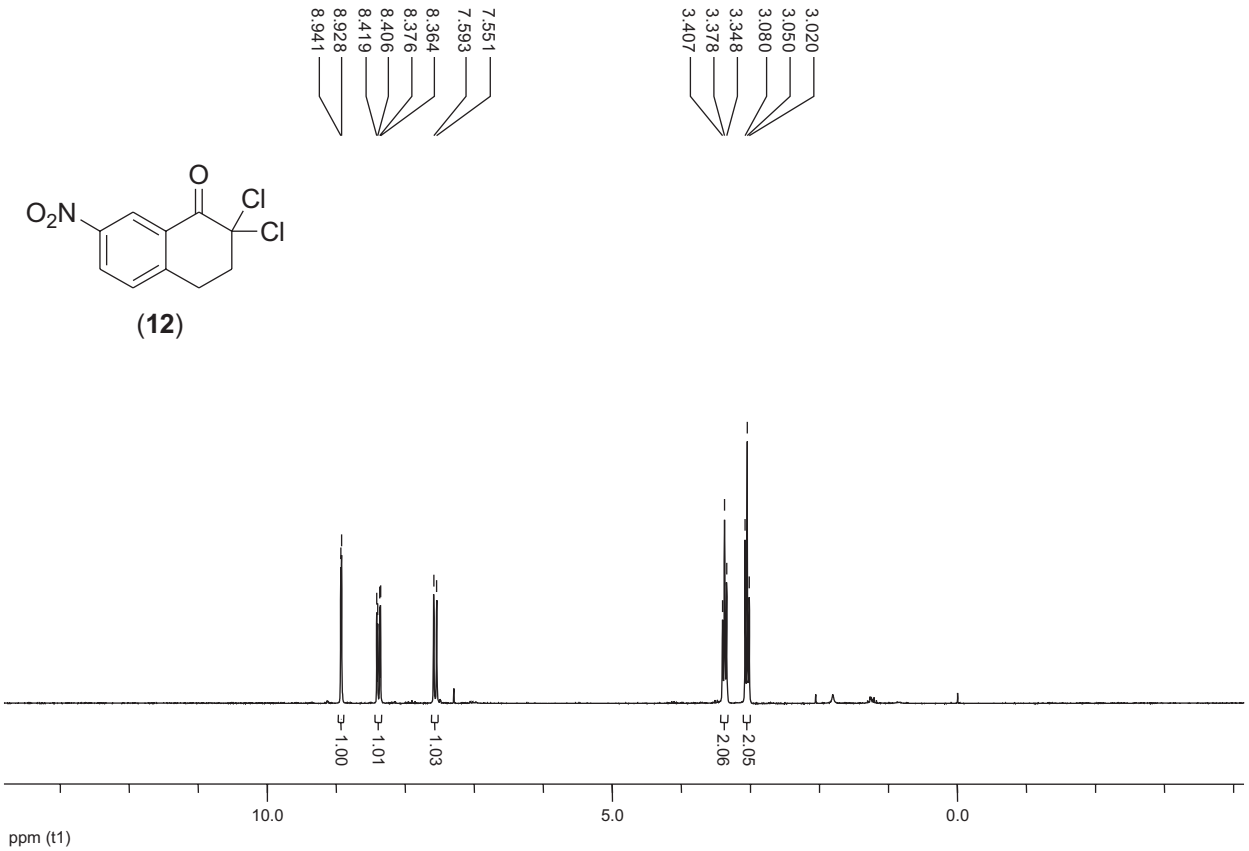

Figure S4. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **12**.

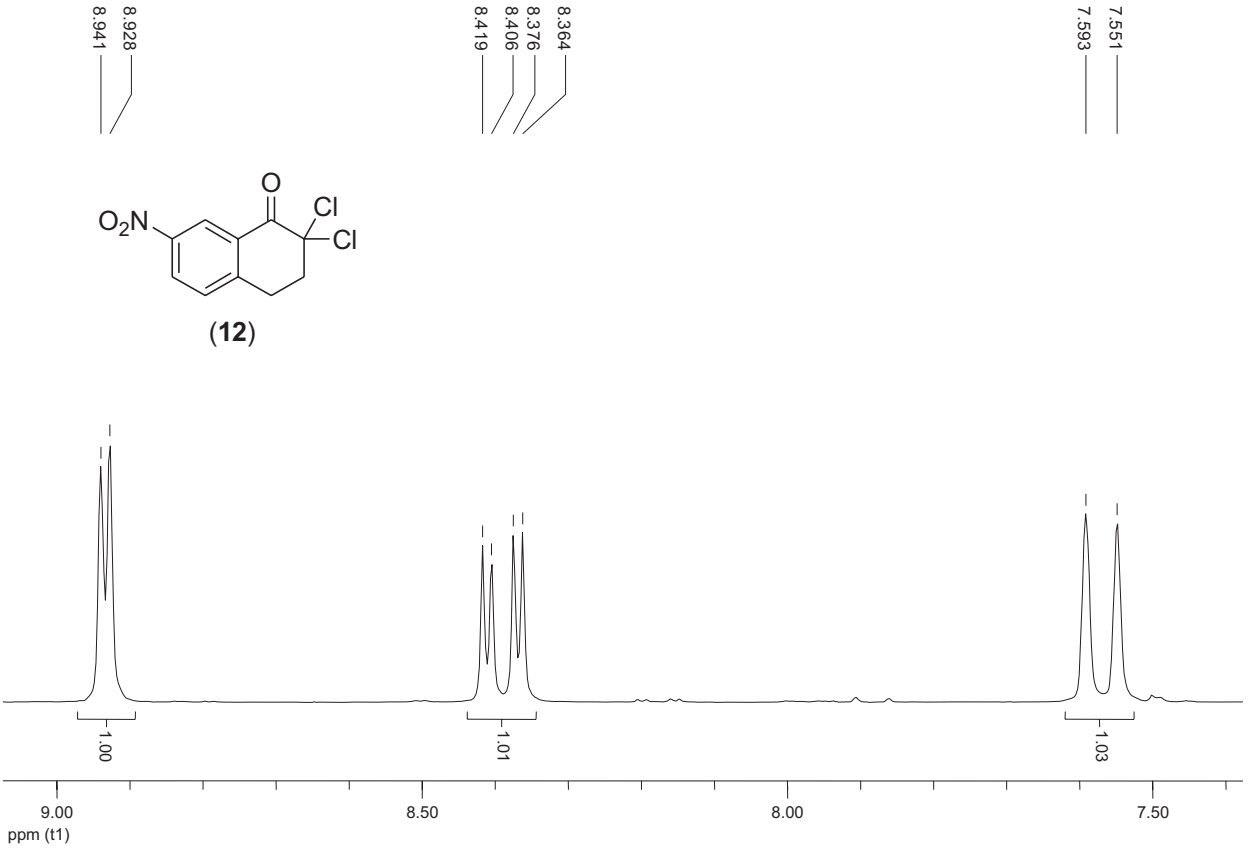

Figure S5. Detail of the ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **12**.

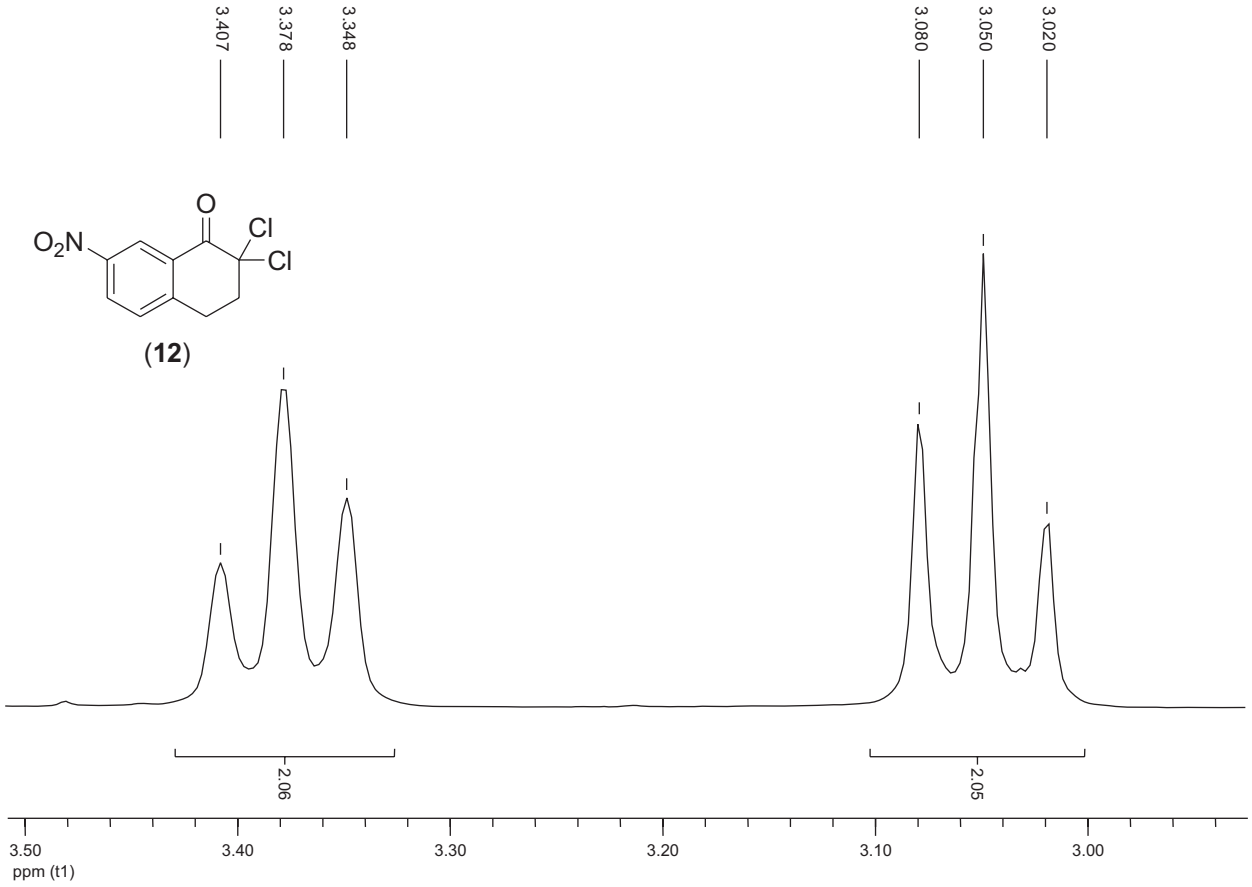

Figure S6. Detail of the ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **12**.

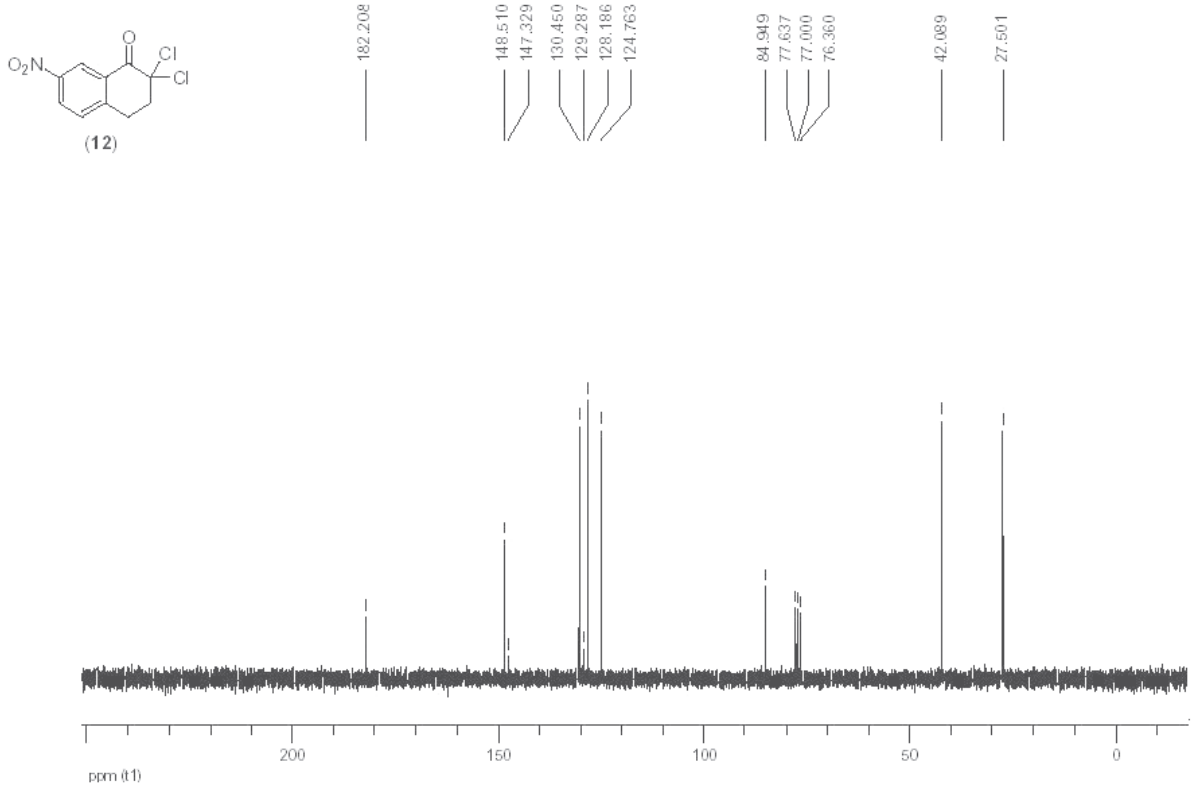

Figure S7. ^{13}C NMR spectrum (50 MHz, $CDCl_3$) of compound **12**.

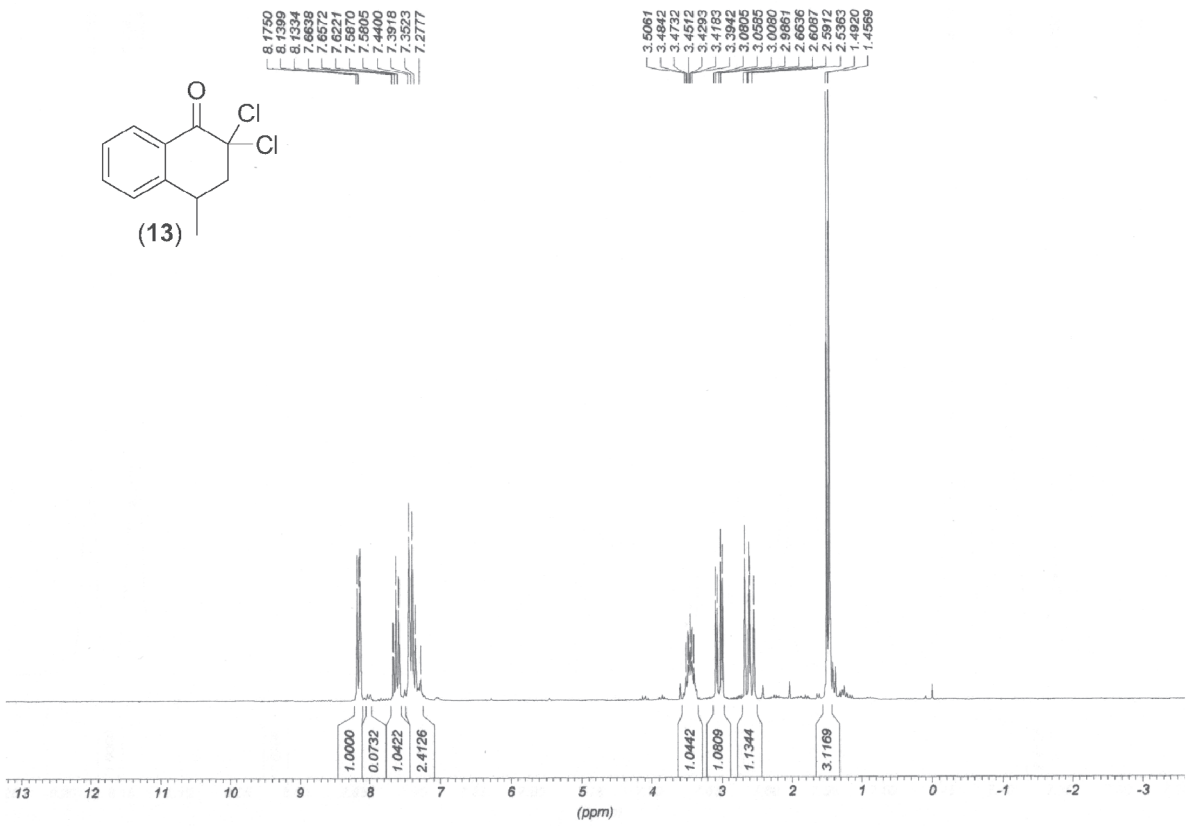

Figure S8. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **13**.

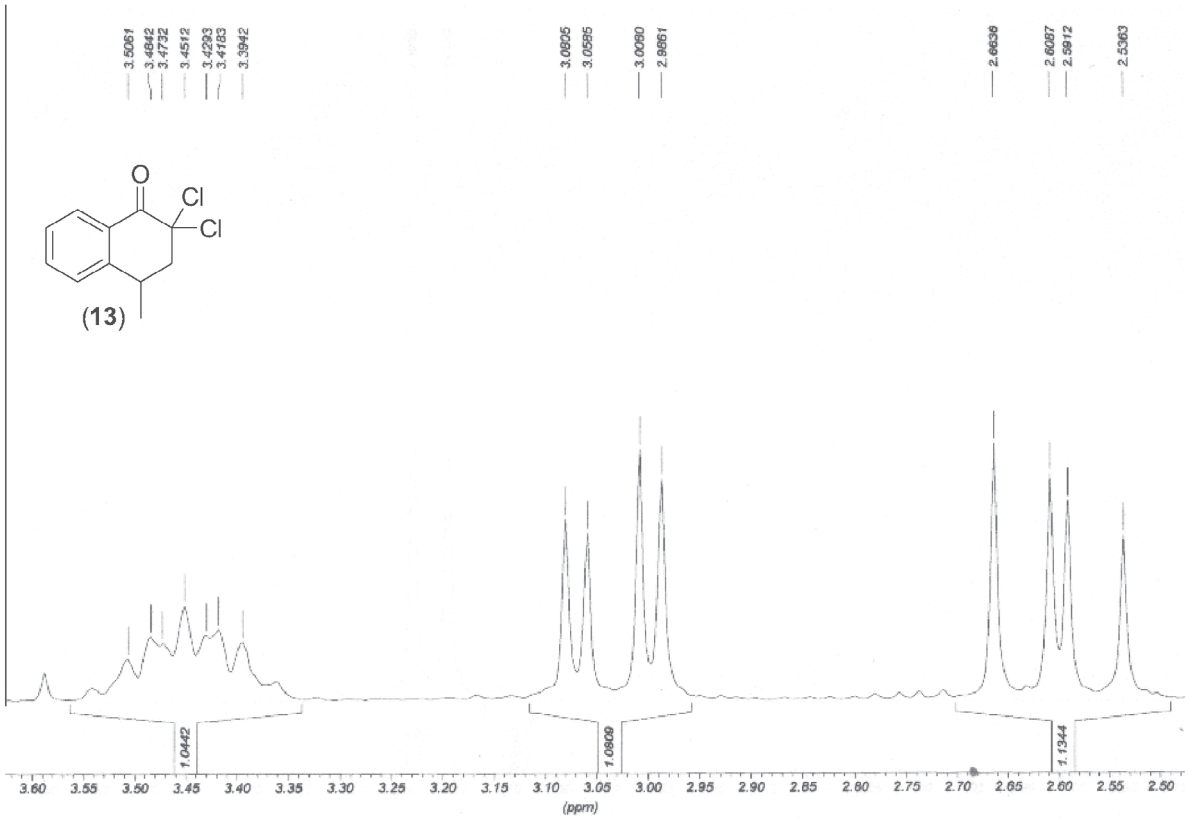

Figure S9. Detail of the ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **13**.

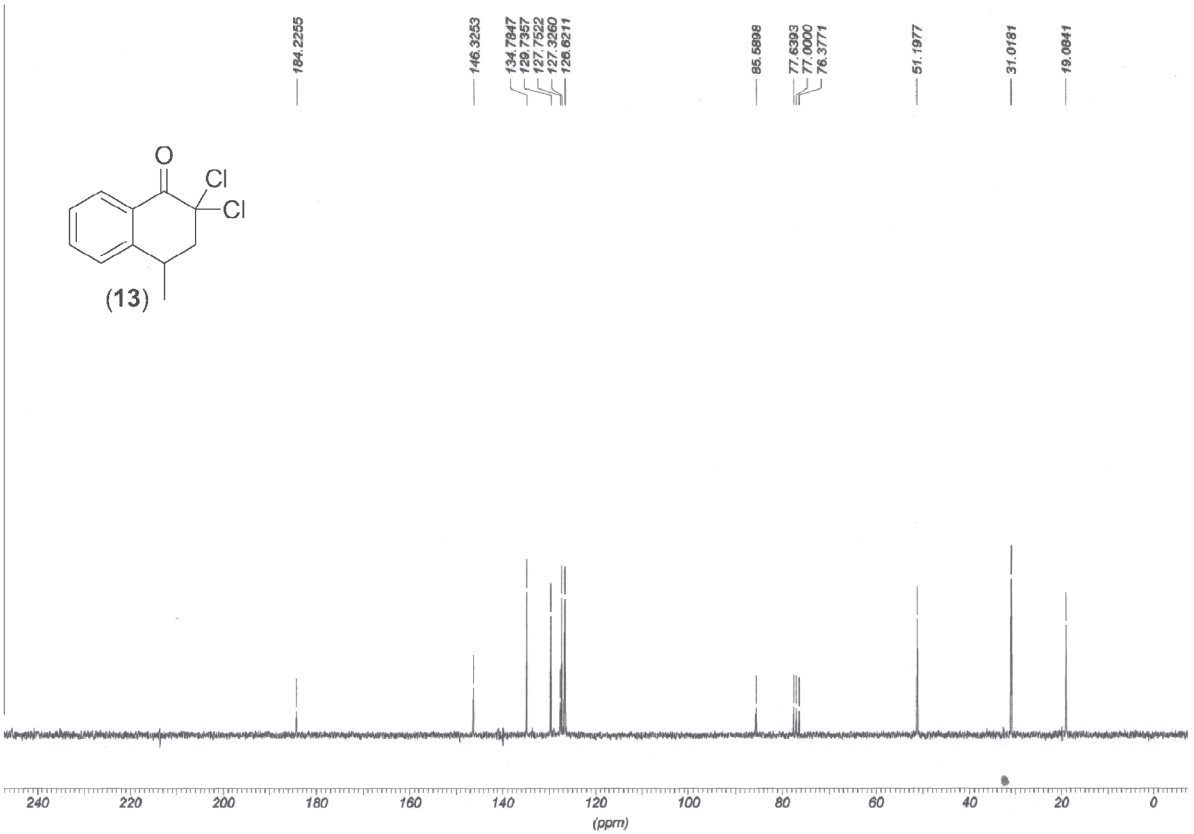

Figure S10. ^{13}C NMR spectrum (50 MHz, $CDCl_3$) of compound **13**.

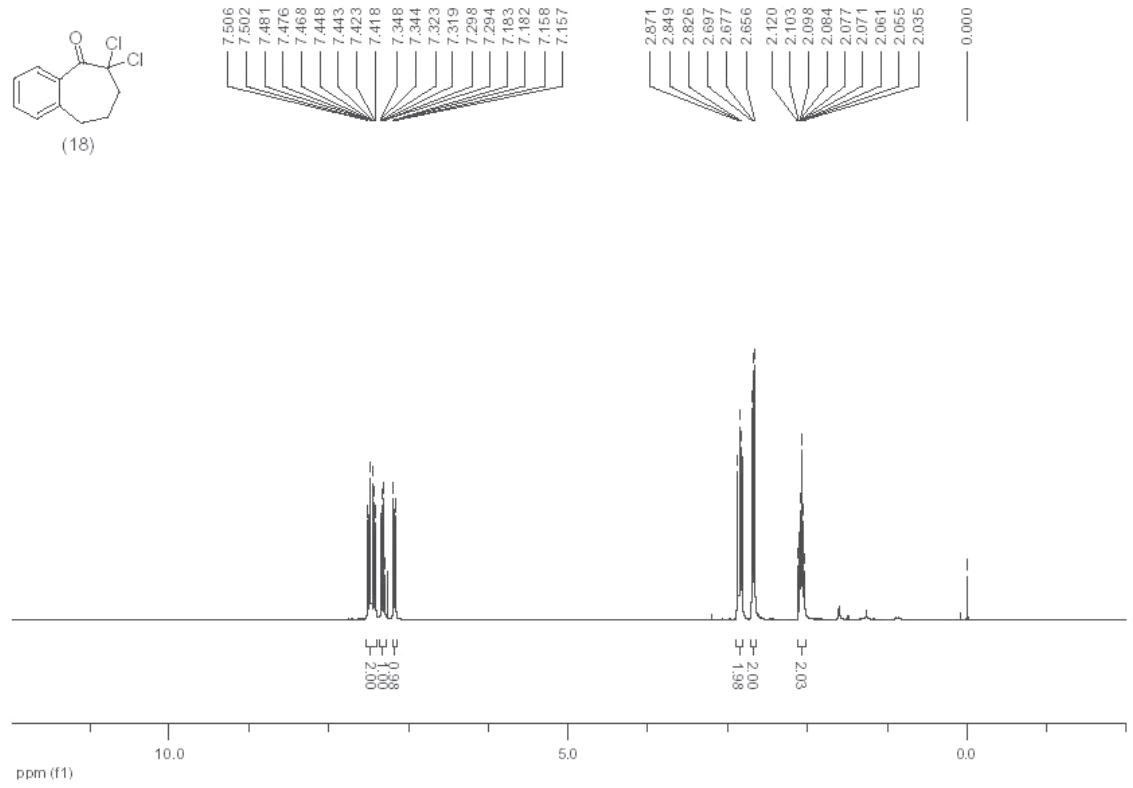

Figure S11. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **18**.

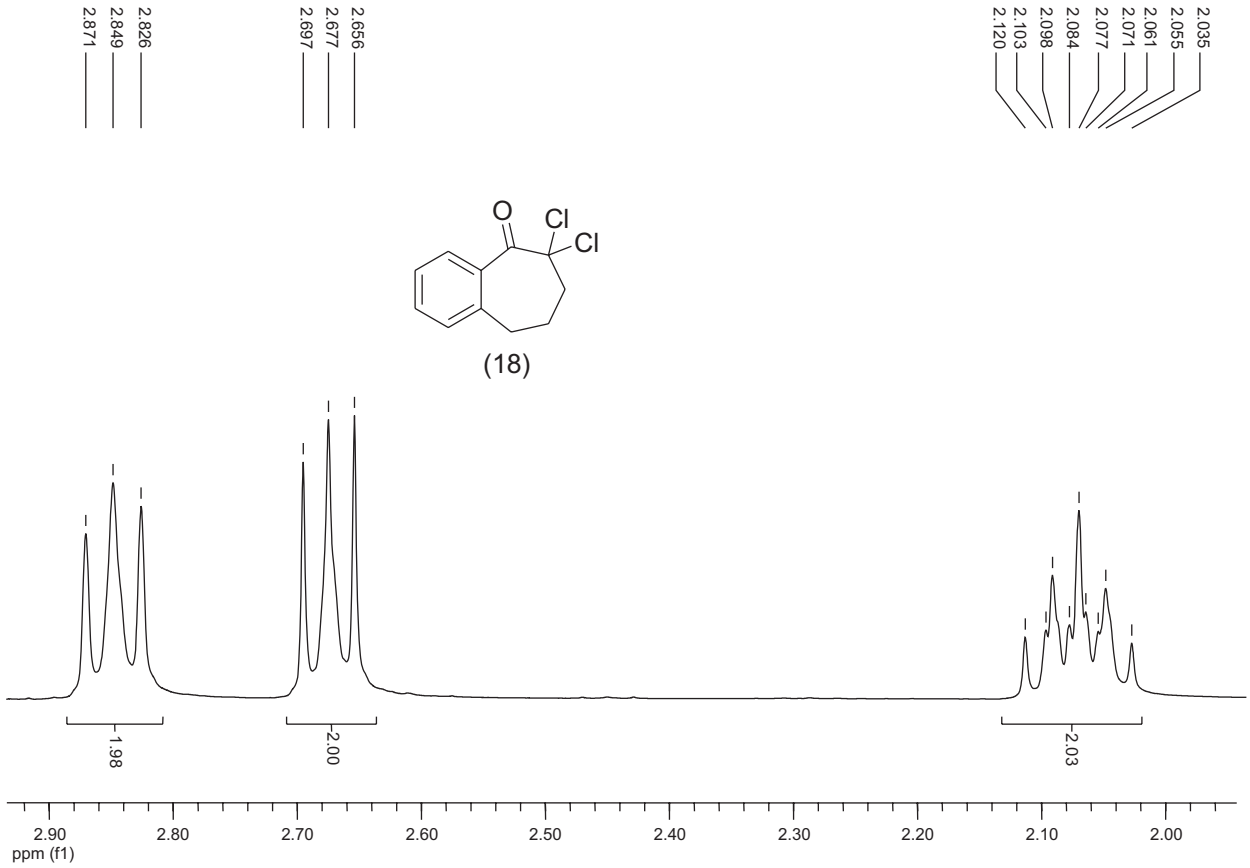

Figure S12. Detail of the ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **18**.

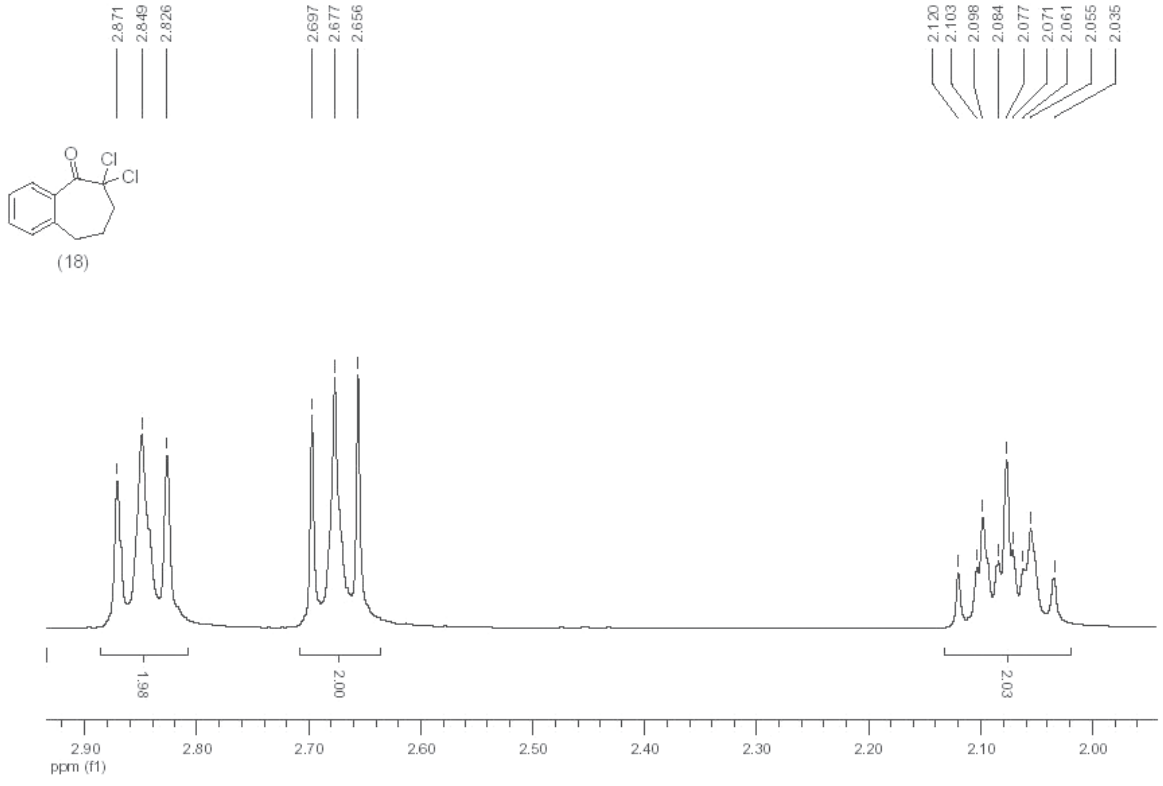

Figure S13. Detail of the ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **18**.

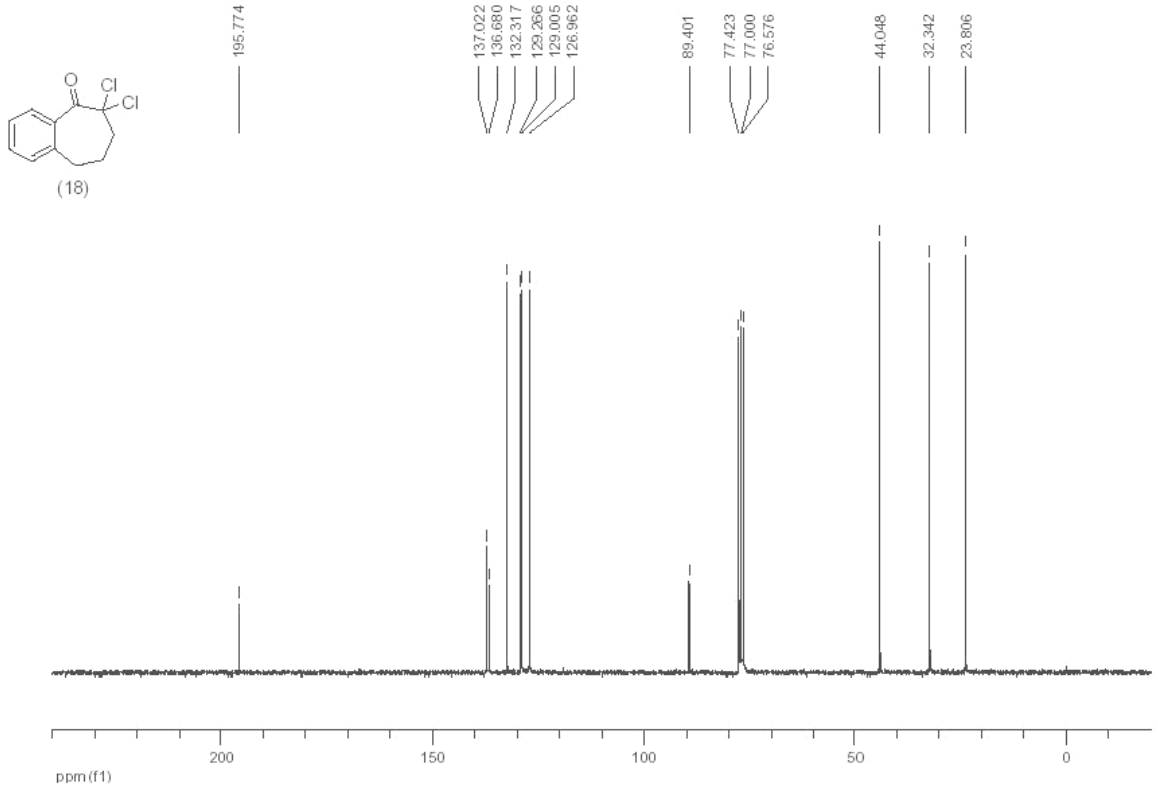

Figure S14. ^{13}C NMR spectrum (50 MHz, $CDCl_3$) of compound **18**.