Simple and quick preparation of α-thiocyanate ketones in hydroalcoholic media. Access to 5-aryl- 2-imino-1,3-oxathiolanes

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Electronic Supplementary Information

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1. General

Ketones **1a**, **2a**, **3a**, **4a** and **5a**, alkyl halides **7a**, **8a** and **9a** and $NaBH_4$ were purchased either from Aldrich or Alfa Aesar. Pure NH_4SCN and KSCN salts were purchased from Riedel-de Haën. All other reagents and solvents were of the highest quality available. Compounds **1b**,[1,2] **2b**,[3,4] **4b**,[4,5] **5b**,[4] **6b**,[6,7] **7b**,[8,9] **8b**[10] and **9b**[11] are known and their physical properties were in agreement with those previously reported.

Flash chromatography was performed using silica gel 60 (230-400 mesh). IR spectra were recorded on a Perkin-Elmer 1720-X infrared Fourier transform spectrophotometer on NaCl pellets. ^{1}H-, ^{13}C-NMR, and DEPT were obtained using DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) spectrometer for routine experiments. The chemical shifts (δ) values are given ppm and the coupling constants (J) in Hertz (Hz). ESI$^+$ was used to record routine mass spectra (MS) and ESI- TOF for HRMS.

2. Experimental procedures

2.1. Synthesis of 3'-nitro-α-chloroacetophenone **6a**

To a solution of the corresponding acetophenone derivative (1 equiv.) and *p*-TsOH (1.5 equiv.) in MeCN (5 mL), *N*-chlorosuccinimide (NCS, 1 equiv.) was added.[12] The reaction mixture was heated under gentle reflux and stirred until no starting material was detected (TLC). Then, the solvent was concentrated under vacuo and the residue subjected to column chromatography (silica gel) using CH_2Cl_2 / petroleum ether mixtures as eluent (isolated yield: 85%).

2.2. General procedure for the preparation of α-thiocyanate ketones in alcohol-water mixtures

To a solution of 2.5 mmol of the corresponding α-halo ketone **1a**-**6a** in 2-propanol (1 mL), 2.7 mmol of NH_4SCN dissolved in water (1 mL) were added and the mixture subjected to vigorous stirring at room temperature. When the starting material was totally consumed (TLC), 5 mL of water were added, and the mixture was filtered through a sintered glass funnel. The solid was washed with water and dried under reduced pressure. The purity was excellent (NMR and MS) and no further purification steps were required.

2.3. General procedure for the preparation of α-thiocyanate ketones in pure alcohol

To a solution of 2.5 mmol of α-halo ketone in the alcohol (1 mL), 2.7 mmol of NH_4SCN (as ground solid) were added and the mixture subjected to vigorous stirring at room temperature. When the starting material was totally consumed

(TLC), 5 mL of water were added, and the mixture was filtered through a sintered glass funnel. The solid was washed with water and dried under reduced pressure. The purity was excellent (NMR and MS) and no further purification steps were required.

2.4. General procedure for the preparation of alkyl thiocyanate in alcohol-water mixtures

To a solution of 2.5 mmol of alkyl halide in the corresponding alcohol (1 mL), 2.7 mmol of NH_4SCN dissolved in water (1 mL) were added and the mixture subjected to vigorous stirring at 50ºC in a sealed tube. When the starting material was totally consumed (TLC), 5 mL of water were added and the mixture was partitioned with Cl_2CH_2 (3 x 5 ml). The combined organic layers were dried over Na_2SO_4 and the solvent distilled off at low temperature under reduced pressure. The crude material was subjected to column chromatography in silica gel with EtOAc/petroleum ether mixtures (5-30%) as eluent.

2.5. General procedure for the preparation of alkyl thiocyanate in pure alcohol

To a solution of 2.5 mmol of alkyl halide in the corresponding alcohol (1 mL), 2.7 mmol of NH_4SCN (as ground solid) were added, and the mixture subjected to vigorous stirring at room temperature (except for **8a**: 50º C, sealed tube). When the starting material was totally consumed (TLC), 5 mL of water were added, and the mixture was partitioned. The organic layer was dried over Na_2SO_4. The purity was excellent (NMR) and no further purification steps to obtain pure **8b** were required [in the case of **7b** it was subjected to a column chromatography step in silica gel with EtOAc/petroleum ether mixtures (5-30%) as eluent].

2.6. General procedure for the preparation of 5-aryl-2-imino-1,3-oxathiolane

To a solution of 1.13 mmol of α-thiocyanate ketone in MeOH (2 mL), 0.3 mmol (1.2 equiv.) of $NaBH_4$ were added in portions at 0ºC. When no starting material was detected (TLC), the solvent was distilled off at low temperature under reduced pressure and the crude redissolved in CH_2Cl_2 and partitioned with water. Combined organic layers were dried over Na_2SO_4 and the solvent was distilled off at low temperature under reduced pressure, obtaining thus the pure final compounds with no further purification steps. Products must be stored under N_2 atmosphere at -20ºC.

2.7. Procedure for the preparation of 2-imino-5-phenyl-1,3-oxathiolane in an one-pot three-steps procedure starting from α-bromoacetophenone

To a solution of 500 mg of α-bromoacetophenone (2.5 mmol) in 2 mL of MeOH, 206 mg (2.7 mmol) of NH_4SCN (as ground solid) were added. The mixture was subjected to vigorous stirring and after 3 minutes, 25 mg of $NaBH_4$ (0.3 mmol, 1.2 equiv.) were added in portions at 0º C (ice bath). After the α-thiocyano acetophenone completely reacted, a work-up as described in paragraph *2.5.* was achieved.

2.8. Determination of pH

Different solutions were made (see Table S1) and pH was measured. In case no water was used, 2 mL of the corresponding solution was added to 2 mL of distilled water before measurement.

Table S1. Measurement of different solution pHs at 20ºC.

Solution	pH
1b in H_2O/2-propanol 1:1 v v^{-1}	6
1b+$NaBH_4$ in H_2O/2-propanol 1:1 v v^{-1}	9
1b+$NaBH_4$ in H_2O	9.5
1b+$NaBH_4$ in MeOH	9.5
1b+$NaBH_4$ in THF/MeOH 90:10 v v^{-1}	7

As can be noted, when adding sodium borohydride, solution pH turned basic in all cases due to the presence of hydride and hydroxide/methoxide species. Only in case of THF pH remained neutral, due to the fact that the salt did not solubilise in a high extent, due to this, cyclisation reaction was much slower than in case of pure MeOH (as noted through ^{1}H-NMR).

3. Compounds characterisation

3.1. 2-imino-5-phenyl-1,3-oxathiolane **1c**

White solid; **m.p.** (CH_2Cl_2) 89-91ºC; **IR** (nujol) 3163, 1690, 1639 and 1570 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ 3.43 (*dd*, 1H, $|^2J_{HH}|$ 11, $^3J_{HH}$ 9 Hz), 3.61 (*dd*, 1H, $|^2J_{HH}|$ 11, $^3J_{HH}$ 6 Hz), 5.56 (*dd*, 1H, $^3J_{HH}$ 9, $^3J_{HH}$ 6 Hz) and 7.38 (*m*, 5H); **^{13}C-NMR** ($CDCl_3$, 75.5 MHz) δ 39.6, 84.1, 125.5, 128.6, 128.8, 136.8 and 168.9; **HRMS** (ESI-TOF) *calculated for* $C_9H_{10}NOS$ $[M+H]^+$: 180.0483, *found*: 180.0478.

3.2. 2-imino-5-(4-nitrophenyl)-1,3-oxathiolane **2c**

Yellow solid; **m.p.** (CH_2Cl_2) 116-118º C; **IR** (nujol) 3344, 1663, 1568 and 1522 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ 3.42 (*dd*, 1H, $|^2J_{HH}|$ 11, $^3J_{HH}$ 9 Hz), 3.75 (*dd*, 1H, $|^2J_{HH}|$ 11, $^3J_{HH}$ 6 Hz), 5.69 (*dd*, 1H, $^3J_{HH}$ 9, $^3J_{HH}$ 6 Hz), 7.59 (*d*, 2H, $^3J_{HH}$ 9 Hz) and 8.24 (*d*, 2H, $^3J_{HH}$ 9 Hz); **^{13}C-NMR** ($CDCl_3$, 75.5 MHz) δ 39.4, 82.3, 124.0, 126.4, 144.0, 148.0 and 168.1; **HRMS** (ESI-TOF) *calculated for* $C_9H_9N_2O_3S$ $[M+H]^+$: 225.0334, *found*: 225.0328.

3.3. 5-(4-chlorophenyl)-2-imino-1,3-oxathiolane **4c**

Colourless oil; **IR** (neat) 3203, 1634 and 1053 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ 3.42 (*dd*, 1H, $|^2J_{HH}|$ 11, $^3J_{HH}$ 9 Hz), 3.63 (*dd*, 1H, $|^2J_{HH}|$ 11, $^3J_{HH}$ 6 Hz), 5.57 (*dd*, 1H, $^3J_{HH}$ 9, $^3J_{HH}$ 6 Hz), 7.34 (*d*, 2H, $^3J_{HH}$ 9 Hz) and 7.38 (*d*, 2H, $^3J_{HH}$ 9 Hz, 2H); **^{13}C-NMR** ($CDCl_3$, 75.5 MHz) δ 39.7, 83.4, 127.0, 129.0, 134.9, 135.4 and 168.7; **HRMS** (ESI-TOF) *calculated for* C_9H_9ClNOS $[M+H]^+$: 214.0093, *found*: 214.0088.

3.4. 5-(3,4-dichlorophenyl)-2-imino-1,3-oxathiolane **5c**

Pale yellow oil; **IR** (neat) 3335, 1638, 1566, 1030 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ 3.40 (*dd*, 1H, $|^2J_{HH}|$ 11, $^3J_{HH}$ 9 Hz), 3.66 (*dd*, 1H, $|^2J_{HH}|$ 11, $^3J_{HH}$ 6 Hz), 5.54 (*dd*, 1H, $^3J_{HH}$ 9, $^3J_{HH}$ 6 Hz), 7.24 (*dd*, 1H, $^3J_{HH}$ 8, $|^4J_{HH}|$ 2 Hz), 7.47 (*d*, 1H, $^3J_{HH}$ 8 Hz), 7.51 (*d*, 1H, $|^4J_{HH}|$ 2 Hz); **^{13}C-NMR** ($CDCl_3$, 75.5 MHz) δ 39.5, 82.4, 124.8, 127.8, 130.8, 133.1 (2C), 137.1 and 168.2; **HRMS** (ESI-TOF) *calculated for* $C_9H_8Cl_2NOS$ [M+H]$^+$: 247.9704, *found*: 247.9698.

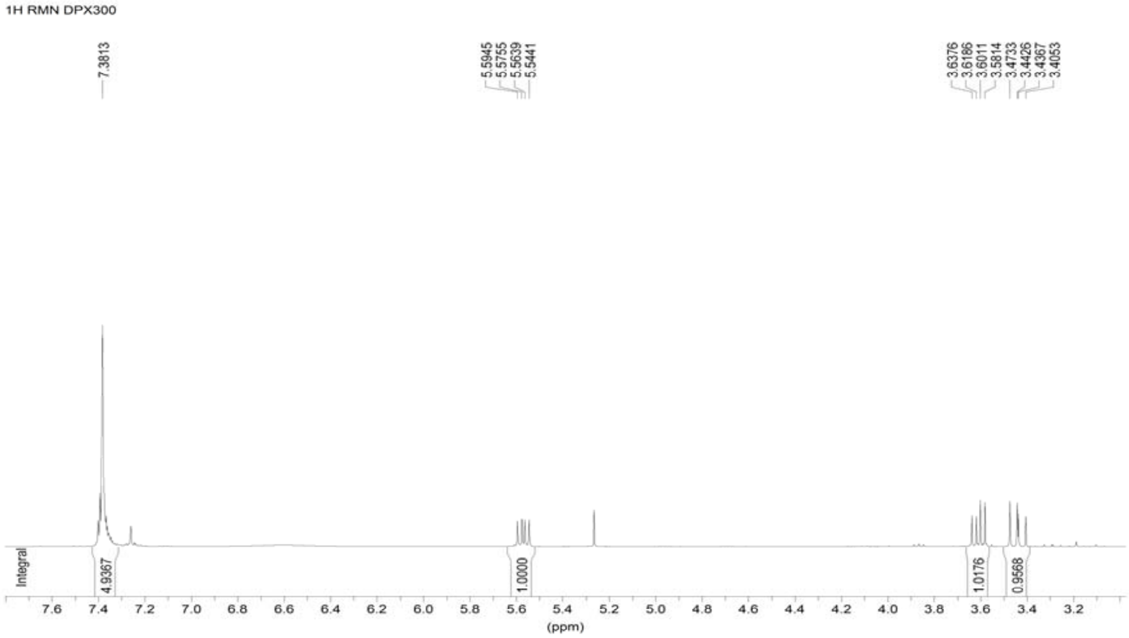
3.5. 2-imino-5-(3-nitrophenyl)-1,3-oxathiolane **6c**

White solid; **m.p.** (CH_2Cl_2) 112-113ºC; **IR** (nujol) 3419, 1630, 1526 and 1307 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ 3.46 (*dd*, 1H, $|^2J_{HH}|$ 11, $^3J_{HH}$ 9 Hz), 3.76 (*dd*, 1H, $|^2J_{HH}|$ 11, $^3J_{HH}$ 6 Hz), 5.69 (*dd*, 1H, $^3J_{HH}$ 9, $^3J_{HH}$ 6 Hz), 7.60 (*apparent t*, 1H, $^3J_{HH}$ 8 Hz), 7.77 (*d*, 1H, $^3J_{HH}$ 8 Hz), 8.23 (*dd*, 1H, $^3J_{HH}$ 8, $|^4J_{HH}|$ 2 Hz) and 8.27 (*d*, 1H, $|^4J_{HH}|$ 2 Hz); **^{13}C-NMR** ($CDCl_3$, 75.5 MHz) δ 39.5, 82.4, 120.7, 123.8, 130.0, 131.5, 139.2, 148.3 and 168.1; **HRMS** (ESI-TOF) *calculated for* $C_9H_9N_2O_3S$ [M+H]$^+$: 225.0334, *found*: 225.0327.

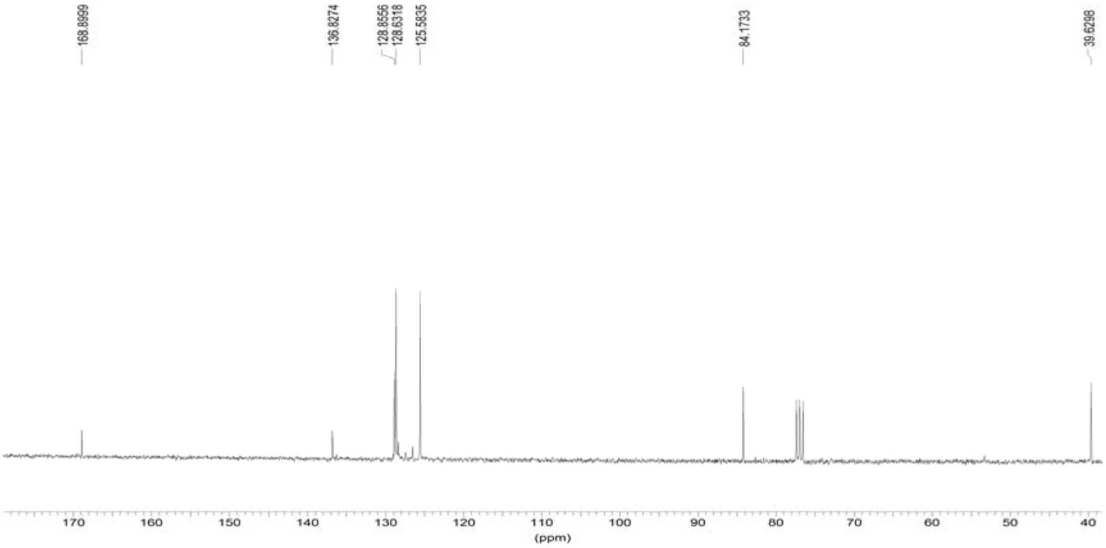
4. NMR Spectra

4.1. 2-imino-5-phenyl-1,3-oxathiolane **1c**

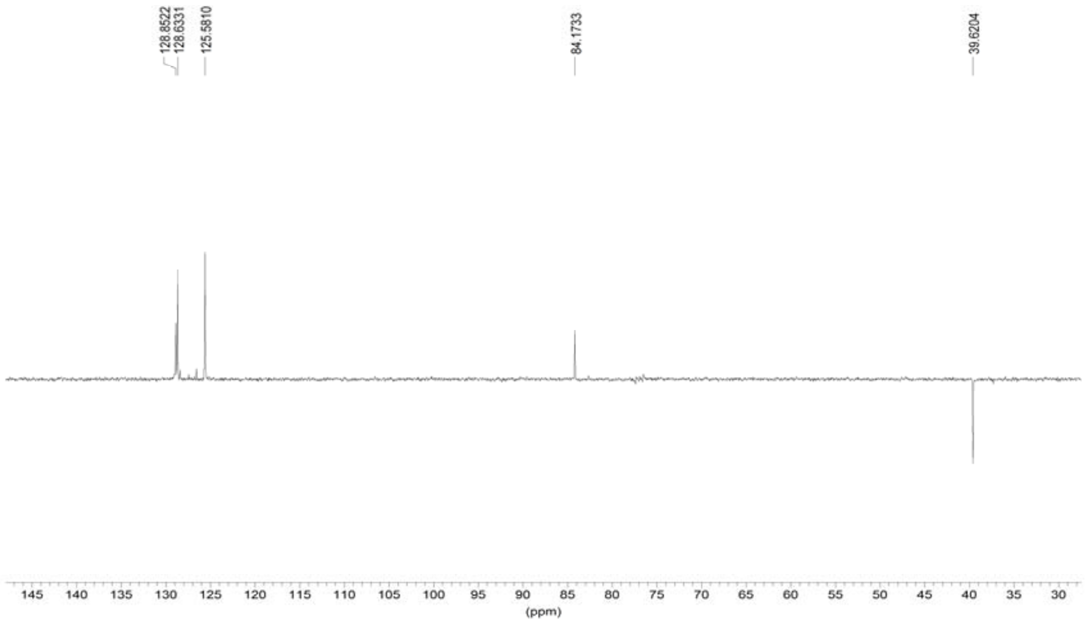
^{1}H-NMR



^{13}C-NMR

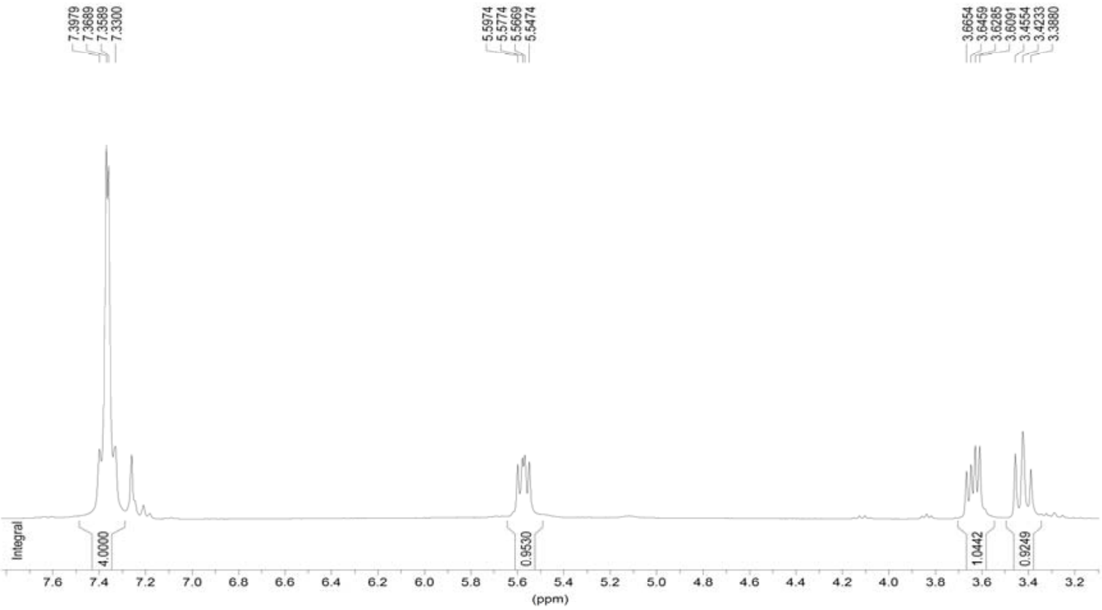


DEPT 135º-NMR



4.2. 5-(4-chlorophenyl)-2-imino-1,3-oxathiolane **4c**

^{1}H-NMR



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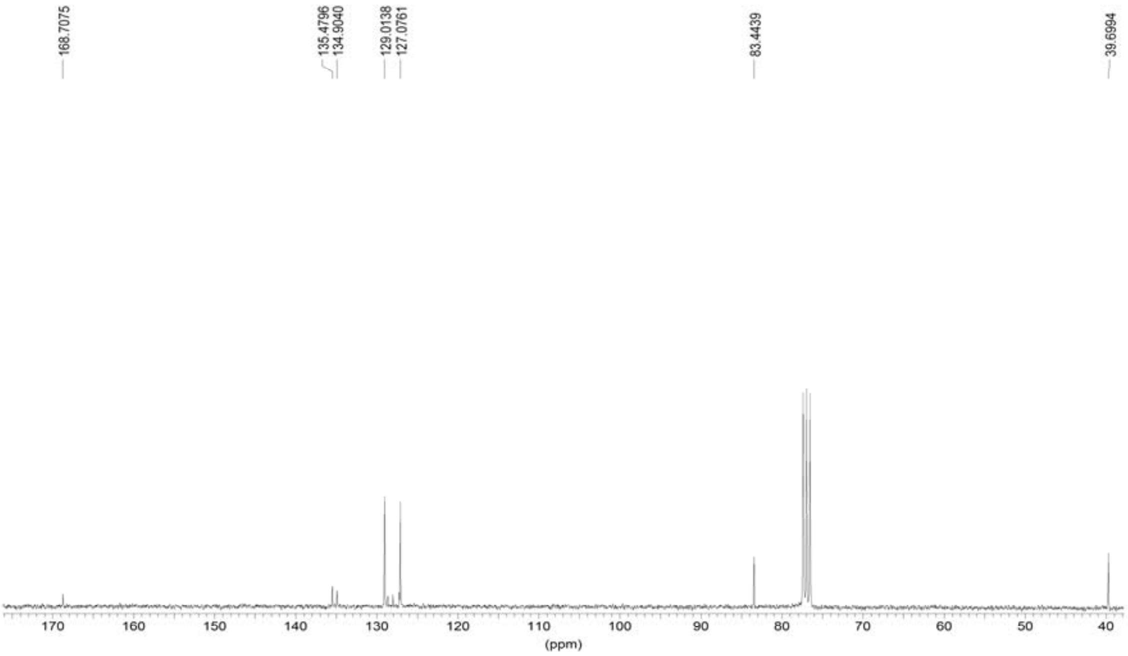

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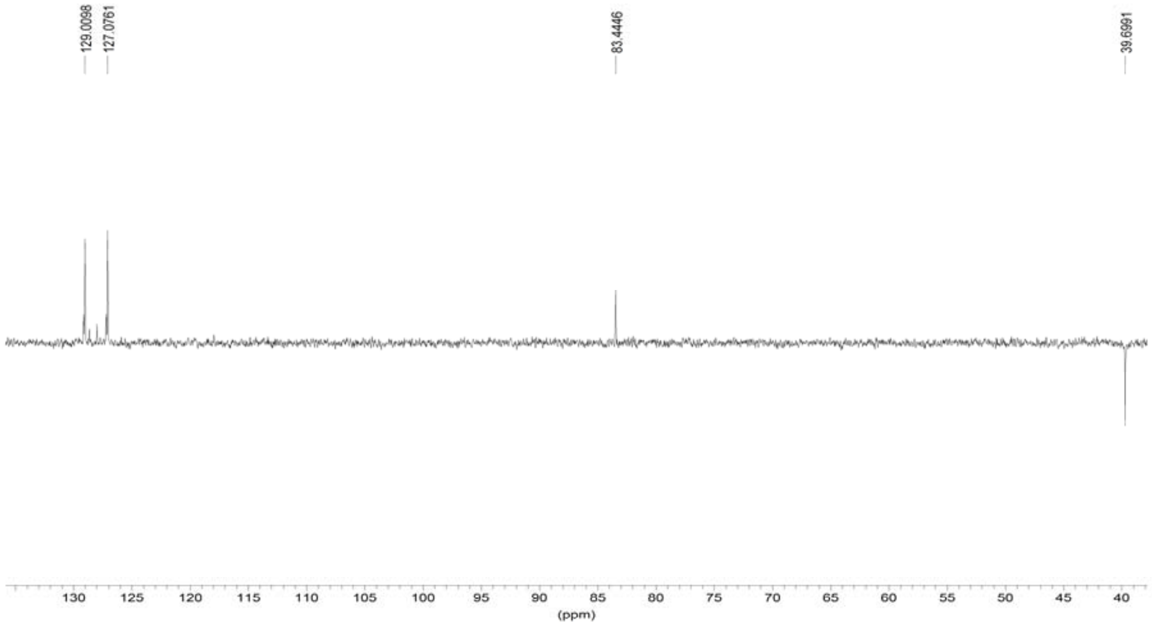

4.3. 5-(3,4-dichlorophenyl)-2-imino-1,3-oxathiolane **5c**

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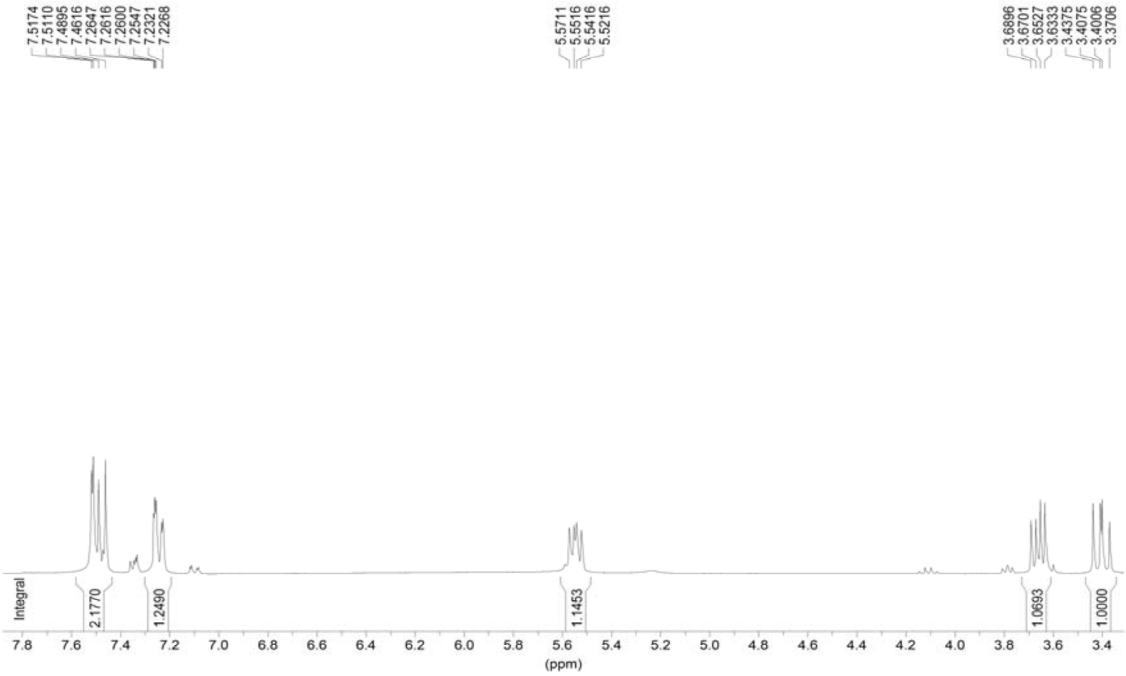

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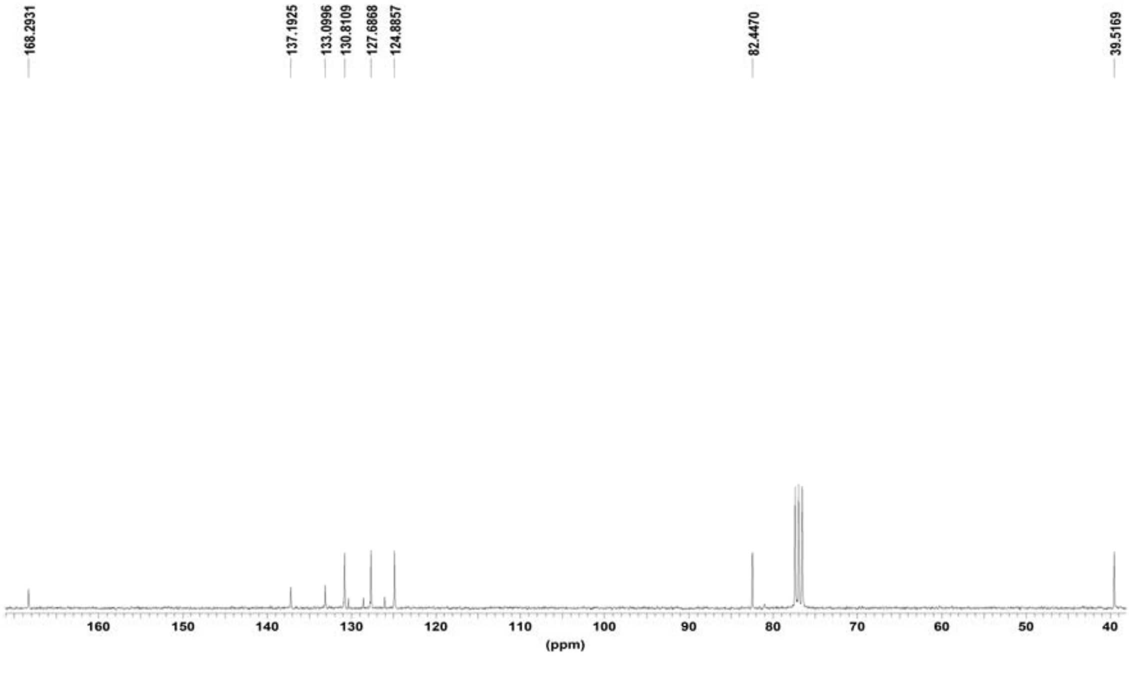

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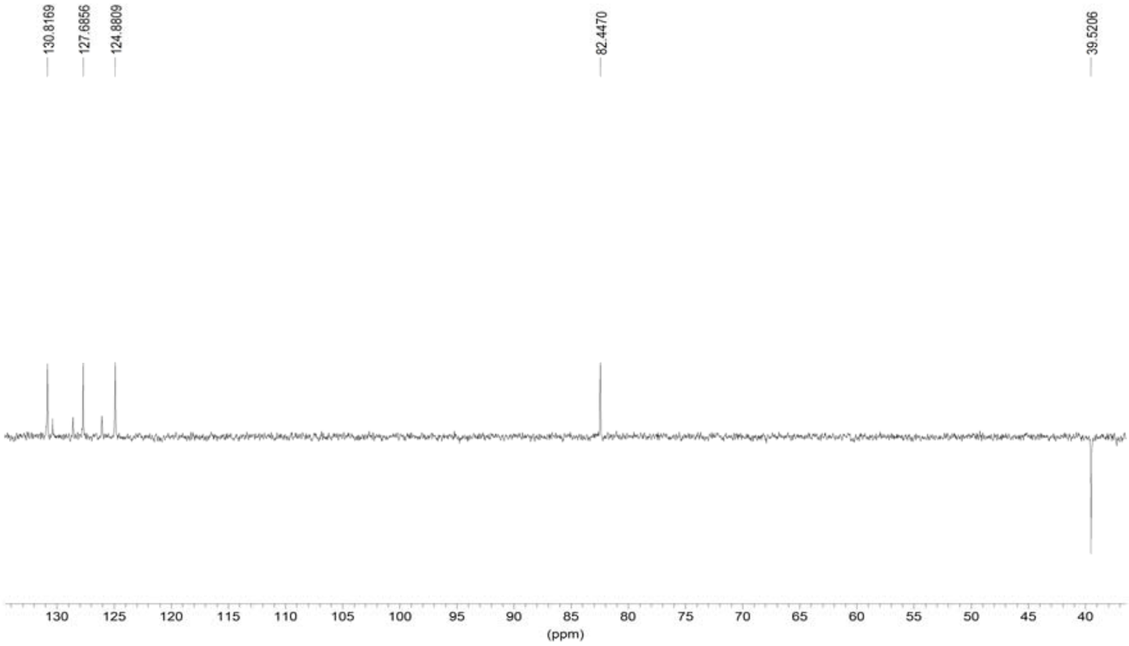
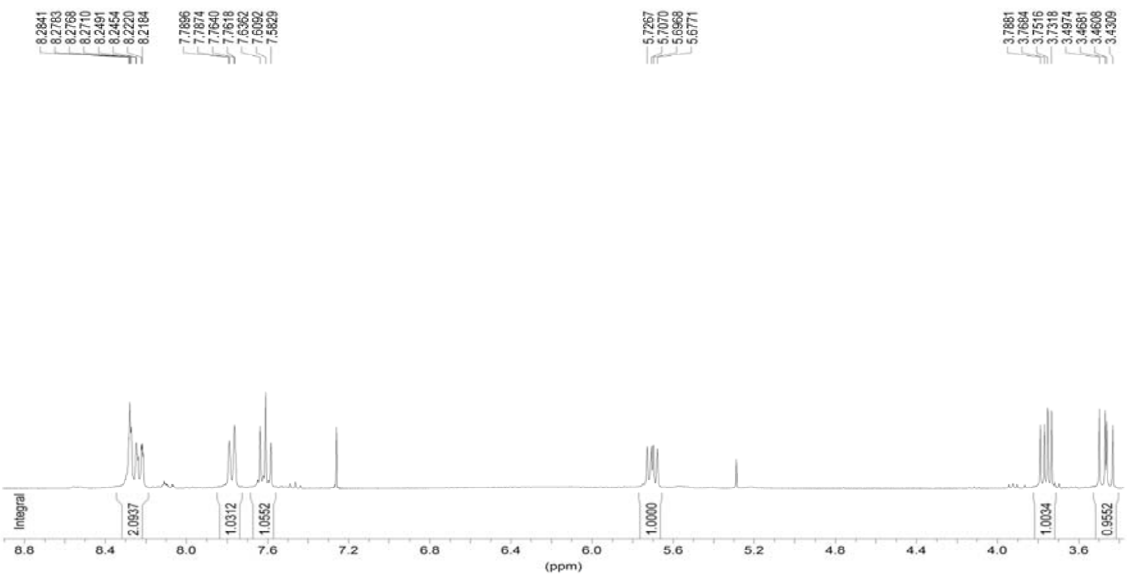


4.4. 2-imino-5-(3-nitrophenyl)-1,3-oxathiolane **6c**

^{1}H-NMR



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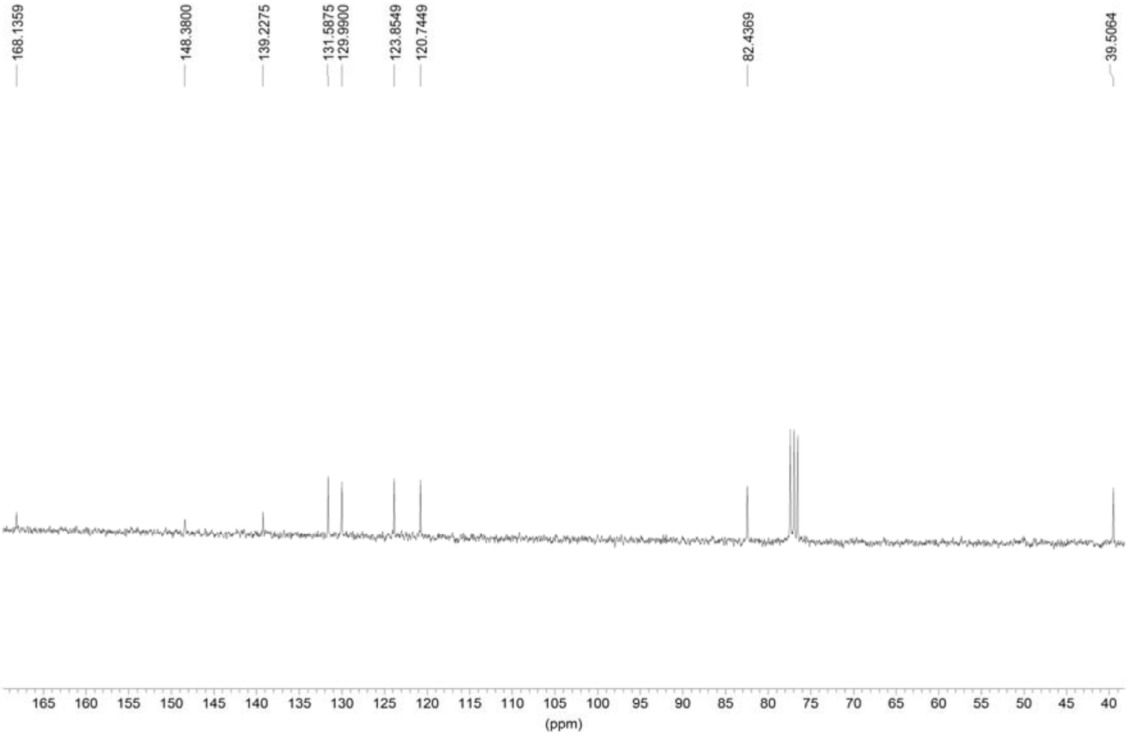

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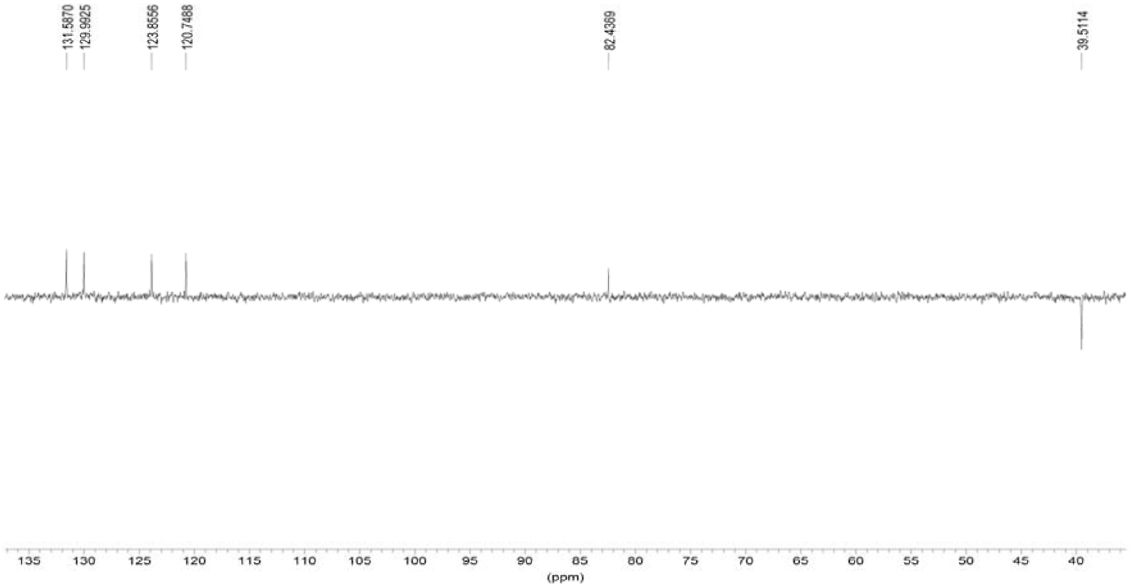

5. References

1. O. Prakash, H. Kaur, H. Batra, N. Rani, S. P. Singh and R. M. Moriarty, *J. Org. Chem.*, 2001, **66**, 2019.

2. J. S. Yadav, B. V. S. Reddy, U. V. S. Reddy and D. N. Chary, *Synthesis*, 2008, **8**, 1283.

3. J. Rudolph, H. Theis, R. Hanke, R. Endermann, L. Johannsen and F.-U. Geschke, *J. Med. Chem.*, 2001, **44**, 619.

4. H. Boehland, I. Berg, K. Heutzenroeder, H. Dehne and J. Teller, Germany (East), DD 284223, A5 19901107, CAN 1991, 115:40790.

5. V. Nair, L. G. Nair, T. G. George and A. Augustine, *Tetrahedron*, 2000, **56**, 7607.

6. G. E. Lukes and G. P. Wilsey, Jr., USA, US 3222248, 19651207, CAN 1966, 64:35662.

7. M. H. Elnagdi, A. H. H. Elghandour and K. U. Sadek, *Spectrochim. Acta A*, 1990, **46A**, 51.

8. P.-Y. Renard, H. Schwebel, P. Vayron, E. Leclerc, S. Dias and C. Mioskowski, *Tetrahedron Lett.*, 2001, **42**, 8479.

9. T. Ando, J. H. Clark, D. G. Cork, M. Fujita and T. Kimura, *J. Org. Chem.*, 1987, **52**, 681.

10. I. Norihito, I. Tatsue, Y. Masae and N. Akira, Earth Chemical CO, Japan, JP 56086109, 19810713, CAN 1981, 95:145287.

11. Y. Ju, D. Kumar and R. S. Varma, *J. Org. Chem.*, 2006, **71**, 6697.

12. J. C. Lee, Y. H. Bae and S. K.Chang, *Bull. Korean Chem. Soc.* 2003, **24**, 407.