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

Fabricio R. Bisogno, Aníbal Cuetos, Iván Lavandera and Vicente Gotor*

Electronic Supplementary Information

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1. General

Ketones 1a, 2a, 3a, 4a and 5a, alkyl halides 7a, 8a and 9a and NaBH₄ were purchased either from Aldrich or Alfa Aesar. Pure NH₄SCN and KSCN salts were purchased from Riedel-de Haën. All other reagents and solvents were of the highest quality available. Compounds 1b, 2b, 4b, 5b, 6b, 7b, 8b, 9b, 10 and 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. ¹H-, ¹³C-NMR, and DEPT were obtained using DPX-300 (¹H, 300.13 MHz and ¹³C, 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. 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$_2$Cl$_2$ / 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$_4$SCN 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$_4$SCN (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 NH₄SCN dissolved in water (1 mL) were added and the mixture subjected to vigorous stirring at 50°C in a sealed tube. When the starting material was totally consumed (TLC), 5 mL of water were added and the mixture was partitioned with Cl₂CH₂ (3 x 5 ml). The combined organic layers were dried over Na₂SO₄ 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 NH₄SCN (as ground solid) were added, and the mixture subjected to vigorous stirring at room temperature (except for 8a: 50° 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 Na₂SO₄. 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 NaBH₄ were added in portions at 0°C. When no starting material was detected (TLC), the solvent was distilled off at low temperature under reduced pressure and the crude redissolved in CH₂Cl₂ and partitioned with water. Combined organic layers were dried over Na₂SO₄ 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 N₂ atmosphere at -20°C.

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 NH₄SCN (as ground solid) were added. The mixture was subjected to vigorous stirring and after 3 minutes, 25 mg of NaBH₄ (0.3 mmol, 1.2 equiv.) were added in portions at 0°C (ice bath). After the α-thiocyanate 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.

<table>
<thead>
<tr>
<th>Solution</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b in H₂O/2-propanol 1:1 v v⁻¹</td>
<td>6</td>
</tr>
<tr>
<td>1b+NaBH₄ in H₂O/2-propanol 1:1 v v⁻¹</td>
<td>9</td>
</tr>
<tr>
<td>1b+NaBH₄ in H₂O</td>
<td>9.5</td>
</tr>
<tr>
<td>1b+NaBH₄ in MeOH</td>
<td>9.5</td>
</tr>
<tr>
<td>1b+NaBH₄ in THF/MeOH 90:10 v v⁻¹</td>
<td>7</td>
</tr>
</tbody>
</table>

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 ¹H-NMR).
3. Compounds characterisation

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

White solid; m.p. (CH$_2$Cl$_2$) 89-91°C; IR (nujol) 3163, 1690, 1639 and 1570 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ 3.43 (dd, 1H, $^3$J$_{HH}$ 11, $^3$J$_{HH}$ 9 Hz), 3.61 (dd, 1H, $^2$J$_{HH}$ 11, $^3$J$_{HH}$ 6 Hz), 5.56 (dd, 1H, $^3$J$_{HH}$ 9, $^3$J$_{HH}$ 6 Hz) and 7.38 (m, 5H); $^{13}$C-NMR (CDCl$_3$, 75.5 MHz) $\delta$ 39.6, 84.1, 125.5, 128.6, 128.8, 136.8 and 168.9; HRMS (ESI-TOF) calculated for C$_9$H$_{10}$NOS [M+H]$^+$: 180.0483, found: 180.0478.

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

Yellow solid; m.p. (CH$_2$Cl$_2$) 116-118°C; IR (nujol) 3344, 1663, 1568 and 1522 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ 3.42 (dd, 1H, $^3$J$_{HH}$ 11, $^3$J$_{HH}$ 9 Hz), 3.75 (dd, 1H, $^2$J$_{HH}$ 11, $^3$J$_{HH}$ 6 Hz), 5.69 (dd, 1H, $^3$J$_{HH}$ 9, $^3$J$_{HH}$ 6 Hz), 7.59 (d, 2H, $^3$J$_{HH}$ 9 Hz) and 8.24 (d, 2H, $^3$J$_{HH}$ 9 Hz); $^{13}$C-NMR (CDCl$_3$, 75.5 MHz) $\delta$ 39.4, 82.3, 124.0, 126.4, 144.0, 148.0 and 168.1; HRMS (ESI-TOF) calculated for C$_9$H$_{10}$N$_2$O$_3$S [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) $\delta$ 3.42 (dd, 1H, $^3$J$_{HH}$ 11, $^3$J$_{HH}$ 9 Hz), 3.63 (dd, 1H, $^2$J$_{HH}$ 11, $^3$J$_{HH}$ 6 Hz), 5.57 (dd, 1H, $^3$J$_{HH}$ 9, $^3$J$_{HH}$ 6 Hz), 7.34 (d, 2H, $^3$J$_{HH}$ 9 Hz) and 7.38 (d, 2H, $^3$J$_{HH}$ 9 Hz, 2H); $^{13}$C-NMR (CDCl$_3$, 75.5 MHz) $\delta$ 39.7, 83.4, 127.0, 129.0, 134.9, 135.4 and 168.7; HRMS (ESI-TOF) calculated for C$_9$H$_{9}$ClNOS [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) $\delta$ 3.40 ($dd$, 1H, $^{2}J_{HH}$ 11, $^{3}J_{HH}$ 9 Hz), 3.66 ($dd$, 1H, $^{2}J_{HH}$ 11, $^{3}J_{HH}$ 6 Hz), 5.54 ($dd$, 1H, $^{3}J_{HH}$ 9, $^{3}J_{HH}$ 6 Hz), 7.24 ($dd$, 1H, $^{3}J_{HH}$ 8, $^{4}J_{HH}$ 2 Hz), 7.47 (d, 1H, $^{3}J_{HH}$ 8 Hz), 7.51 (d, 1H, $^{4}J_{HH}$ 2 Hz); $^{13}$C-NMR (CDCl$_3$, 75.5 MHz) $\delta$ 39.5, 82.4, 124.8, 127.8, 130.8, 133.1 (2C), 137.1 and 168.2; HRMS (ESI-TOF) calculated for C$_9$H$_8$Cl$_2$NOS [M+H]$^+$: 247.9704, found: 247.9698.

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

White solid; m.p. (CH$_2$Cl$_2$) 112-113ºC; IR (nujol) 3419, 1630, 1526 and 1307 cm$^{-1}$; $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ 3.46 ($dd$, 1H, $^{2}J_{HH}$ 11, $^{3}J_{HH}$ 9 Hz), 3.76 ($dd$, 1H, $^{2}J_{HH}$ 11, $^{3}J_{HH}$ 6 Hz), 5.69 ($dd$, 1H, $^{3}J_{HH}$ 9, $^{3}J_{HH}$ 6 Hz), 7.60 (apparent t, 1H, $^{3}J_{HH}$ 8 Hz), 7.77 (d, 1H, $^{3}J_{HH}$ 8 Hz), 8.23 ($dd$, 1H, $^{3}J_{HH}$ 8, $^{4}J_{HH}$ 2 Hz) and 8.27 (d, 1H, $^{4}J_{HH}$ 2 Hz); $^{13}$C-NMR (CDCl$_3$, 75.5 MHz) $\delta$ 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$_9$H$_9$N$_2$O$_3$S [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 135°-NMR
4.2. 5-(4-chlorophenyl)-2-imino-1,3-oxathiolane 4c

$^1$H-NMR

$^{13}$C-NMR
DEPT 135°-NMR
4.3. 5-(3,4-dichlorophenyl)-2-imino-1,3-oxathiolane 5c

\(^1\)H-NMR

\(^{13}\)C-NMR
DEPT 135°-NMR
4.4. 2-imino-5-(3-nitrophenyl)-1,3-oxathiolane $6c$

$^1$H-NMR

$^{13}$C-NMR
DEPT 135°-NMR
5. References


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


