One-Pot Synthesis of 7-Hydroxythieno[3,2-b]pyridin-5(4H)-ones

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Abstract: Substituted 7-hydroxythieno[3,2-b]pyridin-5(4H)-ones were prepared from the corresponding β-chloropropenonitriles in one step.

Key words: 7-hydroxythieno[3,2-b]pyridin-5(4H)-one, β-substituted β-chloropropenonitrile, ethyl 4-choloracetoacetate, NMDA receptor

4-Hydroxy-2(1H)-quinolinones (I) are well known and have been studied by several groups. Moreover, 4-hydroxy-3-phenyl-2(1H)-quinolinones (II) belong to the most potent inhibitors of glycine binding to the N-methyl-D-aspartate (NMDA) receptor (Scheme 1). However, only two examples of 7-hydroxythieno[3,2-b]pyridin-5(4H)-one (III and IV) have been described. Furthermore, the synthesis of III and IV requires at least two steps, starting from ethyl or methyl-3-amino-2-thiophene-carboxylate (Scheme 1).

On the other hand, Rodinovskya et al., 5 showed that the synthesis of 4-hydroxy-7-methylpyridino[2,3-d]thieno[3,2-b] pyridin-2(1H)-one (VI) was possible in one step (Scheme 2). The starting material was the salt of 2-thioxo-1,2-dihydro-3-pyridinecarbonitrile (V).

Recently, we published the synthesis of substituted 3-amino-2-cyanothiophenes,6 starting from the corresponding β-substituted β-chloropropenonitrile (Scheme 3).

In this work, we show the possibility of the rapid synthesis of 7-hydroxythieno[3,2-b]pyridin-5(4H)-ones and related compounds, in a one-pot synthesis, from the corresponding β-substituted β-chloropropenonitriles. The reaction occurred smoothly in a one-pot, three-step procedure by reaction of I with sodium sulfide followed by substitution of the intermediate sodium salt with ethyl 4-chloroacetate.

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to acetate. Cyclisation under basic conditions and hydrolysis, afforded the final compounds in yields ranging from 72% to 98% (Table 1). However, when $\alpha,\beta$-disubstituted $\beta$-chloropropenonitriles 1j–l were reacted under the same conditions, target compounds 2j–l were either not obtained (only an inseparable mixture of derivatives was isolated) or, in the case of 1j, 2j was obtained in only a trace amount (Table 1). This may be related to a problem of steric hindrance, which has already been shown in an earlier publication. This problem does not occur when the $\alpha$-substituted $\beta$-chloropropenonitrile is rigid (1i).

We have extended this reaction to 2-chloro-6-methylnicotinonitrile through the use of potassium carbonate, instead of sodium ethanolate, in order to avoid reaction of the ethanolate at the activated position of the starting material (Scheme 4). The expected product 3 was thus obtained in 80% yield.

### Scheme 4

**Reagents and conditions:** (a) Na$_2$S·9H$_2$O, DMF, ClCH$_2$COCH$_2$COOEt, K$_2$CO$_3$.  

In conclusion, we have synthesized in an easy, one-pot reaction, novel 7-hydroxythieno[3,2-b]pyridin-5(4H)-ones, starting from $\beta$-substituted $\beta$-chloropropenonitrile. We have also shown that an extension to 2-chloronicotinonitrile was possible.

Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a AC Bruker 250 MHz spectrometer in DMSO-$d_6$. Elemental analyses were determined with a ThermoFinnigan FlashEA 1112. IR spectra were collected on a Perkin–Elmer Spectrum BX FT-IR spectrophotometer.

### Synthesis of Substituted 7-Hydroxythieno[3,2-b]pyridinones 2a–j; General Procedure

A suspension of sodium sulfide nonahydrate (0.01 mol, 1 equiv) in DMF (14 mL) was heated at 40 °C for 30 min. $\beta$-Substituted $\beta$-chloropropenonitrile (0.01 mol, 1 equiv) dissolved in DMF (4 mL) was added in one portion and the solution was heated at 60 °C for 90 min. Ethyl 4-chloroacetoacetate (0.01 mol, 1 equiv) in DMF (1 mL) was added and the solution was stirred at 60 °C for 90 min. A solution of NaOEt (0.02 mol, 2 equiv) in absolute EtOH (14 mL) was added in one portion and the solution was stirred at 60 °C for 30 min. The reaction was monitored by TLC. The reaction mixture was cooled to r.t. and poured into iced H$_2$O (150 mL). The pH was adjusted to 1 with HCl (37%) and the precipitate was filtered and washed with cold H$_2$O (2 × 25 mL). A suspension of the product in Et$_2$O (25 mL) was heated to reflux for 30 min then the solid was filtered while hot and washed with Et$_2$O (2 × 25 mL).

**7-Hydroxy-2-phenylthieno[3,2-b]pyridin-5(4H)-one (2a)**  

Yield: 72%; brown solid; mp 220–222 °C (dec.).  

IR (KBr): 2814 (br s), 1621 (s), 1516 (s) cm$^{-1}$.  

$^1$H NMR (250 MHz, DMSO-$d_6$): $\delta$ = 5.61 (s, 1 H, CH), 7.28 (s, 1 H, CH), 7.50 (m, 3 H, 3 × CH), 7.72 (d, $J$ = 7.5 Hz, 2 H, 2 × CH), 11.52 (s, 1 H, NH), 11.78 (s, 1 H, OH).
Yield: 98%; brown solid; mp 230–232 °C (dec.).
Anal. calcd for C_{13}H_{8}FNO_{2}S: C, 59.76; H, 3.09; N, 5.36. Found: C, 64.32; H, 3.59; N, 5.61.

7-Hydroxy-2-(4-methylphenyl)thieno[3,2-b]pyridin-5(4H)-one (2b)
Yield: 74%; brown solid; mp 204–206 °C (dec.).
IR (KBr): 2916 (br s), 1620 (s), 1523 (cm–1).

7-Hydroxy-2-(4-chlorophenyl)thieno[3,2-b]pyridin-5(4H)-one (2c)
Yield: 88%; brown solid; mp 212–214 °C (dec.).
IR (KBr): 2892 (br s), 1671 (s), 1524 (cm–1).

7-Hydroxy-2-(4-nitrophenyl)thieno[3,2-b]pyridin-5(4H)-one (2f)
Yield: 98%; brown solid; mp 230–232 °C (dec.).
IR (KBr): 3559 (br s), 1731 (s), 1519 (s) cm–1.

Yield: 80%; brown solid; mp 208–210 °C (dec.).
Anal. calcd for C_{14}H_{11}NO_{2}S: C, 65.35; H, 4.31; N, 5.12. Found: C, 65.23; H, 4.37; N, 5.19.

Yield: 70%; brown solid; mp 210–212 °C (dec.).
IR (KBr): 2963 (br s), 1639 (s), 1507 (s) cm–1.

Yield: 8%; brown solid; mp 212–214 °C (dec.).
IR (KBr): 2892 (br s), 1671 (s), 1524 (s) cm–1.

Yield: 2%; brown solid; mp 220–222 °C (dec.).
IR (KBr): 3062 (br s), 1660 (s), 1520 (s) cm–1.

Yield: 1%; brown solid; mp 228–230 °C (dec.).
Anal. calcd for C_{15}H_{11}NO_{2}S: C, 66.89; H, 4.12; N, 5.04. Found: C, 66.63; H, 4.36; N, 5.35.
4-Hydroxy-7-methylpyridino[2,3-d]thieno[3,2-b]pyridin-2(1H)-one (3)
Synthesised as for substituted 2a–j, using 2-chloro-6-methylnicotinonitrile as starting material, K₂CO₃ as base and 85% phosphoric acid as acid to adjust the pH to 1.
Yield: 80%; brown solid; mp 214–216 °C (dec.).
IR (KBr): 3247 (br s), 1639 (s), 1543 (s) cm⁻¹.
¹H NMR (250 MHz, CDCl₃): δ = 2.49 (s, 3 H, CH₃), 5.87 (s, 1 H, CH), 7.40 (d, J = 7.5 Hz, 1 H, CH), 8.56 (d, J = 7.5 Hz, 1 H, CH), 11.70 (s, 2 H, NH and OH).
¹³C NMR (62.5 MHz, DMSO-d₆): δ = 24.16, 97.39, 107.92, 120.16, 121.31, 130.46, 136.19, 158.62, 159.43, 162.01, 164.29.
Anal. calcd for C₁₁H₈N₂O₂S: C, 56.88; H, 3.47; N, 12.06. Found: C, 56.76; H, 3.12; N, 12.30.

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References