# A NEW SYNTHESIS OF 1,3-THIAZINE DERIVATIVES HAVING A DITHIOLANE RING AND THEIR REDUCTIVE CLEAVAGE WITH SODIUM CYANOBOROHYDRIDE

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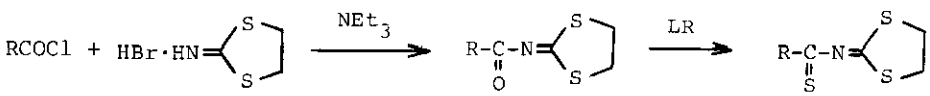
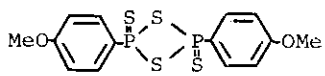
Abstract ——— Some new 1,3-thiazines containing 1,3-dithiolane were synthesized by [4+2] cycloaddition of 2-thioacylimino-1,3-dithiolanes with methyl vinyl ketone and allowed to react with sodium cyanoborohydride to give unusual reduction product with a loss of the dithiolane ring together with normal C=N reduction products.

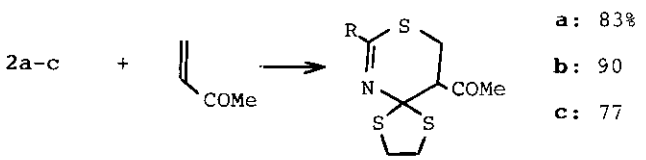
1,3-Thiazines are an important class of compounds contained in a cephalosporin skeleton and have been studied extensively.[1-3] Previously we reported the for-



| | | | |
|---|---|---|---|
| | | **1a-c** | **2a-c** |
| **a:** | R = Me | 78% | 84% |
| **b:** | R = $CH_2OCH_2Ph$ | 54 | 75 |
| **c:** | R = $CH_2OSiMe_2t$-Bu | 52 | 65 |

LR =





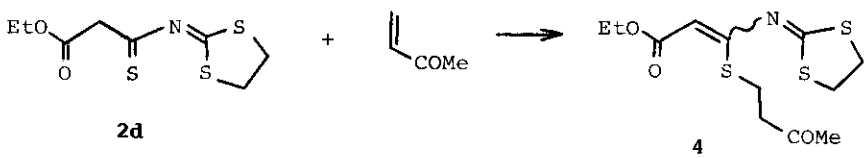
**3a-c**

**a:** 83%
**b:** 90
**c:** 77

Scheme 1

mation of 2-thioacyliminodithiolane derivatives from the photoreaction of 1,2,4-dithiazole-3-thiones with olefins and their cycloaddition with some electron-deficient olefins and acetylenes.[4] In continuation of these studies on 1,3-thiazines and related compounds, we now wish to report a new synthetic method for 2-thioacylimino-1,3-dithiolanes, their cycloadditions leading to 1,3-thiazines, and a novel reductive cleavage of 1,3-dithiolane ring in the 1,3-thiazine derivatives.

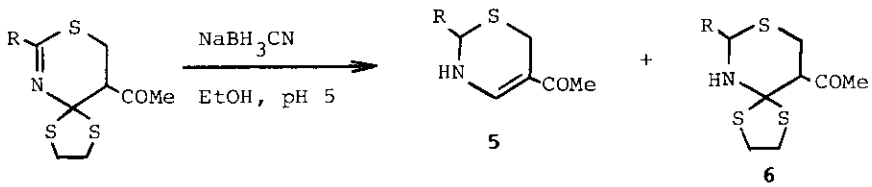
1,3-Thiazine derivatives **3a-c** having a dithiolane ring were synthesized as shown in Scheme 1 by the cycloaddition of methyl vinyl ketone with 2-thioacylimino-1,3-dithiolanes **2** obtained by sulfurization of 2-acylimino-1,3-dithiolanes **1** with Lawesson Reagent.[5] The present method for the synthesis of **2** is more general than the previous one[4] and can provide new 1,3-thiazine derivatives **3a-c** with a substituent containing a functional group at the 2-position. We also attempted the reaction of **2d** with methyl vinyl ketone, but the product was **4** (43%), Michael addition product of ene-thiol of **2d** (Scheme 2).[6]




**2d** **4**

Scheme 2

When **3a-c** were reduced with sodium cyanoborohydride in ethanol at pH 5, interesting products **5a-c** without the dithiolane ring were formed along with normal reduction products of the C=N bond, **6a-c** (Scheme 3).[7]




**3** **5** **6**

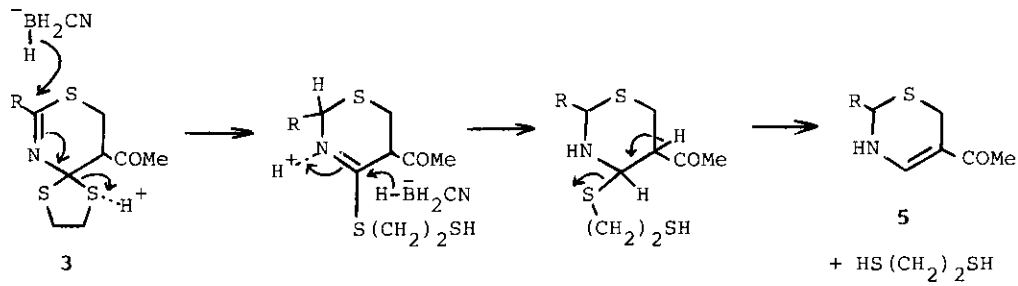
| | | |
|---|---|---|
| **a:** | 24% | 53% |
| **b:** | 17 | 52 |
| **c:** | 45 | 28 |

Scheme 3

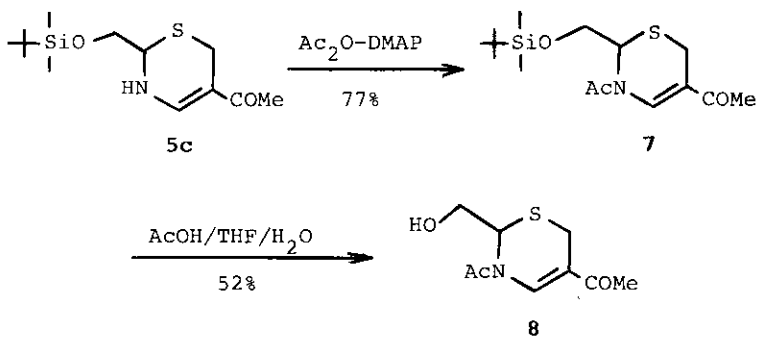
The dithiolanes are useful heterocycles in organic syntheses and the reductive cleavage into the corresponding hydrocarbons and the hydrolytic conversion into the corresponding carbonyl conversion are well known.[8] The reductive cleavage is mostly carried out using Raney nickel and, as far as we are aware, the present finding represents the first example of reductive removal of a dithiolane ring by hydride reagents.

This unusual reaction most likely proceeds via a pathway as shown in Scheme 4. Compound **6** was not reduced to **5** under the identical reaction conditions.

**5c** thus obtained can be converted into alcohol **8** which is thought to be a potentially useful compound for the synthesis of cephalosporin derivatives (Scheme 5).[9]



Scheme 4



Scheme 5

In conclusion, we have prepared 1,3-dithiazines with a functionalized substituent at the 2-position and a dithiolane ring at the 4-positions, respectively, and found a novel method for the reductive removal of the dithiolane ring used as an

activating group[10] for the cycloaddition of conjugated thioacylimines. We consider that this finding provides a useful approach for the synthesis of a cephem skeleton.

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5. **2a**: $^{1}$H-NMR($CDCl_3$) δ 2.66(s, 3H), 3.48(s, 4H); $^{13}$C-NMR($CDCl_3$) 35.88, 38.92, 184.65, 222.61; IR(neat) 1600, 1460, 1240, 1200cm$^{-1}$; MS(m/z) 177($M^+$), 149, 59(base). **2b**: $^{1}$H-NMR($CDCl_3$) δ 3.46(s, 4H), 4.37(s, 2H), 4.63(s, 2H), 7.20-7.50(br s, 5H); $^{13}$C-NMR($CDCl_3$) δ 35.88, 72.90, 80.49, 127.71, 127.97, 128.36, 137.63, 188.37, 221.21; IR(neat) 1460, 1220, 1100, 960cm$^{-1}$. **2c**: $^{1}$H-NMR($CDCl_3$) δ 0.11(s, 6H), 0.93(s, 9H), 3.51(s, 4H), 4.54(s, 2H); $^{13}$C-NMR($CDCl_3$) δ -0.58, 18.55, 25.94, 35.81, 74.87; IR(KBr disk) 2950, 2850, 1460, 1220, 840 cm$^{-1}$. **2d**: $^{1}$H-NMR($CDCl_3$) δ 1.20(t, J=7.2Hz, 3H), 3.43(s, 4H), 3.81(s, 2H), 4.15(q, J=7.2Hz, 2H); $^{13}$C-NMR($CDCl_3$) δ 14.19, 35.88, 56.59, 60.99, 166.77, 189.61, 214.84; MS(m/z) 249($M^+$), 221(base). **3a** $^{1}$H-NMR($CDCl_3$) δ 2.02(s, 3H),

2.27(s, 3H), 3.00-3.67(m, 7H); $^{13}$C-NMR($CDCl_3$) 27.87, 28.17, 30.09, 39.41, 40.09, 51.44, 84.32, 156.75, 205.75, 205.45; IR(KBr disk) 1710, 1600, 1420, 1360cm$^{-1}$; MS(m/z) 247($M^+$), 206, 59(base), 43. **3b**: $^1$H-NMR($CDCl_3$) $\delta$ 2.33(s, 3H), 3.17-3.70(m, 7H), 4.16(s, 2H), 4.53(s, 2H), 7.33(br s, 5H); $^{13}$C-NMR($CDCl_3$) $\delta$ 27.45, 30.00, 39.45, 40.25, 52.29, 72.96, 74.84, 84.08, 128.17, 128.50, 128.66, 137.67, 160.67, 204.60; IR(neat) 2900, 1700, 1590cm$^{-1}$; MS(m/z) 353($M^+$), 310, 232, 91(base). **3c**: $^1$H-NMR($CDCl_3$) $\delta$ 0.08(s, 6H), 0.91(s, 9H), 3.16-3.73(m, 3H), 3.41(s, 4H), 4.30(s, 2H); $^{13}$C-NMR($CDCl_3$) $\delta$ -5.42, 18.28, 25.79, 27.35, 30.12, 39.49, 40.21, 52.46, 68.12, 84.09, 163.48, 204.56; IR(KBr disk) 2950, 1720, 1610, 1370, 860cm$^{-1}$.

6. Compound **2d** was synthesized also by the reaction of the corresponding amide with Lawesson reagent. It is noteworthy that the amide carbonyl group was selectively sulfurized in the presence of the ester carbonyl group. **4**: a mixture(**A** and **B**) of (E)- and (Z)-isomers with regards to the C=C bond; $^1$H-NMR($CDCl_3$) **A** $\delta$ 1.27(t, J=7.2Hz, 3H), 2.13(s, 3H), 2.82(m, 4H), 4.15(q, J=7.2Hz, 2H), 5.30(s, 1H); **B** $\delta$ 1.25(t, J=7.2Hz, 3H0, 2.13(s, 3H), 2.87(m, 4H), 3.59(s, 4H), 4.08(q, J=7.2Hz, 2H), 5.22(s, 1H); $^{13}$C-NMR($CDCl_3$) **A** $\delta$ 14.41, 23.94, 30.04, 36.79, 44.04, 59.73, 99.08, 166.04, 166.91, 174.98, 206.32; **B** $\delta$ 14.44, 26.65, 30.07, 37.24, 43.41, 59.64, 98.49, 162.82, 163.87, 174.84, 206.05; MS(m/z) 319($M^+$), 291, 221(base) (for both **A** and **B**).

7. **5a**: $^1$H-NMR($CDCl_3$) $\delta$ 1.50(d, J=6.4Hz, 3H), 2.08(s, 3H), 3.50(q, J=16.0Hz, 2H), 4.28(m, 1H), 5.25(br, 1H), 7.35(d, J=6.4Hz, 1H); $^{13}$C-NMR($CDCl_3$) $\delta$ 20.64, 23.97, 24.11, 51.44, 109.21, 143.69, 193.37; MS(m/z) 157($M^+$, base), 114, 98. **5b**: $^1$H-NMR $\delta$ 2.18(s, 3H), 3.55-3.89(m, 4H), 4.57(s, 2H), 4.40-4.71(m, 1H), 5.62(br, 1H), 7.34(s, 5H), 7.48(d, J=7.0Hz, 1H); $^{13}$C-NMR($CDCl_3$) $\delta$ 22.51, 23.84, 53.55, 71.29, 73.54, 108.67, 127.88, 128.63, 137.30, 140.02, 193.24; MS(m/z) 263($M^+$), 142, 98, 91. **5c**: $^1$H-NMR($CDCl_3$) $\delta$ 0.10(s, 6H), 0.91(s, 9H), 3.26-4.12(m, 5H), 5.54(br, 1H), 7.55(d, J=6.2Hz, 1H); $^{13}$C-NMR($CDCl_3$) $\delta$ 22.49, 23.82, 25.72, 25.87, 55.53, 64.82, 143.00, 206.87. **6a**: $^1$H-NMR($CDCl_3$) $\delta$ 1.26(d, J=6.4Hz, 3H), 2.10(s, 3H), 2.80-3.80(m, 7H), 4.55(q, J=6.4Hz, 1H); $^{13}$C-NMR($CDCl_3$) $\delta$ 21.99, 28.58, 31.34, 36.95, 39.41, 54.36, 55.96, 87.60, 206.56; MS(m/z) 249($M^+$), 206. **6b**: $^1$HNMR($CDCl_3$) $\delta$ 2.10(s, 3H), 3.12(m, 7H), 3.43(d, J=5.0Hz, 2H), 4.41(s, 2H), 4.80(dt, 1H), 7.14(s, 5H); $^{13}$C-NMR($CDCl_3$) 28.66, 31.04, 36.86, 39.47, 55.20, 60.48, 72.40, 73.40, 87.73, 127.66,

128.66, 128.74, 137.92, 206.29; MS(m/z) 355($M^+$), 312, 91(base). **6c**: $^1$H-NMR($CDCl_3$) δ 0.06(s, 6H), 0.90(s, 9H), 2.23(s, 3H), 3.2-3.3(m, 7H), 3.72(d, J=4.4Hz, 2H), 4.79(br, 1H); $^{13}$C-NMR($CDCl_3$) δ -5.35, 18.32, 25.83, 28.60, 30.91, 36.76, 39.49, 55.38, 62.43, 65.77, 87.85, 205.97.

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9. **7**: $^1$H-NMR($CDCl_3$) δ 0.09(s, 6H), 0.90(s, 9H), 2.34(s, 3H), 2.36(s, 3H), 3.13(br, 4H), 3.5-4.3(m, 2H). **8**: $^1$H-NMR($CDCl_3$) δ 2.12(s, 3H), 2.20(s, 3H), 3.59(s, 2H), 4.02-4.81(m, 2H), 5.39-5.85(br, 1H), 7.48(d, J=5.9Hz, 1H); $^{13}$C-NMR($CDCl_3$) δ 18.55, 20.75, 21.70, 21.86, 23.92, 24.76, 61.95, 117.56, 134.97, 142.77, 169.21, 170.97, 193.51; MS(m/z) 215($M^+$), 149, 142, 98.
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