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# Novel synthesis and γ-alkylation reactions of 4-(1-pyrrolidinyl)-2(5*H*)-thiophenones

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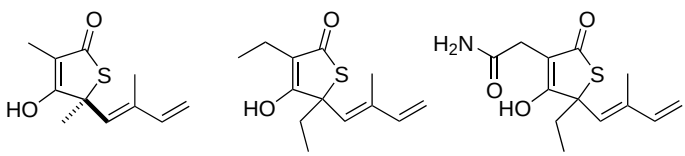
**Abstract**—Four-step synthesis of achiral and chiral 4-(1-pyrrolidinyl)-2(5*H*)-thiophenones with 61 and 66% overall yields are described. The γ-alkylation reaction studies and synthetic applications toward the thiolactomycin analog are also reported.


Substituted thiotetronic acid related compounds such as (+)-thiolactomycin **1**,[1] thiotetromycin **2**,[2] and U-68,204 **3** are a group of compounds with important bioactivities.[3] For example, (+)-thiolactomycin **1** is an antibiotic produced by *Nocardia* sp. No. 2-200, that is active against many species of pathogens including Gram-positive cocci, enteric bacteria, acid-fast bacteria and anaerobic bacteria. It has been found that the combined use of thiolactomycin and β-lactam antibiotics produces a synergistic effect against the inducible β-lactamase-producing microorganism.[4] A common important feature in these three compounds is the γ-disubstitution on the thiotetronic acid. Therefore, the study of the γ-alkylation reaction of similar systems becomes vital to the synthesis of thiotetronic acid related antibiotics.[5]




Thiolactomycin **1** Thiotetromycin **2** U-68,204 **3**

Herein, we first report on a novel procedure for the synthesis of achiral and chiral 4-(1-pyrrolidinyl)-2(5*H*)-thiophenones.[6] Secondly, γ-alkylation reactions of the title compound has been studied and applied in the synthesis of a thiolactomycin analog.[7]

Methyl acetoacetate **4** in benzene was condensed with compound **5** or **5a** to afford vinylogous urethane **6** and **6a** in 81 and 83% yields, respectively.[8] Deprotonation of **6** or **6a** with LDA, followed by chlorination with hexachloroethane afforded chlorinated compound **7** and **7a**, respectively. Subsequent treatment of the chlorinated compounds **7** or **7a** with potassium thioacetate produced thiolated adducts, which without purification were treated with sodium methoxide to facilitate cyclization to produce 2(5*H*)-thiophenones **8** and **8a** in 75 and 80% yields (Scheme 1).

With **8** and **8a** in hand, reaction of compound **8** was studied first under various conditions. Compound **8** was deprotonated with lithium diisopropylamide (LDA) and then treated with alkyl halide to produce mono-alkylated products **9**–**13** in moderate yields. A second alkylation of **9** and **12**, using LDA or *t*-BuLi as a base, provided **14** and **15** in good yields (Scheme 2).

Deprotonation and alkylation of **8a** under similar conditions afforded **9a**–**13a** in 53–93% yields. Though the mono-alkylation reaction was successful in compound **8a**, di-alkylation of **8a** turned out to be problematic, presumably due to the steric hindrance of the bulky substitution on the pyrrolidine. The only success was the hydroxymethylation reaction. Deprotonation of **9a**

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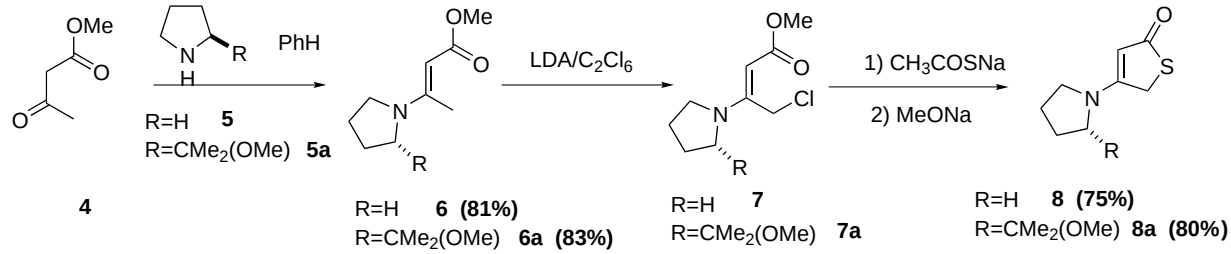
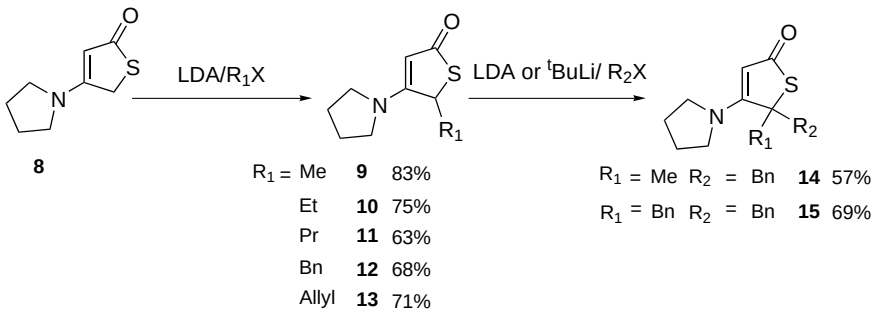



**Scheme 1.**




**Scheme 2.**

with *t*-BuLi followed by treatment with formaldehyde gas at −50°C provided **16** in moderate yield and excellent diastereoselectivity (Scheme 3).

The diastereoselectivities of **9a**–**13a** and **16** were determined using HPLC and NMR as shown in Scheme 3. The stereochemistry of the major diastereomer as determined by single-crystal X-ray analysis of the compounds **9a** and **16** is shown in Fig. 1.[9]

Our synthetic approach toward the thiolactomycin analog started from the second alkylation of the compound **9**. Deprotonation of the compound **9**, followed by the addition–elimination reaction with a mixture (*E*:*Z*/3:1) of 3-bromo-2-methacrylonitrile provided **17*E*** and **17*Z*** in 81% yield with a 4:1 ratio.[10] Reduction of **17*E*** with diisobutylaluminum hydride (DIBAL-H) at −20°C provided aldehyde **18** in 81% yield. Finally, reaction of compound **18** with phosphonium ylide generated by the deprotonation of methyltriphenylphosphonium iodide resulted in thiolactomycin analog **19** in 74% yield.[11] Synthetic efforts using chiral compound **9a** to synthesize the chiral analog are being continuously investigated in our laboratory (Scheme 4).

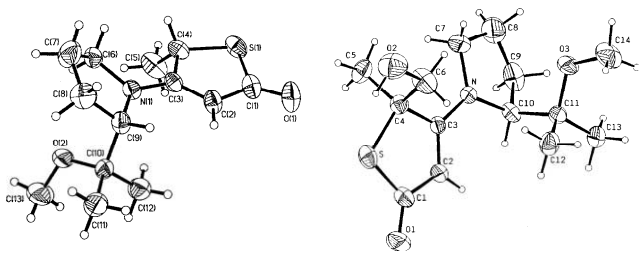


**Figure 1.** Molecule structures of **9a** and **16**.

## Acknowledgements

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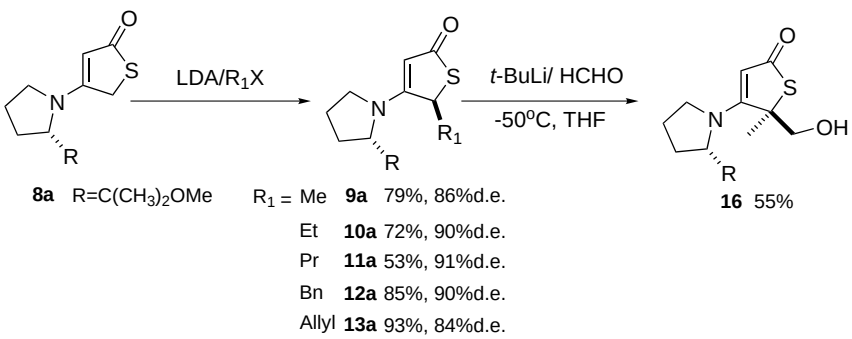
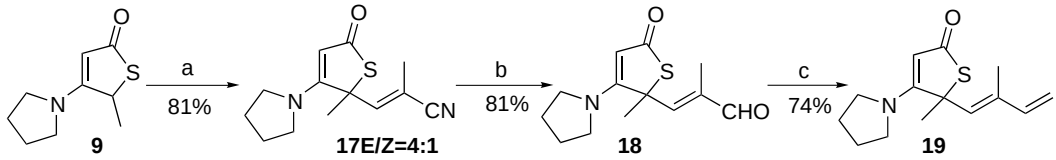



**Scheme 3.**




**Scheme 4.** *Reagents and conditions*: (a) *t*-BuLi, THF, 3-bromo-2-methacrylonitrile (*E*:*Z*/3:1); (b) diisobutylaluminum hydride, heptane; (c) LDA, THF, methyltriphenylphosphonium iodide.

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9. The crystal structure of compounds **9a** and **16** have been deposited at the Cambridge Crystallographic Data Centre as CCDC 158219 and CCDC 158220. The absolute stereochemistry at the γ-position was determined based on the existing chiral center on the pyrrolidine that originated from *L*-proline.
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11. All compounds have been fully characterized. **9**: mp 87–89°C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 4.88 (s, 1H), 4.30 (q, $J=6.96$ Hz, 1H), 3.50 (br, 2H), 3.29 (br, 2H), 1.85–2.18 (br, 4H), 1.66 (d, $J=6.96$ Hz, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 192.7, 172.9, 96.3, 50.6, 48.4, 43.8, 25.8(2C), 21.4. EIMS: 183 ($M^+$, 100), 150(80), 70 (80). Anal. calcd for $C_9H_{13}NOS$: C, 58.98; H, 7.15; N, 7.64. Found: C, 59.04; H, 7.29; N, 7.63. **9a**: $[\alpha]_D^{20}=-49.6$ ($c=1$, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.12 (s, 1H), 4.26 (q, $J=6.87$ Hz, 1H), 3.59 (m, 1H), 3.49 (m, 2H), 3.10 (s, 3H), 1.99 (m, 4H), 1.60 (d, $J=6.87$ Hz, 3H), 1.08 (s, 3H), 1.07 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 195.0, 175.4, 98.6, 78.7, 69.3, 49.8, 49.1, 44.4, 25.3, 24.3, 22.0(2C), 21.6. EIHRMS: ($C_{13}H_{21}NO_2S$) calcd 255.1293; found 255.1295. Anal. calcd for $C_{13}H_{21}NO_2S$: C, 61.14; H, 8.29; N, 5.49; found C, 61.18; H, 8.26; N, 5.48. **17*E***: mp 195–196°C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 6.46 (s, 1H), 4.84 (s, 1H), 3.35 (br, 4H), 1.98 (br, 4H), 1.93 (s, 3H), 1.87 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 190.0, 171.2, 145.9, 119.7, 114.3, 96.8, 55.2, 50.5(2C), 29.5, 25.4(2C), 15.3. EIHRMS: ($C_{13}H_{16}N_2OS$) calcd 248.0984; found 248.0991. **18**: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 9.36 (s, 1H), 6.41 (s, 1H), 4.80 (s, 1H), 3.35 (br, 4H), 1.97 (br, 4H), 1.92 (s, 3H), 1.68 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 194.6, 194.2, 171.7, 151.1, 141.1, 97.2, 55.7, 50.8(2C), 29.2, 26.3(2C), 9.1. EIHRMS: ($C_{13}H_{17}NO_2S$) calcd 251.0980; found 251.0979. **19**: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 6.29 (dd, $J=17.58$, 10.84 Hz, 1H), 5.56 (d, $J=17.58$ Hz, 1H), 5.05 (d, $J=10.84$ Hz, 1H), 4.84 (s, 1H), 3.32 (br, 4H), 1.92 (br, 4H), 1.91 (s, 3H), 1.73 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 194.2, 174.7, 155.4, 140.51, 130.8, 113.7, 96.8, 56.3, 50.8(2C), 30.9, 26.3(2C), 11.6. EIHRMS: ($C_{14}H_{19}NOS$) calcd 249.1187; found 249.1183.