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OBSERVATIONS REGARDING ESCHENMOSER SULFIDE CONTRACTIONS OF β-OXYGENATED THIOLACTAMS

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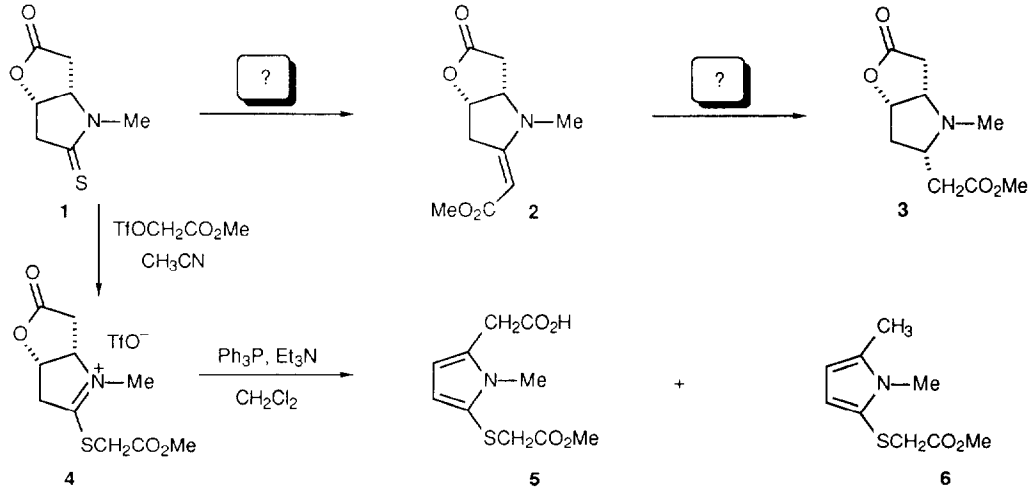
Abstract: *Application of an Eschenmoser sulfide contraction to a thiolactam bearing a β-acyloxy group was complicated by a competitive β-elimination reaction. Changing the β-substituent to an alkoxy group retarded the rate of elimination such that sulfide contraction products could be obtained.*

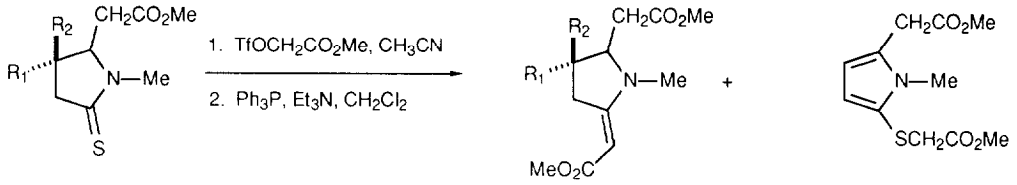
During the course of a project directed toward the synthesis of potential cocaine uptake antagonists we were faced with the task of converting thiolactam **1** to pyrrolidine derivative **3**.[1] We hoped to do this via vinylogous urethane **2** using the Eschenmoser sulfide contraction.[2] Unfortunately this met with failure as treatment of **1** with carbomethoxymethyl trifluoromethanesulfonate in acetonitrile followed by triphenylphosphine and triethylamine in dichloromethane gave a mixture of pyrroles **5** and **6** (Scheme 1).[3,4] Since it is known that thioalkyliminium salts can be deprotonated adjacent to the azomethine carbon under Eschenmoser contraction conditions, it was presumed that pyrroles **5** and **6** were the result of such a deprotonation, followed by β-elimination and aromatization.[5]

Scheme 1



In an attempt to eliminate this problem, it was decided to replace the β-acyloxy group with a worse leaving group. Thus, thiolactams **7** and **8** were prepared and subjected to Eschenmoser sulfide contraction conditions (Scheme 2).[6] Although this did not completely eliminate the aromatization problem, it did afford the desired vinylogous urethanes in a reasonable yield. For example, treatment of **7** with the appropriate triflate followed by triphenylphosphine and triethylamine in dichloromethane gave vinylogous urethane **9** in 66% yield along with 17% of pyrrole **11**. Thiolactam **8** behaved in a similar manner as vinylogous urethane **10** and pyrrole **11** were produced in 65% and 30% yields, respectively. Thus, changing from β-acyloxy group to a β-alkoxy group turned on the sulfide contraction pathway at the expense of the undesired aromatization.[7]

Scheme 2



7 R_1 = OMe R_2 = H
8 R_1 = H R_2 = OMe

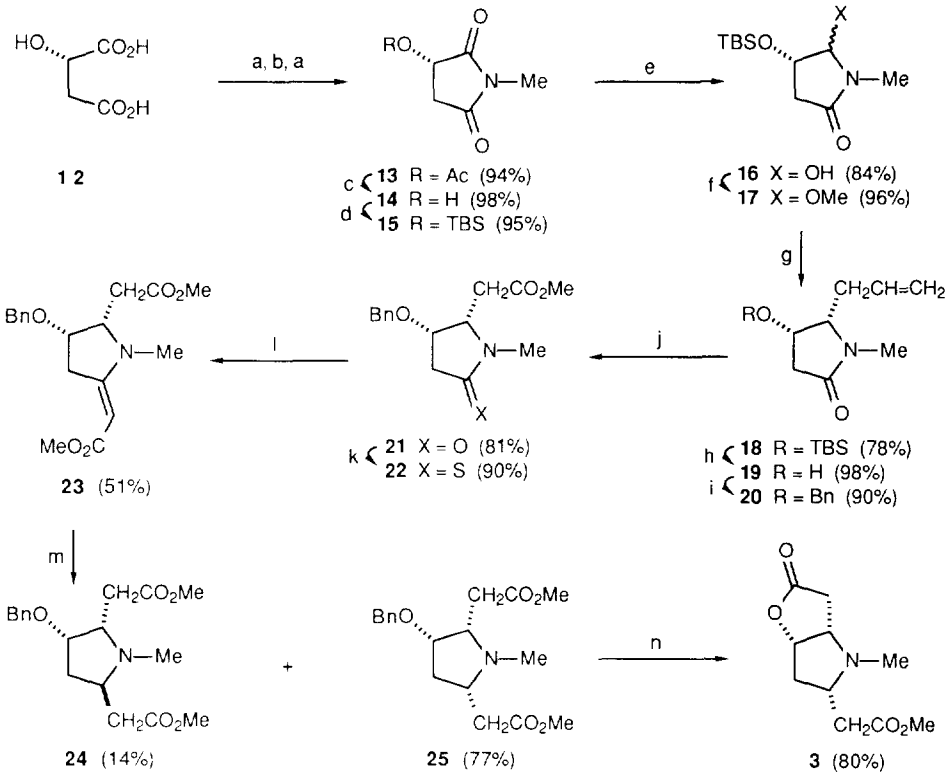
9 R_1 = OMe R_2 = H (66%)
10 R_1 = H R_2 = OMe (65%)

11 (17%)
11 (30%)

It was possible to use this observation to accomplish the original synthetic objective, a synthesis of **3**, as outlined in Scheme 3. Thus, sequential treatment of (*S*)-malic acid with acetyl chloride, methylamine, and acetyl chloride gave imide **13** (94%). Conversion of the **13** to **14** was accomplished in 98% yield using ethanolic HCl and reprotection of the alcohol gave **15** (95%). Regioselective reduction of the imide using sodium borohydride in methanol gave **16** (84%)[8] and a Williamson ether synthesis then provided **17** in 96% yield.[9] Treatment of **17** with allytrimethylsilane and titanium tetrachloride gave **18** in 72% yield along with 12% of the corresponding trans isomer.[10] Removal of the *tert*-butyldimethylsilyl protecting group was followed by benzylation of the resulting alcohol **19** (98%) to provide ether **20** (90%). Ozonolysis of **20** gave ester **21** (81%) which was converted to thiolactam **22** (90%) using Lawesson's reagent.[11,12] Application of the Eschemoser sulfide contraction procedure to **22** did afford vinylogous urethane **23** in 51% yield. Borch reduction of **23** gave the desired all-cis pyrrolidine **25** (77%) along with 14% of **24**.[13] Finally, hydrogenolysis of the benzyl ether using rhodium on alumina afforded lactone **3** in 80% yield.

In summary, it was found that a Eschenmoser sulfide contraction on a thiolactam substrate carrying a β-acyloxy group was complicated by a competitive β-elimination reaction.[14] This problem was overcome, however, by changing the β-substituent to an alkoxy group. This tactic should expand the scope of the sulfide contraction process to include β-oxygenated substrates.[15]

Scheme 3



(a) AcCl (b) $MeNH_2$, CH_2Cl_2 (c) HCl, EtOH (d) TBSCl, imidazole, DMF (e) $NaBH_4$, MeOH
(f) NaH, MeI, THF (g) $TMSCH_2CH{=}CH_2$, $TiCl_4$, CH_2Cl_2, -78°C → rt (h) *n*-Bu_4NF, THF (i) NaH, BnBr, THF
(j) O_3, MeOH-H_2O-NaOH, CH_2Cl_2 (k) $(MeOC_6H_4PS_2)_2$, CH_2Cl_2 (l) $TfOCH_2CO_2Me$; Ph_3P, Et_3N, CH_2Cl_2
(m) $NaBH_3CN$, MeOH, pH4 (n) H_2, $Pd(OH)_2$

References and Notes

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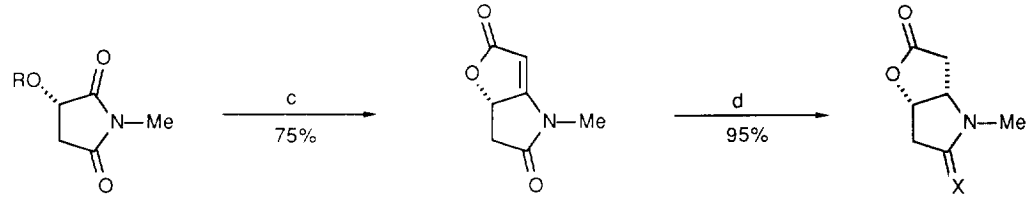
3. The synthesis of starting thiolactam **1** was accomplished from imide **14** (*vide supra*) using an intramolecular Wittig reaction as described below. For other intramolecular Wittig reactions of imides see Flitsch, W.; Wernsmann, P.; *Tetrahedron Lett.* **1981**, *22*, 719. Flitsch, W.; Russkamp, P.; *Annalen* **1983**, 521. Flitsch, W.; Pandl, K.; Russkamp, P. *Annalen* **1983**, 529.



(a) $BrCH_2COCl$, pyridine, CH_2Cl_2 (b) NaI, acetone (c) Ph_3P, CH_3CN; then Et_3N (d) H_2, Rh/Al_2O_3, EtOAc (e) $(p\text{-}MeOC_6H_4PS_2)_2$, CH_2Cl_2

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6. Thiolactams **7** and **8** were prepared by a procedure similar to that described for thiolactam **22** in Scheme 3. Details will be described elsewhere.
7. A substructure search using CAS REACT failed to uncover an example of an Eschenmoser sulfide contraction of a β-oxygenated 2-thiopyrrolidinone.
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14. Acetylation of the hydroxyl group of **19** followed by treatment of the derived lactam with Lawesson's reagent provided a thiolactam which gave only the corresponding pyrrole in 95% yield upon exposure to the aforementioned sulfide contraction conditions. Thus, we are confident that the elimination problem is due to the nature of the β-substituent and not ring strain that might be present in bicyclic thiolactam **1**.

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