Tetrahedron Letters,Vol.24,No.47,pp 5165-5168,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

A NEW AND MILD METHOD FOR THE REDUCTION OF SECONDARY AMIDES TO CARBINOLAMINE ETHERS AND IMINES: A CONVERSION OF OXOTOMAYMYCIN TO TOMAYMYCIN

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Abstract: A new and mild method for reducing 2° amides to carbinolamine ethers and imines and its use in the synthesis of pyrrolo[1,4]benzodiazepine antibiotics is reported.

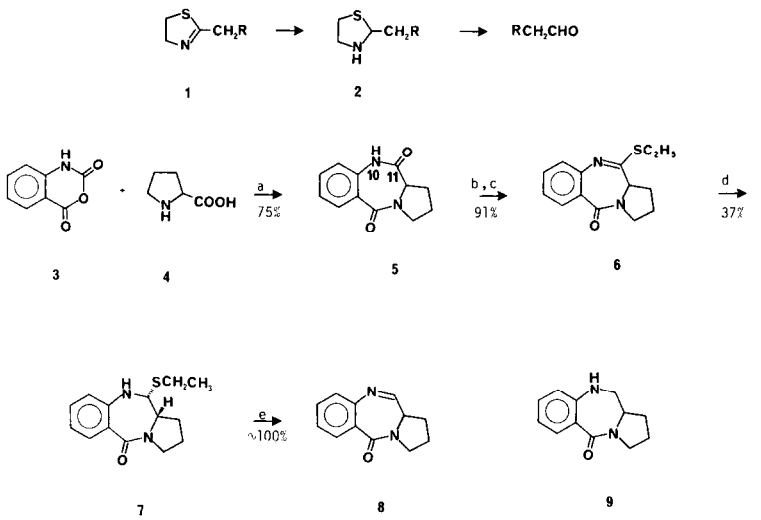
Our recent research was aimed at possible synthetic approaches to pyrrolo[1,4]benzodiazepine antitumor antibiotics such as anthramycin, sibiromycin, tomaymycin, and neothramycin.[1] These compounds contain a rather labile carbinolamine or imine functionality at N10-C11. One attractive route appeared to be utilization of the corresponding amides, since they are relatively easy to prepare. The key step then would be the reduction of a secondary amide to the carbinolamine oxidation level.

There are only a limited number of methods available for such a reduction.[2] Leimgruber[3] and Carey[4] reported difficulty in reducing precursors to anthramycin and sibiromycin, respectively. Similar attempts using hydride reagents were reported recently by Hurley.[5]

In order to find a general and mild method, we focused on the use of imino thioethers which were easily derived from amides. It is well-known that thiazolines (1) can be reduced to thiazolidines (2) using aluminum-amalgam.[6] Since the thiazoline can be considered as an imino thioether, the aluminum-amalgam method should be applicable to regular imino thioethers.

Initially, we tested this concept with the unsubstituted pyrrolo[1,4]benzodiazepein-5,11-dione (5), which was readily synthesized from isatoic anhydride and proline.[7] Treatment of 5 with P_2S_5 followed by alkylation with triethyloxonium tetrafluoroborate afforded imino thioether 6[8a] in 91% yield. Reduction of 6 with excess Al-Hg[9] at 0-5° overnight gave thiocarbinolamine 7,[10] which crystallized upon workup, in 37% yield. As observed with anthramycin[11] and tomaymycin,[12] the C11 proton of 7 was coupled to the N10 proton and not

the C11a proton; consequently, the stereochemistry was determined as shown in 7. Upon silica gel chromatography, conversion to the known[13] imine (8) occurred. Thus, to our best knowledge, this is the first use of Al-Hg for the purpose of reducing a secondary amide to a carbinolamine, and the mild (neutral and low temperature) conditions should make this procedure compatible with many functional groups. A minor byproduct in this reaction was amine 9.[8a,b]



a. DMF/153°/3 h

b. $P_2S_5/C_6H_6/80°/2.5$ h

c. $(C_2H_5)_3OBF_4/CH_2Cl_2/KHCO_3$

d. Al-Hg/Aq THF/0-5°/14 h

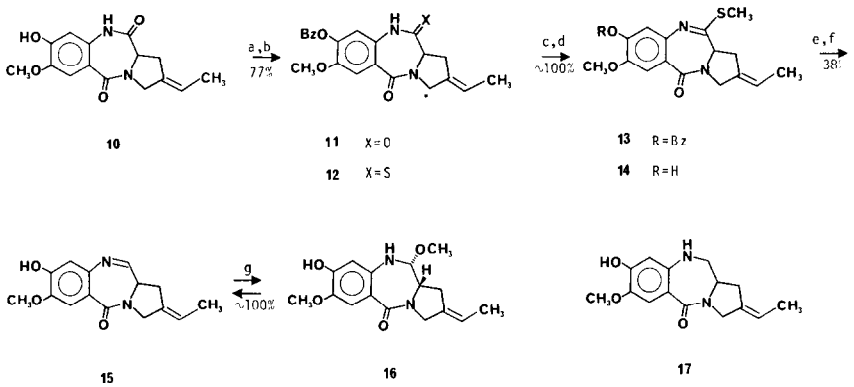
e. SiO_2

We have applied this method to the conversion of oxotomaymycin (10) to tomaymycin (16). Oxotomaymycin is a biologically inactive byproduct of tomaymycin fermentation.[14] It is considerably more stable, and consequently, its isolation is straightforward. Therefore, its chemical conversion to tomaymycin might have some practical significance.

The conversion began with the protection of the C8 hydroxy group as a benzoate (11)[8a,b] (Scheme II). Thiation took place selectively at the C11 amide when 11 was treated with the Lawesson reagent.[15] Thioamide 12[8a,b] was methylated to give imino thioether 13,[8a] whose benzoyl group was subsequently hydrolized without disturbing the imino thioether moiety. Crude 14[8a] was then treated with Al-Hg (prepared from 7 eq of aluminum foil) at 0-5° for

22 h. The initial reaction products were treated with 0.1N methanolic $HgCl_2$ solution at 0° and chromatographed on SiO_2 at 5° to give pretomaymycin **15**[16,17] (38%) and over-reduction product **17** (8%).[8a] When **15** was dissolved in methanol and kept in a freezer overnight, conversion to tomaymycin **16**[18] was quantitative. The overall yield for the 6-step transformation was approximately 29%.

Use of this method in the total synthesis of a new pyrrolo[1,4]benzodiazepine antitumor antibiotic (BBM-2040) will be published elsewhere.[19] Thus, this method appears to have a considerable utility in the synthesis of anthramycin-type compounds.



10 **11** X=O **12** X=S **13** R=Bz **14** R=H **15** **16** **17**

a. $NaH/C_6H_5COCl/DMF/-20°\rightarrow RT$
b. $(p\text{-}CH_3OC_6H_4PS_2)_2/C_6H_6/80°/1.5$ h
c. $CH_3I/K_2CO_3/THF/12$ h
d. $K_2CO_3/CH_3OH/0°$
e. Al-Hg/Aq THF/0-5°/22 h
f. $HgCl_2/CH_3OH/0°$
g. CH_3OH

Acknowledgement. A partial support of this work was provided by the National Cancer Institute through NO1-CM-87180.

References and Footnotes

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8. a. Satisfactory spectroscopic data were obtained on this compound. b. Satisfactory elemental analysis data or high resolution mass spectrum data were obtained.

9. Aluminum amalgam was prepared according to the method of Keck et al.; Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. Syn. Comm., 1979, 9, 281.

10. Mp 125-130°; IR(KBr) 3280, 1608, 1595, 1560, 1485, 1343 cm^{-1}; NMR($CDCl_2$, δ) 1.26(t, 3H, J=7.0 Hz), 1.70-2.40(m, 4H), 2.61(q, 2H, J=7.0 Hz), 3.60-3.94(m, 2H), 4.20(t, 1H, J=8 Hz), 4.80(d, 1H, J=6 Hz), 5.18(bd, 1H, J=6 Hz), 6.59(d, 1H, J=8 Hz), 6.82(t, 1H, J=8 Hz), 7.24(dt, 1H, J=8, 2 Hz), 8.12(dd, 1H, J=8, 2 Hz); Anal. Calcd for $C_{14}H_{18}N_2OS$: C, 64.09; H, 6.91; N, 10.68; Found: C, 63.82; H, 6.49; N, 10.47.

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16. IR(Nujol) 3310, 1630, 1600, 1580, 1285, 1210 cm^{-1}; NMR (360 MHz) ($CDCl_3$, δ) 1.75(dt, 3H, J=6.62, 1.47 Hz), 2.96(d, 2H, J=5.91 Hz), 3.89(dt, 1H, J=5.91, 4.92 Hz), 3.96(s, 3H), 4.26(s, 2H), 5.60(m, 1H), 6.16(s, 1H), 6.89(s, 1H), 7.50(s, 1H), 7.66(d, 1H, J=4.92 Hz); $[\alpha]_D^{24}$ = +240° (C=0.08, pyridine); Observed mass 272.1134, calcd for $C_{15}H_{16}N_2O_3$ 272.1160.

17. We thank Dr. J. Matson of these laboratories for supplying us pretomaymycin and oxotomaymycin.

18. IR(KBr) 3360, 1625, 1580, 1495, 1260 cm^{-1}; NMR (360 MHz) (pyridine-d_6, δ) 1.54(d, 3H, J=6.62 Hz), 2.69(bd, 1H, J=16.91 Hz), 2.87(dd, 1H, J=16.91, 9.20 Hz), 3.31(s, 3H), 3.75(s, 3H), 4.16(dd, 1H, J=9.20, 5.15 Hz), 4.71(s, 2H), 4.75(d, 1H, J=6.25 Hz), 5.33(m, 1H), 6.90(s, 1H), 7.85(d, 1H, J=6.25 Hz), 8.14(s, 1H); Cl mass spectrum (isobutane) 305 (M^++1) (2%), 273 (100%); Observed mass 272.1138; calcd for $C_{16}H_{20}N_2O_4$-CH_3OH = 272.1160.

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(Received in USA 26 August 1983)