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ACID-CATALYZED CYCLIZATIONS OF N-VINYL-α-SULFINYLACETAMIDES A NOVEL SYNTHETIC APPROACH TO ERYTHRINANE

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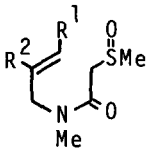
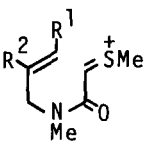
Summary: Under the Pummerer reaction conditions, N-(1-cyclohexenyl)-N-methyl-α-(methylsulfinyl)acetamide (7a) cyclized in a 5-endo trigonal fashion through the intermediary cation (8) to give the tetrahydro-4H-oxindole (10). The reaction was successively applied to a novel synthesis of erythrinane skeleton.

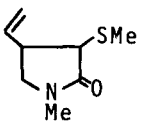
Recently, the Pummerer reaction intermediate of α-sulfinylacetamide has been shown[1] to behave as a highly reactive initiating center for cationic olefin cyclizations. Thus, under the Pummerer reaction conditions, N-allyl-α-sulfinyl-acetamide (1a or 1b) cyclizes in a 5-exo- or 6-endo-trigonal fashion through the intermediary carbocation (2a or 2b) to afford the five- or six-membered lactam (3 or 4). In the present letter, we wish to report a 5-endo-trigonal cyclization of N-vinyl-α-sulfinylacetamide (7a) and an application of the cyclization into new synthesis of erythrinane skeleton.



1a,b



2a,b



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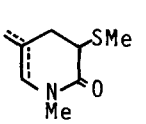

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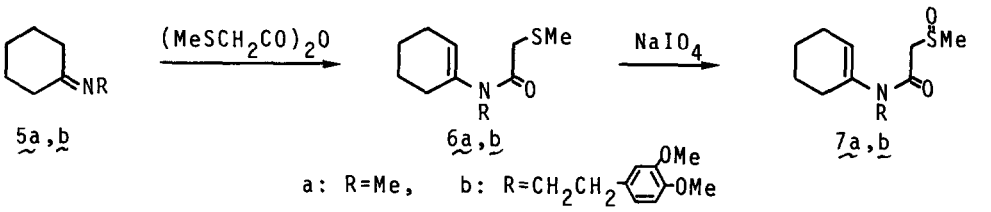
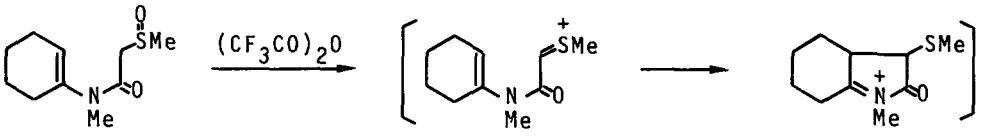
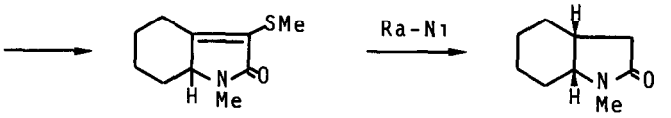
a: R^1=Me R^2=H, b R^1=H R^2=Me

N-(1-Cyclohexenyl)-N-methyl-α-(methylsulfinyl)acetamide (7a) was prepared by N-acylation of N-cyclohexylidenemethylamine (5a) with α-methylthioacetic anhydride in pyridine, followed by oxidation of the resultant sulfide (6a) with sodium metaperiodate in aqueous methanol. Treatment of the amide (7a) with equimolar amount of trifluoroacetic anhydride in methylene chloride at 0° gave the cyclization product, 1-methyl-3-methylthio-5,6,7,7a-tetrahydro-4H-oxindole (10; 22% yield), whose structure was confirmed by its spectroscopic data[2] and chemical transformation into 11[3] by reduction with Raney nickel. The reaction of

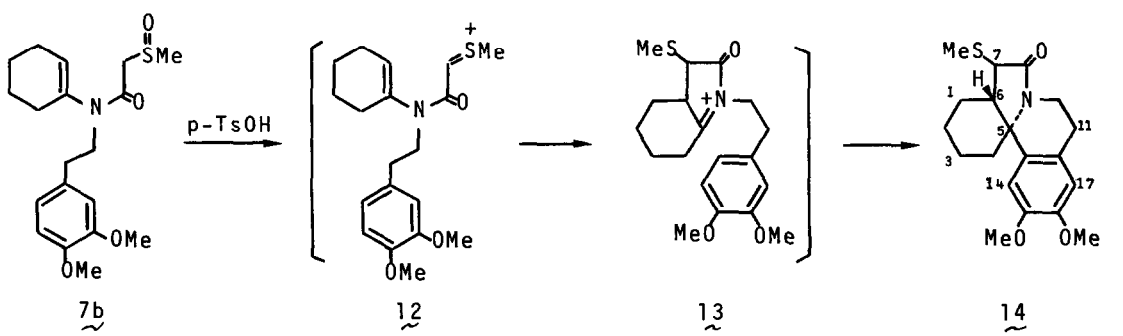
7a into 10 is considered to proceed through a 5-endo-trigonal cyclization[4] of the Pummerer reaction intermediate (8) to 9.



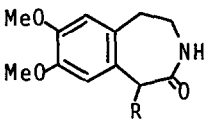




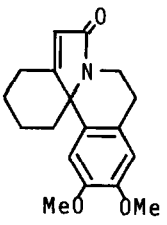
In the above reaction, employment of N-(1-cyclohexenyl)-N-[(3,4-dimethoxyphenyl)ethyl]-α-(methylsulfinyl)acetamide (7b) instead of 7a gave directly the erythrinane skeleton (14), whose formation is explained by a 5-endo-trigonal cyclization of the Pummerer reaction intermediate (12) to the acyliminium ion (13) and successive "acyliminium olefin cyclization"[5] of 13. The amide (7b) was prepared from N-cyclohexylidene-(3,4-dimethoxyphenyl)ethylamine (5b) by the procedure employed for the preparation of 7a. Treatment of 7b with two equivalents of anhydrous p-toluenesulfonic acid in boiling dichloroethane under continuous removal of water afforded 15,16-dimethoxy-7-methylthio-cis-erythrinan-8-one (14;



mp 169.5-170.5°, 60% yield), accompanied by a small amount of 3-benzazepin-2-one derivative (15; mp 124-128°, 8% yield). The structures of 14 and 15 were established by their spectroscopic data[6] and the following chemical transformations. Oxidation of 14 with sodium metaperiodate in aqueous methanol followed by thermolysis of the resultant sulfoxide in boiling toluene brought about syn elimination of methanesulfenic acid to give 15,16-dimethoxyerythrin-6-en-8-one (16; 81% yield), whose spectroscopic data were in good accord with those reported.[7] This ready elimination allows us to assign a relative configuration of the methylthio group and C_6-H in 14 as cis.[8] Reduction of 14 with Raney nickel in boiling ethanol gave 15,16-dimethoxy-cis-erythrinan-8-one (17[9]; 99% yield), which was successively converted into 15,16-dimethoxy-cis-erythrinane (18; mp of picrate 181-183°, lit.[10] 182-183°) by reduction with lithium aluminum hydride in 78% yield. Reduction of 15 with Raney nickel gave the 3-benzazepin-2-one (19; mp 197.5-198°. lit.[11] 192-194°) in 84% yield.



15 R=SMe
19 R=H



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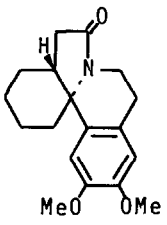

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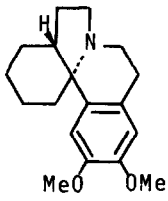

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The present one step construction of erythrinane skeleton involving double olefin-cyclizations is interesting as a new method for the spiro compounds, and is of preparative value.

References and Notes

1 Y. Tamura, H. Maeda, S. Akai, K. Ishiyama, and H. Ishibashi, *Tetrahedron Lett.*, 22, 4301 (1981). For other examples of olefin cyclizations initiated by α-thiocarbocations, see L. N. Mander and P. H. C. Mundill, *Synthesis*, 1981, 620; B. M. Trost and E. Murayama, *J. Am. Chem. Soc.*, 103, 6529 (1981) and references cited therein.

2 IR ($CHCl_3$) cm^{-1}: 1665 (lactam). NMR ($CDCl_3$) δ : 0.8-3.2 (8H, m), 2.41 (3H, s, SMe), 2.95 (3H, s, NMe), 3.62 (1H, dd, J=11 and 6 Hz, C_{7a}-H).

3 IR ($CHCl_3$) cm^{-1}: 1665 (lactam). NMR ($CDCl_3$) δ : 0.9-2.5 (11H, m), 2.78 (3H, s, NMe), 3.45 (1H, q like, J=5 Hz, C_{7a}-H). These data are in good agreement with those reported; see A. Bertho and J. F. Schmidt, *Chem. Ber.*, 97, 3284 (1964).

4 This cyclization is stated to be disfavored, though a few examples have

appeared in the literature; see J. E. Baldwin, *J. C. S. Chem. Comm.*, 1976, 734; R. Grigg, J. Kemp, J. Malone, and A. Tangthongkum, *ibid*, 1980, 648 and references cited therein.

5 a) W. N. Speckamp, "Stereoselective Synthesis of Natural Products - Workshop Conferences Hoechst", Vol 7, pp 50-62, Bartmann and Winterfeldt, Eds., Excerpta Medica (Elsevier), 1979; b) P. M. M. Nossin and W. N. Speckamp, *Tetrahedron Lett.*, 21, 1991 (1980); c) S. J. Veenstra and W. N. Speckamp, *J. Am. Chem. Soc.*, 103, 4645 (1981).

6 (14): IR ($CHCl_3$) cm^{-1}: 1670 (lactam). NMR ($CDCl_3$) δ : 1.4-2.45 (7H, m), 2.12 (3H, s, SMe), 2.7-3.0 (3H, m), 3.05-3.35 (2H, m), 3.38 (1H, d, C_7-H, J=10 Hz), 3.87 and 3.91 (3H×2, 2s, OMe×2), 3.95-4.25 (1H, m), 6.62 and 6.93 (1H×2, 2s, arom). (15): IR ($CHCl_3$) cm^{-1}: 3410 (NH), 1655 (lactam). NMR ($CDCl_3$) δ: 2.33 (3H, s, SMe), 2.95-3.5 (3H, m), 3.85 and 3.87 (3H×2, 2s, OMe×2), 4.05-4.45 (1H, m), 4.53 (1H, d, C_2-H, J=2 Hz), 6.54 and 6.69 (1H×2, 2s, arom), 7.0-7.25 (1H, br, NH).

7 a) A. Mondon, *Liebigs Ann. Chem.*, 628, 123 (1959); b) Ref. 9b. IR ($CHCl_3$) cm^{-1}: 1660 (lactam). NMR ($CDCl_3$) δ : 1.5-4.5 (12H, m), 3.86 and 3.89 (3H×2, 2s, OMe×2), 5.90 (1H, s, C_7-H), 6.73 and 7.08 (1H×2, 2s, arom).

8 Under the present conditions, the thermal isomerization of sulfinyl group is presumed not to occur, see P. A. Bartlett, *J. Am. Chem. Soc.*, 98, 3305 (1976).

9 a) A. Mondon, K. F. Hausen, K. Boehme, H. P. Faro, H. J. Nestler, H. G. Vilhuber, and K. Bottcher, *Chem. Ber.*, 103, 615 (1970); b) A. Mondon and P.-R. Seidel, *ibid.*, 104, 2937 (1971). IR ($CHCl_3$) cm^{-1}: 1660 (lactam). NMR ($CDCl_3$) δ : 1.45-3.4 (14H, m) 3.86 and 3.89 (3H×2, 2s, OMe×2), 4.0-4.3 (1H, m, C_{10}-H), 6.58 and 6.87 (1H×2, 2s, arom). Mass *m/e* (rel. int.): 301 (28, M^+), 272 (3), 259 (18), 258 (100), 246 (2), 245 (13), 244 (14) 217 (3), 216 (4), 214 (3), 202 (1), 200 (2).

10 A. Mondon, H. P. Faro, K. Boehme, K. F. Hansen, and P.-R. Seidel, *Chem. Ber.*, 103, 1286 (1970).

11 O. Yonemitsu, Y. Okuno, Y. Kanaoka, and B. Witkop, *J. Am. Chem. Soc.*, 92, 5686 (1970).

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