INTRAMOLECULAR CYCLIZATION OF METHYLTHIOFUROPYRIDONES

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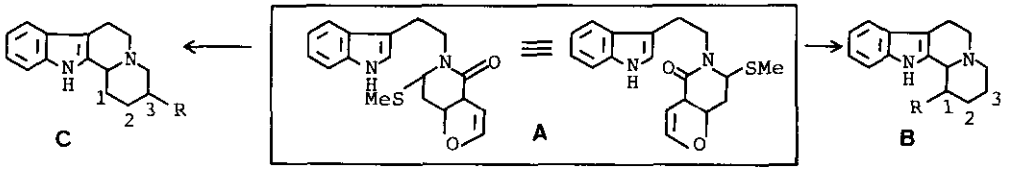
Abstract——Methylthiofuropyridone **4** has been proved as a potential synthon for the construction of indoloquinolizidine structure by the intramolecular cyclization involving methylthio and lactam carbonyl groups.

In continuation of our work[1] on the exploration of a new and general synthetic route for monoterpenoid alkaloids employing alkylthiofuropyridones as a versatile synthon, we have investigated intramolecular cyclization of the system involving α-acyliminium moiety and α-acylamino radical which are expected to be formed in situ from the alkylthiofuropyridone. The alkylthiofuropyridone **A** has carbonyl and methylthio groups on both sides of lactam nitrogen in the molecule. Both groups would be expected to serve as crucial functional groups for the intramolecular cyclization into the indole ring leading to the formation of 1- or 3-substituted indoloquinolizidines **B** and **C** which constitute the basic structures of many of monoterpenoid indole alkaloids.



Treatment of tryptamine with ethyl dithioacetate gave the N-tryptophylthioacetamide (**1**) which was alkylated with dimethyl sulfate to give the thioimidate **2** as an 1:1 mixture of geometrical isomers in 73% yield from tryptamine, which without separation was acylated with 3-furoyl chloride to give the unstable enamide **3** in 52 % yield. Reductive photocyclization[2] of the enamide **3** in the presence of sodium borohydride proceeded smoothly to afford two furopyridones **4**[3] and **5**[4] in 41 and 1 % yields respectively. The major product **4** was employed as a substrate for the following intramolecular cyclizations of the synthon involving

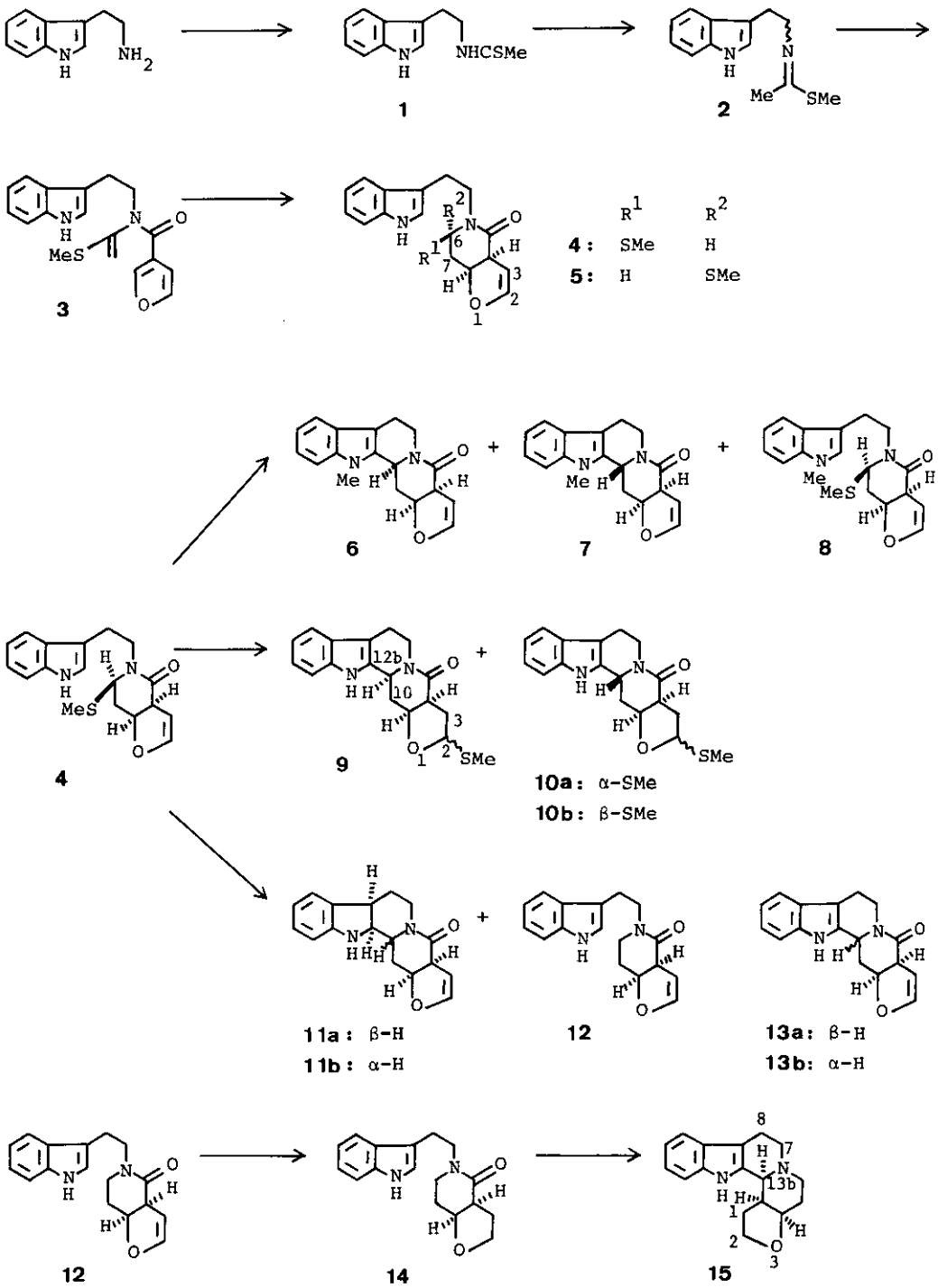
a methylthio group under three different conditions.

Treatment of the methylthiofuropyridone **4** with an excessive amount of methyl iodide in the presence of potassium carbonate gave a mixture of three lactams, **6**,[5] **7**,[4] and **8**[4] in 24, 24, and 21 % yields respectively, of which the former two products **6** and **7** were the intramolecularly cyclized and N-methylated pentacyclic furopyridones and the latter **8** the N-methyl congener of the starting material **4**. Then, we investigated the intramolecular cyclization of the same furopyridone **4** in the presence of p-toluenesulfonic acid and obtained a mixture of three cyclized products **9**,[4,6] **10a**,[4] and **10b**[7] in 10, 40, and 20 % yields respectively. Their structures were deduced from their spectral data as the intramolecularly cyclized products with a methylthio group on the furan ring. The n.O.e measurements suggested the relative configuration of the methylthio group at the 2-position in **10a** and **10b**.

As the third experiment, intramolecular radical cyclization of **4** was investigated. Treatment of the methylthiofuropyridone **4** with tributyltin hydride in the presence of 2,2'-azobisisobutyronitrile (AIBN) gave three products **11a**,[8] **11b**,[4] and **12**[4] in 17, 38, and 40 % yields respectively. The indoline structures for **11a** and **11b** were deduced from both spectral data and chemical evidences including their conversions into the indoloquinolizidines **13a**[4] and **13b**[9] by oxidation with phenylseleninic anhydride.[10] The ratios of three products **11a**, **11b**, and **12** were unaffected by the change of the reaction conditions including relative amount of tributyltin hydride, AIBN, and the reaction temperature. Though some intramolecular cyclizations involving aliphatic olefins have been known in the literature,[11] we could have provided the first example of intramolecular addition of α-acylamino radical to the heterocyclic olefins such as indole.

Demethylthiolactam **12** obtained in the above reaction was catalytically hydrogenated over platinum dioxide to give the tetrahydrolactam **14**[4] which was then subjected to Bischler-Napieralski reaction ($POCl_3$-MeCN) followed by reduction with sodium borohydride to give the pentacyclic product **15**[12] in 65 % yield which is an indoloquinolizidine type of compound with a carbon substituent at the 1-position, often seen in natural indole alkaloids.

In conclusion, we have demonstrated the synthetic utility of the methylthiofuropyridone as a potential and versatile synthon for the synthesis of skeleton of indole alkaloids by intramolecular cyclization based on the high reactivity of two inherent functional groups, methylthio and lactam carbonyl groups.


1
2
3
4 : R1 SMe R2 H
5 : R1 H R2 SMe
6
7
8
4
9
10a : α-SMe
10b : β-SMe
11a : β-H
11b : α-H
12
13a : β-H
13b : α-H
12
14
15

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REFERENCES AND NOTES

1. T. Naito, O. Miyata, and I. Ninomiya, Heterocycles, 1988, **27**, 1321.
2. T. Naito, Y. Tada, Y. Nishiguchi, and I. Ninomiya, J. Chem. Soc., Perkin Trans. 1, 1985, 487.
3. m/z: 328 (M^+); ^{1}H-nmr ($CDCl_3$) δ: 6.36 (br t, J = 2.5 Hz, 2-H), 4.86 (br dt, J = 11 and 3 Hz, 7a-H), 4.12 (br dd, J = 4.5 and 3 Hz, 6-H), 2.06 (s, SMe), and 1.90 (br dt, J = 15 and 4.5 Hz, 7-Hax).
4. Structures of new compounds have been deduced by comparisons of ir, nmr, and mass spectra with those of the related compounds which are shown in ref. 3, 5, 7, 8, and 9.
5. m/z: 294 (M^+); ^{1}H-nmr ($CDCl_3$) δ: 6.20 (t, J = 2 Hz, 2-H), 5.20 (t, J = 2 Hz, 3-H), 5.23-4.53 (m, 6-Heq, 12b-H, and 13a-H), and 3.67 (s, NMe).
6. Configuration of methylthio group in **9** has not been deduced from the spectral data.
7. m/z: 328 (M^+); ^{1}H-nmr ($CDCl_3$) δ: 5.30 (dd, J = 7.5 and 3 Hz, 2-H), 5.12 (br d, J = 12 Hz, 12b-H), 4.52 (br dt, J = 6 and 2.5 Hz, 13a-H), 2.20 (s, SMe), and 1.92 (ddd, J = 14, 12, and 2.5 Hz, 13-Hax). Irradiations of signals due to SMe, 2-H, and 13a-H increased the intensities of signals due to 12b-H (4.8 %), 13a-H (3.2 %), and 2-H (6.5 %) respectively.
8. m/z: 282 (M^+); ^{1}H-nmr ($CDCl_3$) δ: 4.94 (dt, J = 10 and 3.5 Hz, 13a-H), 3.55 (td, J = 10 and 3 Hz, 12b-H), 2.42 (br dt, J = 14 and 3.5 Hz, 13-Heq), and 1.74 (br ddd, J = 14, 10, and 3.5 Hz, 13-Hax).
9. T. Naito, O. Miyata, and I. Ninomiya, Heterocycles, 1987, **26**, 1739.
10. I. Ninomiya, C. Hashimoto, T. Kiguchi, D. H. R. Barton, X. Lusinchi, and P. Milliet, Tetrahedron Lett., 1985, **26**, 4187.
11. J-K. Choi and D. J. Hart, Tetrahedron, 1985, **41**, 3959.
12. Ir ($CHCl_3$) cm^{-1}: 3480, 2852, 2804, and 2748; ^{1}H-nmr ($CDCl_3$) δ: 4.22 (dt, J = 10 and 7 Hz, 3a-H) and 3.59 (brs, 13b-H).

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