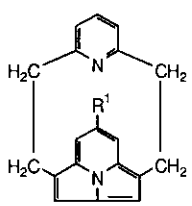
A NEW SYNTHESIS OF 2,12-DITHIA[3.3](1,4)CYCL[3.2.2]AZINOPHANES

Yoshiro Matsuda*, Hiromi Gotou, Keisuke Katou, Hiroshi Matsumoto, Makoto Yamashita, Kimitoshi Takahashi, and Shizuki Ide

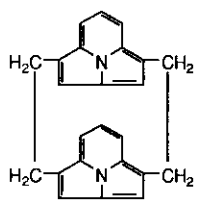
School of Pharmaceutical Sciences, Nagasaki University, 1-14 Bunkyo-machi Nagasaki 852, Japan.

Abstract - 2,12-Dithia[3.3](1,4)cycl[3.2.2]azinophanes (11, 12) which were the key intermediates for the syntheses of [2.2](1,4)-cycl[3.2.2]azinophanes (1, 2) were synthesized by the reaction of bis(mercaptomethyl)cyclazine(10) and dihalogenated compounds (2,6-lutidine dibromide, 8c) with Cs_2CO_3 in N,N-dimethylformamide(DMF).

The syntheses of [2.2]cyclophanes containing heteroaromatic nuclei have been previously reported in the literature.[1] Among some of the common heteroaromatic nuclei which have been incorporated into the [2.2]cyclophane macrocycle are furan, thiophene, pyrrole, and pyridine.[2] However, except for our synthesis of [2.2.2.2](1,4)-cycl[3.2.2]azine derivative,[3] the literature is devoid of [2.2]cyclophane containing cycl[3.2.2]azine nuclei.[4] We now report the first syntheses of 2,12-dithia[3.3]-(1,4)cycl[3.2.2]azinophanes (11,12) which are the key intermediates for the syntheses of [2.2](1,4)cycl[3.2.2]azinophanes (1,2).



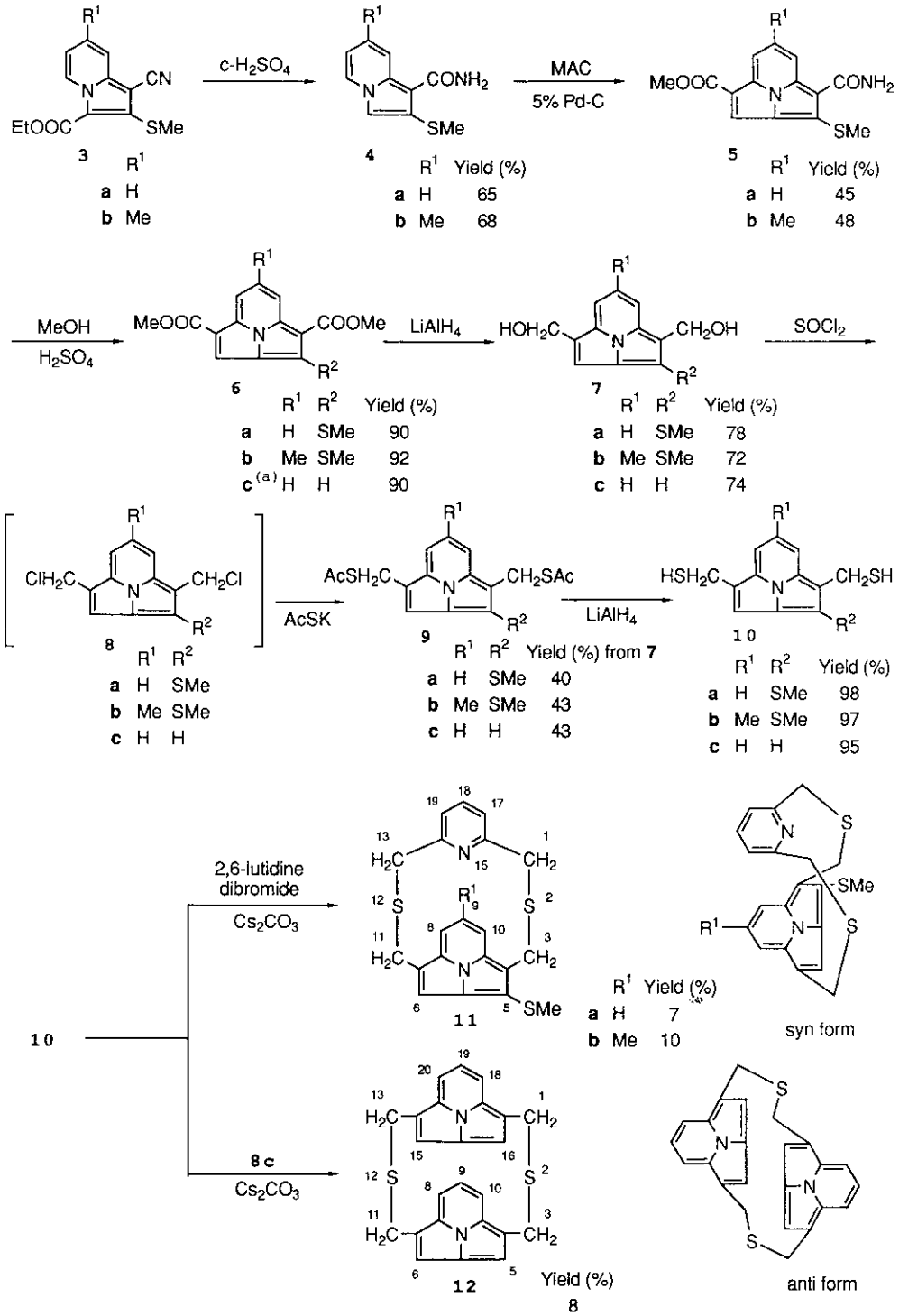
1



2

The starting indolizine derivative (3) used in the present work was prepared according to our previously reported method.[5] Compound 3 was treated with conc. H_2SO_4 at 100 ℃ for 5 h to give the amide derivative (4) with decarboxylation. 1-Carboxyamide-cycl[3.2.2]azine (5) was obtained by the cycloaddition of 4 with methyl acetylenecarboxylate (MAC) in the presence of 5% Pd-C in toluene under nitrogen atmosphere. The diester derivatives (6a,b) were prepared by refluxing 5 in MeOH with conc. H_2SO_4. Compound 6c was obtained by the desulfurization of 6a with Raney Ni in tetrahydrofuran (THF). Compound 6 was reduced by $LiAlH_4$ in THF at room temperature to

Scheme 1



(a) **6a**, Raney-Ni, heating in refluxing THF

give bis(hydroxymethyl)cyclazine (7). Attempt to separate in pure the desired bis-chloromethyl compound (8) from the mixture obtained by the reaction of 7 with thionyl chloride was unsuccessful, because 8 was very unstable to heat. So the crude 8 was treated with potassium thioacetate in acetonitrile to give the desired bis(acetylthiomethyl)cyclazine (9). The key intermediate for the synthesis of cyclazinophanes, bis(mercaptomethyl)cyclazine (10) was obtained by the reduction with $LiAlH_4$ in good yield. The title compounds (11a,b, and 12) were synthesized by the reaction of 10 with dihalogenated compounds (2,6-lutidine dibromide, 8c) in the presence of Cs_2CO_3 in DMF for 48 h, respectively. The assignment of structures of 11a,b[7] and 12[8] was based on spectroscopic analysis. In the ^{1}H-nmr spectrum of 11a, the proton of C_9-H of 11a shows an upfield shift due to the ring current of the opposite pyridine ring and appears as a multiplet at δ 6.52-6.59 (C_6-H of 10a: δ 7.62). In addition, the protons of the 9-methyl group of 11b are also shifted upfield to δ 1.67 (6-CH_3 of 10b: δ 2.77). Thus, it is concluded that the conformer of 11 is the syn form. On the other hand, the assignment of the structure 12 for the anti conformer was readily apparent from its ^{1}H-nmr spectrum. Thus, the protons of $C_{5,6,15,16}$-H of 12 show an upfield shift due to the ring current of the opposite cyclazine ring and appear as a singlet at δ 6.16, whereas the protons of the other ring protons of 12 are normal and appear at δ 7.54, 7.84.

REFERENCES AND NOTES

1. a) M. P. Keehn and S. M. Rosenfold, "Cyclophanes", Academic Press, New York, Vol I and II, 1983. b) M. W. Haenel, B. Lintner, R. Benn, A. Rufinsha, G. Schroth, C. Kruger, S. Hirsch, H. Irngartinger, and D. Schweitzer, Chem. Ber., 1985, 118, 4884. c) R. A. Pascal, C. G. Winans, and D. V. Engen, J. Am. Chem. Soc., 1989, 111, 3007. d) S. Muralidharan, M. Hojjatie, M. Firestone, and H. Freiser, J. Org. Chem., 1989, 54, 393.
2. a) H. Wynberg and R. Helder, Tetrahedron Lett., 1971, 4317. b) J. R. Fletcher and I. O. Sutherland, J. Chem. Soc., Chem. Comm., 1967, 540. c) V. Boekelheide, I. D. Reingold, and M. Tuttle, ibid., 1973, 406. d) S. M. Rosenfold and P. M. Keehn, Tetrahedron Lett., 1973, 4021.
3. H. Gotou, K. Kurata, H. Awaya, Y. Tominaga, Y. Matsuda, and G. Kobayashi, Heterocycles, 1982, 17, 325.
4. a) A. Taurin, Chem. Heterocycl. Compd., 1977, 30, 245. b) W. Flitsh and U. Kramer, Adv. Heterocycl. Chem., 1979, 22, 321. c) K. Matsumoto, T. Uchida, and S. Yamauchi, J. Syn. Org. Chem. Japan, 1977, 35, 739. d) S. J. Lee and J. M.

Cook, Heterocycles, 1983, 20, 87. e) Y. Matsuda and H. Gotou, ibid., 1989, 26, 2757.

5. a) Y. Tominaga and Y. Matsuda, J. Syn. Org. Chem. Japan, 1985, 43, 669. b) S. Hidaki, Y. Tominaga, Y. Matsuda, G. Kobayashi, and K. Sakemi, Yakugaku Zasshi, 1979, 99, 1234. c) C. Maseda, M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, ibid., 1974, 94, 839.

6. a) For 10a, mp 95°C(98%); ^{1}H-nmr($CDCl_3$) δ 1.99(1H, t, J=7Hz, SH), 2.06(1H, t, J=7Hz, SH), 2.85(3H, s, SCH_3), 4.24(2H, d, J=7Hz, CH_2), 4.28(2H, d, J=7Hz, CH_2), 7.49(1H, s, C_3-H), 7.62(1H, t, J=8Hz, C_6-H), 7.85(1H, d, J=8Hz, C_5-H or C_7-H), 7.93(1H, d, J=8Hz, C_5-H or C_7-H); ir(KBr) cm^{-1} 2530(SH); uv(EtOH) λmax nm(log ε) 235(4.29)sh, 252(4.37), 280(4.08)sh, 328(3.94)sh, 338(3.97), 424(4.10). Anal. Calcd for $C_{13}H_{13}NS_3$: C, 55.88; H, 4.69; N, 5.01. Found: C, 55.89; H, 4.56; N, 5.03.

b) For 10b, mp 135°C(97%); ^{1}H-nmr($CDCl_3$) δ 1.97(1H, t, J=7Hz, SH), 2.04(1H, t, J=7Hz, SH), 2.77(3H, s, CH_3), 2.83(3H, s, SCH_3), 4.20(2H, d, J=7Hz, CH_2), 4.25 (2H, d, J=7Hz, CH_2), 7.42(1H, s, C_3-H), 7.66(1H, s, C_5-H or C_7-H), 7.73(1H, s, C_5-H or C_7-H); ir(KBr) cm^{-1} 2550(SH); uv(EtOH) λmax nm(log ε) 215(4.28), 253 (4.36), 330(3.94)sh, 340(3.97), 426(3.78). Anal. Calcd for $C_{14}H_{15}NS_3$: C, 57.30; H, 5.15; N, 4.77. Found: C, 57.37; H, 5.20; N, 4.52.

c) For 10c, mp 70°C(95%); ^{1}H-nmr($CDCl_3$) δ 1.98(2H, t, J=7Hz, 2xSH), 4.30(4H, d, J=7Hz, 2xCH_2), 7.45(2H, s, C_2-H and C_3-H), 7.66(1H, t, J=8Hz, C_6-H), 8.05(2H, d, J=8Hz, C_5-H and C_7-H); ir(KBr) cm^{-1} 2550(SH); uv(EtOH) λmax nm (log ε) 235(4.41), 241(4.39)sh, 257(4.36), 291(3.72), 425(3.75), 444(3.54). Anal. Calcd for $C_{12}H_{11}NS_2$: C, 61.77; H, 4.75; N, 6.00. Found: C, 61.91; H, 4.85; N, 5.94.

7. a) For 11a, mp 170°C(7%); ms($C_{20}H_{18}N_2S_3$) m/z 382(M^+); ^{1}H-nmr($CDCl_3$) δ 2.58(3H, broad s, SCH_3), 3.78-3.80(4H, m, 2xCH_2), 4.14-4.19(4H, m, 2xCH_2), 6.52-6.59(1H, m, C_9-H), 7.21-7.98(6H, m, Ar-H); uv(EtOH) λmax nm 214sh, 233sh, 253, 280 sh, 330sh, 339sh, 420.

b) For 11b, mp 163°C(10%); ms($C_{21}H_{20}N_2S_3$) m/z 396(M^+); ^{1}H-nmr($CDCl_3$) δ 1.67(3H, s, CH_3), 2.57(3H, broad s, SCH_3), 3.83-3.85(4H, m, 2xCH_2), 4.13-4.19(4H, m, 2xCH_2) 7.21-7.79(6H, m, Ar-H); uv(EtOH) λmax nm 216sh, 255, 280sh, 330sh, 342, 425.

8. For 12, mp 220°C(8%); ms($C_{24}H_{18}N_2S_2$) m/z 398(M^+); ^{1}H-nmr($CDCl_3$) δ 4.17(4H, d, J=15Hz, 2xCH_2), 4.40(4H, d, J=15Hz, 2xCH_2), 6.16(4H, s, $C_{5,6,15,16}$-H), 7.54(2H, t, J=7Hz, $C_{9,19}$-H), 7.84(4H, d, J=7Hz, $C_{8,10,18,20}$-H); uv(EtOH) λmax nm 233, 260sh, 274sh, 293sh, 423.

Received, 7th March, 1990