

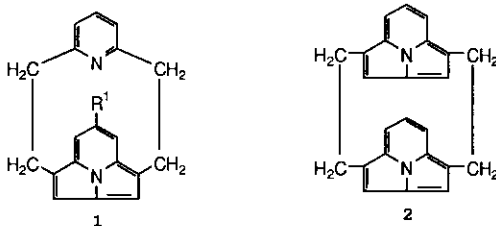
A NEW SYNTHESIS OF 2,12-DITHIA[3.3](1,4)CYCL[3.2.2]AZINOPHANES

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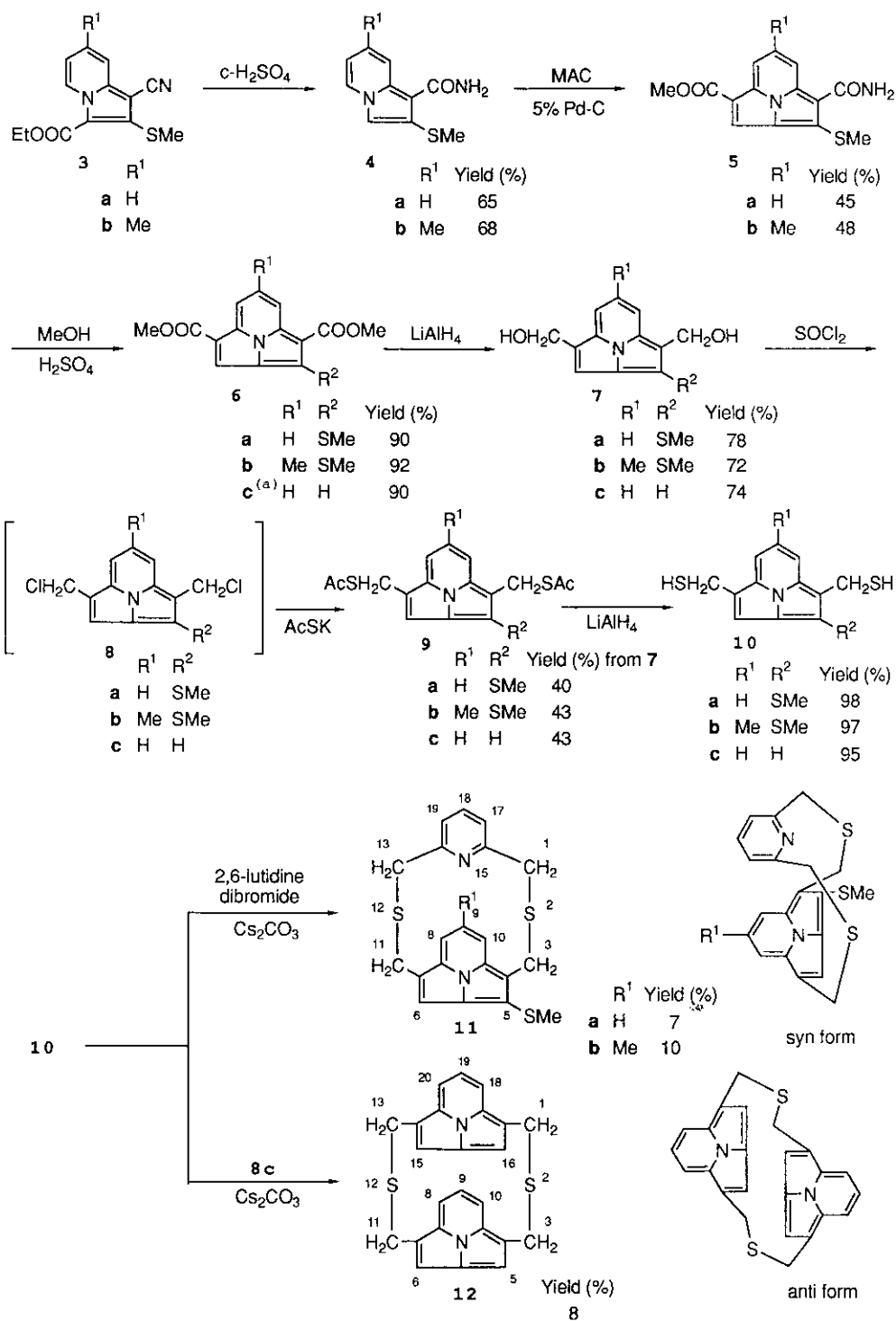
Abstract - 2,12-Dithia[3.3](1,4)cycl[3.2.2]azinophanes (11, 12) which were the key intermediates for the syntheses of [2.2](1,4)-cycl[3.2.2]azinophanes (1, 2) were synthesized by the reaction of bis(mercaptomethyl)cyclazine(10) and dihalogenated compounds (2,6-lutidine dibromide, 8c) with Cs_2CO_3 in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



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 °C 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(acylthiomethyl)cyclazine (9). The key intermediate for the synthesis of cyclazino-phanes, 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,b⁷ and 12⁸ was based on spectroscopic analysis. In the ^1H -nmr spectrum of 11a, the proton of $\text{C}_9\text{-H}$ 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 ($\text{C}_6\text{-H}$ 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 ^1H -nmr spectrum. Thus, the protons of $\text{C}_{5,6,15,16}\text{-H}$ 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.

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6. a) For 10a, mp 95°C(98%); $^1\text{H-nmr}(\text{CDCl}_3)$ δ 1.99(1H, t, $J=7\text{Hz}$, SH), 2.06(1H, t, $J=7\text{Hz}$, SH), 2.85(3H, s, SCH_3), 4.24(2H, d, $J=7\text{Hz}$, CH_2), 4.28(2H, d, $J=7\text{Hz}$, CH_2), 7.49(1H, s, $\text{C}_3\text{-H}$), 7.62(1H, t, $J=8\text{Hz}$, $\text{C}_6\text{-H}$), 7.85(1H, d, $J=8\text{Hz}$, $\text{C}_5\text{-H}$ or $\text{C}_7\text{-H}$), 7.93(1H, d, $J=8\text{Hz}$, $\text{C}_5\text{-H}$ or $\text{C}_7\text{-H}$); $\text{ir}(\text{KBr}) \text{ cm}^{-1}$ 2530(SH); $\text{uv}(\text{EtOH}) \lambda_{\text{max}} \text{ nm}(\log \epsilon)$ 235(4.29)sh, 252(4.37), 280(4.08)sh, 328(3.94)sh, 338(3.97), 424(4.10). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{NS}_3$: 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%); $^1\text{H-nmr}(\text{CDCl}_3)$ δ 1.97(1H, t, $J=7\text{Hz}$, SH), 2.04(1H, t, $J=7\text{Hz}$, SH), 2.77(3H, s, CH_3), 2.83(3H, s, SCH_3), 4.20(2H, d, $J=7\text{Hz}$, CH_2), 4.25(2H, d, $J=7\text{Hz}$, CH_2), 7.42(1H, s, $\text{C}_3\text{-H}$), 7.66(1H, s, $\text{C}_5\text{-H}$ or $\text{C}_7\text{-H}$), 7.73(1H, s, $\text{C}_5\text{-H}$ or $\text{C}_7\text{-H}$); $\text{ir}(\text{KBr}) \text{ cm}^{-1}$ 2550(SH); $\text{uv}(\text{EtOH}) \lambda_{\text{max}} \text{ nm}(\log \epsilon)$ 215(4.28), 253(4.36), 330(3.94)sh, 340(3.97), 426(3.78). Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{NS}_3$: 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%); $^1\text{H-nmr}(\text{CDCl}_3)$ δ 1.98(2H, t, $J=7\text{Hz}$, $2\times\text{SH}$), 4.30(4H, d, $J=7\text{Hz}$, $2\times\text{CH}_2$), 7.45(2H, s, $\text{C}_2\text{-H}$ and $\text{C}_3\text{-H}$), 7.66(1H, t, $J=8\text{Hz}$, $\text{C}_6\text{-H}$), 8.05(2H, d, $J=8\text{Hz}$, $\text{C}_5\text{-H}$ and $\text{C}_7\text{-H}$); $\text{ir}(\text{KBr}) \text{ cm}^{-1}$ 2550(SH); $\text{uv}(\text{EtOH}) \lambda_{\text{max}} \text{ nm}(\log \epsilon)$ 235(4.41), 241(4.39)sh, 257(4.36), 291(3.72), 425(3.75), 444(3.54). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{NS}_2$: 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%); $\text{ms}(\text{C}_{20}\text{H}_{18}\text{N}_2\text{S}_3) m/z$ 382(M^+); $^1\text{H-nmr}(\text{CDCl}_3)$ δ 2.58(3H, broad s, SCH_3), 3.78-3.80(4H, m, $2\times\text{CH}_2$), 4.14-4.19(4H, m, $2\times\text{CH}_2$), 6.52-6.59(1H, m, $\text{C}_9\text{-H}$), 7.21-7.98(6H, m, Ar-H); $\text{uv}(\text{EtOH}) \lambda_{\text{max}} \text{ nm}$ 214sh, 233sh, 253, 280 sh, 330sh, 339sh, 420.
- b) For 11b, mp 163°C(10%); $\text{ms}(\text{C}_{21}\text{H}_{20}\text{N}_2\text{S}_3) m/z$ 396(M^+); $^1\text{H-nmr}(\text{CDCl}_3)$ δ 1.67(3H, s, CH_3), 2.57(3H, broad s, SCH_3), 3.83-3.85(4H, m, $2\times\text{CH}_2$), 4.13-4.19(4H, m, $2\times\text{CH}_2$), 7.21-7.79(6H, m, Ar-H); $\text{uv}(\text{EtOH}) \lambda_{\text{max}} \text{ nm}$ 216sh, 255, 280sh, 330sh, 342, 425.
8. For 12, mp 220°C(8%); $\text{ms}(\text{C}_{24}\text{H}_{18}\text{N}_2\text{S}_2) m/z$ 398(M^+); $^1\text{H-nmr}(\text{CDCl}_3)$ δ 4.17(4H, d, $J=15\text{Hz}$, $2\times\text{CH}_2$), 4.40(4H, d, $J=15\text{Hz}$, $2\times\text{CH}_2$), 6.16(4H, s, $\text{C}_{5,6,15,16}\text{-H}$), 7.54(2H, t, $J=7\text{Hz}$, $\text{C}_{9,19}\text{-H}$), 7.84(4H, d, $J=7\text{Hz}$, $\text{C}_{8,10,18,20}\text{-H}$); $\text{uv}(\text{EtOH}) \lambda_{\text{max}} \text{ nm}$ 233, 260sh, 274sh, 293sh, 423.