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$_2$CO$_3$ 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$_2$SO$_4$ 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 acetylene-carboxylate (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$_2$SO$_4$. 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 thio-
nyl 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(ace-
tylthiomethyl)cyclazine (9). The key intermediate for the synthesis of cyclazino-
phanes, bis(mercaptomethyl)cyclazine (10) was obtained by the reduction with LiAlH4
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
Cs2CO3 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
C9-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 (C6-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-CH3
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 C5,6,15,16-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.

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6. a) For 10a, mp 95°C(96%); \(^1\)H-nmr(CDCl\(_3\)) \(\delta\) 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\(_5\)-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) \(\lambda_{max}\) nm(log \(\epsilon\)) 235(4.29), 252(4.37), 280(4.08), 328(3.94), 338(3.97), 424(4.10). Anal. Calcd for C\(_{13}\)H\(_{13}\)NS: C, 55.88; H, 4.69; N, 5.03.

b) For 10b, mp 135°C(97%); \(^1\)H-nmr(CDCl\(_3\)) \(\delta\) 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, t, J=8Hz, C\(_6\)-H), 7.73(1H, s, C\(_5\)-H or C\(_7\)-H); ir(KBr) cm\(^{-1}\) 2550(SH); uv(EtOH) \(\lambda_{max}\) nm(log \(\epsilon\)) 215(4.28), 253(4.36), 330(3.94), 340(3.97), 426(3.78). Anal. Calcd for C\(_{14}\)H\(_{15}\)NS\(_2\): C, 57.30; H, 4.56; N, 5.03.

c) For 10c, mp 70°C(95%); \(^1\)H-nmr(CDCl\(_3\)) \(\delta\) 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) \(\lambda_{max}\) nm(log \(\epsilon\)) 235(4.41), 241(4.39), 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, 5.94.

7. a) For 11a, mp 170°C(7%); ms(C\(_{20}\)H\(_{18}\)N\(_2\)S\(_3\)) m/z 382(M\(^+\)); \(^1\)H-nmr(CDCl\(_3\)) \(\delta\) 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) \(\lambda_{max}\) nm 214(sh), 233(sh), 253, 280 sh, 330 sh, 339 sh, 420.

b) For 11b, mp 163°C(10%); ms(C\(_{21}\)H\(_{20}\)N\(_2\)S\(_3\)) m/z 396(M\(^+\)); \(^1\)H-nmr(CDCl\(_3\)) \(\delta\) 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) \(\lambda_{max}\) nm 216(sh), 255, 280 sh, 330 sh, 342, 425.

8. For 12, mp 220°C(8%); ms(C\(_{24}\)H\(_{18}\)N\(_2\)S\(_2\)) m/z 398(M\(^+\)); \(^1\)H-nmr(CDCl\(_3\)) \(\delta\) 4.17(4H, d, J=15Hz, 2xCH\(_2\)), 4.40(4H, d, J=15Hz, 2xCH\(_2\)), 6.16(4H, s, C\(_5\), C\(_6\), 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) \(\lambda_{max}\) nm 233, 260 sh, 274 sh, 293 sh, 423.

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