

A NEW SYNTHESIS OF 5-AZA[2.2.3]CYCLAZINES BY [8 + 2]CYCLO-  
ADDITION OF 3-IMINO-3H-PYRROLIZINES WITH DIMETHYL ACETYLENE-  
DICARBOXYLATE

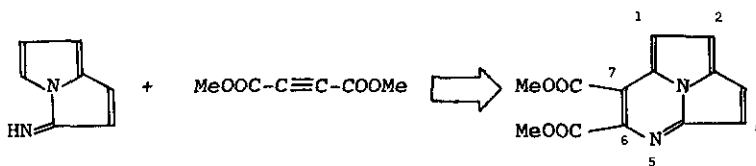
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Abstract—Reaction of 3-imino-3H-pyrrolizines, generated in situ, with dimethyl acetylenedicarboxylate (DMAD) in the presence of palladium on charcoal in toluene gave 5-aza-[2.2.3]cyclazine derivatives in good yields.

5-Aza[2.2.3]cyclazine is an interesting aromatic compound involving delocalized  $10\pi$ -electrons from theoretical point of view, similarly to other 1-, 2-, or 6-aza[2.2.3]cyclazines and [2.2.3]cyclazines.<sup>1-5</sup> Therefore synthesis of a variety of 5-azacyclazines by use of readily available starting materials is highly desirable for the investigation of aza[2.2.3]cyclazine chemistry. Boekelheide and Kertelj have first reported the synthesis of 5-aza[2.2.3]cyclazine derivative by the [8 + 2]cycloaddition reaction of 7-methyl-2-phenylpyrrolo[1,2-c]pyrimidine with DMAD in the presence of palladium on charcoal,<sup>6</sup> which contains a phenyl and a methyl group in the 6- and 2-positions, respectively. However, access to desired 5-aza[2.2.3]cyclazine derivatives from pyrrolo[1,2-c]pyrimidines as the starting materials is difficult at present, because the preparation of suitably designed pyrrolo[1,2-c]pyrimidine derivatives is still limited.

Jessep and Leaver reported a convenient and unique [8 + 2]cycloaddition reaction of 3-dimethylaminomethylene-3H-pyrrolizine bearing an exo-methylene group with DMAD to give dimethyl [2.2.3]cyclazine-5,6-dicarboxylate.<sup>7</sup> Therefore we attempted a novel synthesis of 5-aza[2.2.3]cyclazines by the [8 + 2]cycloaddition reaction of in situ generated cyclic exo-imino tetraene compounds, 3-imino-3H-pyrrolizine derivatives, with DMAD.

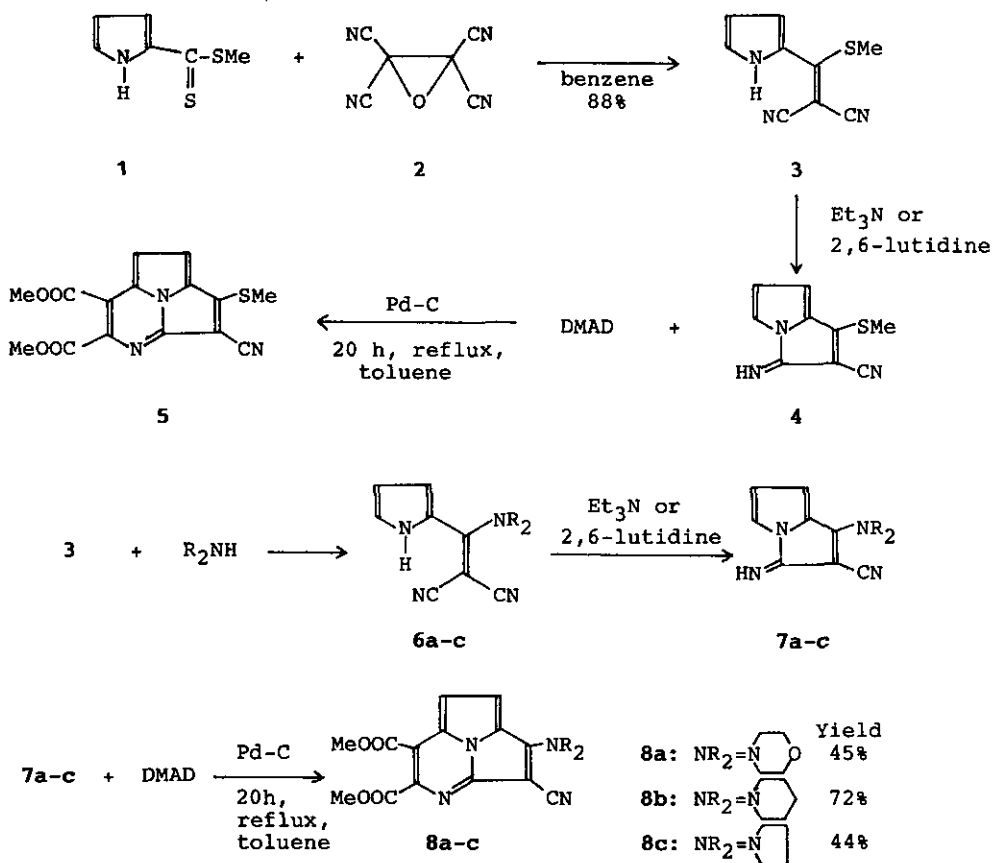
Recently we have reported that the synthesis of polarized ethylenes having both electron-donating and electron-accepting groups on the adjacent two olefinic



carbon atoms.<sup>8</sup> In the extension of the studies on polarized ethylenes, we applied this reaction to the preparation of 2-cyano-3-(2-pyrrolyl)-3-methylthioacrylonitrile which is an important precursor for the synthesis of 5-aza[2.2.3]-cyclazines.

Methyl pyrrolyl-2-dithiocarboxylate (1), readily prepared by the Grignard reaction of pyrrole and carbon disulfide, is allowed to react with tetracyanoethylene oxide (2) in benzene with stirring at room temperature to give a desired dicyanomethylene derivative (3) in 88% yield. Cyclization of 3 to 2-cyano-3-imino-1-methylthio-3H-pyrrolizine (4) occurred smoothly, when the mixture of 3 and triethylamine or 2,6-lutidine was heated at reflux, and then the reaction temperature was elevated ultimately up to ca. 150°C by the removal of the base.<sup>9</sup> Without isolation of 4, treatment of the reaction mixture with DMAD in the presence of 5% palladium on charcoal in toluene at reflux for 20 hr gave the [8 + 2]cycloaddition product, dimethyl 4-cyano-3-methylthio-5-aza[2.2.3]cyclazine-6,7-dicarboxylate (5), in 23% yield. 3-Amino-5-aza[2.2.3]cyclazine derivatives (8a-c) were also obtained from the corresponding 1-amino-3-imino-3H-pyrrolizine derivatives (7a-c) and DMAD. Compounds (7a-c) were readily prepared by displacement of the methylthio group of 3 with the corresponding amines such as morpholine, piperidine, and pyrrolidine, respectively, followed by cyclization under heating in the presence of triethylamine or 2,6-lutidine in a manner similar to the preparation of 4. The vicinal coupling constant between C<sub>1</sub>-H and C<sub>2</sub>-H (7.62 and 7.86 ppm, J<sub>1,2</sub> = 4.5 Hz) of 5 in the <sup>1</sup>H nmr spectrum is similar to the corresponding value of 2-methylthio-1-aza[2.2.3]cyclazine (7.21 and 7.53 ppm, J<sub>3,4</sub> = 4.4 Hz)<sup>10</sup>. The chemical shift of the methyl protons of the methylthio group of 5 is also shown in low field region similar to that of the corresponding methylthio group in 2-methylthio-1-aza[2.2.3]cyclazine<sup>10</sup>. The nmr data apparently indicate that 5-aza[2.2.3]cyclazine derivatives (5 and 8a-c)<sup>11-14</sup> are typical aromatic compounds.

In conclusion, the present synthetic method of aza[2.2.3]cyclazine by the [8 + 2]cycloaddition of heterocycles bearing exo-imino group with DMAD will provide a convenient and useful method for the synthesis of various other aza[2.2.3]-cyclazine derivatives.



Scheme 1

ACKNOWLEDGMENT

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9. Heating at high temperature may be essential for the cyclization of 3. Hartke and Radau reported the preparation of 3 by the Grignard reaction of pyrrole and ketene dithioacetal, 2,2-dicyano-1,1-bis(methylthio)ethylene, in rather low yield and conversion of 3 to 4. However, when we attempted the reaction of 4, thus obtained, with DMAD, only the conjugate addition product of the N-H bond of pyrrole moiety of 3 to DMAD, but not the corresponding cycloadduct, was obtained. See, K. Hartke and S. Radau, Justus Liebigs Ann. Chem., 1974, 2110.
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11. 5, mp 212°C, yellow needles (MeOH), ms(m/z): 329(M<sup>+</sup>, 100), 298(44), 270(17), 240(11), 213(48); ir v(max, KBr)cm<sup>-1</sup>: 2210(CN), 1740, 1715(CO); uv λ(max, EtOH)(log ε): 239(4.45), 278(4.28), 302(4.26), 376(4.32), 440(3.61); <sup>1</sup>H nmr(CDCl<sub>3</sub>) δ: 3.03(3H, s, SMe), 4.08(3H, s, OMe), 4.10(3H, s, OMe), 7.62(1H, d, J=4.5 Hz, 2-H), 7.86(1H, d, J=4.5 Hz, 1-H).
12. 8a, mp 271°C, yellow leaflets(MeOH); ms(m/z): 368(M<sup>+</sup>, 100), 337(21), 252(26), 149(21), 81(31), 71(21), 69(57), 57(50), 55(27); ir v(max, KBr) cm<sup>-1</sup>: 2240(CN), 1738, 1725(CO); uv λ(max, EtOH)(log ε): 222(4.46), 244(4.17), 267(4.26), 273(4.26, shoulder), 297(4.23), 324(4.03, shoulder), 381(4.33); <sup>1</sup>H nmr(CDCl<sub>3</sub>) δ: 4.03(3H, s, OMe), 4.06(3H, s, OMe), 3.90-4.04(8H, m, O-CH<sub>2</sub>-CH<sub>2</sub>-N), 7.33(1H, d, J=4.2 Hz, 2-H), 7.54(1H, d, J=4.2 Hz, 1-H).
13. 8b, mp 253°C, yellow needles(MeOH); ms(m/z): 366(M<sup>+</sup>, 100), 309(58), 250(32), 81(21), 69(35); ir v(max, KBr) cm<sup>-1</sup>: 2205(CN), 1742, 1721(CO); uv λ(max, EtOH) (log ε): 223(4.40), 242(4.09 shoulder), 267(4.25), 272(4.24, shoulder), 297(4.21), 377(4.31); <sup>1</sup>H nmr(CDCl<sub>3</sub>) δ: 1.87(6H, m, 3, 4, 5-H), 4.02(4H, m, N-CH<sub>2</sub>-), 4.05(6H, s, OMe), 7.25(1H, d, J=4.2 Hz, 2-H), 7.50(1H, d, J=4.2 Hz, 1-H).
14. 8c, mp 236°C, yellow needles(MeOH); ms(m/z): 352(M<sup>+</sup>, 19), 236(5), 144(22), 69(28), 57(33), 44(79), 43(100). ir v(max, KBr)cm<sup>-1</sup>: 2205(CN), 1742, 1721(CO); uv λ(max, EtOH)(log ε): 222(4.46), 244(4.15), 265(4.25), 271(4.24), 297(4.24), 325(3.99), 378(4.32). <sup>1</sup>H nmr(CDCl<sub>3</sub>) δ: 2.18-2.33(4H, m, -CH<sub>2</sub>-CH<sub>2</sub>), 4.02(3H, s, OMe), 4.06(3H, s, OMe), 3.80-4.20(4H, m, N-CH<sub>2</sub>-), 7.16(1H, d, J=4.2 Hz, 2-H), 7.41(1H, d, J=4.2 Hz, 1-H).