A NEW SYNTHESIS OF 5-AZA[2.2.3]CYCLAZINES BY [8 + 2]CYCLOADDITION OF 3-IMINO-3H-PYRROLIZINES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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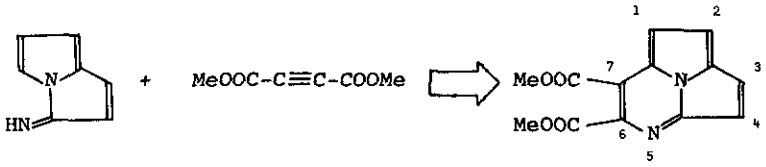
Abstract——Reaction of 3-imino-3H-pyrrolizines, generated in situ, with dimethyl acetylenedicarboxylate (DMAD) in the presence of palladium on charcoal in toluene gave 5-aza-[2.2.3]cyclazine derivatives in good yields.

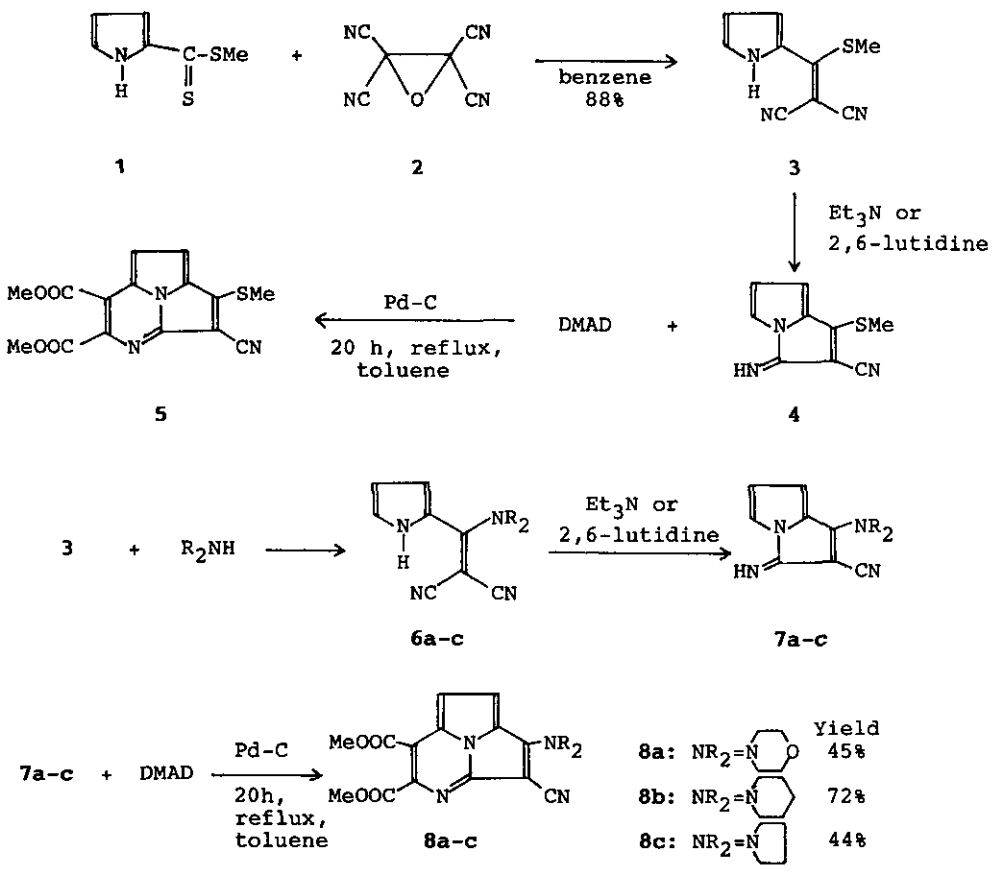
5-Aza[2.2.3]cyclazine is an interesting aromatic compound involving delocalized 10π-electrons from theoretical point of view, similarly to other 1-, 2-, or 6-aza[2.2.3]cyclazines and [2.2.3]cyclazines.[1-5] Therefore synthesis of a variety of 5-azacyclazines by use of readily available starting materials 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,[6] 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.[7] 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.[8] 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.[9] 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_1-H and C_2-H (7.62 and 7.86 ppm, $J_{1,2}$ = 4.5 Hz) of **5** in the ^{1}H nmr spectrum is similar to the corresponding value of 2-methylthio-1-aza[2.2.3]cyclazine (7.21 and 7.53 ppm, $J_{3,4}$ = 4.4 Hz)[10]. 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[10]. The nmr data apparently indicate that 5-aza[2.2.3]cyclazine derivatives (**5** and **8a-c**)[11-14] 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 obatined. 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^+, 100), 298(44), 270(17), 240(11), 213(48); ir ν(max, KBr)cm^{-1}: 2210(CN), 1740, 1715(CO); uv λ(max, EtOH)nm(log ε): 239(4.45), 278(4.28), 302(4.26), 376(4.32), 440(3.61); ^{1}H nmr($CDCl_3$) 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^+, 100), 337(21), 252(26), 149(21), 81(31), 71(21), 69(57), 57(50), 55(27); ir ν(max, KBr) cm^{-1}: 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): ^{1}H nmr($CDCl_3$) δ: 4.03(3H, s, OMe), 4.06(3H, s, OMe), 3.90-4.04(8H, m, O-CH_2-CH_2-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^+, 100), 309(58), 250(32), 81(21), 69(35); ir ν(max, KBr) cm^{-1}: 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); ^{1}H nmr($CDCl_3$) δ: 1.87(6H, m, 3, 4, 5-H), 4.02(4H, m, N-CH_2-), 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^+, 19), 236(5), 144(22), 69(28), 57(33), 44(79), 43(100). ir ν(max, KBr)cm^{-1}: 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). ^{1}H nmr($CDCl_3$) δ: 2.18-2.33(4H, m, -CH_2-CH_2), 4.02(3H, s, OMe), 4.06(3H, s, OMe), 3.80-4.20(4H, m, N-CH_2-), 7.16(1H, d, J=4.2 Hz, 2-H), 7.41(1H, d, J=4.2 Hz, 1-H).

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