# SYNTHESIS OF BENZANNELATED 1-AZACYCL[3.2.2]AZINE: 1-AZABENZO[h]CYCL[3.2.2]AZINE

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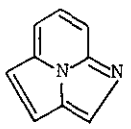
Abstract ——— 1-Azabenzo[h]cycl[3.2.2]azine (3) was synthesized by the reaction sequence starting from 2-[1-ethoxycarbonyl-2,2-bis-(methylthio)vinyl]isoquinolinium iodide (4), involving the cyclo-addition of 2-methylthioimidazo[2,1-a]isoquinoline (8) with dimethyl acetylenedicarboxylate as the key step. It was found that 3 and its 2-methylthio derivative (14) are typical aromatic compounds.

A variety of cycl[3.2.2]azine derivatives have been investigated chiefly because of theoretical interest regarding the relationship between the structure and the aromatic character.[1-8] As for benzannelated cycl[3.2.2]azines, only a few reports are available.[6,9,10] Recently, we prepared benzo[g]cycl[3.2.2]azine (2) and showed that it is a stable aromatic system.[11] As a continuation of our work on benzannelated cyclazines, we carried out the synthetic study of 1-azabenzo[h]cycl-[3.2.2]azine (3), 1-aza-analogue of 2.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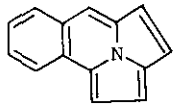
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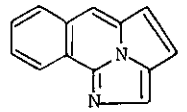
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We chose 2-methylthioimidazo[2,1-a]isoquinoline (8)[12] as the key intermediate, and its preparation was performed by the route shown in Chart 1. Thus, treatment of 2-[1-ethoxycarbonyl-2,2-bis(methylthio)vinyl]isoquinolinium iodide (4)[11] with 1-aminopyridinium mesitylenesulfonate (5)[13] in the presence of triethylamine in ethanol afforded 2-methylthioimidazo[2,1-a]isoquinoline-3-carboxylate (6).[14] This process involves the initial displacement of a methylthio group of 4 with the amino group of 5, followed by intramolecular cyclization and subsequent liberation of the pyridinium moiety to give 6 as illustrated in Chart 1. Hydrolysis of 6 with sodium hydroxide in methanol to the corresponding carboxylic acid (7) and subsequent decarboxylation of 7 by heating in poly phosphoric acid gave the desired compound 8. A solution of 8 and dimethy acetylenedicarboxylate in toluene was refluxed for 30 h using a 50% palladium-charcoal as dehydrogenation catalyst to give the expected

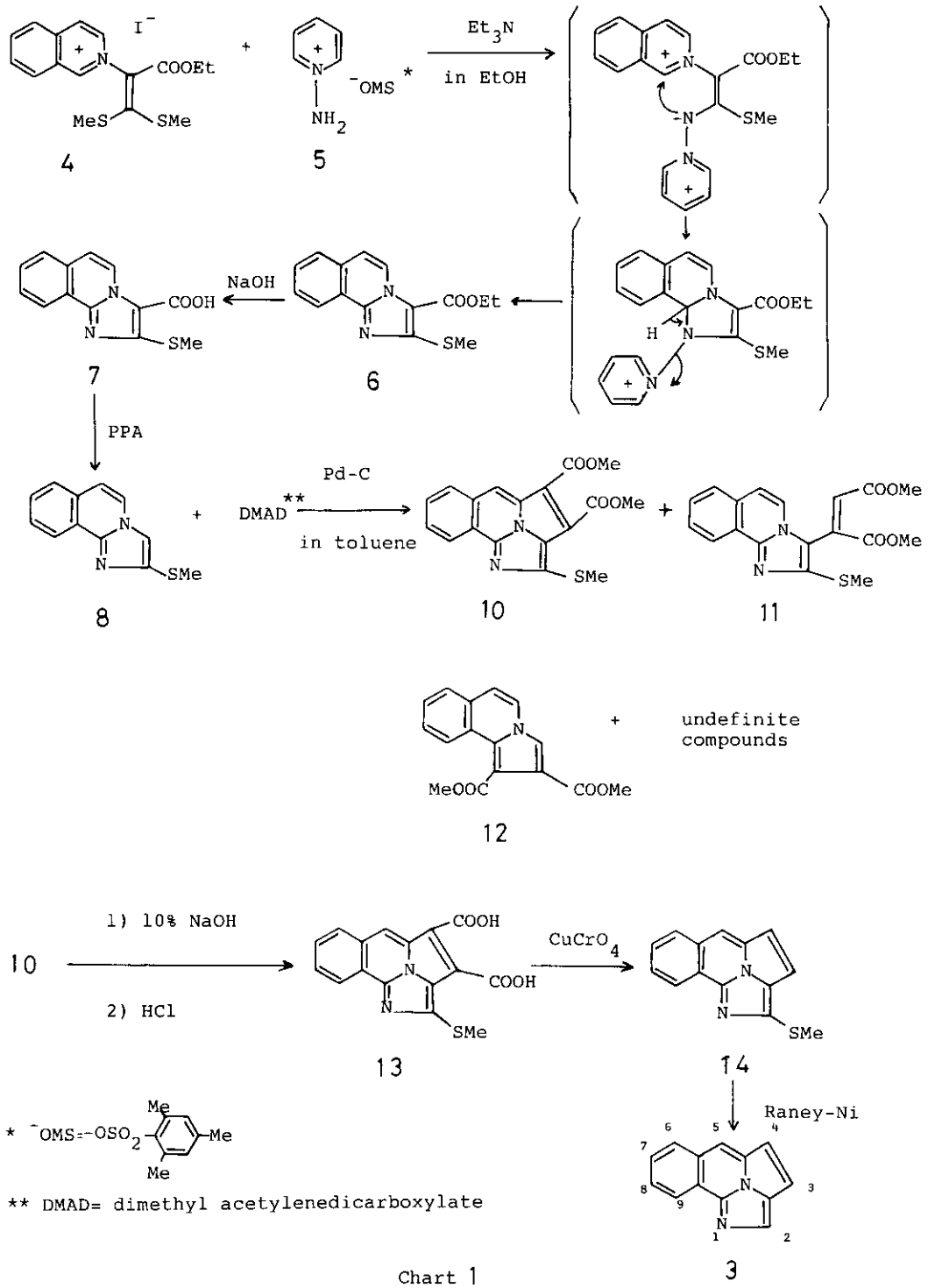
I⁻
COOEt
MeS
SMe
4
+
⁻OMS *
NH2
5
Et3N
in EtOH
COOEt
SMe
NaOH
COOH
SMe
7
COOEt
SMe
6
PPA
Pd-C
DMAD **
in toluene
COOMe
COOMe
SMe
8
10
11
+
undefinite
compounds
MeOOC
COOMe
12
1) 10% NaOH
10
2) HCl
COOH
COOH
SMe
13
CuCrO4
14
Raney-Ni
3
* ⁻OMS=-OSO2
Me
Me
Me
** DMAD= dimethyl acetylenedicarboxylate

Chart 1

product, dimethyl 2-methylthio-1-azabenzo[h]cycl[3.2.2]azine-3,4-dicarboxylate (10),[15] though in a small yield of 6%, together with ethyl 3-(α,β-dimethoxycarbonylvinyl)imidazo[2,1-a]isoquinoline-3-carboxylate (11)[16](4%), dimethyl pyrrolo[2,1-a]isoquinoline-2,3-dicarboxylate (12)[17](33%) and some undefined compounds. Hydrolysis of 10 with 10% sodium hydroxide gave the corresponding diacid (13) almost quantitatively. Decarboxylation of 13 occurred smoothly on heating with copper chromite in diphenyl ether to produce 2-methylthio-1-azabenzo[h]cycl[3.2.2]azine (14)[18] in 34% yield. Finally, the desulfurization of 14 was easily effected with Raney-nickel to afford the desired parent compound, 1-azabenzo[h]cycl[3.2.2]azine (3)[19] in 15% yield (Chart 1).

Both the 1-azabenzo[h]cycl[3.2.2]azines (14 and 3) are yellow crystalls and soluble in most organic solvents giving pale yellow solutions. They are stable to heat, light, and acids.

The aromatic proton chemical shifts (7.40 - 9.04 ppm) of 3 in the $^1$H-NMR spectrum are similar to those of benzo[g]cycl[3.2.2]azine (2) (7.28 - 8.95 ppm)[11] and of 1-azacycl[3.2.2]azine (1) (7.46 - 8.58 ppm)[1]. The vicinal coupling constant for C3-H and C4-H ($J_{3,4}$=5.0 Hz) is slightly larger than the corresponding value in compound 1 and 2 (1: $J_{3,4}$=4.8 Hz; 2: $J_{3,4}$=4.9 Hz).[1,11] The methyl protons (2.94 ppm) of methylthio group of 14 are strongly deshielded relative to those (2.03 - 2.33 ppm) of the non aromatic model compounds such as ketene dithioacetals.[20,21] The above results show that 1-azabenzo[h]cycl[3.2.2]azine derivatives (14, 3) are typical aromatic compounds.

ACKNOWLEDGEMENT

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12) mp 87°C, colorless prisms, NMR δ ($CDCl_3$): 2.60(3H, s, $SCH_3$), 7.22(1H, d, J=7.3 Hz, 6-H), 7.44(1H, s, 3-H), 7.49-7.68(3H, m, 7,8,9-H), 7.80(1H, d, J=7.3 Hz, 5-H), 8.57-8.69(1H, m, 10-H).

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14) Compound 6 was also obtained by the reaction of N-bis(methylthio)methylene-p-toluenesulfonamide with 2-ethoxycarbonylmethylisoquinolinium bromide. This reaction is carried out in the presence of triethylamine in ethanol under refluxing and is superior to the reaction of 4 with pyridinium N-imine in the case of large scale. Y. Tominaga, Y. Matsuda, and G. Kobayashi, Heterocycles, 1976, 4, 939.

15) mp 132°C, orange needles, IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1730, 1705(C=O); UV $\lambda_{max}^{EtOH}$nm(log ε): 258(4.36, shoulder), 275(4.64), 366(3.83), 444(4.16), 468(4.06); MS m/z: 354 ($M^+$); NMR δ($CDCl_3$): 2.97(3H, s, $SCH_3$), 4.08(3H, s, $OCH_3$), 4.13(3H, s, $OCH_3$), 7.69-7.92(2H, m, 6,7,8-H), 8.21-8.32(1H, m, 6-H), 8.60(1H, s,5-H), 8.80-8.91 (1H, m, 9-H).

16) mp 135°C, yellow needles, IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1725, 1695(C=O); UV $\lambda_{max}^{EtOH}$nm(log ε): 250(4.39, shoulder), 266(4.51), 290(4.19, shoulder), 367(4.03); MS m/z: 356 ($M^+$); NMR δ ($CDCl_3$): 2.74(3H, s, $SCH_3$), 3.83(3H, s, $OCH_3$), 3.93(3H, s, $OCH_3$), 6.30(1H, s, vinyl-H), 7.09(1H, d, J=7.5 Hz, 6-H), 7.56-7.72(3H, m, 7,8,9-H), 7.94(1H, d, J=7.5 Hz, 5-H), 8.61-8.71(1H, m, 10-H).

17) mp 130°C, yellow plates; IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1735, 1705(C=O); UV $\lambda_{max}^{EtOH}$nm(log ε): 264(4.68), 323(3.82); MS m/z: 283($M^+$); NMR δ ($CDCl_3$): 3.88(3H, s, $OCH_3$), 4.04 (3H, s, $OCH_3$), 6.87(1H, d, J=7.5 Hz, 6-H), 7.40-7.57(3H, m, 7,8,9-H), 7.65 (1H, d, J=7.5 Hz, 5-H), 7.70(1H, s, 3-H), 8.19-8.30(1H, m, 10-H).

18) mp 113°C, yellow needles, IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1487, 1385, 1270, 1235, 750; UV $\lambda_{max}^{EtOH}$ nm(log ε): 219(4.16), 240(4.26, shoulder), 257(4.50), 261(4.51), 280(4.48), 297(4.28, shoulder), 309(4.16, shoulder), 336(3.86), 349(3.65, shoulder), 398(4.05), 416(4.17); MS m/z: 238($M^+$), 223($M^+$-$CH_3$), 205($M^+$-SH); NMR δ ($CDCl_3$): 2.94(3H, s, $SCH_3$), 7.30(1H, d, J=4.8 Hz, 4-H),7.63(1H, d, J=4.8 Hz, 3-H), 7.69-7.88(2H, m, 7,8-H), 8.11(1H, s, 5-H), 8.16-8.27(1H, m, 6-H), 8.85-8.95(1H, m, 9-H).

19) mp 90°C, yellow prisms, IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1485, 1385, 1110, 1040, 835, 745, 660; UV $\lambda_{max}^{EtOH}$nm(log ε): 225(4.12, shoulder), 257(4.62), 266(4.52), 276(4.40), 292 (3.92), 304(3.94), 317(3.94), 322(3.92, shoulder), 331(3.90),385(3.63), 404 (3.63); MS m/z: 192($M^+$); NMR δ ($CDCl_3$): 7.40(1H, d, J=5.0 Hz, 4-H), 7.68(1H, d, J=5.0 Hz, 3-H), 7.75-7.97(2H, m, 7,8-H), 8.21(1H, s, 5-H),8.26(1H, s, 2-H), 8.21-8.32(1H, m, 6-H), 8.92-9.04(1H, m, 9-H).

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