Communications to the Editor

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SYNTHESIS OF BENZANNELATED CYCL[3.2.2]AZINE: BENZO[g]CYCL[3.2.2]AZINE

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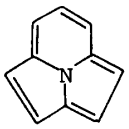
The benzannalated cycl[3.2.2]azine, benzo[g]cycl[3.2.2]azine (2), was synthesized from 2-methylthiopyrrolo[2,1-a]isoquinoline (5) and dimethyl acetylenedicarboxylate. The key intermediate (5) for the synthesis of 2 was prepared using the reaction of isoquinolinium ketene dithioacetal (8) with nitromethane in good yields. Compound 8 was obtained using the reaction of 2-ethoxycarbonylmethylisoquinolinium bromide (6) with carbon disulfide and dimethyl sulfate in the presence of sodium hydroxide followed by methylation with methyl iodide.

KEYWORDS ——— benzannelated annulene; benzannelated cycl[3.2.2]-azine; benzo[g]cycl[3.2.2]azine; ketene dithioacetal; pyrrolo[2,1-a]-isoquinoline; cycloaddition reaction; desulfurization; decarboxylation

Recently there has been considerable effort to try to rationalize the effects of benzo-fusion on aromatic annulenes.[1-5] It is generally recognized that benz-annelation reduces the diatropicity or paratropicity of the macrocyclic system and the reasons for this are indicated in terms of increased bond localisations in the macrocyclic ring.[5,6] In this respect, it seems worth while to prepare some benzo-fused compounds of cycl[3.2.2]azine (1). There are two isomers of benzannelated cycl[3.2.2]azine derivatives, benzo[g]cycl[3.2.2]azine (2) and benzo[a]cycl[3.2.2]-azine (3).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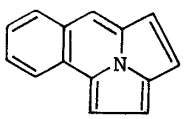
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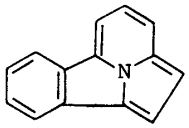
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In this paper we report the facile synthesis of the parent benzo[g]cycl[3.2.2]-azine (2) according to a modification of Boekelheide s method fortl the synthesis of cycl[3.2.2]azines. The Boekelheide s procedure has also been found to be applicable to the preparation of other polycyclic aromatic cyclazines.[7-10] Our approach is illustrated retrosynthetically in Chart 1. It utilizes a [2 + 8]cycloaddition reaction between 2-methylthiopyrrolo[2,1-a]isoquinoline (5) and dimethyl acetylene-dicarboxylate (DMAD), followed by desulfurization and decarboxylation from 4 to give 2.

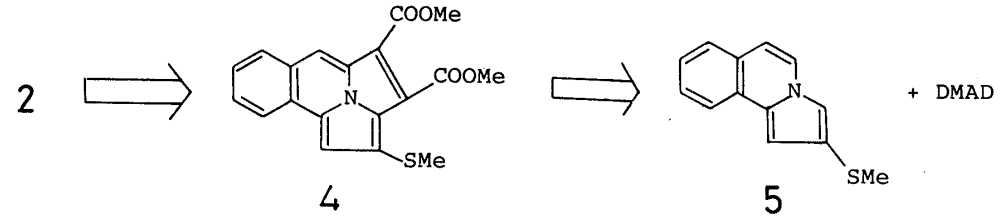

Chart 1

Recently, we reported a convenient synthesis of indolizine derivatives in good yields using the reaction of pyridinium ketene dithioacetals with nitromethane.[11,12] We applied the above reaction to the preparation of pyrrolo[2,1-a]isoquinoline derivatives. The isoquinolinium ketene dithioacetal, 2-[1-ethoxycarbonyl-2,2-bis-(methylthio)vinyl]isoquinolinium iodide (8)[13] was prepared as follows: a solution of sodium hydroxide was added portionwise to a solution of 2-ethoxycarbonylmethyl-isoquinolinium bromide (6), an excess of carbon disulfide, and dimethyl sulfate in ethanol at room temperature under stirring to yield the corresponding methyl dithio-carboxylate derivative (7).[14] The methylation of 7 with methyl iodide in ethanol gave the desired ketene dithioacetal (8) in 70% yield (from 6). The reaction of 8 with nitromethane in the presence of triethylamine as a base in ethanol gave the corresponding ethyl 2-methylthiopyrrolo[2,1-a]isoquinoline-3-carboxylate (9)[15] in 56% yield. Hydrolysis and subsequent decarboxylation of 9 occurred smoothly to give 5,[16] a key intermediate for the synthesis of 2, in 91% yield. The [2 + 8] cycloaddition reaction of 5 with DMAD in the presence of a 5% palladium-on-charcoal as dehydrogenation catalyst under refluxing 30 h in toluene gave two products. One of these is an expected addition product, dimethyl 2-methylthiobenzo[g]cycl[3.2.2]-azine-3,4-dicarboxylate (4)[17] in 27% yield. Another product has the molecular formula $C_{19}H_{17}NO_4S$=255. The determination of the structure will be described in a full publication. The desulfurization of 4 with Raney-nickel occurred easily to give dimethyl benzo[g]cycl[3.2.2]azine-3,4-dicarboxylate (10)[18] in 44% yield. Hydrolysis of the diester with 10% sodium hydroxide proceeded essentially quantitatively to give the diacid 11. Finally, decarboxylation of the diacid using copper chromite in quinoline occurred smoothly to produce the desired benzo[g]cycl[3.2.2]-azine (2)[19] in 45% yield. Similarly, 2-methylthiobenzo[g]cycl[3.2.2]azine[20] was synthesized from 4 in 22% yield.

Properties of Benzo[g]cycl[3.2.2]azine (2) ——— The bnezocyclazine 2 has a sweet smell like naphthalene and is a stable crystalline solid of bright yellow leaflets which are obtained analytically pure after recrystallization from methanol, mp 141°C. In the ^{1}H-NMR spectrum the peripheral protons are shown in the range δ 7.37 - 8.23 for the protons of the cyclazine ring and δ 7.62 - 8.67 for the benzene ring. Thus the effect of benzo fusion is to shift the peripheral protons downfield relative to the cycl[3.2.2]azine (1),[21] implying no reduction in ring current as expected. Their chemical shifts are similar to aceanthrylene.[22]

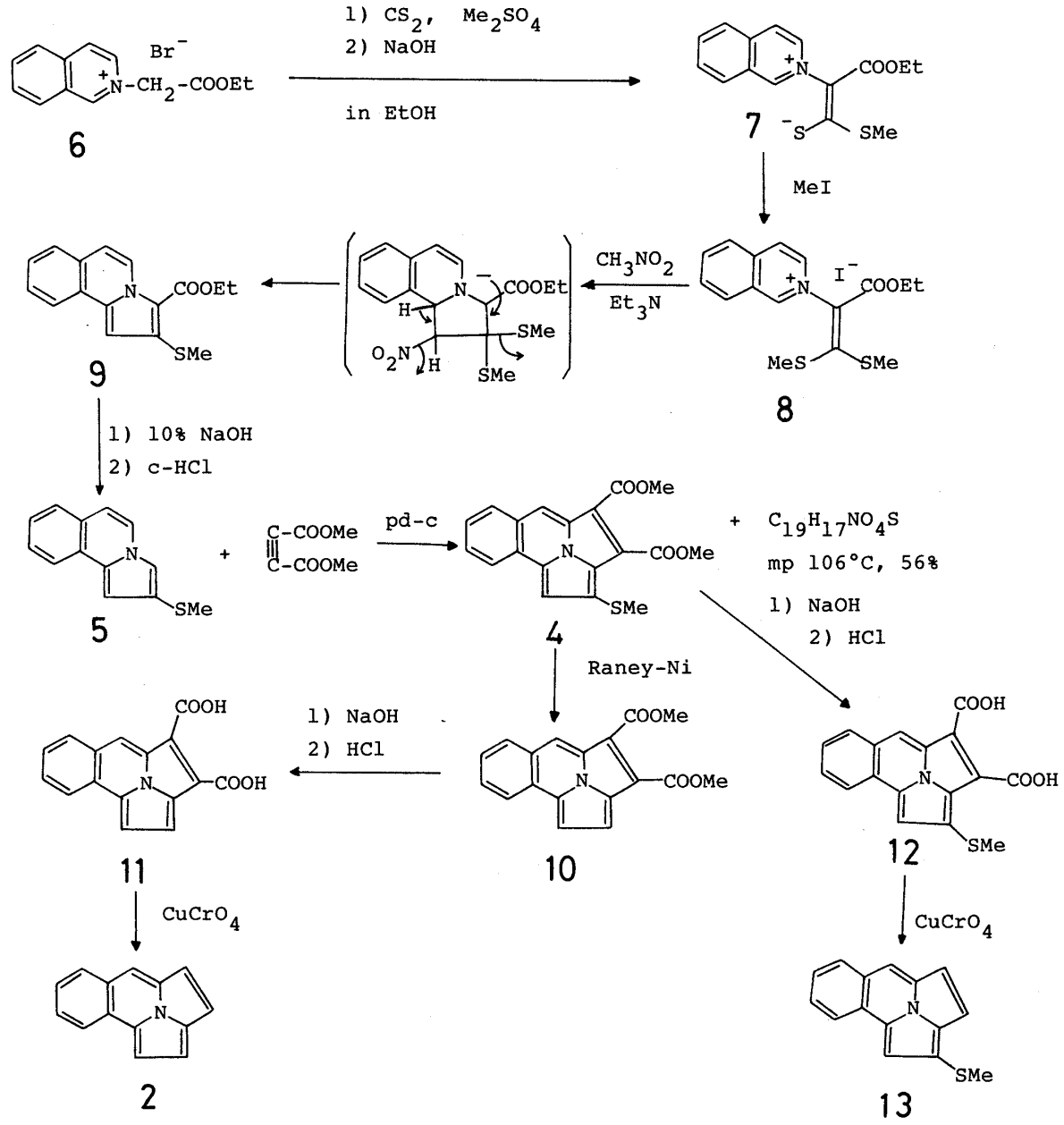

Chart 2

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13) mp 138°C, yellow prisms, IR ν_{max}^{KBr} cm^{-1}: 1690(C=O); NMR(DMSO-d_6) δ: 1.12 (3H, t, J=7 Hz, CH_3), 2.37(3H, s, SCH_3), 2.72(3H, s, SCH_3), 4.19(2H, q, J=7 Hz, O-CH_2), 8.10-8.61(4H, m, 5,6,7,8-H), 8.73(1H, d, J=7.9 Hz, 4-H), 8.96(1H, dd, J=1.5, 7.8 Hz, 3-H), 10.31(1H, s, 1-H).
14) mp 197°C, orange needles, IR ν_{max}^{KBr} cm^{-1}: 1638(C=O); NMR($CDCl_3$) δ: 1.18(3H, t, J=7 Hz, CH_3), 2.65(3H, s, SCH_3), 4.18(2H, q, J=7 Hz, O-CH_2), 7.78-8.25(6H, m, 3,4,5,6,7,8-H), 9.28(1H, s, 1-H).
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16) mp 59°C, colorless prisms, NMR($CDCl_3$) δ: 2.49(3H, s, SCH_3), 6.69(1H, d, J=8 Hz, 6-H), 6.92(1H, dd, J=0.8, 1.5 Hz, 1-H), 7.20(1H, d, J=1.5 Hz,3-H), 7.26-7.58 (3H, m, 7,8,9-H), 7.62(1H, d, J=8 Hz, 5-H), 7.89-8.00(1H, m, 10-H).
17) mp 144°C, orange needles, MS m/z: 353(M^+); IR ν_{max}^{KBr} cm^{-1}: 1728, 1692(C=O); UV λ_{max}^{EtOH}nm(log ε): 275(4.79), 320(3.99, shoulder), 440(4.01,shoulder), 435 (4.05, shoulder), 458(4.18); NMR($CDCl_3$) δ: 2.76(3H, s, SCH_3), 4.06(3H, s, OCH_3), 4.13(3H, s, OCH_3), 7.48(1H, s, 1-H), 7.56-7.85(2H, m, 7,8-H),8.21-8.28(1H, m, 6-H), 8.32-8.54(1H, m, 9-H), 8.67(1H, s, 5-H).
18) mp 134°C, orange needles, IR ν_{max}^{KBr} cm^{-1}: 1735, 1695(C=O); UV λ_{max}^{EtOH}nm(log ε): 260(4.67), 368(4.23), 464(4.27); NMR($CDCl_3$) δ: 4.10(3H, s, OCH_3), 4.11(3H, s, OCH_3), 7.67-7.94(4H, m, 1,2,7,8-H), 8.23-8.39(1H, m, 6-H), 8.56-8.66(1H, m, 9-H), 8.85(1H, s, 5-H).
19) mp 141°C, bright yellow leaflets, MS m/z: 191(M^+); IR ν_{max}^{KBr} cm^{-1}: 1485, 1400, 1375, 1208, 1130, 1020, 1010, 740; UV λ_{max}^{EtOH}nm(log ε): 218(4.28), 258(4.53), 283(4.46), 308(3.88), 316(3.76), 329(3.88), 343(3.90), 440(3.50), 456(3.46, shoulder); NMR($CDCl_3$) δ: 7.37(1H, d, J=4.9 Hz, 4-H), 7.46(1H, d, J=3.9 Hz, 1-H), 7.67(1H, d, J=3.9 Hz, 2-H), 7.54-7.86(2H, m, 7,8-H), 7.75(1H, d, J=4.9 Hz, 3-H), 8.23(1H, s, 5-H), 8.23-8.32(1H, m, 6-H), 8.56-8.67(1H, m, 9-H).
20) mp 89°C, golden yellow leaflets, MS m/z: 237(M^+); IR ν_{max}^{KBr} cm^{-1}: 1470, 1400, 1300, 1255, 1130, 865, 737; UV λ_{max}^{EtOH}nm(log ε): 252(4.44, shoulder), 265(4.53), 292(4.36), 310(4.14), 323(4.10), 374(4.03), 436(3.65), 452(3.64); NMR($CDCl_3$) δ: 2.82(3H, s, SCH_3), 7.33(1H, dd, J=0.9, 4.9 Hz, 4-H), 7.47(1H, d, J=0.9 Hz, 1-H), 7.60-7.70(2H, m, 7,8-H), 7.74(1H, d, J=4.9 Hz, 3-H), 8.14(1H, s, 5-H), 8.17-8.27(1H, m, 6-H), 8.42-8.58(1H, m, 9-H).
21) The protons appear in the δ 7.20-7.86 (CCl_4): L.M. Jackman, Q.N. Poter, and G.R. Underwood, Aust. J. Chem., 18, 1221 (1965).
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