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CYCLOADDITION REACTION OF 3-CYANOINDOLIZINES WITH DIMETHYL ACETYLENEDICARBOXYLATE—FORMATION OF CYCL[3.2.2]AZINES AND 1:2 ADDUCTS

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3-Cyano- and 3-cyano-6,8-dimethylindolizines (1a) and (1b) react with dimethyl acetylenedicarboxylate in refluxing toluene in the presence of Pd-C to give the cycl[3.2.2]azines (4a) and (4b), respectively, while 3-cyano-7-methyl- and 3-cyano-7-benzylindolizines (1c) and (1d) affording the 1:2 adducts (6c) and (6d) along with cycl[3.2.2]azine (4d).

Indolizines have been known to undergo (8+2)π cycloaddition with electron deficient acetylenes and olefins to give such a novel type of heterocycles as cyclazines.[1~3] In this connection, we have previously reported a simple synthesis of 1,2-unsubstituted 3-cyanoindolizines via cycloaddition-extrusion reactions of dicyanomethylids with phenyl vinyl sulfoxide.[4] The ready availability of various 3-cyanoindolizines prompted us to investigate their cycloaddition with dimethyl acetylenedicarboxylate (DMAD); these reactions would provide a complementary method for the synthesis of cycl[3.2.2]azines to Boekelheide et al.'s method[5] since few indolizines substituted only in pyridine moiety have been described.

On heating 3-cyanoindolizine (1a) with an excess of DMAD in toluene in the presence of 5 % Pd-C for 24 h was given the product (4a) in 40 % yield, which was identical with an authentic material[5] and was converted to the parent cycl[3.2.2]-azine[5] by demethoxycarbonylation with lithium bromide in hexamethylphosphoramide.[6]

A similar reaction of 3-cyano-6,8-dimethylindolizine (1b) with DMAD produced 1,2-dimethoxycarbonyl-5,7-dimethylcycl[3.2.2]azine (4b) in 25 % yield as yellow crystals; mp 88°C; m/e 285(M^+); IR(KBr) cm^{-1} 1740, 1685 (C=O); ^{1}H-NMR($CDCl_3$) δ 2.75, 2.83(each s, 6H, CH_3), 4.02(s, 6H, CO_2CH_3), 7.31(s, 1H, H-6), 7.28, 7.54(ABq, J=5 Hz, 2H, H-3,4); ^{13}C-NMR($CDCl_3$) δ 17.2, 18.6(each q, CH_3), 52.2, 52.4(each q, CO_2CH_3), 113.2, 117.6, 128.0(each d, C-3, 4, and 6), 115.5, 117.7, 125.5, 126.7, 126.9, 128.6, 129.4(each s, sp^2 quaternary carbons), 164.6, 166.1(each s, C=O).

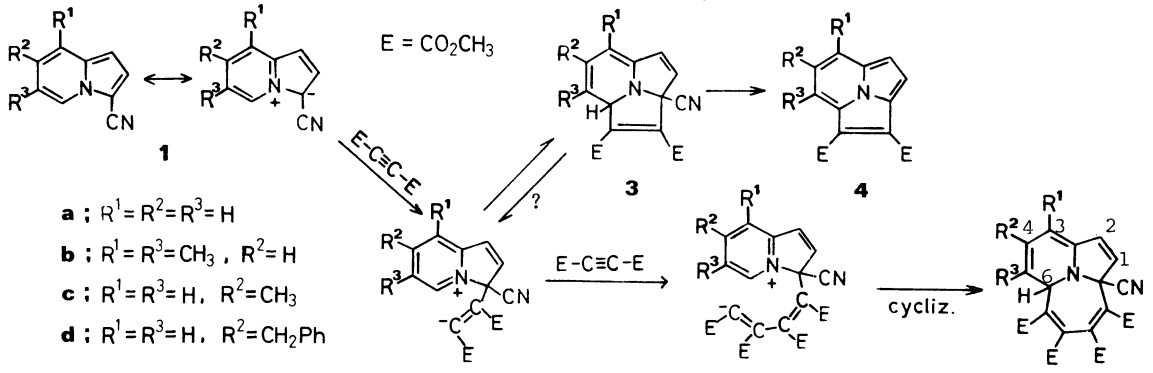
In contrast to these, 3-cyano-7-methylindolizine (1c) reacted with DMAD to give a 1:2 adduct in 39 % yield; mp 155°C; m/e 440(M^+); IR(KBr) cm^{-1} 2250(C≡N), 1770, 1710(ester C=O); ^{1}H-NMR($CDCl_3$) δ 2.25(s, 3H, CH_3), 3.75, 3.84, 3.86, 4.03(each s, 12H, CO_2CH_3), 6.72, 6.96(ABq, J=12 Hz, 2H, H-5a and 5), 7.12, 7.63(each bs, 2H, H-1 and 2), 7.99(s, 1H, H-3); ^{13}C-NMR($CDCl_3$) δ 21.1(q, CH_3), 52.0, 52.6, 55.6(each q, CO_2CH_3), 107.6, 110.9(each s), 118.6(s, C≡N), 120.9, 129.9, 131.6, 133.3(each d), 129.2, 134.8, 135.6, 139.4, 148.3(each s), 162.5, 166.6, 168.9(each s, C=O). It can be assumed that the ring protons and carbons, which are deshielded by ester groups owing to non-planarity of the ring, are at unexpectedly low field. Of the twelve

theoretically possible resonance peaks for the ring carbons of (6c), five sp^2 doublet peaks and seven sp^2 singlet peaks could be discerned, thus suggesting 1:2 adduct structure (6), although their complete assignments are difficult. There are precedents for this type of 1:2 structure being formed from nitrogen heterocycles such as pyridines,[7] azapentalenes,[8] and azaazulenes[9] with DMAD.

Furthermore, reaction of 3-cyano-7-benzylindolizine (1d) with DMAD gave the corresponding cycl[3.2.2]azine (4d) along with the 1:2 adduct (6d); (4d): mp 117°C; 5 %; m/e 347(M^+); IR(KBr) cm^{-1} 1735, 1680; ^{1}H-NMR($CDCl_3$) δ 4.02, 4.07(each s, 6H, CO_2CH_3), 4.41(s, 2H, CH_2), 7.2-7.4(m, 6H), 7.70(part of ABq, J=5 Hz, 1H, H-3 or 4), 7.80, 8.35(each s, 2H, H-7,5); ^{13}C-NMR($CDCl_3$) δ 42.8(t, CH_2), 51.8, 52.6(each q, CO_2CH_3), 115.8, 116.4, 118.0, 121.1, 126.6, 128.8, 129.0(each d, sp^2 -CH=), 111.8, 121.6, 127.0, 129.7, 132.1, 139.7, 140.4(each s, sp^2 -C=C), 164.4, 164.6(each s, C=O), (6d): mp 160°C; m/e 516(M^+); IR(KBr) cm^{-1} 2230, 1770, 1715; ^{1}H-NMR($CDCl_3$) δ 3.76, 3.87, 3.91, 4.04(each s, 12H), 6.65, 6.96(ABq, J=11 Hz, 2H), 7.71(d, J=3 Hz, 1H), 6.9-7.3(m, 6H), 7.84(s, 1H); ^{13}C-NMR($CDCl_3$) δ 41.2(t), 51.9, 52.6, 55.5(each q), 103.2, 110.5, 118.0(each s), 120.9, 126.2, 128.4, 128.9, 129.6 129.9(each d), 134.9, 135.5, 139.4, 142.3, 148.1(each s), 162.3, 166.3, 168.7(each s).

At present, no explanation could not be made as to the differences in the direction of reaction depending on the substituents. In the absence of Pd-C, these reactions did not occur significantly, details of the catalyst action however remaining equivocal.

Thus, 3-cyanoindolizines could serve as key intermediates to cycl[3.2.2]azines though with limited scope and this is the first example in which 1:2 adducts were isolated in the reactions of indolizines with acetylenes and olefins.



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