ADDITION REACTION OF INDOLIZINE DERIVATIVES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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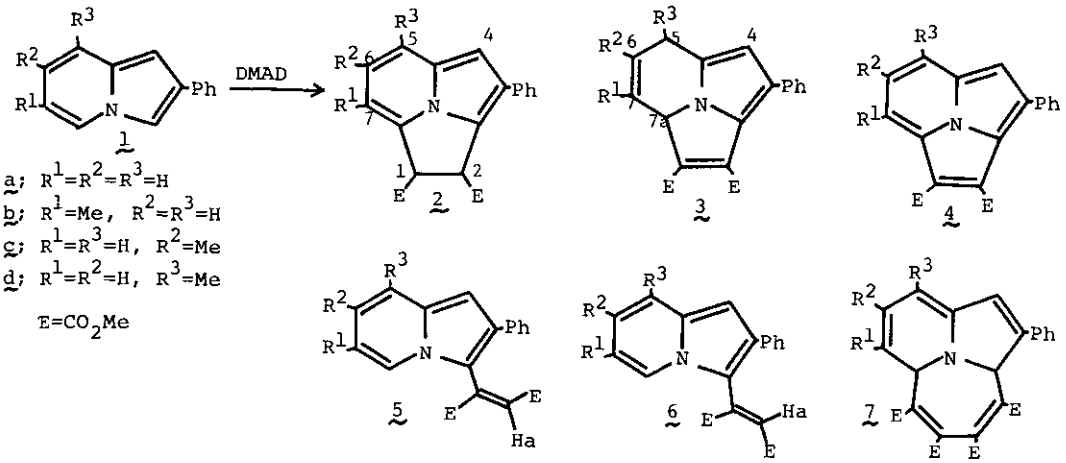
Abstract —— Indolizine derivatives 1 reacted with dimethyl acetylenedicarboxylate to give 1:1 adducts 2-6. In some cases 1:2 adducts 7 were obtained from which cycl[4.3.2]azine derivatives 11 were synthesized by dehydrogenation. The addition reaction was dependent on the substituents and solvents employed.

The reaction of indolizines with electron deficient acetylenes provides a useful method for synthesis of cycl[3.2.2]azines and (8+2)π cycloadducts have been postulated as intermediates to give the cyclazines.[1] The details, however, remain ambiguous because the addition reaction has been carried out under dehydrogenating conditions. We report here the addition reaction of indolizine derivatives 1 with dimethyl acetylenedicarboxylate (DMAD) in the absence of dehydrogenating catalyst. When a dry acetone solution of indolizines 1a-d and DMAD (1.0 : 1.3 equiv) was stirred under N_2 at room temperature for 15 h, several 1:1 adducts 2-6 and 1:2 adducts 7 were obtained in the yields shown in Table 1. These products could be separated by flash column chromatography on silica gel. The structural assignments of these products were based on their spectroscopic data[2,3] along with chemical evidence. The ^{1}H NMR spectrum of 2a, for example, is as follows.[3] 2a; δppm (200 MHz, C_6D_6) 3.58 (s, Me), 3.86 (s, Me), 5.25 (brd, H-1, J=5.0 Hz), 5.32 (d, H-2, J= 5.0 Hz), 6.53 (br d, H-7, J=7.0 Hz), 6.70 (dd, H-6, J=9.0, 7.0 Hz), 7.15 (ddd, H-5, J=9.0, 1.0, 1.0 Hz), 7.28 (s, H-4), 7.26 (m, 1H, Ph), 7.40 (m, 2H, Ph), 7.64 (m, 2H, Ph). The fact that the olefinic proton signal assigned to H-7 is observed as broad doublet and the absorptions of two methine proton couple with each other (J=5.0 Hz) strongly supports this structure. The structures of 1:1 adducts 3 were also deduced from the ^{1}H NMR spectra. The spectrum of 3d, for example, exhibits the methyl signal



a; $R^1=R^2=R^3=H$
b; $R^1=Me$, $R^2=R^3=H$
c; $R^1=R^3=H$, $R^2=Me$
d; $R^1=R^2=H$, $R^3=Me$

E=CO_2Me

Table 1 Yields and melting points of the adducts in the reaction in acetone

Compd number suffix	2 Yield, % (m.p., °C)	3 % (°C)	4 % (°C)	5 % (°C)	6 % (°C)	7 % (°C)
a	4 (107-108)	-a)	8 (138-139)	13 (130-132)	4 (oil)	-a)
b	4 (117-119)	6 (129-131)	1 (126-127)	11 (104-107)	5 (oil)	13 (197-199)
c	5 (oil)	-a)	4 (186-187)	16 (148-151)	-a)	8 (212-214)
d	27 (113-116)	5 (117-120)	8 (141-143)	20 (121-124)	-a)	-a)

a) These products could not be isolated.

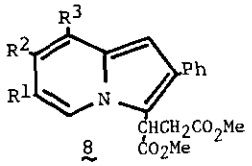
Table 2 Yields (%) of the adducts in the reaction of the indolizines 1b with DMAD in several solvents at room temperature

Compd	C_6H_6	CH_2Cl_2	CH_3COCH_3	CH_3CN	CH_3CH_2OH	CH_3SOCH_3	$HCON(CH_3)_2$
2b	15	9	4	12	-a)	2	2
3b	10	10	6	-a)	-a)	3	15
4b	5	7	2	5	1	1	4
5b	1	1	11	1	30	3	2
6b	-a)	-a)	5	-a)	11	-a)	5
7b	1	3	13	15	4	18	9

a) These products could not be isolated.

as doublet, indicating the presence of a hydrogen at the C_5-position. 3d; δppm (60 MHz, $CDCl_3$) 1.48 (d, Me, J=7.5 Hz), 3.60 (s, Me), 3.78 (s, Me), 3.7-3.8 (m, H-5), 5.01 (d, H-7a, J=4.0 Hz), 6.39 (br s, H-4), 6.41 (dd, H-7, J=9.5, 4.0 Hz), 6.99 (dd, H-6, J=9.5, 2.0 Hz), 7.1-7.6 (m, 5H, Ph). Upon heating a chloroform solution of 3 at 60 °C, 3 isomerized to 2, whereas 2 were stable even in refluxing toluene. When the addition reaction was carried out in refluxing toluene, only 2 were isolated in 25-30 % yields. Treating the adducts 2a-d with 10 % Pd-C in refluxing toluene gave

cyclazines 4a-d in 80-90 % yields, while the reaction of 3b with Pd-C gave 4b in 64 % yield. These results support the structures of 1:1 cycloadducts 2 and 3. The Michael type adducts 5 are geometrical isomers of 6[4,5] because both of them gave the same compounds 8 by reduction with $NaBH_4$ in tetrahydrofuran. Their structures could be determined on the basis of the ^1H NMR spectra. Thus, the singlet signals of the vinylic protons Ha appear at lower field in 5 than in 6. (5a; δ7.02, 5b; 7.10 6a; 6.06, 6b; 6.05). These values of chemical shifts are in good agreement with the values reported for the dimethyl (E)- and (Z)-butendioate derivatives.[6] The structures of 1:2 cycloadducts 7 were suggested by their elemental and mass spectra.[7] Table 1 indicates that the 1:2 adducts 7 were isolated only in the reaction of indolizines bearing a methyl group at the C_6 or C_7 position. The yields of 7 increased when more amounts of DMAD were used. Thus, when indolizines 1b,c and DMAD (1.0 : 3.0 equiv) were reacted in acetone at room temperature, 7b,c were obtained in 50 and 38 % yields, respectively. In contrast, no 1:2 adduct was isolated in the reaction of indolizines 1a,d even if the excess of DMAD was used. The addition reaction was also sensitive to the solvent effects. The reaction of indolizine 1b with DMAD was examined in several solvents as shown in Table 2. In nonpolar solvents, the formation of the Michael type adducts 5 and 6 is depressed, while their formation is favored in ethanol. The better yields of the 1:2 adducts 7 are accomplished in aprotic polar solvents.



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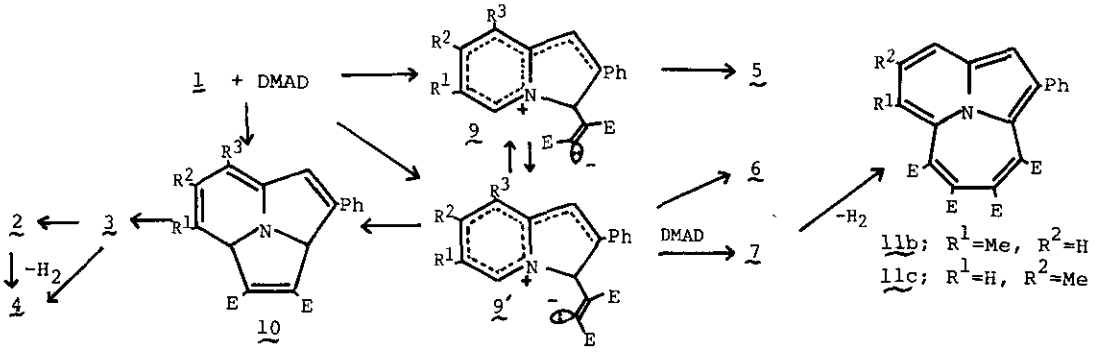
Considering these findings, the following reaction mechanism can be assumed. Indolizines 1 react with DMAD to give dipole intermediate 9 and/or 9', protonation of which leads to the Michael type adducts 5 and 6, respectively. The fact that the anti-addition is preferred is in agreement with the reported results for nucleophilic additions to acetylenes.[8] The 1:1 adducts 3 can be formed by a 1,5-



hydrogen shift from (8+2) π cycloadducts 10 which are formed by a stepwise mechanism via 9' or a concerted cycloaddition. The formation of indolizines 2 can be explained by tautomerization of 3 in which aromatization is considered to drive the reaction. The 1:2 adducts 7 can be formed by attack of another DMAD to 9'. The better yields of 7 obtained in polar solvents such as acetonitrile or acetone can be attributed to the fact that the dipolar intermediate 9' is stabilized in these solvents. The methyl substituents (R^1 or R^2) may also stabilize 9'.
Dehydrogenation of the adducts 7b and 7c with DDQ or chloranil in refluxing benzene afforded cycl[4.3.2]azine derivatives 11b (mp 186-189 °C) and 11c (mp 162-164 °C), respectively, in 60-80 % yields.[9] They are stable red crystals and the longer absorption maxima were observed at 320 nm (logε=4.46) in 11b and 310 nm (logε=4.50) in 11c. Thus, the reaction of indolizines with DMAD provides a convenient method to synthesize cycl[4.3.2]azines besides cycl[3.2.2]azines.

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2. All new compounds obtained here showed satisfactory elemental analyses and spectral data. The stereochemistry of the adducts 2, 3, and 7 has not been unambiguously determined.
3. We thank Professor Toshio Mukai at Tohoku University for providing the measurements of the 200 MHz NMR spectra.
4. The formation of one Michael type adduct has been reported, but the stereochemistry was ambiguous.[5]
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