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ADDITION REACTIONS OF INDOLIZINE DERIVATIVES WITH DIETHYL AZODICARBOXYLATE

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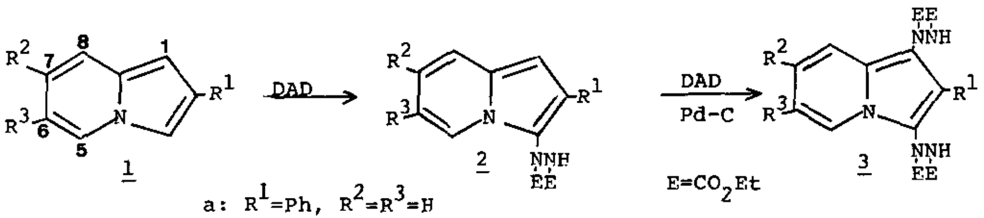
Abstract -- Indolizines reacted with diethyl azodicarboxylate (DAD) to give Michael type adducts 2. These adducts 2 underwent novel addition reactions with DAD to give 1:2 adducts 3. These addition reactions are useful methods for synthesis of indolizine derivatives.

Indolizine is known to undergo cycloaddition reactions with some electron deficient olefins to give (8+2) adducts.[1,2] These reactions provide a useful method for synthesis of tricyclic heterocycles and are also of interest from the viewpoint of the reaction mechanism.[3] In this connection, we have examined the addition reactions of indolizines with several olefins and found the novel reactions of indolizine derivatives 1 with diethyl azodicarboxylate (DAD). When a mixture of 1 and DAD (1:1 equiv) was heated in refluxing ethanol for an hour, 1:1 adducts 2 were obtained in high yields shown in Table 1.[4] These adducts 2 underwent further addition reactions with DAD to give 1:2 adducts 3 upon heating in refluxing ethanol in the presence of 10% Pd-C for 20 hr.[4] The structures of 2 and 3 were deduced on the basis of the spectroscopic data along with elemental analyses. In the IR spectra of 2 and 3, peaks due to NH groups



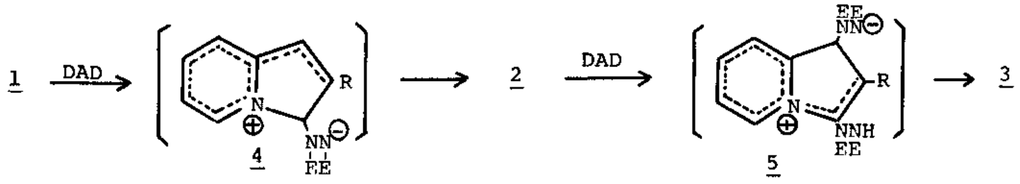
E=CO_2Et

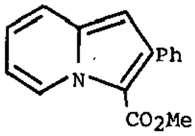
a: R^1=Ph, R^2=R^3=H
b: R^1=Ph, R^2=Me, R^3=H
c: R^1=Ph, R^2=H, R^3=Me
d: R^1=Me, R^2=R^3=H

Table 1 Yields and Melting Points of the Adducts 2 and 3

Compd	Yield, %	M.P., °C	Compd	Yield, %	M.P., °C
2a	78.9	187-188	3a	93.0	203-205
2b	85.0	159-160	3b	83.0	164-166
2c	85.5	142-143	3c	84.5	179-180
2d	59.0	140-141	3d	38.0	200-201

are observed, indicating that the Michael type addition reactions occurred instead of the (8+2) cycloaddition reaction. Their NMR spectra indicate the presence of a indolizine skeleton and the addition sites of DAD to indolizines. The NMR spectra of the methyl derivatives are shown as follows. 2d; δ ppm ($CDCl_3$) 1.18(t, 3H, J=8.0 Hz), 1.23(t, 3H, J=8.0), 2.25(s, 3H), 4.16(q, 4H, J=8.0), 6.18(s, H-1), 6.40 (ddd, H-6, J=7.2, 7.0, 1.5), 6.62(ddd, H-7, J=8.0, 7.0, 1.5), 7.17(dd, H-8, J=8.0, 1.5), 7.47(brs, NH), 8.16(brd, H-5, J=7.2). 3d; δ ppm ($CDCl_3$) 1.0-1.4(m, 12H), 2.18(s, 3H), 4.19(q, 8H, J=8.0), 6.50(ddd, H-6, J=7.5, 7.5, 1.5), 6.78(ddd, H-7, J=8.0, 7.5 1.5), 7.30(brs, NH), 7.42(brs, NH), 7.51(dd, H-8, J=8.0, 1.5), 8.20(brd, H-5, J= 7.5). The H-1 signal appears as singlet in 2d, while it is not observed in 3d. The formation of 2 and 3 can be explained by electrophilic addition of DAD to indolizines followed by a hydrogen shift. The intermediate 4 and 5 can be stabilized by delocalization of the cation. The hydrogen shift in 4 seems to be rapid and intramolecular because the reaction of 1 with DAD giving 2 was insensitive to the solvent effects. On the other hand, the reaction of 2 to 3 requires Pd-C catalyst,[5] indicating that it is more difficult for the hydrogen shift





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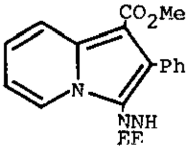

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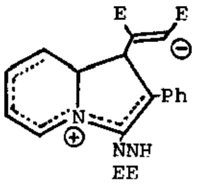

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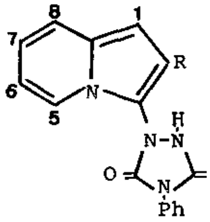
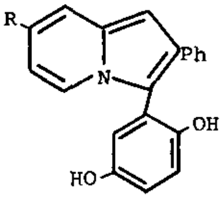
to take place in 5 than in 4.

In contrast, the reaction of DAD with indolizine derivative 6 under the same conditions as above did not occur at all, indicating that the electron donating effect of a hydrazino substituent takes an important role in the Michael type addition. On the other hand, the reaction of indolizine derivative 2 with dimethyl acetylenedicarboxylate gave a complex mixture instead of an adduct 7. This fact seems to indicate that the hydrogen shift from the intermediate 5 takes place more readily than from the corresponding intermediate 8. To our best knowledge, the reaction of DAD to indolizine derivatives 2 is the first example of the Michael type addition reaction at the C_1 position of indolizines.



10a: R=Ph
10b: R=Me



11a: R=H
11b: R=Me

For comparison, the addition reactions of indolizines 1 with 4-phenyl-1,2,4-triazoline-3,5-dione (9) and p-benzoquinone were examined. The reaction of 1a and 1d with 9 in dichloromethane at room temperature gave 1:1 adducts 10a (mp 105-110°C, 90%) and 10b (mp 133-135°C, 43%), respectively.[6] Similarly, the reaction of 1a and 1b with p-benzoquinone in the presence of 10% Pd-C in refluxing toluene gave 11a (mp 114-116°C, 42%) and 11b (mp 160-162°C, 59%), respectively.[6] These addition reactions are similar to those of 1 although 1:2 adducts such as 3 were not obtained. The addition reactions described here are useful methods for synthesis of indolizine derivatives.

References and Notes

1. A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, J. Am. Chem. Soc., 1961, 83, 453; V. Boekelheide and K. Fahrenholtz, ibid., 1961, 83, 458.
2. S. Ikeda, S. Kajigaeshi, and S. Kanemasa, Chem. Lett., 1976, 367.
3. R. Huisgen, Angew. Chem., 1963, 75, 604.
4. Satisfactory elemental analyses were obtained for all new compounds.
5. Details of the catalyst action remain equivocal.

6. The elemental analyses and spectroscopic data of these products are consistent with the structures of the Michael type adducts. (10a); νmax (KBr) 3400, 1760, 1690 cm^{-1}, δppm (60MHz, $CDCl_3$) 6.38 (dd, H-6, J=7.5, 7.0, 1.5 Hz), 6.49 (s, H-1), 6.69 (ddd, H-7, J=7.5, 7.5, 1.5), 7.0-7.6 (m, 12H), 7.60 (brd, H-5, J=7.0), (10b); νmax (KBr) 3150, 1760, 1690 cm^{-1}, δppm (60 MHz, $CDCl_3$) 2.15 (s, Me), 6.19 (s, H-1), 6.38 (ddd, H-6, J=7.5, 7.5, 1.0), 6.70 (ddd, H-7, J=8.0, 7.5, 1.0), 7.0-7.7 (m, 9H), (11a); νmax (KBr) 3350, 1630, 1600 cm^{-1}, δppm (60MHz, $CDCl_3$) 4.76 (brs, OH), 6.25-6.85 (m, 5H), 7.0-7.7 (m, 9H), (11b); νmax (KBr) 3500, 3350, 1640, 1600 cm^{-1}, δppm (60MHz, DMSO) 2.24 (s, Me), 6.2-6.9 (m, 5H), 7.0-7.5 (m, 8H), 8.66 (s, OH), 8.89 (s, OH).

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