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SYNTHESIS OF VINYL-SUBSTITUTED INDOLIZINE DERIVATIVES BY A NOVEL REACTION OF INDOLIZINES WITH ETHOXYETHYLENES HAVING ELECTRON WITHDRAWING SUBSTITUENTS

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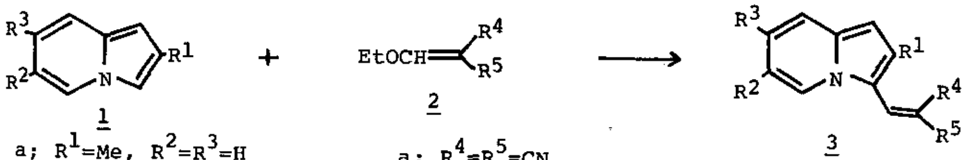
Abstract --- Reactions of indolizine derivatives with electron deficient ethoxyethylenes such as ethoxymethylenemalononitrile gave vinyl-substituted indolizines 3 by the Michael type addition reaction followed by ethanol elimination. Hydrolisis of 3-dicyanovinylindolizines afforded 3-formylindolizines.

Addition reactions of indolizines with electron deficient olefins have been extensively studied.[1] These reactions provide a useful method to prepare a novel type of heterocycles such as cyclazines.[2] In the present paper we report a novel reaction of indolizines with electron deficient vinyl ethers, which provides a mild, simple and versatile entry to vinyl-substituted indolizines.

When a mixture of indolizines 1a-c and ethoxymethylenemalononitrile (2a) (1:1 equiv) was heated in boiling toluene for 15 h, orange crystals 3a-c were obtained in high yields. The structures of the products 3a-c were determined on the basis of the spectroscopic data along with chemical evidence. The elemental analyses and Mass spectra indicate that these are ethanol eliminated products from 1:1 adducts. The NMR spectra show the presence of a indolizine skeleton with the disappearance of H-3 signal of the starting indolizines. The NMR spectrum of 3a, for example, is shown as follows. δppm ($CDCl_3$) 2.48 (s, 3H, Me), 6.52 (br s, H-1), 6.97 (ddd, H-6, J=7.0, 7.0, 1.0 Hz), 7.22-7.55 (m, H-7 & H-8), 7.62 (s, Ha), 8.26 (d, H-5, J=7.0). The high field broad singlet for one proton can be assigned to H-1,[3, 4] indicating that the substitution occurred at 3-position of the indolizine.



a; R^1=Me, R^2=R^3=H
b; R^1=Ph, R^2=R^3=H
c; R^1=Ph, R^2=Me, R^3=H
d; R^1=Ph, R^2=H, R^3=Me
e; R^1=p-BrC_6H_4, R^2=R^3=H

a; R^4=R^5=CN
b; R^4=CN, R^5=CO_2Et
c; R^4=R^5=CO_2Et
d; R^4=COMe, R^5=CO_2Et

Table 1. Melting Points and Yields of the Products 3

Prod.	React.	R^1	R^2	R^3	R^4	R^5	M.P., °C	Yield, %
3a	1a + 2a[a)]	Me	H	H	CN	CN	178-181	60
3b	1b + 2a[a)]	Ph	H	H	CN	CN	182-184	69
3c	1c + 2a[a)]	Ph	Me	H	CN	CN	205-208	44
3d	1b + 2b[a)]	Ph	H	H	CN	CO_2Et	118-120	48
3e	1a + 2c[b)]	Me	H	H	CO_2Et	CO_2Et	oil	22
3f	1b + 2c[b)]	Ph	H	H	CO_2Et	CO_2Et	oil	29
3g	1d + 2c[b)]	Ph	H	Me	CO_2Et	CO_2Et	oil	82
3h	1e + 2c[b)]	p-BrC_6H_4	H	H	CO_2Et	CO_2Et	113-115	34
3i	1b + 2d[b)]	Ph	H	H	COMe[c)] (CO_2Et)	CO_2Et (COMe)	79-81	85
3j	1d + 2d[b)]	Ph	H	Me	COMe[c)] (CO_2Et)	CO_2Et (COMe)	123-125	62

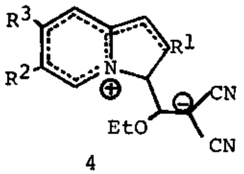
a) toluene reflux b) xylene reflux c) mixture of isomers

The UV spectra of 3 are characteristic. 3a; λmax (ethanol) 228 nm (logε = 4.15), 258 (3.89), 318 (4.05), 347 (3.71), 463 (4.54), λmax (cyclohexane) 216 (4.22), 231 (4.21), 258 (3.85), 315 (4.14), 429 (4.31), 454 (4.45), 3b; λmax (ethanol) 248 (4.41), 261 (4.23), 280 (4.09), 325 (3.88), 465 (4.49), λmax (cyclohexane) 237 (4.47), 278 (4.08), 324 (4.04), 429 (4.20), 453 (4.42). The strong absorption bands in the longer wave length region can be attributed to intramolecular charge transfer transition, in which the indolizine part acts as a π-doner and the vinyl part acts as π-acceptor.[5]

Similar reaction of indolizines 1 with ethyl ethoxymethylenecyanoacetate (2b), diethyl ethoxymethylenemalonate (2c) and ethyl ethoxymethyleneacetoacetate (2d) in refluxing xylene afforded the corresponding vinyl-substituted indolizines 3.[6,7]

These results are shown in Table 1.

The formation of the vinylindolizines 3 can be explained by the initial Michael type addition reaction to give an intermediate 4 followed by elimination of ethanol. This reaction is a new type of reactions of indolizines which reflects their large nucleophilicity. The formation of 3-substituted indolizines in this reaction is in accord with the reported results that the electrophilic substitution reactions occur at the 3-position of indolizines which are supported by the calculations.[8]



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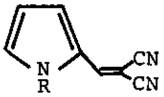
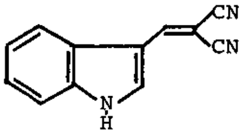


5a; R=H
5b; R=Me



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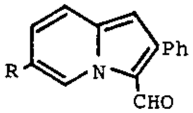

7a; R=H
7b; R=Me

For comparison, the reaction of pyrrole or indole with ethoxymethylenemalononitrile (2a) was examined. When a xylene solution of pyrrole and 2a was heated at reflux for 15 h, they were almost recovered unchanged. Indole did not react with 2a in refluxing xylene either. These results indicate the high reactivity of indolizines toward electrophiles compared with pyrrole or indole. On heating a mixture of pyrrole and 2a (1.2 : 1.0 equiv) in refluxing acetic acid, however, 2-vinylpyrrole 5a (mp 123-125 °C) was obtained in 26 % yield. Similarly, reaction of 1-methylpyrrole and 2a under the same conditions gave the corresponding pyrrole 5b (mp 146-148°C) in 15 % yield. Although reaction of indole with 2a in refluxing acetic acid gave a poor yield of the expected 3-vinylindole 6, the reaction in dry tetrahydrofuran in the presence of sodium hydride afforded 6 (mp 226-228 °C) in 41 % yield. The structures of 5 and 6 were determined on the basis of the spectroscopic data.

The vinylindolizines 3 obtained here seem to be potential starting materials for synthesis of functionalized nitrogen-bridged heterocycles. When the vinylindolizines 3b,c were treated with sodium hydroxide in refluxing ethanol, hydrolysis occurred to give 3-formylindolizines 7a (mp 102-104 °C) and 7b (mp 84-85 °C), respectively, in nearly quantitative yields. This reaction provides a new procedure for formylation of indolizines which is particularly interesting because a dicyanovinyl substituent is known to be a good aldehyde protecting group.[9] Similarly, hydrolysis of vinylpyrrole 5a and vinylindole 6 with sodium hydroxide afforded 1-formylpyrrole and 3-formylindole, respectively, in high yields.

References and Notes

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5. The similar charge-transfer bands are observed in the UV spectra of 3-tricyanovinylindolizines.[4]
6. All new compounds obtained here showed satisfactory elemental analyses and spectral data.
7. The corresponding ketenethioacetal, 1-cyano-2,2'-bismethylthioacrylonitrile, did not react with indolizines 1 in refluxing xylene at all.
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