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MICHAEL ADDITIONS OF INDOLES TO 2-OXOINDOLIN-3-YLIDENE KETONES

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Michael-type additions to (E)-2-oxoindolin-3-ylidene ketones(1) and indoles(2) gave rise to C-1'(3) and/or C-3(4) adducts depending on the oxindolic N-substituents and the C-1' adducts(3) were converted into new 9H-pyridazino[3,4-b]indole derivatives(6).

2-Oxoindolin-3-ylidene ketones(1) are of considerable interests in their reactivities because of the presence of two α,β-unsaturated carbonyl systems in the molecule. Tacconi and co-workers[1)], in a series of investigations, have studied the reactions of (E)-2-oxoindolin-3-ylideneacetophenone(1a) with enamines and ethyl vinyl ethers undergoing heterodiene cycloadditions. It has been concluded that (E)-2-oxoindolin-3-ylideneacetophenone(1a) underwent 1,2 or 1,4-cycloaddition with aldo-enamines depending on the oxindolic nitrogen substituents. These results led us to study the effect of N-substituents on Michael-type additions.

We wish to report here the influence of N-substituents in (E)-

2-oxoindolin-3-ylidene ketones(1) on Michael-type additions[2)] with indole derivatives as typical enamine and the structures of the unusual minor products in these reactions.

Indoles were found to react readily with (E)-2-oxoindolin-3-ylideneacetophenone(1a) in a refluxing acetic acid solution[3)] for 3 hr in N_2 to afford the corresponding adducts in good yields[4)] (Table 1). In a typical experiment evaporation of the solvent and subsequent chromatographic separation on silica gel gave C-1' adduct(3a),75.5%, as the mixture of *dl*-threo and *dl*-erythro isomers and C-3 adduct(4a),mp 251-254°,2.8%,$\lambda_{max}^{95\%EtOH}$nm(log ε):221(4.65), 246(4.36),281(3.98),291(3.91);ν_{max}^{KBr}cm^{-1}:3310,1721;δ(DMSO-d_6):4.26 and 4.51(d,J=18Hz,1H),10.38 and 10.90(s,1H,NH). Recrystallization resulted successfully in isolation of each *dl*-diastereomer, 3a-I, mp 165-179°,71%,$\lambda_{max}^{95\%EtOH}$nm(log ε):218(4.66),245(4.36),283(3.94), 291(3.88);ν_{max}^{KBr}cm^{-1}:3360,1705;δ(DMSO-d_6):4.49 and 5.59(d,J=6Hz,1H), 10.09 and 10.69(s,1H,NH) and 3a-II,mp 224-226°,4.5%,δ(DMSO-d_6): 4.16 and 5.78(d,J=6Hz,1H),10.19 and 10.80(s,1H,NH). The gross structures of C-1' and C-3 adducts were determined easily by their mass spectra, 3a showed intense peaks at M-105(COPh)(A-fission) along with m/e 234(base),206(B-fission) and 4a showed the only intense peak at m/e 247(M-CH_2COPh)(base).

These results(Table 1) indicate that if R_1 is an electron-donating substituent the 3-position of the oxindole becomes more activated and the addition leads to C-3 adduct(4) in a moderate yield together with C-1' adduct(3), whereas, for the electron-attracting substituent the addition leads to C-1' adduct(3) exclusively.

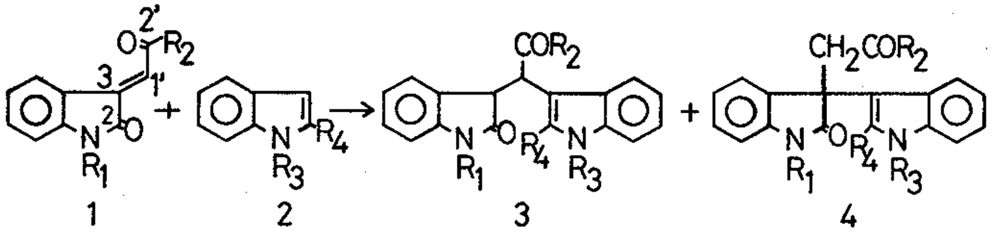
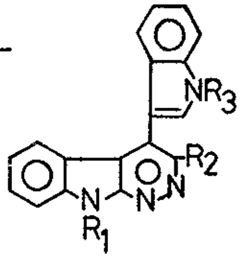


Table 1 Addition of Indoles to 2-Oxoindolin-3-ylidene Ketones

	1		2		Reaction	3		4	5
	R_1	R_2	R_3	R_4	Conditions	Yield (%)	Ratio of Diastereomers	Yield (%)	Yield (%)
a)	H	Ph	H	H	AcOH,reflux 3hr	75.5	15.8:1	2.8	—
b)	H	Ph	H	CH_3		91	2:1	—	—
c)	CH_3	Ph	H	H		45	3:1	31	—
d)	CH_3	Ph	H	CH_3		71	1.7:1	12	—
e)	$COCH_3$	Ph	H	CH_3		38+47(3b)		—	—
f)	COPh	Ph	H	H		—		—	—
g)	H	CH_3	H	H		76		—	11
h)	H	CH_3	CH_3	H		65		—	—
a)	H	Ph	H	H	$BF_3 \cdot Et_2O$	52	1.5:1	5	12
g)	H	CH_3	H	H	90°,10min	30		—	—
h)	H	CH_3	CH_3	H		40		—	—

Table 2 9H-Pyridazino[3,4-b]indole Derivatives(6)

	R_1	R_2	R_3	mp(°C)	Yield(%)
6a	H	Ph	H	>300	33
6c	CH_3	Ph	H	291.5	29
6g	H	CH_3	H	262-6	35
6h	H	CH_3	CH_3	>300	17



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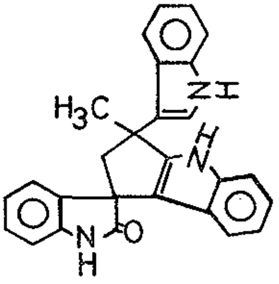
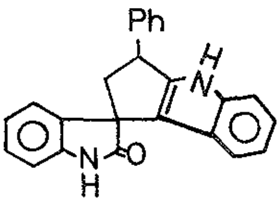
Under similar conditions, (E)-2-oxoindolin-3-ylideneacetone (1g) afforded C-1' adduct(3g),mp 205-208°,76%,m/e 304(M^+,21),261 (45,A) and 172(base),144(49,B);δ(DMSO-d_6):2.16(s,3H),4.37 and 4.7 (d,J=6Hz,1H), together with by-product(5g),mp >300°,11%, whose structural assignment was based on the following evidences, $C_{27}H_{21}ON_3$,m/e 403(M^+,52),388(M-15,base);ν_{max}^{KBr}cm^{-1}:1714,1619;δ(DMSO-d_6) 2.03(s,3H),2.94 and 3.53(d,J=14Hz,1H),10.35,10.50 and 10.55(s,1H, NH); positive to Ehrlich reaction.



5g



5a

Furthermore, we examined this Michael-type addition in $BF_3\cdot Et_2O$ at 90° for 10 min$^{5)}$. Thus 1a gave the C-1' adduct(3a),52%, along with a minor product(5a),mp 284-285.5°,12%, whose structure was determined by the following data, $C_{24}H_{18}ON_2$,m/e 350(M^+,base); $_{max}^{KBr}$cm^{-1}:1712,1620;δ(C_5D_5N):2.95(dd,J=6,14Hz,1H),3.93(dd,J=8,14 Hz,1H),5.39(dd,J=6,8Hz,1H); negative to Ehrlich reaction.

Formation of 5a and 5g can reasonably involve 'C-3 adduct' intermediate followed by intramolecular cyclization during the reaction. Investigation of this point is continuing in our laboratory.

Finally 3a,3c,3g and 3h were converted into new 9H-pyridazino-[3,4-b]indole derivatives(6) on treatment with hydrazine hydrate$^{6)}$

in acetic acid(Table 2).

As the result, we demonstrate that (E)-2-oxoindolin-3-ylidene ketones(1) are the excellent Michael acceptors under acidic conditions and the influence of the oxindolic N-substituents can be regarded as the determinant of the mode of Michael-type addition.

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4 Satisfactory elemental analytical, mass spectral and nmr data have been obtained for all new compounds.

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