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REACTION OF 1-SUBSTITUTED INDOLES WITH CARBOXYLIC ACIDS AND N-IODOSUCCINIMIDE

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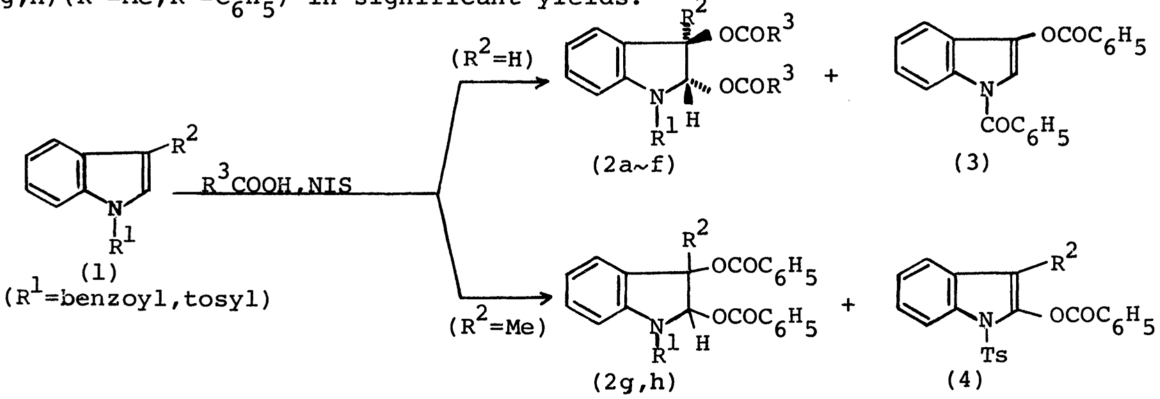
1-Substituted indoles reacted with carboxylic acids and N-iodosuccinimide to give 1-substituted-2,3-diacyloxyindolines in significant yields.

The direct introduction of an acyloxy function to the indole nucleus using carboxylic acids and related reagents is little known.1) The only known example is the benzoyloxylation of 2-phenylindole with benzoylperoxide.2) Previously, it was described that the reaction of indoles and related compounds with puseudo halogens such as IN_3, ISCN or $(SCN)_2$ provided a simple method for the preparation of various indole derivatives containing an azide or a thiocyanate function.3~6)

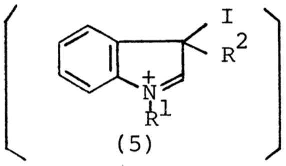
Now we have found that 1-substituted indoles (1)(R^1= benzoyl, tosyl) react with some carboxylic acids and N-iodosuccinimide (NIS)7) to give 1-substituted-trans-2,3-diacyloxyindolines (2a~f)(R^2=H) and 1-substituted-2,3-dibenzoyloxy-3-methylindolines (2g,h)(R^2=Me,R^3=C_6H_5) in significant yields.



A solution of 1-benzoylindole(300mg,1.4mmol), benzoic acid(414mg,3.5mmol), and NIS(997mg,4.2mmol) in dry CH_2Cl_2(25ml) was stirred 24 h at 40°C. The resulting solution was diluted with benzene(200ml), washed with 5% Na_2CO_3,5% $Na_2S_2O_3$, and water, dried,and concentrated in vacuo. The oily residue was separated by preparative TLC using silica gel to give 1-benzoyl-trans-2,3-dibenzoyloxyindoline(2a)(331mg, mp 141-143°C,8) and 1-benzoyl-3-benzoyloxyindole(3)(16mg,3%), mp 182°C 9) as a minor product.10) The structure of (2a) was assigned on the basis of following spectral data. The IR spectrum(KBr) displayed a strong ester absorbtion band at 1720cm^{-1} and the NMR spectrum($CDCl_3$) showed a sharp singlet at δ 6.20(3-H), 6.84(2-H), and a multiplet for aromatic hydrogens between δ 7.0 and 8.1. The trans conformation of two benzoyloxy groups was assigned on the basis of the coupling constant($J_{2,3}$= 0 Hz) between 2-H and 3-H.[11] In contrast to the case of NIS, the reaction using N-bromosuccinimide gave only 1-benzoyl-3-bromoindole, mp 97°C (lit.[12] 97-98°C). Furthermore, no reaction using N-chlorosuccinimide occurred at all after 48 h.

Similar treatment of 1-benzoylindole, 1-tosylindole with carboxylic acids[13] using NIS gave the corresponding 1-substituted-trans-diacyloxyindolines (2a~f). The results were summarized in table 1. Table 1 also showed the physical data of 1-substituted-2,3-dibenzoyloxy-3-methylindolines (2g,h)[14] which were obtained from the reaction of 1-benzoyl-3-methylindole, and 3-methyl-1-tosylindole with benzoic acid. In case of (2h), for example, 2-benzoyloxy-3-methyl-1-tosylindole(4)(14%, mp 133-135°C)[15] was isolated as a by-product.

The formation of (2) may be rationalized by the assumption that the initially formed cationic indolenine intermediate (5) may be attacked by acyloxy anions to give the diacyloxy products.



(5)

Table 1. Physical data of 1-substituted-2,3-diacyloxyindolines[a]

	R^1	R^2	R^3	Solvent	Yield(%)	Mp(°C)[c]	NMR(δ, $CDCl_3$)
a	benzoyl	H	phenyl	CH_2Cl_2	53	142-143	6.84(s,2-H),6.20(s,3-H)
b	benzoyl	H	Me	CH_3COOH [b]	43	94-95	6.48(s,2-H),5.83(s,3-H) 2.05(s,COMe),1.95(s,COMe)
c	benzoyl	H	benzyl	$CHCl_3$	40	oil	6.41(s,2-H),5.82(s,3-H) 3.57(s,$COCH_2$),3.46(s,$COCH_2$)
d	tosyl	H	Me	CH_3COOH [b]	46	143-144	6.56(s,2-H),5.68(s,3-H) 2.02(s,COMe),1.82(s,COMe)
e	tosyl	H	phenyl	CH_2Cl_2	40	171-172	7.00(s,2-H),6.10(s,3-H)
f	tosyl	H	benzyl	CH_2Cl_2	41	oil	6.66(s,2-H),5.74(s,3-H) 3.60(s,$COCH_2$),3.34(s,$COCH_2$)
g	benzoyl	Me	phenyl	CH_2Cl_2	48	157-158	1.90(s,3-Me)
h	tosyl	Me	phenyl	CH_2Cl_2	45	134-135	1.90(s,3-Me)

a) Reaction time ; 24 h for (2a~d) and 48 h for (2e~h).
b) After the reaction, acetic acid was evaporated under reduced pressure. The residue was dissolved in benzene.
c) Recrystallized from MeOH-H_2O or MeOH-THF-H_2O, except for (2c) and (2f).

References and footnotes

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8) All new crystalline compounds gave satisfactory elemental and spectral analyses.
9) (3) : IR(KBr) 1720 cm^{-1}; NMR (δ, $CDCl_3$) 7.00-8.00 ; Mass m/e, 341(M^+).
10) 1-Benzoyl-3-iodoindole(7%, mp 114-115°C) was also isolated as an another by-product.
11) a) F.A.L.Anet and J.M.Muchowski, Chem.and Ind., 1963, 81. b) Y.Tamura, M.Chun, S.Kwon, T.Okada, and M.Ikeda Chem. Pharm. Bull., 26, 3515 (1978).
12) R.Weissgerber, Chem.Ber., 46,651 (1913).
13) Acetic acid was used as a solvent instead of CH_2Cl_2.
14) The stereochemical relationship could not be assigned by NMR data.
15) (4): IR(KBr) 1760 cm^{-1} ; NMR (δ, $CDCl_3$) 2.06(s,3-Me); Mass m/e, 405(M^+).

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