A DIRECT N-ACYLATION OF INDOLE WITH CARBOXYLIC ACIDS

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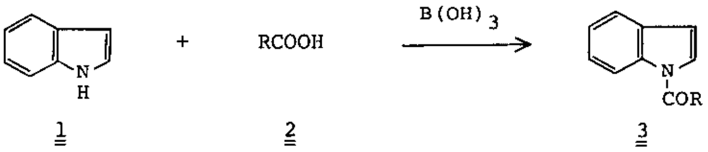
Abstract ——— A simple method for the N-acylation of indole is described. Indole (1) was directly acylated at nitrogen with various carboxylic acids (2) catalyzed by boric acid in moderate yield.

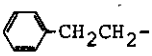
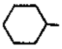
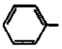
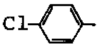
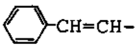
N-Acylation of indole proceeds with divergence in general. Widely used synthetically, acylation of Grignard or sodio derivative of indole is complicated by concomitant formation of 3-acyl and/or 1,3-diacyl derivatives, depending upon the reaction temperature and the acylating reagent, and the yield of N-acylindole is unsatisfactory.1) Recently, Illi reported an efficient N-acylation of indole with acid chloride and sodium hydroxide in dichloromethane using tetrabutylammonium hydrogen sulfate as a phase-transfer catalyst.2) An alternative procedure, involving in situ formation of potassio indole with potassium hydroxide and indole in dimethoxyethane, also reported by Kikugawa.3)



R = alkyl or aryl

All known methods for the N-acylation of indole require activated carboxylic acid derivatives such as acid halides or esters as acylating agents. We have recently observed that indole was directly acylated at nitrogen with carboxylic acid itself in the presence of boric acid. Thus, a mixture of indole (1), an appropriate carboxylic acid (2 , 1.1 equiv.) and boric acid (0.3 equiv.) in mesitylene was heated under refluxing for 48 hr using Dean-Stark water-separator. Purification of the crude product through short column on silica gel developed with isopropyl ether-hexane afforded the desired 1-acylindole (3). Results were summarized in Table.

Table N-Acylindoles (3)*

R	mp (°C) (lit. mp)	yield (%)	IR $\nu_{C=O}$ (cm^{-1})
	78.5-79.5	82	1700 (nujol)
	97.5-98.5	52	1690 (nujol)
$CH_3(CH_2)_4$-	colorless oil[4)]	64	1708 (neat)
	69-69.5 (67-68)[5)]	45	1678 (nujol)
	117.5-118 (114.5-115.5)[6)]	57	1678 (nujol)
	100.5-101.5	50	1670 (nujol)

When the reaction was carried out in xylene as a solvent, a considerable lowering of the yield was observed. Although the role of boric acid in the reaction is not clear, the present procedure offers a facile and economical method for the syntheses of N-acylindoles. Further applications of the reaction are now in progress.

ACKNOWLEGEMENT

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REFERENCES AND NOTES

1. R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York and London, 1970, p 33.
2. V. O. Illi, Synthesis, 1979, 387.
3. Y. Kikugawa, Synthesis, 1981, 460.
4. bp 135°C / 1 mmHg (bath temp) ; By micro-distillation.
5. T. Itahara, Synthesis, 1979, 151.

* Satisfactory elemental analyses were obtained for all new compounds described. Structures of 3 were also confirmed by ^{1}H-NMR spectra.

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