A CONVENIENT SYNTHETIC METHOD OF 1-ACYL-2-ARYL-3,3-DIMETHYL-INDOLINE INVOLVING ISOLABLE DIASTEREOMERIC ATROPISOMERS

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Abstract — The synthesis of 1-acyl-2-aryl-3,3-dimethylindoline was improved by the reaction of 1-acyl-2-hydroxy-3,3-dimethylindoline with an arene in the presence of $BF_3 \cdot O(C_2H_5)_2$ in dioxane, and stable diastereomeric atropisomers were isolated as products when the arene was β-naphthol.

During the course of a study on 3H-indole derivatives, two of the authors obtained, in collaboration with others, a pair of isomeric compounds of the molecular formula, $C_{27}H_{25}ClN_2O$, by pyrolysis of 1-(4-chlorobenzoyl)-3,3-dimethylindolin-2-yl pyridinium chloride (1).[1] They have been proven by ^{13}C nmr data,[2] chemical properties,[1,2] and X-ray diffraction analysis,[3] to be diastereomeric atropisomers of 1-[1-(4-chlorobenzoyl)-3,3-dimethylindolin-2-yl]-2,3-dimethylindole, depicted in structures (2-A) and (2-B), which resulted from the restricted rotation about the C*-N bond (Figure 1). Later, an example of analogous isomerism, due to hindered rotation about the $C_{sp}3 - C_{sp}2$ bond, was reported regarding the compound where the 2-substituent of (2)

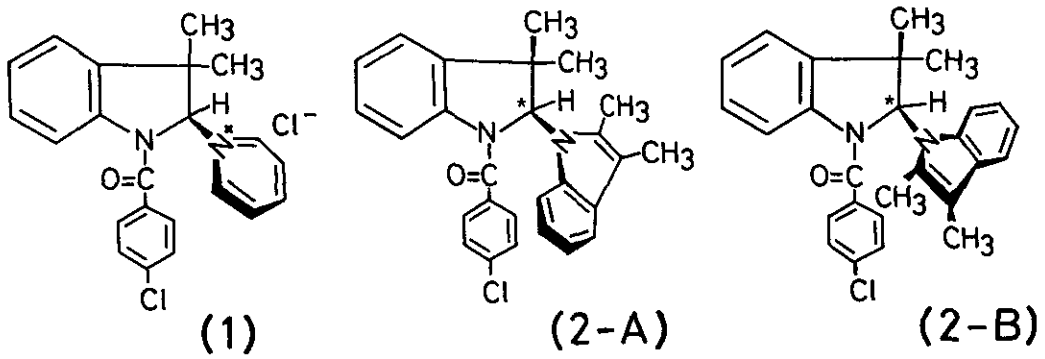
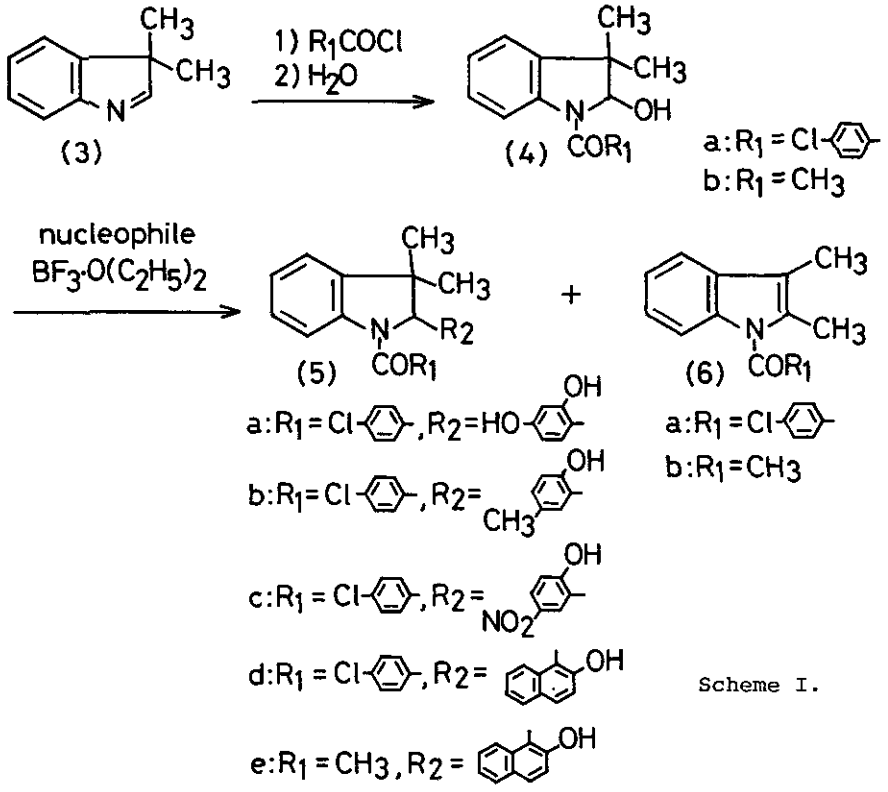


Figure 1.



Scheme I.

was replaced by 2-hydroxynaphth-1-yl.[4]

In developing this series of studies on the molecular design of atropisomer, the improvement of the synthesis is the most urgent problem. So far, we have attempted the synthesis of 1-acyl-2-aryl-3,3-dimethylindoline (5) in several ways. As a result, it has been proven most convenient and widely applicable that the synthesis is performed by boron fluoride etherate-promoted reaction of a nucleophile (arene) with 1-acyl-2-hydroxy-3,3-dimethylindoline (4) which is easily obtained by the method improved by the participation of the authors (Scheme I).[5]

The procedure is, in general, conducted as follows: To a solution of 1-acyl-2-hydroxy-3,3-dimethylindoline (4) (0.4 mmol) and the nucleophile (arene) (0.48 mmol) in dry dioxane (10 ml), $BF_3 \cdot O(C_2H_5)_2$ (2.0 mmol) was added, and the mixture was then stirred under dry nitrogen at 40-70°C for 2-72 h. After cooling, ether (200 ml) was added to the reaction mixture. The ethereal layer was hydrolyzed with saturated aqueous $NaHCO_3$, washed further with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated under a reduced pressure. The residue was fractionated by preparative tlc on a silica gel 60 PF_{254} (Merck) using benzene and ethyl acetate (20:1).

Table I. Synthesis of (5) by Boron Fluoride Etherate-promoted Reaction of (4) with a Nucleophile

Substrate	Nucleophile	Reaction Conditions Temp./°C	Time/h	Product[a]	mp/°C	Yield/%[b]
(4a)	resorcinol	40	10	(5a)	252-254	100
(4a)	p-cresol	60	72	(5b)	231.5-232.0	21
				(6a)	75-76[6]	44
(4a)	p-nitrophenol	reflux	6	(5c)	-	0
(4a)	β-naphthol	50	9	diastereomeric		
				(5d) A (Rf = 0.27)[c]	272.0-272.3	29
				(5d) B (Rf = 0.14)	-[4]	45
				(6a)	75-76	12
(4b)	β-naphthol	70	2	diastereomeric		
				(5e) A (Rf = 0.38)[d]	-[7]	30
				(5e) B (Rf = 0.30)	277-279	18
				(6b)	74-75[8]	33

a) Determined by elemental analysis, mass, ir, and ^{1}H nmr spectral data. b) Isolated yield after preparative tlc. c)-d) On a silica gel F_{254} plate containing a fluorescent indicator (Merck), using benzene-ethyl acetate [10:1 for c) and 2:1 for d)] as eluent.

The results are given in Scheme I and Table I. The table indicates that the reaction conditions and yields of (5) are governed by the nucleophilicity of incoming groups in the order; resorcinol > p-cresol > p-nitrophenol, and that the attacking of the nucleophiles seems not to be inhibited sterically at least by their bulkiness up to the extent of β-naphthol.

In the synthesis of (5d) and (5e) using β-naphthol as a nucleophile, a pair of stable diastereomeric atropisomers were isolated, respectively. Molecular models (Dreiding Model) of (5a-e) indicate that the rotation of the 2-substituent is free in (5a), (5b), and (5c), and not free in (5d) and (5e). In comparison of the structure of (5d) with that of (2), they are analogous in the state that the rotation of the 2-substituent is prevented by the same neighboring amide group, which has a planar

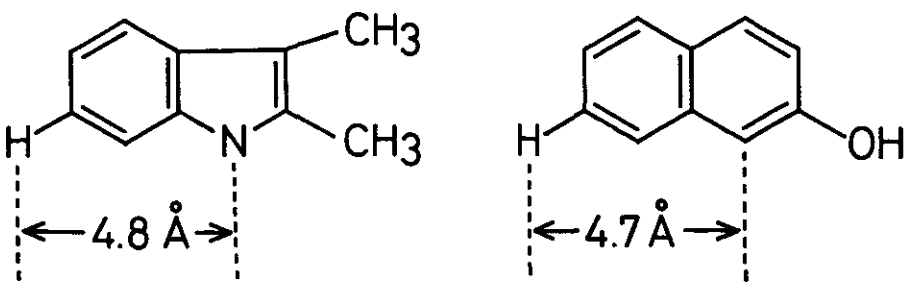


Figure 2.

structure,[3] and the widths of the 2-substituents from their rotation axes closely resemble (4.8 Å and 4.7 Å) (Figure 2), although there is a difference in bonding, as one is C_{sp^3}-N_{sp^2} and the other C_{sp^3}-C_{sp^2}. However, the successful isolation of the isomers in the case of (5e) is quite instructive because it tells us that the amide group is not necessarily to be so bulky as 4-chlorobenzoyl for the prevention of the rotation of the neighboring group. These findings offer useful suggestions empirically to the molecular design in further study of this problem.

REFERENCES AND NOTES

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   A sample of (5d-B) (prisms) begins to liquefy at ca. 210°C, but a clear melt does not result. It solidifies gradually on heating to isomerize to (5d-A) (plates), which melts completely at 272.5-273.0°C.
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6. H. Yamamoto, A. Misaki, and M. Imanaka (Chem. Pharm. Bull., 1968, 16, 2313) listed as mp 78.5-79°C.
7. A sample of (5e-A) (needles) begins to liquefy at ca. 200°C, but a clear melt does not result. It solidifies gradually on heating to isomerize to (5e-B) (prisms), which melts completely at 278-280°C.
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