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A new approach for the synthesis of 2-substituted indole derivatives via Michael type adducts

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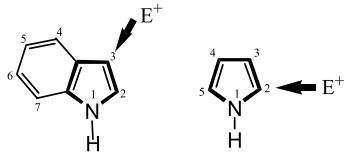
Abstract—4,7-Dihydroindole undergoes regioselective alkylation at the 2-position of the indole nucleus through conjugate addition with α,β-unsaturated carbonyl compounds. The oxidation of the Michael adducts affords the corresponding 2-substituted indole derivatives which were characterized by spectroscopic methods.

1. Introduction

The chemistry of indole is one of the most active areas of heterocyclic chemistry. The indole moiety remains at the forefront of biological and medicinal chemistry. The most ubiquitous of the bioactive alkaloids known are based on the indole nucleus.[1] Since the 3-position of indole is the preferred site for electrophilic substitution reaction, 3-alkyl or acyl indoles are versatile intermediates for the synthesis of a wide range of indole derivatives.[2] The simple and direct method for the synthesis of 3-alkylated indoles involve the conjugate addition of indoles to α,β-unsaturated compounds. 2-Substituted indoles are also potential intermediates for many alkaloids and pharmacologically important substances.[3] While the methods for the preparation of 3-substituted indoles are well established, there is a need for yet easier access to 2-substituted indoles. Generally restricted methods have been reported for the preparation of 2-substituted indoles. α-Lithioindoles have been used to prepare 2-haloindoles and to introduce a variety of substituents by the reaction with appropriate electrophiles such as aldehydes, ketones and chloformates.[4] Another method for the synthesis of 2-substituted indoles involves α-palladation at moderate temperature if C-3 is occupied. The metallated products are allowed to react with acrylates, other alkenes (Heck reaction) or carbon monoxide in situ.[5] Additionally, 2-methylindoles have been elaborated into many 2-substituted indole derivatives using an allylic bromination reaction.[6] However, most of these methods involve protection of the indole 3-position with an ester or benzoyl group and masking the indole nitrogen as a phenyl sulfonyl or acyl.



1 **2**

Indole (**1**) undergoes electrophilic substitution preferentially at β(C3)-position whereas pyrrole (**2**) gives reaction at α(C2)-position.[7] The positional selectivity in these five-membered systems is well explained by the stability of the Wheland intermediates for electrophilic substitution. The intermediate cations from β- for indole (**1**) and α- for pyrrole (**2**) are the more stabilized. Michael reactions are one of the most important carbon–carbon bond-forming reactions in organic synthesis.[8,9] We would like to disclose herein our approach for synthesis of 2-substituted indole derivatives with Michael type adducts. Our synthetic strategy is based on a dipole change by transforming the indole ring into a pyrrole derivative.

2. Results and discussion

Firstly, we carried out Birch reduction reaction of indole with Li in liquid ammonia, which is a very powerful reducing system, and which reduces the benzene ring but not the pyrrole ring to form 4,7-dihydroindole (**3**) and 4,5,6,7-tetrahydroindole (**4**) (Scheme 1).[10] We obtained a mixture consisting of **3** and **4** in a 4:1 ratio, which could be best separated by recrystallization, respectively. Since the

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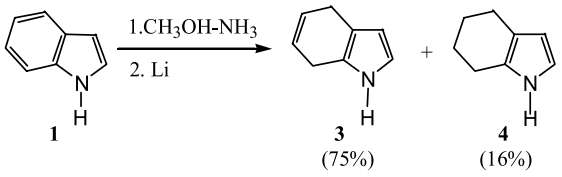


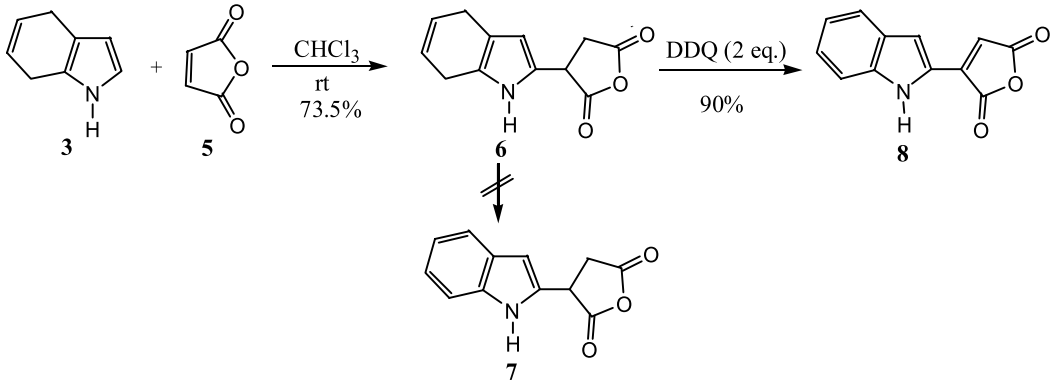
Scheme 1.

reduction products are now pyrrole derivatives, we investigated the Michael reaction of 4,7-dihydroindole (**3**) with α,β-unsaturated carbonyl compounds (Table 1). The reaction of **3** with maleic anhydride (**5**) in $CHCl_3$ gave 3-(4,7-dihydro-1*H*-indol-2-yl)-dihydro-furan-2,5-dione (**6**) in a 73.5% (Scheme 2). For the next step, we attempted the aromatization of the cyclohexadiene ring in **6** to obtain the indole derivative **7**. Whereas, the oxidation of **6** with 1 equiv of 1,2-dicyano-4,5-dichloroquinone (DDQ) gave a complex reaction mixture, the indole derivative **8** was obtained by reaction of **6** with 2 equiv of DDQ in a 90%. Similarly, various α,β-unsaturated carbonyl compounds such as diethyl azodicarboxylate (**9**), 1,3-diphenyl-propenone (**10**),[11] 2-cyclohexenone (**11**)[11] and 2-cyclopentenone (**12**)[11] were reacted with 4,7-dihydroindole (**3**) in order to

Table 1. Michael addition of 4,7-dihydroindole (**3**) with some α,β-unsaturated compounds

Entry	Nucleophile	Electrophile	Catalyst	Oxidant	Product	Yield (%)[a]
1	**3**	**5**	–		**8**	90
2[b]	**3**	**9**	$Bi(NO_3)_3$		**13**	45
3	**3**	**10**	$Bi(NO_3)_3$		**15**	30
4	**3**	**11**	$Bi(NO_3)_3$		**16**	49
5	**3**	**12**	$Bi(NO_3)_3$		**17**	45

[a] Isolated yield.
[b] $EtO_2C–NH–NH–CO_2Et$ (**14**)[12] forms at entry 2.



Scheme 2.