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FACILE SYNTHESIS OF 1-ARYL-2,3-DIHYDRO-1*H*-ISOINDOLES BY CYCLIZATION OF *N*-FORMYLIMINIUM ION *VIA* GEOMETRICALLY DISFAVORED 5-*ENDO*-TRIG PROCESS

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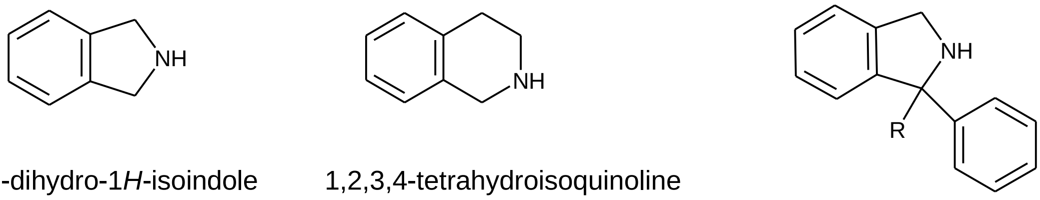
Abstract — Synthesis of 1-aryl-2,3-dihydro-1*H*-isoindoles (isoindolines) (**10**) was achieved in a highly effective manner *via* acid catalyzed cyclization of *N*-formyliminium ion (**8**) obtained from 2,3-dimethoxybenzylamine and carbonyl compounds with acetic-formic anhydride under a one pot procedure. This Pictet-Spengler type reaction provides a convenient method for preparing 1-arylisoindolines.

Compounds containing 2,3-dihydro-1*H*-isoindoles (isoindoline) (**1**) such as 1-methyl-1-phenyl-(**3**) and 1-phenyl-derivative (**4**) are known to be a non-competitive NMDA antagonist[1, 2] and a phencyclidine agonist[3] respectively. However, isoindoline derivatives are very rare in spite of biological interest, when



2,3-dihydro-1*H*-isoindole 1,2,3,4-tetrahydroisoquinoline

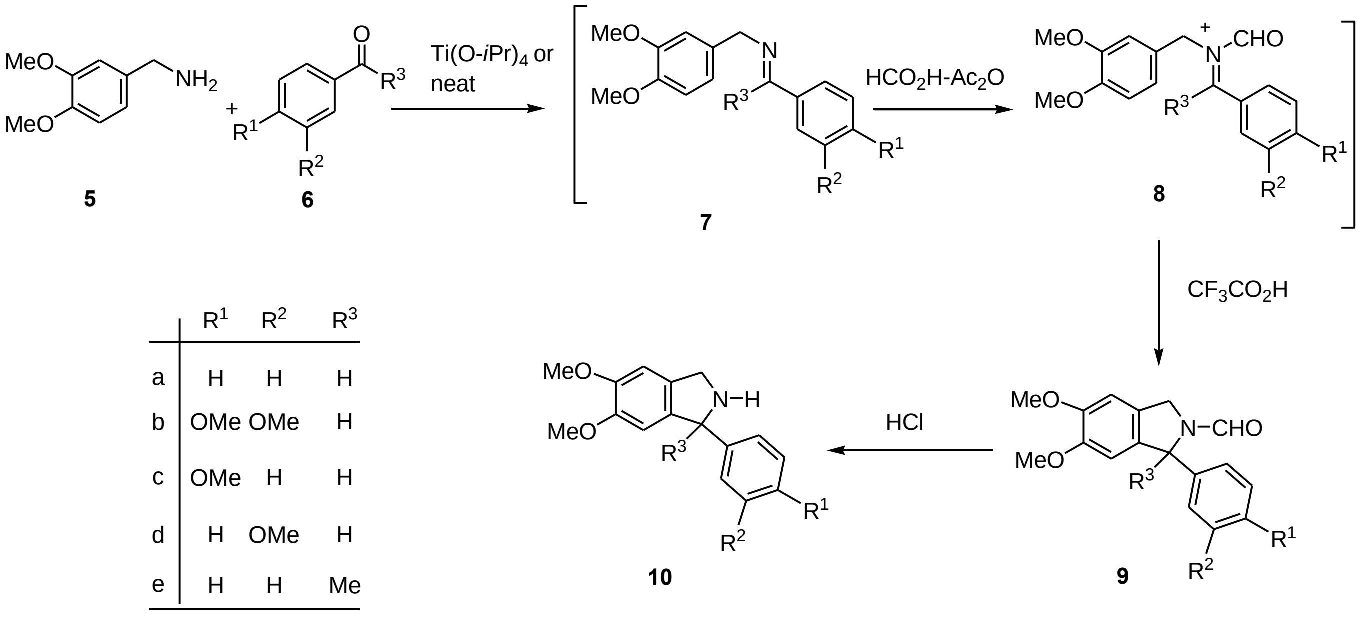
1 **2** **3**: R=Me **4**: R=H

Scheme 1 2,3-Dihydro-1*H*-isoindoles and related compoundes as a NMDA antagonist and a phencyclidine agonist compared to 1,2,3,4-tetrahydroisoquinoline (**2**) derivatives that constitute the fundamental ring system of various medicines. Although there are several syntheses of isoindoline in the literature,[4-10] only one paper which deals with a general methodology leading to the isoindoline ring system is reported.[10]

In this paper we report the synthesis of 1-aryl-2,3-dihydro-1*H*-isoindole (**10**) utilizing a simple and convenient method *via* a Pictet-Spengler type reaction, that is, the intramolecular cyclization of *N*-formyliminium ion (**8**). We have recently developed this methodology for the synthesis of tetrahydroisoquinoline (**2**) producing not only 1-substituted but also 1,1-disubstituted derivatives.[11]

The *N*-formyliminium ions (**8a~e**), substrates of the reaction, were readily prepared by formylation of imines (**7a~e**) with acetic-formic anhydride. The imines (**7a~e**) were obtained by heating a mixture of 3,4-dimethoxybenzylamine (**5**) and arylaldehydes (**6a~d**) or acetophenone (**6e**). The procedures are shown in Table 1.

The intramolecular cyclization of *N*-formyliminium ions (**8**) leading to the isoindoline ring system *via* 5-*endo*-trig process was anticipated to be difficult to achieve when compared with the Pictet-Spengler reaction to 1,2,3,4-tetrahydroisoquinoline *via* 6-*endo*-trig; according to the Baldwin rule[12] the former reaction of 5-*endo*-trig process is geometrically disfavored while the latter 6-*endo*-trig one is favored. This disadvantage was overcome by finding reaction conditions using a large excess of trifluoroacetic acid (TFA) described in Table 1. However, when the process of removing acetic-formic anhydride from the reaction mixture was omitted or inadequate, the cyclization did not occur in a practical sense. This fact revealed that the acidity of the reaction solution is critically important to produce this intramolecular cyclization. Thus, the 1-aryl-2,3-dihydro-2-formyl-1*H*-isoindoles (**9**) were obtained in fairly good yields, as shown in Table 1.[13] Hydrolysis of **9** with hydrochloric acid yielded the corresponding 1-aryl-2,3-dihydro-1*H*-isoindoles (**10**) in a quantitative yield.[13] The direct cyclization of the imine (**7**) to the isoindoline (**10**) did not occur at all even when treated with TFA even under more forced conditions, indicating that the cyclization is the reaction of *N*-formyliminium ions (**8**) activated by *N*-formyl group. These experiments clearly demonstrated that the cyclization of the *N*-formyliminium ion to isoindoline



	R^1	R^2	R^3
a	H	H	H
b	OMe	OMe	H
c	OMe	H	H
d	H	OMe	H
e	H	H	Me

Scheme 2 Synthesis of 1-aryl-2,3-dihydro-1*H*-isoindoles

Table 1. Synthesis of 1-Aryl-2,3-dihydro-2-formyl-1*H*-isoindoles (**9**) by Acid Catalyzed Cyclization of *N*-Formyliminium Ions (**8**).

Run	*N*-Formyliminium ion (**8**)*1				Cyclization*2			
		R^1	R^2	R^3	Reagent	Temp (℃)	Time(h)	Yields of **9** (%)*3
1	**8a**	H	H	H	TFA	90	3	**9a** (65)
2	**8b**	OMe	OMe	H	TFA	90	3	**9b** (80)
3	**8c**	OMe	H	H	TFA	90	3	**9c** (83)
4	**8d**	H	OMe	H	TFA	90	3	**9d** (38)
5	**8e**	H	H	Me	TFA	90	5	**9e** (86)

*1a) **8a~d** were prepared by heating the mixture of **5** (1.2 mol eq.) and **6** (1 mol eq.) without solvent at 80 °C for 1 h, followed by heating at 70 °C for 1 h in acetic-formic anhydride (100 mol eq.) which was prepared from acetic anhydride (100 mol eq.) and formic acid (100 mol eq.)

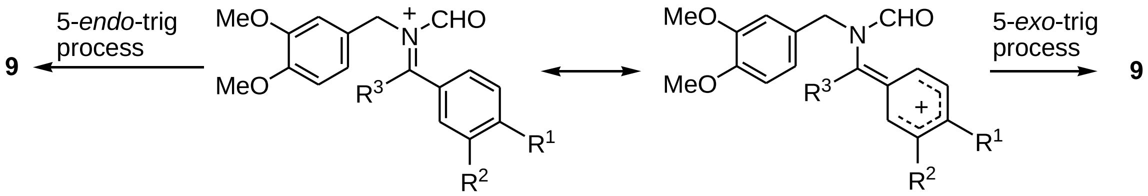
*1b) **8e** was prepared as follows: the mixture of **5** (1.2 mol eq.) and **6e** (1 mol eq.) was heated in Ti(*i*-OPr)$_4$ (1.5 mol eq.) at 80 °C for 1 h, and the resulting imine **7e** was formylated by acetic-formic anhydride (100 mol eq.) at 70 °C for 1 h without removing the Ti catalyst.

*2) The reaction was carried out in large excess of TFA (100 mol eq.) after eliminating excess acetic-formic anhydride by heating *in vacuo*.

*3) The yields of **9** were calculated based on the quantity of the carbonyl compounds (**6**).

occurs through the geometrically disfavored 5-*endo* trigonal process. It is especially noteworthy that the *N*-formyliminium ion (**8e**), in spite of having the congested tetra-substituted C=N$^+$ system, readily caused the cyclization to give **9e** in 86% yield.

The occurrence of this cyclization may be explained in terms of mesomeric effect. The C=N$^+$ bond is conjugated to the benzene ring. Therefore, the energy of the transition state should be lowered by the contribution of mesomeric enamino-structure **8B** featuring 5-*exo* trigonal cyclization. Thus, the 5-*endo* trig process of the imino-structure **8A** to **9**, although geometrically disfavored, will be facilitated by the contribution of **8B** that is geometrically favored. The relatively low yield of isoindoline **9d** probably is attributable to the instability of the cation of **8B** which is induced by the electron attractive *meta* OMe group (R^2) .



imino-sturutrue **8A** enamino-structure **8B**

Scheme 3 Mesomeric structure of N-formyliminium ion

Thus, the Pictet-Spengler type reaction of *N*-formyliminium ions obtained from 3,4-dimethoxybenzylamine and carbonyl compounds under a one pot procedure provides a convenient method for preparing 1-arylisoindolines. Investigation concerning the scope and limitation of this methodology is underway.

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13. The structures of **9** and **10** were determined by elementary and spectral analyses (Mass, ^{1}H-and ^{13}C-NMR data).