APPLICATION OF VARIOUS ACIDS ON SILICA AS GREEN CATALYSTS IN THE REACTION OF ISATIN WITH INDOLE

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Abstract

A simple, highly efficient, and eco-friendly method for obtaining of 1H,1''H-[3,3':3',3''-terbenzo[b]pyrrol]-2'(1'H)-one by the reaction of isatin with indole using a various acids on silica as heterogeneous catalysts has been applied.

Keywords: *isatin, indoline-2,3-dione, indole, heterogeneous catalysis, green chemistry, 1H,1''H-[3,3':3',3''-terbenzo[b]pyrrol]-2'(1'H)-one, TfOH/SiO_2, $HClO_4/SiO_2$, H_2SO_4/SiO_2, PPA/SiO_2.*

INTRODUCTION

Oxindoles owns antibacterial, antiprotozoal, and anti-inflammatory activities and have been patented as agonists to progesterone receptors [1]. The naturally occurring oxindole derivative convolutamydine **1** has been found to exhibit potent activity in the differentiation of HL-60 human plomyelocytic leukemic cells [2].

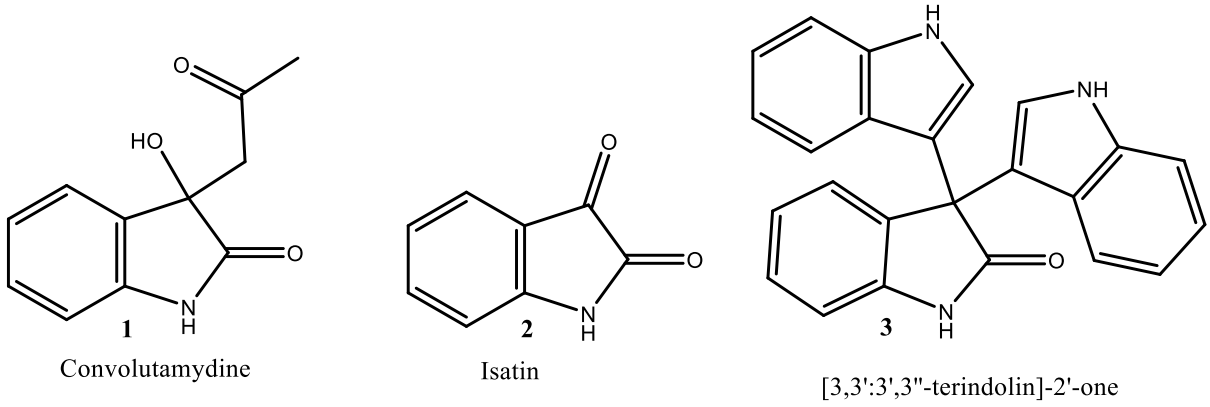


Fig. 1. Naturally occurring isatin compounds.

Isatin **2** is a heterocyclic natural product which is found in plants of the genus *Isatis* [3]. Compounds with indole moieties exhibit antibacterial and antifungal activities [4]. The importance of 3,3'-disubstituted oxindoles lies in their employment as drug candidates. In particular, 3,3-diaryloxindole **3** is frequently found in clinical drugs and biologically active compounds and possesses anti-proliferative, antibacterial, anti-protozoal and anti-inflammatory activities [1, 5, 6].

In the last years have been reported different methods for synthesis of [3,3':3',3"-terindolin]-2'-one using different acid catalysts and reaction conditions. The acid catalysts have been used in a wide number of organic reactions to overcome the limitation, such a volatility, toxicity, hazardous nature of the conventional methods etc. In particular, in the Friedel-Crafts reaction of isatin with different indoles have been involved as catalysts ionic liquids [7,8], $FeCl_3$[9], TfOH [10], CAN [11], H_3PO_4/SiO_2 [12], SiO_2/g-C_3N_4 [13], [Dabco-H][BF_4] and [Dabco-H][HSO_4] [14], Al_2O_3/V_2O_5 [15], Fe_3O_4-SO_3H [16], *β*-CD-SO_3H [17, 18], Fe_3O_4-OSO_3 [19], nano-NiO [20], nano-SiO_2 [21] and many others. Instead of using many different catalysts a wide range of solvents have been used as well. Deb and Bhuyan [22] describes water-promoted synthesis of 3,3'-di(indolyl) oxindoles. The authors received the desired product with 85% yield refluxing the starting materials in water-ethanol mixture (7:3) without any catalysts. Other authors [23] are using rhodium-catalyzed three-component reaction

of azooxoindoles with indoles and isatins to produce a variety of 3,3',3''-trisindoles. Kamal and co-workers [24] are using catalytic amount of $FeCl_3$ for the synthesis of 3,3-diindolyl oxyindoles. The reaction is carrying out with 5 mol % anhydrous $FeCl_3$ in acetonitrile for less than an hour at room temperature. Chinese authors [25] developed a simple and efficient metal-free catalyzed oxidative trimeric reaction of indoles towards different indole derivatives. They were using the radical TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl radical) as highly selective oxidation catalyst for the synthesis of isatin derivatives. The authors manage to obtain [3,2':2',3"-terindolin]-3'-one using different indoles, TEMPO, benzoic acid in acetonitrile at 65°C for 3 days. Ionic liquids were using also for synthesis of symmetrical and unsymmetrical 3,3-di(indolyl)indolin-2-ones [26]. The authors revealed that the interaction between isatin and indoles in [BMIM][BF_4]-LiCl or *N*,*N*,*N*,*N* – tetramethylguanidinium triflate media stops at the step of addition of the two components providing 3-indolyl-3-hydroxyindolin-2-ones while the ionic liquid *N*,*N*,*N*,*N*–tetramethylguanidinium trifluoroacetate runs the reaction further through accompanying Friedel-Crafts substitution to afford symmetrical 3,3-di(indol-3-yl)indolin-2-ones. Other Chinese authors [27] are using ceric ammonium nitrate as catalyst for the reaction of isatin with indoles under sonic waves to obtain symmetrical 3,3-di(indolyl)indolin-2-ones. The initial research of the authors carried out the reaction using different solvents like anhydrous C_2H_5OH and CH_3OH, CH_2Cl_2, and CH_3CN. The yields they obtained were highest using anhydrous C_2H_5OH for an hour. [3,3':3',3"-terindolin]-2'-one derivatives were obtained using *p*-TSA as acid catalyst in CH_2Cl_2 at room temperature [28]. Klumpp and his collaborators [29] are using the super strong triflic acid as catalyst in the reaction of isatin with different aromatics for preparation of 3,3-diaryloxindoles. An efficient procedure via electrophilic substitution reaction of indoles with isatins in presence of a Wells-Dawson tungsten heteropolyacid ($H_6P_2W_{18}O_{62}$) in water is developed from Alimohammadi and co-workers [30]. The authors are obtaining the desire compounds in water as a solvent for 30min at 60°C in presence of $H_6P_2W_{18}O_{62}$.

RESULTS AND DISCUSSION

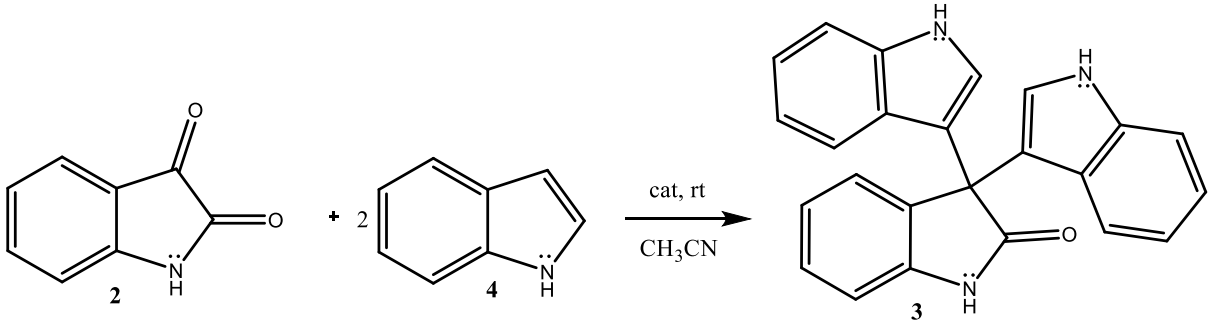
Following the requirement of "green chemistry", the exploration for more environmentally friendly forms of catalysis has created fast-growing interest, and one of the leading contenders for environmentally acceptable alternatives is supported catalysis. Solid supported reagents are unique acid catalysts that have become popular over the last 20 years. Many different heterogeneous catalysts have been used in a large number of organic reactions.

A silica gel supported acids has achieved appreciable interest in organic synthesis because of its unique properties such as high efficiency –related with the surface area, more thermal stability and reusability, low toxicity, greater selectivity, ease of handling and high selectivity. The catalyst immobilization contribute easy separation of the products from the catalysts without tedious experimental workup, and enables the efficient recovery of the catalysts, and potentially allows the adaptation of the immobilized catalysts to continuous flow-type processes.

We have already report [31, 32] the successful application of heterogeneous acid catalysts for obtaining of different heterocyclic compounds. In connection with our ongoing work on using different heteregeneous catalysts in the organic synthesis we now wish to provide a new, "green" and efficient way for synthesis of [3,3';3',3''-terindolin]-2'-one. The heterogeneous catalysts we used in the reaction haven't been used before for the obtaining of the desired and similar products. In relation with that we have selected four acids immobilized on silica as heterogeneous catalysts. The acids - triflic, sulfuric, perchloric and polyphosphoric have been used in the organic chemistry for synthesis of many biologically active organic compounds. Trifluoromethanesulfonic acid, also called triflic acid (TfOH), H_2SO_4, $HClO_4$ and PPA are probably the most versatile Brønsted acid catalysts in a vast array of organic reactions. Because of their highly corroding and fuming liquids, difficulties remain in storage, transportation, handling and waste disposal and acutely restrict their employment in commerce. The binding of these protic acids onto an inorganic material, such as silica gel, allows solid acids which can be easily operated, as they invariably are low toxicity, non-corrosive, free-flowing powders with superior thermal and mechanical stability under catalytic conditions. The catalysts used

in this research $TfOH/SiO_2$ [33], H_2SO_4/SiO_2 [34], $HClO_4/SiO_2$ [35] and PPA/SiO_2 [36] have been obtained using cited literature procedures.

The reaction between isatin **2** (1mmol) and indole **4** (2mmol) in the presence of heterogeneous catalyst (0.06g) in acetonitrile proceeded to give the product of the reaction [3,3';3',3''-terindolin]-2'-one **3** with very good yields for short time (Shown on Table 1). The course of the reaction was monitored by thin layer chromatography. We have investigate four different catalyst in the reaction. After the completion of the reaction the catalyst is separated by simple filtration and washed. The dried catalyst is ready to take part in the next synthesis. The catalysts can be used up to 3 times in the reaction without losing their activity. The solvent is distilled *via* rotary evaporator and in practice we have not got any waste product at the end of the reaction. We have obtained light brown colored crystals which, after recrystallization in ethanol, turn to white crystals with a melting point of 299-302 °C.



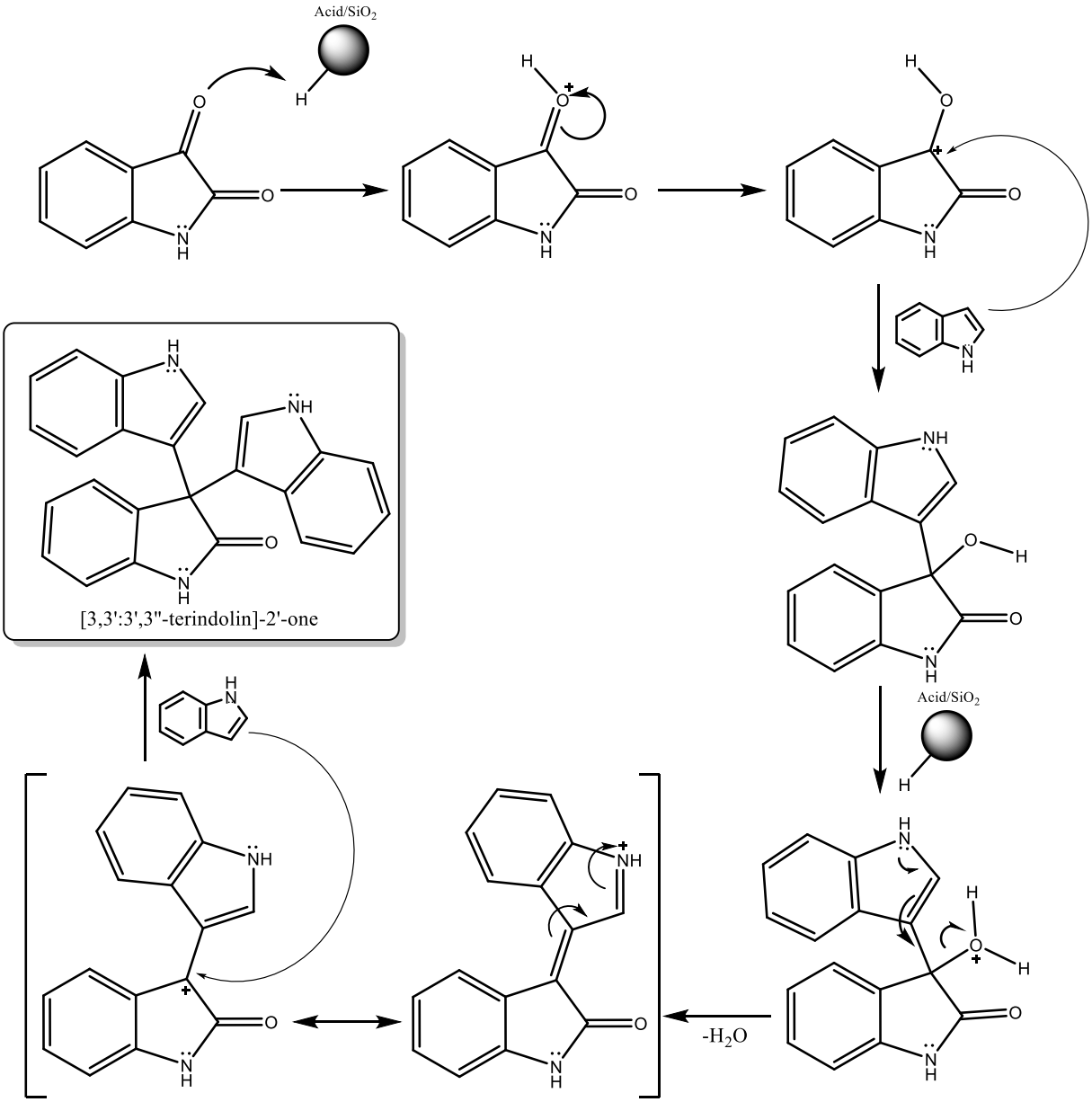
Scheme 1. Reaction between isatin and indole.

In the next table (**Table 1**) are shown the reaction time and the yield of the reaction carried out with different catalysts. Highest yield and shortest reaction time we have observed using the heterogeneous catalyst $TfOH/SiO_2$. The reaction time using PPA/SiO_2 as catalyst in the reaction is doubled – 30 minutes with similar yield and using the catalysts $HClO_4/SiO_2$ and H_2SO_4/SiO_2 the reaction time is tripled and the yields are a little bit lower.

	Catalyst, g	**Quantity of acid taking place, mmol**	**Reaction time, min**	**Yield, %**
$TfOH/SiO_2$	0.06	0.03	15	98
PPA/SiO_2	0.06	0.15	30	97
$HClO_4/SiO_2$	0.06	0.03	45	95
H_2SO_4/SiO_2	0.06	0.20	45	89

Table 1. Yield, reaction time and quantity of acid taking place in the reaction using different catalysts.

The reaction starts with protonation of the carbonyl of third position. The role of the acid catalyst is to protonate the carbonyl group at third position which will provide a better electrophile center for the subsequent nucleophilic attack. The carbonyl at the 2-position is unreactive and this is due to stabilization by the indole nitrogen. Once the better electrophilic center is formed the following step is nucleophilic attack of first indole molecule. After another protonation of the oxygen and leaving of water molecule is obtained better electrophilic center again and second molecule indole is attaching to give the product of the reaction [3,3':3'3''-terindolin]-2'one.



Scheme 2. Proposed mechanism of the reaction between isatin and indole.

EXPERIMENTAL SECTION

Reagents and chemicals were purchased from commercial sources [Aldrich, Merck] and used as received. Melting points were determined on a Boetius hostage apparatus and are uncorrected. Raman spectra was recorded with Vertex 70 Ram II. TLC was carried out on precoated 0.2 mm Fluka silica gel 60 plates.

Synthesis of [3,3':3'3''-terindolin]-2'one 3

To the solution of isatin **2** (1mmol, 0.147g) in acetonitrile, indole **4** (2mmol, 0.234g) and corresponding catalyst (0.06g) was added. The reaction mixture was stirred at room temperature and monitored *via* thin layer chromatography. After completion of the reaction (see Table 1) the catalyst was separated by simple filtration. The solvent was removed *via* rotary evaporator. The obtained light brown crystals were recrystallized with ethanol to white colored ones with melting point of 299-302^{o}C.

As compound **3** is known [37, 38, 39, 40] have ^{1}H and ^{13}C-NMR [37, 38, 39, 40], IR [41], UV [42] and mass [43] data available. In relation with that we have analyzed compound **3** with Raman Spectroscopy as there is none Raman spectra published (Reaxys).

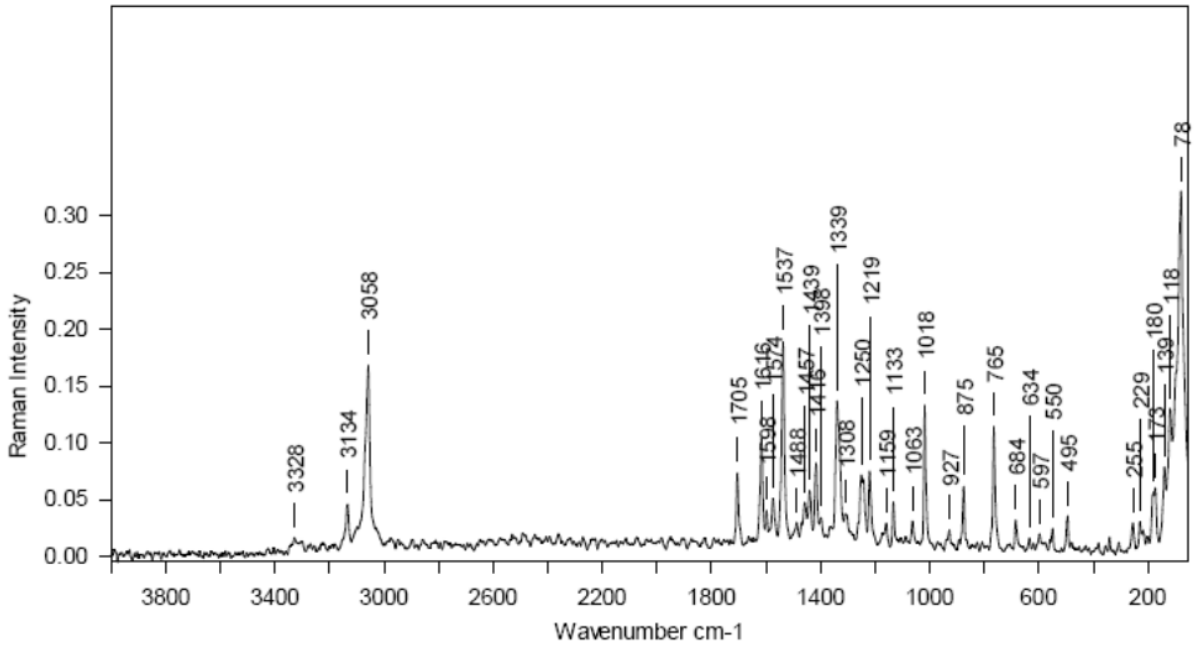


Fig. 2. Raman spectra of [3,3':3'3''-terindolin]-2'one.

Raman: 3328 (NH), 3058 (C-H – Ar), 1705 (C=O), 1616, 3134 (NHCO), 1574, 1598 (Ar ring - stretching), 1537 ν(C=C), 1339 (C-H, Ar - bending), 1018, 1457 (Ar), 495, 550 (C=O, bending).

CONCLUSIONS

In conclusion a green and eco-friendly method for synthesis of [3,3':3'3''-terindolin]-2'one was developed. The procedure we report using the heterogeneous catalysts $TfOH/SiO_2$, $HClO_4/SiO_2$, H_2SO_4/SiO_2 and PPA/SiO_2 offers easy, quick, economical and eco-friendly synthesis of the desired product with high yield for short time without any waste products.

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