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Synthesis of 3-(5-aryl-[1,3,4]oxadiazol-2yl)-1*H*-indazole Derivatives Using Cellulose Sulphuric Acid (CSA) as a Catalyst

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ABSTRACT: Simple synthesis of 3-(5-aryl-[1,3,4]oxadiazole-2-yl)-1*H* indazole derivatives by the condensation of 1*H* indazole-3-carboxylic acid hydrazide and aromatic acids using cellulose sulphuric acid (CSA) as a catalyst. The title compound was characterized by analytical and spectral (IR, ^{1}H NMR and EC-MS) methods.

Keywords: Cellulose Sulphuric Acid; Grinding; Mild Catalyst.

INTRODUCTION: The substituted oxadiazoles are heterocyclic compounds, which serve both as biomimetic and reactive pharmacophores and many are key elements with potential biological activities[1] such as pesticidal,[2] antiperipheral vasomotility,[3] CNS stimulant, anti-inflammatory, hypotensive,[4] insecticidal,[5] bactericidal,[6] hypoglycemic,[7] analgesic, anticonvulsive, antiemetic, diuretic,[8] muscle relaxant[9] and fungicidal[10] activities.

Indazoles constitute an important class of heterocycles that display interesting biological properties,[11] such as anti-depressant,[12] anti-inflammatory,[13] analgesic and antipyretic,[14] dopamine antagonistic,[15] anti-tumor,[16] anti-emetic[17] and anti-HIV activities.[18] The indazole ring system is also present in many other compounds such as herbicides, dyes or sweeteners like guanidine-1*H*-indazole.[11,19]

In recent days the milder conditions were tried and investigated on clean, simple, ecofriendly benign and excellent process became the chemists interesting undertaking.[20,21] Several improved or developed process are reported using modified reagents[22] and solid acid catalysts like clay,[23] zeolites[24] and silica sulfuric acid.[24(c)] However, the reactions are sluggish when they are performed in the liquid phase.[25] Relatively few solid phase methods have been developed.[26]

Biological properties associated with oxadiazole and indazole moieties and importance of solvent-free grinding technique promoted us to synthesize some oxadiazoles with indazole nucleus under grinding.

In continuation of our research on the development of green methodologies for the synthesis of heterocyclic compounds, we report here an efficient and green method for the synthesis of 3-(5-aryl-[1,3,4]oxadiazole-2-yl)-1*H* indazole derivatives at room temperature using cellulose sulfuric acid (CSA) as a catalyst (Scheme 1).

Cellulose is one of the most abundant natural materials in the world and it has been widely studied during the past decades in organic transformations.[27,28]

Cellulose is a biodegradable material, can be obtained from renewable resources and has potential as a catalyst to yield clean, efficient and fast reactions. Cellulose sulfuric acid, a non-hygroscopic solid acid catalyst, is an efficient and environmentally benign catalyst for the synthesis of 3-(5-aryl-[1,3,4]oxadiazole-2-yl)-1*H* indazole derivatives.

MATERIALS AND METHODS:

Experimental Section: All the melting points were determined in open capillaries in a paraffin bath and are uncorrected. The catalyst CSA was prepared according to literature method.[27,28] Products were identified by comparing melting points with those found in literature. ^{1}H NMR spectra were recorded on Mercury Plus Varian at 300 MHz in DMSO-d_6 as a solvent and TMS as an internal standard. The progress of the reactions was monitored by TLC.

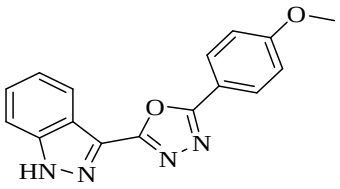
General Procedure:

Conventional Method: The mixture of 1*H*-indazole-3-carboxylic acid hydrazide (10 mmol) and aromatic acids (10 mmol) in the presence of Cellulose Sulfuric Acid (catalytic amount) in methanol was stirred at reflux temperature for the appropriate time (Table 1). After completion of reaction as monitored by TLC, the content was poured on crushed ice and then neutralized by $NaHCO_3$. Resulting solid was filtered, dried and recrystallized from ethanol to afford the pure product.

Preparation of Cellulose Sulfuric Acid [27,28]**:** To a magnetically stirred mixture of 5 g of cellulose (DEAE for column chromatography, Merck) in 20 mL of *n*-hexane, 1.0 g of chlorosulfonic acid (9 mmol) was added dropwise at 0 °C over 2 hrs HCl gas was removed from the reaction vessel immediately. After the addition was complete, the mixture was stirred for 2 hrs at room temperature. The mixture was then filtered and washed with 30 mL of acetonitrile and dried at room temperature to obtain 5.47 g cellulose sulfuric acid as a white powder.

***General Procedure for the Synthesis of 3-(5-aryl-[1,3,4]oxadiazol-2yl)-1H indazole*:** Cellulose sulfuric acid (0.1g) was added to a mixture of (10 mmol) 1*H*-indazole-3-carboxylic acid hydrazide and aromatic acids (10 mmol) in a mortar. The reaction mixture was ground at room temperature using a pestle for appropriate time. After the completion of the reaction (TLC), ethanol (20 mL) was added and the reaction mixture was filtered. The catalyst was washed with ethanol (2x10 mL). The obtained filtrate was evaporated using a rotary evaporator. The removal of solvent from the combined filtrate gave the product in almost pure form. The obtained compounds were analyzed and the results were compared with literature values.

Spectral analysis:



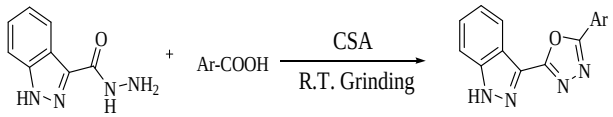
3-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-1*H*-indazole (**3f**)

IR (KBr, cm^{-1}): 3402 (N-H), 1670 (C=N), 1249 (C-O-C).

^{1}H NMR (DMSO-d_6, 300MHz, δ ppm): δ 3.90 (s, 3H, OCH_3), 7.50-7.90 (m, 7H, ArH), 8.22 (d, 1H, ArH), 8.52 (d, 1H, ArH).

ES-MS: m/z 291.2 (M+1).

RESULTS AND DISCUSSION: The titled compounds were synthesized successfully according to reported procedure used for the synthesis of other 1,3,4-oxadiazoles by both conventional and grinding method. In the conventional method 1*H*-indazole-3-carboxylic acid hydrazide **1** was treated with aromatic acids **2a-g** in presence of phosphorous oxychloride to afford the 5-substituted indazolyl oxadiazole derivatives **3a-g** in 6-9 h with good yields (65-76%). The reaction was found to proceed smoothly under reflux condition (Table1).



1 **2a-g** **3a-g**

Scheme 1: Synthesis of 3-(5-aryl-[1,3,4]oxadiazole-2-yl)-1*H* indazole derivatives using at room temperature grinding with cellulose sulfuric acid as a catalyst.

The titled compounds were synthesized successfully according to reported procedure used for the synthesis of other 1,3,4-oxadiazoles by both conventional and grinding. In the conventional method 1*H*-indazole-3-carboxylic acid hydrazide **1** was treated with aromatic acids **2a-g** in presence of cellulose sulfuric acid in methanol to afford the 5-substituted indazolyl oxadiazole derivatives **3a-g** in 6-9 h with good yields (55-73%). The reaction was found to proceed smoothly under reflux condition (Table 1).

Table 1: Characterization data of 3-(5-aryl-[1,3,4]oxadiazol-2yl)-1*H* indazole.

Entry	Ar	Conventional Method		Microwave Method		MP (°C)
		Time (h)	Yield[a] (%)	Time (min)	Yield[a] (%)	
3a	C_6H_5	6	68	08	86	261-263
3b	2-ClC_6H_4	8	73	05	94	145-147
3c	3-ClC_6H_4	5	71	10	88	168-170
3d	2-OHC_6H_4	8	69	07	87	156-158
3e	2,4-$(OCH_3)_2C_6H_3$	7	55	06	90	210-212
3f	4-$OCH_3C_6H_4$	8	72	05	91	175-177
3g	CH=CH-C_6H_5	9	67	11	93	146-148

Reaction conditions: 1 (10 mmol), 2 (10 mmol). [a]Isolated yields

Grinding method synthesis of 3-(5-aryl-[1,3,4]oxadiazol-2yl)-1*H*-indazole derivatives 3**a-g** were carried out by the reaction of 1*H*-indazole-3-carboxylic acid hydrazide **1** with the aromatic acids **2a-g** in the presence of cellulose sulfuric acid as a

catalyst. The reaction was completed within 05-10 min with excellent product yields (86-97%) (Table 1). To establish the generality with respect to carboxylic acid; acid hydrazide were treated with various substituted aromatic acids under the influence of griding to get the corresponding oxadiazoles in excellent yields. The product was confirmed by IR, ^{1}H NMR and Mass spectroscopic analysis.

CONCLUSION: Cellulose sulphuric acid (CSA) is a readily available, inexpensive, and efficient catalyst for the synthesis of variety of 3-(5-aryl-[1,3,4]oxadiazol-2yl)-1*H*-indazole derivatives. The remarkable advantages offered by this method are short reaction times, ease of product isolations, and high yields. We believe that this method is a useful addition to the present methodology for the synthesis of 3-(5-aryl-[1,3,4]oxadiazol-2yl)-1*H*-indazoles.

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