Synthesis of 3-(5-aryl-[1, 3, 4] Oxadiazol-2yl)-1*H*-indazole Derivatives using Silica Supported Sulphamic Acid as a Mild Catalyst in Microwave Irradiation

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Abstract

Simple synthesis of 3-(5-aryl-[1,3,4]oxadiazole-2-yl)-1H indazole derivatives by the condensation of 1H indazole-3-carboxylic acid hydrazide and aromatic acids using silica supported sulphamic acid as a mild catalyst in microwave irradiation. The title compound was characterized by analytical and spectral (IR, ^{1}H NMR and EC-MS) methods.

Keywords: Sulphamic Acid, Indazole, Microwave Irradiation, Mild Catalyst

Introduction

Heterocyclic compounds like substituted oxadiazoles serve as biomimetic and reactive pharmacophores. Substituted oxadiazoles with potential biological activities[1] such as fungicidal[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 pesticidal,[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]

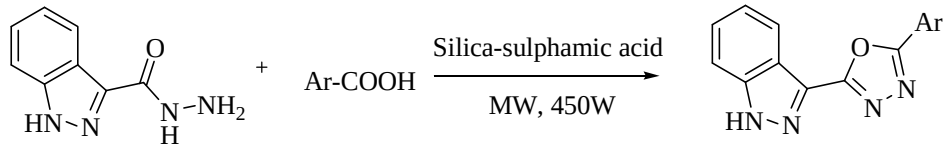
In recent days the milder conditions were tried and investigated on clean, simple, ecofriendly benign and excellent process became the chemists interesting undertaking.[20,21] Several improved or developed process are reported using modified reagents[22] and solid acid catalysts like clay,[23] zeolites[24] 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]

Silica supported sulphamic acid is an excellent mild catalyst over sulphuric acid and chlorosulphonic acid[27] in organic reactions without any limitations such as use of rather toxic, harmful solvents and expensive reagents. Hence, we tried mild acid catalyst sulphamic acid[28] which shows rather slow rate of reaction and higher yield, therefore on using solid support (silica), which gives enhancement in the rate of reaction and better yields. Reaction goes through simple, clean and environmental friendly.

In this paper, we have studied a 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 silica supported sulphamic acid as a mild catalyst in microwave irradiation. (Scheme 1).

Result 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 microwave irradiation method.[29] In the conventional method 1*H*-indazole-3-carboxylic acid hydrazide **1** was treated with aromatic acids **2a-h** in presence of phosphorous oxychloride to afford the 5-substituted indazolyl oxadiazole derivatives **3a-h** in 6-9 h with good yields (65-76%). The reaction was found to proceed smoothly under reflux condition (Table1).



1 **2a-h** **3a-h**

Scheme 1 Solvent-free microwave assisted 3-(5-aryl-[1,3,4]oxadiazole-2-yl)-1*H* indazole derivatives using silica-sulphamic acid.

The titled compounds were synthesized successfully according to reported procedure used for the synthesis of other 1,3,4-oxadiazoles by both conventional and microwave irradiation method.[27] In the conventional method 1*H*-indazole-3-carboxylic acid hydrazide **1** was treated with aromatic acids **2a-h** in presence of Sulphamic acid in methanol to afford the 5-substituted indazolyl oxadiazole derivatives **3a-h** in 6-9 h with good yields (55-73%). The reaction was found to proceed smoothly under reflux condition (Table1).

Entry	Ar	Conventional Method		Microwave Method		MP (°C)
		Time (h)	Yield[a] (%)	Time (min)	Yield[a] (%)	
3a	C_6H_5	6	68	12	85	260-262
3b	2-ClC_6H_4	8	73	10	91	146-148
3c	3-ClC_6H_4	5	71	12	86	170-172
3d	2-OHC_6H_4	8	69	14	84	154-156
3e	2,4-$(OCH_3)_2C_6H_3$	7	55	12	82	208-210
3f	4-$OCH_3C_6H_4$	8	72	13	87	176-178
3g	CH=CH-C_6H_5	9	67	15	84	147-149
3h	2-BrC_6H_4	6	63	09	75	135-137

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

The reaction of 1*H*-indazole-3-carboxylic acid hydrazide **1** with the aromatic acids **2a-h** for the synthesis of various 3-(5-aryl-[1,3,4]oxadiazol-2yl)-1*H*-indazole derivatives **3a-h** using microwave were carried out by in the presence of Sulphamic acid using alumina as a solid support. The reaction was completed within 09-15 min with excellent product yields (82-93%) (Table 1).

To establish the generality with respect to carboxylic acid; acid hydrazide were treated with various substituted aromatic acids under the influence of microwave irradiation to get the corresponding oxadiazoles in excellent yields. The product was confirmed by IR, ^{1}H NMR and Mass spectroscopic analysis.Table-1 Characterization data of 3-(5-aryl-[1,3,4]oxadiazol-2yl)-1*H* indazole

Experimental Section

All the melting points were determined in open capillaries in a paraffin bath and are uncorrected. Microwave oven (LG Smart Chef MS-255R operating at 2450 MHz having maximum output power of 960W) was used for microwave irradiation. ^{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 Sulphamic 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.

General Procedure for the synthesis silica sulphamic acid catalyst.

For this preparation Silica gel (230-400 mesh) about 0.5 gm with 1mmole of sulphamic acid (0.96 gm) was taken and mills that mixture for few minutes by using mortar and pestle at room temperature. The mixture of silica and sulphamic acid used for further reaction.

Microwave Irradiation Method: The mixture of 1*H*-indazole-3-carboxylic acid hydrazide (10 mmol) and aromatic acids (10 mmol) and alumina (1 g) were finely ground with a mortar and pestle, silica sulphamic acid catalyst (1.95gm) was added to this mixture in a glass vial, which was placed in to screw capped Teflon vessel. Microwave irradiation was applied for appropriate time (Table 1) in 30 sec regular time interval. After completion of reaction as monitored by TLC; the product was extracted by ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ solution and concentrate on rota evaporator under reduced pressure to afford the product.

Spectral Analysis

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

Conclusion

Sulphamic acid is a readily available, inexpensive, and efficient catalyst for the synthesis of 3-(5-aryl-[1, 3, 4] oxadiazole-2-yl)-1*H* indazole derivatives. The remarkable advantages offered by this method are solvent-free reaction conditions, Microwave Irradiation method, 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] oxadiazole-2-yl)-1*H* indazole derivatives.

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