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$H_3PW_{12}O_{40}$: An Efficient Catalyst for the Synthesis of Spirooxindoles Under Ultrasound Irradiation

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A simple and efficient one-pot three-component synthesis of the biologically important spirooxindoles scaffold was carried out by the reaction of isatin, malononitrile and 1,3-dicarbonyl compounds in presence of tungstophosphoric acid as a catalyst. This method is of great value because of high yield processing and easy handling.

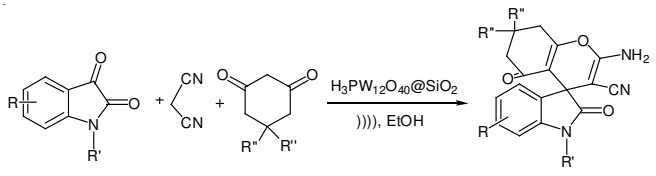
Key Words: Spirooxindole, Heteropoly acids, Ultrasound irradiation, Reusability.

INTRODUCTION

The indole nucleus is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents[1]. Compounds carrying the indole moiety exhibit antibacterial and antifungal activities[2]. Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity[3-5]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids[6-9]. For example, spirotryprostatin A, a natural alkaloid isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly[10] and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors. Due to these properties spirooxindoles have been attention and many procedures have been reported for synthesis of various spirooxindoles[11-15].

Heteropolyacids, catalyze a wide variety of reactions in homogeneous or heterogeneous (liquid-solid, gas-solid or liquid-liquid biphasic) systems, offering strong options for more efficient and cleaner processing compared to conventional mineral acids[16-18]. A major disadvantage of bulk heteropolyacids lies in their low specific surface area, less than 10 $m^2 g^{-1}$ that can be improved by supporting on oxidic carriers especially SiO_2 which is an inexpensive and noncorrosive neutral solid[19,20]. The support provides an opportunity to spread HPAs over a large surface area, which generally increases catalytic activity.

Ultrasound irradiation, an efficient and innocuous technique for reagent activation in the synthesis of organic compounds and in particular heterocyclic compounds, has been applied with success, milder reaction condition and higher yields in comparison to the classical methods[21,22]. Ultrasound-promoted syntheses has attracted much attention during the past few decades. As part of our endeavor development methodology for synthesis spirooxindoles, we investigated a three-component reaction involving isatin **1** with malononitrile and 1,3-dicarbonyl compounds **2** catalyzed with heteropoly acids and silica supported heteropoly acids under Ultrasound (**Scheme-I**).



1 2 3

Scheme-I: Reaction of isatins, 1,3-cyclohexadione and malononitrile in the presence of silica supported of tungstophosphoric acid under ultrasound irradiation

EXPERIMENTAL

All starting materials were purchased from Merck or Fluka. Substituted N-methylisatins were synthesized according to a literature procedure[23]. The supported $H_3PW_{12}O_{40}$ catalyst was prepared by the incipient wetness method according to literature[24].

General procedure for the synthesis of spirooxindoles: A mixture of isatin (1 mmol), malononitrile (1 mmol), cyclohexane-1,3-dione (1 mmol) and $H_3PW_{12}O_{40}$@SiO_2 (8 mol %) in EtOH (5 mL) was irradiated by ultrasonics irradiation for given time in Table-2. Upon completion, monitored by TLC,

TABLE-1
OPTIMIZATION OF REACTION CONDITION IN THE SYNTHESIS OF SPIROOXINDOLE **3a**

Entry	Amouts of catalyst (mmol)	Time (min)	Solvent	Yield (%)[a]
1	$H_3PMo_{12}O_{40}$(20)	10	EtOH	74
2	$H_3PW_{12}O_{40}$(20)	10	EtOH	86
3	$H_7SiW_9V_3O_{40}$(20)	20	EtOH	70
4	$H_3PW_{12}O_{40}$@SiO_2(9)	10	EtOH	86
5	$H_3PW_{12}O_{40}$@SiO_2(8)	10	EtOH	86
6	$H_3PW_{12}O_{40}$@SiO_2(7)	10	EtOH	78
7	$H_3PW_{12}O_{40}$@SiO_2(8)	10	CH_3CN	75
8	$H_3PW_{12}O_{40}$@SiO_2(8)	10	THF	70

[a]Isolated yields.

the catalyst was separated by filteration. The solvent was evaporated and the residue was recrystallized from dioxane/EtOH (1:1) to afford the pure product in 86 % yield. This procedure was followed for the synthesis of all the spirooxindoles (**3a-g**) (Table-1).

(3a): Yield: 86 %; m.p. >300 ºC; ^{1}H NMR (DMSO-d_6, 400 MHZ) δ: 10.39 (s, 1H), 7.21 (br s, 2H,), 7.13 (t, 1H, *J* = 7.6 Hz), 7.01 (d, 1H, *J* = 7.6 Hz), 6.88 (t, 1H, *J* = 7.6 Hz), 6.77 (d, 1H, *J* = 8.0 Hz), 2.63-2.67 (m, 2H), 2.30-2.37 (m, 2H), 1.90-1.93 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHZ) δ: 195.1, 178.2, 166.1, 158.7, 142.0, 134.6, 128.2, 123.3, 121.8, 117.4, 111.9, 109.2, 57.6, 46.9, 36.4, 26.8, 19.8; FT IR (KBr, ν_{max}, cm^{-1}): 3372, 3287, 3133, 2955, 2191, 1698, 1613, 1466, 1350, 1211, 1011, 933, 764, 679.

(3b): Yield: 81 %; m.p. 289-290 ºC; ^{1}H NMR (DMSO-d_6, 400 MHZ) δ: 10.37 (s, 1H), 7.20 (br s, 2H), 7.14 (t, 1H, *J* = 10.0 Hz), 6.97 (d, 1H, *J* = 9.6 Hz), 6.88 (t, 1H, *J* = 10.0 Hz), 6.78 (d, 1H, *J* = 10.0 Hz), 2.56 (d, 2H, *J* = 7.2 Hz), 2.18 (d, 1H, *J* = 21.2 Hz), 2.08 (d, 1H, *J* = 21.6 Hz), 1.03 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHZ) δ: 194.9, 178.1, 164.2, 158.9, 142.1, 134.5, 128.2, 123.1, 121.8, 117.4, 110.9, 109.3, 57.5, 50.1, 46.9, 40.0, 32.0, 27.7, 27.1; FT IR (KBr, ν_{max}, cm^{-1}): 3380, 3310, 3141, 2963, 2192, 1721, 1659, 1605, 1466, 1350, 1219, 1057, 903, 748, 679, 556.

(3c): Yield: 79 %; m.p. >300 ºC; ^{1}H NMR (DMSO-d_6, 400 MHZ) δ: 10.66 (s, 1H,), 7.33 (br s, 2H), 7.11 (t, 1H, *J* = 7.2 Hz), 7.03 (d, 1H, *J* = 8.0 Hz), 6.81 (d, 1H, *J* = 7.6 Hz), 2.62-2.67 (m, 2H), 2.25- 2.32 (m, 2H), 1.94-1.96 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHZ) δ: 195.3, 177.9, 166.7, 158.8, 141.4, 137.0, 130.9, 126.2, 117.3, 113.4, 111.2, 56.9, 47.2, 36.4, 26.8, 19.8; FT IR (KBr, ν_{max}, cm^{-1}): 3357, 3271, 3156, 2963, 2192, 1728, 1651, 1450, 1350, 1219, 1011, 910, 733, 656.

RESULTS AND DISCUSSION

Initially, evaluation of various catalysts and solvent systems was carried out for the synthesis of spirooxindole with fused chromenes. After systematic screening, silica supported of $H_3PW_{12}O_{40}$ ($H_3PW_{12}O_{40}$@SiO_2) and ethanol were found to be the best (entry 5).

Encouraged by this success, we extended this reaction of different isatin 1 and 1,3-dicarbonyl compound in the presence of malononitrile. The corresponding products **3a-g** was synthesized in high yield (74-85 %) and the results are summarized in Table-2.

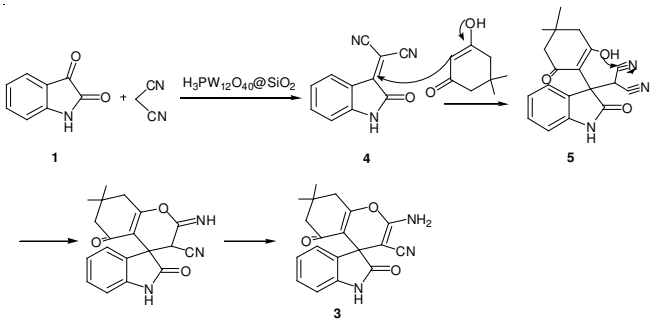
TABLE-2
SYNTHESIS OF SPIROOXINDOLES **3a-g**

Entry	R	R'	R''	Time (min)	Yield (%)[a]
3a	H	H	H	6	86
3b	H	H	Me	10	81
3c	4-Br	H	H	6	79
3d	4-Br	H	Me	8	76
3e	6-Br	H	Me	10	84
3f	H	Me	Me	6	75
3g	H	CH_2Ph	Me	6	79

[a]Isolated yields.

The structures of compounds **3a-g** were deduced from their elemental analysis, IR and high-field ^{1}H and ^{13}C NMR spectra. The IR spectrum of compound 3a showed absorption bands due to the NH_2 and NH groups at 3372, 3287, 3133 and the CH at 2955 and the CN group at 2191and C=O group at 1698 cm^{-1}. The ^{1}H NMR spectrum of **3a** showed two singlet for NH and NH_2 group (δ = 10.39 and 7.21), three multiplet for CH_2 groups (δ = 2.63-2.67, 2.30-2.37 and 1.90-1.93) and the aromatic moieties gave rise to multiplets in the aromatic region of the spectrum (δ = 6.77-7.13 ppm). The ^{1}H decoupled ^{13}C NMR spectrum of **3** showed 17 distinct resonances in agreement with the suggested structure. As shown in Table-2, it was found that this method works with a wide variety of substrates. A series of different position substituted isatins including either electron-withdrawing or electron-donating groups and different substituted 1,3-cyclohexanedione were used in this reaction.

Proposed mechanism for the synthesis of spiro derivative **3** was described in **Scheme-II**. The process represents a typical cascade reaction in which the isatin **1** first condenses with malononitrile to afford isatylidene malononitrile derivative **4** in the presence of heteropolyacids in EtOH. This step was regarded as a fast Knoevenagel condensation. Then, **4** is attacked *via* Michael addition of dimedone **2** to give the intermediate **5** followed by the cycloaddition of hydroxyl group to the cyano moiety to form the desired product **3** (**Scheme-II**).



Scheme-II: Proposed mechanism for synthesis of spirooxindoles

Conclusion

We have described a simple one-pot three component reaction involving isatin, malononitrile reagent and 1,3-dicarbonyl compounds for the synthesis of a series of spirooxindoles derivatives in presence of heteropolyacids. Particularly, valuable features of this method include the higher yields of the products, broader substrate scope, mild reaction conditions, catalyst recyclable and the straight forwardness of

the procedure, which make it a useful and attractive process for the synthesis of these important compounds.

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