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Silica Supported $H_3PW_{12}O_{40}$: An Efficient Catalyst for the Synthesis of Spirooxindoles *via* a One-Pot Reaction under Solvent Free Conditions

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Silica supported tungstophosphoric acid was found to be an efficient catalyst for the solvent-free synthesis of spirooxindoles *via* a one-pot three component reaction of isatin, 1,3-cyclohexadione and 4-hydroxy-6-methyl-2*H*-pyran-2-one. This method has many advantages such as simple work-up, using reusable and heterogeneous catalyst and good yield.

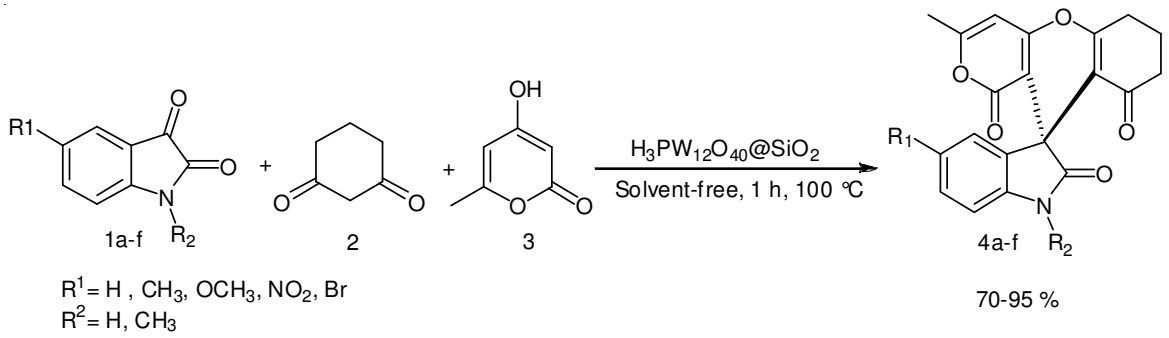
Key Words: Spirooxindole, Tungstophosphoric acid, Heterogeneous catalyst, Solvent-free condition.

INTRODUCTION

The indole ring system is probably the most ubiquitous heterocycle found in nature. Because of the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents. New indole alkaloids with a broad spectrum of biological properties are being discovered rapidly as marine invertebrate metabolites[1]. Moreover, many other analogous indole derivatives[2], demonstrate strong inhibitory effects against a variety of tumor cell lines, including leukemia, non-small cell lung cancer, ovarian cancer, colon cancer, renal cancer and breast cancer. On the other hand, spirooxindole derivatives occupy a special place in organic and medicinal chemistry because these compounds are well-known as microtubule assembly inhibitors (spirotryprostatin A and B)[3] and serotonin receptor modulators (pteropodine and isopteropodine)[4]. Due to these properties spirooxindoles have been attention and many procedure have been reported for synthesis of variousspirooxindoles[5,6]. Recently, new multi-component reaction for the synthesis of spirooxindoles catalyzed by $SiCl_4$ has been reported. The method requires long reaction times, tedious work-ups and the use of toxic solvents[7]. Considering the above reasons, we present an efficient method to synthesize spirooxindoles *via* one-pot three component reaction of isatins, 1,3-cyclohexadione and 4-hydroxy-6-methyl-2*H*-pyran-2-one in the presence of silica-supported tungstophosphoric acid under solvent-free conditions (**Scheme-I**).

EXPERIMENTAL

All starting materials were purchased from Merck or Fluka. Substituted N-methyl isatins were synthesized according to a literature procedure[8]. The supported $H_3PW_{12}O_{40}$ catalyst was prepared by the incipient wetness method according to literature[9].



Scheme-I: Reaction of isatins, 1,3-cyclohexadione and 4-hydroxy-6-methyl-2*H*-pyran-2-one in the presence of silica supported of tungstophosphoric acid

General procedure for the synthesis of spirooxindoles in the presence of silica supported $H_3PW_{12}O_{40}$ under solvent-free conditions: Isatin (1 mmol), 1,3-cyclohexanedione (1 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol) and silica supported $H_3PW_{12}O_{40}$ (4 mol %) were placed in a round bottom flask. The mixture was heated at 100 ºC and heating continued for 1 h. After completion of the reaction, chloroform was added to the mixture and the catalyst was separated by filtration. Thereafter, the solvent was evaporated and the oily residue was recrystallized from ethyl acetate to afford the pure spirooxindoles.

(4a): Yield: 60 %; m.p. > 250 ºC; ^{1}H NMR ($CDCl_3$, 400 MHZ) δ: 7.26-7.22 (m, 1H), 6.94-6.83 (m, 3H), 5.93 (s, 1H), 3.33 (s, 3H), 2.68 (t, 2H), 2.35-2.29 (m, 2H), 2.18 (s, 3H), 2.11-1.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHZ) δ: 195.0, 177.6, 165.0, 162.7, 160.1, 158.9, 142.2, 132.6, 128.9, 123.0, 122.0, 114.6, 109.4, 101.3, 98.0, 45.7, 37.1, 27.5, 19.8; FT IR (KBr, ν_{max}, cm^{-1}): 3011, 1712, 1670, 1634, 1610, 1590, 1498, 1470, 1349, 1308, 1213, 1175, 1130, 1090, 1068, 1002, 977, 934, 887, 751.

(4b): Yield: 70 %; m.p. > 250 ºC; ^{1}H NMR ($CDCl_3$, 400 MHZ) δ: 7.65 (b, 1H), 7.22-7.15 (m, 1H), 6.93-6.82(m, 3H), 5.93 (s, 1H), 2.69 (t, 2H), 2.44-2.29 (m, 2H), 2.21 (s, 3H), 2.17-1.95 (m, 2H)); ^{13}C NMR ($CDCl_3$, 100 MHZ) δ: 195.2, 177.5, 165.0, 162.8, 160.0, 158.8, 142.2, 132.7, 128.9, 123.0, 122.1, 114.7, 109.3, 101.3, 98.0, 45.5, 37.1, 27.5, 19.5; FT IR (KBr, ν_{max}, cm^{-1}): 3349, 3001, 1725, 1675, 1630, 1589, 1486, 1470, 1353, 1327, 1307, 1244, 1213, 1170, 1129, 1068, 1032,1009, 980, 933, 748, 678, 563.

(4c): Yield: 89 %; m.p. > 250 ºC; ^{1}H NMR ($CDCl_3$, 400 MHZ) δ: 8.27-8.23 (m, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz,1H), 6.01 (s, 1H), 3.38 (s, 3H), 2.76-2.72 (m, 2H), 2.38-2.32 (m, 2H), 2.23 (s, 3H), 2.14-2.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHZ) δ: 195.2, 177.0, 166.3, 163.5, 160.2, 159.4, 151.1, 143.1, 132.9, 126.3, 118.4, 113.5, 107.3, 100.3, 98.1, 44.8, 36.8, 27.5, 27.1, 19.8, 19.7; FT IR (KBr, ν_{max}, cm^{-1}): 3450, 2051, 1726, 1675, 1631, 1614, 1593, 1496, 1446, 1331, 1298, 1211, 1176, 1134, 1065, 1009, 753, 684, 552.

RESULTS AND DISCUSSION

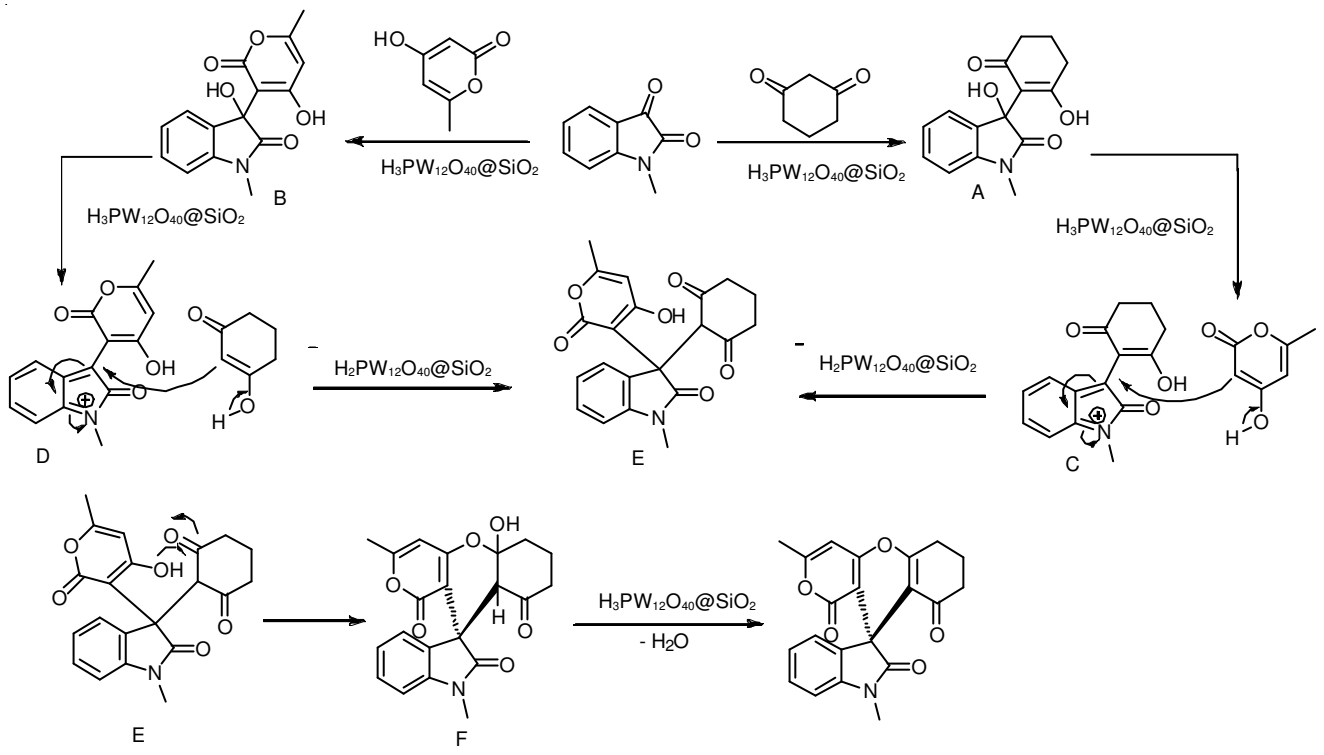
To achieve suitable conditions for the synthesis of the spirooxindoless[4], various amount of catalysts and different solvents were investigated in the model reaction of N-methyl isatin (**1a**), 1,3-cyclohexadione (**2**) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (3). The best overall yield (95 %) was obtained using $H_3PW_{12}O_{40}$ (4 mol %) under solvent free condition at 100 ºC (entry 7).

TABLE-1
OPTIMIZATION OF REACTION CONDITION IN THE SYNTHESIS OF SPIROOXINDOLE **4a**[a]

Entry	Amouts of catalyst (mmol)	Temp. (ºC)	Solvent	Yield (%)[c]
1	$H_3PW_{12}O_{40}$@ SiO_2 (5)	84[b]	DCE	55
2	$H_3PW_{12}O_{40}$@ SiO_2 (4)	84	DCE	55
3	$H_3PW_{12}O_{40}$@ SiO_2 (3)	84	DCE	43
5	$H_3PW_{12}O_{40}$@ SiO_2 (4)	110[b]	Toluene	62
7	$H_3PW_{12}O_{40}$@ SiO_2 (4)	100	Solvent-free	95

[a]N-Isatin (1 mmol), 1,3-cyclohexanedione (1 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol); [b]under reflux conditions; [c]isolated yield.

In order to evaluate the versatility of this protocol, next different isatins containing both electron-withdrawing and electron-releasing substituents were investigated in the reaction. All the desired spirooxindoles were obtained in good yields (70-95 %), as summarized in Table-2.



Scheme-II: Proposed mechanism for synthesis ofspirooxindoles

TABLE-2
EFFICIENT SYNTHESIS OF SPIROOXINDOLES USING VARIOUS ISATINS

Entry	Isatin	Yield (%)	Entry	Isatin	Yield (%)
4a	$R_1 = H\, R_2 = CH_3$	95	**4d**	$R_1 = CH_3, R_2 = CH_3$	84
4b	$R_1 = H, R_2 = H$	70	**4e**	$R_1 = OCH_3, R_2 = CH_3$	77
4c	$R_1 = NO_2, R_2 = CH_3$	89	**4f**	$R_1 = Br, R_2 = CH_3$	92

[a]All of the products were identified by comparing their melting points and FT-IR, ^1H and ^{13}C NMR spectra with those of authentic samples reported in the literature; [b]Isolated yields.

Our investigation showed that all isatin derivatives could be used in this protocol but better results were obtained with isatins containing electron-withdrawing substituents on the aromatic ring. We can conceive of two plausible pathways for this reaction (**Scheme-II**).

Conclusion

We have demonstrated an efficient methodology for the synthesis of spirooxindoles in the presence of a green catalyst under solvent free conditions. Although the products have been reported in the literature but the time reactions is long and the yields are lower[15]. These green syntheses were complete within suitable time with good to high yields that avoided tedious workup isolations due to the high yield products.

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