SHORT COMMUNICATION

A NOVEL ONE-POT SYNTHESIS OF SPIROOXINDOLE DERIVATIVES CATALYZED BY NANO ZnO

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ABSTRACT. Nano zinc oxide was explored as a heterogeneous and reusable catalyst for the one-pot synthesis of spirooxindoles via three-component reaction between urea, isatin, and 1,3-dicarbonyl compounds.
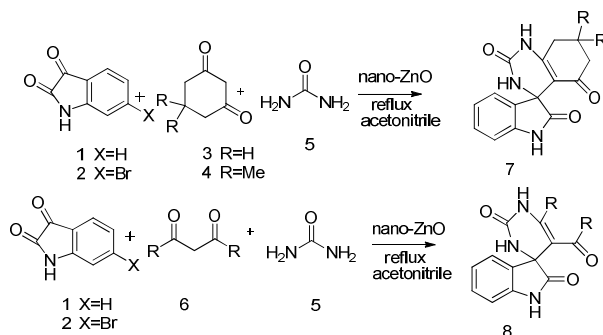
KEY WORDS: Nano-ZnO, Spirooxindoles, Isatin

INTRODUCTION

The indole skeleton occurs in many important natural products, pharmaceuticals, and other synthetic materials exhibiting a variety of biological activities and other properties [1]. Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [2-5]. Spirooxindoles with fused chromenes have been found to have a wide spectrum of activities such as antimicrobial [6], antiviral [7], mutagenicity [8], antiproliferative [9], sex pheromone [10], antitumor [11], and central nervous system activities [12].

One-pot multicomponent reactions (MCRs) by virtue of their convergence, productivity, facile execution and high yield have attracted considerable attention in recent years since they are performed without need to isolate the any intermediate during their processes and this reduces time saves both energy and raw materials [13]. There has been tremendous development in three or four component reaction specially the Bignelli [14], Passerini [15], Ugi [16] and Mannich [17] reactions, which have further led to renaissance of MCRs. MCRs have emerged as valuable tools for the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds [18-20]. Nevertheless, great efforts have been and still are being made to find and develop new MCRs. Zinc oxide is a non-hygroscopic, inexpensive, non-toxic [LD50 = 7950 mg/kg (mouse)] material, which has been utilized as a heterogeneous catalyst for number of organic reactions [21]. Of late, catalysis by nano materials has become an area of interest, as these materials exhibit better catalytic activity compared their bulk sized counterparts [22].

As part of our program aimed at developing new methods for the preparation of new compounds via MCRs [23], Herein, we used nano-ZnO as a catalyst for the synthesis of spirooxindoles **7** and **8** via three-component reaction between urea, isatin, and 1,3-dicarbonyl compounds (Scheme 1).

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Scheme 1. Nano ZnO catalyzed synthesis of spirooxindoles.

RESULTS AND DISCUSSION

In connection with our recent interested aimed at the development of efficient protocols for the preparation of biological active heterocycles, herein, we selected nano-ZnO as a new catalyst to synthesis of these compounds.

In a typical procedure, urea (1 mmol), isatin (1 mmol), and dimedone (1 mmol) in the presence of a catalytic amount of nano-ZnO in CH_3CN at reflux temperature afforded the desired spirooxindoles (**7a**) in 93% yield after 6 h (entry 1, Table 1). Similar trend was also observed with bulk ZnO but the yields were comparatively lower than that for nano-ZnO (82%) (entry 2, Table 2). This more yield with nano-ZnO may be attributed to the more surface area due to size reduction.

The effect of temperature was studied by carrying out the reactions at different temperatures. The yields of reactions increased as the reaction temperature was raised. From these results, it was decided that refluxing temperature would be the best temperature for all reactions. In each reaction, the yield is a function of the reaction time and the best time for all reactions was completed after 5 h. The reaction proceeds very cleanly under reflux condition and free of side products.
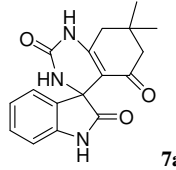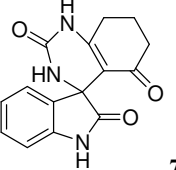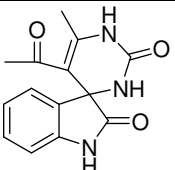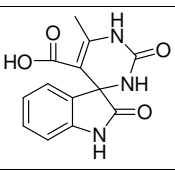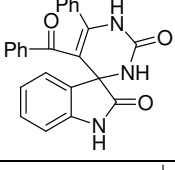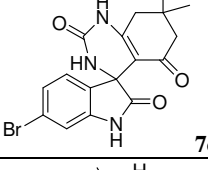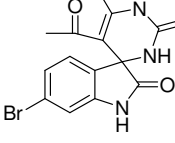
In order to show the generality and scope of this new protocol, we used various isatines with 1,3-dicarbonyl compounds in the presence of PTSA and the results obtained are summarized in Table 1. This reaction was carried out in various solvents such as CH_3CN, chloroform, ethanol and CH_2Cl_2 and the best results in terms of yield and time obtained in CH_3CN.

We evaluated the amount of nano-ZnO required for this transformation and found that as little as 5 mol% of nano-ZnO catalyzed the reaction to some extent, but a longer reaction time (> 5 h) was required. The use of an increased amount of catalyst did not improve the yield significantly.

In order to show the merit of the present work, we compared the result of the synthesis of these compounds in the presence of various catalysts but the best results obtained with nano-ZnO (Table 2).

In conclusion, we have described a highly efficient procedure for the preparation of spirooxindoles using nano-ZnO as a catalyst in good yield. Moreover, the procedure offers several advantages including high yields, operational simplicity, cleaner reaction, minimal environmental impact, and low cost, which make it a useful and attractive process for the synthesis of these compounds.

Table 1. Synthesis of spirooxindoles catalyzed by nano-ZnO.

Entry	X	1,3-Dicarbonyl compounds	Product	Yield (%)[a]		
				25 ˚C	40 ˚C	82 ˚C
1	H	Dimedone	**7a**	55	85	93
2	H	1,3-Cyclohexandione	**7b**	50	76	92
3	H	Acetyl acetone	**8a**	45	70	91
4	H	Ethyl acetoacetate	**8b**	45	72	91
5	H	1,3-Diphenyl-1,3-propandione	**8c**	50	79	91
6	Br	Dimedone	**7c**	50	77	93
7	Br	Acetyl acetone	**8d**	45	70	93

[a] Isolated yields.

Table 2. Comparision of various catalysts for the synthesis of **7a**.

Entry	Catalyst	Yield (%)
1	Nano-ZnO	93
2	Bulk-ZnO	82
3	$HClO_4$	80
4	H_2SO_4	85
5	HCl	82

[a] Isolated yields.

Preparation of catalysts

Bulk zinc oxide was prepared by simple precipitation method wherein aqueous ammonia solution (30%) was added dropwise to zinc nitrate solution under vigorous stirring (till pH of solution reached (7.5–8). The white precipitate of $Zn(OH)_2$ was filtered and washed several times with distilled water till the washings were neutral. The precipitate was then dried overnight at 100 °C in an oven and calcined at 600 °C for 3 h. Nano zinc oxide catalyst was prepared by the gel combustion method as described by Riahi-Noori *et al.* [24]. An appropriate molar ratio of citric acid and zinc nitrate (2:1) were mixed in a minimum amount of distilled water. The aqueous solution was homogenized and further concentrated on a hot plate to a viscous liquid, which was further heated at 100 °C for complete removal of water to obtain a dry mass. This mass was then further heated gradually till its combustion occurred giving a white fluffy powder. The powder obtained was annealed at 600 °C for 3 h to give nano-ZnO. The oxide was further characterized by various analytical techniques to confirm its structural properties. External morphology and particle size of the catalyst was determined by TEM image (Figure 1). It is clear from TEM image that the zinc oxide has polymorphic geometry and the size of the particles is in the range of 50-70 nm.
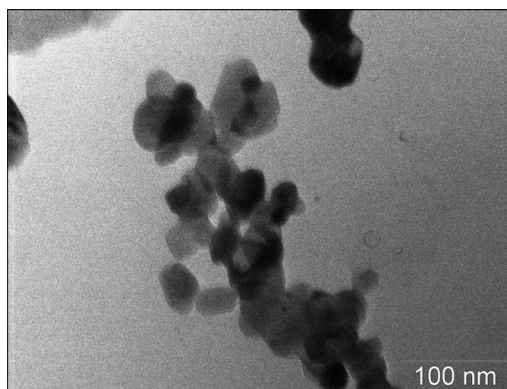

Figure 1. Transmission electron microscopy (TEM) image of nano-ZnO at 100 nm.

Preparation of spirooxindoles

Typical procedure. A mixture of the 1,3-dicarbonyl compounds (1 mmol), isatin (1 mmol), urea (1 mmol) and nano-ZnO (5 mol%) in acetonitrile (5 mL) was refluxed for 6 h. The progress of the reaction was monitored by TLC (ethyl acetate-hexane 1:3). On completion, the reaction

mixture was washed with diethyl ether and the precipitate formed was filtered to give pure product.

7a. M.p. 183-185 °C; GC/MS: 311 (M$^+$). IR (KBr) (ν_{max}, cm^{-1}): 3397, 3347, 3125, 1684, 1670, 1632; ^{1}H NMR (CDC1$_3$, 500 MHz) δ_H (ppm): 1.02 (3H, CH$_3$, s), 1.11 (3H, CH$_3$, s), 2.12 (2H, CH$_2$, s), 2.56 (2H, CH$_2$, s), 7.03-7.65 (4H, m, arom), 7.89 (3H, s, NH). ^{13}C NMR (CDC1$_3$, 125 MHz) δ_C (ppm): 23.45, 26.71, 36.81, 42.56, 52.68, 69.81, 111.26, 116.56, 117.23, 123.56, 140.68, 142.76, 143.62, 148.76, 168.22, 169.78, 170.22.

7b. M.p. 199-201 °C; GC/MS: 283 (M$^+$). IR (KBr) (ν_{max}, cm^{-1}): 3367, 3354, 3200, 1655, 1642, 1629; ^{1}H NMR (CDC1$_3$, 500 MHz) δ_H (ppm): 2.25 (2H, CH$_2$, m), 3.00 (2H, CH$_2$, m), 3.51 (2H, CH$_2$, m),7.01-7.71 (4H, m, arom), 8.01 (3H, s, NH). ^{13}C NMR (CDC1$_3$, 125 MHz) δ_C (ppm): 32.47, 34.67, 38.97, 69.84, 112.55, 117.01, 118.22, 140.09, 142.38, 144.96, 145.77, 148.66, 169.33, 171.71, 174.98.

7c. M.p. 189-191 °C; GC/MS: 390 (M$^+$). IR (KBr) (ν_{max}, cm^{-1}): 3387, 3366, 3205, 1674, 1665, 1622; ^{1}H NMR (CDC1$_3$, 500 MHz) δ_H (ppm): 1.00 (3H, CH$_3$, s), 1.10 (3H, CH$_3$, s), 2.40 (2H, CH$_2$, s), 3.01 (2H, CH$_2$, s), 7.10-7.50 (3H, m, arom), 8.30 (3H, s, NH). ^{13}C NMR (CDC1$_3$, 125 MHz) δ_C (ppm): 22.96, 27.88, 39.97, 43.68, 54.97, 69.96, 112.32, 117.66, 118.48, 140.56, 142.48, 144.96, 146.70, 149.71, 169.21, 172.70, 174.32.

8a. M.p. > 300 °C; GC/MS: 271 (M$^+$). IR (KBr) (ν_{max}, cm^{-1}): 3419, 3400, 3194, 1706, 1661, 1611; ^{1}H NMR (CDC1$_3$, 500 MHz) δ_H (ppm): 2.29 (3H, CH$_3$, s), 2.51 (3H, CH$_3$, s), 7.11-7.40 (4H, m, arom), 7.51 (3H, s, NH). ^{13}C NMR (CDC1$_3$, 125 MHz) δ_C (ppm): 21.33, 25.71, 48.56, 110.16, 111.56, 116.53, 124.06, 140.48, 142.44, 143.55, 148.14, 168.28, 169.66, 170.10.

8b. M.p. 185-188 °C; GC/MS: 273 (M$^+$). IR (KBr) (ν_{max}, cm^{-1}): 3448, 3361, 3267, 3199, 1702, 1673, 1632; ^{1}H NMR (CDC1$_3$, 500 MHz) δ_H (ppm): 2.31 (3H, CH$_3$, s), 7.16-7.53 (4H, m, arom), 8.07 (4H, s, NH, OH). ^{13}C NMR (CDC1$_3$, 125 MHz) δ_C (ppm): 22.93, 49.66, 110.48, 111.33, 117.28, 122.96, 141.08, 142.99, 143.67, 148.93, 168.84, 169.12, 172.17.

8c. M.p. > 300 °C; GC/MS: 395 (M$^+$). IR (KBr) (ν_{max}, cm^{-1}): 3448, 3459, 3229, 1729, 1671, 1639; ^{1}H NMR (CDC1$_3$, 500 MHz) δ_H (ppm): 7.09-7.96 (14H, m, arom), 7.84 (3H, s, NH). ^{13}C NMR (CDC1$_3$, 125 MHz) δ_C (ppm): 48.56, 110.16, 111.57, 111.68, 112.56, 112.69, 112.98, 113.09, 114.01, 114.29, 114.56, 115.01, 115.29, 115.63, 116.12 116.41, 124.11, 140.93, 143.56, 144.65, 147.18, 169.36, 169.66, 171.52.

8d. M.p. > 300 °C; GC/MS: 350 (M$^+$). IR (KBr) (ν_{max}, cm^{-1}): 3425, 3412, 3199, 1716, 1669, 1622, 1252, 998. ^{1}H NMR (CDC1$_3$, 500 MHz) δ_H (ppm): 2.36 (3H, CH$_3$, s), 2.77 (3H, CH$_3$, s), 7.19-7.89 (3H, m, arom), 7.69 (3H, s, NH). ^{13}C NMR (CDC1$_3$, 125 MHz) δ_C (ppm): 21.55, 25.96, 48.96, 110.99, 111.27, 117.61, 127.19, 147.33, 144.57, 146.82, 149.93, 169.23, 171.66, 172.29.

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