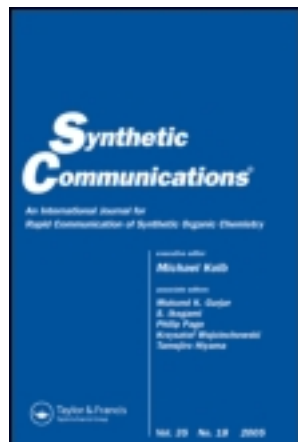


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Novel One-Pot Synthesis of New Oxindole Derivatives Catalyzed by PTSA

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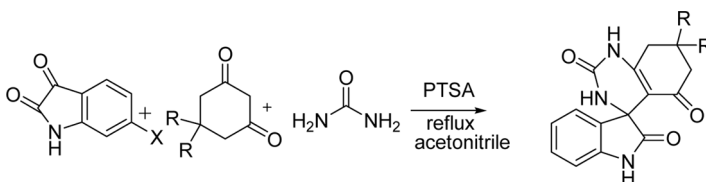
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NOVEL ONE-POT SYNTHESIS OF NEW OXINDOLE DERIVATIVES CATALYZED BY PTSA

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GRAPHICAL ABSTRACT



Abstract The one-pot synthesis of spirooxindoles via three-component reaction of urea, isatin, and 1,3-dicarbonyl compounds in the presence of a catalytic amount of *p*-toluenesulfonic acid in acetonitrile has been carried out.

Keywords Isatin; spirooxindoles; *p*-toluenesulfonic acid

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 excellent yields, have attracted considerable attention in recent years because they are performed without need to isolate the any intermediate during the processes, and this reduces time and saves both energy and raw materials.^[13] There has been tremendous development in three- or four-component reactions, especially the Bignelli,^[14] Passerini,^[15] Ugi,^[16] and Mannich^[17] reactions, which have led to a renaissance of MCRs. MCRs have emerged as valuable tools for the preparation of structurally diverse chemical libraries of drug-like

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heterocyclic compounds.^[18–20] Nevertheless, great efforts have been and still are being made to find and develop new MCRs.

As part of our program aimed at developing new methods for the preparation of new compounds via MCRs,^[21] herein, we describe the use of *p*-toluenesulfonic acid (PTSA) as a catalyst for the synthesis of spirooxindoles **7** and **8** (Scheme 1).

In a typical procedure, urea (1 mmol), isatin (1 mmol), and dimesone (1 mmol) in the presence of a catalytic amount of PTSA in CH₃CN at reflux temperature afforded the desired spirooxindoles (**7a**) in 90% yield after 6 h (entry 4, Table 1). To the best of our knowledge, there are no reports on the synthesis of these compounds.

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.

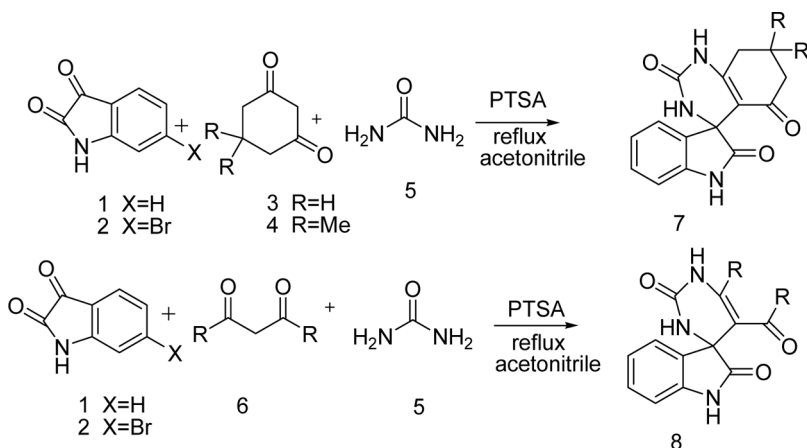
From these results, it was decided that refluxing temperature would be the best temperature for all reactions. In each reaction, the yield is a function of the reaction time, and the best time for all reactions was completed after 6 h. The reaction proceeds very cleanly under reflux condition and is free of side products.

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 CH₃CN, chloroform, ethanol, and CH₂Cl₂, and the best results in terms of yield and time were obtained in CH₃CN.

We evaluated the amount of PTSA required for this transformation and found that as little as 5 mol% of PTSA catalyzed the reaction to some extent, but a longer reaction time (>6 h) was required. The use of an increased amount of catalyst did not improve the yield significantly.

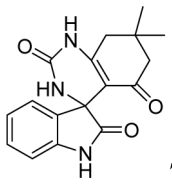
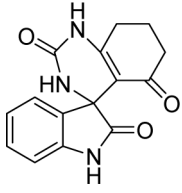
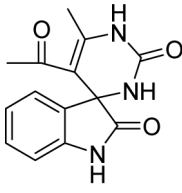
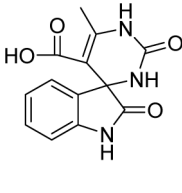
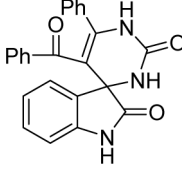
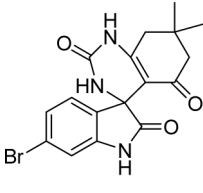
The yields of the reactions decreased when mineral acids were used.

In conclusion, we have described a highly efficient procedure for the preparation of spirooxindoles using PTSA as a catalyst in good yield. Moreover, the procedure offers several advantages including excellent yields, operational



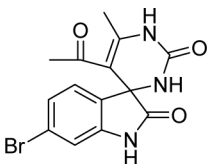
Scheme 1.

Table 1. Synthesis of spirooxindoles catalyzed by PTSA

Entry	X	1,3-Dicarbonyl compounds	Product	Yield (%) ^a		
				25 °C	40 °C	82 °C
1	H	Dimedone	 7a	55	85	92
2	H	1,3-Cyclohexandione	 7b	50	75	91
3	H	Acetyl acetone	 8a	45	70	91
4	H	Ethyl acetoacetate	 8b	45	72	90
5	H	1,3-Diphenyl-1,3-propanedione	 8c	50	79	90
6	Br	Dimedone	 7c	50	77	93

(Continued)

Table 1. Continued

Entry	X	1,3-Dicarbonyl compounds	Product	Yield (%) ^a		
				25 °C	40 °C	82 °C
7	Br	Acetyl acetone	 8d	43	70	92

^aIsolated yields.Table 2. Comparison of various catalysts for the synthesis of **7a**

Entry	Catalyst	Yield (%)
1	PTSA	92
2	HClO ₄	80
3	H ₂ SO ₄	85
4	HCl	82

simplicity, clean reaction, minimal environmental impact, and low cost, which make it a useful and attractive process for the synthesis of these compounds.

EXPERIMENTAL

Preparation of Spirooxindoles: Typical Procedure

A mixture of the 1,3-dicarbonyl compounds (1 mmol), isatin (1 mmol), urea (1 mmol), and PTSA (5 mol%) in acetonitrile (5 mL) was refluxed for 6 h. The progress of the reaction was monitored by thin-layer chromatography (TLC; ethyl acetate–hexane 1:3). On completion, the reaction mixture was washed with diethyl ether, and the precipitate that formed was filtered to give the pure product.

Selected Data

Compound 7a. Mp: 183–185 °C; GC/MS: 311 (M⁺). IR (KBr) (ν_{\max} , cm⁻¹): 3397, 3347, 3125, 1684, 1670, 1632; ¹H NMR (CDCl₃, 500 MHz) δ_{H} (ppm): 1.02 (3H, CH₃, s), 1.11 (3H, CH₃, s), 2.12 (2H, CH₂, s), 2.56 (2H, CH₂, s), 7.03–7.65 (4H, m, arom), 7.89 (3H, s, NH). ¹³C NMR (CDCl₃, 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.

Compound 7b. Mp: 199–201 °C; GC/MS: 283 (M⁺). IR (KBr) (ν_{\max} , cm⁻¹): 3367, 3354, 3200, 1655, 1642, 1629; ¹H NMR (CDCl₃, 500 MHz) δ_{H} (ppm): 2.25 (2H, CH₂, m), 3.00 (2H, CH₂, m), 3.51 (2H, CH₂, m), 7.01–7.71 (4H, m, arom), 8.01 (3H, s, NH). ¹³C NMR (CDCl₃, 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.

Compound 7c. Mp: 189–191 °C; GC/MS: 390 (M⁺). IR (KBr) (ν_{\max} , cm⁻¹): 3387, 3366, 3205, 1674, 1665, 1622; ¹H NMR (CDCl₃, 500 MHz) δ_{H} (ppm): 1.00 (3H, CH₃, s), 1.10 (3H, CH₃, s), 2.40 (2H, CH₂, s), 3.01 (2H, CH₂, s), 7.10–7.50 (3H, m, arom), 8.30 (3H, s, NH). ¹³C NMR (CDCl₃, 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.

Compound 8a. Mp > 300 °C; GC/MS: 271 (M⁺). IR (KBr) (ν_{\max} , cm⁻¹): 3419, 3400, 3194, 1706, 1661, 1611; ¹H NMR (CDCl₃, 500 MHz) δ_{H} (ppm): 2.29 (3H, CH₃, s), 2.51 (3H, CH₃, s), 7.11–7.40 (4H, m, arom), 7.51 (3H, s, NH). ¹³C NMR (CDCl₃, 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.

Compound 8b. Mp: 185–188 °C; GC/MS: 273 (M⁺). IR (KBr) (ν_{\max} , cm⁻¹): 3448, 3267, 3199, 1702, 1673, 1632; ¹H NMR (CDCl₃, 500 MHz) δ_{H} (ppm): 2.31 (3H, CH₃, s), 7.16–7.53 (4H, m, arom), 8.07 (4H, s, NH, OH). ¹³C NMR (CDCl₃, 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.

Compound 8c. Mp > 300 °C; GC/MS: 395 (M⁺). IR (KBr) (ν_{\max} , cm⁻¹): 3448, 3459, 3229, 1729, 1671, 1639; ¹H NMR (CDCl₃, 500 MHz) δ_{H} (ppm): 7.09–7.96 (14H, m, arom), 7.84 (3H, s, NH). ¹³C NMR (CDCl₃, 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.

Compound 8d. Mp > 300 °C; GC/MS: 350 (M⁺). IR (KBr) (ν_{\max} , cm⁻¹): 3425, 3412, 3199, 1716, 1669, 1622, 1252, 998. ¹H NMR (CDCl₃, 500 MHz) δ_{H} (ppm): 2.36 (3H, CH₃, s), 2.77 (3H, CH₃, s), 7.19–7.89 (3H, m, arom), 7.69 (3H, s, NH). ¹³C NMR (CDCl₃, 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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