

One-Pot, Pseudo Four-Component Synthesis of a Spiro[diindeno[1,2-*b*:2',1'-*e*]pyridine-11,3'-indoline]-trione Library

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Received August 22, 2009

A one-pot, pseudo four-component method for the efficient and simple synthesis of spiro[diindeno[1,2-*b*:2',1'-*e*]pyridine-11,3'-indoline]-2',10,12-trione derivatives in refluxing acetonitrile is reported. The features of this procedure are mild reaction conditions, high yields of products, and operational simplicity.

1. Introduction

Multicomponent reactions (MCRs), in which multiple reactions are combined into the synthetic operation, have been used extensively to form carbon–carbon bonds in synthetic chemistry.¹ Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. In the past decade, there has been tremendous development in three- and four-component reactions, and great efforts continue to be made to develop new MCRs.² In this context, heterocycles containing an indenone moiety show interesting features that make them attractive for use in MCRs.

Indenone-fused heterocycles represent important biological and medicinal scaffolds. Thus, the indenopyridine skeleton is present in the 4-azafluorenone group of alkaloids, represented by its simplest member onychnine (Figure 1).³ Indenopyrazoles (**A**) and indenopyridazines (**B**) have been investigated as cyclin-dependent kinase⁴ and selective monoamine oxidase B (MAO-B)⁵ inhibitors, respectively.

Further, indenopyridines (**C**) exhibit cytotoxic,^{6a} phosphodiesterase inhibitory,^{6b} adenosine A2a receptor antagonistic,^{6c} antiinflammatory/antiallergic,^{6d} coronary dilating,^{6e} and calcium modulating activities.^{6f} These compounds have also been investigated for the treatment of hyperlipoproteinemia and arteriosclerosis,^{6g} as well as neurodegenerative diseases.^{6h} Lastly, indenopyridone NSC 314622 is serving as a lead compound for the development of anticancer agents targeting topoisomerase I. Its polycyclic planar structure allows for DNA intercalation and inhibition of DNA religation by topoisomerase I in a manner similar to the polycyclic natural product camptothecin and its clinically useful derivative topotecan.⁷

The indole moiety is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents.⁸ Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives can highly

enhance biological activity.⁹ The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.¹⁰ For example, spirotryprostatin A and B, two natural alkaloids isolated from the fermentation broth of *Aspergillus fumigatus*, have been identified as novel inhibitors of microtubule assembly,^{10d} and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors (Figure 1).^{10a}

Considering the above reports, and as part of our program aimed at developing new methodologies for the preparation of heterocyclic compounds,¹¹ very recently, we have reported some procedures for the synthesis of spirooxindole fused heterocycles.¹² We are currently investigating the synthesis of various spiro[diindeno[1,2-*b*:2',1'-*e*]pyridine-11,3'-indoline]-2',10,12-triones via a facile, atom-economical, and one-pot pseudo four-component condensation reaction.

2. Results and Discussion

The choice of an appropriate reaction media is of crucial importance for successful synthesis. Initially, the pseudo four-component reaction of 1,3-indandione **1**, aniline **2a**, and isatin

Table 1. Model Reaction, Conditions, and Yields^a

entry	conditions	catalyst (mol %)	time (h)	yield (%)
1	CHCl ₃ (reflux)	<i>p</i> -TSA (30)	4	<30
2	water (reflux)	<i>p</i> -TSA (30)	4	<30
3	CH ₃ CN (reflux)	<i>p</i> -TSA (20)	1	74
4	CH ₃ CN (reflux)	<i>p</i> -TSA (30)	1	81
5	CH ₃ CN (reflux)	<i>p</i> -TSA (40)	1	82
6	CH ₃ CN (reflux)		10	<30
7	CH ₃ CN/ r.t.	<i>p</i> -TSA (30)	10	<40
8	EtOH (reflux)	<i>p</i> -TSA (30)	1	60
9	MeOH (reflux)	<i>p</i> -TSA (30)	1	53
10	CH ₃ CN (reflux)	LiCl (30)	1	<30
11	CH ₃ CN (reflux)	ZnCl ₂ (30)	1	<30
12	CH ₃ CN (reflux)	AlCl ₃ (30)	1	66

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^a 1,3-Indandione (2 mmol), aniline (1 mmol), isatin (1 mmol).

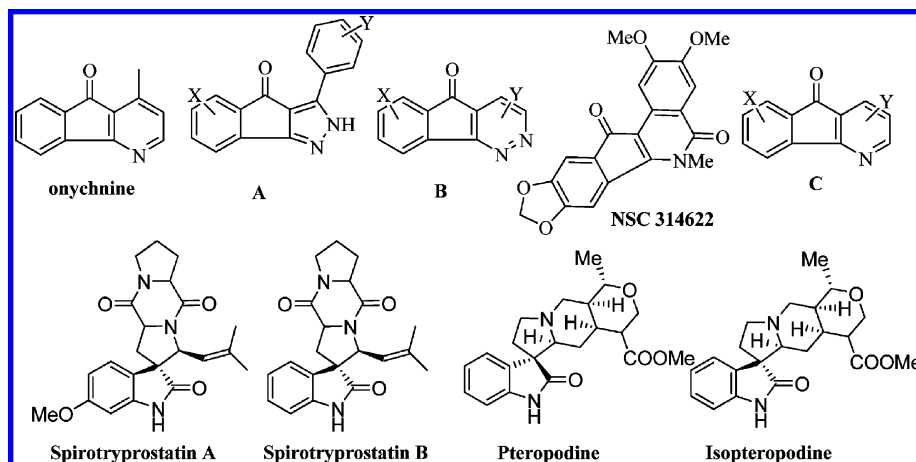
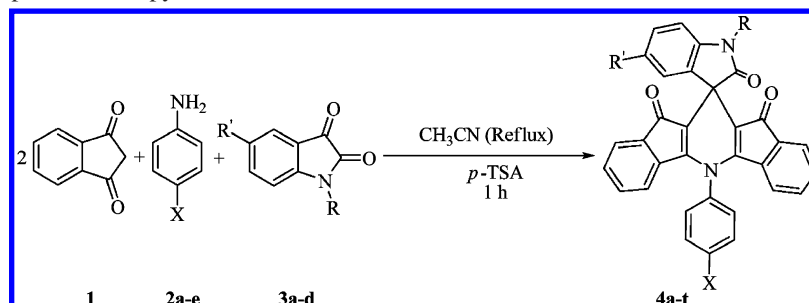
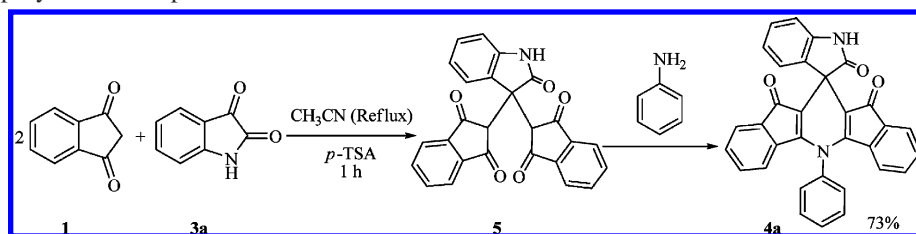


Figure 1. Representatives of important indenone-fused heterocycles and spirooxindoles.

Scheme 1. Synthesis of Spiro[diindenopyridine-indoline]-triones **4**



Scheme 2. Two-Step Synthesis of Spirooxindole **4a**



3a as a simple model substrate was investigated to establish the feasibility of the strategy and optimize the reaction conditions. Different solvents in the presence of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and available catalyst and various Lewis acids were screened in the model reaction. As can be seen from Table 1, in the presence of *p*-TSA, acetonitrile is the solvent of choice for the reaction, and the desired product is obtained in excellent yields and high purity (Entry 3), while without *p*-TSA and over long period of time (10 h) the yield of product was very low (Entry 4).

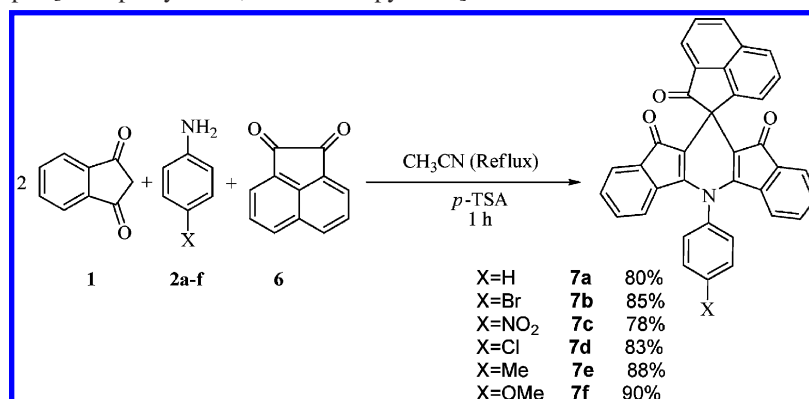
Encouraged by this success, we extended this reaction of 1,3-indandione **1** with a range of other aromatic amines **2a–e** and isatins **3a–d** with both electron withdrawing and electron releasing substituents under similar conditions (MeCN, *p*-TSA), and corresponding spiro[diindenopyridine-11,3'-indoline]-2',10,12-triones **4a–t** were synthesized in high yields (Scheme 1). We have shown that the use of a wide diversity of substituents in aromatic amines **2** and isatins **3** in this pseudo four-component reaction makes possible the synthesis of libraries under similar circumstances (Table 2).

The reaction proceeds very cleanly under mild conditions and is compatible with a wide range of functional groups. In addition, the advantage of such methodology is that products sedimented from the reaction medium after cooling it to room temperature and spirooxindoles **4** were obtained with high purity.

When this reaction was carried out with aliphatic amines such as *n*-propylamine or ethylamine, TLC and ¹H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products; the yield of the expected product was very poor.

Given the large number of commercially available isatins and aromatic amines, the present method should be applicable to synthesis of libraries with high diversity. We expect this method to find extensive application in the field of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

For the investigation of the reaction mechanism, it is notable that when 1,3-indandione **1** and isatin **3a** were reacted for 1 h, the intermediate **5** was isolated and characterized by spectroscopic methods. When intermediate **5** and aniline **2a** were reacted in the presence of *p*-TSA under the same

Scheme 3. Synthesis of Spiro[acenaphthylene-1,11'-diindenopyridine]-triones **7**Table 2. Spiro[diindenopyridine-indoline]-triones **4**

compound 4	X	R'	R	yield (%) ^a
a	H	H	H	82
b	Br	H	H	85
c	NO ₂	H	H	80
d	Me	H	H	90
e	OMe	H	H	92
f	H	H	Me	78
g	Br	H	Me	78
h	NO ₂	H	Me	75
i	Me	H	Me	84
j	OMe	H	Me	87
k	H	Br	H	80
l	Br	Br	H	80
m	NO ₂	Br	H	76
n	Me	Br	H	85
o	OMe	Br	H	88
p	H	NO ₂	H	84
q	Br	NO ₂	H	82
r	NO ₂	NO ₂	H	77
s	Me	NO ₂	H	88
t	OMe	NO ₂	H	91

^a Isolated yields.

reaction conditions, the product **4a** was obtained in 73% yield (Scheme 2). According to the results, a reasonable possibility for the formation of spiro[diindenopyridine-indoline]-triones **4** is shown in the Supporting Information.

As expected, when the isatin **3** was replaced by acenaphthylene-1,2-dione **6**, 5'-aryl-2*H*,5'*H*-spiro[acenaphthylene-1,11'-diindenopyridine]-2,10',12'-triones **7a–f** was obtained in good yield under the same reaction conditions (Scheme 3).

Compounds **4** and **7** are stable solids whose structures were established by IR, ¹H NMR, ¹³C NMR spectroscopy, and elemental analysis.

In conclusion, an efficient, atom-economical, and simple method for the preparation of spiro[diindenopyridine-indoline]-triones and spiro[acenaphthylene-diindenopyridine]-triones using readily available starting materials is reported. Prominent among the advantages of this new method are operational simplicity, good yields in short reaction times, and easy workup procedures employed.

Typical Procedure for Preparation of 5-Phenyl-5*H*-spiro[diindenopyridine-11,3'-indoline]-2',10,12-trione (4a**).** A mixture of 1,3-indandione (0.30 g, 2 mmol), aniline (0.09 g, 1 mmol), isatin (0.15 g, 1 mmol), and *p*-TSA (30 mol %) in refluxing acetonitrile (5 mL) was stirred for 30 min. After completion of the reaction confirmed by TLC (eluent: EtOAc/*n*-hexane, 1:3), the reaction mixture was

cooled to room temperature. Then, the precipitated product was filtered and washed with water (10 mL) and ethanol (5 mL) to afford the pure product **4a** as a red powder (0.39 g, 82%); mp >300 °C. IR (KBr) (ν_{max} /cm⁻¹): 3437, 3132, 1703, 1624. ¹H NMR (300 MHz, DMSO-*d*₆): δ_{H} (ppm) 5.46 (2H, d, ³*J*_{HH} = 6.0 Hz, H–Ar), 6.45–8.14 (15H, m, H–Ar), 10.65 (1H, s, NH). ¹³C NMR (75 MHz, DMSO-*d*₆): δ_{C} (ppm) 46.1, 109.5, 111.9, 121.8, 121.9, 122.7, 124.9, 125.9, 128.5, 129.0, 130.7, 132.1, 132.8, 134.8, 136.5, 138.2, 142.6, 156.2, 178.0, 190.0. Anal. Calcd for C₃₂H₁₈N₂O₃: C, 80.32; H, 3.79; N, 5.85. Found: C, 80.41; H, 3.71; N, 5.76.

Acknowledgment. We gratefully acknowledge financial support from the Research Council of Shahid Beheshti University.

Supporting Information Available. Experimental procedures, and IR, ¹H NMR, and ¹³C NMR spectra for compounds **4** and **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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CC900130A