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Grindstone chemistry: one-pot synthesis of spiro[diindenopyridine-indoline] triones and spiro[acenaphthylene-diindenopyridine]triones

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ABSTRACT

A one-pot, pseudo four-component, and simple synthesis of spiro[diindenopyridine-indoline]triones and spiro[acenaphthylene-diindenopyridine]triones via the reaction of 1,3-indandione, aromatic amines and isatins or acenaphthylene-1,2-dione using a 'Grindstone Chemistry' method is reported.

Indenopyridine derivatives represent important biological and medicinal scaffolds. The indenopyridine skeleton is present in the 4-azafluorenone group of alkaloids, represented by its simplest member onychnine (Fig. 1).[1] Indenopyrazoles **A** and indenopyridazines **B** have been investigated as cyclin-dependent kinase[2] and selective monoamine oxidase B (MAO-B)[3] inhibitors, respectively. Indenopyridines **C** exhibit cytotoxic,[4a] phosphodiesterase inhibitory,[4b] adenosine A2a receptor antagonistic,[4c] antiinflammatory/antiallergic,[4d] coronary dilating[4e], and calcium-modulating activities.[4f] These compounds have also been investigated for the treatment of hyperlipoproteinemia and arteriosclerosis[4g] as well as neurodegenerative diseases.[4h]

Indole and indoline are important fragments of a large number of natural products and medicinal agents,[5] and several indolines, spiro-annulated with heterocycles at the 3-position, have shown good biological activity.[6–8] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[9–11] For example, spirotryprostatins A and B, two natural alkaloids isolated from the fermentation broth of *Aspergillus fumigatus*, have been identified as novel inhibitors of microtubule assembly.[11] As a consequence, a number of methods have been reported for the preparation of spirooxindole-fused heterocycles.[12–17]

Recently, the 'Grindstone Chemistry' technique has been used as a green and rapid method for the synthesis of organic compounds.[18,19] The 'Grindstone Chemistry' procedure is a slight modification of a method described by Toda et al. who demonstrated that many reactions can be performed in high yields by simply grinding two or more solids together.[20] These reactions were usually carried out on a very small scale in an agate mortar and grinding with a pestle. Bose et al. extended this approach to chemical reactions on large scale, a method they termed a 'Grindstone Chemistry' modified approach.[18]

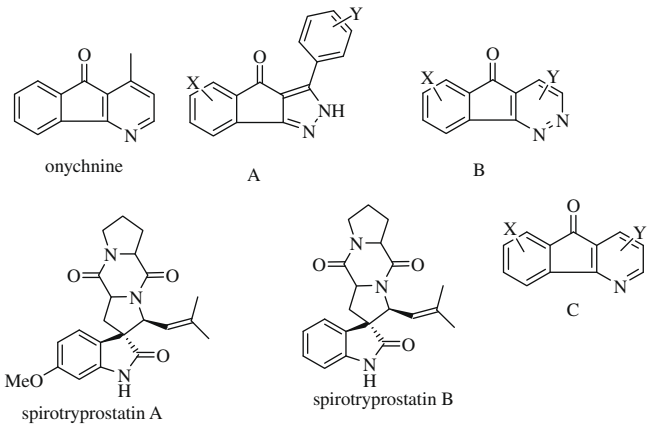

Figure 1. Representative important indenone-fused heterocycles and spirooxindoles.

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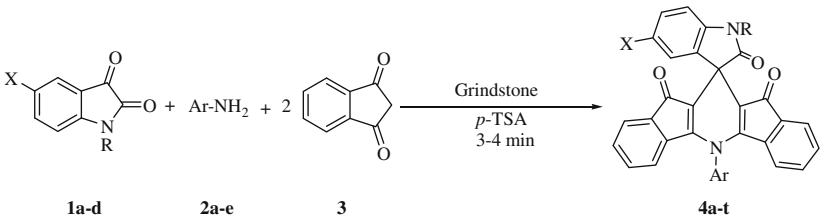


Scheme 1. One-pot synthesis of spirodiindenopyridine-indolines **4**.

Table 1
Spiro[diindenopyridine-indoline]triones **4**

Product	Ar	X	R	Yield[a] (%)
4a	C_6H_5	H	H	85
4b	4-Br–C_6H_4	H	H	82
4c	4-O_2N–C_6H_4	H	H	87
4d	4-Me–C_6H_4	H	H	89
4e	4-MeO–C_6H_4	H	H	90
4f	C_6H_5	H	Me	81
4g	4-Br–C_6H_4	H	Me	84
4h	4-O_2N–C_6H_4	H	Me	80
4i	4-Me–C_6H_4	H	Me	88
4j	4-MeO–C_6H_4	H	Me	86
4k	C_6H_5	Br	H	83
4l	4-Br–C_6H_4	Br	H	84
4m	4-O_2N–C_6H_4	Br	H	90
4n	4-Me–C_6H_4	Br	H	91
4o	4-MeO–C_6H_4	Br	H	87
4p	C_6H_5	NO_2	H	90
4q	4-Br–C_6H_4	NO_2	H	86
4r	4-O_2N–C_6H_4	NO_2	H	87
4s	4-Me–C_6H_4	NO_2	H	91
4t	4-MeO–C_6H_4	NO_2	H	82

[a] Isolated yield, reaction time = 3–4 min.

In 'Grindstone Chemistry', exothermic reactions can be performed by grinding the reactants together for a few minutes without using any organic solvent; apparently this method is not very effective for endothermic reactions. Since spirodiindenopyridine-indoline formation is an exothermic reaction, and as part of our program aimed toward the preparation of heterocyclic compounds,[21–29] especially spirooxindoles,[30–34] we report herein the synthesis of spiro[diindenopyridine-indoline]triones and spiro[acenaphthylene-diindenopyridine]triones via 'Grindstone Chem istry'.

In a pilot experiment,[35] a mixture of isatin **1a** (10 mmol), aniline **2a** (10 mmol), and 1,3-indanedione **3** (20 mmol) in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) (an inexpensive and readily available catalyst) was ground using a mortar and pestle of appropriate size (Scheme 1). Grinding for about 3–4 min led to red colored 5-phenyl-5*H*-spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridin-11,3′-indoline]-2′,10,12-trione **4a** in 85% yield. The reaction was performed at ambient temperature during which almost a 10 °C increase in temperature was observed. This increase in reaction temperature indicated that spirodiindenopyridine-indoline formation was an exothermic process.

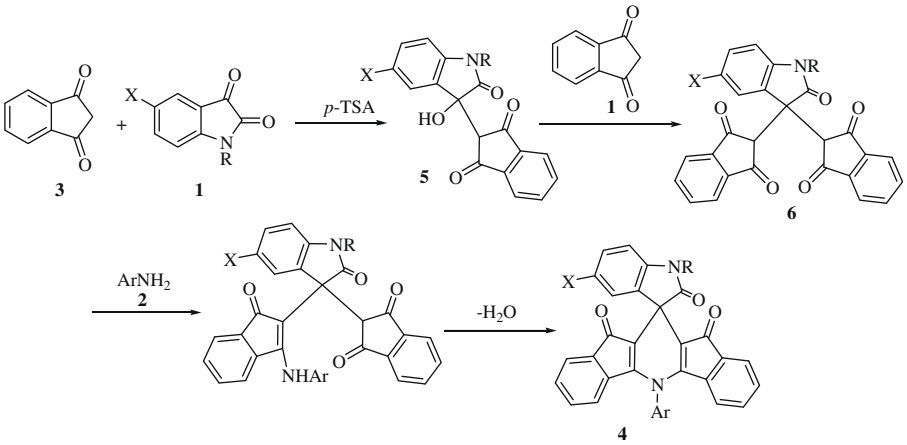
Next, to delineate the scope of this approach, particularly with regard to library construction, this method was evaluated using four substituted isatins **1a–d**, five substituted anilines **2a–e**, and 1,3-indanedione **3**. The corresponding spiro[diindeno[1,2-*b*:2′,1′-*e*]pyridin-11,3′-indoline]-2′,10,12-triones **4a–t** were obtained in good yields under similar conditions, (Table 1). The reaction proceeds very cleanly under mild conditions and is compatible with a wide range of functional groups.

The ^1H and ^{13}C NMR spectra of the crude products indicated the formation of spirooxindole-fused diindenopyridines **4**. The nature of these compounds as 1:1:2 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at the appropriate *m/z* value. Compounds **4a–t** are stable solids whose structures were established by IR, ^1H and ^{13}C NMR spectroscopy, and elemental analysis.

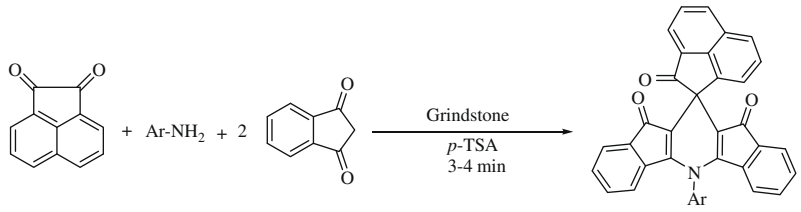
The results were good in terms of yields and product purity in the presence of *p*-TSA, while without *p*-TSA, the yields of products were low (<40%) even after 30 min.

When this reaction was carried out with aliphatic amines such as *n*-propylamine or ethylamine under the same conditions, the TLC and ^1H NMR spectra of the reaction mixtures showed the presence of a combination of starting materials and numerous by-products, the yield of the expected product being very poor.

We have not established an exact mechanism for the formation of spiro[diindenopyridine-indoline]triones **4**, however, a reasonable possibility is shown in Scheme 2. It is thought that product **4** results from initial addition of 1,3-indanedione **3** to the isatin **1**



Scheme 2. Proposed mechanism for the synthesis of spirodiindenopyridine-indolines **4**.



7 2a-e 3 8a-e

Product	Ar	Yield (%) [a]
8a	C_6H_5	87
8b	4-Br-C_6H_4	88
8c	4-O_2N-C_6H_4	82
8d	4-Me-C_6H_4	86
8e	4-MeO-C_6H_4	89

[a] Isolated yield

Scheme 3. One-pot synthesis of spiro[acenaphthylene-diindenopyridine]triones **6**.

to yield intermediate **5**, which reacted further with another molecule of **3**. Finally, addition of the substituted aniline **2** to the intermediate **6**, followed by cyclization afforded the product **4**.

A large-scale synthesis of spiro[diindenopyridine-indoline]trione **4a** was carried out on 100 mmol scale (a total of 60 g) in a large glass bowl. The reaction mixture was ground by a mechanical stirrer for just under five minutes and the desired product was obtained in 85% yield.

To further explore the potential of this protocol for spirooxindole synthesis, we investigated the reaction of anilines **2** and 1,3-indanedione **3** with acenaphthylen-1,2-dione **7**. Spiro[acenaphthylene-diindenopyridine]triones **8a–e** were obtained in good yields (Scheme 3).

In conclusion, we have described an efficient, one-pot, and pseudo four-component method for the synthesis of spiro[diindenopyridine-indoline]triones and spiro[acenaphthylene-diindenopyridine]triones using 'Grindstone chemistry'. Prominent among the advantages of this new method are operational simplicity, good yields of products in short reaction times, and easy work-up procedures.

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35. *Typical procedure for the preparation of 5-phenyl-5H-spiro[diindeno[1,2-b:2′,1′-e]pyridin-11,3′-indoline]-2′,10,12-trione* (**4a**)*:* A mixture of 1,3-indandione (2.92 g, 20 mmol), aniline (0.93 g, 10 mmol), isatin (1.47 g, 10 mmol), and *p*-TSA (0.62 g, 3 mmol) was ground for 3–4 min using a mortar and pestle. After storage at rt for 10 min, the solid was washed with H_2O (20 mL) and EtOH (15 mL) to afford the pure product **4a** as a red powder (4.06 g, 85%); mp >300 °C. IR (KBr) (ν_{max}, cm^{-1}): 3437, 3132, 1703, 1624. ^1H NMR (300 MHz, DMSO-d_6): δ_H = 5.46 (2H, d, $^3J_{HH}$ = 6.0 Hz, H-Ar), 6.45–8.14 (15H, m, H-Ar),

10.65 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C = 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 $C_{32}H_{18}N_2O_3$: C, 80.32; H, 3.79; N, 5.85. Found: C, 80.41; H, 3.71; N, 5.76.Selected characterization data:*5-(4-Bromophenyl)-5H-spiro[diindeno[1,2-b:2′,1′-e]pyridin-11,3′-indoline]-2′,10,12-trione* (**4b**)*:* Red powder (yield 82%); mp >300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3495, 1708, 1629. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 5.56 (2H, d, $^3J_{HH}$ = 6.0 Hz, H-Ar), 6.84–8.15 (14H, m, H-Ar), 10.65 (1H, s, NH). Anal. Calcd for $C_{32}H_{17}BrN_2O_3$: C, 68.95; H, 3.07; N, 5.03. Found: C, 68.92; H, 3.02; N, 4.96.Due to the very low solubility of **4b**, we were unable to obtain ^{13}C NMR data.*1′-Methyl-5-p-tolyl-5H-spiro[diindeno[1,2-b:2′,1′-e]pyridin-11,3′-indoline]-2′,10,12-trione* (**4i**)*:* Red powder (yield 88%); mp >300 °C. IR (KBr) (ν_{max} /cm^{-1}): 3059, 1702, 1614. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.57 (3H, s, CH_3), 3.25 (3H, s, NCH_3), 5.54 (2H, d, $^3J_{HH}$ = 7.4 Hz, H-Ar), 6.97–8.03 (14H, m, H-Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 21.5, 26.9, 45.6, 108.4, 111.6, 121.9, 122.0, 122.7, 124.6, 129.2, 130.1, 130.8, 131.2, 132.7, 132.9, 133.9, 135.6, 136.6, 142.0, 144.0, 156.5, 176.5, 190.0. Anal. Calcd for $C_{34}H_{22}N_2O_3$: C, 80.62; H, 4.38; N, 5.53. Found: C, 80.53; H, 4.31; N, 5.44.*5′-Bromo-5-phenyl-5H-spiro[diindeno[1,2-b:2′,1′-e]pyridin-11,3′-indoline]-2′,10,12-trione* (**4k**)*:* Red powder (yield 83%); mp >300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3342, 3064, 1729, 1694. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 5.45 (2H, d, $^3J_{HH}$ = 7.2 Hz, H-Ar), 6.83–8.24 (14H, m, H-Ar), 10.80 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 46.3, 111.2, 111.4, 113.9, 121.9, 122.0, 127.8, 130.2, 130.7, 130.9, 131.7, 132.1, 132.7, 132.9, 136.5, 136.9, 138.2, 142.0, 156.6, 177.7, 190.0. Anal. Calcd for $C_{32}H_{17}BrN_2O_3$: C, 68.95; H, 3.07; N, 5.03. Found: C, 68.83; H, 3.13; N, 5.10.*5-(4-Methoxyphenyl)-5′-nitro-5H-spiro[diindeno[1,2-b:2′,1′-e]pyridin-11,3′-indoline]-2′,10,12-trione* (**4t**)*:* Red powder (yield 82%); mp >300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3301, 3064, 1740, 1698. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.96 (3H, s, OCH_3), 5.61 (2H, d, $^3J_{HH}$ = 6.6 Hz, H-Ar), 7.08–8.43 (13H, m, H-Ar), 11.40 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 46.2, 56.2, 109.6, 110.5, 115.5, 115.7, 120.9, 122.0, 122.3, 126.6, 130.6, 131.0, 131.2, 131.7, 132.7, 133.1, 135.4, 136.6, 143.0, 149.2, 157.6, 161.5, 190.1. Anal. Calcd for $C_{33}H_{19}N_3O_6$: C, 71.61; H, 3.46; N, 7.59. Found: C, 71.70; H, 3.52; N, 7.65.*5′-Phenyl-5′,5a′-dihydro-2H,4b′H-spiro[acenaphthylene-1,11′-diindeno[1,2-b:2′,1′-e]pyridin]-2,10′,12′(10a′H,11a′H)-trione* (**8a**): Red powder (yield 87%); mp >300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3442, 1725, 1687, 1621. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 5.48 (2H, d, $^3J_{HH}$ = 7.2 Hz, H-Ar), 7.09–8.32 (17H, m, H-Ar). Anal. Calcd for $C_{36}H_{19}NO_3$: C, 84.20; H, 3.73; N, 2.73. Found: C, 84.33; H, 3.67; N, 2.65.Due to the very low solubility of **8a**, we were unable to obtain ^{13}C NMR data.*5′-p-Tolyl-5′,5a′-dihydro-2H,4b′H-spiro[acenaphthylene-1,11′-diindeno[1,2-b:2′,1′-e]pyridin]-2,10′,12′(10a′H,11a′H)-trione* (**8d**)*:* Red powder (yield 86%); mp >300 °C. IR (KBr) (ν_{max} /cm^{-1}): 3500, 1697, 1619, 1610. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.57 (3H, s, CH_3), 5.56 (2H, d, $^3J_{HH}$ = 7.4 Hz, H-Ar), 7.14–8.33 (16H, m, H-Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 21.3, 50.9, 109.7, 113.1, 113.5, 117.3, 121.1, 121.8, 122.0, 125.2, 128.9, 129.2, 129.9, 130.6, 131.0, 131.8, 132.6, 132.8, 135.7, 136.7, 141.2, 142.0, 156.6, 158.0, 158.6, 159.1, 159.6, 190.3, 204.5, 206.7. Anal. Calcd for $C_{37}H_{21}NO_3$: C, 84.23; H, 4.01; N, 2.65. Found: C, 84.10; H, 3.94; N, 2.71.