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ORIGINAL PAPER

Solvent-free multicomponent assembling of isatins, malononitrile, and dimedone: fast and efficient way to functionalized spirooxindole system

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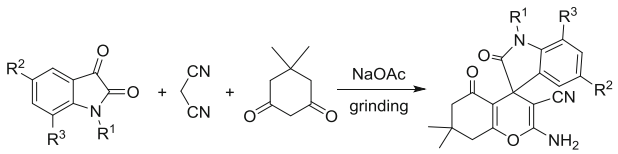
Abstract Solvent-free sodium acetate catalyzed multicomponent reaction of isatins, malononitrile, and dimedone initiated by grinding in mortar results in the fast and efficient formation of substituted spirooxindoles in 90–99 % yields. The developed solvent-free fast multicomponent approach to the substituted spirooxindoles—the pharmacologically perspective substances with spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic activities—is beneficial from the viewpoint of diversity-oriented large-scale processes and represents fast efficient and environmentally benign solvent-free synthetic concept for multicomponent reactions strategy.

Graphical abstract



Keywords Solvent-free · Catalysis · Carbanions · Cyclization · Heterocycles · Green chemistry

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Introduction

The multicomponent reactions (MCRs) are known as a new simple and efficient methodology to produce biologically active compounds and has become an important area of research in organic, combinatorial, and medicinal chemistry [1]. The MCR strategy offers significant advantages over conventional linear-type synthesis due to its flexible, convergent, and atom efficient nature [2, 3]. Thus, the success of combinatorial chemistry in drug discovery process is considerably dependent on further advances in heterocyclic MCR methodology and, according to the current synthetic requirements of 'green chemistry', environmentally benign solvent-free multicomponent procedures are particularly welcome.

The heterocyclic spirooxindole ring system is a widely distributed structural framework in a number of pharmaceuticals and natural products [4], including such cytostatic alkaloids as spirotryprostatins A, B, and strychnophylline [5]. The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole compounds have made them attractive synthetic targets [6–8]. Among the oxygen-containing heterocycles spiro-fused with oxindole ring system, 4*H*-chromenes are of particular utility as they belong to 'privileged medicinal scaffolds'—certain molecular frameworks serving for the generation of ligands for functionally and structurally discreet biological receptors [9, 10]. Functionally substituted 4*H*-chromenes have received considerable attention due to their useful biological properties, which include spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic activities [11–13]. The current interest to 5,6,7,8-tetrahydro-4*H*-chromene derivatives bearing nitrile functionality, especially to 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-

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3-carbonitriles, arises from their potential application in the treatment of human neurodegenerative disorders [14, 15].

In recent years, multicomponent condensation reactions have been reported for the synthesis of spirooxindoles via condensation of isatin, 1,3-cyclic diketones, and malononitrile under different catalytic conditions [16–21]. Among the catalysts are tetrabutylammonium fluoride (10 mol%) [16] (2008), sodium stearate (12 mol%) (2010) [17], lipase from porcinepancreas (20 mol%) (2011) [18], triphenylphosphine (10 mol%) (2012) [19], SBA-15-DABCO (10 mol%) (2014) [20], and even $HAuCl_4$ (5 mol%) in polyethylene glycol as solvent (2012) [21]. Multicomponent condensation under catalytic conditions and ultrasound irradiation was also used to ensure decreasing reaction time of this process to 10–20 min [22–24]. Electrocatalytic variant for this process is also known [25] as well as non-catalytic process by reflux reagents in propanol [26].

The demand for both clean and efficient chemical syntheses in the last decade is becoming more urgent. Thus, solvent-free multicomponent reactions are one of the most usual solutions to modernize classical procedures by making them cleaner, safer and easier to perform. It is often claimed that the best solvent is no solvent [27].

The only known solvent-free process for synthesis of spirooxindole uses complex ZnO nano-rods catalyst especially prepared by multistep procedure from $Zn(OAc)_2$ and PEG 2000 by the action of ammonium hydroxide in deionized water (reflux, 6 h) [28]. The crude catalyst was centrifuged and washed twice with deionized water and absolute ethanol. Then, again deionized water was added and the mixture was refluxed for the additional 9 h. At the final step, catalyst was dried at 100 °C in an oven over the night. But in the end of this solvent-free procedure, ethanol is needed for isolation and crystallization desired spirooxindoles [28].

Thus, each of the known procedures for the synthesis of corresponding spiro[4*H*-chromene-4,3′-oxindole] system from isatin, 1,3-cyclic diketones, and malononitrile has its merits; however, fast, facile, and efficient solvent-free multicomponent method for this process has yet to be developed.

Considering our results on the 'solvent-free' multicomponent transformations of carbonyl compounds and C–H acids [29–36] as well as the certain biomedical application of spirooxindoles mentioned above, we were prompted to design a convenient fast and facile 'solvent-free' methodology for the efficient synthesis of substituted spirooxindoles based on multicomponent assembling of isatins, malononitrile, and dimedone.

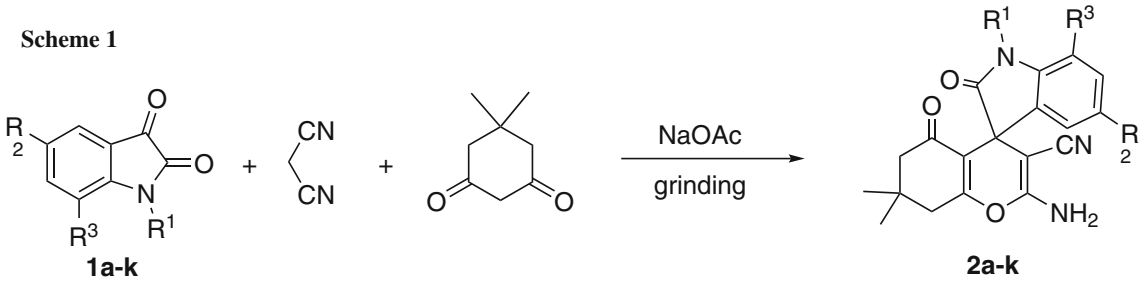
Results and discussion

As it follows from introduction, we were interested in designing a 'one-pot' fast convenient and facile 'solvent-free' methodology for the efficient synthesis of functionalized spirooxindole system based on isatins **1a**–**1k**, malononitrile, and dimedone assembling (Scheme 1; Tables 1 and 2).

On the first stage of our research, the direct transformation of isatin **1a**, malononitrile, and dimedone into 2-amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (**2a**) by grinding in mortar without any catalyst and solvent was studied (Table 1, entries 1 and 2).

Under these simple conditions, spirooxindole **2a** was obtained in 79 and 90 % yields, respectively, in 15 and 30 min reaction time. With 10 mol% of KF or NaOAc as catalysts, 15 min reaction time is sufficient to ensure 92 and 95 % yields of **2a** (Table 1, entries 3 and 4). Addition

Scheme 1



a: R^1 = H, R^2 = H, R^3= H
b: R^1 = H, R^2 = Cl, R^3 = H
c: R^1 = H, R^2 = Br, R^3 = H
d: R^1 = H, R^2 = NO_2, R^3 = H
e: R^1 = H, R^2 = Me, R^3 = Me
f: R^1 = H, R^2 = Br, R^3 = Br
g: R^1 = Me, R^2 = H, R^3 = H
h: R^1 = 4-Cl-Bn, R^2 = H, R^3 = H
j: R^1 = Ac, R^2 = H, R^3 = H
k: R^1 = Ts, R^2 = H, R^3 = H

Scheme 2

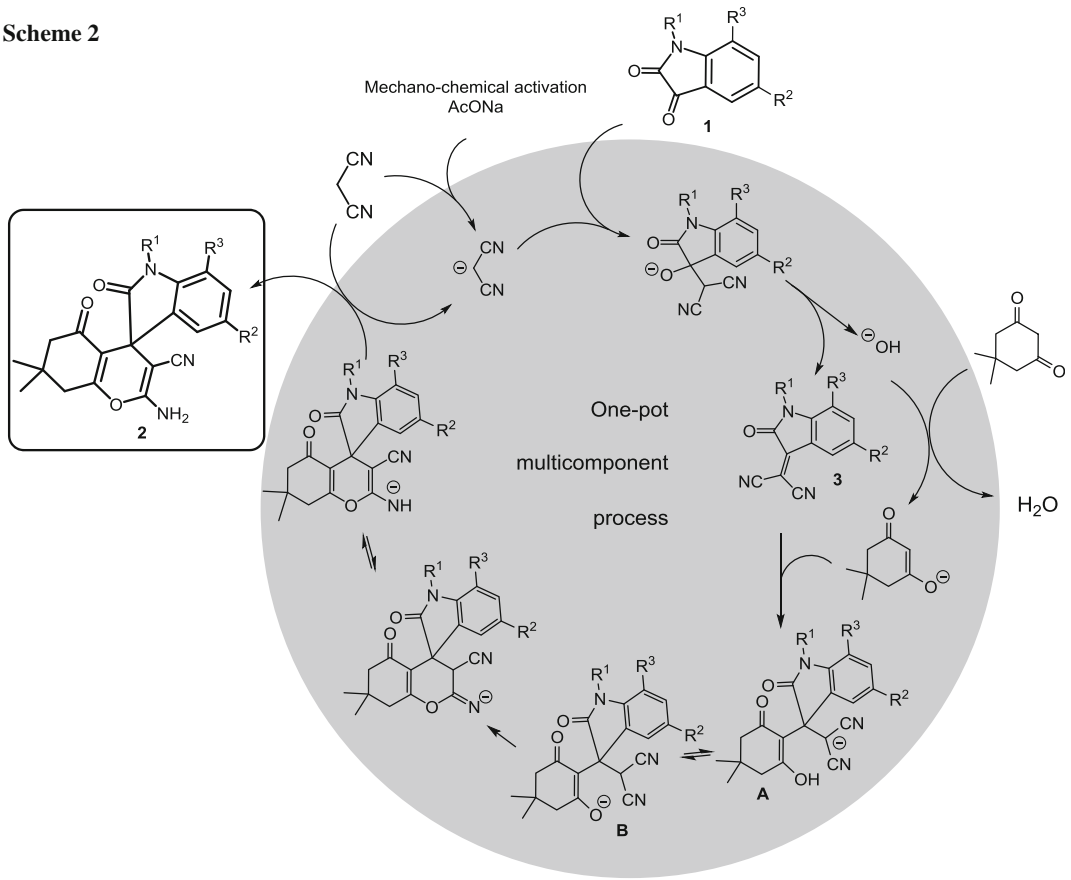


Table 1 Multicomponent transformation of isatin **1a**, malononitrile, and dimedone into 2-amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (**2a**)

Entry	Additive of water/cm^3	Base	Quantity of base/mol%	Time/min	Product	Yield/%
1	–	–	–	15	**2a**	79[b]
2	–	–	–	30	**2a**	90[a]
3	–	KF	10	15	**2a**	92[a]
4	–	NaOAc	10	15	**2a**	95[a]
5	1	NaOAc	10	15	**2a**	93[a]

3 mmol of isatin **1a**, 3 mmol of dimedone, 3 mmol of malononitrile grinding at 25 °C

[a] Isolated yield

[b] NMR data

of small quantity of water in this case has no noticeable influence on the result of the reaction.

Under the optimal conditions thus found (10 mol% NaOAc as catalysts, 15 min grinding in mortar), isatins **1a**–**1k**, malononitrile, and dimedone were transformed into corresponding substituted spirooxindoles **2a**–**2k** in 90–99 % yields (Table 2). But, in the case of **2j** and **2k**, reaction time was increased to 20 and 30 min, respectively, to reach more than 90 % yield. The necessity to use prolonged reaction time for isatins **1j**, **1k** may be due to the electron withdrawing substituent at N-atom of isatin.

With the above results taken into consideration and the mechanistic data on NaOAc-catalyzed catalytic solvent-free multicomponent processes [30–32], the following mechanism for the sodium acetate catalyzed assembling of isatins **1**, malononitrile, and dimedone into substituted spirooxindoles **2** is proposed. The initiation step of the catalytic cycle begins with the sodium acetated induced deprotonation of a molecule of malononitrile, which leads to the malononitrile anion formation (Scheme 2).

The following process represents a typical multicomponent reaction. Knoevenagel condensation of the malononitrile anion with isatin **1** takes place with the elimination of a hydroxide anion and formation of Knoevenagel adduct **3** [37]. The subsequent hydroxide-promoted Michael addition of dimedone to electron-deficient Knoevenagel adduct **3** results in the anions **A** and **B** formation. Further cyclization of anion **B** and protonation with the participation of the next molecule

Table 2 Multicomponent transformation of isatins **1a–1k**, malononitrile, and dimedone into 2-amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitriles **2a–2k**

Entry	Isatin	R^1	R^2	R^3	Time/min	Product	Yield/%[a]
1	**1a**	H	H	H	15	**2a**	95
2	**1b**	H	Cl	H	15	**2b**	96
3	**1c**	H	Br	H	15	**2c**	90
4	**1d**	H	NO_2	H	15	**2d**	95
5	**1e**	H	Me	Me	15	**2e**	91
6	**1f**	H	Br	Br	15	**2f**	95
7	**1g**	Me	H	H	15	**2g**	98
8	**1h**	4-Cl-Bn	H	H	15	**2h**	95
9	**1j**	Ac	H	H	15	**2j**	85
10	**1j**	Ac	H	H	20	**2j**	99
11	**1k**	Ts	H	H	15	**2k**	51
12	**1k**	Ts	H	H	30	**2k**	91

3 mmol of isatin **1**, 3 mmol of dimedone, 3 mmol of malononitrile, 0.3 mmol NaOAc grinding at 25 °C

[a] Isolated yield

of malononitrile leads to the corresponding spirooxindole **2** formation with the regeneration of malononitrile anion at the last step of the catalytic cycle (Scheme 2).

Thus, the simple NaOAc-catalyzed procedure can produce a fast efficient and selective solvent-free multicomponent transformation of isatins, malononitrile, and dimedone into substituted spirooxindoles in excellent 90–99 % yields. This new process opens an efficient and convenient solventless multicomponent way to create substituted spirooxindoles, the pharmacologically active substances with known spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic activities and promising compounds for different biomedical applications. This new solvent-free multicomponent procedure utilizes simple equipment; it is easily carried out and is valuable from the viewpoint of environmentally benign diversity-oriented large-scale processes.

Experimental

All melting points were measured with a Gallenkamp melting-point apparatus. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 with a Bruker Avance II 300 spectrometer at ambient temperature. Chemical shift values are relative to Me_4Si. IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Mass spectra (EI, 70 eV) were obtained directly with a Kratos MS-30 spectrometer. HRMS (ESI) was measured on a Bruker micrOTOF II instrument; external or internal calibration was done with Electrospray Calibrant Solution (Fluka). All chemicals used in this study were commercially available.

General procedure

Isatin **1** (3 mmol), 0.198 g malononitrile (3 mmol), 0.420 g dimedone (3 mmol), and 0.025 g sodium acetate (0.3 mmol) were grinded with the pestle in mortar at ambient temperature for 15 min. The resulting mixture was air dried. Crude solid was then put on filter, rinsed with water (2 × 2 cm^3), and dried with water pump.

2-Amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile
(**2a**)
Yield 95 %; *m.p.*: 305–307 °C (Ref. [25] 305–307 °C).

2-Amino-5′-chloro-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile
(**2b**)
Yield 96 %; *m.p.*: 293–295 °C (Ref. [23] 294–296 °C).

2-Amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile
(**2c**)
Yield 90 %; *m.p.*: 305–307 °C (Ref. [23] 306–308 °C).

2-Amino-7,7-dimethyl-5′-nitro-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile
(**2d**)
Yield 95 %; *m.p.*: 302–304 °C (Ref. [23] 302–304 °C).

2-Amino-5′,7,7,7′-tetramethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile
(**2e**)
Yield 91 %; *m.p.*: >360 °C (Ref. [3] >360 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.00 (s, 3H, CH_3), 1.03 (s, 1H,

CH_3), 2.08–2.16 (m, 2H, CH_2), 2.17 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.55 (s, 2H, CH_2), 6.58 (s, 1H, Ar), 6.76 (s, 1H, Ar), 7.16 (s, 2H, NH_2), 10.31 (s, 1H, NH) ppm.

2-Amino-5′,7′-dibromo-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (**2f**, $C_{19}H_{15}Br_2N_3O_3$)
Yield 95 %; *m.p.*: 301–303 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.02$ (s, 6H, $2CH_3$), 2.17 (s, 2H, CH_2), 2.50–2.63 (m, 2H, CH_2), 7.30 (s, 1H, Ar), 7.42 (s, 2H, NH_2), 7.60 (s, 1H, Ar), 10.91 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 27.1$, 27.6, 32.0, 32.5, 41.5, 45.8, 48.2, 49.8, 56.3, 102.4, 113.8, 117.1, 125.4, 132.9, 137.8, 141.1, 158.9, 164.9, 195.2 ppm; IR (KBr): $\bar{\nu} = 3285$, 2194, 1736, 1659, 1598, 1461, 1351, 1148, 1054, 557 cm^{-1}; HRMS (ESI): $m/z = 515.9351$ [M + Na], calcd for $C_{19}H_{15}BrN_3O_3Na$ 515.9353; MS (EI, 70 eV): *m/z* (%) = 409 (4), 353 (6), 305 (12), 277 (47), 249 (14), 188 (10), 168 (27), 112 (16), 83 (100), 39 (95).

2-Amino-1′,7,7-trimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (**2g**)
Yield 98 %; *m.p.*: 248–250 °C (Ref. [25] 248–250 °C).

2-Amino-1′-(4-chlorobenzyl)-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (**2h**, $C_{26}H_{22}ClN_3O_3$)
Yield 95 %; *m.p.*: 239–241 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.02$ (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.09–2.24 (m, 2H, CH_2), 2.60–2.61 (m, 2H, CH_2), 4.91 (s, 2H, CH_2), 6.73 (d, 1H, $J = 7.6$ Hz, Ar), 6.97 (t, 1H, $J = 7.6$ Hz, Ar), 7.08–7.17 (m, 2H, Ar), 7.32 (s, 1H, NH_2), 7.37 (d, 2H, $J = 8.2$ Hz, Ar), 7.52 (d, 2H, $J = 8.2$ Hz, Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 27.0$, 27.6, 27.7, 31.9, 42.6, 46.4, 49.9, 57.2, 108.7, 110.5, 117.3, 122.6, 123.0, 128.2 (2C), 128.5, 129.1, 129.3 (2C), 131.8, 133.5, 135.2, 158.9, 164.5, 176.6, 195.0 ppm; IR (KBr): $\bar{\nu} = 3384$, 2957, 2197, 1737, 1670, 1610, 1490, 1467, 1352, 479 cm^{-1}; HRMS (ESI): $m/z = 482.1238$ [M + Na], calcd for $C_{26}H_{22}ClN_3O_3Na$ 482.1242; MS (EI, 70 eV): *m/z* (%) = 461 (1), 459 (3), 375 (1), 334 (12), 319 (10), 271 (11), 214 (5), 180 (8), 125 (100), 83 (32), 28 (32).

1′-Acetyl-2-amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (**2j**)
Yield 99 %; *m.p.*: 233–234 °C (Ref. [25] 233–234 °C).

2-Amino-7,7-dimethyl-2′,5-dioxo-1′-tosyl-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (**2k**, $C_{26}H_{23}N_3O_5S$)
Yield 91 %; *m.p.*: 248–250 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.97$ (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.00–2.14 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.56–2.57 (m, 2H, CH_2), 7.16 (s, 2H, NH_2), 7.34–7.45 (m, 4H, Ar), 7.70–7.92 (m, 4H, Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.1$, 27.0 (2C), 27.4 (2C), 32.0, 49.3, 56.5, 110.3, 112.4, 112.5, 116.5, 123.8, 125.1, 127.5, 127.5, 128.9, 129.7, 132.4, 138.2, 145.4, 167.7, 174.7, 194.6, 204.7 ppm; IR (KBr): $\bar{\nu} = 3320$, 2197, 1753, 1686, 1667,1353, 1225, 1190, 1180, 572 cm^{-1}; HRMS (ESI): $m/z = 512.1247$ [M + Na], calcd for $C_{26}H_{23}N_3O_5SNa$ 512.1251; MS (EI, 70 eV): *m/z* (%) = 334 (2), 291 (1), 234 (1), 155 (48), 91 (100), 84 (21), 83 (48), 66 (19), 65 (51), 56 (29).

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