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Pot, atom and step-economic (PASE) synthesis of medicinally relevant spiro[oxindole-3,4′-pyrano[4,3-*b*]pyran] scaffold

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Abstract: Fast (3 min) pot, atom and step economics (PASE) potassium fluoride catalyzed multicomponent reaction of isatins, malononitrile and 4-hydroxy-6-methyl-2*H*-pyran-2-one results in efficient formation of substituted spirooxindole-3,4′-pyrano[4,3-*b*]pyrans in 92–96% yields. The developed 'on-solvent' approach to the substituted spirooxindole-3,4′-pyrano[4,3-*b*]pyrans – the pharmacologically perspective substances with known antiviral, antileishmanial, anticonvulsant and anti-HIV activities – is beneficial from the viewpoint of diversity-oriented large-scale processes and represents fast and environmentally benign synthetic concept for the multicomponent reactions strategy.

Keywords: 4-hydroxy-6-methyl-2*H*-pyran-2-one; catalysis; isatins; malononitrile; multicomponent reaction; spirooxindole-3,4′-pyrano[4,3-*b*]pyrans.

Introduction

The concept of pot, atom and step economy (PASE) [1] is a new approach towards developing environmentally friendly synthetic technologies. The PASE concept is based on combining the pot economy with the already known ideas of atom and step economy. An atom economic procedure takes into consideration the number of atoms of all the reagents that constitute the final compound, thereby regulating the waste of the process [2]. The step economic procedure regulates the efficiency of synthesis by minimization of the number of steps required to synthesize the target molecule [3]. The pot economic process should be accomplished in single reaction vessel without the requirements of workup and isolation of the intermediate species [4]. The advantage of the PASE concept is that it brings together divergent aspects of green chemistry so that one can plan and execute organic synthesis in a way that leads to minimal waste generation.

The design of functional organic and hybrid molecular systems has experienced outstanding recent growth and has become a high priority in the development of new technologies and novel functional materials. In this connection, the concept of 'privileged medicinal structures or scaffolds' has emerged as one of the guiding principles of drug discovery design [5]. These privileged scaffolds commonly consist of rigid hetero ring system that assigns well-defined orientation of appended functionalities for target recognition [6].

The heterocyclic spirooxindole scaffold is a widely distributed structural framework in a number of pharmaceuticals and natural products [7], including such cytostatic alkaloids as spirotryprostatins A, B, and strychnophylline [8]. The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole compounds have made them attractive synthetic targets [9–12].

Among the oxygen-containing heterocycles system, functionalized pyrano[4,3-*b*]pyranes have received considerable attention owing to their wide range of diverse pharmacological activity, such as antiviral, antileishmanial and anticonvulsant activity [13, 14] as well as non-peptide human immunodeficiency virus (HIV) protease inhibition [15].

In recent years, multicomponent reactions have been reported for the synthesis of spirooxindole-3,4′-pyrano[4,3-*b*]pyran scaffold via assembling isatin, 4-hydroxy-6-methyl-2*H*-pyran-2-one and malononitrile in solution under different catalytic conditions. Some of them can be carried out only with unsubtituted isatin (only one example in each publication) [16–20], other suffer from low yields of target compound [21, 22] or long reaction time at elevated temperature [23, 24]. Although each of the known procedures for the synthesis of spirooxindole-3,4′-pyrano[4,3-*b*]pyran system has its merits, fast and efficient PASE method for this process has yet to be developed.

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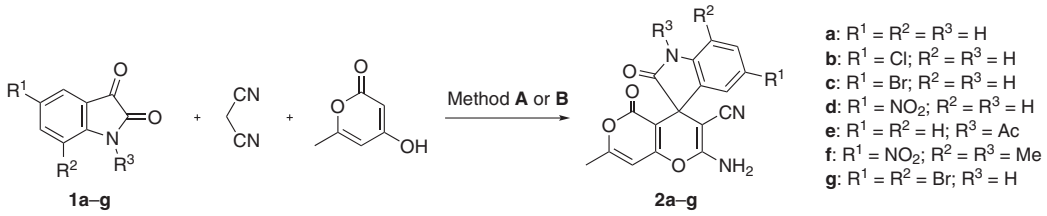


Scheme 1 Synthesis of spirooxindole-3,4′-pyrano[4,3-*b*]pyrans **2a–g**. Method A: grinding in a mortar. Method B: refluxing in ethanol.

Considering our results on the 'solvent-free' multicomponent transformations of carbonyl compounds and C-H acids [25–32] as well as the certain biomedical application of spirooxindole-3,4′-pyrano[4,3-*b*]pyrans mentioned above, we were prompted to design a convenient, fast and facile PASE methodology for the efficient and clean multicomponent assembling of isatins, malononitrile and 4-hydroxy-6-methyl-2*H*-pyran-2-one.

Results and discussion

The reactions of isatins **1a–g** with malononitrile and 4-hydroxy-6-methyl-2*H*-pyran-2-one are summarized in Scheme 1 and Tables 1 and 2. In the model reaction, spirooxindole-3,4′-pyrano[4,3-*b*]pyran **2a** was obtained by grinding the corresponding reactants in a mortar in the presence of NaOAc or KF as catalyst and in the absence of solvent (method A, Table 1, entries 1 and 2). With 10 mol % KF as catalyst, a 90% yield of **2a** was obtained after 15 min (Table 1, entry 2). The alternative thermal reaction (method B, 60°C, 15 min) yielded 67% of **2a**. Recently we have found that small additives of water or alcohols improve similar thermal or grinding-induced processes [33–35] (so called 'on-water' [36] or 'on-solvent' [35, 37] reactions).

Table 1 Multicomponent transformation of isatin **1a**, malononitrile and 4-hydroxy-6-methyl-2*H*-pyran-2-one into spirooxindole-3,4′-pyrano[4,3-*b*]pyran **2a**.[a]

Entry	Additive	Catalyst	Time (min)	Yield of 2a (%)[b]
1	Neat	AcONa,10%	15	83
2	Neat	KF 10%	15	90
3	Neat	KF 10%, 60°C	15	67
4	H_2O, 2 mL	KF 10%, 60°C	15	56
5	MeOH, 2 mL	KF 10%, 60°C	15	83
6	EtOH, 2 mL	KF 10%, 78°C	15	95
7	EtOH, 2 mL	KF 10%, 78°C	5	94
8	EtOH, 2 mL	KF 10%, 78°C	3	94
9	EtOH, 2 mL	KF 10%, 78°C	1	88

[a]A mixture of satin **1a** (3 mmol), malononitrile (3 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (3 mmol) and sodium acetate or potassium fluoride (0.3 mmol) was grinded with a pestle in a mortar (entries 1 and 2) or heated (entries 3–9).
[b]Isolated yield.

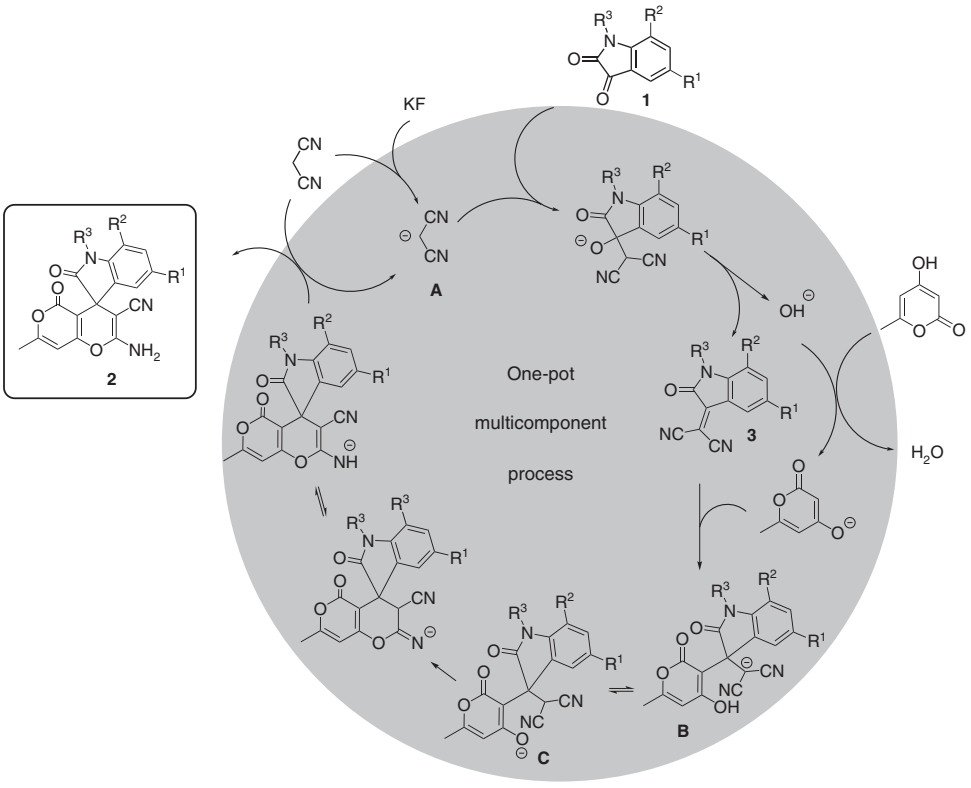
Table 2 Multicomponent transformation of isatins **1a–g**, malononitrile and 4-hydroxy-6-methyl-2*H*-pyran-2-one into spirooxindole-3,4′-pyrano[4,3-*b*]pyrans **2a–g**.[a]

Entry	Isatin	Product	Yield (%)[b]
1	**1a**	**2a**	94
2	**1b**	**2b**	96
3	**1c**	**2c**	92
4	**1d**	**2d**	94
5	**1e**	**2e**	93
6	**1f**	**2f**	95
7	**1g**	**2g**	94

[a]A mixture of isatin **1** (3 mmol), malononitrile (3 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (3 mmol), potassium fluoride (0.3 mmol) and EtOH (2 mL) was heated at 78°C for 3 min.
[b]Isolated yield.

Accordingly, the next thermal experiments were conducted in the presence of a small amount of water or alcohol. Under the thermal conditions with KF as catalyst and EtOH as additive at 78°C product **2a** was obtained in 94% yield after 3 min. Under these conditions (10 mol % KF, 2 mL of EtOH, 78°C, 3 min reaction time), isatins **1a–g** were transformed into the corresponding substituted spirooxindole-3,4′-pyrano[4,3-*b*]pyrans **2a–g** in 92–96% yields (Table 2).

Taking into accounts the literature reports on related transformations [18, 38, 39], the following mechanism for the 'on solvent' assembly of isatins **1a–g**, malononitrile and 4-hydroxy-6-methyl-2*H*-pyran-2-one into substituted spiroxindole-3,4′-pyrano[4,3-*b*]pyrans **2a–g** can be proposed (Scheme 2). The initiation step of the catalytic cycle begins with potassium fluoride induced deprotonation of a molecule of malononitrile, which leads to the formation of malononitrile anion **A**. Then Knoevenagel condensation of the anion **A** with isatin **1** takes place with the elimination of a hydroxide anion and formation of



Scheme 2 Mechanism of multicomponent transformation of isatin **1**, malononitrile and 4-hydroxy-6-methyl-2*H*-pyran-2-one into spirooxindole-3,4′-pyrano[4,3-*b*]pyran **2**.

Knoevenagel adduct **3** [40]. The subsequent hydroxide-promoted Michael addition of 4-hydroxy-6-methyl-2*H*-pyran-2-one to electron-deficient Knoevenagel adduct **3** results in generation of anion **B** which is in equilibrium with its tautomer **C**. Subsequent cyclization of anion **C** followed by protonation with the participation of a molecule of malononitrile leads to the formation of the corresponding spirooxindole **2** with the regeneration of malononitrile anion at the last step of the catalytic cycle.

Conclusion

The new, highly efficient 'on-solvent' multicomponent PASE process provides a convenient route to substituted spirooxindole-3,4′-pyrano[4,3-*b*]pyrans – promising compounds with known antiviral, antileishmanial and anticonvulsant activity. This method utilizes facile procedure, simple equipment; it is easy to be carried out and is valuable from the 'green chemistry' viewpoint and large-scale processes. This very fast and highly efficient approach to substituted spirooxindole-3,4′-pyrano[4,3-*b*]pyrans represents a new synthetic concept for multicomponent reactions.

Experimental

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in DMSO-d_6 with a Bruker Avance II 300 spectrometer at ambient temperature. Chemical shifts values are relative to Me_4Si. IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Electron-impact mass spectra were obtained at 70 eV using a direct inlet system at a Finningan MAT INCOS 50 spectrometer. All chemicals used in this study were commercially available.

Typical grinding procedure (method A)

A mixture of isatin **1a–g** (3 mmol), malononitrile (0.198 g, 3 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (0.378 g, 3 mmol) and sodium acetate (0.025 g, 0.3 mmol) or potassium fluoride (0.017 g, 0.3 mmol) was grinded with a pestle in a mortar at ambient temperature for 15 min. Crude product was rinsed with water (2×2 mL), dried with suction and crystalized from ethanol.

Typical procedure with ethanol (method B)

A mixture of isatin **1a–g** (3 mmol), malononitrile (0.198 g, 3 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (0.378 g, 3 mmol) and potassium

fluoride (0.017 g, 0.3 mmol) and ethanol (2 mL) was heated under reflux for 3 min. After cooling, the solid material was filtered, dried under suction and crystallized from ethanol.

2′-Amino-7′-methyl-2,5′-dioxo-1,2-dihydro-5′*H*-spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitrile (2a) White solid; yield 0.91 g (94%); mp 283–285°C (Lit. mp 278–280°C [24]); ^{1}H NMR: δ_H δ 2.24 (s, 3H, CH_3), 6.35 (s, 1H, CH), 6.82 (d, *J* = 7.6 Hz, 1H, Ar), 6.93 (t, *J* = 7.6 Hz, 1H, Ar), 7.10 (d, *J* = 7.6 Hz, 1H, Ar), 7.19 (t, *J* = 7.6 Hz, 1H, Ar), 7.44 (s, 2H, NH_2), 10.57 (s, 1H, NH).

2′-Amino-5-chloro-7′-methyl-1,2-dihydro-2,5′-dioxo-5′*H*-spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitrile (2b) Brownish solid; yield 1.02 g (96%); mp >300°C (Lit. mp >300°C [24]); ^{1}H NMR: δ_H δ 2.25 (s, 3H, CH_3), 6.37 (s, 1H, CH), 6.84 (d, *J* = 8.4 Hz, 1H, Ar), 7.25 (d, J = 8.4 Hz, 1H, Ar), 7.32 (s, 1H, Ar), 7.56 (s, 2H, NH_2), 10.73 (s, 1H, NH).

2′-Amino-5-bromo-7′-methyl-1,2-dihydro-2,5′-dioxo-5′H-spiro[indole-3,4′-pyra-no[4,3-b]pyran]-3′-carbonitrile (2c) White solid; yield 1.10 g (92%); mp >300°C (Lit. mp >300°C [24]); ^{1}H NMR: δ_H δ 2.26 (s, 3H, CH_3), 6.37 (s, 1H, CH), 6.80 (d, *J* = 7.6 Hz, 1H, Ar), 7.38 (d, *J* = 7.6 Hz, 1H, Ar), 7.43 (s, 1H, Ar), 7.56 (s, 2H, NH_2), 10.75 (s, 1H, NH).

2′-Amino-7′-methyl-5-nitro-1,2-dihydro-2,5′-dioxo-5′*H*-spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitrile (2d) White solid; yield 1.03 g (90%); mp >320°C (Lit. mp >320°C [21]); ^{1}H NMR: δ_H δ 2.25 (s, 3H, CH_3), 6.39 (s, 1H, CH), 7.03 (d, *J* = 8.6 Hz, 1H, Ar), 7.46 (s, 2H, NH_2), 7.99 (s, 1H, Ar), 8.21 (d, *J* = 8.6 Hz, 1H, Ar), 11.35 (s, 1H, NH).

1-Acetyl-2′-amino-7′-methyl-1,2-dihydro-2,5′-dioxo-5′*H*-spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitrile (2e) White solid; yield 1.01 g (93%); mp: 265–267°C; IR: ν_{max} 3395, 3206, 2199, 1699, 1610, 1272, 1211, 1162, 1035, 754 cm^{-1}; ^{1}H NMR: δ_H 2.31 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 6.49 (s, 1H, CH), 7.21–7.42 (m, 3H, Ar), 7.76 (s, 2H, NH_2), 8.12 (d, *J* = 8.0 Hz, 1H, Ar); ^{13}C NMR: δ_c 19.3, 25.9, 47.7, 56.5, 98.0, 115.1, 115.3, 116.7, 124.1, 125.7, 129.2, 131.4, 139.5, 158.6, 159.8, 160.4, 164.5, 170.2, 177.3. ESI-HR-MS. Calcd for $C_{19}H_{13}N_3NaO_5$ ([M+Na]$^+$): *m/z* 386.0747. Found: *m/z* 386.0740.

2′-Amino-1,7′-dimethyl-5-nitro-1,2-dihydro-2,5′-dioxo-5′*H*-spiro[indole-3,4′-pyrano[4,3-*b*]pyran]-3′-carbonitrile (2f) White solid; yield 1.09 g (95%); mp 270–272°C, dec., (Lit. mp 269–271°C [21]); ^{1}H NMR: δ_H δ 2.25 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 6.41 (s, 1H, CH), 7.30 (s, 2H, NH_2), 7.31–8.32 (m, 3H, Ar).

2′-Amino-5,7-dibromo-7′-methyl-1,2-dihydro-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyra-no[4,3-*b*]pyran]-3′-carbonitrile (2g) White solid; yield 1.35 g (94%); mp >300; ν_{max} 3351, 3164, 2198, 1722, 1675, 1605, 1462, 1367, 1138, 563 cm^{-1}; HRMS (ESI): 501.8821 [M+Na]$^+$, calcd for $C_{17}H_9Br_2N_3NaO_4$: 501.8833; ^{1}H NMR: δ_H δ 2.26 (s, 3H, CH_3), 6.39 (s, 1H, CH), 7.51 (s, 1H, Ar), 7.60 (s, 2H, NH_2), 7.65 (s, 1H, Ar), 11.08 (s, 1H, NH); ^{13}C NMR: δ_c 19.3, 48.3, 55.9, 97.5, 98.1, 102.5, 114.2, 116.9, 126.3, 133.5, 136.4, 141.3, 158.8, 160.0, 160.2, 164.1, 177.0. ESI-HR-MS. Calcd for $C_{17}H_9Br_2N_3NaO_4$ ([M+Na]$^+$): *m/z* 501.8833. Found: *m/z* 501.8821.

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