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Multicomponent assembling of isatins, malononitrile and 4-hydroxy-6-methylpyridin-2(1*H*)-ones: one-pot efficient approach to privileged spiro[indoline-3,4′-pyrano[3,2-*c*]pyridine]-2,5′(6′*H*)-dione scaffold

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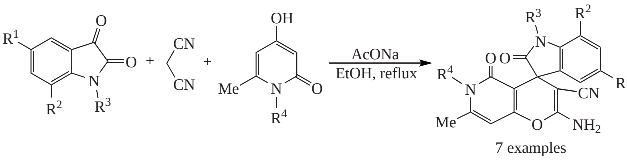
The new one-pot multicomponent assembling of isatins, malononitrile and 4 hydroxy-6-methylpyridin-2(1*H*)-ones into previously unknown 2′-amino-7′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-*c*]pyridine]-3′-carbonitriles in 80–98% yields has been accomplished by their reflux in ethanol in the presence of sodium acetate.



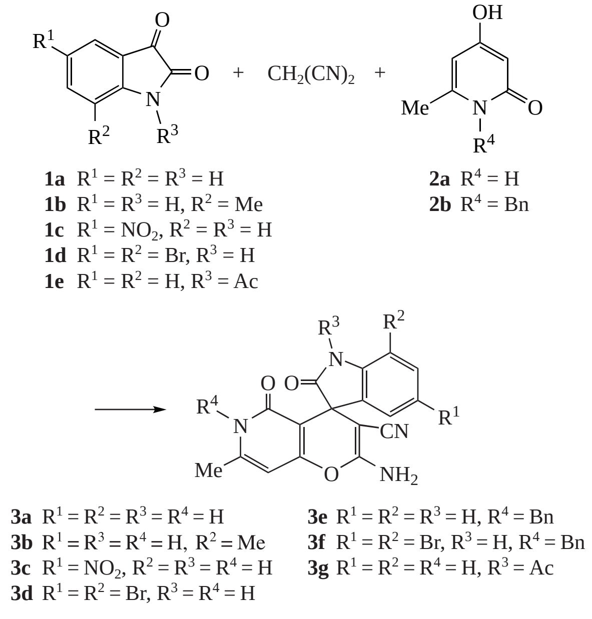
One-pot reactions are known as efficient tool for synthesis of medicinally privileged structures by performing all processes in one reactor without any mesne work up.[1] One-pot domino and multicomponent processes are of special interest since at least three different substrates compose a new molecule. Multicomponent strategy has gained significant importance as an access to complex heterocyclic targets providing higher yields, lower cost and reducing time of reaction.[2]

The design of functional organic and hybrid molecular systems has shown outstanding recent growth and is a high priority in the development of new technologies and novel functional materials.[3] In this connection the concept of 'privileged medicinal structures or scaffolds' has emerged as one of the guiding principles of drug discovery design. These privileged scaffolds commonly consist of rigid hetero ring system that assigns well-defined orientation of appended functionalities for target recognition.[4]

As widely spread in natural compounds, spirooxindole fragment presented in such cytostatic alkaloids as spiro-tryprostatins A, B, and strychnophylline. They are characterized by unique structural array and possess different types of pharmacological activities such as, antiviral,[5] apoptotic,[6] antitubercular,[7] antitumor,[8] and antiproliferative.[9] Spirooxindoles are also important synthetic target exhibiting extended pharmacological activity, such as analgesic,[10] as well as properties useful for fever,[11] colic,[12] and infestations treatment.[13] Pyridin-2(1*H*)-one moiety has been found in some alkaloids, *e.g.* zanthosimuline or YCM1008A.[13–15]

The combinations of biologically active spirooxindole ring system with a pharmacologically active pyridin-2(1*H*)-one fragment can force, evolve and multiplicate properties of both fragments. Recently we have found different types of multicomponent reactions using isatin as active carbonyl compound to accomplish synthesis of potentially pharmacologically active spirooxindoles.[16–20] In the present study we report our results on the novel efficient multicomponent assembling of isatins, malononitrile and 4 hydroxy-6-methylpyridin-2(1*H*)-ones under simple catalytic conditions (Scheme 1, Tables 1, 2).

At the first stage of investigation, according to success in solvent-free non-catalytic synthesis,[21] the reaction was carried out by grinding the reactants in a mortar with a pestle for 15 min at ambient temperature (Table 1, entry 1). Recently we have found that small additives of water or alcohols have improved multicomponent processes or assembling initiated by grinding[22–24] (so called 'on-water'[25] or 'on solvent'[26] reactions), therefore the next non-catalytic 'on-water' reaction in mortar was carried out for 15 min with addition of 2 ml of water without

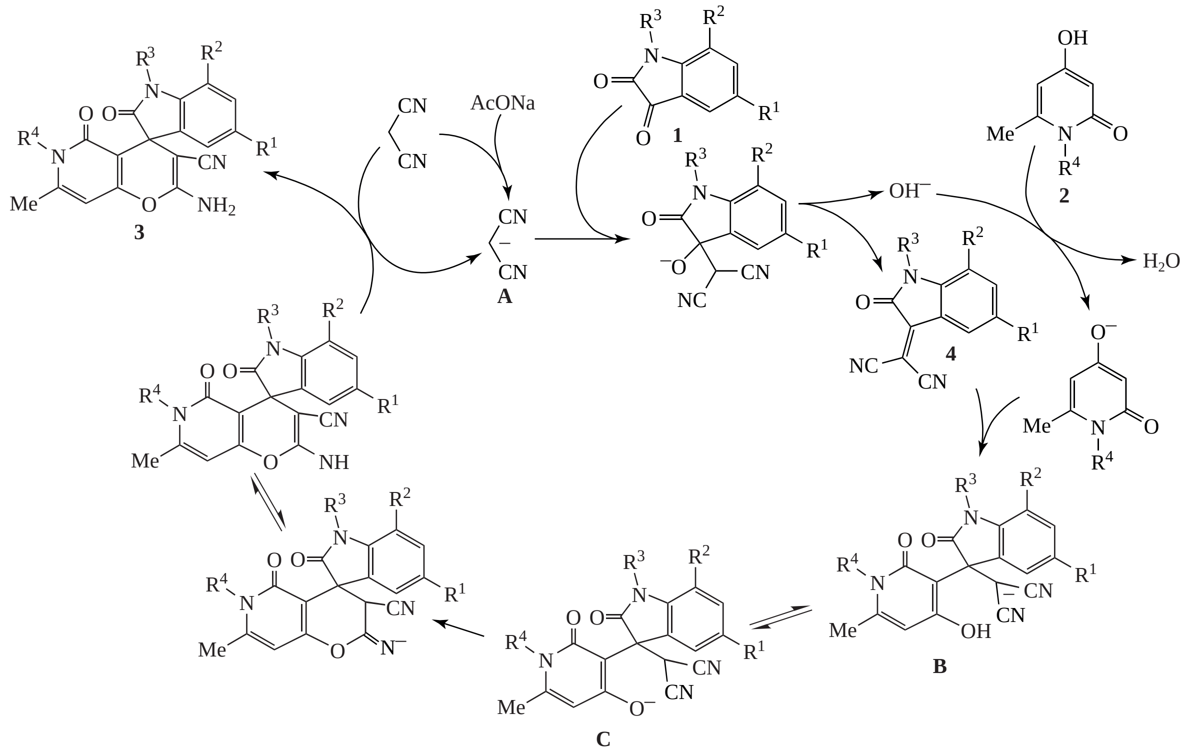


1a R^1 = R^2 = R^3 = H
1b R^1 = R^3 = H, R^2 = Me
1c R^1 = NO$_2$, R^2 = R^3 = H
1d R^1 = R^2 = Br, R^3 = H
1e R^1 = R^2 = H, R^3 = Ac

2a R^4 = H
2b R^4 = Bn

3a R^1 = R^2 = R^3 = R^4 = H
3b R^1 = R^3 = R^4 = H, R^2 = Me
3c R^1 = NO$_2$, R^2 = R^3 = R^4 = H
3d R^1 = R^2 = Br, R^3 = R^4 = H
3e R^1 = R^2 = R^3 = H, R^4 = Bn
3f R^1 = R^2 = Br, R^3 = H, R^4 = Bn
3g R^1 = R^2 = R^4 = H, R^3 = Ac

Scheme 1



Scheme 2

Table 1 Multicomponent transformation of isatin **1a**, malononitrile and 4-hydroxy-6-methylpyridin-2(1*H*)-one **2a** into spiro[indoline-3,4′-pyrano-[3,2-*c*]pyridine] **3a**.[a]

Entry	Solvent (volume/ml)	Base (mol%)	*T*/°C	*t*/h	Yield of **3a** (%)
1	Solvent-free[b]	Catalyst-free	25	0.25	10[c]
2	H_2O (2)[b]	Catalyst-free	25	0.25	15[c]
3	H_2O (10)	Catalyst-free	80	1	37[c]
4	EtOH (5)	Catalyst-free	78	1	48[c]
5	H_2O (10)	AcONa (10)	80	1	88[d]
6	EtOH (5)	AcONa (10)	78	1 (0.5)	98[d] (95[d])

[a] Isatin **1a** (3 mmol), malononitrile (3 mmol), 4-hydroxy-6-methylpyridin-2(1*H*)-one **2a** (3 mmol), catalyst, and solvent were stirred at appropriate temperature. [b] Isatin **1a** (3 mmol), malononitrile (3 mmol), 4-hydroxy-6-methylpyridin-2(1*H*)-one **2a** (3 mmol), and catalyst were grinded with a pestle in mortar for 15 min. [c] According to ^{1}H NMR data. [d] Isolated yields.

Table 2 Multicomponent transformation of isatins **1a**–**e**, malononirile and 4-hydroxy-6-methylpyridin-2(1*H*)-ones **2a**,**b** into spiro[indoline-3,4′-pyrano-[3,2-*c*]pyridines] **3a**–**g**.[a]

Entry	R^1	R^2	R^3	R^4	Yield of **3** (%)[c]
1	H	H	H	H	**3a**, 98
2	H	Me	H	H	**3b**, 95
3	NO_2	H	H	H	**3c**, 90
4	Br	Br	H	H	**3d**, 95
5	H	H	H	Bn	**3e**, 80
6	Br	Br	H	Bn	**3f**, 85
7	H	H	Ac	H	**3g**, 68[d]
8[b]	H	H	Ac	H	**3g**, 84

[a] Isatin **1a**–**e** (3 mmol), malononitrile (3 mmol), 4-hydroxy-6-methylpyridin-2(1*H*)-ones **2a**,**b** (3 mmol), AcONa (10 mol%), and EtOH (5 ml) were refluxed for 1 h. [b] Isatin **1a**–**e** (3 mmol), malononitrile (3 mmol), 4-hydroxy-6-methylpyridin-2(1*H*)-ones **2a**,**b** (3 mmol), and pyridine (5 ml) were refluxed for 1 h. [c] Isolated yields. [d] According to ^{1}H NMR data.

any catalyst (Table 1, entry 2). However, in both these cases the yields of spiro[indoline-3,4′-pyrano[3,2-*c*]pyridine] did not exceed 10–15%.

The thermal activation, ensured success earlier,[19,27] led to spiro[indoline-3,4′-pyrano[3,2-*c*]pyridine] **3a** in 37% (water) and 48% (ethanol) yields (Table 1, entries 3, 4). Next, to improve activation sodium acetate was tested as cheap, mild, non-toxic base catalyst.[28,29] This catalyst raised the yield under 'on water' conditions up to 88% (Table 1, entry 5). The same 'on-solvent' reaction with ethanol provided 98% yield of spiro[indoline-3,4′-pyrano[3,2-*c*]pyridine] **3a** (entry 6).

Thus, under these conditions (ethanol, 78° C, 1 h) with sodium acetate as a catalyst spiro[indoline-3,4′-pyrano[3,2-*c*]pyridines] **3b**–**f** were formed in 80–95% yields (Table 2, entries 2–6).[†] However, compound **3g** in ethanol was obtained in somewhat lower (68%) yield (entry 7). This yield was improved to 84% by application of more severe conditions: using pyridine not only as catalyst, but also as a solvent (reflux for 1 h, entry 8).

Based on the above results and data on the mechanisms of multicomponent transformation of isatins and CH acids,[30,31] the following mechanism for the assembling $\mathbf{1} + \mathbf{2} + CH_2(CN)_2 \rightarrow \mathbf{3}$ was proposed (Scheme 2). The initiation step of the catalytic cycle begins with the sodium acetate induced deprotonation of a molecule of malononitrile, which leads to anion **A**. Then Knoevenagel condensation of anion **A** with isatin **1** occurs with the elimination of a hydroxide anion and formation of the Knoevenagel adduct **4**.[32] The subsequent hydroxide-promoted Michael addition of 4-hydroxy-6-methylpyridin-2(1*H*)-one to electron-deficient Knoevenagel adduct **4** affords anions **B** and **C**. Further cyclization of anion **C** and protonation with the participation of the next molecule of malononitrile yields corresponding spiro[indoline-3,4′-pyrano[3,2-*c*]pyridine] **3** with the regeneration of malononitrile anion at the last step of the catalytic cycle (see Scheme 2).

[†] *General (typical) procedure.* Isatin **1** (3 mmol), malononitrile (3 mmol), 4-hydroxy-6-methylpyridin-2(1*H*)-one **2** (3 mmol) were refluxed for 60 min in ethanol (5 ml) with sodium acetate (10 mol%) or in pyridine (without any catalyst). After the reaction was finished, the solid was filtered, washed with ice ethanol and dried to isolate pure products **3**. For their characteristics, see Online Supplementary Materials.

To conclude, the new one-pot multicomponent assembling of isatins, malononitrile and 4-hydroxy-6-methylpyridin-2(1*H*)-ones into previously unknown 2′-amino-7′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-*c*]pyridine]-3′-carbonitriles in 80–98 % yields has been developed. The products obtained seem promising compounds with potential activity for tuberculosis and tumor treatment. The catalytic procedure utilizes simple equipment; it is easily carried out and is valuable from the viewpoint of environmentally benign and diversity-oriented large-scale processes.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.09.011.

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