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Mendeleev Commun., 2024, **34**, 865–867

Mendeleev Communications

First example of isatin used in four-component synthesis of ionic unsymmetrical scaffold with three different heterocyclic rings

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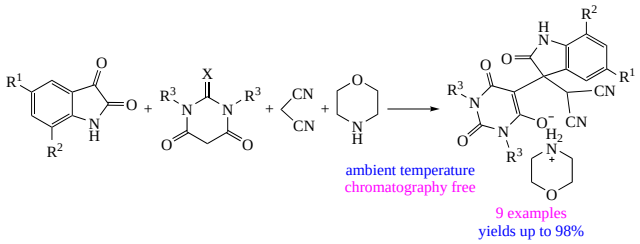
DOI: 10.1016/j.mencom.2024.10.030

The new type of four-component tandem Knoevenagel–Michael reaction was found: isatins, barbituric acids, malononitrile and morpholine at ambient temperature and without catalysts selectively form new non-symmetrical ionic scaffold, namely, morpholin-4-ium 5-(3-dicyanomethyl-2-oxoindolin-3-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate derivatives, in 80–98% yields. Their structure was confirmed using 2D NMR such as ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, and ^{1}H–^{13}C HMBC correlation experiments. The products seem promising as they contain three different pharmacologically active heterocyclic rings.



Keywords: multicomponent reaction, isatin, barbituric acid, malononitrile, morpholine, tandem Knoevenagel–Michael reaction, four-component reaction, ionic scaffold.

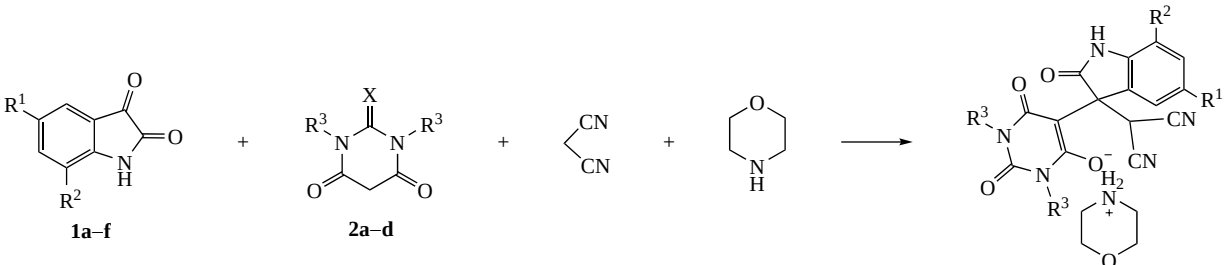
In the last decades, multicomponent reactions (MCRs) became the main synthetic way in diversity-oriented synthesis with maximum structural complexity in minimum steps.[1] MCRs that involve multiple starting compounds typically react in a stepwise manner to yield complex products in a greener and more economical manner due to having greater than three highly diversifiable starting reagents. Unlike traditional methods, MCRs increase the accessible chemical space exponentially with each additional reaction component. The discovery of MCRs, especially with a 'higher order' variant, is challenging and has emerged as the frontiers in contemporary organic synthesis. Thus, the ideal synthetic protocol could be the simple mixing of the only participating compounds without catalyst and heating to achieve the desired result in one step.[2] In tandem reactions several stages follow one after another, and each subsequent stage is strongly dependent on the type of new functional groups or moieties formed in the previous one.[3] Tandem Knoevenagel–Michael reaction is known in classical organic chemistry,[3] and until now, investigations in this area have been in progress.[4–6]

The use of privileged structures or scaffolds in drug discovery is a rapidly developing area in medicinal chemistry. This type of molecules is capable of binding to multiple receptors with high affinity, and its exploitation should allow medicinal chemists more effectively discover biologically active compounds with a broad range of therapeutic areas with a reasonable time scale.[7]

Isatin (1*H*-indole-2,3-dione) and its derivatives have a lot of applications in medicinal chemistry.[8] Isatin contains an indole nucleus bearing both lactam and keto moieties, which exert biological effects, such as antimicrobial, antitubercular, anticonvulsant, and anticancer.[9] In particular, substituted isatins are present in several biologically active alkaloids and pharmacological agents.[10] They are also applied as antioxidants, and anticancer remedies, as well as other useful biomedical agents.[11] Barbiturates also privileged medicinal scaffold[12] in different central nervous system drugs, sedatives, anticonvulsants, and anaesthetic agents.[13] Nowadays, a renewed interest has arisen to them, because pyrimidinetrione template is an efficient zinc-chelating moiety, and thus, such derivatives demonstrate high selectivity toward matrix metalloproteinases responsible for cancer progression.[14] Similarly, barbiturates have shown inhibitory activity against uridine phosphorylase, which catalyses the reversible phosphorolysis in ribosides of uracil to nucleobases and found at an elevated level in selected human tumor cells.[15] Among N-containing heterocycles, morpholine is a privileged pharmacophore with wide ranges of pharmacological activities with different mechanisms of action. It is one of the most useful scaffolds for the development of central nervous system drug candidates because of its well-balanced lipophilic−hydrophilic profile, the reduced pK_a value, and the chair-like flexible conformation.[16] Doxapram,[17] phendimetrazine,[18] moclobemide,[19] and aprepitant[20] containing a morpholine fragment are applied in medicine, mainly as anxiolytics and/or antidepressants.

Solubility plays a significant role in the action of drugs, especially those intended for oral administration.[21] Currently, about 40% of drugs are classified as practically insoluble. One of the methods for increasing solubility is the chemical modification of the drug substance *via* the formation of salts or ion pairs.[21] Due to their special physicochemical properties, the salts and ion pairs of barbiturates became important types of compounds in the development of new drugs.[22,23]

Considering our experience in tandem and multicomponent reactions with the formation of complex heterocyclic compounds[24–28] and biomedical applications of heterocyclic ionic scaffolds, we intended to design a convenient and efficient tandem Knoevenagel–Michael strategy for assembling isatins, barbituric acids, malononitrile, and morpholine into non-



1a–f

a $R^1 = R^2 = H$
b $R^1 = R^2 = Me$
c $R^1 = MeO$, $R^2 = H$
d $R^1 = Cl$, $R^2 = H$
e $R^1 = Br$, $R^2 = H$
f $R^1 = R^2 = Br$

2a–d

a $R^3 = Me$, X = O
b $R^3 = H$, X = O
c $R^3 = Et$, X = O
d $R^3 = Et$, X = S

a $R^1 = R^2 = H$, $R^3 = Me$, X = O, 91%
b $R^1 = R^2 = R^3 = H$, X = O, 80%
c $R^1 = R^2 = H$, $R^3 = Et$, X = O, 87%
d $R^1 = R^2 = H$, $R^3 = Et$, X = S, 83%
e $R^1 = R^2 = R^3 = Me$, X = O, 98%

3a–i

f $R^1 = MeO$, $R^2 = H$, $R^3 = Me$, X = O, 85%
g $R^1 = Cl$, $R^2 = H$, $R^3 = Me$, X = O, 91%
h $R^1 = Br$, $R^2 = H$, $R^3 = Me$, X = O, 92%
i $R^1 = R^2 = Br$, $R^3 = Me$, X = O, 95%

Scheme 1 *Reagents and conditions*: i, isatin (1 mmol), barbituric acid (1 mmol), malononitrile (1 mmol), morpholine (1 mmol), ethanol (4 ml), ambient temperature, 1 h.

symmetrical ionic scaffold with three pharmacologically active heterocyclic rings. Herein, we report on the selective and efficient four-component assembling isatins **1a–f**, barbituric acids **2a–d**, malononitrile, and morpholine into an unsymmetrical ionic scaffold **3a–i** with three heterocyclic rings (Scheme 1). First, to estimate multicomponent reaction conditions, we have carried out assembling of isatin **1a**, *N*,*N*′-dimethylbarbituric acid **2a**, malononitrile and morpholine in ethanol with the formation of ionic product **3a** (Table 1, entries 1–5). Initially the reaction was performed in ethanol at ambient temperature, and 60 min processing was found to be the optimal reaction time when **3a** was obtained in 91% yield (entry 4). Among other alcohols, *n*-propanol was found to be the best solvent, with the formation of **3a** in 88% yield (entries 6–8). Reasonable yields of **3a** were achieved in acetonitrile (75%) and chloroform (83%) (entries 9, 10).

Under the optimal conditions thus found (ethanol as a solvent, 60 min reaction time at ambient temperature), compounds **3a–i** were isolated in 80–98% yields (see Scheme 1).† Their structures were confirmed by ^{1}H, ^{13}C NMR, and IR spectroscopy, as well as high-resolution mass spectrometry (see Online Supplementary Materials). For all compounds, only one set of signals was observed in ^{1}H and ^{13}C NMR spectra. The structure of compound **3a** was additionally confirmed by 2D NMR spectroscopy (Figure 1). The full assignment of all signals was carried out using ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, and ^{1}H–^{13}C HMBC. The ^{1}H NMR spectrum contained two broadened signals, indicating the presence of dynamics in the sample. Morpholinium NH_2^+ was in exchange with water, so both proton signals had a large width. Also, there was a broad singlet at 3.02 ppm from NCH_3 groups due to keto–enol tautamerism. In the ^{13}C NMR spectrum, signals for C4′ and C6′ have the same chemical shifts and appear as a broad signals also because of tautomrism. It is noteworthy that the CH proton from the malononitrile moiety appeared at low field (6.91 ppm), and the assignment was made on the basis of the HSQC cross-peak with the high field carbon signal (at 28.9 ppm).

Table 1 One-pot assembling isatin **1a**, *N*,*N*′-dimethylbarbituric acid **2a**, malononitrile, and morpholine.[a]

Entry	Solvent	Time/min	Yield of **3a** (%)
1	EtOH	5	13
2	EtOH	15	55
3	EtOH	30	85
4	EtOH	60	91
5	EtOH	120	87
6	MeOH	60	88
7	Pr^nOH	60	86
8	Pr^iOH	60	88
9	MeCN	60	75
10	$CHCl_3$	60	83

[a] Benzaldehyde **1a** (1 mmol), *N*,*N*′-dimethylbarbituric acid **2a** (1 mmol), malononitrile (1 mmol), and morpholine (1 mmol) were stirred in solvent (4 ml) at ambient temperature.

† *General (typical) procedures*. Isatin **1** (1 mmol), barbituric acid **2** (1 mmol), malononitrile (1 mmol), and morpholine (1 mmol) were stirred in ethanol (4 ml) for 1 h at ambient temperature. In the cases of **3a**,**e**,**j**–**l**, the reaction mixture was evaporated to the volume 2 ml, cooled to 0 °C for 2 h. The formed solid was filtered, rinsed with an ice-cold ethanol/water solution (1 : 1, 2 ml) and dried. In the cases of **3b**–**d**,**f**, after the end of the reaction, the solvent was evaporated and the solid was crystallized from ethanol to afford pure compound.

Morpholin-4-ium 5-(3-dicyanomethyl-2-oxoindolin-3-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate **3a**. Yield 0.40 g (91%), mp 147–149 °C.

With all these results and taking into consideration the mechanistic data on tandem Knoevenagel–Michael reactions,[29–31] the following mechanism for the four-component assembling isatins **1**, barbituric acids **2**, malononitrile, and morpholine into compound **3** was proposed (Scheme 2). First, the reaction of isatin **1** and malononitrile in the presence of morpholine affords the Knoevenagel adduct **A**. The following addition of barbituric acid **2** leads to the unsymmetrical compound **B**. The final step is the formation of morpholin-4-ium salt **3** which occurs in the reaction between CH acid **5** and morpholine.

Thus, the new type of four-component tandem Knoevenagel–Michael reaction was found, *viz.* isatins, barbituric acids, malononitrile, and morpholine have been successfully transformed in alcohols and other organic solvents without catalyst or any other additives at ambient temperature with the selective formation of the new substituted unsymmetrical ionic scaffold **3** with three different heterocyclic rings in 80–98% yields. This new four-component reaction is a facile and efficient

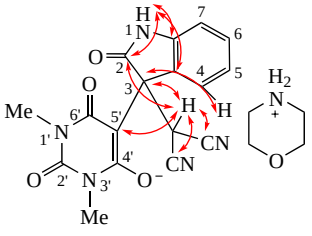
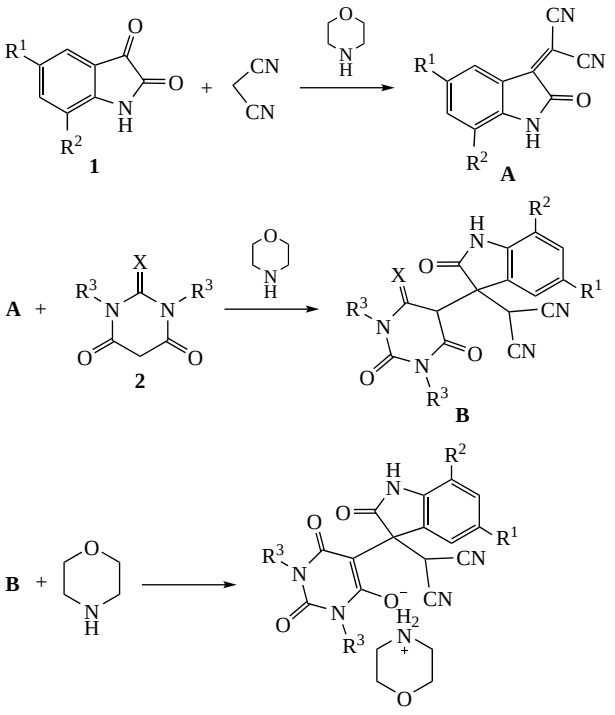


Figure 1 The structure and numbering of compound **3a**. Key ^{1}H–^{13}C HMBC spectrum correlations established by NMR are shown by arrows.



Scheme 2

way to the earlier unknown substituted unsymmetrical scaffold containing both isatin, babituric acid, malononitrile, and morpholine fragments, which are promising compounds for biomedical applications, among them anticonvulsants, anti-AIDS agents, and anti-inflammatory remedies. This synthetic four-component procedure utilizes simple equipment, does not use heating or a long reaction time, catalyst, or any other additives; it is easily carried out, and the isolation procedure is very simple. Thus, this new method is valuable both from the viewpoint of environmentally benign diversity-oriented large-scale processes and for the synthesis of new potential drug libraries.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.10.030.

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Received: 23rd May 2024; Com. 24/7503