Multi-component supramolecular synthesis of spirooxindoles catalyzed by β-cyclodextrin in water

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Abstract: A neutral and efficient one-pot three-component aqueous-phase synthesis is developed for various spirooxindole derivatives from isatin, malononitrile, and 1,3-dicarbonyl compounds in high yields by supramolecular catalysis involving β-cyclodextrin. The β-cyclodextrin can be recovered and reused a number of times without any loss of activity.

Key words: spirooxindole, isatin, dimedone, 4-hydroxy coumarin, barbituric acid, biomimetic synthesis, β-cyclodextrin, water.

Résumé : On a mis au point une synthèse monotope neutre et efficace, à trois composants et en milieu neutre qui permet d'obtenir avec des rendements élevés des dérivés spirooxindoles de l'isatine à partir du malononitrile et de composés 1,3-dicarbonylés et faisant appel à une supracatalyse impliquant la β-cyclodextrine. La β-cyclodextrine peut être récupérée et réutilisée un certain nombre de fois sans aucune perte d'activité.

Mots-clés : spirooxindole, isatine, dimédone, 4-hydroxycoumarine, acide barbiturique, synthèse biomimétique, β-cyclodextrine, eau.

[Traduit par la Rédaction]

Introduction

The spirooxindole is an important structure present in a number of natural bioactive compounds, such as coerulescine, elacomine, horsfiline, welwitindolinone A, spirotryprostatin A, alstonisine, and surugatoxin.[1] They display potent cytotoxic activity and are also known as h5-HT6 serotonin receptors, estrogen-receptor modulators, antiproliferative agents, and oxytocin antagonists.[2] In view of their significance, various methodologies have been developed for the construction of spirooxindole frameworks.[2] However, our interest in the synthesis of heterocyclic compounds involving supramolecular chemistry[3] and the growing focus on environment-friendly processes prompted us to revisit the synthesis of spiroxindoles.

It is highly desirable to develop a chemical system that can mimic the action of enzymes and effect organic reactions in water with excellent efficiency and selectivity. Water is a safe, inexpensive, and environment-friendly solvent, which makes its use favorable in both academic laboratories and industry. The pioneering studies of organic reactions in water by Breslow[4] in the early 1980s triggered a more widespread interest in the use of water as a medium for organic synthesis, not only because these reactions eliminate the necessity for vigorously drying solvents and substrates, but also because of the unique reactivity and selectivity often observed in aqueous reactions. However, the synthesis of spirooxindoles described so far by the three-component reaction of isatin, malononitrile or methyl cyanoacetate, and 1,3-dicarbonyl compounds have limited scope because of the use of transition-metal catalysts, microwave irradiation, surfactants, acidic or basic conditions, and hazardous solvents.[5] As a consequence, the development of environmentally benign practical synthetic routes under neutral conditions using a recyclable catalyst in water for accessing these spirooxindole derivatives still remains a major goal.

These aqueous reactions can be made more sophisticated if they can be performed under supramolecular catalysis, such as β-cyclodextrin, overcoming many of the drawbacks observed in the previous methodologies. Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities which bind substrates and catalyze chemical reactions with high selectivity. They catalyze reactions by supramolecular catalysis involving reversible formation of host-guest complexes by non-covalent bonding as seen in enzymes.

In continuation of our interest in the β-cyclodextrin catalyzed biomimetic synthesis of heterocyclic compounds in aqueous phase,[3] we have explored the aqueous-phase synthesis of spiooxindole derivatives by the three-component reaction of isatin, malononitrile, and dimedone under neutral conditions catalyzed by β-cyclodextrin (Scheme 1).

Results and discussion

In general, the reactions were carried out by forming an in situ β-CD complex of the isatin in water, followed by the

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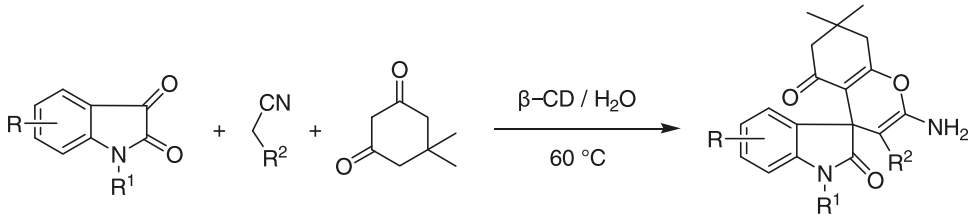
Scheme 1.

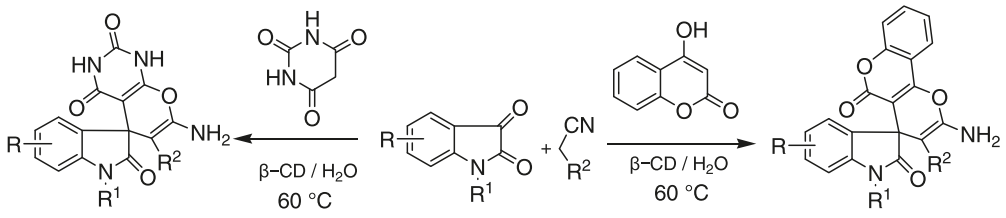


R = H, 4-Br, 6-Br, 5-CH_3, 5-NO_2
R^1= CH_3, CH_2Ph, Ph
R^2= CN, COOMe

Table 1. β-CD-catalyzed multi-component synthesis of spirooxindoles **1**–**10**.

Entry	R	R^1	R^2	Time (h)	Yield (%)
1	H	H	CN	5	90
2	4-Br	H	CN	5	89
3	6-Br	H	CN	5	85
4	5-CH_3	H	CN	5	88
5	5-NO_2	H	CN	6	84
6	H	CH_3	CN	4	91
7	H	CH_2Ph	CN	4	90
8	H	Ph	CN	4	89
9	H	H	COOMe	6	85
10	6-Br	H	COOMe	5	87

Scheme 2.



14-16

R = H, Br
R^1= H, CH_3
R^2= CN, COOMe

11-13

Table 2. β-CD-catalyzed multi-component synthesis of spirooxindoles **11**–**16**.

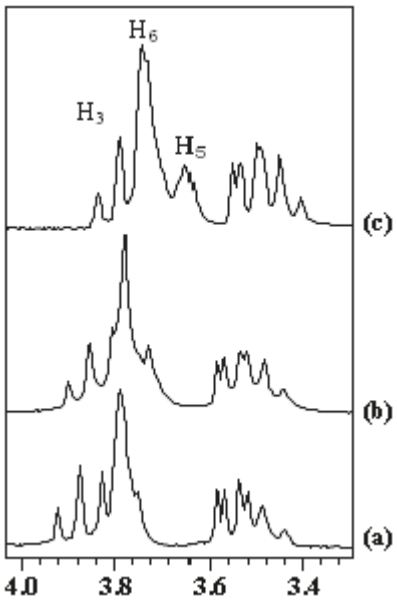
Entry	R	R^1	R^2	Time (h)	Yield (%)
11	H	H	CN	8	88
12	4-Br	H	CN	7	88
13	H	CH_3	COOMe	8	85
14	H	H	CN	8	86
15	H	CH_3	CN	7	85
16	H	H	COOMe	8	84

addition of malononitrile and dimedone, and stirring at 60 °C. The corresponding spirooxindole compounds were obtained in impressive yields (84%–91%) after 4–6 h by simple filtration. This methodology is compatible with various substituted isatins having different functionalities such as bromo, methyl, nitro, phenyl, and benzyl groups (Table 1, entries 1–8). It was found that methyl cyanoacetate also underwent condensation with isatin and dimedone to give the desired product in impressive yields (Table 1, entries 9–10, 85%–87%) under similar conditions. These reactions proceeded efficiently under neutral conditions. No byproduct formation was observed. β-Cyclodextrin can be easily recovered and reused.

Further applications of this methodology involve the reactions of 4-hydroxy coumarin and barbituric acid under the above optimized conditions (Scheme 2) to produce spirooxindole derivatives (Table 2, entries 11–16) efficiently in yields ranging from 84–88%.

The complexation of isatin with β-CD was confirmed by the isolation of the β-CD–isatin complex and the study of its ^{1}H NMR spectrum, which shows an upfield shift of H3 and H5 of β-CD as observed by us earlier.[3a] The ^{1}H NMR spectra (D_2O) of β-CD, the β-CD–isatin complex, and the freeze-dried reaction mixture of the β-CD–isatin complex after the addition of malononitrile and dimedone were studied. It was observed from Fig. 1 that there was an upfield shift of H3 (0.02 ppm) and H5 (0.02 ppm) protons of cyclodextrin in the β-CD–isatin complex as compared to β-CD, indicating the formation of an inclusion complex of isa-

Fig. 1. [1]H NMR spectra of (a) β-CD; (b) β-CD–isatin complex; and (c) reaction mixture after 2 h. The spectra were recorded in D_2O at 25 °C.



tin with β-CD from the secondary side of cyclodextrin.[6] In the spectra of the reaction mixture of the β-CD–isatin complex after the addition of malononitrile and dimedone after 2 h, an upfield shift of the CD H6 proton by 0.048 ppm was also observed. This indicated that the reaction proceeded by complexation of malononitrile and dimedone from the primary side of cyclodextrin (Fig. 1). This clearly demonstrates that the isatin is ideally located for the condensation with malononitrile and dimedone in the hydrophobic environment of the β-cyclodextrin cavity.

The catalytic activity of cyclodextrins for these reactions is established by the fact that in the absence of cyclodextrin, the reaction was observed to proceed in very poor yields (20%) even after long reaction times (24 h). The complexation of isatin with β-CD increases the reactivity of the keto group due to intermolecular hydrogen bonding with the CD-hydroxyl groups[7] facilitating the Knoevenagel condensation with malononitrile to form an isatylidene malononitrile derivative. It then undergoes the established sequence of reactions such as Michael addition of dimedone followed by the cycloaddition of hydroxyl group to the cyano moiety to form the spiro compound.[5] Here, β-CD not only forms the inclusion complex with isatin but is also involved in the intermolecular hydrogen bonding with the guest to promote the condensation and cycloaddition of the hydroxyl group to the cyano moiety.

In summary, we have developed a neutral aqueous-phase synthesis of various spirooxindole derivatives by the one-pot three-component reaction of the corresponding isatin, activated methylene reagent, and 1,3-dicarbonyl compounds under biomimetic conditions in the presence of β-cyclodextrin. These cyclodextrin mediated water solvent reactions are very useful from both economical and environmental points of view. β-Cyclodextrin, apart from being nontoxic, is also considered as metabolically safe. This straightforward, environmentally benign methodology may find widespread applications in organic and medicinal chemistry.

Experimental

General

Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FT-IR 240-c spectrometer using KBr optics. [1]H NMR spectra were recorded on Gemini-200/Avance-300/Inova-400 spectrometer in DMSO or $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on an Agilent 1200 spectrometer. Starting materials were obtained commercially from Sigma-Aldrich or Lancaster and were used without purification.

General procedure for the synthesis of spirooxindole

β-CD (1 mmol) was dissolved in water (15 mL) by warming to 60 °C until a clear solution was formed. Then, isatin (1 mmol) dissolved in methanol (0.5 mL) was added dropwise followed by malononitrile (1.2 mmol) and dimedone (1 mmol), and the mixture was stirred at 60 °C until the reaction was complete (as monitored by TLC) (Table 1). The mixture was cooled to 40 °C and the solid was filtered off, washed with water (10 mL), and recrystallized from EtOH to yield colorless crystals. The filtrate of the reaction mixture was cooled to 5 °C to recover β-CD.

Characterization data

*2-Amino-5-oxo-7,7-dimethyl-spiro[(4**H**)-5,6,7,8-tetrahydrochromene-4,3′-(3′**H**)-indol]-(1′**H**)-2′-one-3-carbonitrile (1)*

Colorless solid; mp 287–289 °C. IR (cm^{-1}) : 3380, 3308, 3142, 2195, 1723, 1659, 1608, 1466, 1350, 1219, 1059, 908, 748. [1]H NMR (DMSO-d_6, 300 MHz) δ: 10.41 (s, 1H, NH), 7.22 (br s, 2H, NH_2), 7.11 (t, 1H, J = 10.0 Hz, ArH), 7.01–6.73 (m, 3H, ArH), 2.56 (s, 2H, CH_2), 2.23–2.03 (m, 2H, CH_2), 1.03 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). EIMS *m/z*: 335 [M^+]. Anal. calcd. for $C_{19}H_{17}N_3O_3$: C 68.05, H 5.11, N 12.53; found: C 68.24, H 5.22, N 12.61.

*2-Amino-5-oxo-7,7-dimethyl-spiro[(4**H**)-5,6,7,8-tetrahydrochromene-4,3′-(3′**H**)-4′-bromo-indol]-(1′**H**)-2′-one-3-carbonitrile (2*

Colorless solid; mp 312–315 °C. IR (cm^{-1}): 3363, 3310, 3152, 2962, 2199, 1724, 1659, 1605, 1497, 1350, 1219, 1048, 928. [1]H NMR (DMSO-d_6, 300 MHz) δ: 10.41 (s, 1H, NH), 7.28 (br s, 2H, NH_2), 7.14 (t, 1H, J = 7.6 Hz, ArH), 6.98 (d, 1H, J = 7.2 Hz, ArH), 6.78 (d, 1H, J = 7.6 Hz, ArH), 2.56 (d, 2H, J = 7.6 Hz, CH_2), 2.17 (d, 1H, J = 15.6 Hz, CH), 2.08 (d, 1H, J = 16.0 Hz, CH), 1.03 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). Anal. calcd. for $C_{19}H_{16}BrN_3O_3$: C 55.09, H 3.89, N 10.14; found: C 55.19, H 3.97, N 10.19.

*Methyl 2-amino-5-oxo-7,7-dimethyl-spiro[(4**H**)-5,6,7,8-tetrahydrochromene-4,3′-(3′**H**)-indol]-(1′**H**)-2′-one-3-carboxylate (9)*

Colorless solid; mp 255–256 °C. IR (cm^{-1}): 3366, 3241, 3187, 2955, 1690, 1614, 1520, 1471, 1304, 1225, 1167, 1054, 928, 746. [1]H NMR ($CDCl_3$, 400 MHz) δ: 10.22 (s, 1H, NH), 7.88 (br s, 2H, NH_2), 7.05–7.11 (m, 1H, ArH),

6.90 (d, 1H, *J* = 6.0 Hz, ArH), 6.82 (t, 1H, *J* = 7.8 Hz, ArH), 6.76 (d, 1H, *J* = 6.9 Hz, ArH), 3.32 (s, 3H, CH_3), 2.66 (d, 1H, *J* = 17.4 Hz, CH), 2.55 (d, 1H, *J* = 17.4 Hz, CH), 2.23 (d, 1H, *J* = 15.66 Hz, CH), 2.07 (d, 1H, *J* = 15.66 Hz, CH), 1.10 (s, 3H, CH_3), 1.01 (s, 3H, CH_3). EIMS *m*/*z*: 368 [M^+]. Anal. calcd. for $C_{20}H_{20}N_2O_5$: C 65.21, H 5.47, N 7.60; found: C 65.47, H 5.35, N 7.68.

2-Amino-5,7-dioxo-spiro[(3′H)-indol-3′,4,4(H)-5,6,7,8-tetrahydropyrano(2,3-d)pyrimidine]-(1′H)-2′-one-3-carbonitrile (11)

Colorless solid; mp 273–274 °C. IR (cm^{-1}): 3448, 3280, 3142, 3033, 2204, 1697, 1643, 1511, 1443, 1396, 1242, 1114, 1003, 846, 663. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 12.40 (br s, 1H, NH), 12.02 (br s, 1H, NH), 10.52 (br s, 1H, NH), 7.41 (br s, 2H, NH_2), 7.17 (t, 2H, *J* = 8.0 Hz, ArH), 6.91 (t, 1H, *J* = 7.6 Hz, ArH), 6.79 (d, 1H, *J* = 7.6 Hz, ArH). EIMS *m*/*z*: 323 [M^+]. Anal. calcd. for $C_{15}H_9N_5O_4$: C 55.73, H 2.81, N 21.66; found: C 55.40, H 2.89, N 21.68.

2-Amino-5-oxo-spiro[(3′H)-indol-3′,4-4(H)-pyrano(3,2-c)chromen]-(1′H)-2′-one-3-carbonitrile (14)

Colorless solid; mp 290–292 °C. IR (cm^{-1}): 3350, 3300, 3195, 2954, 2199, 1720, 1667, 1613, 1522, 1474, 1364, 1224, 1132, 1072, 972, 748. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.64 (s, 1H, NH), 7.95 (d, 1H, *J* = 8.0 Hz, ArH), 7.77 (t, 1H, *J* = 7.6 Hz, ArH), 7.67 (br s, 2H, NH_2), 7.57 (t, 1H, *J* = 7.6 Hz, ArH), 7.50 (d, 1H, *J* = 8.4 Hz, ArH), 7.22 (t, 2H, *J* = 7.6 Hz, ArH), 6.93 (t, 1H, *J* = 7.6 Hz, ArH), 6.85 (d, 1H, *J* = 8.0 Hz, ArH). EIMS *m*/*z*: 357 [M^+]. Anal. calcd. for $C_{20}H_{11}N_3O_4$: C 67.23, H 3.10, N 11.76; found: C 67.49, H 3.02, N 11.86.

Supplementary data

Supplementary data for this article are available on the journal Web site (canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5305. For more information on obtaining material, refer to cisti-icist.nrc-cnrc.gc.ca/cms/unpub_e.shtml.

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