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A novel organocatalytic multi-component reaction: an efficient synthesis of polysubstituted pyrano-fused spirooxindoles

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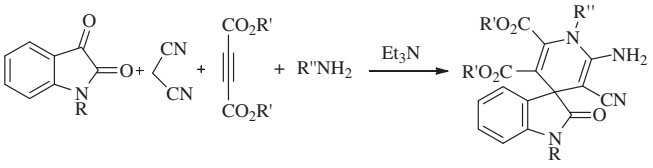
ABSTRACT

A practical, simple, and efficient method for the synthesis of pyrano-fused spirooxindoles via an organocatalytic three-component reaction of isatins, malononitrile, and dialkyl acetylenedicarboxylate in the presence of 3,4-dimethylaniline as an organocatalyst in ethanol is reported. The structures of these products are confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry, and single-crystal X-ray diffraction studies.

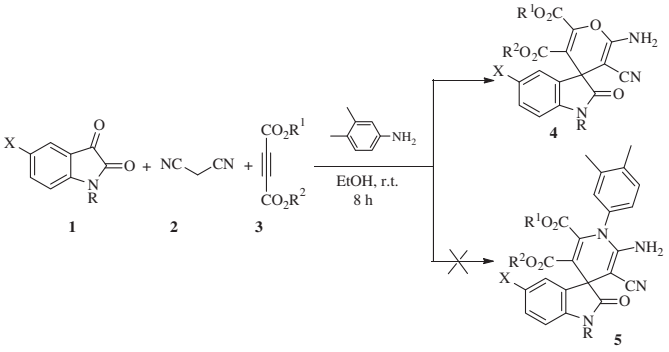
The synthesis of novel heterocyclic compounds with potential biological activity is one of the main challenges in chemical biology and medicinal chemistry. The search for new and efficient synthetic methodologies to access small molecules of privileged structures is of significant interest.[1] Multicomponent reactions (MCRs) have proved to be very influential and efficient bond-forming tools in organic, combinatorial, and medicinal chemistry.[2] In addition to the fundamental atom economy and selectivity underlying such reactions, the simpler procedures, shorter reaction times, energy savings, and environmental friendliness have all led to numerous efforts to design and execute MCRs in both academia and industry.[3]

The spirooxindole moiety is an important heterocycle found in many pharmacological agents and natural products such as coerulescine, horsfiline, welwitindolinone A, spirotryprostatin A, elacomine, and alstonisine.[4] Spirotryprostatin A, a natural alkaloid isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly, and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors.[5,6]

Compounds having the pyran structural motif exhibit a wide range of biological activities, such as diuretic, analgesic, myorelaxant,[7] anticoagulant,[8] anticancer,[9] anti-tumor,[10] and anti-HIV.[11] In addition, they are also useful for the treatment of neurodegenerative disorders including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease.[12] Pyran-annulated oxindoles are widely distributed in Nature and exhibit diverse physiological activities.[13] Several synthetic spiroheterocyclic compounds, containing both indole and pyran moieties possess anticonvulsant, analgesic,[14] herbicidal,[15] and antimicrobial activities.[16]



Scheme 1. Synthesis of spirooxindole-fused dihydropyridines by Perumal et al.



Scheme 2. Synthesis of polyfunctionalized pyrano-fused spirooxindoles **4**.

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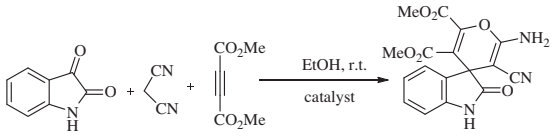
Table 1
Effect of catalyst on the reaction



1a **2** **3a** **4a**

Entry	Catalyst[a]	Time (h)	Yield (%)
1	Aniline	15	43
2	*p*-Toluidine	15	51
3	4-Aminophenol	10	75
4	*N*,*N*-Dimethylbenzene-1,4-diamine	9	85
5	4,5-Dimethylbenzene-1,2-diamine	10	83
6	3,4-Dimethylaniline	8	90
7	3,4-Dimethylaniline	8	75[b]
8	3,4-Dimethylaniline	8	55[c]
9	4-Nitroaniline	15	Trace[d]
10	Triethylamine	15	Trace[d]
11	Diethylamine	15	Trace[d]
12	None	15	0

[a] Catalyst = 1 mmol.
[b] Catalyst = 0.7 mmol.
[c] Catalyst = 0.5 mmol.
[d] The Perumal product was obtained in <20% yield.

Table 2
Effect of solvent on the reaction

Entry	Solvent	Time (h)	Yield (%)
1	CH_3CN	12	48
2	1,4-Dioxane	12	35
3	THF	12	43
4	MeOH	8	68
5	EtOH	8	90
6	H_2O	12	55

The multi-component reactions of amines, acetylenic esters, active carbonyl compounds, and malononitrile based on a Huisgen 1,4-dipole intermediate have been reported for the synthesis of new heterocyclic compounds.[17–19] Perumal and co-workers described the synthesis of spirooxindole-fused dihydropyridines via the reaction of isatins, malononitrile, primary amines, and acetylenic esters in the presence of Et_3N (Scheme 1).[20]

Due to the important biological activities of spirooxindoles and pyrans, we hypothesize that the synthesis of new heterocycles containing both spirooxindole and pyran moieties may result in the discovery of new drug candidates. Therefore, in continuation of our efforts on the design and efficient synthesis of new spirooxindoles,[21–24] herein, we report a novel and efficient method for the synthesis of polyfunctionalized pyrano-fused spirooxindoles **4** via the three-component condensation of isatins **1**, malononitrile (**2**), and dialkyl acetylenedicarboxylates **3** in the presence of 3,4-dimethylaniline (DMA) as an organocatalyst (Scheme 2). It was interesting that spirooxindole-fused dihydropyridines **5** were not detected at all, while pyrano-fused spirooxindoles **4** were obtained in good yields.

Our initial experiments focused on the three-component reaction of isatin (**1a**) (1 mmol), malononitrile (**2**) (1 mmol), and dimethyl acetylenedicarboxylate (**3a**) (1 mmol) as a model reaction, in the presence of various aliphatic and aromatic amines as organocatalysts in EtOH at room temperature (Table 1). It was found that the reaction using an equimolar amount of DMA resulted in a higher yield and short reaction time (Table 1, entry 6). When this reaction was carried out without a catalyst product **4a** was not detected (Table 1, entry 12).

To find the optimal reaction solvent, various examples were investigated on the DMA-catalyzed model reaction at room temperature (Table 2). The results showed that the solvent affected

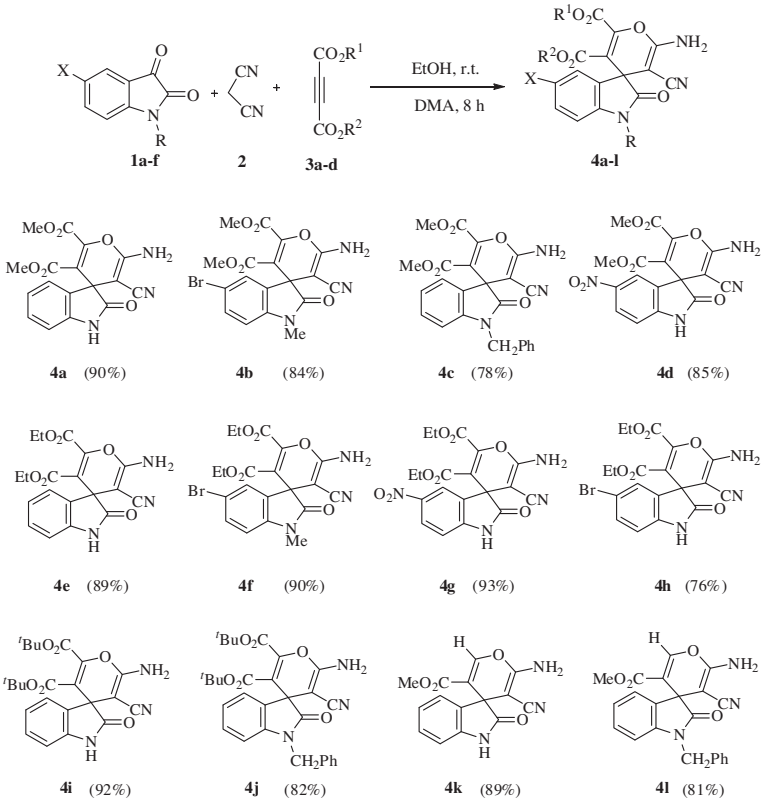


Figure 1. Synthesis of pyranospirooxindoles **4**.

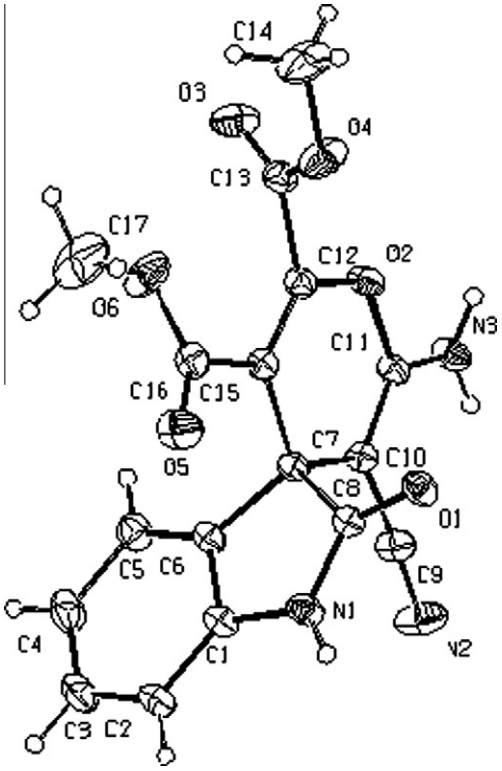
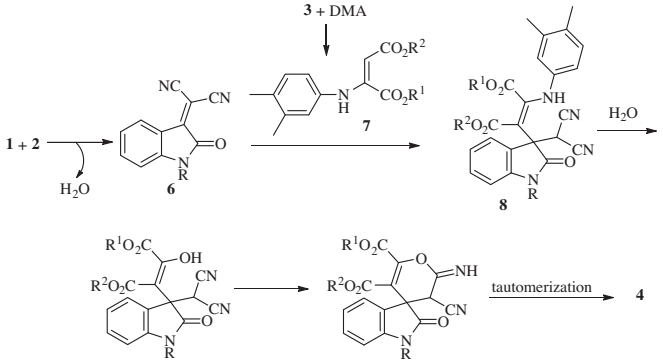


Figure 2. X-ray crystal structure (ORTEP) of compound **4a**.



Scheme 3. Possible mechanism for the formation of product **4**.

the efficiency of the reaction and EtOH proved to be the best choice (Table 2, entry 5).

Using the optimized conditions, a variety of isatins **1a–f** and dialkylacetylenedicarboxylates **3a–d** were employed to evaluate the substrate scope of the reaction. Pyranospirooxindoles **4a–l** were obtained in good yields (Fig. 1).[25] As anticipated, these reactions proceeded very cleanly at room temperature and no side reactions were observed. All the compounds described in this Letter have been synthesized for the first time.

The products **4** were stable solids, the structures of which were fully characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The structure of **4a** was confirmed by single-crystal X-ray analysis[26] (Fig. 2).

We have not established an exact mechanism for the formation of **4**, however, a reasonable possibility is shown in Scheme 3. It is reasonable to assume that product **4** results from the initial formation of intermediate isatylidene malononitrile **6** by standard Knoevenagel condensation of **1** and **2**. Subsequent Michael-type addition of the β-enamino ester **7** (formed in situ by reaction of **3** and DMA) to **6** yields intermediate **8**. Finally, intermolecular nucleophilic substitution of H_2O on **8**, followed by cyclization and tautomerization affords the corresponding product **4**. To help clarify the proposed mechanism, first, the isatylidene malononitrile **6a** was synthesized via condensation of isatin **1a** and malononitrile, and then reaction of **6a** with DMAD in the presence of DMA afforded the corresponding product **4a** in 83% yield.

In conclusion, an efficient, atom-economic, and environmentally friendly method for the preparation of polysubstituted pyrano-fused spirooxindoles using readily available starting materials in EtOH is reported. Prominent among the advantages of this method are operational simplicity, good yields, and the easy work-up procedure employed.

Acknowledgement

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25. *General procedure for preparation of pyran-annulated spirooxindoles* (**4**). A mixture of isatin **1** (1 mmol) and malononitrile (**2**) (1 mmol) in EtOH (3 mL) was stirred for 15 min then treated with a solution of dialkyl acetylenedicarboxylate **3** (1 mmol) and 3,4-dimethylaniline (1 mmol) in EtOH (1 mL). The mixture was stirred at room temperature for 8 h. After completion of the reaction (TLC, eluent: EtOAc/hexane, 1:2), the mixture was filtered and the precipitate washed with H_2O (5 mL) and EtOH (5 mL) to afford the pure product **4**. *Dimethyl 2′-amino-3′-cyano-2-oxospiro[indoline-3,4′-pyran]-*

5′,6′-dicarboxylate (**4a**). White powder (90%); mp 216–218 °C. IR (KBr) (ν_{max}/cm^{-1}): 3391, 3301, 3167, 2200, 1751, 1725, 1706. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.39 (3H, s, OMe), 3.83 (3H, s, OMe), 6.82 (1H, d, $^3J_{HH}$ = 7.4 Hz, H–Ar), 6.98 (1H, t, $^3J_{HH}$ = 7.2 Hz, H–Ar), 7.15 (1H, d, $^3J_{HH}$ = 7.2 Hz, H–Ar), 7.23 (1H, t, $^3J_{HH}$ = 7.4 Hz, H–Ar), 7.52, (2H, s, NH_2), 10.56, (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 49.5, 52.9, 53.9, 55.7, 110.2, 111.9, 117.3, 122.7, 124.9, 130.0, 132.0, 142.3, 145.7, 159.7, 161.0, 163.6, 177.2. MS, *m*/*z*: 355 (M^+). Anal. Calcd for $C_{17}H_{13}N_3O_6$: C, 57.47; H, 3.69; N, 11.83. Found: C, 57.36; H, 3.75; N, 11.73. *Dimethyl 2′-amino-5-bromo-3′-cyano-1-methyl-2-oxospiro[indoline-3,4′-pyran]-5′,6′-dicarboxylate* (**4b**). White powder (yield 84%); mp 222–224 °C. IR (KBr) (ν_{max}/cm^{-1}): 3407, 3310, 2209, 1761, 1649, 1604. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.14 (3H, s, NMe), 3.41 (3H, s, OMe), 3.82 (3H, s, OMe), 7.04 (1H, s, H–Ar), 7.53 (2H, s, H–Ar), 7.64 (2H, s, NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 27.1, 49.0, 53.1, 54.0, 54.9, 109.6, 111.3, 115.2, 117.1, 127.5, 132.8, 134.0, 143.1, 147.4, 159.6, 161.0, 163.4, 175.4. MS, *m*/*z*: 449 (M^+, ^{81}Br), 447 (M^+, ^{79}Br). Anal. Calcd for $C_{18}H_{14}BrN_3O_6$: C, 48.23; H, 3.15; N, 9.37. Found: C, 48.07; H, 3.08; N, 9.24. *Diethyl 2′-amino-5-bromo-3′-cyano-1-methyl-2-oxospiro[indoline-3,4′-pyran]-5′,6′-dicarboxylate* (**4f**). Cream powder (yield 90%); mp 190–192 °C. IR (KBr) (ν_{max}/cm^{-1}): 3455, 3280, 2191, 1719, 1634, 1604. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.81 (3H, s, Me), 1.25 (3H, s, Me), 3.14 (3H, s, NMe), 3.83 (2H, s, OCH_2), 4.27 (2H, s, OCH_2), 7.03–7.06 (1H, m, H–Ar), 7.50–7.58 (4H, m, H–Ar and NH_2).^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 13.6, 14.0, 49.0, 55.0, 61.8, 63.2, 63.3, 109.4, 111.2, 115.1, 117.1, 127.5, 132.8, 134.0, 143.2, 147.5, 159.7, 160.5, 162.8, 175.5. MS, *m*/*z*: 477 (M^+, ^{81}Br), 475 (M^+, ^{79}Br). Anal. Calcd for $C_{20}H_{18}BrN_3O_6$: C, 50.44; H, 3.81; N, 8.82. Found: C, 50.32; H, 3.73; N, 8.89. *Di-tert-butyl 2′-amino-3′-cyano-2-oxospiro[indoline-3,4′-pyran]-5′,6′-dicarboxylate* (**4i**). White powder (yield 92%); mp 178–180 °C. IR (KBr) (ν_{max}/cm^{-1}): 3415, 3310, 3155, 2208, 1745, 1610. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.00 (9H, s, 3Me), 1.45 (9H, s, 3Me), 6.84 (1H, d, $^3J_{HH}$ = 7.4 Hz, H–Ar), 6.99 (1H, t, $^3J_{HH}$ = 7.4 Hz, H–Ar), 7.12 (1H, d, $^3J_{HH}$ = 7.2 Hz, H–Ar), 7.26 (1H, t, $^3J_{HH}$ = 7.2 Hz, H–Ar), 7.44 (2H, s, NH_2), 10.61 (1H, s, NH).^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 27.1, 27.6, 49.3, 55.8, 82.8, 84.5, 110.1, 111.6, 114.0, 117.5, 122.6, 124.9, 129.8, 132.5, 133.5, 142.8, 146.8, 159.8, 159.9, 162.3, 177.5. MS, *m*/*z*: 439 (M^+). Anal. Calcd for $C_{23}H_{25}N_3O_6$: C, 62.86; H, 5.73; N, 9.56. Found: C, 62.93; H, 5.79; N, 9.48.

26. *X-ray data for* ***4a***: $C_{17}H_{13}N_3O_6$, M = 355.30 g/mol, triclinic system, space group Pī, a = 6.8979(5), b = 11.0423(9), c = 12.3365(10) Å, α = 64.503(6), β = 84.134(6), γ = 79.308(6)°, V = 833.15(11) Å^3, Z = 2, Dc = 1.416 g cm^{-3}, μ(Mo Kα) = 0.110 mm^{-1}, crystal dimensions: 0.50 × 0.40 × 0.35 mm. The structure was solved using SHELXS. The structure refinement and data reduction were carried out with SHELXL from the X-Step32 suite of programs.[27] The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final $R1$ = 0.0434, $wR2$ = 0.1337 and S = 1.065 with 243 parameters using 4453 independent reflections (θ range = 1.83–29.25°). Crystallographic data for **4a** have been deposited with the Cambridge Crystallographic Data Centre, CCDC 859396. Copies of the data can be obtained, free of charge, on application to The Director, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
27. X-STEP32 Version 1.07b, X-ray structure evaluation package, 2000, Stoe & Cie, Darmstadt, Germany.