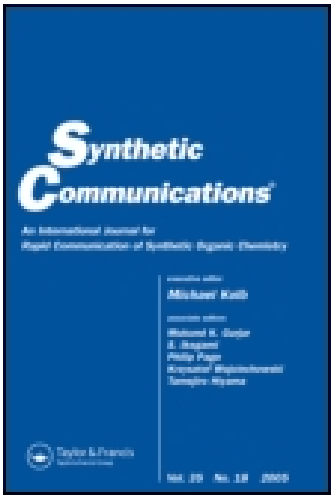

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# ONE-POT, CATALYST-FREE SYNTHESIS OF SPIROOXINDOLE AND 4*H*-PYRAN DERIVATIVES

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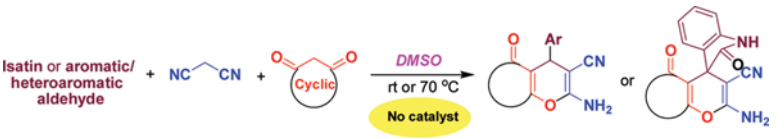
## GRAPHICAL ABSTRACT




**Abstract** *The synthesis of biologically valuable spirooxindoles and 4H-pyrans is described under catalyst-free conditions through sequential Knoevenagel–Michael–cyclization reactions from isatin or aromatic aldehyde, malononitrile, and 1,3-dicarbonyl compounds. The reaction conditions are very simple, providing excellent yield.*
*[Supplementary materials are available for this article. Go to the publisher's online edition of* Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

**Keywords** Catalyst-free; isatin; malononitrile; 4H-pyrans; spirooxindoles

## INTRODUCTION

Spirooxindole[1] and 4*H*-pyrans[2] are structural units of natural products and also display a wide range of biological activities such as anti-cancer, anti-HIV, antiviral, antiancaphylactia, antifungal, and antibacterial activities. A sequential Knoevenagel–Michael–cyclization reaction was one of the more convenient protocols for the construction of these skeletons from readily available starting materials such as isatin or aromatic aldehyde, malononitrile, and 1,3-dicarbonyl compounds. This class of reaction has been carried out in the presence of quaternary ammonium salt, base, Lewis acid, or ionic liquids such as $InCl_3$,[3a] 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU),[3b] triethylbenzylammonium chloride,[3c] piperidine,[3d] $NH_4Cl$,[3e]

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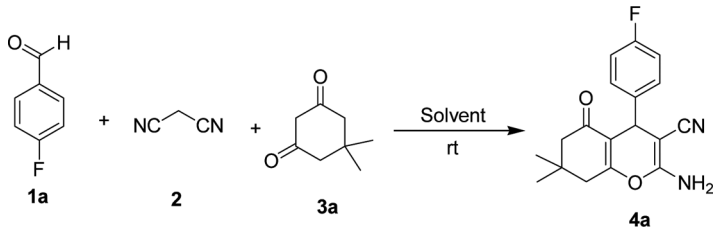
dimethylaminopyridine (DMAP),[3f] tetrabutylammonium bromide (TBAB),[3g] hexadecyltrimethylammonium bromide,[3h] alum,[3i] *S*-proline,[3j] β-CD,[3k] ethylenediammonium diacetate (EDDA),[3l] hexadecyldimethylbenzyl ammonium bromide,[3m] $K_3PO_4$,[3n] hexamethylenetetramine,[3o] KF-alumina,[3p] and nano-ZnO[3q] and ionic liquids such as $[BMIm]BF_4$,[3r] tetramethylguanidinium triflate,[3s] and $[DMDBSI]\cdot 2HSO_4$.[3t] The role of catalyst in this reaction was to catalyze the Knoevenagel as well as Michael addition reactions. Recently Elinson et al. [4a] and Khaksar et al.[4b] reported the noncatalytic thermal synthesis of 4*H*-pyrans in isopropyl alcohol (IPA) or water and 2,2,2-trifluoroethanol under reflux condition respectively. Each of the protocols has its own merits, with at least one drawback such as poor yield, harsh reaction condition, long reaction time, and high catalyst loading. With this literature background, we planned to develop an improved, catalyst-free, and easy method to access the spirooxindoles and 4*H*-pyrans, and the results are presented here.

## DISCUSSION

For optimization of the conditions, the reaction of 4-fluorobenzaldehyde, malononitrile, and dimedone was considered as the model. Here all the starting materials were mixed together, and the reaction was performed in different solvents at room temperature. Initially water, the polar protic environmentally friendly solvent, was tried and the expected product **4a** was obtained in 75% after 24 h (Table 1, entry 1) but ethanol yielded 72% of **4a** after 15 h (Table 1, entry 2). Previously this class of reaction was performed with different catalysts or without

**Table 1.** Optimization of reaction conditions




| Entry | Solvent | Time (h) | Yield (%)[a] |
|---|---|---|---|
| 1 | Water | 24 | 75 |
| 2 | EtOH | 15 | 72 |
| 3 | Cyclohexane | 24 | N/R |
| 4 | Toluene | 24 | N/R |
| 5 | THF | 24 | Trace |
| 6 | DCM | 24 | Trace |
| 7 | Acetone | 24 | Trace |
| 8 | $CH_3CN$ | 24 | 15 |
| 9 | Dioxane | 24 | 18 |
| 10 | DMA | 6 | 65 |
| 11 | DMF | 6 | 68 |
| 12 | DMSO | 1 | 98 |

[a]Isolated yield.

any catalyst in polar protic solvents such as water, ethanol, and isopropanol with limited success. The nonpolar solvents (cyclohexane and toluene) and borderline polar-aprotic solvents (tetrahydrofuran and methylene dichloride) were totally ineffective in this sequential reaction (Table 1, entries 3 to 6), whereas polar aprotic solvents (DMF and DMA) gave moderate yields of **4a** (Table 1, entries 10 and 11). Dioxane, acetonitrile, and acetone were not successful (Table 1).

The highly polar aprotic solvent dimethylsulfoxide (DMSO) worked well in this reaction, giving quantitative yield (98%) of 4*H*-pyran **4a** in a short reaction time (Table 1, entry 12) and hence was identified as the solvent of choice. The mild basic character of the oxygen in DMSO facilitates the reaction efficiently and also the product was isolated in a pure form by simple filtration. DMSO is a versatile and powerful solvent for organic reactions involving displacement, elimination, condensation, and polymerization reactions, and it can facilitate a reaction without a catalyst.[5] Recently, Xue et al.[5a] have reported the uncatalyzed Knoevenagel condensation of isatin and rhodanines in DMSO, and Dash et al.[5b] have reported the aldol reaction of thiazolidinedione in DMSO medium without the use of any catalyst.

The substrate scope was then explored with different aromatic aldehydes and 1,3-dicarbonyl components, and the results are presented in Table 2. The reaction has gone smoothly in the presence of strong electron-releasing ($OCH_3$) and electron-withdrawing ($NO_2$) groups in the phenyl ring (Table 2, entries 2 to 5). The reaction went well even with a free carboxylic acid group in the phenyl ring, requiring no protection (Table 2, entry 6). Heteroaromatic aldehydes also participated well in this reaction (Table 2, entries 7 and 8). When cyclohexan-1,3-dione and 4-hydroxycoumarin were employed instead of dimedone, the reaction took more time for completion with poor yield. When the reaction was carried out at 70 °C, the reaction was completed in 3–10 h in these cases (Table 2, entries 9 to 14).

The plausible mechanism of this uncatalyzed sequential reaction is given in Scheme 1. The mild basic nature of oxygen of DMSO may facilitate the Knoevenagel condensation and the Knoevenagel product can then undergo Michael addition with 1,3-dicarbonyl compound. The subsequent cyclization leads to the 4*H*-pyran skeleton **4**.

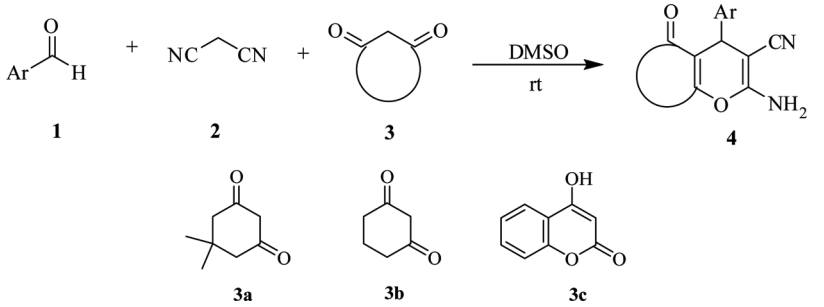
The established protocol was extended to isatin, and the reaction of isatin, malononitrile, and dimedone or cyclohexan-1,3-dione was carried out in DMSO at 70 °C for 1 h. The desired products **6a** and **6b** were obtained in 85% and 74% respectively (Scheme 2). The reaction of isatin, malononitrile, and 4-hydroxycoumarin yielded the products **7a** and **7b** in good yield, but required more reaction time compared to that for **6**.

## EXPERIMENTAL

### Typical Procedure for the Synthesis of 4*H*-Pyrans (4) as Exemplified for 2-Amino-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile (4a)

A mixture of 4-fluoro benzaldehyde (0.5 g, 4.0 mmol), malononitrile (0.29 g, 4.4 mmol), and dimedone (0.56 g, 4.0 mmol) in DMSO (5 mL) was stirred at room temperature for 1 h. The resulting mixture was poured into ice and stirred for

**Table 2.** Catalyst-free synthesis of 4*H*-pyran skeleton

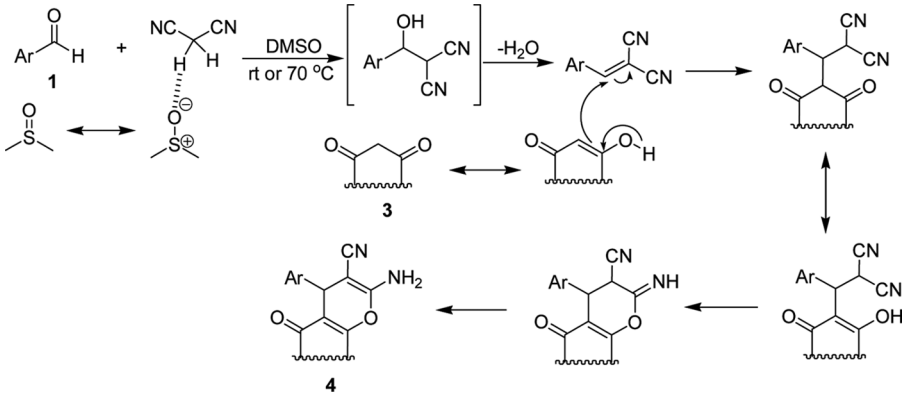



1 2 3 4

3a 3b 3c

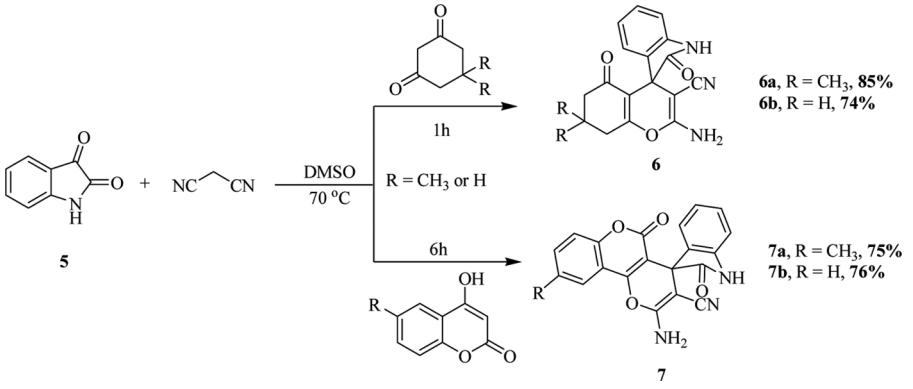
| Entry | Ar | 3 | Time (h) | Product | Yield (%)[a] | Mp (°C) observed | Mp (°C) reported |
|---|---|---|---|---|---|---|---|
| 1 | Phenyl | **3a** | 1.5 | **4b** | 96 | 228–230 | 226–228[3p] |
| 2 | 4-Chlorophenyl | **3a** | 1.5 | **4c** | 98 | 238–240 | 237–239[3m] |
| 3 | 4-Nitrophenyl | **3a** | 1 | **4d** | 90 | 177–179 | 178–180[3m] |
| 4 | 4-Methoxyphenyl | **3a** | 5 | **4e** | 85 | 195–197 | 194–196[3m] |
| 5 | 4-Methylphenyl | **3a** | 2 | **4f** | 86 | 217–219 | 218–220[3m] |
| 6 | 3-Carboxyphenyl | **3a** | 1 | **4g** | 92 | 238–240 | — |
| 7 | 2-Thienyl | **3a** | 2 | **4h** | 88 | 211–213 | 210–212[3n] |
| 8 | 1-Acetyl-indol-3-yl | **3a** | 3 | **4i** | 87 | 206–208 | — |
| 9 | 4-Chlorophenyl | **3b** | 10 | **4j** | 72[b] | 225–227 | 224–226[3m] |
| 10 | 4-Chlorophenyl | **3c** | 3 | **4k** | 88[b] | 259–261 | 260–262[3b] |
| 11 | 4-Methylphenyl | **3c** | 6 | **4l** | 78[b] | 254–256 | 253–255[3b] |
| 12 | 4-Hydroxy-3-methoxyphenyl | **3c** | 10 | **4m** | 62[b] | 241–243 | — |
| 13 | Phenyl | **3c** | 10 | **4n** | 73[b] | 257–259 | 256–258[3b] |
| 14 | 2-Thienyl | **3c** | 10 | **4o** | 69[b] | 229–231 | 228–229[3o] |

[a]Isolated yield.
[b]The reaction was carried out at 70 °C.




1 3 4

**Scheme 1.** Mechanism for the formation of 4*H*-pyran skeleton.




**Scheme 2.** Synthesis of spirooxindole skeleton.

15 min, and the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.21 g, 98%) as a white powder. Mp 188–190 °C; IR $\nu_{max}$ (KBr) 3356, 3179, 2190, 1674, 1637, 1604, 1507, 1464, 1410, 1367 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 1.03 (s, 3H), 1.11 (s, 3H), 2.22 (d, $J = 6.6$ Hz, 2H), 2.45 (s, 2H), 4.40 (s, 1H), 4.56 (s, 2H), 6.97 (t, $J = 8.6$ Hz, 2H), 7.20 (dd, $J = 8.6$ Hz, 2.8 Hz, 2H); $\delta_C$ (100 MHz, DMSO-$d_6$) 26.8, 28.3, 31.8, 34.9, 50.0, 58.1, 112.6, 115.0, 119.6, 129.0, 140.9, 158.5, 159.7, 162.1, 162.5, 195.7. Anal. calcd. for $C_{18}H_{17}FN_2O_2$: C, 69.22; H, 5.49; N, 8.97. Found: C, 69.28; H, 5.51; N, 8.99%. ESI-m/z calcd. for $[C_{18}H_{17}FN_2O_2+H]^+$ 313.1; found 313.1.

### Typical Procedure for the Synthesis of Spirooxindoles (6 and 7) as Exemplified for 2-Amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (6a)

A mixture of isatin (0.6 g, 4.0 mmol), malononitrile (0.29 g, 4.4 mmol), and dimedone (0.56 g, 4.0 mmol) in DMSO (5 mL) was stirred at 70 °C for 1 h. The resulting mixture was poured into ice and stirred for 15 min; the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.16 g, 85%) as a pale yellow solid. Mp 267–269 °C (lit.[31] 268–270 °C); IR $\nu_{max}$ (KBr) 3378, 3315, 3143, 2192, 1722, 1683, 1657, 1621, 1605, 1472, 1349 $cm^{-1}$; $\delta_H$ (400 MHz, DMSO-$d_6$) 1.00 (s, 3H), 1.03 (s, 3H), 2.11 (q, $J = 16.1$ Hz, 2H), 2.54–2.61 (m, 2H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.89 (t, $J = 7.4$ Hz, 1H), 6.97 (d, $J = 7.2$ Hz, 1H), 7.14 (t, $J = 7.6$ Hz, 1H), 7.22 (s, 2H), 10.39 (s, 1H); $\delta_C$ (100 MHz, DMSO-$d_6$) 27.4, 28.0, 32.3, 47.2, 50.4, 57.9, 109.6, 111.2, 117.7, 122.1, 123.4, 128.5, 134.8, 142.4, 159.1, 164.5, 178.4, 195.2. Anal. calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.11; H, 5.12; N, 12.55%. ESI-m/z calcd. for $[C_{19}H_{17}N_3O_3$- H]$^+$ 334.1; found 334.1.

## SUPPORTING INFORMATION

Full experimental details, analytical data, and copies of $^1H$ and $^{13}C$ spectra can be found via the Supplementary Content section of this article's Web page.

## ACKNOWLEDGMENTS

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