An efficient one-pot method for a highly stereoselective base-catalysed synthesis of novel trans-spirocyclopropane-indanedione derivatives

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A one-pot, efficient, synthesis of six novel *trans*-spirocyclopropane-indanedione derivatives with high stereoselectivity has been achieved *via* the reaction of acetopyridinium chloride with 1,3-indandione and an araldehyde in the presence of triethylamine in acetonitrile under reflux conditions. The attractive features of the method are excellent yields and high purity, short reaction times, and easy work-up.

Keywords: spiro-cyclopropanes, triethylamine, acetopyridinium chloride, aryl aldehydes, 1,3-indandione, stereoselective synthesis

Cyclopropanes are one of the most important strained small ring cyclic hydrocarbons that have attracted much attention.[1,2] Multicomponent reactions can be an ideal way for the preparation of cyclopropanes, in which one-pot transformations take place to yield the final product.[3–5] Cyclopropanes are one of the most important and fundamental groups in many naturally occurring compounds and pharmaceutical and agrochemical products.[6,7] Moreover, they exhibit a wide range of biological activity[8] ranging from enzyme inhibition to antibiotic, herbicidal, antitumor,[9] anticancer,[10] antibacterial, antiviral, antimycotic, antineoplastic, antimetastatic, thyromimetic, anti-HIV, phytotoxic, and insecticidal activities, as well as carboxy peptidase inhibition properties[11] and antiviral properties.[12]

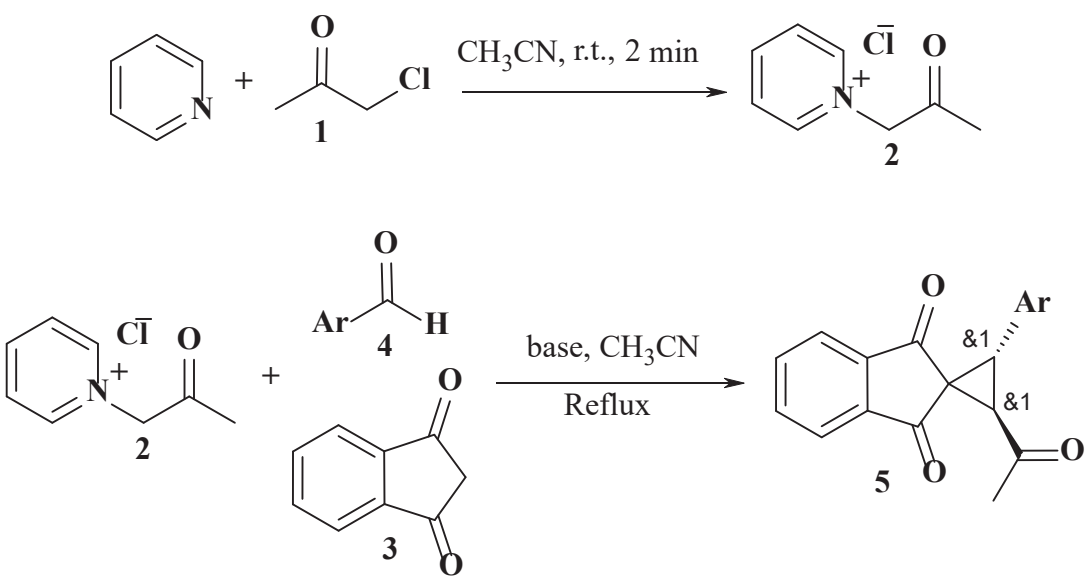
In this study, we planned to prepare some cyclopropane compounds for bio-testing. We were guided in our choice of method by some recent work by Bavantula and co-workers[13] in which a series of polysubstituted cyclopropane compounds were prepared in a highly stereoselective way. The synthesis involved the reaction between 4-chlorophenacylpyridinium bromide (prepared *in situ* from the reaction between pyridine and 4-chlorophenacyl bromide) and indan-1,3-dione and an araldehyde in the presence of trimethylamine in acetonitrile. It occurred to us that an interesting series of related polycyclic cyclopropane compounds could be formed by using most of the same reactants under similar conditions but replacing 4-chlorophenacylpyridinium bromide with acetopyridinium chloride. Here we report on the successful synthesis of a series of six novel cyclopropane compounds.

Results and discussion

We chose benzaldehyde (**4**; Ar = Ph) as a model compound to optimise the reaction conditions. We first used the reaction conditions similar to those described previously by Bavantula and co-workers.[13] Accordingly, we treated acetyl chloride **1** with pyridine at room temperature to form acetopyridinium chloride **2** (Scheme 1). This salt **2** was then reacted with 1,3-indandione **3** and benzaldehyde (**4**; Ar = Ph) in acetonitrile at reflux using triethylamine as catalyst (Scheme 2). The expected product was formed in high yield (92%). Other bases were tried, but showed no improvement on triethylamine (Table 1), so the use of 2 equiv. Et_3N and a reaction time of 1.5 h (entry 6) were chosen as the optimum conditions.

Using these optimised reaction conditions, we then investigated the scope and efficiency of this methodology by the preparation of spirocyclopropane-indanedione derivatives *via* different aromatic aldehydes and the results are shown in Table 2.

The structure of compounds **5a–f** were deduced from their IR, ^{1}H, and ^{13}C NMR spectra and their MS and elemental analyses. The mass spectra of compounds **5a–f** were fairly similar and displayed molecular ion peaks. In their ^{1}H NMR spectra, the two protons at the 2,3-position of the cyclopropane



Scheme 1

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Table 1 Optimisation of the reaction conditions (catalyst, duration of reaction) for the reaction between pre-formed acetopyridinium chloride **2** (1.5 mmol), 1,3-indanedione **3** and benzaldehyde (**4**; Ar = Ph) in the presence of a base catalyst in MeCN (5 ml) (Scheme 1)[a]

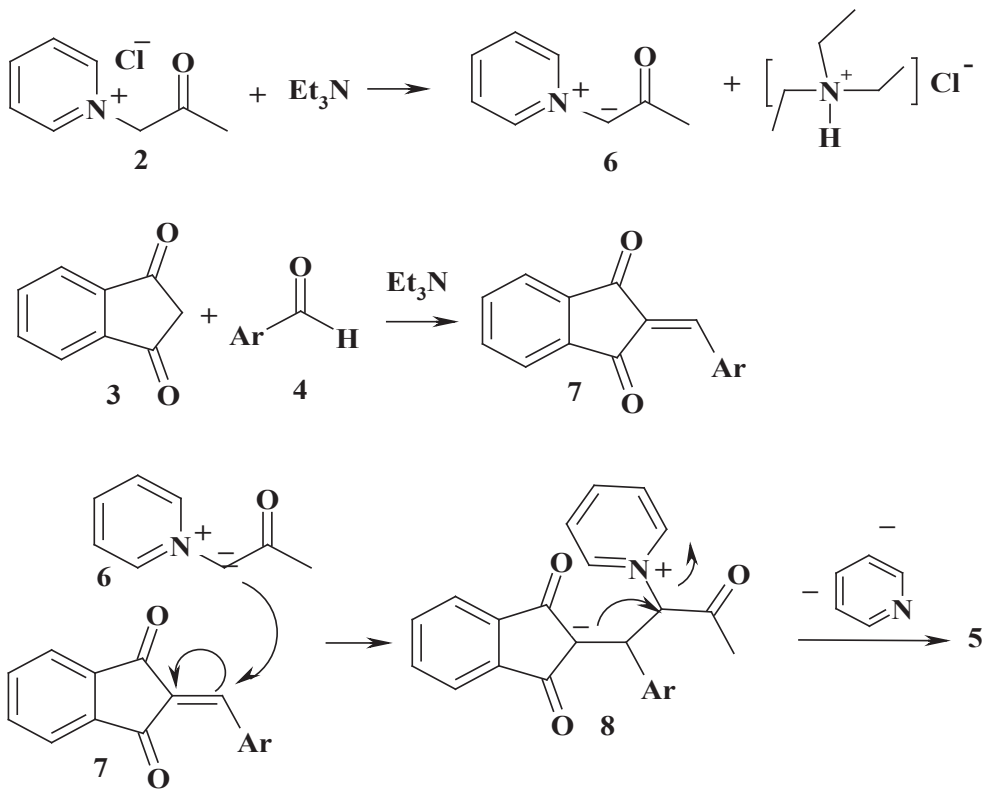
Entry	Catalyst	Amount (equiv.)	Conditions/solvent	Time (h)	Yield[b] (%)
1	No catalyst	–	Reflux/CH_3CN	24	–
2	*p*-TSA	2	Reflux/ CH_3CN	2	10
3	DABCO	2	Reflux/ CH_3CN	1.5	50
4	Piperidine	2	Reflux/ CH_3CN	1.5	65
5	Et_3N	1	Reflux/ CH_3CN	2	78
6	**Et_3N**	**2**	**Reflux/ CH_3CN**	**1.5**	**92**
7	Et_3N	3	Reflux/ CH_3CN	1.5	93

[a]Reaction conditions: to a stirred mixture of pre-formed acetopyridinium chloride **2** (1.5 mmol), indan-1,3-dione **3** (1 mmol) and benzaldehyde **4** (Ar = Ph) (1 mmol) in MeCN (5 mL) was added a base (2 mmol) and the mixture heated at reflux for various times. [b]Isolated yields.

Table 2 Yields of a series of *trans*-spirocyclopropane-indanedione derivatives **5** (Ar = various) prepared from acetopyridinium chloride **2**, indan-1,3-dione **3** and an araldehyde **4** (Ar = various) (Scheme 1)[a]

Entry	Ar	Product	Yield (%)[b]	M.p. (°C)
1	C_6H_5	**5a**	92	173–175
2	4–ClC_6H_4	**5b**	95	157–159
3	4-CNC_6H_4	**5c**	91	103–105
4	4–BrC_6H_4	**5d**	94	161–163
5	4–Cl–3–$NO_2C_6H_3$	**5e**	93	199–201
6	2–$NO_2C_6H_4$	**5f**	94	149–151

[a]Reaction conditions: to a stirred mixture of pre-formed acetopyridinium chloride **2** (1.5 mmol), indan-1,3-dione **3** (1 mmol) and an araldehyde **4** (Ar = various) (1 mmol) in MeCN (5 mL) was added triethylamine (2 mmol) and the mixture heated at reflux for 1.5 h. [b]Isolated yields.



Scheme 2

ring displayed two doublets at 3.70 and 4.01 ppm with a vicinal coupling constant of 8.8 Hz. It has been documented that in *cis*-2,3-cyclopropane ring the vicinal coupling constant of the two methine protons is 6–12 Hz, while in a *trans*-2,3-cyclopropane ring the vicinal coupling constant is 4–9 Hz. So we concluded that the thermodynamically stable *trans* isomer of 2,3-cyclopropane derivatives were formed. An X-ray crystallographic study has confirmed the *trans* assignment.[13] The mechanism of the reaction is probably similar to that published by Bavantula and co-workers[13] (Scheme 2). The reaction for the formation of spiro-cyclopropane derivatives occurs through a Knoevenagel condensation, Michael addition and finally S_N2 substitution reaction.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. NMR spectra were obtained on a Bruker DRX-400 MHz spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) in $CDCl_3$ using TMS as an internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) are given in Hz. Others chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

In a 25 mL round bottom flask, acetyl chloride (1.5 mmol), pyridine (1.5 mmol) and acetonitrile (5 mL) were added and stirred at room temperature for 2 min. A white solid, acetopyridinium chloride precipitate formed; to this the aromatic aldehyde (1 mmol), 1,3-indandione (1 mmol) and triethylamine (2 mmol) as catalyst were added and refluxed for 1.5 h. After completion of the reaction, monitored by TLC, The mixture was then cooled and crystallisation was performed by ethanol to afford the pure product.

2-Acetyl-3-phenylspiro-[cyclopropane-1,2'-indene]-1',3'-dione (**5a**): Pink powder; m.p. 173–175 °C; IR (ν_{max}, cm^{-1}) KBr: 1737, 1710,

1698 (3 × C=O); ^{1}H NMR δ 2.39 (3H, s, CH_3), 3.73 (1H, d, *J* = 8.8 Hz, CH), 4.08 (1H, d, *J* = 8.8 Hz, CH), 7.31–7.37 (5H, m, 5 × ArH), 7.80–7.88 (3H, m, 3 × ArH), 8.00–8.02 (1H, m, ArH); ^{13}C NMR δ 30.3 (CH_3), 42.5 (CH), 43.9 (CH), 47.1, 122.9, 123.0, 128.2, 128.3, 129.1, 132.1, 135.2, 135.3, 141.9, 141.9, 193.7, 194.0, 199.7; MS *m/z* (%): 290 (7); Anal. calcd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86; found: C, 78.76; H, 4.95%.

2-Acetyl-3-(4-chlorophenyl)-spiro[cyclopropane-1,2'-indene]-1',3'-dione (**5b**): Violet powder; m.p. 157–159 °C; IR (ν_{max}, cm^{-1}) KBr: 1735, 1708, 1692 (3 × C=O); ^{1}H NMR δ 2.37 (3H, s, CH_3), 3.68 (1H, d, *J* = 8.8 Hz, CH), 4.02 (1H, d, *J* = 8.8 Hz, CH), 7.23 (2H, d, *J* = 8.0 Hz, 2 × ArH), 7.30 (2H, d, *J* = 8.0 Hz, 2 × ArH), 7.81–7.89 (3H, m, 3 × ArH), 8.00–8.02 (1H, m, ArH); ^{13}C NMR δ 30.3 (CH_3), 41.3 (CH), 43.8 (CH), 46.8, 123.0, 123.1, 128.6, 130.4, 130.6, 134.1, 135.4, 135.4, 141.9, 193.6, 194.7, 199.2; MS *m/z* (%): 324 (5); Anal. calcd for $C_{19}H_{13}ClO_3$: C, 70.27; H, 4.03; found: C, 70.40; H, 4.14%.

4-(2-Acetyl-1',3'-dioxo-1',3'-dihydrospiro-[cyclopropane-1,2'-inden]-3-yl)benzonitrile (**5c**): Grey powder; m.p. 103–105 °C; IR (ν_{max}, cm^{-1}) KBr: 1733, 1711, 1685 (3 × C=O); ^{1}H NMR δ 2.37 (3H, s, CH_3), 3.70 (1H, d, *J* = 8.8 Hz, CH), 4.06 (1H, d, *J* = 8.8 Hz, CH), 7.42 (2H, d, *J* = 8.4 Hz, 2 × ArH), 7.63 (2H, d, *J* = 8.4 Hz, 2 × ArH), 7.84–7.91 (3H, m, 3 × ArH), 8.01–8.03 (1H, m, ArH); ^{13}C NMR δ 30.4 (CH_3), 40.6 (CH), 43.5 (CH), 46.5, 112.0, 118.5, 123.1, 123.2, 130.0, 132.1, 135.7, 137.6, 141.7, 141.8, 193.4, 194.2, 198.6; MS *m/z* (%): 315 (3); Anal. calcd for $C_{20}H_{13}NO_3$: C, 76.18; H, 4.16; N, 4.44; found: C, 76.29; H, 4.27; N, 4.53%.

2-Acetyl-3-(4-bromophenyl)-spiro[cyclopropane-1,2'-indene]-1',3'-dione (**5d**): Brown powder; m.p. 161–163 °C; IR (ν_{max}, cm^{-1}) KBr: 1736, 1709, 1690 (3 × C=O); ^{1}H NMR δ 2.37 (3H, s, CH_3), 3.67 (1H, d, *J* = 8.8 Hz, CH), 4.00 (1H, d, *J* = 8.8 Hz, CH), 7.17 (2H, d, *J* = 8.0 Hz, 2 × ArH), 7.46 (2H, d, *J* = 8.0 Hz, 2 × ArH), 7.81–7.89 (3H, m, 3 × ArH), 8.00–8.02 (1H, m, ArH); ^{13}C NMR δ 30.3 (CH_3), 41.4 (CH), 43.7 (CH), 46.8, 122.3, 123.0, 123.1, 130.8,131.1, 131.5, 135.4, 135.5, 141.8, 193.6, 194.6, 199.2; MS *m/z* (%): 369 (8); Anal. calcd for $C_{19}H_{13}BrO_3$: C, 61.81; H, 3.55; found: C, 61.96; H, 3.70%.

2-Acetyl-3-(4-chloro-3-nitrophenyl)-spiro[cyclopropane-1,2'-indene]-1',3'-dione (**5e**): Brown powder; m.p. 199–201 °C; IR (ν_{max}, cm^{-1}) KBr: 1737, 1713, 1695 (3 × C=O); ^{1}H NMR δ 2.40 (3H, s, CH_3), 3.62 (1H, d, *J* = 8.8 Hz, CH), 4.22 (1H, d, *J* = 8.8 Hz, CH), 7.52–7.59 (2H, m, 2 × ArH), 7.80–7.90 (3H, m, 3 × ArH), 8.06 (1H, s, ArH), 8.04–8.08 (1H, m, ArH); ^{13}C NMR δ 30.3 (CH_3), 38.3 (CH), 44.1 (CH), 46.3, 122.9, 123.3, 125.2, 128.9, 129.4, 131.8, 133.6, 135.4, 135.6, 141.5, 142.1, 148.9, 194.1, 194.5, 199.4; MS *m/z* (%): 369 (5); Anal. calcd for $C_{19}H_{12}ClNO_5$: C, 61.72; H, 3.27; N, 3.79; found: C, 61.84; H, 3.38; N, 3.90%.

2-Acetyl-3-(2-nitrophenyl)-spiro[cyclopropane-1,2'-indene]-1',3'-dione (**5f**): Dark brown powder; m.p. 149–151 °C; IR (ν_{max}, cm^{-1}) KBr: 1736, 1711, 1694, (3 × C=O). ^{1}H NMR δ 2.36 (3H, s, CH_3), 3.69 (1H, d, *J* = 8.8 Hz, CH), 4.02 (1H, d, *J* = 8.8 Hz, CH), 7.46–7.55 (2H, m, 2 × ArH), 7.85–7.92 (4H, m, 4 × ArH), 8.02–8.04 (1H, m, ArH); ^{13}C NMR δ 30.4 (CH_3), 39.2 (CH), 43.4 (CH), 46.2, 123.2, 123.3, 126.4, 126.9, 131.8, 132.8, 133.78, 135.8, 135.8, 141.7, 141.9, 147.5, 193.4, 193.8, 198.2; MS *m/z* (%): 335 (7); Anal. calcd for $C_{19}H_{13}NO_3$: C, 68.06; H, 3.91; N, 4.18; found: C, 68.17; H, 4.06; N, 4.30%.

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