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# Tandem [5 + 1] annulation–isocyanide cyclization: efficient synthesis of hydroindolones†

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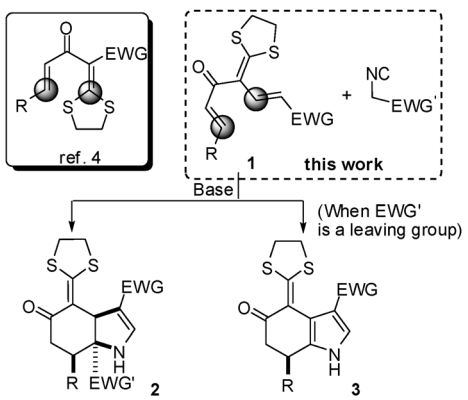
**A new strategy for the rapid construction of functionalized reduced indoles starting from activated methylene isocyanides and 1,5-dielectrophilic 5-oxohepta-2,6-dienoates (and their equivalents) through a [5 + 1] annulation–isocyanide cyclization cascade under basic conditions has been developed. This strategy allows the synthesis of polysubstituted dihydroindolones and tetrahydroindolones in high to excellent yields under extremely mild conditions in a single step.**

Domino reactions are attractive to industry and research laboratories because of their potential to save solvents, reagents, time and energy.[1,2] In our research to develop new domino reactions using ethyl isocyanoacetate as Michael donors,[3,4] two-carbon-tethered pyrrole/oxazole pairs[4a] and pyrrolizidines[4b] were synthesized with α-alkenoyl ketene dithioacetals (Scheme 1, box) as 1,5-dielectrophiles based on the [5 + 1] annulation strategy.[5] On the basis of these results[4] combined with the choice of suitable 1,5-dielectrophiles,[2a,d,4,5] we envisioned that compounds containing the indole core, for example tetrahydroindolones **2** and dihydroindolones **3**, could be constructed through a domino sequence involving an initial [5 + 1] annulation of the 1,5-dielectrophilic substrates **1** with activated methylene isocyanides, followed by pyrrole ring formation (Scheme 1, EWG = electron-withdrawing group). We report herein our preliminary results, which have led to a practical method for the rapid construction of these bicyclic systems (Scheme 1) in a single step.[1]

In the present study, initially, the model reaction of 5-oxohepta-2,6-dienoate **1a** (1.0 mmol) with ethyl isocyanoacetate (1.2 mmol) was examined to optimize the reaction conditions (Table 1).[6] Indeed, the desired tetrahydroindolone **2a** could be obtained in high yields with either NaOH or *t*-BuOK as the catalyst in DMF solvent at room temperature (entries 2–4). In comparison, $K_2CO_3$ was a less effective catalyst than NaOH or *t*-BuOK (entry 5). Among the solvents tested, DMF seemed to be the best choice although comparable results were produced with acetonitrile as the solvent (entry 6). No desired product **2a** was detectable (monitored by TLC) when the reaction was carried out in dichloromethane or toluene (entries 7 and 8).

Clearly, product **2a** can be obtained in high yield in a short time under the reaction conditions as in Table 1, entry 2.‡ Under the optimal conditions, the scope of the reaction was then investigated and the results are summarized in Table 2. It is obvious that the tandem reaction showed broad tolerance for various R substituents of **1**. All selected substrates **1a–j**, bearing phenyl (entry 2), electron-rich (entries 3, 7 and 8), electron-deficient (entries 1 and 4–6) aromatics, and hetero-aromatic R groups (entries 9 and 10), reacted smoothly with ethyl isocyanoacetate to give the corresponding tetrahydroindolones **2a–j** in high to excellent yield under very mild conditions over 18 to 60 min. In addition, the reaction of substrate **1k** bearing a phenylvinyl R group can give the desired **2k** in 74% yield in the presence of stoichiometric amounts of NaOH in acetonitrile (entry 11). Similarly, the desired tetrahydroindolones **2l** and **2m** could be prepared in high yields from substrates **1l** and **1m** bearing an ethoxycarbonyl (entry 12) and cyano groups (entry 13), respectively. According to $^1$H and $^{13}$C NMR data of the products **2**, it was found that the tandem reaction proceeds in a highly regio- and diastereoselective manner and creates simultaneously three adjacent stereocenters.[7] The configuration of **2** was further confirmed by the X-ray diffraction analysis of **2m** (Fig. 1).[8]

The tandem process mentioned above (Table 2) represents a very simple and highly efficient methodology for the construction of polyfunctionalized tetrahydroindolone derivatives from readily available acyclic precursors under mild reaction conditions in an




**Scheme 1** Domino reactions based on [5 + 1] annulation.

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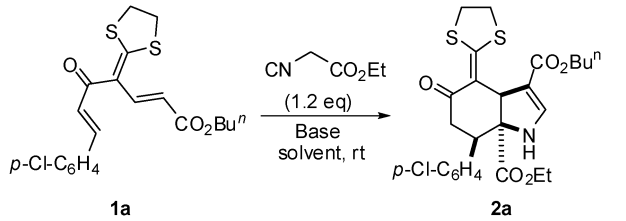
† Electronic supplementary information (ESI) available: Detailed experimental procedures and analytical data. CCDC 824546 (**2m**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc14916d

**Table 1** Optimization of reaction conditions

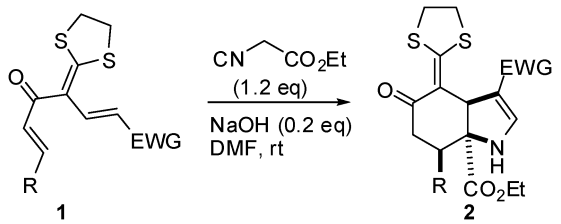



1a 2a

| Entry | Base (equiv.) | Solvent | *t*/h | **2a**[a] (%) | **1a**[a] (%) |
|---|---|---|---|---|---|
| 1 | NaOH (0.1) | DMF | 12 | 70 | 16 |
| **2** | **NaOH (0.2)** | **DMF** | **0.3** | **90** | **0** |
| 3 | NaOH (0.3) | DMF | 0.3 | 87 | 0 |
| 4 | *t*-BuOK (0.2) | DMF | 0.3 | 89 | 0 |
| 5 | $K_2CO_3$ (0.2) | DMF | 5 | 70 | 20 |
| 6 | NaOH (0.2) | $CH_3CN$ | 1 | 87 | 0 |
| 7 | NaOH (0.2) | $CH_2Cl_2$ | 12 | 0 | 93 |
| 8 | NaOH (0.2) | Toluene | 12 | 0 | 97 |

[a] Isolated yield.

**Table 2** Synthesis of tetrahydroindolones **2**[a]




1 2

| Entry | 1 | R | EWG | *t*/min | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | 4-$ClC_6H_4$ | $CO_2Bu^n$ | 18 | **2a** (90) |
| 2 | **1b** | $C_6H_5$ | $CO_2Bu^n$ | 18 | **2b** (87) |
| 3 | **1c** | 4-$MeOC_6H_4$ | $CO_2Bu^n$ | 20 | **2c** (80) |
| 4 | **1d** | 2-$ClC_6H_4$ | $CO_2Bu^n$ | 18 | **2d** (84) |
| 5 | **1e** | 4-$BrC_6H_4$ | $CO_2Bu^n$ | 18 | **2e** (90) |
| 6[c] | **1f** | 4-$NO_2C_6H_4$ | $CO_2Bu^n$ | 60 | **2f** (75) |
| 7 | **1g** | 4-$MeC_6H_4$ | $CO_2Bu^n$ | 30 | **2g** (91) |
| 8 | **1h** | 3,4-$O_2CH_2C_6H_3$ | $CO_2Bu^n$ | 40 | **2h** (83) |
| 9[c] | **1i** | 2-Furyl | $CO_2Bu^n$ | 30 | **2i** (85) |
| 10 | **1j** | 2-Thienyl | $CO_2Bu^n$ | 30 | **2j** (89) |
| 11[d] | **1k** | PhCH=CH | $CO_2Bu^n$ | 40 | **2k** (74) |
| 12 | **1l** | 4-$ClC_6H_4$ | $CO_2Et$ | 20 | **2l** (88) |
| 13 | **1m** | 4-$ClC_6H_4$ | CN | 30 | **2m** (83) |

[a] *Reaction conditions*: **1** (1.0 mmol), isocyanoacetate (1.2 mmol), NaOH (0.2 mmol), DMF (4.0 mL), room temperature. [b] Isolated yield. [c] 0.3 equiv. NaOH was used. [d] 1.0 equiv. NaOH was used in $CH_3CN$ (4.0 mL) instead of DMF.

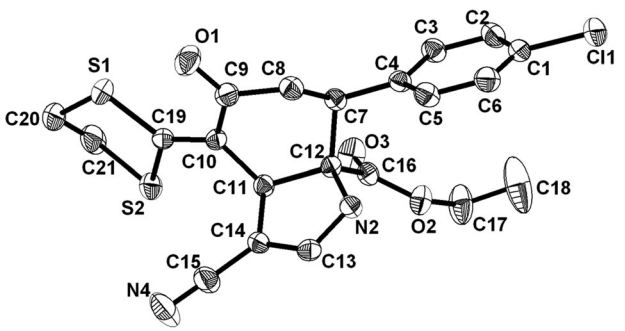


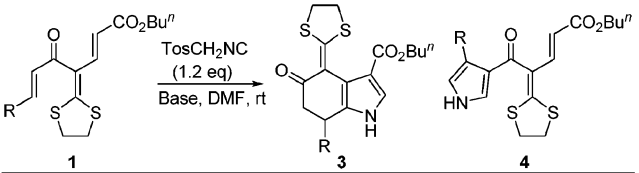

**Fig. 1** ORTEP drawing of **2m**.

atom-economic manner. It should be emphasized that the above reactions define a practical method for the construction of the bicyclic systems by combining the [5 + 1] annulation and pyrrole ring formation into one pot.[1,3–5,9,10] To test the generality of this new approach for the construction of the indole core, the reactions of tosylmethyl isocyanide (TosMIC) with selected 5-oxohepta-2,6-dienoates **1** were further examined (Table 3, Tos = *p*-toluenesulfonyl). However, under the optimized reaction conditions (Table 1, entry 2), the reaction of **1a** (1.0 mmol) with TosMIC (1.2 mmol) was very sluggish. In this case, the desired product, dihydroindolone **3a**, was isolated only in 8% yield along with the [3 + 2] cycloaddition adduct **4a** in 5% yield (entry 1).[11] It was found that the desired product **3a** could be obtained in 53% yield as the major product when the above reaction was performed in the presence of 1.5 equivalents of NaOH (entry 2). After further optimization of the reaction conditions, fortunately, **3a** was produced in 80% yield under otherwise identical conditions as above but with DBU (1.5 eq, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) as the base (entry 3). Under similar conditions, dihydroindolones **3b**, **3c** and **3i** were prepared in high yields from the reactions of **1b**, **1c** and **1i** with TosMIC, respectively (entries 4–6).

On the basis of the above results (Tables 2 and 3) together with previous observations,[4,5] the possible mechanisms for the formation of tetrahydroindolones **2** and dihydroindolones **3** are proposed in Scheme 2. The overall process may involve: (1) the diastereoselective double Michael addition ([5 + 1] annulation) of ethyl isocyanoacetate (or TosMIC) to 1,5-dielectrophile **1** under basic conditions to provide cyclohexanone anion intermediate **A**;[4,5] (2) subsequent intramolecular cyclization of the resulting anion onto the isocyanide carbon and protonation followed by isomerization to furnish tetrahydroindolones **2** (Table 2);[3] (3) in the cases of using TosMIC as the isocyanide component, a further elimination of tosylic acid resulting in the formation of dihydroindolones **3** (Table 3) in the presence of excess base.[11]

In conclusion, we have developed a new strategy for the rapid and highly efficient synthesis of polysubstituted dihydroindolone and tetrahydroindolone derivatives. The domino reaction combines [5 + 1] annulation with pyrrole ring formation and allows the construction of the fused bicyclic systems in a single step from the easily available acyclic substrates in high to

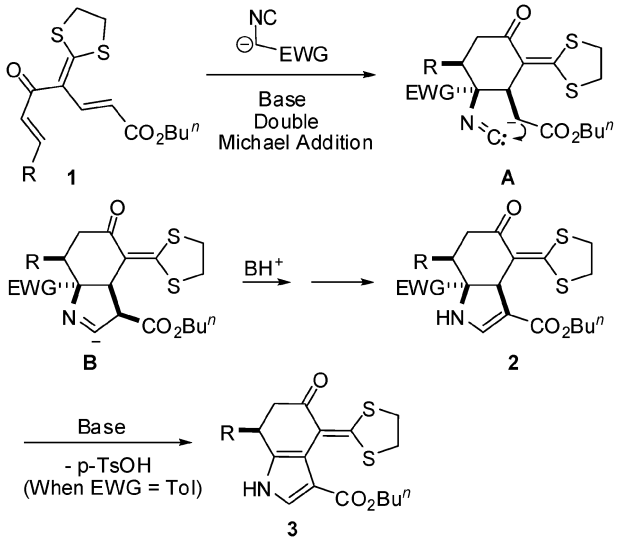
**Table 3** Synthesis of dihydroindolones **3**




1 3 4

| Entry | 1 | Base (equiv.) | *t*/h | Yield[a] (%) | |
|---|---|---|---|---|---|
| 1[b] | **1a** | NaOH (0.2) | 12 | **3a** (8) | **4a** (5) |
| 2 | **1a** | NaOH (1.5) | 0.5 | **3a** (53) | **4a** (29) |
| 3 | **1a** | DBU (1.5) | 1 | **3a** (80) | **4a** (0) |
| 4 | **1b** | DBU (1.5) | 1 | **3b** (78) | **4b** (0) |
| 5 | **1c** | DBU (1.5) | 1 | **3c** (75) | **4c** (0) |
| 6 | **1i** | DBU (1.5) | 3 | **3i** (83) | **4i** (0) |

[a] Isolated yield. [b] **1a** was recovered in 65% yield.




**Scheme 2** Proposed mechanisms for formation of **2** and **3**.

excellent yields under mild metal-free conditions. This strategy exhibits a highly efficient use of the reactive sites of the substrates and expands the synthetic potential of the [5 + 1] annulation. Further studies are in progress.

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## Notes and references

‡ *General procedure* for the synthesis of **2** (taking **2a** as an example): To a solution of 5-oxohepta-2,6-dienoate **1a** (1.0 mmol, 408 mg) and ethyl isocyanoacetate (1.2 mmol, 0.13 ml) in DMF (4.0 ml) was added NaOH (0.2 mmol, 8 mg) in one portion. The reaction mixture was stirred for 18 min at room temperature. After **1a** was consumed (monitored by TLC), the reaction mixture was poured into ice-water (45 mL) under stirring. The precipitated solid was collected by filtration, and dried *in vacuo* to afford the crude product, which was purified by flash chromatography (silica gel, petroleum ether–acetone = 5 : 1, v/v) to give **2a** (469 mg, 90%) as a white solid.


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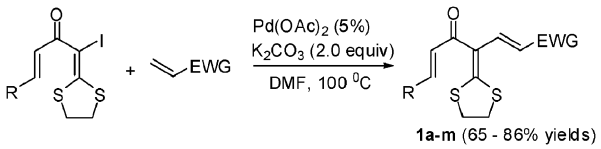
6 Substrates **1a–m** were easily prepared in high yields by $Pd(OAc)_2$-catalyzed C–C coupling reaction of α-iodo-α-cinnamoyl ketene dithioacetals with terminal alkenes, see ESI†.




7 In these reactions (Table 2), no diastereomers of **2a–m** were detected.

8 *Crystal data* for **2m**: $C_{21}H_{19}ClN_2O_3S_2$, white crystal, $M$ = 446.82, monoclinic, space group $C2/c$, $a$ = 40.139(6), $b$ = 9.4559(13), $c$ = 11.1246(14) Å, $\beta$ = 100.587(2)°, $V$ = 4150.5(10) Å$^3$, $Z$ = 8, $T$ = 293(2) K, $F_{000}$ = 1856, $R_1$ = 0.0486, $wR_2$ = 0.1252. CCDC 824546.

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