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COMMUNICATION

A multicomponent synthetic strategy for two-carbon-tethered 1,3-oxathiole–indole pairs†

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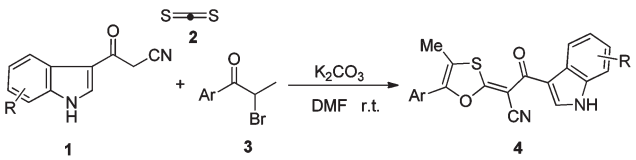
An efficient methodology for the multicomponent synthesis of new and highly functionalized heterocycles containing 1,3-oxathiole and indole units which are connected through an sp^2-C_2 bridge has been developed. This domino reaction enables successful assembly of three new sigma bonds including a C–S bond and a C–O bond in a one-pot operation. Features of this strategy include mild conditions, convenient one-pot operation, and high stereo- and regioselectivity.

Heterocyclic compounds embedded with oxygen and sulfur are prevalent in numerous natural products and pharmaceutical leads. Among the oxygen and sulfur heterocycles, the partially 1,3-oxathiole derivatives are important motifs, displaying remarkable pharmaceutical or biochemical activities.[1] On the other hand, the indole moiety has been found in various pharmacologically and biologically active compounds.[2] Many indole alkaloids are recognized as one of the rapidly growing groups of marine invertebrate metabolites for their broad spectrum of biological properties,[3] such as anticancer, anti-tumour,[4] anti-inflammatory, hypoglycemic, analgesic and anti-pyretic activities.[5] Thus, a assembly of these two motifs could potentially lead to a series of structurally and biologically interesting compounds. Although the synthesis and application of 1,3-oxathioles[6] and indole[7,8] derivatives have been reported, respectively, in the literature, to the best of our knowledge, the direct synthesis of two-carbon-tethered 1,3-oxathiole–indole pairs has not been achieved so far.

Multicomponent domino reactions (MDRs), which involve several bond-forming reactions in a one-pot manipulation, represent an attractive strategy in the facile assembly of molecular architecture.[9] Such reactions provide efficient access to complex molecules from readily available starting materials. They also form an ideal platform for rapid generation of both complexity and diversity in a collection of compounds with predefined functionality, *e.g.*, ligands for catalysis or bioactive compounds. Very recently, we have developed a series of new multicomponent domino reactions (MDRs) that provide easy access to multiple functionalized ring structures of chemical and pharmaceutical interest.[10,11] During our continuous efforts on the development of useful multi-component domino reactions, herein, we would like to report another new synthetic strategy for the regioselective preparation of polyfunctionalized heterocycles containing 1,3-oxathiole and indole skeletons through three-component domino reactions. This reaction was achieved from the available starting materials such as indol-3-yl substituted β-oxopropanenitrile, carbon disulfide, and α-bromo propiophenones in the presence of K_2CO_3 under mild condition (Scheme 1). The great aspect of the present domino reaction is shown by the fact that the synthesis of new polyfunctionalized heterocycles containing 1,3-oxathiole and indole units which connected through *a* sp^2-C_2 *bridge* was readily achieved *via* base-promoted three-component reaction in a single step, and *spatial configuration of exocyclic double bond* was controlled well in an intermolecular manner.



Scheme 1 The synthesis of fully substituted (*Z*)-1,3-oxathioles.

We planned to link two biologically important nuclei, 1,3-oxathioles and indoles, to generate a new set of compounds, two-carbon-tethered 1,3-oxathiole–indole pairs, using three-component domino [3 + 2] heterocyclization of indol-3-yl substituted β-oxopropanenitrile **1** with carbon disulfide **2** and substituted α-bromo propiophenones **3**. It should be mentioned that indol-3-yl substituted β-oxopropanenitriles are versatile and readily obtainable reagents, and their chemistry has received considerable attention in recent years.[12] We started this study by subjecting a preformed indol-3-yl substituted β-oxopropanenitrile **1a** and carbon disulfide **2** to the reaction with α-bromo propiophenones **3a** in DMF at room temperature using different bases (2.5 equiv.). The reaction scarcely proceeded in the present of EtONa or piperidine, and an incomplete reaction was observed using NaOH or triethylamine as a base catalyst (Table 1, entries 3 and 4). K_2CO_3 as a mild base gave the fully substituted (*Z*)-1,3-oxathioles **4a** in 69% yield (Table 1, entry 5).

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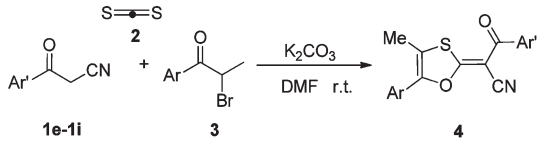
Table 1 Screening of various bases in DMF

Entry	Base	Time (h)	Yield (%)
1	EtONa	5	Trace
2	Piperidine	5	Trace
3	NaOH	5	35
4	Triethylamine	5	58
5	K_2CO_3	5	69

Table 2 The domino synthesis of compounds **4**[14]

Entry	4	1	Ar	Time (h)	Yield (%)
1	**4a**	**1a**	Phenyl (**3a**)	5	69
2	**4b**	**1a**	4-Tolyl (**3b**)	5.5	65
3	**4c**	**1a**	4-Bromophenyl (**3c**)	4.5	70
4	**4d**	**1b**	Phenyl (**3a**)	5	64
5	**4e**	**1b**	4-Tolyl (**3b**)	6	67
6	**4f**	**1b**	4-Bromophenyl (**3c**)	5.5	68
7	**4g**	**1c**	Phenyl (**3a**)	4.5	60
8	**4h**	**1c**	4-Tolyl (**3b**)	5	63
9	**4i**	**1c**	4-Bromophenyl (**3c**)	5.5	69
10	**4j**	**1d**	Phenyl (**3a**)	6	68
11	**4k**	**1d**	4-Tolyl (**3b**)	5.5	63
12	**4l**	**1d**	4-Bromophenyl (**3c**)	5	66
13	**4m**	**1e**	4-Tolyl (**3b**)	6	73
14	**4n**	**1e**	4-Bromophenyl (**3c**)	4.5	70
15	**4o**	**1f**	Phenyl (**3a**)	6	77
16	**4p**	**1f**	4-Tolyl (**3b**)	5	72
17	**4q**	**1f**	4-Bromophenyl (**3c**)	4.5	71
18	**4r**	**1g**	Phenyl (**3a**)	5	79
19	**4s**	**1g**	4-Tolyl (**3b**)	6	78
20	**4t**	**1g**	4-Bromophenyl (**3c**)	5.5	76
21	**4u**	**1h**	Phenyl (**3a**)	6	78
22	**4v**	**1h**	4-Tolyl (**3b**)	5.5	73
23	**4w**	**1h**	4-Bromophenyl (**3c**)	5	82
24	**4x**	**1i**	4-Tolyl (**3b**)	6	78
25	**4y**	**1i**	4-Bromophenyl (**3c**)	5.5	80

With this result in hand, we went on to study the scope of the methodology. Using the optimized reaction conditions, a variety of structurally diverse β-oxopropanenitrile were investigated, and a series of new fully substituted 1,3-oxathioles were afforded in good yields. As shown in Table 2, at the beginning, we made a search for the α-bromo propiophenone substrate scope, β-oxopropanenitrile **1a** were used as model substrates (Table 2, entries 1–3), and the results indicated that α-bromo propiophenones bearing either electron donating or electron withdrawing functional groups such as bromo, or methyl were suitable for this reaction. To further expand the scope of β-oxopropanenitrile substrates, different α-bromo propiophenones were as model substrates and examined various β-oxopropanenitriles including 5-bromoindol-3-yl **1b**, 5-methoxyindol-3-yl **1c**, 2-methylindol-3-yl **1d**, phenyl **1e**, 4-tolyl **1f**, 4-methoxyphenyl **1g** and 4-chlorophenyl **1h**. In all these cases, the reactions proceeded smoothly to give the corresponding polyfunctionalized 1,3-oxathioles substituted at multiple sites in good yields with very high stereoselectivities. The thien-2-yl substituted β-oxopropanenitriles **1i** were converted into the corresponding two-carbon-tethered 1,3-oxathiole/thiofuran pairs **4x** and **4y** in 78% and 80% yields, respectively (Scheme 2; Table 2, entries 24 and 25). Indeed, the protocol provides a straightforward pathway to construct highly functionalized 1,3-oxathiole substituted at multiple



Scheme 2 The continuous synthesis of 1,3-oxathioles **4**.

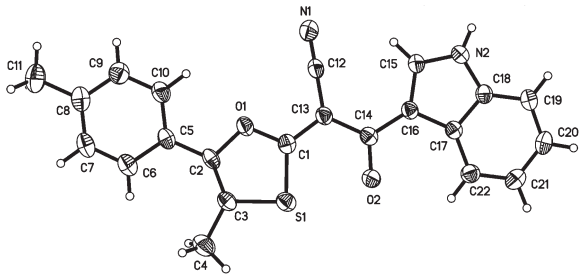
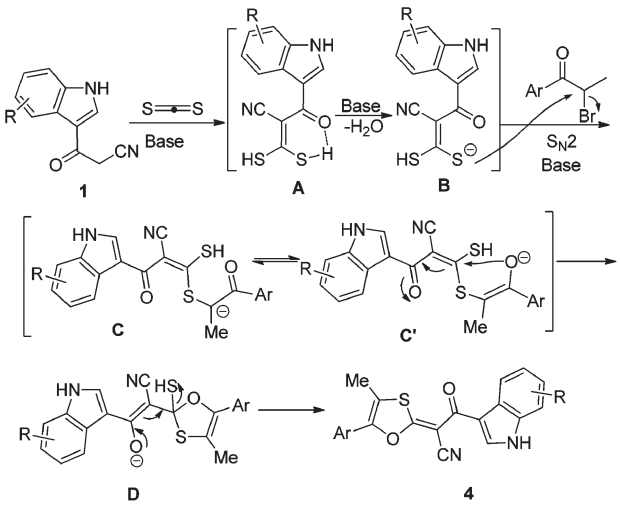


Fig. 1 The ORTEP drawing of **4b**.



Scheme 3 Proposed mechanism for formation of products **4**.

sites. It should be noted that this reaction can be performed on a multigram scale under the simple conditions described above. Additionally, functional groups like bromide and chloride were well tolerated. These functional groups provide ample opportunity for further functional group manipulations, for example, by modern cross-coupling reactions.

In all cases, the complexity of resulting products from this new reaction illustrates the remarkable stereo-, and regioselectivity of the sequence starting from very common and easily accessible starting materials. Furthermore, the reaction occurred under mild condition; in fact, all cases can be finished at room temperature. The structural elucidation and the attribution of stereoselectivity were unequivocally determined by NMR spectroscopic analysis and X-ray diffraction of single crystal **4b** (Fig. 1 and see ESI†).

During these domino processes, the formation of 1,3-oxathiole skeleton and *Z*-configuration of the exocyclic double bond were readily achieved *via* three-component domino reaction in a one-pot operation. Up to three sigma-bonds including a C–S bond and a C–O bond were formed accompanied by the cleavage of C=S in the carbon disulfide (Scheme 3).

On the basis of all the above results, reasonable mechanism has been proposed for the formation of fully substituted (*Z*)-1,3-oxathioles as shown in Scheme 3. The initial double nucleophilic additions between indol-3-yl substituted β-oxopropanenitrile **1** and carbon disulfide **2** generated intermediate **A** with intramolecular H-bonding. The intramolecular H-bonding can stabilize configuration of the C=C double bond and make S–H bond polarization to improve its acidity.[13] Under basic condition, the proton with stronger acidity prefers to be deprotonated to give thiol anion. So, the intermediate **A** was deprotonated by K_2CO_3 to generate thiol anion **B**, which successively underwent S_N2-type reaction (**B** to **C**), enolization (**C** to **C′**) and cyclization (addition–elimination, **C′** to **D**) generating the final (*Z*)-1,3-oxathiole derivative **4**.

Conclusion

In summary, we have described K_2CO_3-catalyzed domino heterocyclization as an alternative method for the synthesis of a set of two-carbon-tethered 1,3-oxathiole–indole pairs with concomitant formation of exocyclic double bond in one-pot manner. This three-component reaction provides a facile and efficient strategy for construction of structurally diverse 1,3-oxathiole skeleton. The ready accessibility of the starting materials, the broad compatibility of β-oxopropanenitrile substrates, and the generality of this process make the reaction highly valuable in view of the synthetic and medicinal importance of multi-heterocyclic framework of this type. Features of this strategy include the mild condition, convenient one-pot operation, and high stereo- and regioselectivity. Further investigations are in progress in our laboratory to evaluate the process with a broader range of substrates, and to synthesize more complex products and test their biological activity.

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14 General procedure for the synthesis of products **4**: β-oxopropanenitriles (**1**, 1.0 mmol,) was introduced in a 20 mL reaction vial, carbon disulfide (**2**, 2.0 mmol), α-bromo propiophenones (**3**, 1.1 mmol), K_2CO_3 (2.5 mmol), and DMF (8 mL) were then successively added. Subsequently, the reaction vial was capped and then stirred at room temperature for a given time until TLC (petroleum ether : acetone 4 : 1) revealed that conversion of the starting material **1** was complete. The reaction mixture was diluted with cold water (50 ml) and then extracted by acetic ester. Next, the organic phase was concentrated by vacuum distillation and dissolved in EtOH (95%) to afford the desired pure 1,3-oxathioles **4**.

