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A Multipathway Coupled Domino Strategy: Metal-free Oxidative Cyclization for One-Pot Synthesis of 2-Acylbenzothiazoles from Multiform Substrates

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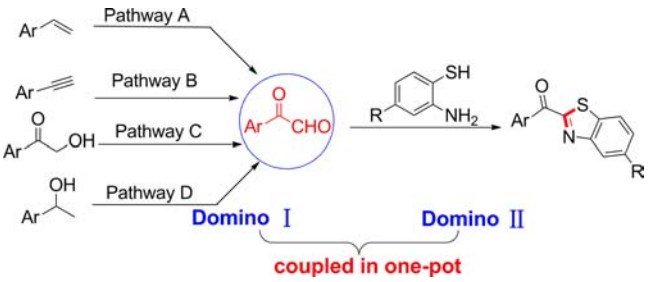
ABSTRACT



A multipathway coupled domino strategy has been developed for the efficient synthesis of 2-acylbenzothiazoles from multiform substrates arylethenes, arylacetylenes, 2-hydroxy-aromatic ketones, and carbinols via four distinct pathways. Through a logical coupled oxidation/heterocyclization domino process, a variety of 2-acylbenzothiazoles were synthesized free of metal in one pot.

Domino reactions, by virtue of their significant advantages, have emerged as a powerful tool in synthetic organic chemistry.[1] Up to now, many novel domino reaction strategies have been proposed.[2] More recently, coupled domino reactions,[3] wherein two or more domino processes are sequentially assembled in the same reaction vessel, have attracted much attention as a valuable synthetic approach. García-Tellado first demonstrated the graceful strategy for the synthesis of tetronic acids, tetrasubstituted pyrroles, and 1,3-oxazolidines by a chain of two coupled processes.[3a−c] In our previous work, we also demonstrated the power and potential of this strategy in the process of constructing multisubstituted hydantoins.[2d] As we know, the development of a multipathway synthesis strategy to access the same product is greatly desirable. However, the multipathway synthesis approach has not yet been sufficiently studied by chemists. Indeed, the strategy is prevalent in nature and organisms.[4] Inspired by the above graceful strategy, we herein developed a multipathway coupled domino strategy to access 2-acylbenzothiazoles from multiform substrates (Scheme 1).

Benzothiazole derivatives act as important heterocyclic scaffolds and are frequently found in natural products.

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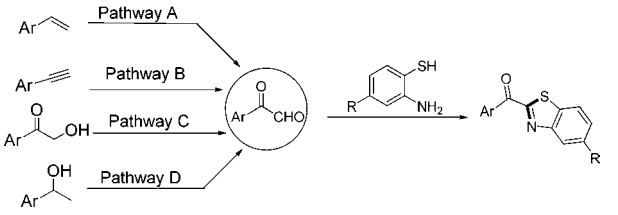
Scheme 1. Multipathway Coupled Domino Strategy



Moreover, many compounds containing a benzothiazole motif exhibit potential biological activities and medicinal significance.[5] However, only a few methods have been reported to access 2-acylbenzothiazoles.[6] In addition, no examples have been reported for the synthesis of 2-acylbenzothiazole from multiform substrates arylethenes or arylacetylenes, or 2-hydroxy-aromatic ketones or carbinols. Herein, we reported a simple, metal-free, and multipathway method to synthesize 2-acylbenzothiazoles from different substrates.

To initiate our study, the reaction of styrene (**1a**) with 2-aminobenzenethiol (**2a**) was chosen as a model reaction in the presence of different oxidants and additives in DMSO. The reaction of styrene (**1a**, 1 mmol) and 2-aminobenzenethiol (**2a**, 1 mmol) with I_2/IBX (1.1 mmol/1.2 mmol) could only afford the desired product in very low yield at 70 °C in DMSO (Table 1, entry 1). It was found, however, that the desired product could be obtained in 50% yield when styrene (**1a**, 1 mmol) and I_2/IBX (1.1 mmol/1.2 mmol) were mixed and heated at 70 °C for 1.5 h, with the subsequent addition of 2-aminobenzenethiol (**2a**, 1 mmol) to the mixture for another 1 h at 70 °C. Then, sequential addition coupled domino methodology was adopted to form the product. Different temperatures were scanned to improve the yield, and 80 °C was found to be the most optimal for the domino reaction (Table 1, entries 2–4). The additive NIS was also found to promote the reaction, allowing a moderate yield (Table 1, entry 5). In addition, the other oxidants, such as TBHP, H_2O_2, DMP, DIB, BTI, and HTIB, were tested for this reaction in the presence of molecular iodine. Among them, IBX was found to be the most optimal oxidant for the transformation (Table 1, entries 6–11). Finally as concluded above, the optimal reaction conditions for the reaction turned out to be styrene **1a** (1.1 mmol) and 2-aminobenzenethiol **2a** (1.2 mmol), at 80 °C with I_2/IBX (2.0 mmol/1.5 mmol) in DMSO (entry 15).

With the optimal conditions in hand, the scope of the transformation was investigated, mediated with I_2/IBX, and the results were summarized in Scheme 2. As shown in

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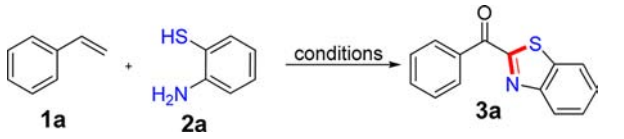
Table 1. Optimization Studies in the Synthesis of 2-Acylbenzothiazole



entry	additive (mmol)	oxidant (mmol)	temp (°C)	yield (%)[c]
1[a]	I_2 (1.1)	IBX (1.2)	70	10
2[b]	I_2 (1.1)	IBX (1.2)	70	50
3[b]	I_2 (1.1)	IBX (1.2)	80	56
4[b]	I_2 (1.1)	IBX (1.2)	90	55
5[b]	NIS (1.1)	IBX (1.2)	80	40
6[b]	I_2 (1.1)	TBHP (1.2)	80	<20
7[b]	I_2 (1.1)	H_2O_2 (1.2)	80	n.r.
8[b]	I_2 (1.1)	DMP (1.2)	80	n.r.
9[b]	I_2 (1.1)	DIB (1.2)	80	n.r.
10[b]	I_2 (1.1)	BTI (1.2)	80	n.r.
11[b]	I_2 (1.1)	HTIB (1.2)	80	n.r.
12[b]	I_2 (1.5)	IBX (1.2)	80	68
13[b]	I_2 (1.5)	IBX (1.5)	80	74
14[b]	I_2 (2.0)	IBX (2.0)	80	75
15[b]	I_2 (2.0)	IBX (1.5)	80	75

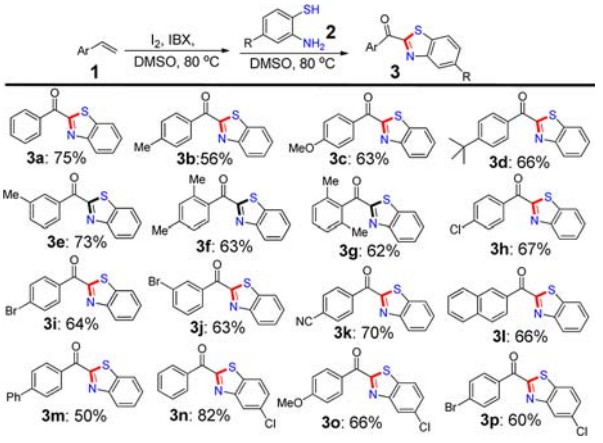
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), I_2 (1.1 mmol), IBX (1.2 mmol) was heated at 70 °C in DMSO. [b] Reaction conditions: **1a** (1.0 mmol), I_2, oxidant was heated for 1.5 h and then added **2a** (1.2 mmol) in DMSO. [c] Isolated yield. IBX = *o*-iodoxy-benzoic acid, TBHP = *tert*-butyl hydroperoxide, DMP = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, DIB = (diacetoxyiodo)benzene, BTI = [bis-(trifluoroacetoxy)iodo]benzene, HTIB = [Hydro(tosyloxy)iodo]benzene.

Scheme 2, both electron-donating and -withdrawing groups attached to arylethenes **1** were all suitable for this protocol. Arylethenes with different substituents, such as Me, OMe, *t*-Bu, Me_2, Cl, Br, and CN, could all provide the corresponding products with 56–75% yields (Scheme 2, **3a**–**k**). In addition, 2-naphthyl ethene **1l** and biphenyl ethene **1m** also reacted with 2-aminobenzenethiol **2a** to obtain the desired products in 66% and 50% yields (Scheme 2, **3l** and **3m**). This indicated that the electronic and steric nature of the arylethenes had little influence on the reaction efficiency. In addition, 2-amino-4-chlorobenzenethiol (**2b**) could also react with arylethenes **1** to afford the corresponding products in moderate to good yields (**3n**–**p**, 60–82%).

Encouraged by the results obtained with arylethenes, we focused our attention on the terminal aromatic alkynes. Then, we optimized the reaction conditions on the basis of phenylacetylene **4a** and 2-aminobenzenethiol **2a** (see Supporting Information). The reaction gave a moderate yield in the presence of I_2 and IBX. The other oxidants, however, only gave a trace amount of desired product. To our delight, the yield was increased when NIS was selected as an additive. After extensive optimization, it was found that the reaction could perform at 80 °C with the additive NIS (1.5 mmol) in the absence of an oxidant in DMSO.

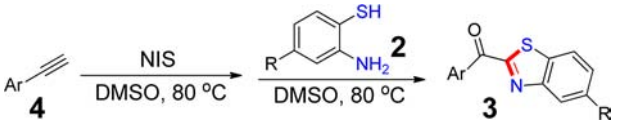
The scope of both terminal aryl alkynes (**4**) and *o*-aminobenzenethiols (**2**) was also explored (Table 2). The results demonstrated that the electronic nature of the

Scheme 2. Scope of Arylethenes and *o*-Aminobenzenethiols[a]



[a] Reaction conditions: **1** (1.0 mmol), I_2 (2.0 mmol), IBX (1.5 mmol) in DMSO at 80 °C for 1−3 h, and then added **2** (1.2 mmol) in DMSO at 80 °C. Isolated yields provided.

Table 2. Scope of Arylacetylenes and *o*-Aminobenzenethiols[a]



entry	Ar	R	products	yield (%)[b]
1	C_6H_5 (**4a**)	H	**3a**	62
2	4-Me-C_6H_5 (**4b**)	H	**3b**	55
3	4-OMe-C_6H_5 (**4c**)	H	**3c**	58
4	4-Br-C_6H_5 (**4d**)	H	**3i**	60
5	C_6H_5 (**4a**)	Cl	**3n**	63
6	4-Me-C_6H_5 (**4b**)	Cl	**3r**	58
7	4-OMe-C_6H_5 (**4c**)	Cl	**3o**	45
8	4-Br-C_6H_5 (**4d**)	Cl	**3p**	60

[a] Reaction conditions: **4** (1.0 mmol), NIS (1.5 mmol) heated at 80 °C for 2 h in DMSO, and then added **2a** (1.5 mmol). [b] Isolated yields.

arylacetylenes (**4**) and *o*-aminobenzenethiols (**2**) had little influence on the reaction efficiency, as all the desired products were obtained in moderate yields (45−63%; entries 1−8).

To further expand the scope of the substrates, 2-hydroxy-aromatic ketones such as **5a**−**5e** were also investigated. To our delight, 2-hydroxy-aromatic ketones in the presence of IBX in DMSO could easily be transformed to arylglyoxals, which then reacted with *o*-aminobenzenethiols (**2**) in the presence of I_2 to afford the corresponding products in one pot. The results indicated that 2-hydroxy-aromatic ketones, bearing either an electron-donating or -withdrawing group on the aromatic ring, performed smoothly with *o*-aminobenzenethiols in DMSO, and all the desired products were obtained in good yields (68−85%; Table 3).

To our delight, 1-arylethanols **6** were also compatible for the transformation in the presence of IBX and I_2 in

Table 3. Scope of 2-Hydroxy-Aromatic Ketones and *o*-Aminobenzenethiols[a]

entry	Ar	R	products	yield (%)[b]
1	C_6H_5 (**5a**)	H	**3a**	75
2	4-Me-C_6H_4 (**5b**)	H	**3b**	80
3	4-Cl-C_6H_4 (**5c**)	H	**3h**	78
4	4-Br-C_6H_4 (**5d**)	H	**3i**	72
5	4-F-C_6H_4 (**5e**)	H	**3q**	80
6	C_6H_5 (**5a**)	Cl	**3n**	82
7	4-Br-C_6H_4 (**5d**)	Cl	**3p**	68
8	4-F-C_6H_4 (**5e**)	Cl	**3r**	85

[a] Reaction conditions: **1a** (1.1 mmol), IBX (1.0 mmol) was heated at 80 °C for 2.0 h in DMSO and then added **2** (1.0 mmol), I_2 (1.0 mmol). [b] Isolated yields.

Table 4. Scope of 1-Arylethanol and *o*-Aminobenzenethiols[a]

entry	Ar	R	products	yield (%)[b]
1	C_6H_5 (**6a**)	H	**3a**	75
2	4-Me-C_6H_4 (**6b**)	H	**3b**	80
3	4-Br-C_6H_4 (**6c**)	H	**3i**	78
4	2-OMe-C_6H_4 (**6d**)	H	**3s**	60
5	C_6H_5 (**6a**)	Cl	**3n**	72
6	4-Me-C_6H_4 (**6b**)	Cl	**3r**	82
7	4-Br-C_6H_4 (**6c**)	Cl	**3p**	80
8	2-OMe-C_6H_4 (**6d**)	Cl	**3t**	58

[a] Reaction conditions: **6** (1.1 mmol), IBX (0.75 mmol), and I_2 (1.0 mmol) heated at 80 °C for 2.0 h in DMSO, and then added **2** (1.5 mmol). [b] Isolated yields.

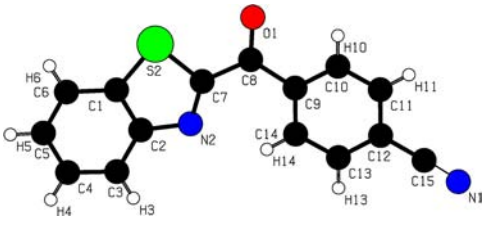
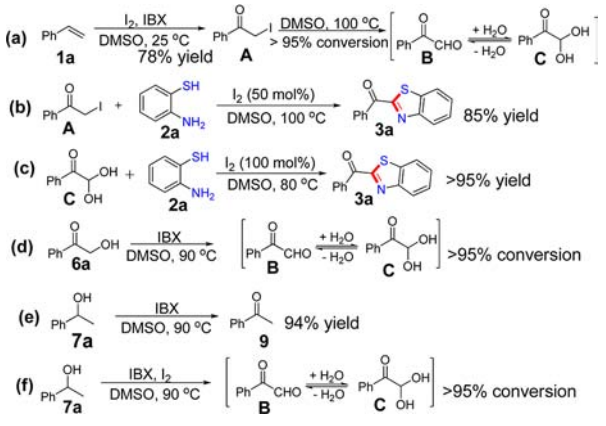


Figure 1. X-ray crystal structure of compound **3k**.

DMSO. The results were summarized in Table 4. 1-Arylethanols **6** were treated with 0.75 equiv of IBX and 1.0 equiv of I_2 in DMSO at 80−90 °C, and then 1.5 equiv of *o*-aminobenzenethiols **2** were added to the mixture.

Scheme 3. Control Experiments

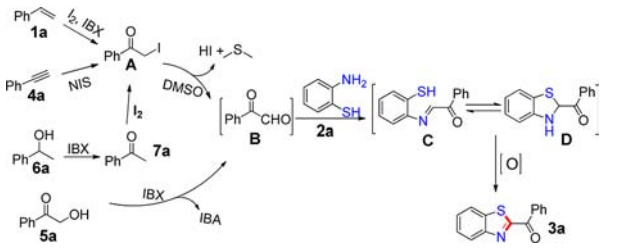


The corresponding product was afforded in moderate to good yields (58−82%, Table 4, entries 1−8). Furthermore, the target compound **3k** was further determined by X-ray crystallographic analysis (Figure 1).

To gain insight into the mechanism, control experiments were also performed (Scheme 3). When styrene (**1a**) was treated with I_2 and IBX at 25 °C in DMSO, phenacyl iodine (**A**) was obtained in 78% yield (Scheme 3a). Furthermore, phenacyl iodine (**A**) could be converted into phenylglyoxal (**B**) or hydrated hemiacetal (**C**) in a quantitative conversion in DMSO at 100 °C. Previous reports also demonstrated that styrene (**1a**) and phenylacetylene (**4a**) could be transformed to phenacyl iodine (**A**) in the presence of I_2/NIS and an oxidant.[7] In addition, phenacyl iodine (**A**) could react with **2a** and I_2 to obtain the product (**3a**) in 85% yield (Scheme 3b). The reaction of hydrated hemiacetal (**C**) with **2a** also proceeded smoothly in excellent yield (>95%) (Scheme 3c). 2-Hydroxy-1-phenylethanone **6a** was oxidized to phenylglyoxal (**B**) or hydrated hemiacetal (**C**) by IBX in a quantitative conversion as well (Scheme 3d). Moreover, IBX could efficiently oxidize 1-phenylethanol to furnish acetophenone in 94% yield (Scheme 3e). If IBX and I_2 were added to 1-phenylethanol, the ensuing product would be phenylglyoxal **B** or hydrated hemiacetal (**C**) (Scheme 3f).[8] These results clearly demonstrated that phenacyl iodine (**A**) and phenylglyoxal (**B**) may be important intemediates in the transformation.

On the basis of the experimental results and previous works,[2c−e,7a,9] we proposed a possible mechanism as follows (Scheme 4). Initially, styrene (**1a**) or phenylacetylene (**4a**) was converted into phenacyl iodine (**A**) through consecutive iodination and oxidation in I_2/IBX or NIS. Subsequently, phenacyl iodine (**A**) was further converted into phenylglyoxal (**B**) in DMSO.[10] Carbinol **6a** was oxidized by IBX to afford acetophenone **7a**, which was followed by iodination and oxidation to give phenylglyoxal (**B**). In addition, 2-hydroxy-1-phenylethanone **5a** was easily oxidized to phenylglyoxal (**B**) by oxidant IBX.[11] Finally, phenylglyoxal (**B**) reacted with **2a** via a condensation, Michael addition, and oxidative dehydrogenation sequence to afford the desired product **3a**.[12]

Scheme 4. Proposed Mechanism



In conclusion, we developed a multipathway coupled domino strategy for the synthesis of 2-acylbenzothiazoles from multiform substrates arylethenes, arylacetylenes, 2-hydroxy-aryl ketones, and 1-arylethanol. The protocol embodied four distinct reaction pathways. It provided a diverse synthetic approach to access 2-acylbenzothiazoles, which should be of great utility in the fields of combinatorial chemistry and organic methodology. Further studies on the applications of this strategy will be reported in due course.

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Supporting Information Available. Spectrascopic data and general procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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