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Direct Synthesis of Substituted Naphthalenes from 1,3-Dicarbonyl Compounds and 1,2-Bis(halomethyl)benzenes Including a Novel Rearrangement Aromatization of Benzo[*c*]oxepine

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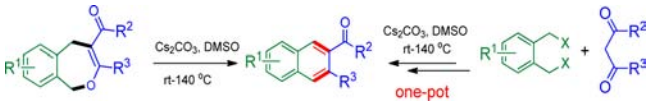
ABSTRACT



An unexpected rearrangement aromatization of benzo[*c*]oxepine has been revealed to synthesize substituted naphthalenes. This observation was further exploited to develop an efficient approach for the construction of naphthalenes from simple and commercially available 1,3-dicarbonyl compounds and 1,2-bis(halomethyl)benzene compounds via a new domino reaction sequence.

Substituted naphthalenes have attracted considerable attention as important basic building blocks for the synthesis of pharmaceuticals[1] and polycyclic aromatic electronic materials.[2] Therefore, substantial effort has been devoted to the development of synthetic methodologies for the construction of these privileged structural motifs.[3] A variety of methods have been reported, including Diels–Alder reactions,[3a,4] annulation via Fischer carbenes (the Dötz reaction),[5] cyclization of aromatic enynes or enediynes,[6] ring-closing metathesis,[7] annulations using alkynes,[8] rearrangements of strained rings,[9] Lewis acid catalyzed cyclization,[10] and many others.[11] In this paper, we report an effective route for the synthesis of substituded naphthalenes from simple and commercially available 1,3-dicarbonyl

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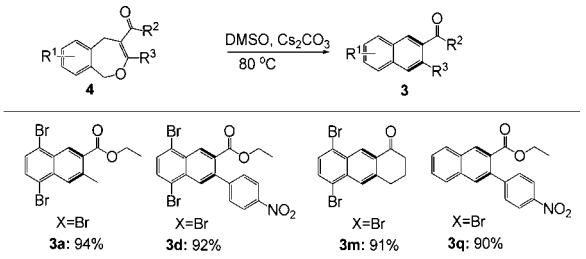
compounds and 1,2-bis(halomethyl)benzene compounds. In addition, we report a novel rearrangement process that transforms benzo[*c*]oxepines into napthalene derivatives.

Scheme 1. Rearrangement of Benzo[*c*]oxepine[a]



[a] Reaction conditions: **4** (1.0 mmol), Cs_2CO_3 (2.0 mmol) in DMSO at 80 °C for 2 h. Isolated yields.

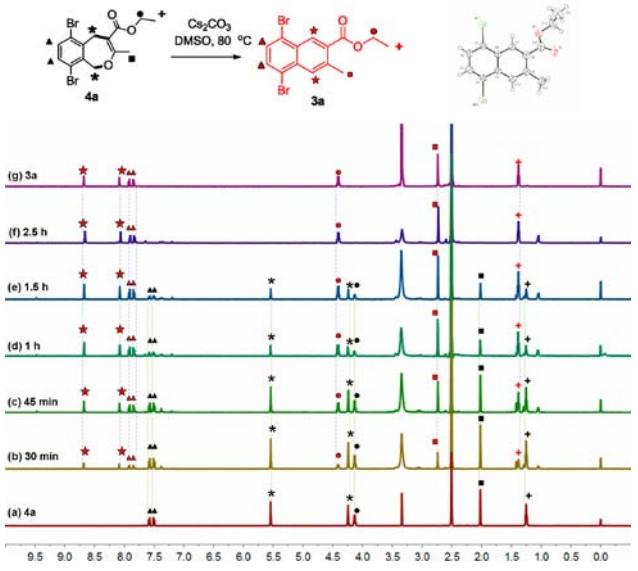
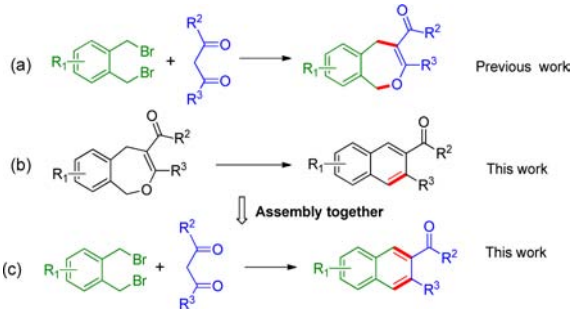


Figure 1. Reaction process of **4a** (0.1 mmol) in the presence of Cs_2CO_3 (0.2 mmol) at 80 °C was monitored by ^{1}H NMR spectroscopy (600 MHz, DMSO-d_6, 298 ± 0.5 K).

Initially, our investigation focused on the reactivity of the benzo[*c*]oxepine skeleton. To our surprise, a naphthalene-based product **3a** was obtained when ethyl 6,9-dibromo-3-methyl-1,5-dihydrobenzo[*c*]oxepine-4-carboxylate (**4a**) mixed with 2 equiv of Cs_2CO_3 in DMSO at 80 °C (Scheme 1, **3a**). Other substituted naphthalenes were also obtained from corresponding benzo[*c*]oxepine compounds (Scheme 1, **3d**, **3m**, and **3q**). The reaction process of **4a** was

Scheme 2. Merger of Two Fundamental Reactions



monitored by ^{1}H NMR spectroscopy (Figure 1). The formation of product **3a** was clearly observed after 30 min and the concentration subsequently increased over time, which was directly related to the consumption of **4a**. This conversion continued for about 2.5 h until starting material **4a** was consumed. We did not observe the formation of intermediates in this transformation. Moreover, the structures of product **3a** and **3q** were determined by X-ray crystallographic analysis.[12] These results established a fascinating rearrangement−aromatization of benzo[*c*]oxepine, which could lead to an efficient approach toward substituted naphthalenes under mild conditions.

The efficient formation of substituted naphthalenes prompted us to study the reaction further. Based on the previously reported synthesis of benzo[*c*]oxepines under basic conditions (Scheme 2a)[13] and this novel rearrangement aromatization (Scheme 2b) also under basic conditions, we considered whether it would be possible to construct naphthalenes directly via a one-pot domino reaction that merges these two fundamental reactions (Scheme 2c). To our delight, the reaction of 1,4-dibromo-2,3-bis(bromomethyl)benzene (**1a**) with ethyl 3-oxobutanoate (**2a**) performed smoothly to give the desired product **3a** in the presence of Cs_2CO_3 (2 equiv) at 20−140 °C in DMSO (Table1, entries 1−3). Other bases, such as K_3PO_4, *t*-BuOK, KOH, Na_2CO_3, Et_3N, and DBU provided lower yields (Table 1, entries 6−11). Interestingly, acids such as CH_3COOH and Lewis acid $ZnCl_2$ also promoted the conversion in low yields (Table 1, entries 13−14). The desired product was also obtained in DMF, EtOH, and toluene in moderate yields (Table S1, Supporting

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(12) Crystal data of **3a**, **3g**, **3l**, **3q**, **4d**, **4q**, **5q**. See SI for details.

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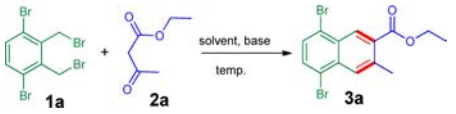
Information (SI)). After the above experimental optimizations, we found that **1a** (1 mmol) could react with **2a** (1 mmol) in the presence of Cs_2CO_3 (2 mmol) in DMSO at 80 °C to afford the desired product in 86% yield after 2 h (Table 1, entry 2).

Table 1. Optimization of the Reaction Conditions[a]



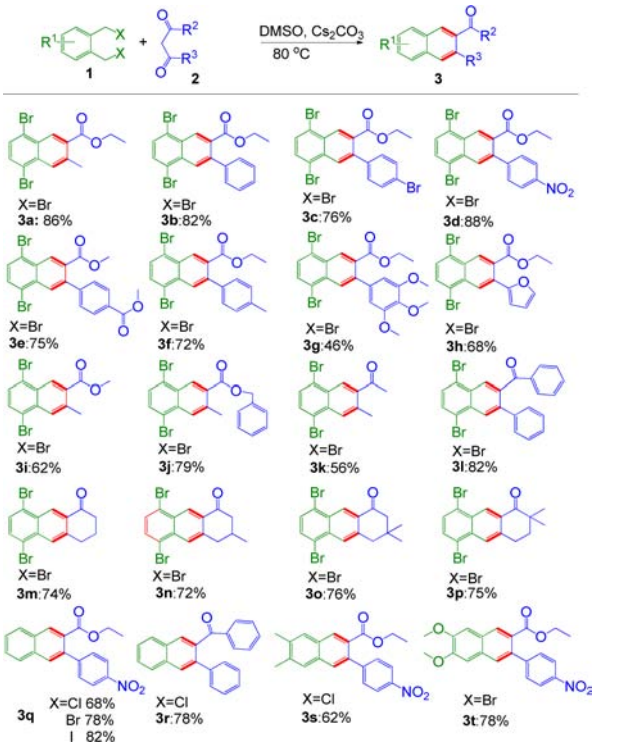
entry	solvent	base	temp/°C	molar ratio	yield[b] (%)
1	DMSO	Cs_2CO_3	20	1:1	84
2	**DMSO**	**Cs_2CO_3**	**80**	**1:1**	**86**
3	DMSO	Cs_2CO_3	140	1:1	86
4	DMSO	Cs_2CO_3	80	1:0.5	84
5	DMSO	Cs_2CO_3	80	1:2	86
6	DMSO	K_3PO_4	80	1:1	68
7	DMSO	*t*-BuOK	80	1:1	64
8	DMSO	KOH	80	1:1	45
9	DMSO	Na_2CO_3	80	1:1	26
10	DMSO	Et_3N	80	1:1	<5
11	DMSO	DBU	80	1:1	64
12	DMSO	HCl	80	1:1	<5
13	DMSO	CH_3COOH	80	1:1	15
14	DMSO	$ZnCl_2$	80	1:1	25

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), base (2 mmol), solvent (5 mL). The reaction was performed for 2 h. [b] Isolated yields.

Under the optimal conditions, a wide range of 1,3-dicarbonyl compounds and 1,2-bis(halomethyl)benzene compounds were investigated. As shown in Scheme 3, different 1,3-dicarbonyl compounds reacted smoothly with **1a** to afford the desired products in moderate to good yields. For example, derivatives of ethyl benzoylacetate substituted with electron-withdrawing or -donating groups on the phenyl ring exhibited good reactivity (Scheme 3, entries **3c**−**g**, 46%−88%). Ethyl 3-(furan-2-yl)-3-oxopropanoate also gave a satisfying result (Scheme 3, **3h**, 68%). Furthermore, the reactions of methyl 3-oxobutanoate, benzyl 3-oxobutanoate, pentane-2,4-dione, and 1,3-diphenylpropane-1,3-dione also took place smoothly to furnish the desired products in moderate to good yields (Scheme 3, **3i**−**3l**, 56−82%). In addition, cyclohexanedione and substituted cyclohexanediones also delivered the corresponding aromatic products in good yields (Scheme 3, **3m**−**p**, 72−76%).

The scope of this reaction was further extended to various 1,2-bis(halomethyl)benzene compounds. For example, when different benzyl halides, such as 1,2-bis(chloromethyl)benzene, 1,2-bis(bromomethyl)benzene, or 1,2-bis(iodomethyl)benzene were used, naphthalene **3q** was isolated in 68%, 78%, and 82% yields, respectively. When different substituents were attached to the aromatic rings of the 1,2-bis(halomethyl)benzene starting materials, the reaction afforded the analogous products in moderate yields (Scheme 3, **3s**−**t**, 62−78%).

Scheme 3. Scope of 1,3-Dicarbonyl Compounds and 1,2-Bis(halomethyl)benzene Compounds[a]

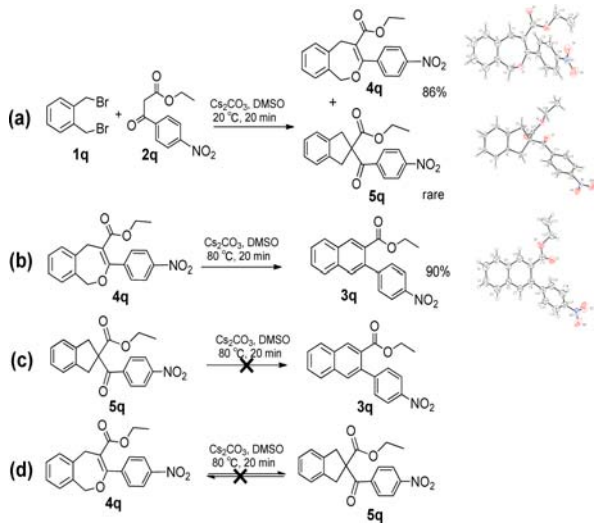


[a] Isolated yields.

To gain some insight into the mechanism of the reaction process, the following experiments were performed (Scheme 4). First, we conducted the reaction of 1-(bromomethyl)-2-ethylbenzene (**1q**) with ethyl 3-(4-nitrophenyl)-3-oxopropanoate (**2q**) with Cs_2CO_3 in DMSO at rt. The reaction was monitored by TLC and stopped after 20 min to obtain ethyl 3-(4-nitrophenyl)-1,5-dihydrobenzo[*c*]oxepine-4-carboxylate (**4q**) and ethyl 2-(4-nitrobenzoyl)-2,3-dihydro-1*H*-indene-2-carboxylate (**5q**) (Scheme 4a), whose structures were confirmed by X-ray diffraction.[12] When benzo[*c*]oxepine **4q** was subsequently treated with Cs_2CO_3 in DMSO at 80 °C, the aromatic product **3q** was obtained in good yield after 20 min (90%, Scheme 4b). However, when the byproduct indene **5q** was treated under the same conditions, the aromatic product **3q** was not observed in the experiment (Scheme 4c). Moreover, there were no indications that the seven-membered ring **4q** and the five-membered ring **5q** interconvert under the reaction conditions (Scheme 4d).

To further probe the reaction process, we monitored the reaction of **1a** and **2a** by ^1H NMR spectroscopic studies (Figure 2). All of the signals were assigned by marked symbols. As shown in the figure, the consumption of **1a** and **2a** occurred during the first 10 min, providing the intermediate seven-membered ring **4a** (Figure 2c and 2d). Then, the naphthalene-based product **3a** began to appear after about 1 h and the concentration subsequently increased over time (Figure 2e−2g). The rearrangement

Scheme 4. Control Experiments



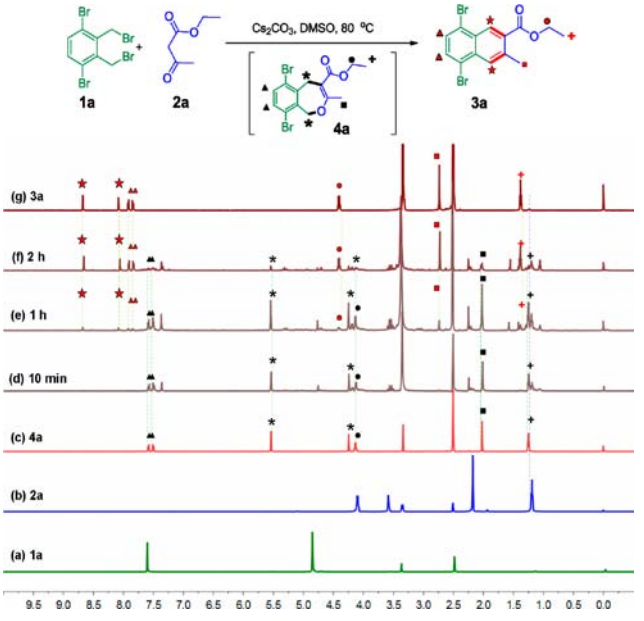


Figure 2. Reaction process of **1a** (0.1 mmol) and **2a** (0.1 mmol) in the presence of Cs_2CO_3 (0.2 mmol) at 80 °C was monitored by ^{1}H NMR spectroscopy (600 MHz, DMSO-d_6, 298 ± 0.5 K).

aromatization of the seven-membered ring **4q** in the presence of Cs_2CO_3 was also monitored by ^{1}H NMR spectroscopic studies (Figure S2, SI).

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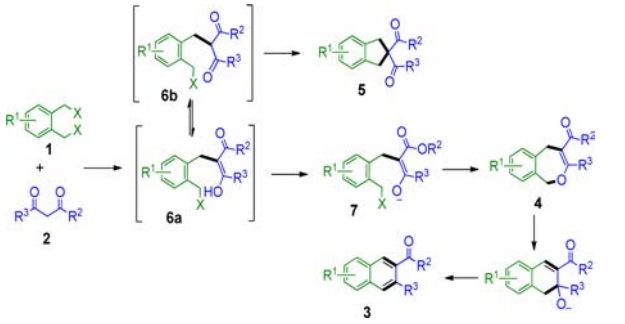
Scheme 5. Proposed Reaction Pathway



On the basis of the results described above and in the literature,[13a,14] a plausible mechanism of this reaction is described in Scheme 5. Due to the presence of an active methylene group, the first C-alkylation in 1,3-dicarbonyl compounds gave intermediate **6**, which could exist in two tautomeric forms **6a** and **6b**. The existence of monalkylated **6** in enolic forms caused a competition between C-alkylation to give the five-membered ring **5** and O-alkylation to present the seven-membered ring **4**.[13a] The stability of seven-membered benzo[*c*]oxepine provided **4** as the major product. Finally, rearrangement of **4** followed by aromatization in the presence of Cs_2CO_3 afforded the desired naphthalene-based product **3**.

In summary, we have illustrated an efficient and novel rearrangement aromatization of benzo[*c*]oxepine to construct substituted naphthalenes. This process was further developed to a route that integrates C-alkylation/O-alkylation/rearrangement/aromatization sequences to directly synthesize substituted naphthalene products from simple and commercially available 1,3-dicarbonyl compounds and 1,2-bis(halomethyl)-benzenes. A variety of functional groups were tolerated under these reaction conditions. Investigations into the detailed mechanism and synthetic applications of this reaction are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.