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Formation of Benzo[*f*]-1-indanone Frameworks by Regulable Intramolecular Annulations of *gem*-Dialkylthio Trienynes

Zhongxue Fang,[†] Ying Liu,[†] Badru-Deen Barry,[†] Peiqiu Liao,[†] and Xihe Bi*[,†,‡]

[†]Department of Chemistry, Northeast Normal University, Changchun 130024, China

[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

Supporting Information

ABSTRACT: An atom-economic route to benzo[*f*]-1-indanone frameworks has been developed starting from the readily available *gem*-dialkylthio trienynes by intramolecular annulations. The chemoselectivity of the intramolecular cyclizations can be regulated by both the base and the type of gas atmosphere used in the reaction, thus allowing the divergent synthesis of the corresponding functionalized benzo[*f*]-1-indanones in good to excellent yields.

The indan ring framework is the major niche in natural products and bioactive and pharmaceutically relevant molecules.[1] It has distinguished utility in organic light-emitting devices, dyes, and photoremovable protecting groups.[2] Distinctly, benzo[*f*]indanones constitute the core structural motif in naturally occurring bioactive compounds, such as euplectin, coneuplectin and ligustrones A–C (Figure 1).[3]

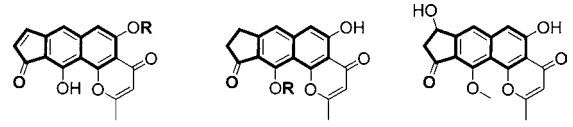

Figure 1. Natural products containing benzo[*f*]-1-indanones.

Euplectin possesses moderate cytotoxicity toward the growth of murine P-815 mastocytoma cells, and ligustrones are the major metabolite of the fungus, while the bioactivity of coneuplectin has not been evaluated due to the paucity of this natural compound. Even though the synthesis of benzo[*f*]indanones has attracted much attention, the available methods suffer from remarkable disadvantages such as harsh conditions (>150 °C) and noneasily available starting materials.[4] As a consequence, the need for further efforts to unravel new strategies with selective and controlled substitution patterns that are promotable by environmentally benign and atom-economic catalyst systems is compelling.

The Diels–Alder (DA) approach is irrefutably the most impressive synthetic technique for the formation of six-membered carbo- and heterocyclic frameworks.[5] Over the past decade, the potency of this method is peculiarly manifested from the versatility of the dehydro-Diels–Alder (DDA) reaction; a valuable extension of the classical Diels–Alder reaction.[6] Most of these reactions are triggered by heat,[7] transition metals,[8] microwave,[9] base,[10] or photochemical conditions.[11] Besides the single products obtained from starting materials, the technique is often constrained by its utility of higher temperatures[12] or its dependence on substrates bearing specific functional groups such as silicon group.[13] Consequently, the design of novel substrates that can submit to a range of functionalities capable of affording various products remain highly desirable. α-Oxo ketene dithioacetals have been shown to be versatile intermediates in organic synthesis since the first report by Kelber in 1910.[14] Due to the unique structural character, they are ideal scaffolds to construct polyenyne systems, which are the basis for intramolecular cyclization reactions. However, such utilizations are rather rare.[15] As our continued efforts to develop novel organic reactions by strategic use of functionalized alkynes,[16] we herein report a regulable DDA reaction of *gem*-dialkylthio trienynes, thus allowing the divergent synthesis of a range of benzo[*f*]-1-indanones.

In our preliminary investigations for optimal reaction conditions, we evaluated the DDA reaction of *gem*-dialkylthio trienyne **1a** on various reaction parameters including temperature, base, and atmospheric gas (Table 1). The reaction afforded 90% of **3a** and a trace amount of **2a** when **1a** (1.0 equiv) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.0 equiv) in open-air conditions at 120 °C for 12 h (Table 1, entry 1). However, replacement of the DBU with 1,4-diazabicyclo[2.2.2]octane (DABCO) in the reaction offered a mixture of regioisomers with the following composition: **3a** (35%), **4a** (35%), and **2a** (15%) were obtained (Table 1, entry 2). Further, two products with identical selectivity for types **2a** and **4a** were obtained for the same reaction when $BnN(CH_3)_2$ and Et_3N were each used as base for 4 and 6 h, respectively (entries 3 and 4). Delightfully, an appealing result that offered 83% yield of **4a** was obtained when the reaction of **1a** was performed in the presence of 2.0 equiv of DBU for 30 min under nitrogen atmosphere (Table 1, entry 5). By varying

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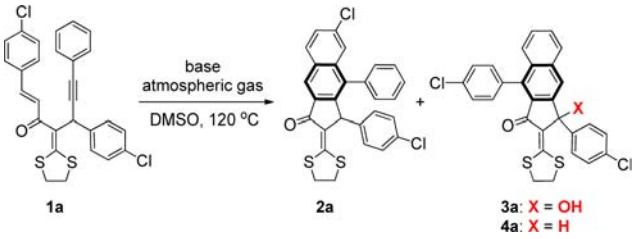
Table 1. Optimization of the Reaction Conditions[a]



entry	base (2.0 equiv)	O_2/N_2/ air	time (h)	2a[b] (%)	3a[b] (%)	4a[b] (%)
1	DBU	air	12	5	90	0
2	DABCO	air	5	15	35	35
3	$BnN(CH_3)_2$	air	4	20	0	70
4	Et_3N	air	6	20	0	70
5	DBU	N_2	0.5	15	0	83
6[c]	DBU	O_2	1	5	90	0
7		air	24	86[d]	0	0

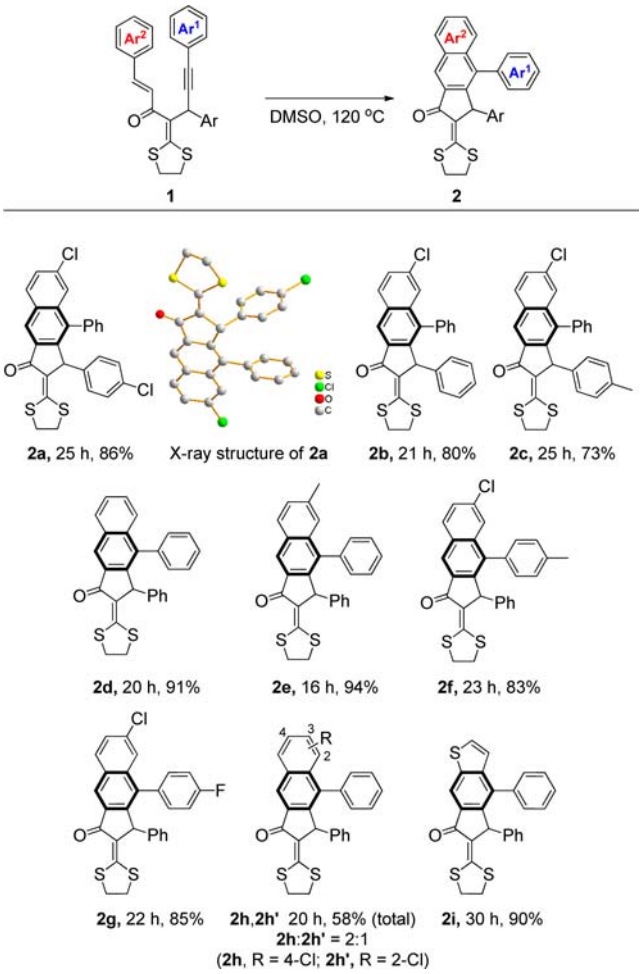
[a]The reaction was run with 0.3 mmol of **1a**. [b]The ratio of regioisomers was determined by ^1H NMR spectral analysis of the reaction mixture. [c]0.3 equiv of DBU was used. [d]Isolated yield.

different conditions that utilized 30 mol % of DBU as the catalyst under oxygen atmosphere, **3a** was obtained in 90% yield in 60 min (Table 1, entry 6). Interestingly also, when the reaction was run without a base, isomer **2a** was obtained as the sole product in 86% yield, albeit over a much longer reaction time (24 h) (Table 1, entry 7). In line with these observations, the reaction conditions listed in entries 5−7 are optimal for the regioselective formation of benzo[*f*]-1-indanone isomers and were selected for further investigations on the reaction scope.

Given the novelty of this reaction and the possibility to selectively produce some unusual benzo[*f*]-1-indanone motifs of type **2**, we decided to explore its scope. As a result, the set of experimental conditions listed in entry 7 of Table 1 was utilized for this purpose. First, we found that the reactions of substrates **1a−i** all smoothly proceeded to efficiently afford the corresponding products **2a−i** in good to excellent yields (Scheme 1). Systematic variation of substituents on the Ar, Ar^1, and Ar^2 showed no dramatic influence on the results. It is worth mentioning that substrate **1h** with an unsymmetrical Ar^2 group gave rise to a regioisomer mixture of **2h** and **2h′** in a ratio of **2**:**1**. Furthermore, the 2-thienyl group, a heteroaryl unit, imparted no effect on the reaction outcome, and as a result, the corresponding thieno[*f*]-1-indanone **2i** was obtained in 90% yield. In addition to the structural analysis by $^1H/^{13}C$ NMR and HRMS spectra, the indanone structure was further unambiguously confirmed by the X-ray diffraction (XRD) analysis of product **2a** (CCDC No. 1022437).

Further, aiming for the selective synthesis of product **3**, the reaction conditions listed in Table 1, entry 6, were used to explore the reaction scope and limitations. As summarized in Scheme 2, when *gem*-dialkylthio trienynes **1** were subjected to 30 mol % DBU catalysis in DMSO under oxygen atmosphere, 3-hydroxybenzo[*f*]-1-indanones **3a−k** were obtained in good to high yields. From our scrutiny of the substituent effects on the Ar group, the reaction was submitted to various electron-donating and -withdrawing substituents on the Ar group, thus affording the corresponding 3-hydroxybenzo[*f*]-1-indanones **3a−c** in excellent yields (86−90%). Next, the systematic variation of Ar^1 and Ar^2 groups was carried out. We were pleased to find that good to excellent yields (61−90%) of the

Scheme 1. Synthesis of Benzo[*f*]-1-indanones 2



desired 3-hydroxybenzo[*f*]-1-indanones (**3d−k**) were obtained with good functional group tolerance. Notably, when substrate **1k** with an unsymmetrical Ar^1 group, a mixture of 3-hydroxybenzo[*f*]-1-indanone **3k** and **3k′** with a ratio of 1.7:1 was obtained. Structure elucidation of the 3-hydroxybenzo[*f*]-1-indanones **3** by $^1H/^{13}C$ NMR and HRMS spectra were further supported and confirmed by XRD analysis of compound **3a** (CCDC No. 1022438). Finally, the benzo[*f*]-1-indanones **4** produced from the DBU (2.0 equiv) catalyzed intramolecular cyclization of *gem*-dialkylthio trienynes **1** under nitrogen atmosphere were examined. It was found that the reactions all smoothly proceeded and afforded the corresponding benzo[*f*]-1-indanones **4a−k** in 56−81% yields. Similarly, the formation of a mixture of products **4k** and **4k′** in a ratio of 1:2 was also obtained.

Notably, all products contain a characteristic ketene dithioacetal group. Therefore, the further functional group transformations were investigated. To our delight, a highly efficient and complete conversion of compound **2b** into a bis-sulfone **5** was realized through the oxidation simply using *m*-CPBA at room temperature (eq 1). To our knowledge, this is the first example to achieve such kind of reaction in ketene dithioacetal chemistry.[14b] The structure of product **5** was unambiguously confirmed by XRD analysis (CCDC No. 1022439).

On the basis of these results and related precedents,[17] a plausible mechanism for the benzo[*f*]-1-indanone synthesis is

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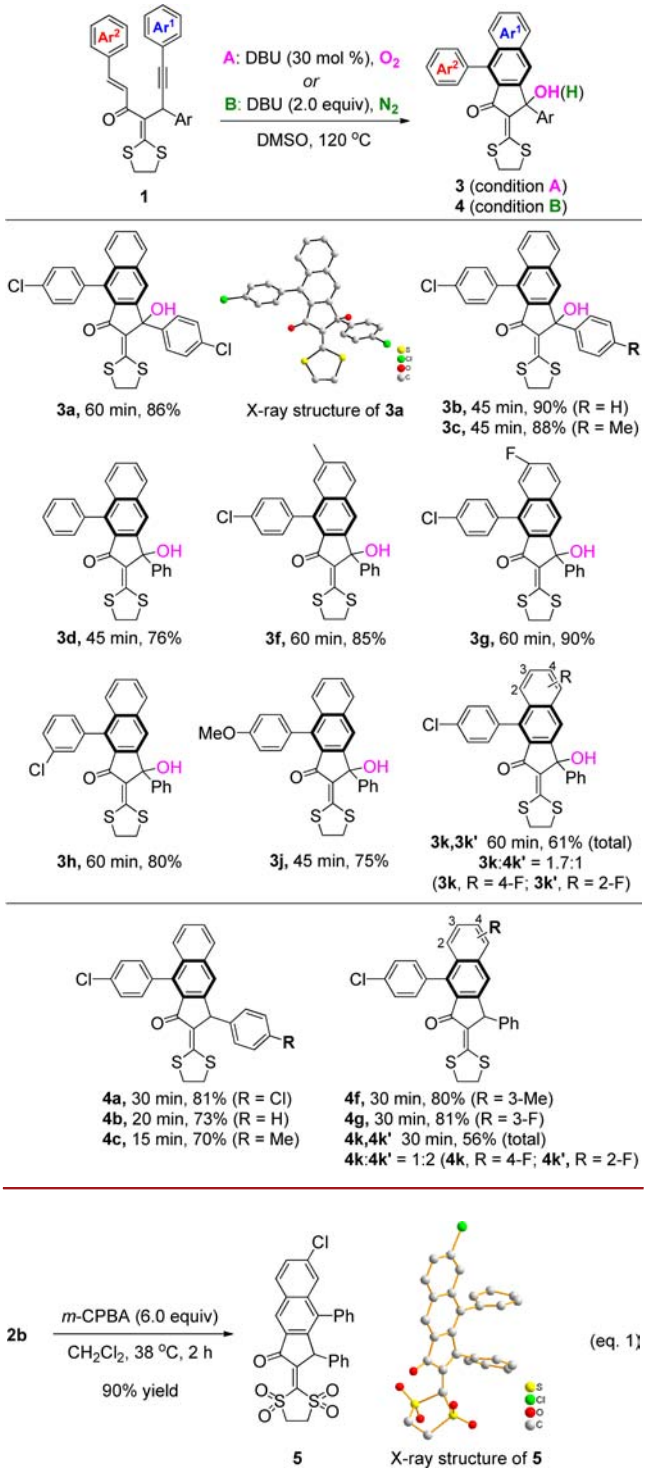
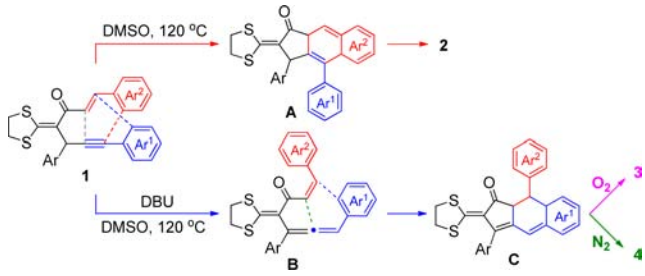
Scheme 2. Synthesis of Benzo[*f*]-1-indanones 3 and 4



thus proposed (Scheme 3). First, in the absence of DBU, the interaction between a styrene group and an alkyne moiety of the dieneyne **1** initiated by the intramolecular Diels–Alder reaction gives the intermediate **A**.[18] The intermediate **A** then undergoes aromatization by the facile loss of two hydrogen atoms to offer the final product, benzo[*f*]-1-indanone **2**. On the other hand, when DBU is present, the initial step involves the isomerization of propargyl unit to give allene intermediate **B**.[19] In this case, the C–C double bond of the electron-deficient cinnamoyl group of the intermediate **B** acts as the dienophile,

Scheme 3. Plausible Reaction Mechanism



whereas the Ar^1 and C–C double bond of the allene acts as the diene component for the DDA reaction producing intermediate **C**.[20] This unstable and highly conjugated species then undergoes aromatization via loss of two hydrogen atoms to yield the 3-hydroxy-substituted product **3** in the presence of oxygen atmosphere,[21] whereas the benzo[*f*]-1-indanones **4** are obtained under nitrogen atmosphere.

In conclusion, we have reported the first example of an intramolecular regulable DDA reaction starting from the easily available *gem*-dialkylthio trienynes, thus leading to the synthesis of diverse indanone derivatives. Modulation on the reaction parameters such as base and the type of atmospheric gas used directly regulates the regioselective formation of benzo[*f*]-1-indanone isomers. Several features in this reaction are noteworthy, such as the ready availability of substrates, regulable chemo- and regioselectivity, atom economy, high efficiency and product yields, and highly functionalized products that are potential for further synthetic derivatization. The discovery described here therefore represents a significant advance in the chemistry of the DDA reaction and opens a new reaction manifold for further exploitation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bixh507@nenu.edu.cn.

Notes

The authors declare no competing financial interest.

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