

Transition-Metal-Free Ring Expansion Reactions of Indene-1,3-dione: Synthesis of Functionalized Benzoannulated Seven-Membered Ring Compounds

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S Supporting Information

ABSTRACT: A novel ring expansion reaction of indene-1,3dione with alkynyl ketones under transition-metal-free conditions has been developed. This process offers an efficient and direct way to synthesize benzoannulated seven-membered rings or fused-ring compounds through C-C σ -bond activation. Notable features of the procedure include easily accessible starting materials, good functional group tolerance, and high atom economy.

hemical transformations initiated by the cleavage of C–C bonds are important and highly efficient methods to synthesize organic compounds because they can reorganize the skeletons and afford versatile scaffolds that are otherwise difficult to prepare. However, activation of C-C bonds is highly challenging because of the inert and stable properties of these bonds. Thus, such transformations have been restricted to highly strained molecules, such as three- or four-membered rings.¹ For unstrained systems, the C-C activation reactions are limited to transition-metal catalysis, using rhenium,² nickel,³ or others.⁴ Nevertheless, transition-metal-free C-C cleavage reactions, in particular, the insertion of alkynes into C–C σ -bonds, are rare,⁵ with the exception of in situ generated arynes⁶ or cyclohexynes.⁷ Recently, we developed a general and efficient base-promoted protocol for the insertion of alkynyl ketones into the C–C σ bonds of 1,3-diketone compounds, which represents the first example of insertion of a normal alkyne triple bond into a C-C σ -bond under transition-metal-free conditions.⁵ We envisioned that indene-1,3-dione would serve as a platform for the production of a variety of benzoannulated seven-membered ring compounds. It is known that benzoannulated sevenmembered ring skeletons widely occur in natural products⁸ and exhibit interesting biological activities,⁹ for example, purpurogallin, theaflavic acid, and hamigeran G (Figure 1). Cyclization strategies to seven-membered rings are often inhibited due to entropic factors and transannular interactions. Accordingly, development of new and efficient synthetic approaches using easily accessible starting materials is of considerable interest. We report herein a transition-metal-free procedure which involves the insertion of ynones into carboncarbon σ -bonds of indene-1,3-dione, resulting in ring expansion by two atoms, for the synthesis of benzoannulated sevenmembered rings. In addition, when alkynes bearing an orthohalogenated aryl ring are used, the reaction affords seven-





Figure 1. Selected examples of naturally occurring compounds containing a benzoannulated seven-membered ring skeleton.

membered, ring-fused cyclic compounds in good to high yields, which are otherwise difficult to prepare (Scheme 1c,d).

We initially attempted the reactions of 1-phenyl-3-(*p*-tolyl)prop-2-yn-1-one (1a) bearing a tolyl substituent at the alkyne terminus with indene-1,3-dione (2a) (1.2 equiv) in the presence of 2.0 equiv of Cs_2CO_3 at 60 °C in DMSO (3.0 mL). The results are shown in Table 1. The expected C–C σ -bond insertion/ring expansion product 3a could be formed in 60% yield within 3 h (Table 1, entry 1). Formation of 3a suggested that the C-Cbond α to a carbonyl group in 2a was activated during the reaction process. When 1.4 equiv of 2a was used, the yield of 3a was increased to 79% (entry 2). However, 2.0 equiv of 2a resulted in lower yield (Table 1, entry 3). Increasing the reaction temperature to 110 °C afforded 3a in a higher yield of 81% within 1 h in the presence of 3.0 equiv of Cs_2CO_3 (entry 5). Interestingly, the yield of 3a was further increased to 84% when the reaction was carried out in 5.0 mL of solvent at 110 °C (entry 6), indicating that both the concentration of the substrates and reaction temperature have a large influence on the reaction

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Scheme 1. Insertion of Triple Bonds into a Carbon–Carbon σ -Bond

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Table 1. Screening of Reaction Conditions⁴

Ph	+ C 1a		base vent, temp		Dh
entry	base (equiv)	solvent	temp (°C)	time (h)	yield (%)
1 ^b	Cs_2CO_3 (2.0)	DMSO	60	3	60
2 ^c	Cs_2CO_3 (2.0)	DMSO	60	3	79
3 ^d	Cs_2CO_3 (2.0)	DMSO	60	3	75
4 ^e	Cs_2CO_3 (3.0)	DMSO	60	2	80
5 ^e	Cs_2CO_3 (3.0)	DMSO	110	1	81
6	Cs_2CO_3 (3.0)	DMSO	110	1	84
7	Cs_2CO_3 (3.0)	toluene	110	1	NR
8	Cs_2CO_3 (3.0)	DMF	110	1	78
9	Cs_2CO_3 (3.0)	DMA	110	1	68
10	Cs_2CO_3 (3.0)	NMP	110	1	51
11	DABCO (3.0)	DMSO	110	1	NR
12	$\mathrm{KO}^{t}\mathrm{Bu}$ (3.0)	DMSO	110	1	trace
13	K_2CO_3 (3.0)	DMSO	110	1	74
14	KOH (3.0)	DMSO	110	1	32

^{*a*}Unless otherwise noted, the reactions were conducted on a 0.2 mmol scale with the ratio of 1a/2a = 1:1.4 in 5.0 mL of solvent under N₂. ^{*b*}1a/2a = 1:1.2 in 3.0 mL of DMSO. ^{*c*}1a/2a = 1:1.4 in 3.0 mL of DMSO. ^{*d*}1a/2a = 1:2.0 in 3.0 mL of DMSO. ^{*c*}3.0 mL of DMSO. ^{*f*}No reaction.

process. Toluene as the solvent gave no desired product at all. The reactions could also proceed in dipolar aprotic solvents such as DMF, DMA, or NMP, albeit with lower product yields (entries 8-10). An organic base such as DABCO was ineffective for this reaction (entry 11). Other bases, such as K₂CO₃ and KOH, afforded **3a** in 32–74% yields (entries 13 and 14). However, a stronger base such as KO^tBu gave only a trace amount of **3a** (entry 12).

With the optimal reaction conditions in hand (Table 1, entry 6), we next explored the substrate scope of this C-C activation reaction (Figure 2). The reaction worked well with alkynyl



Figure 2. Synthesis of 3. Unless otherwise noted, the reactions were carried out using 3.0 equiv of Cs_2CO_3 in 5.0 mL of DMSO at 110 °C under N_2 on a 0.2 mmol scale with the ratio of 1/2a = 1:1.4.

ketones bearing various substituents (R^2) on the terminal aryl rings (3a-3e). Substrates with both electron-withdrawing and electron-donating groups on the aryl ring were suitable for the reaction, offering the desired ring expansion products in good to high yields. Notably, a substrate with p-Cl aryl groups was tolerable to the reactions conditions, affording 3d in 78% yield. Interestingly, a methyl-substituted substrate could also react with 2a smoothly to give 3e in 47% yield, in which a 1,5-H shift isomer was formed as the major product. Subsequently, the R^1 substituent on the carbonyl carbon was explored (Table 2, 3f-31). It was found that \mathbb{R}^1 with electron-donating $(3.4.5 - (MeO)_3)$ 4-MeO, 4-Me) aryl groups afforded the corresponding products 3f, 3g, and 3h in 80, 73, and 85% yields, respectively. Electronwithdrawing (4-F, 4-Cl, 4-Br) aryl groups also provided the desired benzoannulated seven-membered rings 3i, 3j, and 3k in good yields. Ring-fused substituents such as 1-naphthyl could be successfully employed as well to give the corresponding 31 in very high yield. Other aryl substituents, such as 2-fural or 2-pyrrolyl, offered the desired products 3m and 3n in 54 and 76% yields, respectively. When both R^1 and R^2 were 4-Cl phenyl groups, the corresponding 30 was formed in 77% yield. Other fivemembered cyclic 1,3-dicarbonyl compounds were also tested. When 1,3-cyclopentanedione was reacted with 3-phenyl-1-(ptolyl)prop-2-yn-1-one at the optimal reaction conditions, the desired product 3p was formed in 68% yield. However, when tetronic acid was used, no desired product was obtained.

It is worth noting that when substrate 1 bearing an *ortho*bromo-substituted aryl ring on the carbonyl carbon, namely, 1-(2-bromophenyl)-3-(p-tolyl)prop-2-yn-1-one (4a), was used, a subsequent intramolecular cyclization reaction occurred to give a seven-membered, fused-ring compound 5a. Structural identification of 5a was carried out by X-ray crystallography. To improve the yield of 5a, different reaction parameters, such as Table 2. Screening of Reaction Conditions for the Synthesis of $5a^a$

B	4a 2	base, solv 110 °C	rent	
entry	base (equiv)	solvent	time (h)	yield (%)
1 ^b	Cs_2CO_3 (3.0)	DMSO	2	30
2 ^b	Cs_2CO_3 (2.0)	DMSO	2	37
3	Cs_2CO_3 (2.0)	DMSO	2	61
4 ^{<i>c</i>}	Cs_2CO_3 (2.0)	DMSO	2	31
5	Cs_2CO_3 (2.0)	DMA	2	55
6	Cs_2CO_3 (2.0)	THF	2	-d
7	Cs_2CO_3 (2.0)	DMF	2	61
8	Cs_2CO_3 (2.0)	CH ₃ OH	2	-d
9	Cs_2CO_3 (2.0)	1,4-dioxane	2	-d
10	NaOH (2.0)	DMSO	2	47
11	KO ^t Bu (2.0)	DMSO	5	trace
12	K_2CO_3 (2.0)	DMSO	2	69
13 ^e	K_2CO_3 (2.0)	DMSO	2	77
14 ^e	K_2CO_3 (3.0)	DMSO	2	84
15 ^e	K_2CO_3 (4.0)	DMSO	2	84

^{*a*}Unless otherwise noted, the reactions were conducted on a 0.3 mmol scale with the ratio of 4a/2a = 1.2:1.0 in 3.0 mL of solvent under N₂. ^{*b*}4a/2a = 1:1.4. ^{*c*}Under air. ^{*d*}No product. ^{*e*}5.0 mL of DMSO was used.

bases, solvents, and ratio of the reactants, were screened (Table 2). It was found that the best result for the synthesis of **5a** was to use 3.0 equiv of K_2CO_3 as the base and DMSO as the solvent at 110 °C (Table 2, entry 14). Thus, the scope of the reaction was explored using various ortho-bromo-substituted arenes on the carbonyl carbon with different electronic properties (Figure 3). For the substituents R^3 on the triple bond, substrates with both electron-withdrawing and electron-donating groups on the aryl ring were suitable for the reaction, offering the desired products (5a-5f) in yields of 58-94%. Electron-rich aryl groups gave yields (5a, 84% yield; 5b, 94% yield; 5c, 93% yield) much higher than those with electron-poor or electron-neutral aryl groups (5e, 69%; 5d, 77%). When chloro- or fluoro-substituted ynone was used instead of bromo-substituted ones, the desired 5d could also be produced in 58 and 67% yields, respectively. A 1-naphthyl group was compatible during the reaction to produce the desired product 5f in 59% yield. With regard to substituents on the carbonyl carbon, an electron-donating group, $3,4-(OMe)_2$, resulted in the formation of 5g in 82% yield. The functionality of -F and -Cl on the various positions of the aryl ring could also be accommodated well during the reaction, and the corresponding products of 5h-5k were formed in 41-92% yields. However, when other electron-withdrawing functionalities, such as 4-CN or 4-NO₂, were employed, only complex mixtures were observed. Ynone bearing a pyridine ring also reacted with 2a to provide the corresponding 51 in 31% yield. To demonstrate the practical utility of this methodology, the gram scale reactions were conducted for the preparation of both 3a and 5a, and the corresponding 3a and 5d were obtained in 77% (2.82 g) and 71% (0.995 g) yields, respectively (see the Supporting Information).

To clarify the reaction mechanism, the reaction of **4a** with **2a** was performed under the optimized reaction conditions at room temperature. An intermediate **6a**, the structures of which were characterized by X-ray crystallography, was obtained in 52% yield



Figure 3. Synthesis of **5**. Unless otherwise noted, the reactions were carried out using 3.0 equiv of K_2CO_3 in 5.0 mL of DMSO at 110 °C under N_2 on a 0.3 mmol scale with the ratio of 4/2a = 1.2:1.

(Scheme 2a). Treatment of 6a with the general reaction conditions of our system led to the formation of desired 5a in

Scheme 2. Control Experiments



92% isolated yield within 2 h (Scheme 2b). This indicates that the desired seven-membered, fused-ring compound 5a was produced through a stepwise path.

Based on the above observation and our previous reports, a plausible reaction mechanism was proposed with model substrates **4a** and **2a**, as depicted in Scheme 3. In the presence of a base, **4a** was attacked by indene-1,3-dione (**2a**) to give an intermediate **A**, which undergoes an intramolecular nucleophilic addition/ring opening to offer a formal alkyne insertion product **C**. Tautermerization of **C** followed by hydrolysis leads to product **6a**, which undergoes nucleophilic aromatic substitution (S_NAr) or conjugate addition followed by elimination of Br^- to afford the final product **5a**.

In summary, we have developed a novel base-promoted ringexpansion reaction of indene-1,3-diones with ynones. This method provides rapid and efficient access to functionalized

Scheme 3. Plausible Reaction Mechanism



benzoannulated seven-membered rings or fused-ring compounds, which are usually difficult to prepare. The C–C σ bond cleavage of common indene-1,3-dione occurred during the reaction process, and the reaction likely proceeds via the formation of a highly reactive cyclobutenol intermediate. This method offers several advantages such as easily accessible starting materials, good functional group tolerance, and mild reaction conditions. Further studies to extend this transition-metal-free alkynyl ketone insertion chemistry are in progress in our group.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00206.

Experimental details and spectroscopic characterization of all new compounds (PDF)

Accession Codes

CCDC 1815272–1815273 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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