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PII: S0040-4039(19)30640-9
DOI: https://doi.org/10.1016/j.tetlet.2019.07.001
Reference: TETL 50910

To appear in: *Tetrahedron Letters*

Received Date: 20 May 2019
Revised Date: 29 June 2019
Accepted Date: 2 July 2019

Please cite this article as: Kanie, M., Ikawa, Y., Yoshimura, T., Matsuo, J-i., Formal [4+4] cycloaddition of 3-arylcyclobutanones with anthracene and their acid-promoted intramolecular cyclization with skeletal rearrangement, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.07.001

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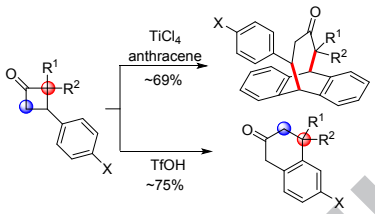

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Formal [4+4] cycloaddition of 3-arylcyclobutanones with anthracene and their acid-promoted intramolecular cyclization with skeletal rearrangement

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

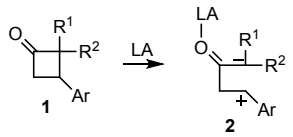
Keywords:
cyclobutanone
anthracene
Lewis acid
[4+4] cycloaddition

ABSTRACT

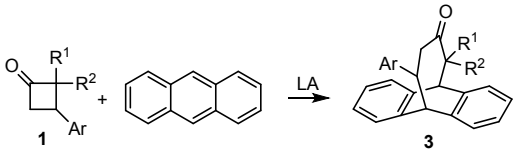
A reaction of 3-arylcyclobutanones with anthracene in the presence of $TiCl_4$ gave 14-aryl-9,10-dihydro-9,10-butanoanthracen-12-ones as a formal [4+4] cycloadduct of anthracenes with a C4 unit formed by cleaving the more substituted C2-C3 bond of cyclobutanones. On the other hand, activation of 3-arylcyclobutanones with TfOH in the absence of nucleophiles gave 2-tetralones with skeletal rearrangement.

Cyclobutanones have been used as a useful building block in organic chemistry particularly by utilizing facile ring cleavage of their four-membered rings.[1] Recently, 3-arylcyclobutanones **1** were activated with a Lewis acid to from a zwitterionic intermediate **2** by cleaving the more substituted C2-C3 cyclobutanone bond (Scheme 1).[2,3] The zwitterionic intermediate **2** reacted with various arenes to give Friedel-Crafts adducts[2]and reacted with nitriles to give the corresponding [4+2] adducts.[3] During our investigation on the above-mentioned Friedel-Crafts reaction, we found that Friedel-Crafts reaction of 3-arylcyclobutanones **1** to anthracene did not occur and formal [4+4] cycloadducts **3** were obtained (Scheme 2). The photochemical dimerization of anthracenes[4] and photochemical cycloaddition of dienes[5] have been reported as suprafacial [4π+4π] photocycloaddition.[6] Except for photochemical cycloaddition, there have been no reports about formal [4+4] cycloaddition to anthracenes.[7]

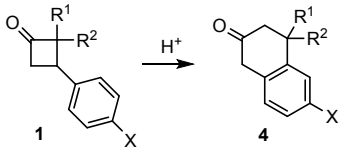
Moreover, during the optimization of the reaction conditions for the [4+4] cycloaddition of **1** and anthracene, activation of 3-arylcyclobutanones **1** with TfOH was found to give 2-tetralones **4** by cycloisomerization with skeletal rearrangement (Scheme 3). In the literature, cyclization of 2-arylcyclobutanones to 2-tetralones and 2-naphthols was reported.[8] However, isomerization of 3-arylcyclobutanones to 2-tetralones has not been reported. We describe here details of these two new reactions of 3-arylcyclobutanones **1**.



Scheme 1. Activation of **1** to a zwitterionic intermediate **2**.



Scheme 2. Formal [4+4] cycloaddition

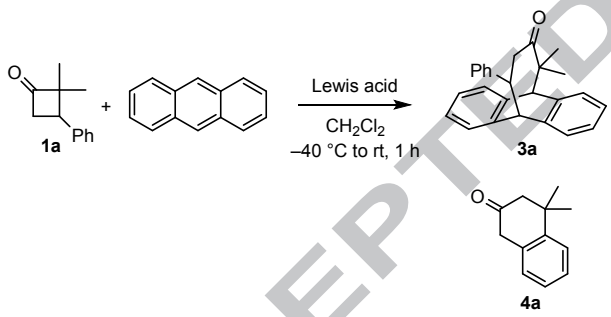


Scheme 3. Cycloisomerization

First, suitable reaction conditions for the formal [4+4] cycloaddition reaction of cyclobutanone **1** and anthracene were screened (Table 1). A solution of cyclobutanone **1a** in dichloromethane was added to a mixture of an equimolar amount of anthracene and 1.1 equivalent of $TiCl_4$ at –40 °C, and then the reaction temperature was allowed to rise to room temperature.

Under these reaction conditions, cyclobutanone **1a** was completely consumed, and a formal [4+4] adduct **3a** was obtained in 69% yield by purification with silica gel preparative TLC (entry 1). The structure of **3a** was confirmed by X-ray crystallography.[9] The order of addition was important for effective cycloaddition between **1a** and anthracene: addition of $TiCl_4$ to a mixture of **1a** and anthracene at –40 °C and then raising the reaction temperature to rt for 1 h gave **3a** in a lower yield (35%) along with many byproducts which were difficult to be isolated. Activation of **1a** with other Lewis acids such as $AlCl_3$, $SnCl_4$, $SiCl_4$, and Me_3SiOTf was found to be less effective compared with $TiCl_4$ (entries 2-5). Effects of Lewis acids including BF_3•OEt_2 and $EtAlCl_2$ were not studied in the reaction of **1a** with anthracene since we knew that ring cleavage of **1a** with BF_3•OEt_2 or $EtAlCl_2$ did not proceed at rt.[2,3] Interestingly, a reaction of **1a** with anthracene in the presence of five equivalents of TfOH at –40 °C to rt for 1 h gave a formal [4+4] adduct **3a** in 36% yield along with 2-tetralone derivative **4a** in 32% yield (entry 6). This result suggested that the carbon skeleton of **1a** rearranged during the formation of **4a** from **1a**. Solvents which can be used in this reaction were limited because Friedel-Crafts reaction of aromatics[2] and formal [4+2] cycloaddition with nitriles[3] proceeded when aromatics and nitriles were used as a solvent. Then, effects of solvents were investigated by using CS_2, nitromethane, and 1,2-dichloroethane (DCE). It was found that these solvents were less effective compared with dichloromethane (entries 7-9). Therefore, optimal Lewis acid and solvent were $TiCl_4$ and dichloromethane.

Table 1. Effects of Lewis acids for formal [4+4] cycloaddition of **1a** and anthracene.[a]

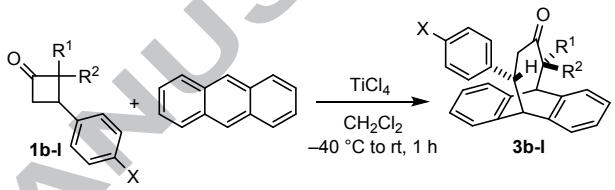


entry	Lewis acid	solvent	yield (%)[b]
1	$TiCl_4$	CH_2Cl_2	69
2	$AlCl_3$	CH_2Cl_2	34
3	$SnCl_4$	CH_2Cl_2	3
4	$SiCl_4$	CH_2Cl_2	NR[c]
5	Me_3SiOTf	CH_2Cl_2	<2
6	TfOH[d]	CH_2Cl_2	36[e]
7	$TiCl_4$	CS_2	22
8	$TiCl_4$	$MeNO_2$	56
9	$TiCl_4$	DCE	21

[a]Cyclobutanone **1a** (1 equiv), anthracene (1 equiv), and Lewis acid (1.1 equiv) were used.
[b]Isolated yield.
[c]No reaction.
[d]Five equivalents of TfOH were used.
[e]Compound **4a** was obtained in 32% yield.

The scope and limitations of the present formal [4+4] cycloaddition were studied by using various 3-arylcyclobutanones **1b-l** (Table 2). Cycloaddition of 2,2-diethyl- and 2,2-dibenzylcyclobutanones **1b**,**c** with anthracene proceeded less efficiently than that with 2,2-dimethylcyclobutanone **1a** probably due to their steric hindrance (entries 1 and 2). Spirocyclobutanones **1d-f** having five-, six-, and seven-membered rings reacted with anthracene to afford the corresponding cycloadducts **3d-f** in good to moderate yields (entries 3-5). The present cycloaddition was greatly influenced by substitution patterns at the 2-position of cyclobutanones: 2-monoalkyl substitution and 2-nonsubstitution resulted in low yields of cycloadducts (entries 6-8). It was noted that *trans*-2-methoxycyclobutanone **1h** gave **3h** in 24% yield as a single diastereomer and the stereochemistry of **3h** was determined by X-ray crystallography (entry 7).[9] Reactions of 3-arycyclobutanones **1j-l** having methyl, methoxy, and bromo groups on the *para*-position of the 3-aryl group proceeded in 30-47% yields (entries 9-11). Apparent differences in reactivities of these three cyclobutanones **1j-l** were not observed.

Table 2 Formal [4+4] cycloaddition of 3-arylcyclobutanones **1b-l** and anthracene.[a]



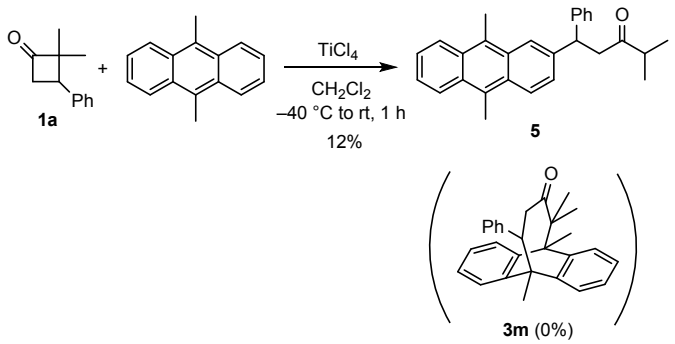
entry	R^1	R^2	X	**3**	yield (%)[b]
1	Et	Et	H	**3b**	42
2	Bn	Bn	H	**3c**	26
3	$-(CH_2)_4-$		H	**3d**	60
4	$-(CH_2)_5-$		H	**3e**	47
5	$-(CH_2)_6-$		H	**3f**	48
6	H	Me	H	**3g**	trace
7	H	OMe	H	**3h**	24[c]
8	H	H	H	**3i**	trace
9	Me	Me	Me	**3j**	30
10	Me	Me	OMe	**3k**	47
11	Me	Me	Br	**3l**	37

[a]Cyclobutanone **1** (1 equiv), anthracene (1 equiv), and $TiCl_4$ (1.1 equiv) were used. [b]Isolated yield.

[c]Compound **3h** was a single diastereomer. Compound **1h** was a single *trans*-isomer.

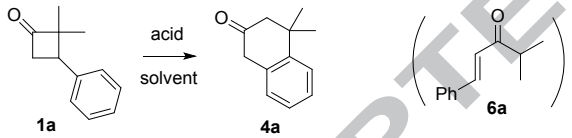
Besides anthracene, we tested a reaction of **1a** with 9,10-dimethylanthracene (Scheme 4). However, the desired [4+4] product **3m** was not formed but a Friedel-Crafts adduct **5** was isolated in 12% yield.[10] Steric hindrance of the methyl group of 9,10-dimethylanthracene caused Friedel-Crafts alkylation with **1a** at sterically less hindered position to give **5**.

Scheme 4. A $TiCl_4$-promoted reaction of **1a** with 9,10-dimethylanthracene.



As described above, activation of **1a** with TfOH in the presence of anthracene gave 2-tetralone derivative[11] **4a** as well as a formal [4+4] adduct **3a** (Table 1, entry 6). Reaction conditions for isomerization of **1a** to **4a** were screened in the absence of anthracene (Table 3). It was found that treatment of **1a** with an equimolar amount of TfOH in refluxing DCE gave a 2-tetralone derivative **4a** in 35% yield (entry 1).[12] A stoichiometric amount of $TiCl_4$, a catalytic amount of $Sc(OTf)_3$, and excess TFA were used instead of TfOH, but these reagents did not effectively promote the conversion of **1a** to **4a** (entries 2-4). Activation of **1a** with a stoichiometric amount of $TiCl_4$ did not give **4a** but afforded enone **6a** in 10% yield (entry 2). The rearrangement of **1a** to **4a** took place at room temperature by using three equivalents of TfOH (entry 5) and the use of five equivalents of TfOH gave **4a** in 75% yield (entry 6). The catalysis of Tf_2NH was less effective compared with TfOH (entry 7).

Table 3. Optimization of reaction conditions for cyclization of **1a** with skeletal rearrangement to **4a**.



entry	acid (equiv)	solvent	conditions	yield (%)[a]
1	TfOH (1.0)	DCE	rt to reflux, 3 h	35
2	$TiCl_4$ (1.0)	DCE	rt to reflux, 3 h	0[b]
3	$Sc(OTf)_3$ (0.2)	DCE	reflux, 4 h	trace
4	TFA (50)	none	reflux, 4 h	7
5	TfOH (3.0)	DCM	rt, 75 min	31
6	TfOH (5.0)	DCM	rt, 75 min	75
7	Tf_2NH (5.0)	DCM	rt, 75 min	40[c]

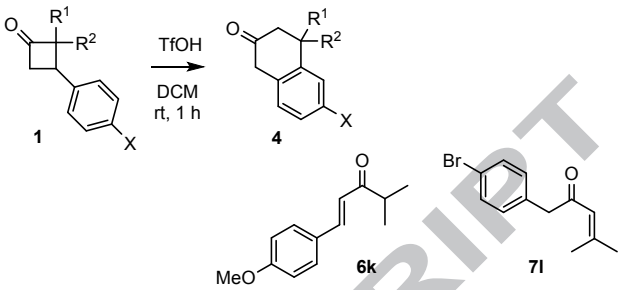
[a]Isolated yield.

[b]Compound **6a** was obtained in 10% yield.

[c]Determined by ^1H NMR analysis by using an internal standard.

The generality of the present TfOH-promoted cycloisomerization was studied by using various 3-arylcyclobutanones **1** (Table 4). 2,2-Diethylcyclobutanone **1b** and spirocyclobutanones **1d**,**e** were isomerized smoothly to the corresponding 2-tetralone derivatives **4b**,**d**,**e** (entries 1-3). Treatment of 2-monomethylcyclobutanone **1g** with TfOH gave a complex mixture of products, though the disappearance of **1g** was checked by TLC analysis (entry 4). *p*-Methoxy substitution on the 3-aryl group resulted in the formation of undesired enone **6k** in 79% yield (entry 6). A cyclobutanone **1l** bearing a *p*-bromophenyl group gave the desired product **4l** in 51% yield along with enone **7l** that was formed by skeletal rearrangement in less than 25% yield (entry 7).

Table 4. TfOH-promoted cycloisomerization of 3-arylcyclobutanones **1** to **4**.[a]



entry	R^1	R^2	X	**4**	yield (%)[b]
1	Et	Et	H	**4b**	72
2	-$(CH_2)_4$-		H	**4d**	45
3	-$(CH_2)_5$-		H	**4e**	57
4	Me	H	H	**4g**	mixture
5	Me	Me	Me	**4j**	66
6	Me	Me	OMe	**4k**	0[c]
7	Me	Me	Br	**4l**	51[d]

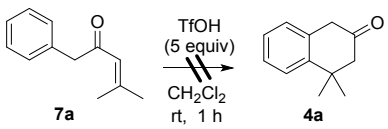
[a]TfOH (5 equiv) was used.

[b]Isolated yield.

[c]Compound **6k** was obtained in 79% yield.

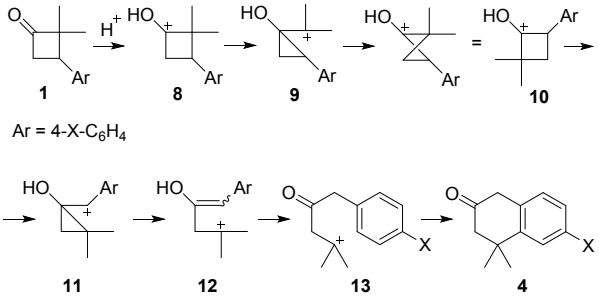
[d]Compound **7l** was obtained in less than 25% yield.

To obtain mechanistic information on the present cycloisomerization, enone **7a**, a simplified structure of **7l** that was obtained as a byproduct (Table 4, entry 7), was treated with five equivalents of TfOH at room temperature (Scheme 5). However, it was found that cyclization of **7a** to **4a** did not proceed.[13] This result suggested that the present cycloisomerization of **1a** to **4a** with TfOH did not procced via enone **7a**.[14]



Scheme 5. Attempted cyclization of **7a** to **4a** with TfOH

A proposed mechanism for the TfOH-promoted cycloisomerization of cyclobutanones **1** to 2-tetralone **4** is shown in Scheme 6. Cyclobutyl cation **8,** which is formed by protonation of **1,** is rearranged to **10**. Carbon-carbon bond cleavage of **10** proceeds to give cyclopropylcarbinyl cation **11**, and isomerization occurs to form homoallyl cation **12**.[15] Cyclization of the aryl group of **12** or **13** proceeds to give **4a**.[16]



Scheme 6. Proposed reaction mechanism from **1** to **4**

In conclusion, we have developed two reactions of 3-arylcyclobutanones: (1) $TiCl_4$-catalyzed formal [4+4] cycloaddition with anthracene and (2) TfOH-promoted cycloisomerization to 2-tetralones with skeletal rearrangement. These two reactions will broaden the synthetic utility of 3-arylcyclobutanones.

Acknowledgments

This work was supported by Kanazawa University SAKIGAKE project.

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9. CCDC1900307 (compound **3a**) and CCDC 1936724 (compound **3h**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.uk/getstructures.
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13. It has been reported that cyclization of **7a** with $AlCl_3$ gave **4a** in 78% yield: Colonge, J.; Chambion, J. *Bull. Soc. Chim. Fr.* **1947**, 1002.
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16. It was thought that compound **6k** was formed via an intermediate **9** and compound **7l** was formed via **12** or **13**.

Supplementary Material

Supplementary data associated this article can be found in the online version at_.