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Ring-opening cyclization of spirocyclopropanes with stabilized sulfonium ylides for the construction of a chromane skeleton

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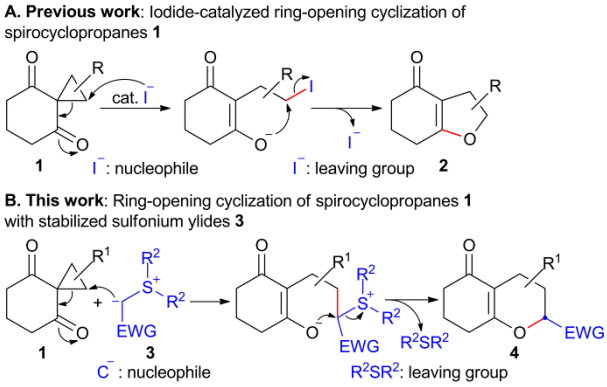
Hisanori Nambu,*[a] Yuta Onuki,[a] Naoki Ono,[a] Kiyoshi Tsuge[b] and Takayuki Yakura*[a]

Regioselective ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes with stabilized sulfonium ylides provided 2,3-*trans*-disubstituted 2,3,4,6,7,8-hexahydro-5*H*-1-benzopyran-5-ones in high yields without the formation of any isomers. The obtained product was readily converted into highly substituted chromane.

Doubly activated cyclopropanes have been shown to be useful synthetic precursors that can be widely applied in the synthesis of a variety of carbo- and heterocyclic compounds.[1] Consequently, the development of ring-forming reactions employing these cyclopropanes continues to attract considerable attention.[2] In this context, we recently reported that the acid-[3] and iodide-catalyzed[4] ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes **1** proceeded in a regioselective manner to afford 3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-ones **2** with excellent yields (Scheme 1, A).[5] It is noteworthy that the iodide-catalyzed reaction could be applied to a variety of nonsubstituted and electron-withdrawing group (EWG)-substituted spirocyclopropanes **1**. In this catalytic system, an iodide ion acts as a nucleophile for the ring opening of cyclopropane and subsequently as a leaving group for the cyclization to provide dihydrofuran.

Meanwhile, sulfonium ylide containing a nucleophilic carbanion and an adjacent electrophilic sulfonium cation is often used as a versatile methylene synthon in the synthesis of diverse carbo- and heterocyclic compounds.[6] Since this type of sulfonium ylide has both a nucleophilic part and a leaving group, we envisioned that it could behave in a similar manner as the iodide ion, that is, the ring-opening cyclization of spirocyclopropanes **1** with sulfonium ylide **3** could provide 2,3,4,6,7,8-hexahydro-5*H*-1-benzopyran-5-ones **4** with the concomitant release of the corresponding sulfide (R^2SR^2, Scheme 1, B). Herein, we describe the ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes **1** using EWG-stabilized sulfonium ylides **3** as nucleophiles for the construction of a chromane skeleton. To the best of our knowledge, no examples of the ring opening of cyclopropanes using a sulfonium ylide as a carbon nucleophile have been reported to date.[7]



Scheme 1 Ring-opening cyclization of spirocyclopropanes **1** with iodide catalyst and sulfonium ylides **3** as nucleophiles.

Initially, we examined the reaction of 2'-phenylcyclohexane-1,3-dione-2-spirocyclopropane (**1a**)[8] with dimethylsulfonium benzoylmethylide (**3a**)[9] as a stabilized sulfonium ylide (Table 1). The ring-opening cyclization of **1a** proceeded using 2.0 equiv of **3a** in CH_2Cl_2 at room temperature to afford 2-benzoyl-3-phenyl-2,3,4,6,7,8-hexahydro-5*H*-1-benzopyran-5-one (**4a**) after 15 h in 95% yield with no evidence of the formation of any diastereoisomer or regioisomer such as the 4-phenyl-substituted product (entry 1). The stereochemistry of **4a** was determined by ^{1}H NOE experiments to be 2,3-*trans* (see ESI† for details). Increasing the reaction temperature to reflux resulted in complete conversion within 3 h and afforded **4a** in 94% yield (entry 2). We next investigated the optimal amount of **3a** in CH_2Cl_2 under reflux. The reaction with 1.5 equiv of **3a** gave **4a** in 95% yield, albeit with a prolonged reaction time (7 h, entry 3). Unfortunately, the use of 1.2 equiv of **3a** diminished the product yield, and a

[a] *Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan.*
[b] *Graduate School of Science and Engineering, University of Toyama, Gofuku, Toyama 930-8555, Japan.*
E-mail: nambu@pha.u-toyama.ac.jp, yakura@pha.u-toyama.ac.jp

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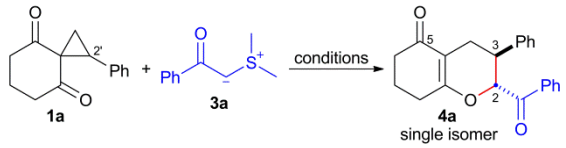
significantly longer reaction time was required to achieve full conversion (90% yield, 18 h, entry 4). Then, a screening of solvents at 50 °C revealed that CH_2Cl_2 was the most effective solvent for this reaction (entry 3 vs entries 5–8) and that CH_3CN could be used as an alternative solvent (entry 8).

Table 1 Ring-opening cyclization of spirocyclopropane **1a** with sulfonium ylide **3a**

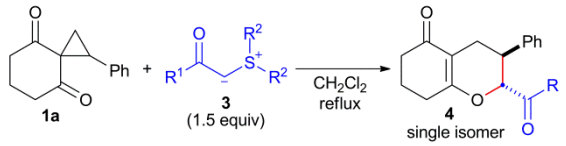


Entry	Equiv of **3a**	Solvent	Temp.	Time (h)	Yield[a] (%)
1	2.0	CH_2Cl_2	rt	15	95
2	2.0	CH_2Cl_2	reflux	3	94
3	1.5	CH_2Cl_2	reflux	7	95
4	1.2	CH_2Cl_2	reflux	18	90
5	1.5	EtOAc	50 °C	8	88
6	1.5	THF	50 °C	11	78
7	1.5	toluene	50 °C	12	84
8	1.5	CH_3CN	50 °C	8	91

[a] Isolated yield.

With the optimized conditions in hand, we investigated the reaction of spirocyclopropane **1a** using a range of sulfonium ylides **3** stabilized by acyl groups (Table 2). The use of 1.5 equiv of *p*-methoxy- and *p*-chlorobenzoyl sulfonium ylides **3b** and **3c** in refluxing CH_2Cl_2 provided the corresponding hexahydrobenzopyran-5-ones **4b** and **4c** as the sole products in 94% and 93% yields, respectively (entries 1 and 2). In contrast, the reaction using **3d** bearing a *p*-nitro group as a strong EWG did not reach completion even after 24 h, affording **4d** in 63% yield along with 30% of recovered starting material **1a** (entry 3). Nevertheless, we were pleased to find that the use of 3 equiv of **3d** improved the product yield, providing **4d** in 82% yield after 48 h (entry 4). We also examined the suitability of an acetyl sulfonium ylide for this reaction. To this aim, we used tetrahydrothiophenium acetylmethylide (**3e**) due to the difficult preparation of dimethylsulfonium acetylmethylide. The reaction of **1a** with **3e** furnished the corresponding product **4e** as a single isomer in 89% yield after 24 h (entry 5). Treatment of pivaloyl sulfonium ylide **3f**[10] for 2 h under the same conditions gave the corresponding product **4f** in 84% yield (entry 6).

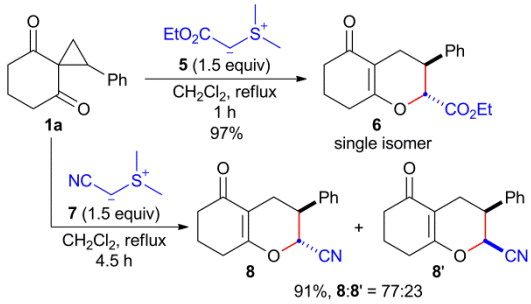
Table 2 Ring-opening cyclization of spirocyclopropane **1a** with sulfonium ylides **3b–f**



	Sulfonium ylide				Product	
Entry		R^1	R^2	Time (h)		Yield[a] (%)
1	**3b**	*p*-$MeOC_6H_4$	Me	4.5	**4b**	94
2	**3c**	*p*-ClC_6H_4	Me	9.5	**4c**	93
3	**3d**	*p*-$NO_2C_6H_4$	Me	24	**4d**	63 (30)[b]
4[c]	**3d**	*p*-$NO_2C_6H_4$	Me	48	**4d**	82
5	**3e**	Me	-$(CH_2)_4$-	24	**4e**	89
6	**3f**	^{t}Bu	Me	2	**4f**	84

[a] Isolated yield. [b] Yield of recovered starting material (**1a**). [c] 3 equiv of sulfonium ylide **3d** was used.

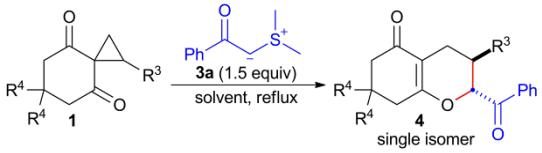
Next, we turned our attention to sulfonium ylides stabilized by other EWG groups (Scheme 2). The reaction of **1a** with dimethylsulfonium ethoxycarbonylmethylide (**5**)[11] under the optimized conditions proceeded smoothly to completion within 1 h, affording the corresponding product **6** as a sole product in 97% yield. The structure of **6** was confirmed by a single-crystal X-ray diffraction analysis (see ESI†). Moreover, cyano sulfonium ylide **7**[12] could be applied to the present protocol, and a 77:23 mixture of diastereomers **8** and **8'** was obtained in 91% combined yield after 4.5 h.



Scheme 2 Ring-opening cyclization of spirocyclopropane **1a** with sulfonium ylides **5** and **7**.

We then investigated the scope of the reaction with respect to the spirocyclopropane substrates **1** using benzoyl-substituted sulfonium ylide **3a** as the nucleophile (Table 3). Treatment of spirocyclopropanes **1b** and **1c**, which possess a *p*-methyl and *p*-bromophenyl group on the cyclopropane, respectively, with **3a** under the optimized conditions provided the corresponding products **4g** and **4h** in 89% and 93% yields with perfect diastereoselectivities, respectively (entries 1 and 2). Meanwhile, the reaction of 2',3'-nonsubstituted cyclohexane-1,3-dione-2-spirocyclopropane **1d** (R^3 = H)[13] under the same conditions was not complete even after 24 h and gave **4i** in 74% yield along with recovered starting material **1d** in 24% yield (entry 3). To our delight, when the reaction was conducted in CH_3CN at reflux, product **4i** was obtained in 91% yield after 8 h (entry 4). The reaction of *n*-butyl-substituted spirocyclopropane **1e** in refluxing CH_2Cl_2 also proceeded slowly, giving the product **4j** in only 22% yield, and the starting material **1e** was recovered in

Table 3 Ring-opening cyclization of spirocyclopropanes **1b–f** with sulfonium ylide **3a**

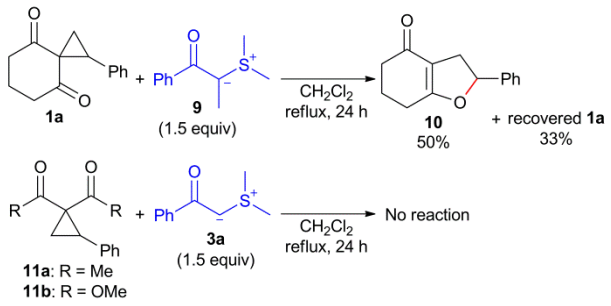


	Spirocyclopropane					Product	
Entry		R^3	R^4	Solvent	Time (h)		Yield[a] (%)
1	**1b**	*p*-MeC_6H_4	H	CH_2Cl_2	6	**4g**	89
2	**1c**	*p*-BrC_6H_4	H	CH_2Cl_2	13	**4h**	93
3	**1d**	H	H	CH_2Cl_2	24	**4i**	74 (24)[b]
4	**1d**	H	H	CH_3CN	8	**4i**	91
5	**1e**	^{n}Bu	H	CH_2Cl_2	24	**4j**	22 (64)[b]
6	**1e**	^{n}Bu	H	CH_3CN	24	**4j**	4
7	**1f**	Ph	Me	CH_2Cl_2	9.5	**4k**	91

[a] Isolated yield. [b] Yields of recovered starting materials **1d** and **1e**.

64% yield (entry 5). However, in this case, switching the solvent from CH_2Cl_2 to CH_3CN did not improve the product yield (4%), and the starting material **1e** decomposed under the reaction conditions (entry 6). The use of dimedone-derived spirocyclopropane **1f** (R^4 = Me) in refluxing CH_2Cl_2 proceeded uneventfully and afforded the desired product **4k** in 91% yield (entry 7).

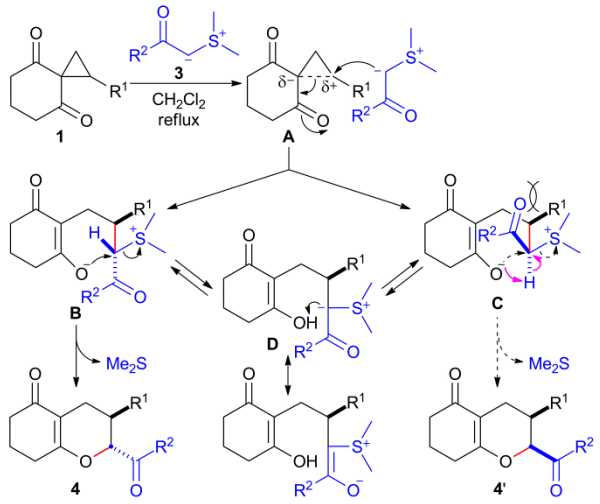
Furthermore, we examined the reaction of spirocyclopropane **1a** with dimethylsulfonium 1-benzoylethylide (**9**)[14] under the optimized conditions (Scheme 3). Unfortunately, the expected product was not obtained. Instead, tetrahydrobenzofuran-4-one **10**[3] was produced in 50% yield, together with 33% unreacted **1a**, which indicates that the nucleophilic attack of the tertiary carbanion **9** to the cyclopropane carbon hardly occurs.[15] On the other hand, the reaction of 1,1-diacetyl-2-phenylcyclopropane (**11a**) and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**11b**) with **3a** did not proceed at all. These results suggest that the spiro structure is crucial for the success of this ring-opening cyclization reaction. Although the reason for the higher reactivity of spirocyclopropane is unclear at present, it is speculated that it has a higher ring strain energy than non-spiro ones.



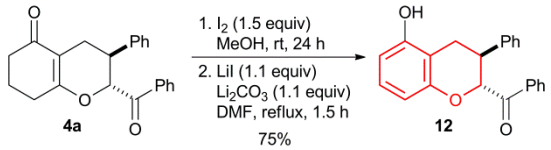
Scheme 3 Unsuccessful reactions of cyclopropanes **1a**, **11a** and **11b** with sulfonium ylides **9** and **3a**.

A plausible mechanism for the ring-opening cyclization of spirocyclopropane **1** with EWG-stabilized sulfonium ylide **3** is shown in Scheme 4. The ring opening of spirocyclopropane **1** would proceed through a nucleophilic attack of the carbanion in **3** to the electrophilic cyclopropane carbon possessing an R^1 substituent in **A**, leading to betaine intermediates **B** and **C**. The S_N2-type cyclization of **B** would occur smoothly to afford the *trans*-product **4** with the concomitant release of the dimethyl sulfide. In contrast, the cyclization of **C** would hardly proceed owing to the severe steric repulsion between the acyl group (R^2CO) and the substituent R^1 in **C**. Consequently, intermediate **C** could be converted into cyclization precursor **B** through reversible intramolecular proton transfer via the sulfonium ylide **D**,[16,17] finally providing the *trans*-isomer **4**.[18]

To demonstrate the utility of the present protocol, we examined the conversion of hexahydrobenzopyran-5-one **4a** into highly substituted chromane **12** (Scheme 5), since chromane is a prevalent structural motif in a range of biologically active natural products and pharmaceuticals.[19–21] On the basis of a reported procedure,[22] reaction of **4a** with iodine in methanol followed by aromatization using a



Scheme 4 Plausible reaction mechanism.



Scheme 5 Conversion of hexahydrobenzopyran-5-one **4a** into chromane **12**.

combination of LiI and Li_2CO_3 afforded 5-hydroxychromane **12** in 75% yield.

In conclusion, we have developed a regioselective ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes using stabilized sulfonium ylides as nucleophiles, which affords the corresponding hexahydrobenzopyran-5-ones in up to 97% yields. The present reaction provides an efficient route to highly substituted chromanes. To the best of our knowledge, this is the first example of a ring-opening cyclization of cyclopropanes with sulfonium ylides, which can be envisaged as a formal [5+1] cycloaddition to construct the six-membered ring system. We believe that this protocol could be extended to a [5+n]-type reaction using other reagents having both nucleophile and leaving group moieties. Further application of the present method to the synthesis of a variety of chromane natural products is currently in progress.

This research was supported, in part, by a Research Funding from the First Bank of Toyama.

Conflicts of interest

There are no conflicts to declare.

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