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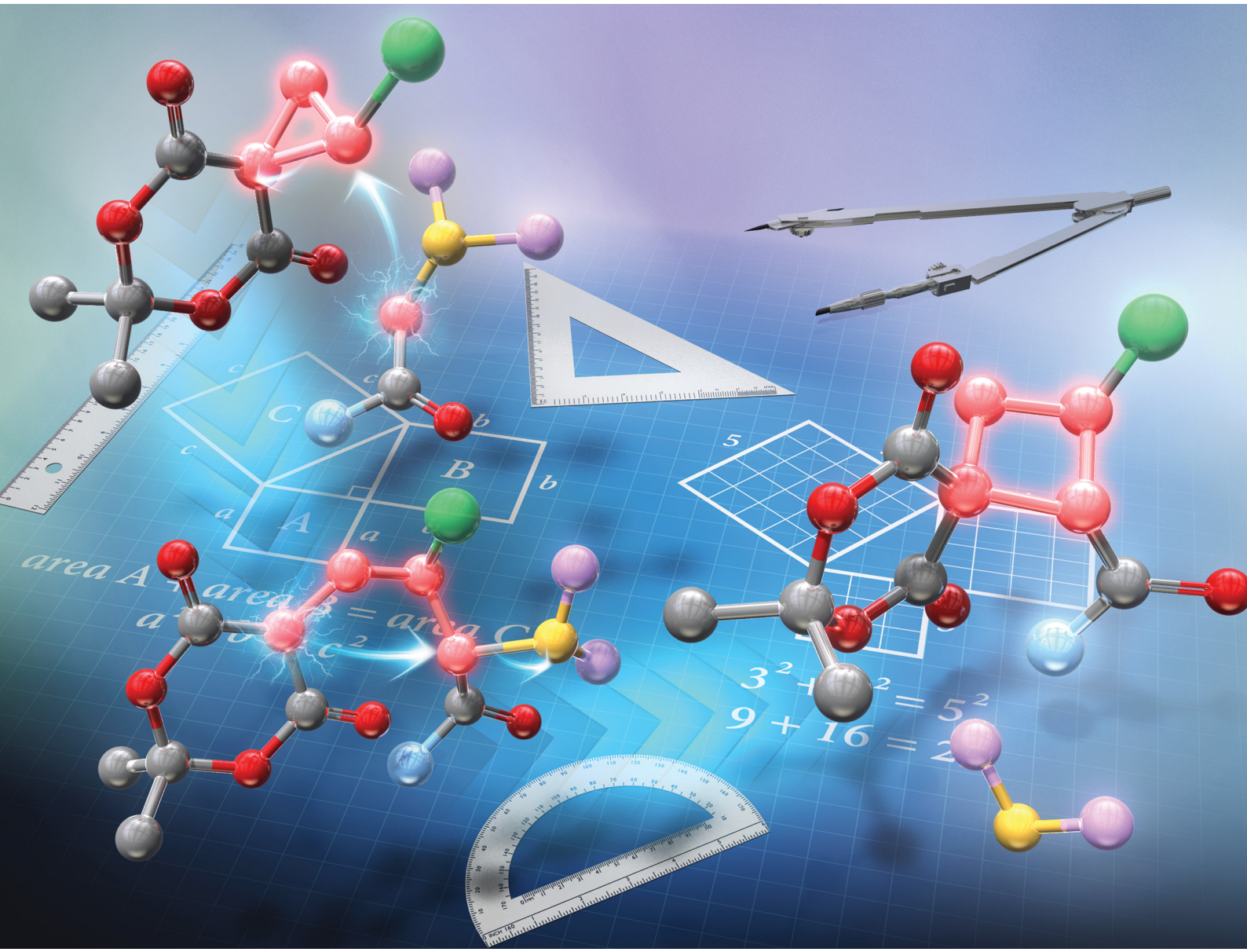

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Ring expansion of spirocyclopropanes with stabilized sulfonium ylides: highly diastereoselective synthesis of cyclobutanes†

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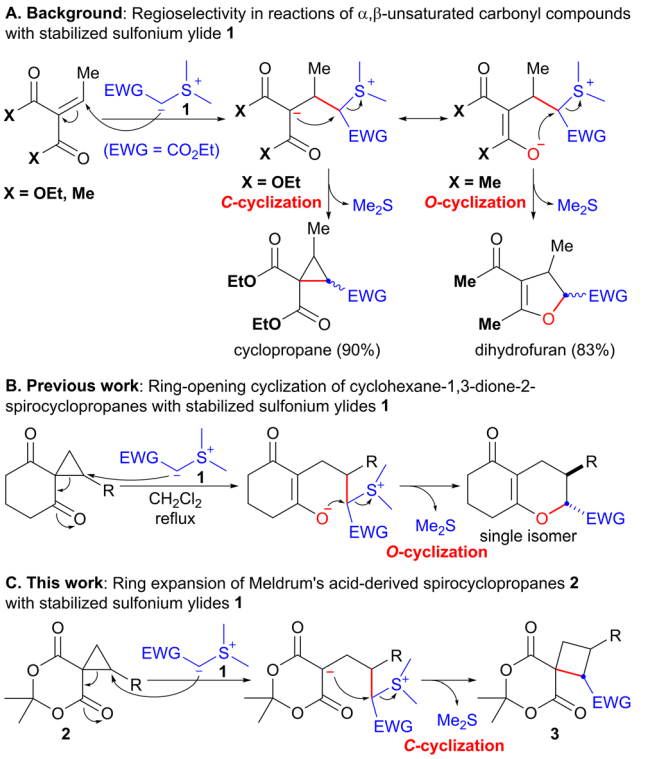
A novel method was devised for regioselective ring expansion of Meldrum's acid-derived spirocyclopropanes to spirocyclobutanes with stabilized sulfonium ylides, affording 1,2-*trans*-disubstituted 6,8-dioxaspiro[3.5]nonane-5,9-diones in up to 87% yields without the formation of any isomers. The aforementioned reaction was also applied to the barbituric acid-derived spirocyclopropane, resulting in the formation of the corresponding cyclobutanes.

Sulfonium ylides stabilized by electron-withdrawing groups (EWG) have been used as a versatile methylene synthon in the synthesis of a variety of carbo- and heterocyclic compounds.[1,2] As a pioneering work, Payne reported that the reaction of α,β-unsaturated diethylmalonate with EWG-stabilized sulfonium ylide **1** (EWG = CO_2Et) afforded cyclopropane in 90% yield (Scheme 1A).[3] In this reaction, the Michael addition of **1** followed by S_N2-type cyclization of the carbanion (*C*-cyclization) proceeded with the concomitant release of the sulfide. In contrast, the reaction of the corresponding 1,3-diketone with stabilized sulfonium ylide **1** unexpectedly produced dihydrofuran in 83% yield through enolate cyclization (*O*-cyclization, Scheme 1A).[3] The regioselectivity of these reactions may be attributed to the inherent difference between esters and ketones. Recently, we reported the ring-opening cyclization of spirocyclopropanes[4] with EWG-stabilized sulfonium ylides **1** to afford hexahydrobenzopyranone as a single isomer *via* the regioselective ring-opening of cyclopropane with sulfonium ylide **1** and subsequent S_N2-type *O*-cyclization (Scheme 1B, eqn (1)).[4f] Considering the similar reactivity of cyclopropane and carbon–carbon double bonds, we expected that the reaction of ester-derived spirocyclopropane **2** with stabilized sulfonium ylide **1** would provide spirocyclobutane **3** through *C*-cyclization (Scheme 1C). Because cyclobutane is a useful scaffold found in several biologically active natural products and pharmaceutically active compounds,[5] the development of a synthetic method for cyclobutane is currently the subject of intense research.[6] Although several instances of



Scheme 1 Reactions of various carbonyl compounds with stabilized sulfonium ylides **1** as nucleophiles.

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† Electronic supplementary information (ESI) available: General procedures, analytical data, and NMR spectra (PDF). CCDC 2312076 (**3a**). For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3cc06033k

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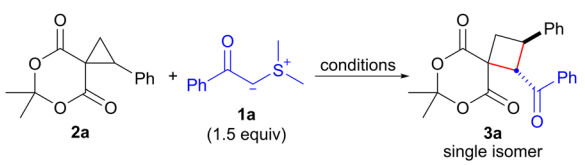
cyclopropane to cyclobutane ring expansion have been documented thus far,[7,8] to the best of our knowledge, there have been no examples of sulfonium ylide-mediated ring expansion (*C*-cyclization).[9] Herein, we describe the ring expansion of Meldrum's acid-derived spirocyclopropanes **2** to spirocyclobutanes **3** using EWG-stabilized sulfonium ylides **1** (Scheme 1C).

Initially, we examined the reaction of 6,6-dimethyl-1-phenyl-5,7-dioxaspiro[2.5]octane-4,8-dione (**2a**)[10] with dimethylsulfonium benzoylmethylide (**1a**) as an EWG-stabilized sulfonium ylide (Table 1). The ring expansion of **1a** proceeded under the reaction conditions previously reported by our group (1.5 equiv. of **1a** in refluxing CH_2Cl_2),[4f] affording 1-benzoyl-7,7-dimethyl-2-phenyl-6,8-dioxaspiro[3.5]nonane-5,9-dione (**3a**) after 24 h in 75% yield (entry 1). Notably, no isomer formation was observed during this process. The structure of **3a** including its stereochemistry was confirmed by a single-crystal X-ray diffraction analysis. This analysis revealed that the structure corresponds to that of cyclobutane with a 1,2-*trans* configuration (see ESI† for details). Screening of the solvents at reflux revealed that benzene and halogenated solvents, such as dichloromethane and 1,2-dichloroethane, were suitable for this reaction (entry 1 *vs.* entries 2–5). Finally, we found that chlorobenzene at 80 °C was the most effective and afforded **3a** in 86% yield after 6 h (entry 6).

After determining the optimal conditions, we investigated the reaction of spirocyclopropane **2a** using a range of sulfonium ylides **1** that are stabilized by carbonyl functional groups (Table 2). The reaction with 1.5 equiv. of *p*-methoxybenzoyl sulfonium ylide **1b** in chlorobenzene at 80 °C afforded the corresponding spirocyclobutane **3b** as the sole product after 6 h in 74% yield (entry 2). The use of *m*- and *o*-methoxybenzoyl sulfonium ylides **1c**[11] and **1d**[12] provided the corresponding products **3c** and **3d** in 86% and 87% yields, respectively (entries 3 and 4). The reaction with sulfonium ylide **1e** bearing a *p*-nitro group as a strong EWG decreased the product yield, and a significantly longer reaction time was required to achieve full conversion (61% yield, 24 h, entry 5 *vs.* entry 1). In contrast, the reaction with *p*-chlorobenzoyl sulfonium ylide **1f** under the optimized conditions proceeded smoothly to completion within 5 h, furnishing **3f** in 83% yield (entry 6). We also investigated the suitability of an acetyl sulfonium ylide for this reaction. To this end, we used tetrahydrothiophenium acetylmethylide (**1g**) because of the difficulty in preparing dimethylsulfonium acetylmethylide. The reaction of **2a** with **1g** afforded the desired product **3g** as a single isomer, albeit with a prolonged reaction time and lower yield (24 h, 36% yield, entry 7 *vs.* entry 1). Moreover, ethoxycarbonyl group-substituted sulfonium ylide **1h** was used in the present protocol, and the corresponding cyclobutane **3h** was obtained in 53% yield after 23 h (entry 8).

Next, we examined the scope of the reaction with the spirocyclopropane substrates **2** using benzoyl-substituted sulfonium ylide **1a** (Table 3). Treatment of spirocyclopropanes **2b**, **2c** and **2d**, which possess *p*-acetoxy-, *p*-methyl-, and *p*-bromophenyl groups on the cyclopropane, respectively, with **1a** under the optimized conditions (chlorobenzene at 80 °C), afforded the corresponding products **3i**, **3j**, and **3k** in 64%–80% yields with perfect diastereoselectivities (entries 1–3). The

Table 1 Ring expansion of spirocyclopropane **2a** with sulfonium ylide **1a**

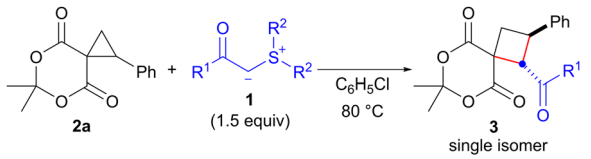


2a **1a** (1.5 equiv) **3a** single isomer

Entry	Solvent	Temp.	Time (h)	Yield[a] (%)
1	CH_2Cl_2	Reflux	24	75
2	EtOAc	Reflux	4.5	60
3	Benzene	Reflux	5	74
4	CH_3CN	Reflux	24	59
5	$ClCH_2CH_2Cl$	Reflux	7	75
6	C_6H_5Cl	80 °C	6	86

[a] Isolated yield.

Table 2 Ring expansion of spirocyclopropane **2a** with sulfonium ylides **1a–h**

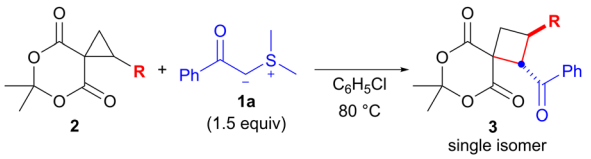


2a **1** (1.5 equiv) **3** single isomer

	Sulfonium ylide			Product	
Entry		R^1	R^2	Time (h)	Yield[a] (%)
1	**1a**	C_6H_5	Me	6	**3a** 86
2	**1b**	*p*-$MeOC_6H_4$	Me	6	**3b** 74
3	**1c**	*m*-$MeOC_6H_4$	Me	6	**3c** 86
4	**1d**	*o*-$MeOC_6H_4$	Me	6	**3d** 87
5	**1e**	*p*-$NO_2C_6H_4$	Me	24	**3e** 61
6	**1f**	*p*-ClC_6H_4	Me	5	**3f** 83
7	**1g**	Me	$-(CH_2)_4-$	24	**3g** 36
8	**1h**	EtO	Me	23	**3h** 53

[a] Isolated yield.

Table 3 Ring expansion of spirocyclopropanes **2b–h** with sulfonium ylides **1a**



2 **1a** (1.5 equiv) **3** single isomer

	Spirocyclopropane			Product	
Entry		R	Time (h)		Yield[a] (%)
1	**2b**	*p*-$AcOC_6H_4$	3	**3i**	64
2	**2c**	*p*-MeC_6H_4	6	**3j**	74
3	**2d**	*p*-BrC_6H_4	6	**3k**	80
4	**2e**	*m*-$MeOC_6H_4$	12	**3l**	69
5	**2f**	2-naphthyl	48	**3m**	80
6	**2g**	Vinyl	24	**3n**	68
7	**2h**	H	24	**3o**	26

[a] Isolated yield.

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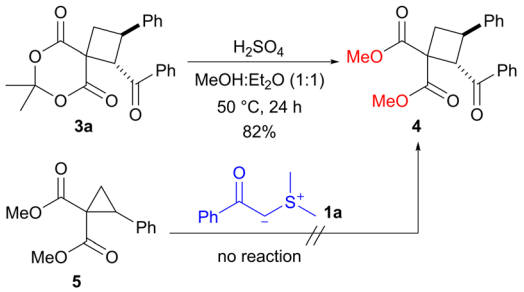
reaction of *m*-methoxyphenyl-substituted spirocyclopropane **2e** for 12 h provided cyclobutane **3l** in 69% yield (entry 4). Although spirocyclopropane **2f**, which possesses a 2-naphthyl group, required a relatively long reaction time (48 h), **3m** was obtained in a good yield (80%, entry 5). There was a concern that the use of vinyl-substituted spirocyclopropane **2g** would compete with the conjugate addition, but the reaction of **2g** proceeded uneventfully and afforded the desired product **3n** in 68% yield (entry 6). Finally, the reaction of the simple spirocyclopropane **2h** (R = H)[13] was investigated (entry 7). A 2′,3′-nonsubstituted spirocyclopropane was found to be less reactive than an aryl-substituted one,[4e] which resulted in a lower yield of product **3o** (26% yield).

A plausible mechanism for the ring expansion of spirocyclopropane **2** with sulfonium ylide **1**, stabilized by an acyl group, is shown in Scheme 2. The ring opening of spirocyclopropane **2** would proceed through the nucleophilic attack of the carbanion in **1** on the electrophilic cyclopropane carbon possessing an R^1 substituent in **A**. This reaction would lead to the formation of betaine intermediates **B** and **C**. S_N2-type *C*-cyclization of the carbanion in **B** would occur smoothly to afford *trans*-product **3** with the concomitant release of dimethyl sulfide. In contrast, the *C*-cyclization of **C** would hardly proceed owing to the severe steric repulsion between the acyl group (R^2CO) and substituent R^1 in **C**. Consequently, intermediate **C** could be converted into cyclization precursor **B** through reversible intramolecular proton transfer *via* the stabilized sulfonium ylide **D**,[14,15] finally providing *trans*-isomer **3**.

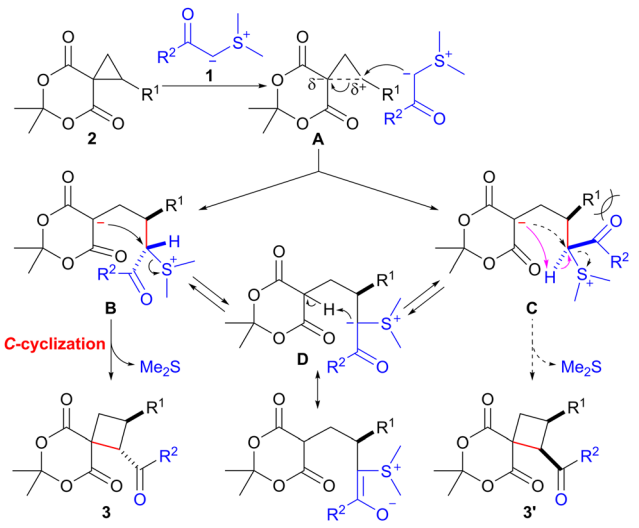
To demonstrate the utility of the present protocol, we examined the conversion of spirocyclobutane **3a** into highly substituted non-spiro cyclobutane **4** (Scheme 3). The treatment of **3a** with sulfuric acid in methanol/diethyl ether (1 : 1) at 50 °C led to a transesterification process, resulting in the formation of dimethyl ester. The reaction yielded the corresponding cyclobutane **4** in 82% yield. Since the reaction of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**5**) with sulfonium ylide **1a** did not proceed,[4f,16] spiro form **3a** was required for the synthesis of diester **4**. This ring-expansion reaction of spirocyclopropanes could be a useful method for the preparation of substituted cyclobutanes.



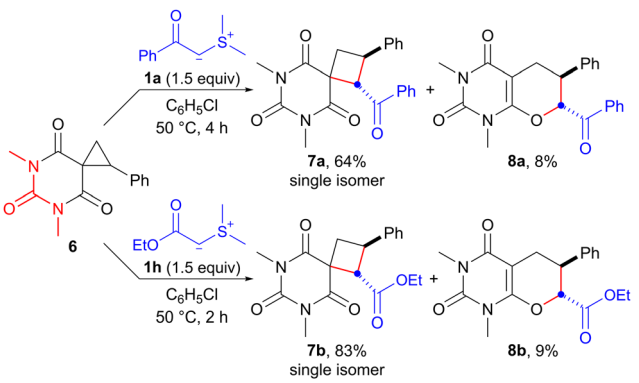
Scheme 3 Conversion of spirocyclobutane **3a** into cyclobutane **4**.

Having achieved ring expansion of ester-derived spirocyclopropanes, we further investigated the reaction of an amide-derived spirocyclopropane with an EWG-stabilized sulfonium ylide. The reaction of spirocyclopropane **6**,[17] derived from barbituric acid, with sulfonium ylides **1a** and **1h** in chlorobenzene proceeded smoothly at 50 °C to provide the corresponding spirocyclobutanes **7a** and **7b** in 64% and 83% yields, respectively (Scheme 4). Interestingly, unexpected products **8a** and **8b**, which indicated that S_N2-type *O*-cyclization of the enolate ion instead of the carbanion would occur, were also obtained in 8% and 9% yields, respectively. Although the results are still preliminary, the reaction of barbituric acid-derived spirocyclopropane with sulfonium ylide exhibits promise as a synthetic method of spirobarbiturate cyclobutane analogs. These compounds have potential as pharmaceutical agents.[18]

In conclusion, we devised a novel method for regioselective ring expansion of cyclopropanes to cyclobutanes using stabilized sulfonium ylides. Meldrum's acid-derived spirocyclobutanes with EWG-stabilized sulfonium ylides afforded the corresponding spirocyclobutanes as single diastereomers in yields of up to 87%. The present reaction provides an efficient route to highly substituted cyclobutanes. To the best of our knowledge, this is the first example of a ring expansion of cyclopropanes with sulfonium ylides. This reaction may be envisaged as a



Scheme 2 Plausible reaction mechanism.



Scheme 4 Ring expansion of barbituric acid-derived spirocyclopropane **6** with sulfonium ylides **1a** and **1h**.

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formal [3+1] cycloaddition, facilitating the construction of the four-membered ring system.[19] The expansion reaction could be applied to the transformation of barbituric acid-derived spirocyclopropane into the corresponding spirocyclobutane. Ongoing efforts are being made to apply the present method to the synthesis of a variety of cyclobutane derivatives.

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Conflicts of interest

There are no conflicts to declare.

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