

Thermally Induced [2+2] Cycloadditions of (Benzyloxymethylene)cyclopropane with Alkylidenemalononitriles^[‡]

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Keywords: Cycloaddition / Cyclobutanes / Enols / Cyclopropanes

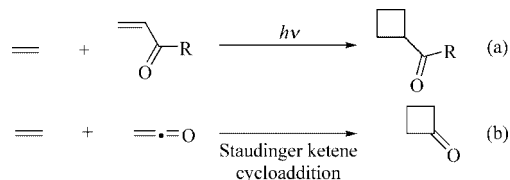
The reaction of (benzyloxymethylene)cyclopropane (**1a**) with alkylidenemalononitriles **2** at ambient pressure afforded the corresponding cyclobutane derivatives **3** in good-to-high yields. For example, the reaction of **1a** with benzylidenemalononitrile (**2a**), (2-naphthylmethylene)malononitrile (**2e**), and *tert*-butylmethylenemalononitrile (**2f**) in acetonitrile at

80 °C gave the corresponding cyclobutanes **3a**, **3e**, and **3f** in 96, 96, and 91 % yield, respectively. Control experiments proved that the reaction proceeds via well-stabilized zwitterionic intermediate **6**.

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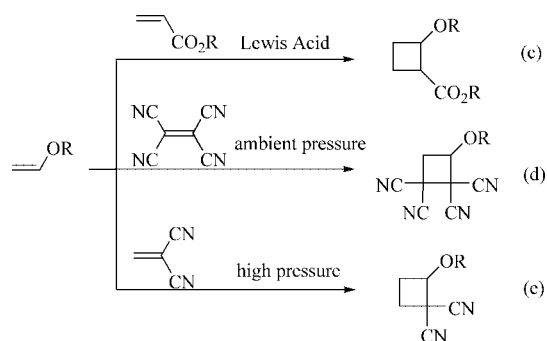
Introduction

Cyclobutane moieties are present in a variety of biologically active compounds,^[1] and cyclobutane derivatives are widely utilized as starting materials in organic synthesis.^[2] These molecules have been primarily synthesized by photochemical [2+2] cycloadditions of alkenes and enones [Scheme 1, type (a)]^[3] as well as thermal [2+2] cycloadditions of ketenes and alkenes [Staudinger ketene cycloadditions, Scheme 1, type (b)].^[4] However, [2+2] cycloadditions of enol ethers have rarely been utilized owing to the insufficient nucleophilicity of the enol ethers. Recently, the group of Takasu and Ihara reported [2+2] cycloadditions



Scheme 1. Various known [2+2] cycloadditions: (a) photochemical reactions of alkenes with enones; (b) Staudinger ketene cycloadditions.

of enol ethers with α,β -unsaturated esters that were enabled by acid catalysts [Scheme 2, type (c)].^[5] Some time ago, Scheeren's group reported that the cycloaddition of 1,1-dicyanoalkenes to enol ethers required high pressure [12 kbar, Scheme 2, type (e)],^[6] whereas that of tetracyanoethylene proceeded at ambient pressure [Scheme 2, type (d)].^[7]



Scheme 2. [2+2] Cycloadditions of enol ethers: (c) with α,β -unsaturated esters in the presence of Lewis acid catalysts; (d) with tetracyanoethylene at ambient pressure; and (e) with methylenemalononitrile under high pressure.

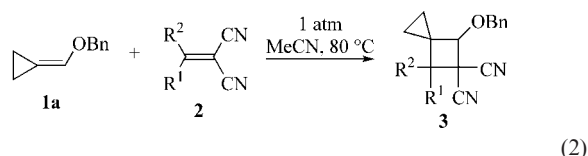
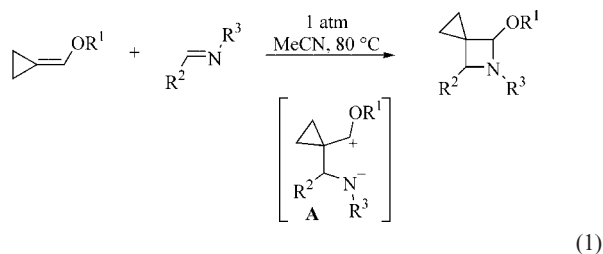
Recently, we found that [2+2] cycloadditions of (alkoxy)methylene)cyclopropanes **1**, which are easily accessible and storable at room temperature,^[8] with imines proceeded at ambient pressure [Equation (1)].^[9] We envisioned that the formation of the zwitterionic intermediate **A**, in which the cation center is doubly stabilized by the cyclopropyl and the alkoxy groups, facilitated the cycloaddition. Herein, we report that the [2+2] cycloaddition of (benzyloxymethylene)cyclopropane (**1a**) with alkylidenemalononitriles **2** proceeds at ambient pressure to afford the corresponding cyclobutanes **3** in good-to-high yields [Equation (2)].

[‡] For A. d. M.: Cyclopropyl Building Blocks for Organic Synthesis, 144. Part 143: B. Yücel, N. V. Valentić, A. de Meijere, *Eur. J. Org. Chem.* **2007**, in press. Part 142: H. Schill, A. de Meijere, *Org. Lett.* **2007**, in press.

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Results and Discussion

Treatment of (benzyloxymethylene)cyclopropane (**1a**) with benzylidenemalononitrile (**2a**) in acetonitrile at 80 °C for 2 h afforded 4-benzyloxy-6-phenylspiro[2.3]hexane-5,5-dicarbonitrile (**3a**) in 96% yield with a *trans/cis* ratio of 1.5:1 (Table 1, Entry 2). The *trans/cis* ratio depended on the reaction temperature; when the reaction was carried out at 30 °C, the *trans/cis* ratio was 3.7:1, whereas the reaction at 130 °C gave **3a** with a *trans/cis* ratio of 1.4:1 (Table 1, Entries 2 and 3). At 0 °C, the reaction was very slow (8 d, 65% yield; Table 1, Entry 4).

Table 1. [2+2] Cycloaddition of **1a** to **2a**.^[a]

Entry	Temperature [°C]	Time [h]	Yield [%] ^[b]	<i>trans/cis</i> ^[c]
1	130	1.5	>99	1.4:1
2	80	2	96	1.5:1
3	30	50	>99	3.7:1
4	0	8 d	65	3.6:1

[a] The reaction of **1a** (0.2 mmol) and **2a** (0.2 mmol) was carried out in acetonitrile. [b] Yields were determined by NMR spectroscopy by using 1,4-dioxane as an internal standard. [c] The diastereomeric ratio was determined by ¹H NMR spectroscopy.

The results of the reaction of **1a** with different alkyldienemalononitriles at 80 °C are summarized in Table 2. The reaction of (arylmethylene)malononitrile **2b** bearing an electron-withdrawing group on the aryl moiety proceeded smoothly, whereas the reaction of **2c** having an electron-donating group was very slow (Table 2, Entries 2 and 3). The reaction of **2d**, which had an electron-rich furan ring as R¹, also proceeded slowly (Table 2, Entry 4). The reaction of (2-naphthylmethylene)malononitrile (**2e**) with **1a** gave **3e** in a high yield (Table 2, Entry 5). Substrate **2f** having a bulky *tert*-butyl group as R¹ was smoothly converted into the corresponding cyclobutane **3f** in 91% yield, whereas the reaction of **2g**, which had a *geminal* dimethyl group, with **1a** took 3 d to afford **3g** in 54% yield (Table 2, Entries 6 and 7). Other substrates, such as dimethyl benzylidenemalonate (**4**) and 3-benzylidenepentane-2,4-dione (**5**), did not react with (benzyloxymethylene)cyclopropane (**1a**); in the attempted reaction of **1a** with **4** or **5**, the latter were

recovered quantitatively, whereas **1a** decomposed under the reaction conditions. The constitutions of the spirocyclopropanated cyclobutanes **3** were confirmed by spectroscopic methods (see Supporting Information). Furthermore, the structure of the *trans* isomer of **3e** was unambiguously established by an X-ray crystallographic analysis (Figure 1).^[10]

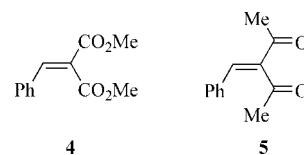


Table 2. [2+2] Cycloadditions of (benzyloxymethylene)cyclopropane (**1a**) with alkyldienemalononitriles **2**.^[a]

Entry	2	R ¹	R ²	Time [h]	Product	Yield [%] ^[b]	<i>trans/cis</i> ^[c]
1	2a	Ph	H	2	3a	96	1.5:1
2	2b	<i>p</i> -O ₂ NC ₆ H ₄	H	1	3b	93	2.0:1
3	2c	<i>p</i> -MeOC ₆ H ₄	H	54	3c	91	1.3:1
4	2d	2-furyl	H	50	3d	89	1.3:1
5	2e	2-naphthyl	H	15	3e	96	1.8:1
6	2f	<i>t</i> Bu	H	33	3f	91	3.4:1
7	2g	Me	Me	72	3g	54	–

[a] The reactions of **1a** (0.2 mmol) and **2** (0.2 mmol) were carried out in acetonitrile (2 mL) at 80 °C. [b] Yields of isolated products. [c] The diastereomeric ratio was determined by ¹H NMR spectroscopy.

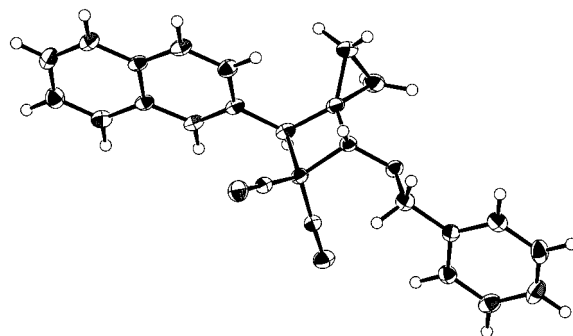
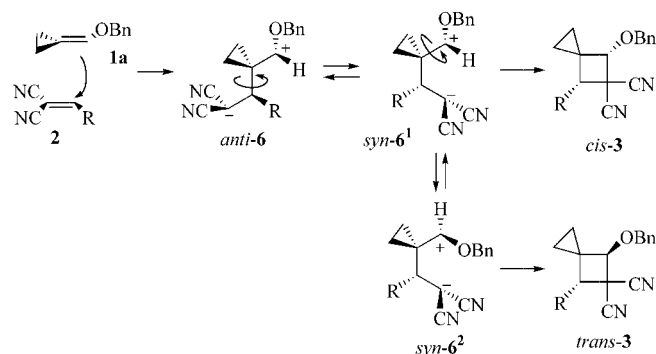


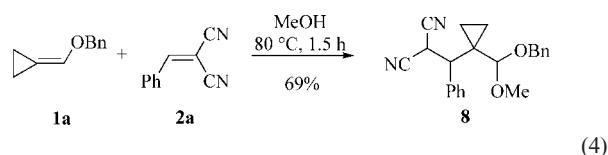
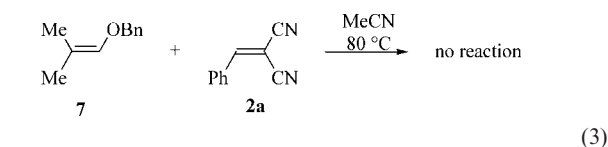
Figure 1. Crystal structure of 4-benzyloxy-6-(2-naphthyl)spiro[2.3]hexane-5,5-dicarbonitrile (*trans*-**3e**). ORTEP representation with thermal ellipsoids set at 50% probability.

A plausible mechanism for the [2+2] cycloadditions of **1a** to **2** is illustrated in Scheme 3. Initially, nucleophilic attack of the carbon–carbon double bond in **1a** on the β-position of the alkyldienemalononitrile would lead to the *anti*-oriented zwitterion *anti*-**6**, which, after internal rotation, cyclizes to the cyclobutane *trans*-**3** or *cis*-**3**. The stabilization of the zwitterionic intermediate **6** by the cyclopropyl group adjacent to the cationic center is essential, as the enol ether **7**, which does not contain a cyclopropane ring, did not react with benzylidenemalononitrile **2a** under thermal conditions. When the reaction of **1a** and **2a** was carried out in methanol, the open chain benzyl methyl acetal **8** was obtained in 69% yield [Equation (3)] and [Equation (4)].^[11]

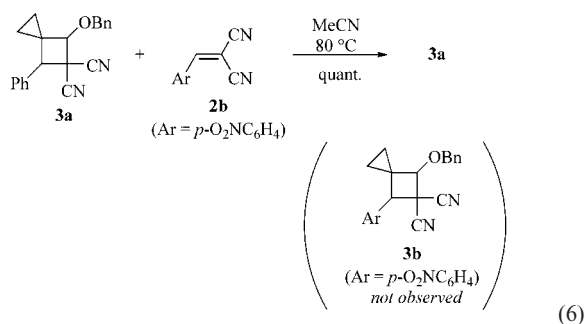
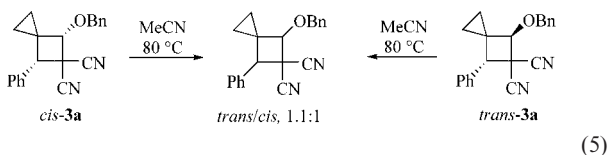
This result proves that the 1,4-zwitterion *anti*-**6** is an intermediate that can be captured by an external nucleophile such as methanol.^[12]



Scheme 3. Mechanistic rationalization of the [2+2] cycloadditions of (benzyloxymethylene)cyclopropane (**1a**) with alkylidenemalononitriles **2**.



When the isolated *trans* and *cis* isomers of **3a** were heated at 80 °C individually, both were converted to a 1.1:1 mixture of *trans* and *cis* isomers, which suggests that the ring closure is reversible [Equation (5)]. To test whether a complete [2+2] cycloreversion can occur, **3a** in acetonitrile was heated in the presence of (*p*-nitrophenylmethylene)ma-



lononitrile (**2b**) at 80 °C for 40 h; however, **3a** was quantitatively recovered, and none of the expected crossover product **3b** was observed by ¹H NMR spectroscopy or GC–MS [Equation (6)].

Conclusions

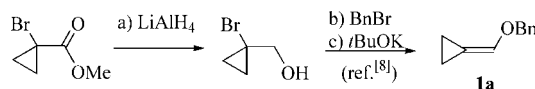
For the [2+2] cycloadditions of (benzyloxymethylene)-cyclopropane with alkylidenemalononitriles, which proceed at ambient pressure, the twofold stabilization of the cationic center in the zwitterionic intermediates **6** plays a crucial role.^[12] Further development of these cycloaddition reactions by employing (alkoxymethylene)cyclopropanes is now in progress in our laboratory.

Experimental Section

Preparation of (Benzyloxymethylene)cyclopropane (**1a**)

(1-Bromocyclopropyl)methanol:^[13] A solution of methyl 1-bromocyclopropanecarboxylate^[14] (100.0 g, 0.50 mol) in anhydrous diethyl ether (200 mL) was added dropwise to a suspension of lithium aluminum hydride (12.00 g, 0.30 mol) in diethyl ether (500 mL) at such a rate that the ether kept boiling gently under reflux. The mixture was then stirred at ambient temperature for an additional 24 h before the excess amount of LiAlH₄ was hydrolyzed by the addition of a slurry of magnesium sulfate (20 g) and water. The solids were filtered off and carefully washed with diethyl ether (250 mL). The combined organic phase was dried with MgSO₄ and concentrated in vacuo. The residue was distilled under reduced pressure through a 20-cm Vigreux column to give 69.93 g (83%) of (1-bromocyclopropyl)methanol, b.p. 86–89 °C/10 mbar (ref.^[13] 64–70 °C/12 Torr). The spectroscopic data were identical with the published ones.^[13]

(1-Bromocyclopropyl)methanol was converted to (benzyloxymethylene)cyclopropane (**1a**) (Scheme 4) according to a literature procedure.^[8]



Scheme 4. Preparation of (benzyloxymethylene)cyclopropane (**1a**): (a) LiAlH₄, Et₂O; (b) PhCH₂Br, NaH, *n*Bu₄NI (cat.), THF, 0 to 25 °C, then 25 °C, 70 h; (c) *t*BuOK, DMSO, 10 to 25 °C, then 25 °C, 2 h.^[8]

General Procedure for the [2+2] Cycloaddition of (Benzyloxymethylene)cyclopropane (1a**) to Alkylidenemalononitriles **2**:** To the alkylidenemalononitrile **2** (0.2 mmol) in acetonitrile (2 mL) was added (benzyloxymethylene)cyclopropane **1a** (0.2 mmol). The mixture was stirred at 80 °C with monitoring by GC–MS. After the starting materials were consumed completely, the solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford product **3**.

***trans*-4-(Benzyloxy)-6-phenylspiro[2.3]hexane-5,5-dicarbonitrile (*trans*-**3a**):** ¹H NMR (270.05 MHz, CDCl₃): δ = 0.62–0.81 (m, 3 H), 1.40–1.48 (m, 1 H), 3.94 (s, 1 H), 4.56 (d, *J* = 11.7 Hz, 1 H), 4.80 (s, 1 H), 4.83 (d, *J* = 11.7 Hz, 1 H), 7.32–7.46 (m, 10 H) ppm. ¹³C NMR (67.80 MHz, CDCl₃): δ = 8.8, 9.7, 28.3, 39.4, 52.3, 72.4, 81.4, 113.0, 114.0, 128.3, 128.6, 128.7, 128.9, 129.1, 134.5, 135.6 ppm. IR

(neat): $\tilde{\nu}$ = 3032–2867, 2248, 1455, 1345, 1091, 1014 cm^{-1} . HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{NaO}$ 337.1317; found 337.1311.

cis-4-(Benzyloxy)-6-phenylspiro[2.3]hexane-5,5-dicarbonitrile (cis-3a): ^1H NMR (270.05 MHz, CDCl_3): δ = 0.52–0.80 (m, 3 H), 1.19–1.27 (m, 1 H), 3.98 (s, 1 H), 4.58 (d, J = 11.7 Hz, 1 H), 4.65, (s, 1 H), 4.87 (d, J = 11.7 Hz, 1 H), 7.39–7.41 (m, 10 H) ppm. ^{13}C NMR (67.80 MHz, CDCl_3): δ = 5.2, 8.8, 29.9, 40.1, 48.8, 72.5, 81.0, 111.8, 115.2, 128.4, 128.6, 128.7, 129.1, 129.4, 132.1, 135.6 ppm. IR (neat): $\tilde{\nu}$ = 3032–2867, 2372, 2243, 1497, 1455, 1142, 1111, 1026, 746 cm^{-1} . HRMS (ESI): $\text{C}_{21}\text{H}_{18}\text{N}_2\text{NaO}$ 337.1317; found 337.1311.

Supporting Information (see footnote on the first page of this article): General procedure for the [2+2] cycloadditions of (benzyloxymethylene)cyclopropane (**1a**) to alkylidenemalononitriles **2**, spectroscopic data of **3** and **8**.

Acknowledgments

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