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

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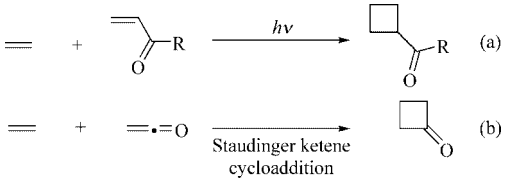
Keywords: Cycloaddition / Cyclobutanes / Enols / Cyclopropanes

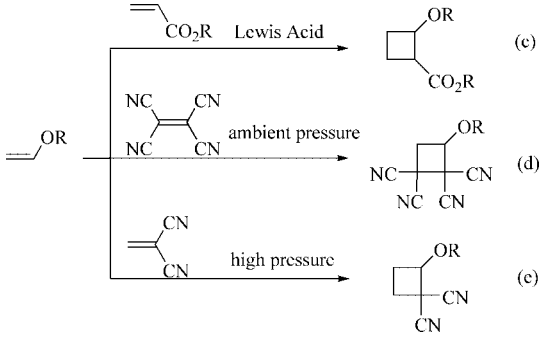
The reaction of (benzyloxymethylene)cyclopropane (**1a**) with alkylidenemalononitriles **2** at ambient pressure afforded the corresponding cyclobutane derivatives **3** in good-to-high yields. For example, the reaction of **1a** with benzylidenemalononitrile (**2a**), (2-naphthylmethylene)malononitrile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

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



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 (alkoxymethylene)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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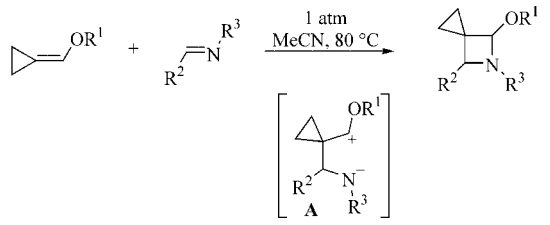

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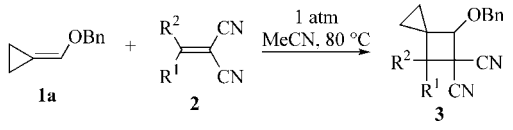


(2)

Results and Discussion

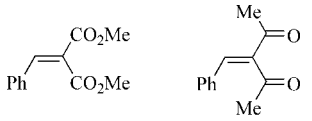
Treatment of (benzyloxymethylene)cyclopropane (**1a**) with benzylidenemalononitrile (**2a**) in acetonitrile at 80 °C for 2 h afforded 4-benzyloxy-6-phenylspiro[2.3]hexane-5,5-dicarbonitrile (**3a**) in 96% yield with a *trans*/*cis* ratio of 1.5:1 (Table 1, Entry 2). The *trans*/*cis* ratio depended 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]	*trans*/*cis*[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 ^{1}H NMR spectroscopy.

The results of the reaction of **1a** with different alkylidenemalononitriles 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 R^1, 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 R^1 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]



4 **5**

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

Entry	**2**	R^1	R^2	Time [h]	Product	Yield [%][b]	*trans*/*cis*[c]
1	**2a**	Ph	H	2	**3a**	96	1.5:1
2	**2b**	*p*-$O_2NC_6H_4$	H	1	**3b**	93	2.0:1
3	**2c**	*p*-$MeOC_6H_4$	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**	*t*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 ^{1}H NMR spectroscopy.

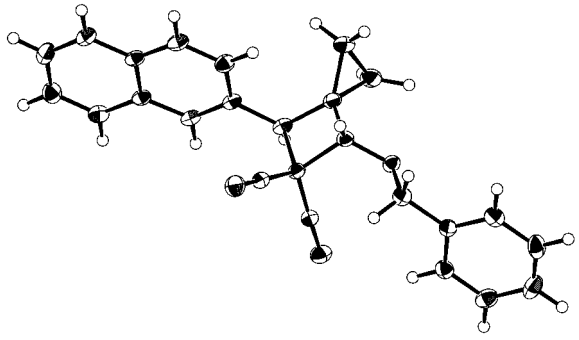
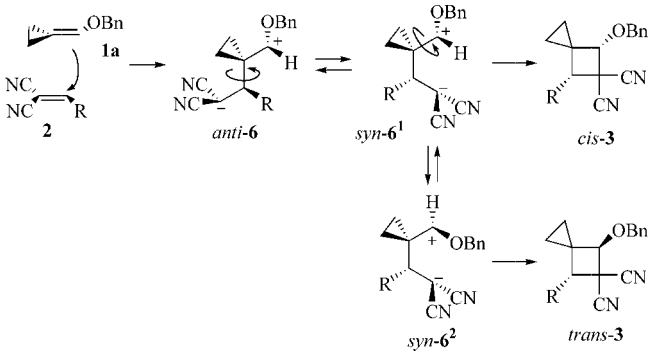


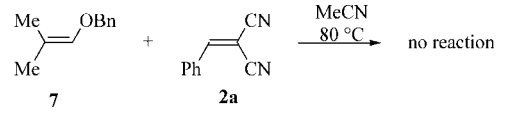
Figure 1. Crystal structure of 4-benzyloxy-6-(2-naphthyl)spiro[2.3]-hexane-5,5-dicarbonitrile (*trans*-**3e**). ORTEP representation with thermal ellipsoids set at 50% probability.

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 alkylidenemalononitrile 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**.



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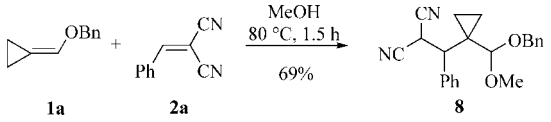
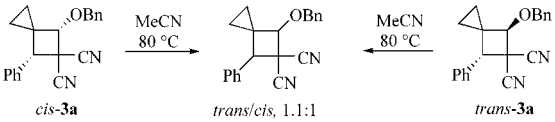


(4)

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



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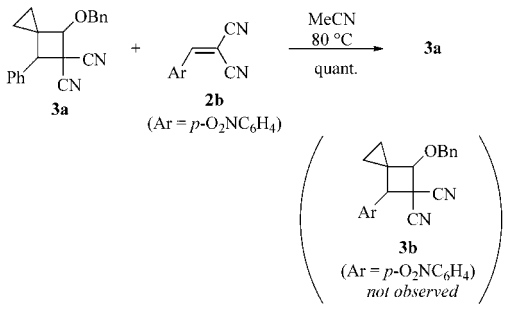


(6)

Conclusions

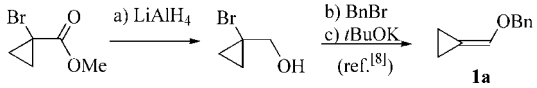
For the [2+2] cycloadditions of (benzyloxymethylene)cyclopropane with alkylidenemalononitriles, which proceed at ambient pressure, the twofold stabilization of the cationic center in the zwitterionic intermediates **6** plays a crucial role.[12] Further development of these cycloaddition reactions by 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 $LiAlH_4$ 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 $MgSO_4$ 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) $LiAlH_4$, Et_2O; (b) $PhCH_2Br$, NaH, nBu_4NI (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):** ^{1}H NMR (270.05 MHz, $CDCl_3$): 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. ^{13}C NMR (67.80 MHz, $CDCl_3$): 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 $C_{21}H_{18}N_2NaO$ 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): $C_{21}H_{18}N_2NaO$ 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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[10] CCDC-643852 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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