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First Domino Mukaiyama-Aldol Cyclizations of 1,3-Bis(trimethylsiloxy)-1,3-butadienes with 1,2-Diketones

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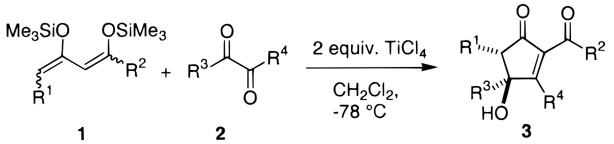
ABSTRACT



The first domino Mukaiyama-aldol cyclization of 1,3-bis(trimethylsiloxy)-1,3-dienes with enolizable 1,2-diketones provides a convenient and regioselective access to substituted cyclopent-2-en-1-ones.

The Diels−Alder reaction represents one of the most convenient methods for generating molecular complexity in the cyclohexane area.[1] The obvious need to extend equally efficient cycloaddition strategies to the construction of five-membered carbocyclic ring systems has led to many elegant studies of [3 + 2] annulation processes.[2] Surprisingly, despite the simplicity of the idea, only few reactions of 1,3-dianionic synthons with 1,2-dielectrophiles have been reported so far. Several drawbacks are possible for these reactions: on the one hand, dianions are highly reactive compounds which can react both as a nucleophile and a base; on the other hand, 1,2-dielectrophiles often represent rather labile compounds. To the best of our knowledge, no cyclization reactions of 1,3-dianions with *enolizable* 1,2-diones have been reported so far, presumably due to deprotonation of the latter by the dianion.[3,4] We have recently developed[5] a Lewis acid-catalyzed cyclization of oxalyl chloride with 1,3-bis(trimethylsiloxy)-1,3-dienes, synthons of 1,3-dicarbonyl-dianions,[6] to give γ-alkylidene butenolides. Herein, we wish to report the first domino Mukaiyama-aldol cyclization of 1,3-bis(trimethylsiloxy)-1,3-dienes with enolizable 1,2-diketones.[7,8] These reactions proceed not only with very good chemoselectivities but also with very good regioselectivities. The products, cyclo-2-penten-4-ones, are of pharmacological relevance and represent versatile building blocks for the synthesis of natural products.[9]

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(1) Review: Tietze, L. F.; Beifuss, U. *Angew. Chem.* **1993**, *105*, 137; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.

(2) Trost, B. M. *Angew. Chem.* **1986**, *98*, 1; *Angew. Chem., Int. Ed.* **1986**, *25*, 1.

(3) For the reaction of 1,3,5-tricarbonyl compounds with glyoxal in aqueous alkaline medium, see: Gawish, A.; Mitschka, R.; Cook, J. M. *Tetrahedron Lett.* **1981**, 211.

(4) For recent base-mediated cyclizations of nonenolizable aromatic 1,2-diones, see: (a) Morgenroth, F.; Berresheim, A. J.; Wagner, M.; Müllen, K. *Chem. Commun.* **1998**, 1139. For a cyclization reaction of the nonenolizable homoadamantane-4,5-dione, see: (b) Eguchi, S.; Ishiura, K.; Noda, T.; Sasaki, T. *J. Org. Chem.* **1987**, *52*, 496.

(5) (a) Langer, P.; Stoll, M. *Angew. Chem.* **1999**, *111*, 1919; *Angew. Chem., Int. Ed.* **1999**, *38*, 1803. (b) Langer, P.; Schneider, T.; Stoll, M. *Chem. Eur. J.*, in press.

(6) (a) Chan, T.-H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 578. (b) Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534. (c) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830.

(7) For the reaction of simple silyl enol ethers with ketones, see: Mukaiyama, T. *Angew. Chem.* **1977**, *89*, 858; *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817.

(8) For the reaction of 1,2-diones with 3-iodo-2-[(trimethylsilyl)methyl]-propene, a synthon of the trimethylenemethane dianion, see: Molander, G. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1986**, *108*, 4683.

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Because of deprotonation rather than nucleophilic attack, all attempts to induce a cyclization reaction of dilithiated ethyl acetoacetate with butane-2,3-dione **2a** failed. Therefore, we decided to react dione **2a** with 1,3-bis(trimethylsiloxy)-1,3-diene **1a**, which was prepared from ethyl acetoacetate in two steps, in the presence of a Lewis acid. Unfortunately, only starting materials could be isolated when trimethylsilyl trifluoromethanesulfonate (TMSOTf) or $BF_3{\cdot}OEt_2$ were used as the Lewis acid. Similarly, only starting materials were obtained when the reaction was carried out at −78 °C using $TiCl_4$. A complex mixture was formed when the reaction temperature was 0 → 20 °C.

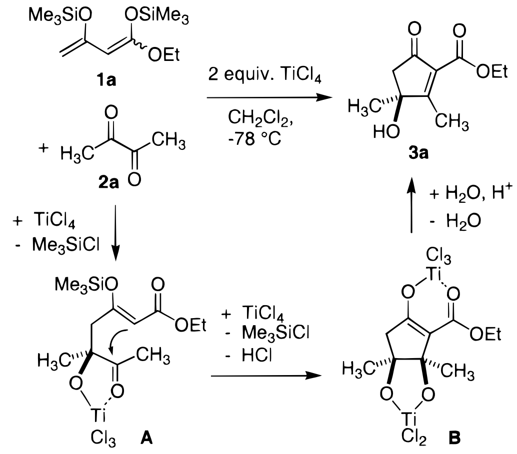
Much to our satisfaction, a cyclization could be induced when the reaction was carried out at −78 → 20 °C to give the 1-hydroxycyclo-2-penten-4-one **3a**. After much experimentation (Table 1), optimal yields (up to 63%) were obtained when the reaction mixture was warmed to ambient during 6 h and when the mixture was stirred at 20 °C for 2 h.[10] The success of this protocol can be explained by the assumption that the initial condensation of the diene with the 1,2-diketone takes place at low temperature and that the cyclization step occurs at 20 °C. The product was formed by a double Mukaiyama-aldol reaction and subsequent elimination of water: the cyclization proceeded by regioselective attack of the terminal carbon atom of the diene onto the dielectrophile and regioselective cyclization via the central carbon atom of the diene (Scheme 1). It is noteworthy that the TMSOTf-catalyzed cyclization of **1a** with oxalyl chloride proceeded via the oxygen rather than the central carbon atom of the diene.[5]

Table 1. Optimization of the Reaction of Diene **1a** with Dione **2a**

entry	Lewis acid	*T* [°C]	*t* [h]^a	equiv of **1a**	yield [%]^b
1	TMSOTf	−78 → 20	6 + 2	1.0	0
2	$BF_3{\cdot}OEt_2$	−78 → 20	6 + 2	1.0	0
3	$TiCl_4$	−78	3	1.0	0
4	$TiCl_4$	−78	12	1.0	0
5	$TiCl_4$	−78 → 20	6 + 0	1.0	38
6	$TiCl_4$	−78 → 20	6 + 2	1.0	63
7	$TiCl_4$	−78 → 20	6 + 12	1.0	26
8	$TiCl_4$	−78 → 20	1 + 2	1.0	18
9	$TiCl_4$	−78 → 20	6 + 2	1.5	41
10	$TiCl_4$	0 → 20	2 + 2	1.0	0

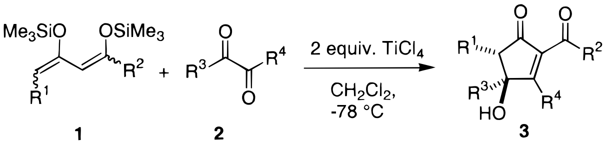
^{a} Reaction time (−78 → 20 °C) + reaction time at 20 °C. ^{b} Isolated yields.

Scheme 1



To study the preparative scope of the reaction, the substituents of the diene were systematically varied (Scheme 2, Table 2). Reaction of dione **2a** with the 1,3-bis(trimethylsiloxy)-1,3-dienes derived from ethyl acetoacetate, acetylacetone, and 1-methoxyacetylacetone afforded the cyclo-2-penten-4-ones **3a**−**c** in good yields. Cyclization of **2a** with the dienes derived from methyl 3-oxopentanoate and ethyl 3-oxohexanoate afforded the cyclopentenones **3d**−**e**. Reaction of **2a** with the dienes derived from methyl 4-methoxyacetoacetate and 1-methoxyacetylacetone (containing a methoxy group at the terminal carbon atom) afforded the methoxy-substituted cyclopentenones **3f** and **3g**, respectively. Because of the similar steric demand of the methyl and the hydroxy group, only low 1,2-stereoselectivities were observed in the case of **3d** and **3f**−**g**. A moderate 1,2-stereoselectivity was observed in the formation of cyclopentenone **3e**.

Scheme 2



To vary the substituents of the 1,2-dione, cyclization reactions of hexane-3,4-dione **2b** were next studied. Reaction of **2b** with the 1,3-bis(trimethylsiloxy)-1,3-dienes derived from ethyl acetoacetate and acetylacetone regioselectively afforded the cyclopentenones **3h** and **3i**. Reaction of **2b** with

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[9] (a) Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, 1475. (b) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7550. (c) Filippini, M.-H.; Faure, R.; Rodriguez, J. *J. Org. Chem.* **1995**, *60*, 6872.

[10] **Preparation of cyclopentenone 3a.** To a CH_2Cl_2 solution (30 mL) of dione **2a** (1.5 mmol, 0.13 g) and 1,3-bis(trimethylsiloxy)-1,3-diene **1a** (1.5 mmol, 0.39 g) was added a CH_2Cl_2 solution (5 mL) of $TiCl_4$ (3 mmol) at −78 °C. The temperature of the reaction mixture was allowed to rise to 20 °C during 6 h. After 2 h of stirring at 20 °C, a saturated solution of NaCl was added, the organic layer was separated, and the aqueous layer was repeatedly extracted with ether. The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, ether/petroleum ether = 1/1). ^1H NMR (acetone-d_6, 200 MHz): δ 1.27 (t, 3 H, $J = 7$, CH_3), 1.45 (s, 3 H, CH_3), 2.24 (s, 3 H, CH_3), 2.55 (s, 2 H, CH_2), 4.21 (q, 2 H, $J = 7$, OCH_2), 4.62 (s, 1 H, OH). ^{13}C NMR (acetone-d_6, 50 MHz): δ_C 11.68, 13.62, 25.31, 51.07, 60.22, 75.02, 131.57, 162.97, 182.60, 198.45. MS (70 eV): 198 (36, M^+). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found.: C, 60.28; H, 7.36. All compounds were characterized by spectroscopic methods and gave correct elemental analyses and/ or high-resolution mass spectra.

Table 2. Synthesis of 1-Hydroxycyclo-2-penten-4-ones **3**

3	R^1	R^2	R^3	R^4	%[a]	selectivity[b]
a	H	OEt	Me	Me	63	
b	H	Me	Me	Me	57	
c	H	CH_2OMe	Me	Me	58	
d	Me	OMe	Me	Me	47	1.2:1
e	Et	OEt	Me	Me	45	3.5:1
f	OMe	OMe	Me	Me	60	1:1.4
g	OMe	Me	Me	Me	25	1:1.2
h	H	OEt	Et	Et	28	
i	H	Me	Et	Et	16	
j	Me	OMe	Et	Et	21	3:1
k	OMe	OMe	Et	Et	20	1:3
l	H	OEt	Me	Et	62	9:1
m	H	CH_2OMe	Me	Et	54	4:1
n	H	Me	Me	Et	51	2:1

[a] Isolated yields. [b] For **3d**−**g** and **3j**−**k**, diastereoselectivities in favor of the drawn isomers. For **3l**−**n**, regioselectivities in favor of the drawn isomers. The ratios were determined by integration of the corresponding ^{1}H NMR signals of the crude products.

the dienes derived from methyl 3-oxopentanoate and methyl 4-methoxyacetoacetate afforded the cyclopentenones **3j** and **3k** with diastereoselectivities of 5:1 and 3:1, respectively. In the case of the cyclization reactions of dione **2b**, the yields were generally lower than in the case of **2a**, presumably due to the increased steric hindrance. In addition, extended reaction times (6 + 12 h) were necessary. Open-chain compounds were isolated as the side products in the formation of cyclopentenones **3j** and **3k**. These compounds were isolated as the major products when the reactions were quenched by addition of water directly after warming of the reaction mixture to ambient. Reaction of diene **1a** with benzile resulted in formation of a complex mixture. Reaction of pentane-2,3-dione **2c**, an unsymmetrical 1,2-dione, with the 1,3-bis(trimethylsiloxy)-1,3-dienes derived from ethyl acetoacetate, 1-methoxy-2,4-pentanedione, and acetylacetone afforded the cyclopentenones **3l**−**n** in good yields. The reactions leading to **3l** and **3m** proceeded with good regioselectivities. This is noteworthy, since the two carbonyl groups of **2c** are very similar sterically.

In summary, we have reported the first Lewis acid-mediated domino Mukaiyama-aldol cyclizations of 1,3-bis-(trimethylsiloxy)-1,3-dienes, 1,3-dicarbonyl dianion synthons, with 1,2-diones. These reactions allow for a convenient and regioselective preparation of cyclo-2-penten-4-ones which are of pharmacological relevance and represent versatile building blocks for the synthesis of natural products.

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