Efficient Synthesis of Functionalized 4,5-Benzotropones by Regioselective Cyclization of 1,3-Bis(trimethylsilyloxy)-1,3-butadienes with Phthalic Dialdehyde

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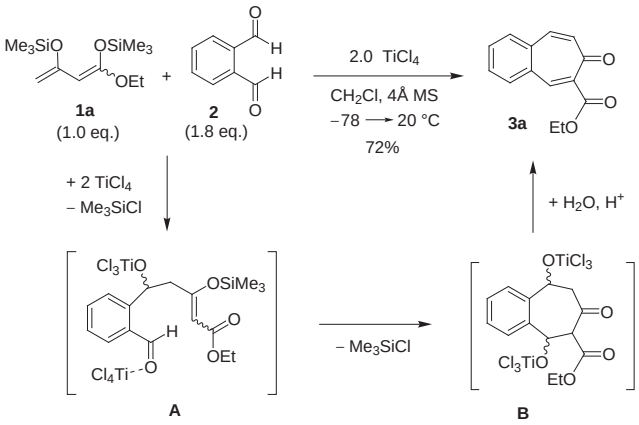
Abstract: The reaction of 1,3-bis(trimethylsiloxy)-1,3-butadienes with phthalic dialdehyde resulted in regioselective formation of functionalized 4,5-benzotropones.

Key words: aldol reactions, benzotropones, cyclizations, regioselectivity, silyl enol ethers

Benzocycloheptanones and benzocycloheptatrienones (benzotropones) are present in a variety of pharmacologically relevant natural products including colchicone, colchicine, allocolchicine or purpurogalline.[1] 4,5-Benzotropones have been previously prepared mainly by base-mediated cyclization of ketones with aromatic dialdehydes.[2,3] Since tropones readily undergo base-mediated Michael additions with the starting materials these reactions are often problematic. In addition, a number of structural limitations exist: whereas 1,3,5-tricarbonyl compounds generally react rather selectively, 1,3-dicarbonyl derivatives such as acetyl acetone and substrates containing base-labile functional groups fail to give the desired products.[3c] Acid-mediated cyclizations are known,[3d] but require harsh conditions (the reactions have to be carried out in neat 96-98% sulfuric acid). In addition, only highly activated substrates, such as 1,3-dimethoxycarbonylacetone, can be successfully transformed into 4,5-benzotropones. Due to the pharmacological relevance of benzotropone derivatives, we herein disclose our findings related to a new synthesis of 4,5-benzotropones. Our methodology is based on the Lewis-acid mediated cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes **1**, electroneutral 1,3-dianion equivalents,[4] with phthalic dialdehyde **2**. Previously, cyclizations of dienes **1** with aliphatic 1,4-dicarbonyl compounds to give bridged oxacycles have been reported by Molander and co-workers.[4b] We have recently reported [3+2] cyclizations of dienes **1** with 1,2-dielectrophiles such as oxalyl chloride, 1,2-diketones and epoxides.[5] The reactions reported herein represent to our knowledge the first Mukaiyama-type [4+3] cyclizations of bis-silyl enol ethers **1** with aromatic 1,4-dicarbonyl compounds to give 4,5-benzotropones.

Our starting point was the reaction of the dianion of ethyl acetoacetate with phthalic dialdehyde **2**. Due to overaddition, polymerization and reduction of the aldehyde, only a complex mixture was formed. The reaction of ethyl acetoacetate with **2** in the presence of KOH, NaOEt or sulfuric acid were equally disappointing. The $TiCl_4$-mediated reaction of **2** with 1,3-bis(trimethylsilyloxy)-1,3-butadiene **1a**, which was readily prepared from ethyl acetoacetate in two steps,[4] resulted in formation of the 4,5-benzotropone **3a**, however, in only low yield. The Lewis acid, temperature, reaction time, concentration and the presence of molecular sieves (MS) proved important parameters during the optimization of the reaction conditions (Table 1). After much experimentation (Table 1) we have found that best results (up to 72% yield) were obtained when the Lewis acid $TiCl_4$ (2.0 equiv.) and an excess of the aldehyde were used. The reaction was carried out in the presence of 4 Å MS at −78 °C → 20 °C using a relatively low concentration of **1a** (0.01 mol/L).[6]



Scheme 1 Mechanism of the formation of 4,5-benzotropone **3a**

The formation of 4,5-benzotropone **3a** can be explained 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 1,4-dielectrophile and subsequent regioselective cyclization via the central carbon atom of the diene (Scheme 1).

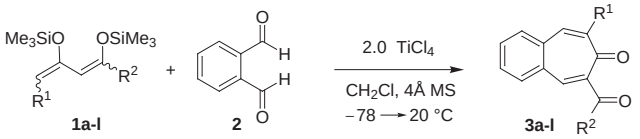
In order to study the preparative scope of the reaction, the substituents of the diene were systematically varied (Scheme 2, Table 2). Reaction of phthalic dialdehyde **2** with the 1,3-bis(trimethylsiloxy)-1,3-dienes **1a-e** derived from ethyl-, methyl-, methoxyethyl-, benzyl-, and isobutyl acetoacetate afforded the 4,5-benzotropones **3a-e** in good yields and with very good regioselectivities. The cyclization of **2** with dienes **1f-h**, containing an alkyl group

Table 1 Optimization of the reaction of diene **1a** with phthalic dialdehyde **2**

entry	4Å MS	*T* [°C]	Lewis acid [c]	Equiv. (**2**)	*c* (**1a**) [mol/l]	Yield (%) [d]
1	No	−78 → 20 [a]	$TiCl_4$	1.3	0.1	15
2	No	−78 → 20 [a]	$TiCl_4$	1.3	0.01	11
3	Yes	−78 → 20 [a]	$TiCl_4$	1.3	0.1	44
4	Yes	−78 → 20 [a]	$TiCl_4$	1.3	0.01	70
5	Yes	−78 → 20 [a]	$TiCl_4$	1.0	0.01	58
6	Yes	−78 → 20 [a]	$TiCl_4$	1.8	0.01	72
7	Yes	−78 → 20 [b]	$TiCl_4$	1.8	0.01	62
8	Yes	−78 → 20 [a]	Me_3SiOTf	1.0	0.01	14
9	Yes	−78 → 20 [a]	Me_3SiOTf	1.0	0.1	17
10	Yes	−78 → −30 [a]	$TiCl_4$	1.8	0.01	0
11	Yes	−78 → 0	$TiCl_4$	1.8	0.01	33

[a] Reaction time: 12 h+2 h (20 °C). [b] 12 h+12 h (20 °C). [c] $TiCl_4$: 2.0 equiv., Me_3SiOTf: 0.3 equiv. [d] Isolated yield

at the terminal carbon atom, gave the methyl-, ethyl- and butyl-substituted 4,5-benzotropones **3f-h**. The reaction of **2** with dienes **1i-k**, which were prepared from acetyl acetone, benzoyl acetone and 1-methoxyacetyl acetone, regioselectively afforded the 4,5-benzotropones **3i-k**. The methoxy-substituted 4,5-benzotropone **3l** was obtained by cyclization of **2** with diene **1l** (a regioisomer of **1k**).



Scheme 2 Cyclization of dienes **1a-l** with phthalic dialdehyde **2**

Table 2 Synthesis of 4,5-benzocycloheptatrien-1-ones **3a-l**

3	R^1	R^2	yield (%) [a]
a	H	OEt	72
b	H	OMe	45
c	H	$O(CH_2)_2OMe$	54
d	H	OCH_2Ph	44
e	H	O(*i*-Bu)	60
f	Me	OMe	41
g	Et	OEt	53
h	Bu	OEt	56
i	H	Me	34
j	H	Ph	51
k	H	CH_2OMe	40
l	OMe	Me	40

[a] Isolated yields.

In conclusion, we have developed a new method for the synthesis of a wide range of functionalized 4,5-benzotropones which are of pharmacological relevance and of interest for the synthesis of natural products. The cyclization products reported herein were not available by base-mediated reactions. Our current work is directed towards exploring the preparative scope of our cyclization reaction and towards its application to the synthesis of alkaloids.

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(6) General procedure for the preparation of 4,5-benzotropones **3**: A CH_2Cl_2-solution (110 mL) of **2** (2.0 mmol, 0.268 g) and molecular sieves (4 Å, 1.0 g) was stirred for 15 min at −78 °C. To the solution was added a CH_2Cl_2-solution (5 mL) each of diene **1a** (1.1 mmol, 0.301 g) and of $TiCl_4$ (2.2 mmol, 0.417 g, 0.43 mL) at −78 °C. The temperature of the reaction mixture was allowed to rise to 20 °C during 12 h. After stirring for 2 h at 20 °C water and subsequently an aqueous solution of hydrochloric acid (100 mL, 10%) was added. The organic layer was separated and the aqueous layer was extracted with ether (100 mL). The combined organic extracts were extracted with brine, dried ($MgSO_4$), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, ether/petroleum ether = 5:1→2:1) to give **3a** as a light yellow oil (0.180 g, 72%). For **3e, 3i** and **3l**: 1.0 equiv. of **2** was used. For **3f-g**, 1.3 equiv. of **2** was used. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7 Hz, 3 H, OCH_2CH_3), 4.34 (q, *J* = 7 Hz, 2 H, OCH_2CH_3), 6.78 (d, *J* = 13 Hz, 1 H, CH=CHCO), 7.37 (d, *J* = 13 Hz, 1 H, CH=CHCO), 7.56−7.61 (m, 4 H, Ar), 7.85 (s, 1 H, −CH=); ^{13}C NMR (200 MHZ, $CDCl_3$): δ 13.99 (OCH_2CH_3), 61.60 (OCH_2CH_3), 130.4, 131.58, 133.55 (CH, Ar), 133.77 (C, Ar), 135.09, 135.24 (CH, Ar), 135.92, 137.26 (C, Ar), 140.28, 141.93 (CH, Ar), 167.42, 184.43 (C=O); IR (KBr): ν 3172 (w), 3059 (w), 2891 (w), 1726 (s), 1631 (s), 1596 (s), 1556 (m), 1426 (m), 1312 (s) cm^{-1}; MS (EI, 70 eV): 228 (M^+, 14), 200 (70), 183 (34), 155 (100), 127 (74); the exact molecular mass m/z = 228.0786±2 mD (M^+) was confirmed by HRMS (EI, 70 eV). All new compounds gave satisfactory spectroscopic and analytical and/ or high resolution mass data.

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