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Synthesis and reactions of 2-chloro-1,3-bis(trimethylsilyloxy)-1,3-butadienes

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ABSTRACT

The reaction of 2-chloro-1,3-bis(trimethylsilyloxy)-1,3-butadienes with various electrophiles allows a convenient synthesis of chlorinated molecules which are not readily available by other methods.

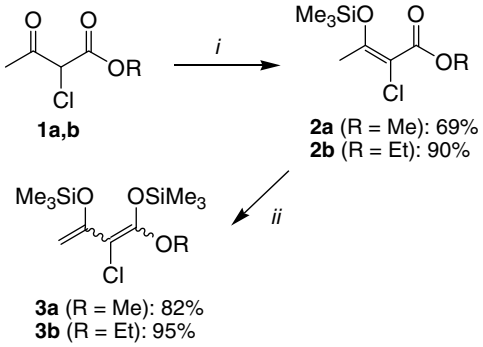
Chlorinated molecules are of considerable pharmacological relevance and occur in a number of natural products.[1] In fact, arenes and hetarenes containing a chloride group often show a better pharmacological activity compared to their non-halogenated analogues.[2] Chlorinated arenes and hetarenes also represent versatile building blocks in transition metal-catalyzed cross coupling reactions.[3] However, the direct chlorination of arenes, hetarenes and open-chained molecules often suffers from several drawbacks, such as low regioselectivity or multiple chlorination. An alternative strategy for the regioselective synthesis of organochlorine compounds relies on the use of appropriate chlorine-containing building blocks in condensation and cyclization reactions. For example, Manzanares and co-workers reported the synthesis of a 4-chlorophenol by [4+2] cycloaddition of a chlorinated thiophene with dimethyl acetylenedicarboxylate.[4]

1,3-Bis(trimethylsilyloxy)-1,3-butadienes (e.g., Chan's diene)[5,6] represent important synthetic building blocks, which have been used in formal [3+2], [3+3], [4+2] and [4+3] cyclizations and other transformations.[7] Herein, we report the synthesis and synthetic application of 2-chloro-1,3-bis(silyloxy)-1,3-butadienes.[8] Their reaction with various electrophiles provides a convenient and regioselective approach to a variety of organochlorine compounds, which are not readily available by other methods.

The reaction of commercially available methyl and ethyl 2-chloroacetoacetate (**1a**,**b**) with Me_3SiCl and triethylamine afforded silyl enol ethers **2a**,**b** (Scheme 1). The 2-chloro-1-alkoxy-1,3-bis(silyloxy)-1,3-butadienes **3a**,**b** were prepared by deprotonation (LDA) of **2a**,**b** at −78 °C and subsequent addition of trimethylchlorosilane. It is noteworthy that the chloride group proved to be compatible with the reaction conditions.

3-Chloro-2,4-bis(silyloxy)-1,3-pentadiene (**3c**) and 2-chloro-1-phenyl-1,3-bis(silyloxy)-1,3-butadiene (**3d**) were prepared by reaction of an ether solution of **1c** and **1d**, respectively, with 2.0 equiv of trimethylsilyl-trifluoromethanesulfonate (Me_3SiOTf) and triethylamine (Scheme 2). This method of silylation was first developed by Simchen and Krägeloh.[6b] Dienes **3a**–**d** can be stored at −20 °C under inert atmosphere for several weeks.

The reaction of **3a** with benzoyl chloride, following our recently reported protocol,[9] afforded methyl 2-chloro-5-phenyl-3,5-dioxopentanoate (**4**) in 82% yield (Scheme 3). The best yields were



Scheme 1. Synthesis of dienes **3a**,**b**. Reagents and conditions: (i) Me_3SiCl, NEt_3, benzene, 20 °C, 48 h; (ii) (1) LDA, THF, −78 °C, 1 h, (2) Me_3SiCl, −78→20 °C, 14h.

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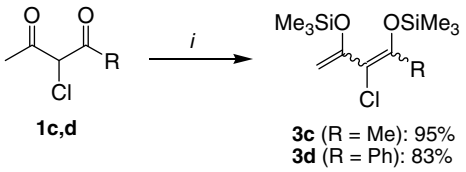
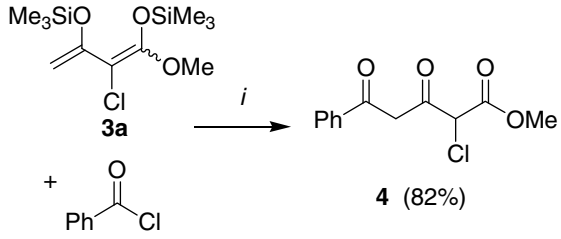


Scheme 2. Synthesis of dienes **3c**,**d**. Reagents and conditions: (i) Me_3SiOTf, NEt_3, Et_2O, 0→20 °C, 4 h.

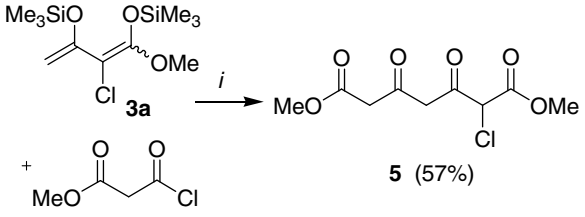
obtained when the reactions were carried out in the *absence* of Lewis acid. It is noteworthy that products such as **4** are not available by direct chlorination of 3,5-dioxoalkanoates, due to the formation of a mixture of regioisomers.

The Me_3SiOTf-catalyzed condensation of **3a** with methyl malonyl chloride afforded dimethyl 2-chloro-3,5-dioxopimelate (**5**) (Scheme 4). The synthesis of **5** by direct chlorination of dimethyl 3,5-dioxopimelate is not possible, due to the formation of regioisomers and multiple chlorination.

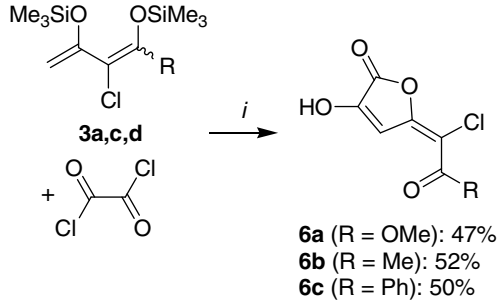
The Me_3SiOTf-catalyzed cyclization[10] of 2-chloro-1,3-bis(silyloxy)-1,3-butadienes **3a**, **3c**, and **3d** with oxalyl chloride afforded the novel chlorinated γ-alkylidenebutenolides **6a**–**c** (Scheme 5). The exocyclic double bond of all products was formed with excellent *Z*-diastereoselectivity (due to thermodynamic reasons). Products **6a**–**c** are not readily available by other methods.



Scheme 3. Synthesis of **4**. Reagents and conditions: (i) CH_2Cl_2, −78→20 °C.



Scheme 4. Synthesis of **5**. Reagents and conditions: (i) Me_3SiOTf (0.2 equiv), CH_2Cl_2, −78→20 °C.

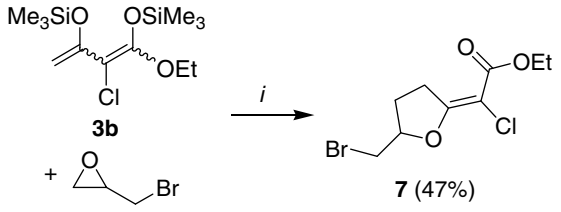


Scheme 5. Synthesis of butenolides **6a**–**c**. Reagents and conditions: (i) Me_3SiOTf (0.3 equiv), CH_2Cl_2, −78→20 °C, 14 h, *Z*/*E* (**6a**–**c**) > 98:2.

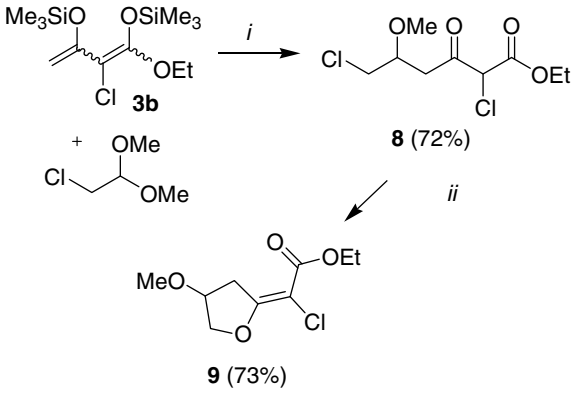
The $TiCl_4$-mediated cyclization of **3b** with epibromohydrin, following our recently reported protocol,[11] afforded the halogenated 2-alkylidenetetrahydrofuran **7** (Scheme 6). The exocyclic double bond was again formed with excellent *Z*-diastereoselectivity.

The Me_3SiOTf-catalyzed condensation of **3b** with 1-chloro-2,2-dimethoxyethane gave ethyl 2,6-dichloro-5-methoxy-3-oxohexanoate (**8**) in good yield as a 1:1 mixture of diastereomers (Scheme 7). The DBU-mediated cyclization[12] of **8** afforded the *Z*-configured 4-methoxy-2-alkylidenetetrahydrofuran **9**. Noteworthy, this product is not available by direct halogenation.[13]

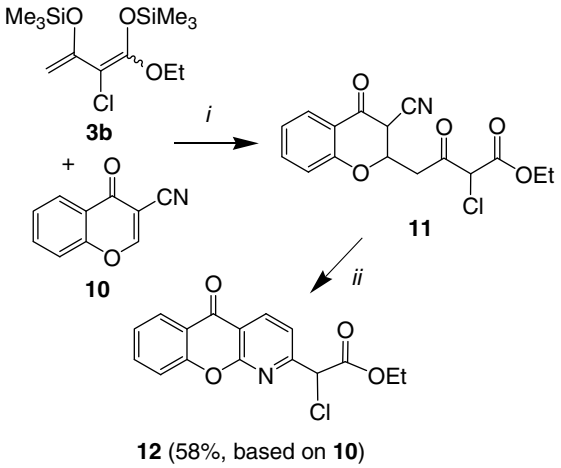
The Me_3SiOTf-mediated condensation of **3b** with 3-cyanochromone (**10**) gave product **11** by regioselective attack of the terminal



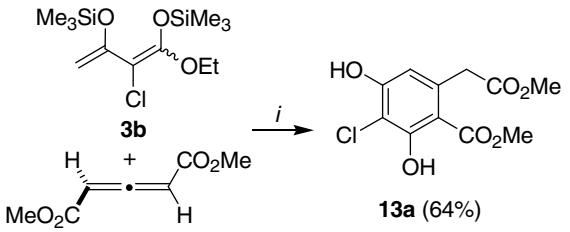
Scheme 6. Synthesis of 2-alkylidenetetrahydrofuran **7**. Reagents and conditions: (i) $TiCl_4$ (2.0 equiv), 4 Å MS, CH_2Cl_2, −78→20 °C, *Z*/*E* (**7**) > 98:2.



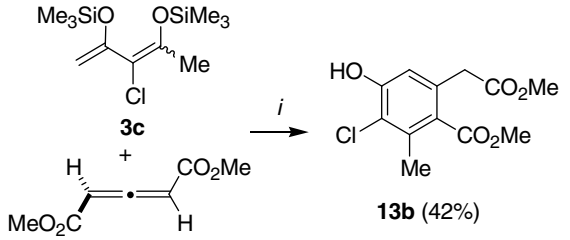
Scheme 7. Synthesis of 2-alkylidenetetrahydrofuran **9**. Reagents and conditions: (i) Me_3SiOTf (0.5 equiv), CH_2Cl_2, −78→20 °C, dr (**8**) = 1:1; (ii) DBU (2.0 equiv), THF, 20 °C, *Z*/*E* (**9**) > 98:2.



Scheme 8. Synthesis of 1-azaxanthone **12**. Reagents and conditions: (i) (1) **10**, Me_3SiOTf, 1 h, 20 °C; (2) **3b**, CH_2Cl_2, 0→20 °C, 12 h; (3) HCl (10%); (ii) (1) NEt_3, EtOH, 20 °C, 12 h, (2) HCl (1 M).



Scheme 9. Synthesis of homophthalate **13a**. Reagents and conditions: (i) (1) neat, 40 °C, 14 h; (2) $HNEt_3F$, EtOH.



Scheme 10. Synthesis of homophthalate **13b**. Reagents and conditions: (i) (1) neat, 40 °C, 14 h; (2) $HNEt_3F$, EtOH.

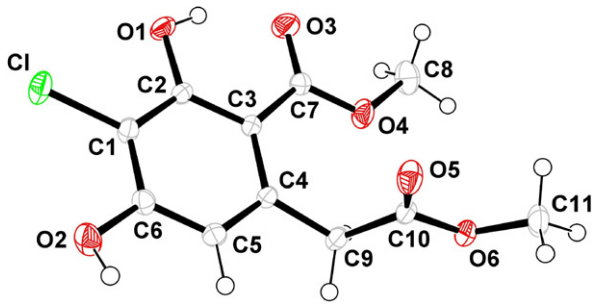
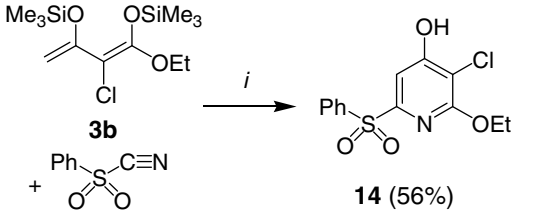


Figure 1. Crystal structure of **13a**.

carbon atom of the diene onto carbon atom C-2 of the cyanochromone and subsequent hydrolysis upon aqueous work-up. Treatment of an ethanol solution of crude **11** with triethylamine afforded the novel chlorinated 1-azaxanthone **12** (Scheme 8). This type of product is again not available by direct chlorination. The transformation of **A** into **12** can be explained by a domino 'retro-Michael/nitrile-addition/heterocyclization' reaction.[14]

The [4+2] cycloaddition[15] of 1,3-bis(trimethylsiloxy)-1,3-butadiene **3b** with dimethyl allene-1,3-dicarboxylate afforded the novel chlorinated 2,4-dihydroxy-homophthalate **13a** in good yield and with very good regioselectivity (Scheme 9). The cycloaddition of dimethyl allene-1,3-dicarboxylate with **3c** gave the homophthalate **13b** (Scheme 10). Products **13a**,**b** are not available by direct halogenation of the corresponding homophthalate because of the formation of a regioisomeric mixture. The structure of **13a** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[16]



Scheme 11. Synthesis of pyridine **14**. Reagents and conditions: (i) (1) neat, 45 °C, 48 h; (2) NH_4Cl, H_2O.

The hetero-Diels–Alder reaction[17] of 1,3-bis(silyloxy)-1,3-butadienes **3b** with phenylsulfonylcyanide afforded the chlorinated 2-(arylsulfonyl)pyridine **14** (Scheme 11).[18] This type of product is again not available by direct chlorination.

In conclusion, we reported the synthesis of 2-chloro-1,3-bis(trimethylsilyloxy)-1,3-butadienes and their reaction with various electrophiles. These reactions provide a regioselective approach to a variety of chlorinated carba- and heterocycles and of chlorinated tri- and tetracarbonyl compounds. The products are not available by direct chlorination reactions. The preparative scope of the methodology is currently being studied.

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References and notes

1. For pharmacologically active chlorinated natural products and drugs: Griseofulvin: (a) Osborne, C. S.; Leitner, I.; Hofbauer, B.; Fielding, C. A.; Favre, B.; Ryder, N. S. *Antimicrob. Agents Chemother.* **2006**, *50*, 2234; (b) Takano, R.; Sugano, K.; Higashida, A.; Hayashi, Y.; Machida, M.; Aso, Y.; Yamashita, S. *Pharm. Res.* **2006**, *23*, 1144; (c) Xue, C.; Li, T.; Deng, Z.; Fu, H.; Lin, W. *Pharmazie* **2006**, *61*, 1041; (d) Phelps, J. B.; Hoffman, W. P.; Lee, C.; Murphy, G. P.; Garriott, M. L. *Mutat. Res.* **2004**, *561*, 153; (e) Rosefort, C.; Fauth, E.; Zankl, H. *Mutagenesis* **2004**, *19*, 277; (f) Kinobe, R. T.; Dercho, R. A.; Vlahakis, J. Z.; Brien, J. F.; Szarek, W. A.; Nakatsu, K. *J. Pharmacol. Exp. Ther.* **2006**, *319*, 277; (g) Albaugh, D.; Albert, G.; Bradford, P.; Cotter, V.; Froyd, J. *J. Antibiot.* **1998**, *51*, 317; Dihydronidulin: (h) Finlay-Jones, P. F.; Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans.* **1981**, *1*, 874.
2. For an example from our laboratory, see: (a) Albrecht, U.; Lalk, M.; Langer, P. *Bioorg. Med. Chem.* **2005**, *13*, 1531; (b) Nguyen, V. D.; Wolf, C.; Mäder, U.; Lalk, M.; Langer, P.; Lindequist, U.; Hecker, M.; Antelmann, H. *Proteomics* **2007**, *7*, 1391.
3. de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004.
4. Corral, C.; Lissavetzky, J.; Manzanares, I. *Synthesis* **1997**, 29.
5. For a review of 1,3-bis(silyl enol ethers), see: Langer, P. *Synthesis* **2002**, 441.
6. (a) Chan, T.-H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 578; (b) Krägeloh, K.; Simchen, G. *Synthesis* **1981**, 30.
7. For a review of [3+3] cyclizations, see: Feist, H.; Langer, P. *Synthesis* **2007**, 327.
8. For the synthesis and reactions of a 4-chloro-1,3-bis(trimethylsilyloxy)-1,3-butadiene, see: (a) Reim, S.; Langer, P. *Tetrahedron Lett.* **2008**, *49*, 2329. For an isolated example of a 2-chloro-1,3-bis(trimethylsilyloxy)-1,3-butadiene, see: (b) Savard, J.; Brassard, P. *Tetrahedron Lett.* **1979**, *20*, 4911. For [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-dienes with 2-chloro-3-silyloxy-2-en-1-ones, see: (c) Yawer, M. A.; Hussain, I.; Reim, S.; Ahmed, Z.; Ullah, E.; Iqbal, I.; Fischer, C.; Reinke, H.; Görls, H.; Langer, P. *Tetrahedron* **2007**, *63*, 12562.
9. Rahn, T.; Nguyen, V. T. H.; Dang, T. H. T.; Ahmed, Z.; Methling, K.; Lalk, M.; Fischer, C.; Spannenberg, A.; Langer, P. *J. Org. Chem.* **2007**, *72*, 1957.
10. Langer, P.; Stoll, M.; Schneider, S. *Chem. Eur. J.* **2000**, *6*, 3204.
11. Langer, P.; Armbrust, H.; Eckardt, T.; Magull, J. *Chem. Eur. J.* **2002**, *8*, 1443.
12. (a) Bellur, E.; Görls, H.; Langer, P. *Eur. J. Org. Chem.* **2005**, 2074. See also: (b) Langer, P.; Krummel, T. *Chem. Eur. J.* **2001**, *7*, 1720.
13. The synthesis of a difluoro-(furan-2-yl)acetate by a different approach has been recently reported: (a) Eto, H.; Kanwko, Y.; Sakamoto, T. *Chem. Pharm. Bull.* **2000**, *48*, 982; (b) Murakami, S.; Kim, S.; Ishii, H.; Fuchigami, T. *Synlett* **2004**, 815.
14. (a) Langer, P.; Appel, B. *Tetrahedron Lett.* **2003**, 5133; (b) Rashid, M. A.; Rasool, N.; Appel, B.; Adeel, M.; Karapetyan, V.; Mkrtchyan, S.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2008**, *64*, 5416.
15. Langer, P.; Kracke, B. *Tetrahedron Lett.* **2000**, *41*, 4545.
16. CCDC-684862 (**13a**) 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.
17. Emmrich, T.; Reinke, H.; Langer, P. *Synthesis* **2006**, 2551.
18. *Synthesis of 3-chloro-2-phenylsulfonyl-4-hydroxypyridine* **14**: To the phenylsulfonyl cyanide (0.167 g, 1.0 mmol) was added dropwise **3b** (0.617 g, 2.0 mmol) at −78 °C. The mixture stirred at 45 °C for 48 h. To the mixture was added an aqueous solution of ammonium chloride (1 M, 20 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane/EtOAc) to give **14** as a yellow viscous oil

(0.175 g, 56%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.22 (t, ^{3}J = 7.1 Hz, 3H, OCH_2CH_3), 4.27 (q, ^{3}J = 7.1 Hz, 2 H, OCH_2CH_3), 7.19 (br s, 1H, OH_{Heter}), 7.44–7.49 (m, 2H, CH_{Ph}), 7.52 (m, 1H, CH_{Ph}), 7.55 (s, 1H, CH_{Heter}), 7.96 (dd, ^{3}J = 8.4 Hz, ^{4}J = 1.5 Hz, 2H, CH_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (OCH_2CH_{3Heter}), 64.1 (OCH_2CH_3), 105.6 (CH_{Heter}), 106.9 (C_{Heter}), 128.9 ($2CH_{Ph}$), 129.0 ($2CH_{Ph}$), 133.8 (CH_{Ph}), 138.4 (C_{Ph}), 153.6 (COH_{Heter}), 159.9, 160.4 (C_{Heter}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3312 (w), 1731 (br, w), 1608 (m), 1417 (m), 1385 (m), 1347 (m), 1304 (m), 1251 (m), 1159 (m), 1093 (s), 1076 (s), 840 (s), 725 (s), 592 (s). HRMS (ESI): calcd for $C_{13}H_{13}ClNO_4S$ ($[M+H]^+$, ^{35}Cl): 314.02483; found: 314.02486. Calcd for $C_{13}H_{12}ClNO_4SNa$ ($[M+Na]^+$, ^{35}Cl): 336.006433; found: 336.00678.