Tetrahedron Letters 51 (2010) 5106–5108

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis and reactions of the first fluoroalkylated 1,3-bis(trimethylsilyloxy)-1,3-butadienes

Stefan Büttner [a], Franziska Bendrath [a], Peter Langer [a,b,*]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
[b] Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

ARTICLE INFO

Article history:
Received 21 March 2010
Revised 15 May 2010
Accepted 19 May 2010
Available online 8 June 2010

Keywords:
Arenes
1,3-Dicarbonyl dianions
Organofluorine compounds
Regioselectivity
Silyl enol ethers

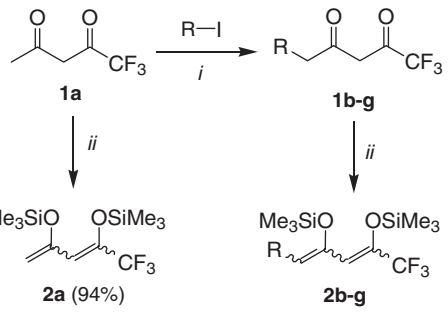
ABSTRACT

The first fluoroalkylated 1,3-bis(silyloxy)-1,3-butadienes have been prepared. Their reaction with oxalyl chloride provides a convenient approach to fluoroalkylated γ-alkylidenebutenolides.

Organofluorine compounds play an important role in medicinal and agricultural chemistry, due to their stereoelectronic properties, solubility, bioavailability, and metabolic stability.[1] Prominent clinically used fluorinated molecules include, for example, 5-fluorouracil (an antineoplastic agent),[2] ciprofloxacin and flurithromycin (antibiotics), fluoxetine (prozac, an antidepressant), faslodex (an antitumor drug), and efavirenz (an antiviral drug).[3,4] Several perfluoroalkyl-substituted molecules show amphiphilic properties and represent promising liquid crystals.[5] Fluoroalkylated compounds are also used as ligands[6] in catalytic reactions, as organocatalysts,[7] and as substrates in palladium catalyzed reactions.[8]

Direct fluorination reactions of arenes and heteroarenes often suffer from low chemo- and regioselectivity or multiple fluorination. An alternative approach to fluorinated molecules relies on the application of a building block strategy. For example, aryl fluorides have been prepared by [4+2] cycloaddition reactions of fluorinated dienes.[9] The synthesis of fluorophenols by annulation reactions of 2,2-difluoro-1,5-diketones has been developed by Portella and co-workers.[10] In recent years, we have studied[11,12] the synthesis of fluorinated arenes based on cyclocondensation reactions of 1,3-bis(trimethylsilyloxy)-1,3-butadienes.[13] Herein, we report the synthesis and reactions of what are, to the best of our knowledge, the first fluoroalkylated 1,3-bis(trimethylsilyloxy)-1,3-butadienes. In this context we also report chain elongation reactions of fluoroalkylated 1,3-diketones by reaction of their dianions with alkyl halides. The cyclization of the new dienes with oxalyl chloride provides a convenient approach to fluoroalkylated γ-alkylidenebutenolides. While butenolides are of considerable pharmacological relevance,[14,15] the fluoroalkylated derivatives reported herein have not been prepared so far. It can be anticipated that they are not readily available by other methods.

The silylation of commercially available 1,1,1-trifluoro-pentane-2,4-dione (**1a**) with trimethylsilyl-trifluoromethanesulfonate (Me_3SiOTf), using the conditions reported by Simchen and coworkers for the silylation of acetylacetone,[16,17] afforded the novel diene **2a** in high yield (Scheme 1). The reaction of the dianion of **1a**, generated by means of LDA (2.3 equiv), with various alkyl



Scheme 1. Synthesis of diketones **1b–g** and dienes **2a–g**: (i) (1) LDA (2.3 equiv), THF, 0 °C, 1 h; (2) R–I, 78 °C→20 °C, 16 h; (ii) NEt_3 (3.0 equiv), TMSOTf (3.0 equiv), Et_2O, 20 °C, 72 h.

* Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412.
E-mail address: peter.langer@uni-rostock.de (P. Langer).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.082

Table 1
Synthesis of diketones **1b–g** and dienes **2b–g**

1,2	R	% (**1**)[a]	% (**2**)[a]
b	*n*Bu	33	98
c	*n*Hex	42	96
d	*n*Oct	59	75
e	*n*Dec	41	95
f	*n*Dodec	55	94
g	CH_2Ph	40	91

[a] Yields of isolated products.

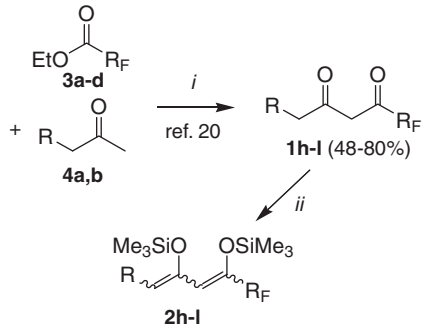
iodides afforded the novel trifluoromethylated 1,3-diketones **1b–g**.[18,19] Diketones **1b–g** were transformed into the dienes **2b–g** in high yields[17] (Table 1).

The reaction of the dianion of **1a** with alkyl halides has, to the best of our knowledge, not been previously reported.[20,21] Röschenthaler and co-workers reported the condensation of **1a** with esters by application of a sequential deprotonation protocol (use of LiH).[22] However, the application of these conditions to the synthesis of **1b–g** proved to be unsuccessful.

Perfluoroalkylated molecules are of relevance as building blocks for the synthesis of liquid crystals and of ligands in fluorinated solvent systems.[5–7] The perfluoroalkylated 1,3-diketones **1h–l** were prepared, following a modified known procedure,[20] by Claisen reaction of the fluorinated esters **3a–d** with acetone (**4a**, R = H) or butan-2-one (**4b**, R = Et) in 48–80% yield (Scheme 2, Table 2). The synthesis of derivatives **1h–k** has been previously reported.[20,23] Diketones **1h–l** were transformed into the novel dienes 2h–**l** in 73–97% yield.[17] 1,3-Diketones **1a–l** exist exclusively in their enol tautomeric form. Dienes **2a–l** exist as inseparable mixtures of *E*/*Z* isomers.

The reaction of dienes **2a–l** with oxalyl chloride in the presence of Me_3SiOTf (0.5 equiv) afforded the novel fluoroalkylated γ-alkylidenebutenolides **5a–l** (Scheme 3, Table 3).[24–26] In contrast, the reaction of the monoanions or dianions of 1,3-diketones **1a–l** with oxalyl derivatives (oxalyl chloride or diethyl oxalate) failed. During the optimization, it proved to be important to use 2.0 equiv of the diene. Butenolides **5a** and **5i**, containing a hydrogen atom located at carbon atom C-4 of the butenolide, were isolated as *E*-configured isomers. The other derivatives, containing an alkyl group located at carbon atom C-4, were isolated as *Z*-configured isomers, due to the steric effect of the alkyl group. The configuration of the products was established based on NOESY experiments. All products were isolated in moderate to good yields (except for **5f**). No systematic trend of the yields could be observed.

In conclusion, we have reported the synthesis of the first fluoroalkylated 1,3-bis(silyloxy)-1,3-butadienes and their application to the synthesis of fluoroalkylated γ-alkylidenebutenolides. Our current studies are directed toward the application of perfluoroalkylated dienes in other cyclocondensation and cycloaddition reactions.

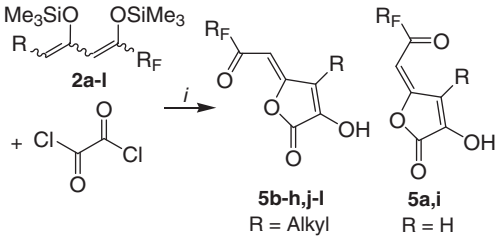


Scheme 2. Synthesis of diketones **1h–l** and dienes **2h–l**: (i) Na, MeOH, 0→20 °C, 16 h; (ii) NEt_3 (3.0 equiv), TMSOTf (3.0 equiv), Et_2O, 20 °C, 72 h.

Table 2
Synthesis of diketones **1h–l** and dienes **2h–l**

3	4	1,2	R_F	R	% (**2**)[a]
a	**b**	**h**	C_2F_5	Et	80
b	**a**	**i**	C_3F_7	H	97
b	**b**	**j**	C_3F_7	Et	80
c	**b**	**k**	C_6F_{13}	Et	77
d	**b**	**l**	C_7F_{15}	Et	73

[a] Yields of isolated products.



Scheme 3. Synthesis of butenolides **5a–l**: (i) TMSOTf (0.5 equiv), CH_2Cl_2, −78 °C→ 20 °C, 16 h.

Table 3
Synthesis of butenolides **5a–l**

5	R_F	R	% (**5**)[a]
a	CF_3	H	54
b	CF_3	*n*Bu	67
c	CF_3	*n*Hex	60
d	CF_3	*n*Oct	35
e	CF_3	*n*Dec	42
f	CF_3	*n*Dodec	20
g	CF_3	CH_2Ph	52
h	C_2F_5	Et	53
i	C_3F_7	H	68
j	C_3F_7	Et	50
k	C_6F_{13}	Et	40
l	C_7F_{15}	Et	54

[a] Yields of isolated products.

Acknowledgment

Financial support by the State of Mecklenburg-Vorpommern is gratefully acknowledged.

References and notes

1. (a)*Fluorine in Bioorganic Chemistry*; Filler, R., Kobayasi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993; (b) Filler, R. *Fluorine Containing Drugs in Organofluorine Chemicals and their Industrial Application*; Pergamon: New York, 1979. Chapter 6; (c) Hudlicky, M. *Chemistry of Organic Compounds*; Ellis Horwood: Chichester, 1992; (d) Kirsch, P. *Modern Fluoroorganic Chemistry*; VCH: Weinheim, 2004; (e) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell Publishing CRC Press, 2004; (f) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Heidelberg, 2008; (g) Tressaud, A.; Haufe, G. *Fluorine and Health*; Elsevier: Amsterdam, 2008.
2. Heidelberger, C.; Chaudhuri, K. N.; Danneberg, P.; Mooren, D.; Griesbach, L.; Duschinsky, R.; Schnitzer, J. R. *Nature* **1957**, *179*, 663.
3. Wong, T. D.; Bymaster, P. F.; Engleman, A. E. *Life Sci.* **1995**, *57*, 411.
4. Roman, L. D.; Walline, C. C.; Rodriguez, J. G.; Barker, L. *Eur. J. Pharmacol.* **2003**, *479*, 53.
5. (a) Stegemeyer, H.; Steinkopff, K. *Liquid Crystals*; Springer: New York, 1994; (b) Miethchen, R.; Hein, M. *Carbohydr. Res.* **2000**, *327*, 169; (c) Hein, M.; Miethchen, R.; Schwäbisch, D.; Schick, C. *Liq. Cryst.* **2000**, *27*, 163; (d) Schwäbisch, D.; Wille, S.; Hein, M.; Miethchen, R. *Liq. Cryst.* **2004**, *31*, 1143; (e) Nicoletti, M.; Bremer, M.; Kirsch, P.; O'Hagan, D. *Chem. Commun.* **2007**, 5075; (f) Kirsch, P.; Hahn, A.;

Fröhlich, R.; Haufe, G. *Eur. J. Org. Chem.* **2006**, 4819. and references cited therein.
6. (a) Schmidbaur, H.; Kumberger, O. *Chem. Ber.* **1993**, *126*, 3; (b) Dinger, M. B.; Henderson, W. *J. Organomet. Chem.* **1998**, *560*, 233; (c) Liedtke, J.; Loss, S.; Widauer, C.; Grützmacher, H. *Tetrahedron* **2000**, *56*, 143; See for example: (a) Schneider, S.; Tzschucke, C. C.; Bannwarth, W. In *Multiphase Homogeneous Catalysis*; Cornils, B., Herrmann, W. A., Horvath, I. T., Leitner, W., Mecking, S., Olivier-Bourbigou, H., Vogt, D., Eds.; Wiley VCH, 2005; p 346. Chapter 4; (b) Clarke, D.; Ali, M. A.; Clifford, A. A.; Parratt, A.; Rose, P.; Schwinn, D.; Bannwarth, W.; Rayner, C. M. *Top. Med. Chem.* **2004**, *7*, 729.
7. Reviews: (a) Wittkopp, A.; Schreiner, P. R.. In *The Chemistry of Dienes and Polyenes*; John Wiley & Sons Ltd, 2000; Vol. 2; (b) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289; See also: (c) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407; (d) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315; (e) Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779; Review: Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.
8. *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.
9. (a) Shi, G.-q.; Cottens, S.; Shiba, S. A.; Schlosser, M. A. *Tetrahedron* **1992**, *48*, 10569; (b) Shi, G.-q.; Schlosser, M. *Tetrahedron* **1993**, *49*, 1445; (c) Patrick, T. B.; Rogers, J.; Gorrell, K. *Org. Lett.* **2002**, *4*, 3155.
10. Lefebvre, O.; Brigaud, T.; Portella, C. *Tetrahedron* **1998**, *54*, 5939.
11. Review: Langer, P. *Synlett* **2009**, 2205.
12. For [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-dienes with 2-fluoro-3-silyloxy-2-en-1-ones, see: (a) Hussain, I.; Yawer, M. A.; Lau, M.; Pundt, T.; Fischer, C.; Reinke, H.; Görls, H.; Langer, P. *Eur. J. Org. Chem.* **2008**, 503; For [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-dienes with trifluoromethyl-substituted 3-ethoxy-2-en-1-ones, see: (b) Mamat, C.; Pundt, T.; Dang, T. H. T.; Klassen, R.; Reinke, H.; Köckerling, M.; Langer, P. *Eur. J. Org. Chem.* **2008**, 492; For reactions of 2-fluoro-1-alkoxy-1,3-bis(silyloxy)-1,3-butadienes, see: (c) Adeel, M.; Reim, S.; Wolf, V.; Yawer, M. A.; Hussain, I.; Villinger, A.; Langer, P. *Synlett* **2008**, 2629; For the synthesis of 3-(perfluoroalkyl)phenols by [3+3] cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 3-silyloxy-1-(perfluoroalkyl)prop-2-en-1-ones, see: (d) Büttner, S.; Lubbe, M.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2008**, *64*, 7968.
13. For a review of 1,3-bis(silyl enol ethers) in general, see: Langer, P. *Synthesis* **2002**, 441.
14. Reviews: (a) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625; (b) Pattenden, G. *Prog. Chem. Nat. Prod.* **1979**, *35*, 133; (c) Gill, M.; Steglich, W. *Prog. Chem. Org. Nat. Prod.* **1987**, *51*, 1; (d) Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287; (e) Negishi, E.-i.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707; For reviews of syntheses of γ-alkylidenebutenolides, see: (f) Brückner, R. *Chem. Commun.* **2002**, 141; (g) Brückner, R. *Curr. Org. Chem.* **2001**, *5*, 679.
15. For a review of the synthesis of butenolides by cyclization reactions of silyl enol ethers with oxalyl chloride, see: Langer, P. *Synlett* **2006**, 3369.
16. Krägeloh, K.; Simchen, G. *Synthesis* **1981**, 30.
17. *General procedure for the synthesis of 1,3-bis(silyloxy)-1,3-butadienes* **2a–l**: To a stirred diethyl ether solution (2 mL per 1.0 mmol of **1**) of **1a–l** (1.0 equiv) were added triethylamine (3.0 equiv) and TMSOTf (3.0 equiv) at 0 °C under an argon atmosphere. The solution was stirred for 30 min at 0 °C. The temperature of the reaction mixture was allowed to rise to 20 °C and the stirring was continued for 3 days. A liquid salt layer separated at the bottom of the flask. The upper layer (ether solution containing the product) was transferred to a dry flask by syringe under argon atmosphere. Diethyl ether (1.5 mL per 1.0 mmol of **1**) was added to the liquid salt layer, the mixture was stirred for 2 min and the layers were allowed to separate by standing for 2 h. The combined ether solutions were concentrated in vacuo to give the pure dienes **2a–l**. Due to their unstable nature, the products had to be immediately used after their preparation.
18. *General procedure for the synthesis of diketones* **1b–g**: To a solution of *n*-butyllithium (2.3 equiv) in THF (3 mL per 1.0 mmol of **1a**) was added diisopropylamine (2.3 equiv) at 0 °C and the mixture was stirred for 30 min followed by dropwise addition of **1a** (1.0 equiv) and subsequent stirring for 1 h at 0 °C. The mixture was cooled to −78 °C and the iodoalkane (1.0 equiv) was added. The temperature of the reaction mixture was allowed to rise to 20 °C during 14 h and, subsequently, hydrochloric acid (10%, 40 mL) was added. The organic layer was separated and extracted with diethylether (3 × 40 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-heptane/EtOAc = 20:1) or by distillation.
19. *1,1,1-Trifluoro-6-phenyl-2,4-hexanedione* (**2g**): Starting with **1a** (1.541 g, 10 mmol), benzyl bromide (1.710 g, 10 mmol), *n*-butyllithium (9.2 mL of a 2.5 M solution in hexanes), and diisopropylamine (3.2 mL, 23 mmol) in THF (30 mL), **2g** was isolated as a colorless liquid (0.966 g, 40%) by distillation; bp = 113–115 °C/1.1 Torr; ^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.73–2.82 (m, 2H, CH_2), 2.99 (t, ^3J = 7.6 Hz, 2H, CH_2), 5.90 (s, 1H, C*H*), 7.15–7.38 (m, 5H, Ar*H*); ^{19}F NMR (235 MHz, DMSO-d_6): δ = −76.6 (CF_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 31.2 (CH_2), 40.2 (CH_2), 96.1 (q, ^3J = 2.0 Hz, C*H*), 117.0 (q, ^1J = 282.3 Hz, CF_3), 126.6 (*C*H), 128.2 (*C*H), 128.7 (*C*H), 139.6 (*C*), 174.9 (q, ^2J = 36.5 Hz, *C*OCF_3), 196.4 (*C*O); IR (ATR, cm^{-1}): ν = 3109 (w), 3088 (w), 3065 (w), 3030 (w), 2932 (w), 2866 (w), 1593 (m), 1497 (w), 1454 (m), 1275 (m), 1196 (s), 1146 (s), 1105 (s), 1077 (m), 1030 (w); MS (EI, 70 eV): *m*/*z* (%) = 244 (M$^+$, 16), 175 (28), 139 (12), 105 (20), 91 (100); HRMS (EI, 70 eV): calcd for $C_{12}H_{11}F_3O_2$ (M$^+$): 244.07057, found 244.06985.
20. The synthesis of **1d** by a different approach has been reported: Hemmilä, I. *Anal. Chem.* **1985**, *57*, 1676.
21. For an isolated example of the reaction of the dianion of **1a** with an aldehyde, see: Tius, M. A.; Hu, H.; Kawakami, J. K.; Busch-Petersen, J. *J. Org. Chem.* **1998**, *63*, 5971.
22. (a) Chizhov, D. L.; Pashkevich, K. I.; Röschenthaler, G.-V. *J. Fluorine Chem.* **2003**, *123*, 267; (b) Sevenard, D. V.; Kazakova, O.; Chizhov, D. L.; Röschenthaler, G.-V. *J. Fluorine Chem.* **2006**, *127*, 983.
23. (a) Moore, R. A.; Levine, R. *J. Org. Chem.* **1964**, *29*, 1439; (b) Park, J. D.; Brown, H. A.; Lacher, J. R. *J. Am. Chem. Soc.* **1953**, *75*, 4753; (c) Nikolaev, V. A.; Kantin, G. P.; Utkin, P. Y. *Russ. J. Org. Chem.* **1994**, 1354; (d) Krokhalev, V. M.; Saloutin, V. I.; Pashkevich, K. I. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1987**, *36*, 1962.
24. Langer, P.; Stoll, M.; Schneider, S. *Chem. Eur. J.* **2000**, *6*, 3204.
25. *General procedure for the synthesis of butenolides* **5a–l**: To a CH_2Cl_2 solution (10 mL) of oxalyl chloride (1.0 mmol) and **2a–l** (2.0 mmol) was added TMSOTf (0.5 mmol) at −78 °C under argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20 °C during 14 h, and, subsequently, a saturated aqueous solution of ammonium chloride (50 mL) was added. The organic layer was separated and extracted with diethylether (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by washing with CH_2Cl_2 or by crystallization.
26. (*Z*)-4-(*n*-Butyl)-3-hydroxy-5-(3,3,3-trifluoro-2-oxopropylidene)furan-2(5*H*)-one (**5b**): Starting with oxalyl chloride (0.296 g, 2.33 mmol), **2b** (1.702 g, 4.8 mmol), and TMSOTf (0.22 mL, 1.2 mmol), **5b** was obtained as a yellowish solid (0.415 g, 67%); mp = 185–187 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.87 (t, ^3J = 7.1 Hz, 3H, CH_3), 1.23–1.44 (m, 4H, CH_2), 2.70 (t, ^3J = 7.4 Hz, 2H, CCH_2), 7.08 (s, 1H, CH); ^{19}F NMR (282 MHz, DMSO-d_6): δ = −70.3 (CF_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.7 (CH_3), 22.3 (CH_2), 23.3 (CH_2), 30.2 (CH_2), 113.5 (q, ^3J = 2.4 Hz, CH), 118.3 (q, ^1J = 273.9 Hz, CF_3), 133.2 (C), 150.0 (C), 150.4 (q, ^2J = 39.2 Hz, $COCF_3$), 161.3 (COH), 177.8 (CO); IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3078 (w), 2959 (m), 2934 (w), 2875 (w), 2747 (w), 2437 (w), 1881 (w), 1721 (m), 1657 (m), 1585 (m), 1468 (w), 1423 (m), 1360 (m), 1328 (w), 1273 (m), 1236 (s), 1229 (s), 1215 (s), 1173 (s), 1154 (s), 1103 (m), 1070 (m), 1029 (m); MS (EI, 70 eV): *m*/*z* (%) = 264 (M$^+$, 68), 247 (26), 235 (20), 219 (100); HRMS (ESI, TOF/MS): calcd for $C_{11}H_{12}F_3O_4$ ([M+H]$^+$): 265.06822, found 265.06809.