Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2745–2747

One-pot synthesis of aryl fluorides by [3+3] cyclization of 1,3-bis(silyl enol ethers) with 2-fluoro-3-silyloxy-2-en-1-ones

Thomas Pundt,[a] Matthias Lau,[a] Ibrar Hussain,[a] Mirza A. Yawer,[a] Helmut Reinke[a] and 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*

Received 19 January 2007; revised 7 February 2007; accepted 9 February 2007
Available online 15 February 2007

Abstract—Functionalized aryl fluorides were regioselectively prepared by [3+3] cyclization of 1,3-bis(silyl enol ethers) with 2-fluoro-3-silyloxy-2-en-1-ones.

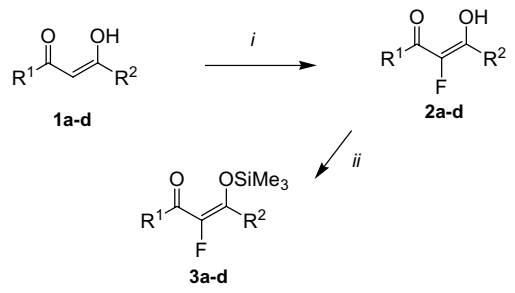
Aryl fluorides are of considerable relevance in medicinal chemistry and also represent important synthetic building blocks.[1] The fluoro group strongly increases the lipophilicity of arenes and heterocycles.[1] In fact, a wide range of important pharmaceutical lead structures contain a functionalized aryl fluoride moiety. Organic fluorides are, in principle, available by fluorination of suitable substrates ('fluorination method') or by synthetic transformation of fluorinated compounds ('building block method') or by combination of these methods.[2] To date, aryl fluorides have been prepared mainly by fluorination of arenes using strong electrophilic fluorination agents (such as fluorine or xenon fluorides).[2] However, these reagents are difficult to obtain or handle, dangerous or (in some cases) very expensive. Selectfluor represents an 'easy-to-handle', commercially available electrophilic fluorination agent.[3] However, the fluorination of non-activated arenes was reported to be unsuccessful (low conversion).[3,4] The fluorination of (activated) anisol has been reported to proceed with 72% conversion. However, a 1:1 regioisomeric mixture of 2- and 4-fluoromethoxyphenol was formed.[4] The reaction of Selectfluor with phenols has been reported to give 4-fluorocyclohexadienones.[5] Therefore, the development of new strategies for the regioselective synthesis of functionalized aryl fluorides is of considerable current interest. Some years ago, Chan and Brownbridge reported[6] an elegant approach to salicylates by cyclization of 1,3-bis(silyl enol ethers)[7] with 3-(silyloxy)alk-2-en-1-ones.[8] Herein, we report a new synthesis of aryl fluorides by formal [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 2-fluoro-3-silyloxy-2-en-1-ones. From a preparative viewpoint, these transformations offer a convenient and regioselective approach to functionalized and sterically encumbered aryl fluorides which are not readily available by other methods. The starting materials—2-fluoro-1,3-diones—are readily available.

2-Fluoro-1,3-diones are available by reaction of 1,3-diketones with, for example, fluorine[9] or *N*-fluorobis(trifluoromethyl)sulfonimide.[10] Recently, a practical method based on the use of Selectfluor has been reported.[11] The microwave mediated reaction of Selectfluor with heptane-3,5-dione (**1a**), 1,3-diphenylpropane-1,3-dione (**1b**), and benzoylacetone (**1c**) afforded 2-fluoro-1,3-diones **2a**–**c** (method A). The reaction of Selectfluor with 2-(methoxybenzoyl)acetone (**1d**)—carried out at 75 °C (4 h)—gave **2d** (method B). The synthesis of 2-fluoro-1,3-dione **2c** has been previously reported (by a different method).[9] The synthesis of **2a**, **2b** and **2d** has, to the best of our knowledge, not yet been reported. The reaction of **2a**–**d** with Me_3SiCl/NEt_3 afforded 2-fluoro-3-silyloxy-2-en-1-ones **3a**–**d** (Scheme 1, Table 1).

The $TiCl_4$ mediated formal [3+3] cyclization of **3a**–**d** with 1,3-bis(silyl enol ethers) **4a**–**g**—prepared from the corresponding 1,3-dicarbonyl compounds in one or two steps[12]—afforded 4-fluorophenols **5a**–**o** in moderate

Keywords: Arenes; Cyclizations; Organic fluorides; Silyl enol ethers.
* Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412; e-mail: peter.langer@uni-rostock.de

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.02.057



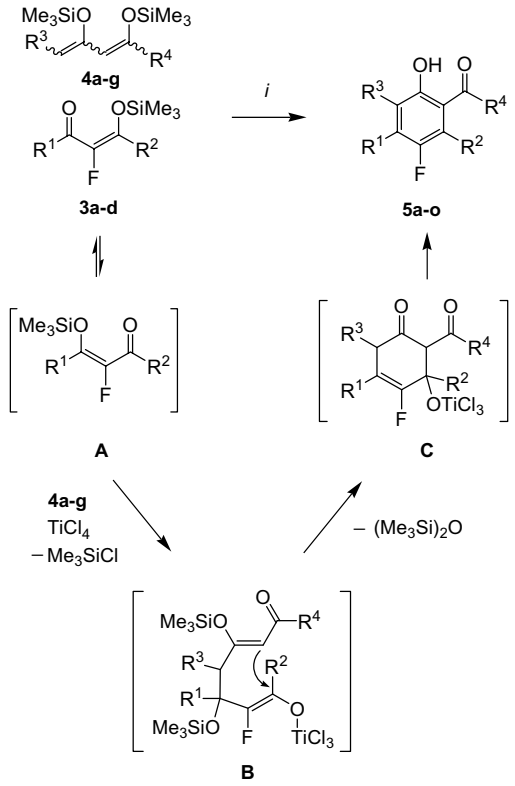
Scheme 1. Synthesis of 3-silyloxy-2-fluoro-2-en-1-ones **3a**–**d**, (i) method A: Selectfluor, microwave, 10 min, 82 °C, CH_3CN; method B: Selectfluor, CH_3CN, 75 °C, 4 h; (ii) Me_3SiCl, NEt_3, C_6H_6, 20 °C.

Table 1. Products and yields

2, 3	R^1	R^2	% (**2**)[a]	% (**3**)[a]
a	Et	Et	71[b]	98
b	Ph	Ph	77[b]	89
c	Me	Ph	88[b]	98
d	Me	2-(MeO)C_6H_4	72[c]	99

[a] Isolated yields.
[b] Method A.
[c] Method B.

to good yields (Scheme 2, Table 2).[13] During optimization of this reaction, the (high) concentration and the temperature played an important role. The cyclization of **4** with **3** proceeds by $TiCl_4$ mediated isomerization of **3** by shift of the silyl group (intermediate **A**), $TiCl_4$



Scheme 2. Synthesis of aryl fluorides **5a**–**o**, (i) $TiCl_4$, CH_2Cl_2, −78→20 °C.

Table 2. Products and yields

3	4	5	R^1	R^2	R^3	R^4	% (**5**)[a]
a	**a**	**a**	Et	Et	H	OMe	32
a	**b**	**b**	Et	Et	H	OEt	42
a	**c**	**c**	Et	Et	H	$O(CH_2)_2OMe$	51
a	**d**	**d**	Et	Et	H	Me	50
a	**e**	**e**	Et	Et	H	Ph	52
b	**a**	**f**	Ph	Ph	H	OMe	82
b	**b**	**g**	Ph	Ph	H	OEt	68
b	**d**	**h**	Ph	Ph	H	Me	30
c	**a**	**i**	Me	Ph	H	OMe	40
c	**c**	**j**	Me	Ph	H	$O(CH_2)_2OMe$	42
c	**d**	**k**	Me	Ph	H	Me	31
c	**e**	**l**	Me	Ph	H	Ph	40
d	**a**	**m**	Me	2-(MeO)C_6H_4	H	OMe	44
d	**f**	**n**	Me	2-(MeO)C_6H_4	Me	OMe	54
d	**g**	**o**	Me	2-(MeO)C_6H_4	Et	OEt	44

[a] Isolated yields.

mediated attack of the terminal carbon atom of **4** onto the carbon located next to substituent R^1 to give intermediate **B** (conjugate addition), cyclization (intermediate **C**), and subsequent aromatization.[6,8] Notably, aryl fluorides **5i**–**o** were formed with very good regioselectivity.

The structure of aryl fluorides **5** was established by spectroscopic methods. The structure of **5f** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[14] The structure of **5i**–**o** was confirmed by NOESY measurements or—for **5i**–**m**—by inspection of the ^4J couplings between the methyl group attached to the benzene moiety and the neighboured aromatic proton. An independent proof was obtained by BBr_3 mediated lactonization of **5m**,**n**. Treatment of **5m** and **5n**

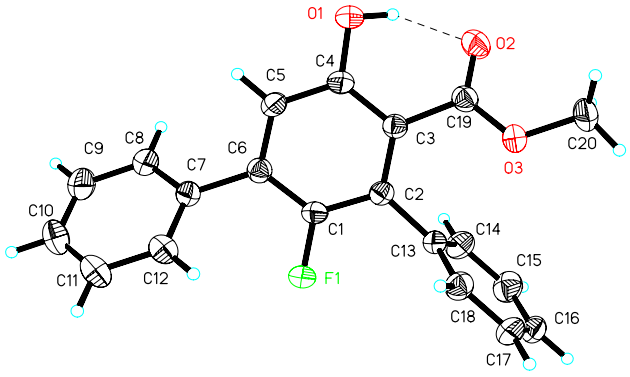
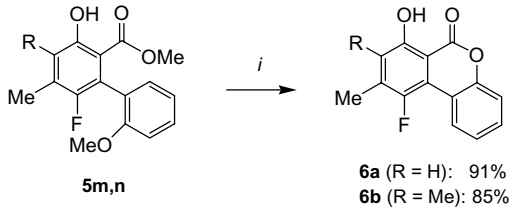


Figure 1. ORTEP plot of **5f**.



Scheme 3. Synthesis of dibenzo[*b*,*d*]pyran-6-ones **6a**,**b**, (i) (1) BBr_3 (4.0 equiv), CH_2Cl_2, 0→20 °C, 18 h; (2) KO*t*Bu, H_2O, 15 min, 20 °C.

with BBr_3 and subsequent addition of an aqueous solution of potassium *tert*-butanolate afforded the novel fluorinated dibenzo[*b*,*d*]pyran-6-ones **6a** and **6b** in good yields, respectively (Scheme 3).

We have reported a new and regioselective synthesis of functionalized 4-fluorophenols based on [3+3] cyclizations of 1,3-bis(silyl enol ethers) with novel 2-fluoro-3-silyloxy-2-en-1-ones.

Acknowledgements

Financial support by the state of Pakistan (HEC scholarships for I.H. and for M.A.Y.) is gratefully acknowledged.

References and notes

1. (a) Kirsch, P. *Modern Fluoroorganic Chemistry*; VCH: Weinheim, 2004; (b) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell Publishing CRC Press, 2004; (c) *Fluorine in Bioorganic Chemistry*; Filler, R., Kobayasi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993; (d) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; Ellis Horwood: Chichester, 1992; (e) Filler, R. *Fluorine Containing Drugs in Organofluorine Chemicals and Their Industrial Application*; Pergamon: New York, 1976, Chapter 6.
2. Reviews: (a) Tredwell, M.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 26; (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119; (c) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, *17*, 2561; (d) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431; (e) Purrington, S. T.; Kagen, B. S.; Patrick, T. B. *Chem. Rev.* **1986**, *86*, 997.
3. Reviews: (a) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem.* **2005**, *117*, 196; *Angew. Chem., Int. Ed.* **2005**, *44*, 192; (b) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31.
4. Banks, R. E.; Besheesh, M. K.; Mohialdin-Khaffaf, S. N.; Sharif, I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2069.
5. Stavber, S.; Jereb, M.; Zupan, M. *Synlett* **1999**, *9*, 1375.
6. Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534.
7. For a review of 1,3-bis(silyl enol ethers) in general, see: Langer, P. *Synthesis* **2002**, 441.
8. For a review of the synthesis of carbacycles by [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 1,3-dielectrophiles, see: Feist, H.; Langer, P. *Synthesis* **2007**, 327.
9. Purrington, S. T.; Bumgardner, C. L.; Lazaridis, N. V.; Singh, P. *J. Org. Chem.* **1987**, *52*, 4307.
10. Xu, Z.-Q.; DesMarteau, D. D.; Gotoh, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 179.
11. Xiao, J.-C.; Shreeve, J. M. *J. Fluorine Chem.* **2005**, *126*, 475, and references cited therein.
12. Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830.
13. *General procedure for the synthesis of aryl fluorides* **5**: To a CH_2Cl_2 solution (2 mL/1 mmol of **3**) of **3** (10.0 mmol) was added **4** (10.0 mmol) and, subsequently, $TiCl_4$ (1.1 mL, 10.0 mmol) at −78 °C. The temperature of the solution was allowed to warm to 20 °C during 14 h with stirring. To the solution was added hydrochloric acid (10%, 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). *Synthesis of methyl 2′-fluoro-5′-hydroxy-[1,1′;3′,1″]terphenyl-4′-carboxylate* (**5f**). Starting with **3b** (0.630 g, 2.0 mmol), **4a** (0.520 g, 2.0 mmol) and $TiCl_4$ (0.25 ml, 2.2 mmol), **5f** was isolated as a colourless solid (0.528 g, 82%); mp = 114–115 °C; $R_f = 0.60$ (toluene). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.46$ (s, 3H, OCH_3), 7.12 (d, $^4J = 6.6$ Hz, 1H, Ar), 7.20–7.50 (m, 8H, Ph), 7.53–7.63 (m, 2H, Ph), 10.64 (s, OH). ^{13}C NMR (75.5 MHZ, $CDCl_3$): $\delta = 51.9$ (OCH_3), 111.6 (d, $^3J = 1.8$ Hz, *C*$COOCH_3$), 118.2 (br s, CH_{Ar}), 127.4, 127.7, 128.5, 128.6 (CH_{Ph}), 128.9 (br s, CH_{Ph}), 129.1 (d, $^4J = 2.9$ Hz, CH_{Ph}), 131.1 (d, $^2J = 20.5$ Hz, C_{Ar}), 134.7 (d, $^3J = 1.4$ Hz, C_{Ph}), 135.6 (br s, C_{Ph}), 135.9 (d, $^2J = 17.6$ Hz, C_{Ar}), 150.0 (d, $^1J = 238.3$ Hz, CF), 157.4 (d, $^4J = 2.4$ Hz, COH), 170.6 ($^4J = 2.4$ Hz, $COOCH_3$). ^{19}F NMR (235 MHz, Cl_3CF): $\delta = -127.6$ (CF). IR (Nujol, cm^{-1}): $\tilde{\nu} = 1669$ (m), 1616 (m), 1601 (m), 1336 (m), 1254 (m), 1222 (m), 1208 (m), 1114 (m). MS (EI, 70 eV): *m*/*z* (%) = 322 (M^+, 62), 291 (30), 290 (100), 262 (34), 233 (48). HRMS (EI, 70 eV): calcd for $C_{20}H_{15}FO_3$ (M^+): 322.09997; found: 322.09939. All products gave satisfactory spectroscopic and analytical and/ or high resolution mass data.
14. CCDC-634352 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; fax: (+44)1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.