Synthetic Methods

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Fluorinating Cleavage of Solid Phase Linkers for Combinatorial Synthesis**

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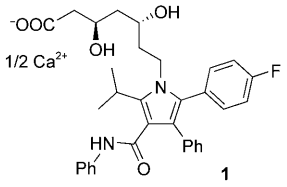
Organofluorine compounds play an increasingly important role in the modern drug discovery process. While the first fluorine-containing agent was developed in the late 1950s,[1] today fluorinated pharmaceuticals and agrochemicals make up about 20% and 30% of their respective global markets.[2] In 2006 two fluorinated drugs, the cholesterol-reducer Lipitor (**1**) and the asthma agent Advair, were the top-selling prescription drugs.[3] Another fluorine-containing blockbuster drug of the last years is the antidepressant Prozac (**2**).



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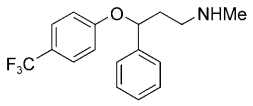

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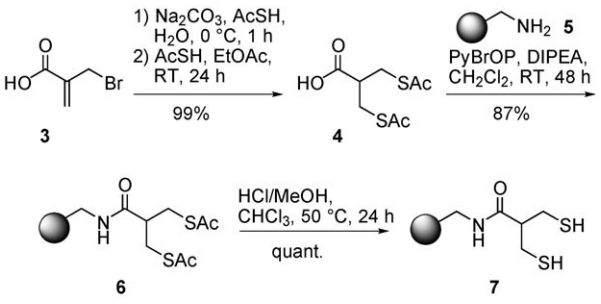
Fluorinated compounds represent a class of particular interest as dramatic changes in the physical properties, the chemical reactivity, and especially the biological activity can be achieved by the introduction of fluorine-containing substituents.[4] However, fluorinated compounds occur only very rarely in nature. A few hundred chlorinated natural products are known but there are only about a dozen fluorine-containing natural products.[5] Therefore, interest in synthesizing organofluorine compounds is steadily increasing and several interesting methods have been developed, particularly in the recent past, for the introduction of fluorine atoms into organic molecules.[6]

The incorporation of fluorine substituents often leads to difficulties in subsequent synthetic steps as a result of the changed electron density in the molecule. For example, fluorine-containing substituents drastically lower the reactivity of aromatic systems in electrophilic substitution reactions, and nucleophilic substitution on aliphatic carbon atoms bearing fluorine groups is hardly possible.[7] Hence, it is advantageous to introduce fluorine atoms into the target structures at a late stage in the synthesis, if possible in the last synthetic step.

We present herein a novel strategy for the preparation of geminal difluoro compounds by using solid-phase synthesis (SPOS) which combines the advantages of SPOS as a well-established method in combinatorial chemistry with the incorporation of fluorine substituents at the end of the synthesis. For this purpose we have developed a linker system that enables the release of the target structures from the resin under simultaneous fluorination.[8]

Kollonitsch and Marburg as well as Katzenellenbogen and co-workers first reported that C–F bonds can be easily generated starting from the corresponding C–S units; an oxidized sulfur species is formed as the leaving group which is displaced by fluoride ion.[9] Based on these observations, we synthesized a dithiane linker on which different aldehydes and ketones were attached, modified, and finally cleaved from the solid support to give *gem*-difluoro compounds.

The precursor **4** of the linker was synthesized starting from 2-(bromomethyl)acrylic acid (**3**) in 99% yield over two steps[10] and subsequently attached to aminomethyl polystyrene resin (**5**, loading 2.06 mmol g^{-1}, 1% DVB = divinylbenzene) using bromotrispyrrolidinophosphonium hexafluorophosphate (PyBrOP) and diisopropylethylamine (DIPEA; Scheme 1). The conversion and the resultant loading of resin **6** with the linker molecule were determined by sulfur elemental analysis. The resin is very stable and can be stored at room temperature. As basic hydrolysis inevitably leads to the formation of the disulfide, the two thioester groups must be cleaved under acidic conditions. The cleavage



Scheme 1. Synthesis of the dithiol linker **7** starting from 2-(bromomethyl)acrylic acid (**3**).

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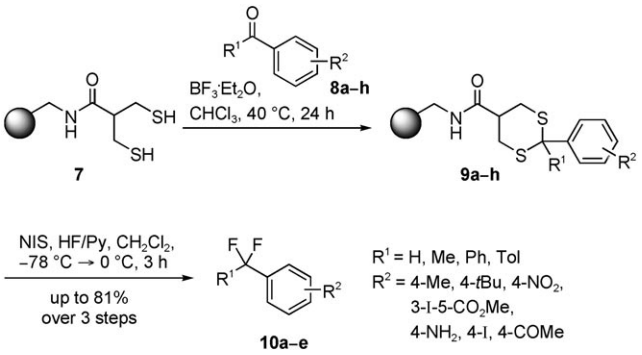
reaction proceeded readily in HCl/methanol at 50 °C to yield the free dithiol linker **7** quantitatively (Scheme 1) and could be monitored by gel-phase ^{13}C NMR spectroscopy.[11]

Aromatic aldehydes and ketones **8a–h** were attached to the free dithiol unit furnishing the corresponding dithanes **9a–h** under Lewis acidic conditions.[12] For cleavage with fluorination, the resins were treated with a combination of *N*-iodosuccinimide (NIS) as the oxidizing agent and HF/pyridine (70 %) as the fluoride source; the *gem*-difluoro compounds **10a–e** were obtained in up to 81 % yield over three steps based upon the loading of resin **6** (Scheme 2).

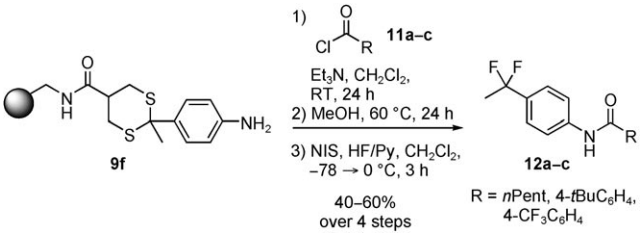


Scheme 2. Attachment of various aldehydes and ketones to a solid support and subsequent cleavage to give *gem*-difluoro compounds.

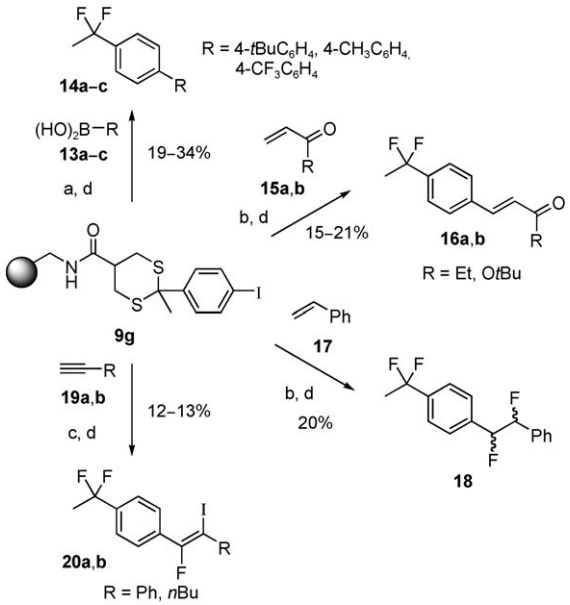
When NIS was replaced by *N*-bromosuccinimide (NBS) or by 1,3-dibromo-5,5-dimethyl-hydantoin (DBH), additional bromination, especially of electron-rich aromatic substrates, was observed as a side reaction. Notable was the high purity of the crude products (> 90 %), which was quantified by ^1H NMR spectroscopy. Besides traces of the corresponding carbonyl compound arising from hydrolysis, only small amounts of succinimide could be detected as impurities. The crude products could be easily purified by column chromatography or by flash filtration when necessary.

To investigate the scope of the novel linker system, compounds **9a** and **9f–h** were modified in different reactions on the solid support and then cleaved from the resin under fluorinating conditions. Resin-bound 4-aminoacetophenone (**9f**) was treated with three different acid chlorides **11a–c** to yield the corresponding amides. As partial double acylation of the amino group caused by an excess of acid chloride was observed, the resins were shaken in methanol for 24 h at 60 °C and the monoacylated products were obtained exclusively. The successful course of the on-bead reactions was monitored qualitatively by gel-phase ^{13}C NMR spectroscopy. The *gem*-difluorinated amides **12a–c** were obtained in 40–60 % yield after cleavage from the resin (Scheme 3). The crude products showed a high purity of 85–90 %.

Different palladium-catalyzed cross-coupling reactions for the formation of C–C bonds were also performed on the dithiane linker system (Scheme 4). The Suzuki coupling was demonstrated on resin-bound 4-iodoacetophenone (**9g**) with the phenyl boronic acids **13a–c**. Fluorinating cleavage afforded the biphenyl derivatives **14a–c** in 19–34 % yield over four steps. The same resin-bound aryl iodide **9g** was



Scheme 3. Amide coupling and subsequent fluorinating cleavage.



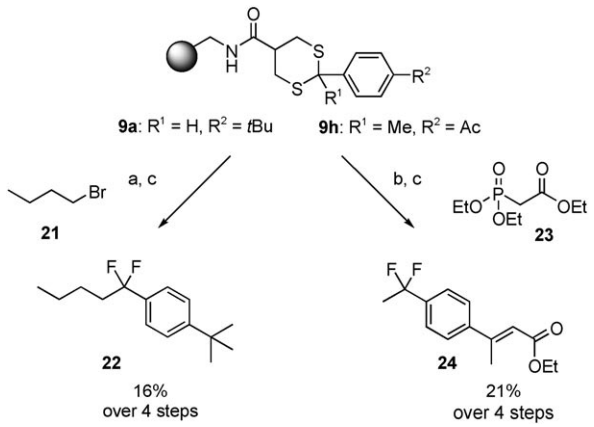
Scheme 4. Palladium-catalyzed cross-coupling reactions and subsequent cleavage: a) **13**, $[Pd(PPh_3)_4]$, K_3PO_4, DMF, 100 °C, 2 d; b) **15** or **17**, $Pd(OAc)_2$, PPh_3, Et_3N, DMF, 100 °C, 2 d; c) **19**, $[Pd(PPh_3)_4]$, CuI, Et_3N, DMF, 80 °C, 2 d; d) NIS, HF/py, −78→0 °C, 3 h (yields over 4 steps).

coupled successfully with terminal olefins in Heck reactions. Olefins bearing electron-withdrawing substituents like a carbonyl or a carboxy group (**15a** and **15b**) proved to be appropriate substrates. The corresponding *gem*-difluorinated compounds **16a** and **16b** were obtained in yields of up to 21 % over four steps. With the olefin **17** bearing an electron-donating phenyl substituent, a vicinal difluorination of the double bond was also observed. Most likely, the electron-rich double bond is initially iodofluorinated under the cleavage conditions. In a second step the iodine exchanges quantitatively with the fluorine, since no iodofluorinated byproduct could be detected in the crude product, which was analyzed by ^1H NMR spectroscopy and GC mass spectrometry.

The solid-supported alkynes obtained by a Sonogashira coupling also underwent an additional iodofluorination reaction to yield selectively the 1-fluoro-2-iodoolefins **20a** and **20b**. These results are consistent with past reports about the reactivity of double and triple bonds in the presence of halogen cations and fluoride sources.[13] Generally the crude products of the cross-coupling reactions showed lower purity after cleavage than those of the amide formation (about 50–

60%) because of residual palladium catalyst, but purification was easily accomplished by using flash filtration.

As dithianes are well established for the umpolung of the carbonyl C atom, this reaction was also investigated. Such transformations on the solid support are quite difficult and only a few examples have been reported.[14] After attachment of 4-*tert*-butylbenzaldehyde to the resin, the resulting dithiane **9a** was deprotonated with *n*-butyllithium and alkylated with butyl bromide (**21**). The corresponding fluorinated compound **22** was obtained in 16% yield over four steps after cleavage (Scheme 5). In another example of the formation of C–C



Scheme 5. Umpolung on the dithiane linker and HWE reaction followed by fluorinating cleavage: a) **9a**, *n*BuLi, THF, −50→−20°C, 4 h, then **21**, −50°C→RT, 15 h; b) **9h**, **23**, KHMDS, [18]crown-6, THF, −78→40°C, 15 h; c) NIS, HF/py, −78→0°C, 3 h.

double bonds on the linker system, solid-supported 4-acetylacetophenone (**9h**) underwent a Horner–Wadsworth–Emmons (HWE) reaction with triethylphosphonoacetate (**23**) in the presence of KHMDS and [18]crown-6. The double bond is stable under the cleavage conditions because of the electron-withdrawing carboxy substituent. The *gem*-difluoro acrylate **24** was isolated in 21% yield over four steps.

In summary, a novel linker system for solid-phase synthesis was developed that enables for the first time the introduction of fluorine substituents into target structures during the cleavage step. This dithiane linker proved to be compatible with different important organic transformations and hence has great potential for the combinatorial synthesis of fluorinated drug structures. We are currently working on the extension of our strategy to other linker systems.

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[1] J. Fried, P. A. Diassi, R. M. Palmers, E. F. Sabo, *J. Am. Chem. Soc.* **1961**, *83*, 4249–4256.
[2] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1887; b) A. M. Thayer, *Chem. Eng. News* **2006**, *23*, 15–24; c) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303–319; d) K. C. Lowe, R. L. Powell, *J. Fluorine Chem.* **2001**, *109*, 1–94.
[3] A. Humphreys, *Med. Ad. News* **2007**, *13*.
[4] a) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637–643; b) P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589; c) J. F. Liebman, A. Greenberg, J. W. R. Dolbier, *Fluorine-containing Molecules: Structure. Reactivity, Synthesis and Applications*, VCH, New York, **1988**; d) R. E. Banks, *J. Fluorine Chem.* **1998**, *87*, 1–17; e) D. O'Hagan, H. S. Rzepa, *Chem. Commun.* **1997**, 645–652; f) F. D. M. Ismail, *J. Fluorine Chem.* **2002**, *118*, 27–33.
[5] D. B. Harper, D. O'Hagan, *J. Fluorine Chem.* **1999**, *100*, 127–133.
[6] a) P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579–2586; b) Y. Hamashima, M. Sodeoka, *Synlett* **2006**, 1467–1478; c) L. Hintermann, A. Togni, *Angew. Chem.* **2000**, *112*, 4530–4533; *Angew. Chem. Int. Ed.* **2000**, *39*, 4359–4362; for a review: d) M. Shimizu, T. Hiyama, *Angew. Chem.* **2005**, *117*, 218–234; *Angew. Chem. Int. Ed.* **2005**, *44*, 214–231; e) M. Schlosser, *Angew. Chem.* **2006**, *118*, 5558–5572; *Angew. Chem. Int. Ed.* **2006**, *45*, 5432–5446; f) J.-A. Ma, D. Cahard, *J. Fluorine Chem.* **2007**, *128*, 975–996.
[7] a) A. D. Allen, F. Shahidi, T. T. Tidwell, *J. Am. Chem. Soc.* **1982**, *104*, 2516–2518; b) H. Matsutani, H. Poras, T. Kusumoto, T. Hiyama, *Chem. Commun.* **1998**, 1259–1260.
[8] There are a few linkers that can be cleaved by fluoride ions, but with none of these systems is fluorine introduced into the target structures. See e.g.: a) R. Ramage, C. A. Barron, S. Bielecki, D. W. Thomas, *Tetrahedron Lett.* **1987**, *28*, 4105–4108; b) M. J. Plunkett, J. A. Ellman, *J. Org. Chem.* **1995**, *60*, 6006–6007; c) M. Wagner, H. Kunz, *Angew. Chem.* **2002**, *114*, 315–319; *Angew. Chem. Int. Ed.* **2002**, *41*, 317–321.
[9] a) J. Kollonitsch, S. Marburg, L. M. Perkins, *J. Org. Chem.* **1976**, *41*, 3107–3111; b) S. C. Sondej, J. A. Katzenellenbogen, *J. Org. Chem.* **1986**, *51*, 3508–3513; c) C. York, G. K. S. Prakash, G. A. Olah, *Tetrahedron* **1996**, *52*, 9–14; d) K. C. Nicolaou, R. Dolle, D. Papahatjis, J. L. Randall, *J. Am. Chem. Soc.* **1984**, *106*, 4189–4192; e) M. Kuroboshi, T. Hiyama, *Synlett* **1991**, 909–910; f) S. Furuta, M. Kuroboshi, T. Hiyama, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 805–819; g) D. P. Matthews, J. P. Whitten, J. R. McCarthy, *Tetrahedron Lett.* **1986**, *27*, 4861–4864; h) T. Fuchigami, T. Fujita, *J. Org. Chem.* **1994**, *59*, 7190–7192.
[10] R. Singh, G. M. Whitesides, *J. Am. Chem. Soc.* **1990**, *112*, 1190–1197.
[11] P. Grice, A. G. Leach, S. V. Ley, A. Massi, D. M. Mynett, *J. Comb. Chem.* **2000**, *2*, 491–495.
[12] a) C. M. Huwe, H. Künzer, *Tetrahedron Lett.* **1999**, *40*, 683–686; b) For an example of a photolabile dithiane linker, see: H. B. Lee, S. Balasubramanian, *J. Org. Chem.* **1999**, *64*, 3454–3460.
[13] G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, I. Kerekes, J. Olah, *J. Org. Chem.* **1979**, *44*, 3872–3881.
[14] a) V. Bertini, F. Lucchesini, M. Porci, A. De Munno, *J. Org. Chem.* **2000**, *65*, 4839–4842; b) Review: N. Ljungdahl, K. Bromfield, N. Kann, *Top. Curr. Chem.* **2007**, *278*, 89–134. For important organometallic reactions on solid supports see, e.g.: c) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem.* **1998**, *110*, 1801–1803; *Angew. Chem. Int. Ed.* **1998**, *37*, 1701–1703; d) C. Milburn, R. R. Milburn, V. Snieckus, *Org. Lett.* **2005**, *7*, 629–631.

