COMMUNICATION

OBC
www.rsc.org/obc

Nucleophilic trifluoromethylation of cyclic imides using (trifluoromethyl)trimethylsilane CF_3SiMe_3†

Anja Hoffmann-Röder, Paul Seiler and François Diederich*
Laboratorium für Organische Chemie, ETH-Hönggerberg, CH-8093, Zürich, Switzerland.
E-mail:diederich@org.chem.ethz.ch

Received 19th May 2004, Accepted 8th July 2004
First published as an Advance Article on the web 27th July 2004

A variety of cyclic five-membered imides was trifluoromethylated in good to excellent chemical yields using (trifluoromethyl)trimethylsilane CF_3SiMe_3 under fluoride ion catalysis. The method was successfully applied to the stereoselective synthesis of trifluoromethylated bi- and tricyclic lactams which could serve as precursors for designed thrombin inhibitors.

The incorporation of fluorinated residues into organic molecules often leads to remarkable changes in their physical, chemical and biological properties and consequently has become a well-established synthetic strategy for the development of new pharmaceuticals, agrochemicals and materials.[1] Among fluorinated bioactive compounds, trifluoromethylated ones have attracted much attention due to the enhanced lipophilicity (*e. g.*, indicated by the Hansch–Leo substituent parameter[2] $\pi_{CF_3} = 0.88$ *vs.* $\pi_{CH_3} = 0.56$) and metabolic stability associated with the trifluoromethyl substituent.[3] Therefore, a wide variety of trifluoromethylation protocols have been developed,[4] among which the use of (trifluoromethyl)-trimethylsilane[5] (Ruppert's reagent, CF_3SiMe_3) as a nucleophilic trifluoromethylating agent has rapidly emerged as the method of choice.[6] Consequently, a quite impressive number of electrophiles, *e.g.*, aldehydes, ketones, esters, imines, enones and alkyl triflates, have been successfully transformed into the desired trifluoromethylated products utilising CF_3SiMe_3 under fluoride ion initiation.[6,7] However, nucleophilic trifluoromethylation reactions of cyclic imides have only been scarcely reported in the literature, despite the fact, that the latter represent important structural elements for natural products and pharmacologically active compounds.[8] Thus, due to deactivation resulting from electron donation from the nitrogen atom to the carbonyl group, nucleophilic trifluoromethylation procedures using CF_3SiMe_3 have so far been mainly described for activated imides such as α-keto amides[9] and imidazolidinetriones.[10] Moreover, it was already shown that protected succinimide,[6a] maleimide,[11] as well as phthalimide,[11] can undergo such trifluoromethylation reactions (Fig. 1), although experimental details for these transformations are not broadly available. Thus, given the relevance of imide-type structural elements for medicinal chemistry together with an increasing interest in fluorinated compounds, a reliable protocol towards the synthesis of trifluoromethylated amides and lactams would be highly desirable.

In the course of our research program directed towards the *de novo* design and synthesis of novel fluorinated non-peptidic thrombin inhibitors,[12] we recently became interested in the selective incorporation of a trifluoromethyl group into the cyclic imide core of some of our designed bi- and tricyclic inhibitor precursors.[13] We therefore decided at first to re-examine the nucleophilic trifluoromethylation reaction of five-membered cyclic imides as model substrates utilising CF_3SiMe_3 under fluoride ion initiation as the trifluoromethide equivalent. After screening of various reaction conditions we were pleased to find that smooth trifluoromethylation of benzylated phthalimide **1** took place upon treatment with two equivalents of CF_3SiMe_3 in the presence of 10 mol% of tetra-*n*-butylammonium fluoride (TBAF·$3H_2O$) in dry

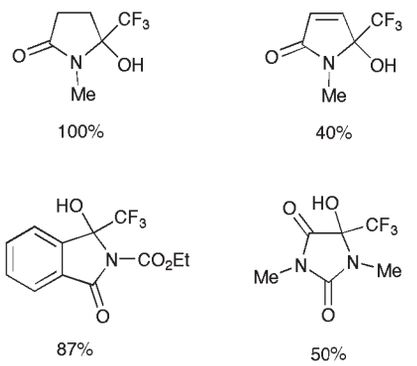
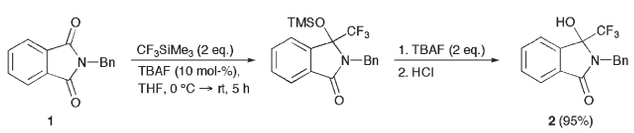


Fig. 1 Trifluoromethylated cyclic imides reported in the literature.

THF. Thus, under these conditions the desired trifluoromethylated lactam **2** was obtained with an excellent chemical yield of 95% after removal of the excess of CF_3SiMe_3 and cleavage of the initially formed silyl ether by equivalent amounts of TBAF (Scheme 1). Interestingly, desilylation was best achieved with 1–2 equivalents of TBAF whereas hydrolysis of the rather stable silyl ether under acidic conditions using aqueous HCl (4 M) did not proceed smoothly but led to mixtures of silylated and non-silylated adducts.



Scheme 1 Nucleophilic trifluoromethylation of cyclic imide **1** with CF_3SiMe_3.

The yield of **2** was found to be substantially higher when solid TBAF·$3H_2O$ was used as fluoride source instead of its conventionally employed solution in THF, which in our hands led to considerable amounts of ring-opened by-products. Moreover, clean conversions were obtained when CF_3SiMe_3 was added to a THF solution of the imide prior to the addition of solid TBAF.‡ In this context, it is also noteworthy, that a reduced amount of CF_3SiMe_3 (1.2–1.5 equivalents) resulted only in sluggish reactions furnishing the desired product **2** in substantially lower chemical yields.

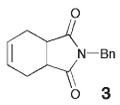
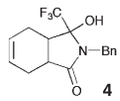
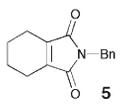
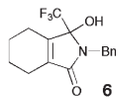
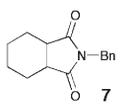
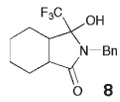
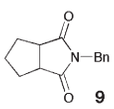
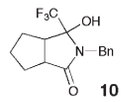
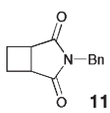
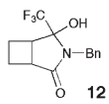
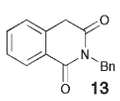
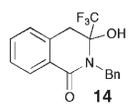
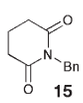
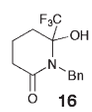
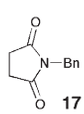
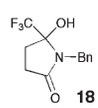
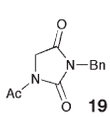
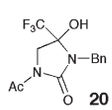
Next, we applied this protocol to a variety of benzylated mono- and bicyclic imides, prepared either by condensation of the corresponding anhydrides with benzylamine or *via* alkylation reactions,[14] and found, that for some substrates the use of CsF or tetramethylammonium fluoride (TMAF) proved to be advantageous over TBAF, leading to cleaner conversions and higher yields of the CF_3-adducts (Table 1). Furthermore, while most of the tested substrates provided the desired trifluoromethylated lactams in good to excellent chemical yields, the corresponding six-membered homophthalimide **13** and glutarimide **15** failed almost completely to undergo the trifluoromethylation reaction (entry 6 and 7). However, in case of hydantoin derivative **20** the low chemical yield should be a consequence of the reduced reactivity resulting from electron donation of the second amide N atom as is further reflected in the longer reaction time and a regioselective attack of the CF_3SiMe_3 at the more reactive upper carbonyl group (entry 9).

Generally, attack of the rather bulky CF_3-nucleophile occurred selectively at the less hindered face of the bicyclic imides provid-

† Electronic supplementary information (ESI) available: synthetic protocols and spectroscopic data for compounds **2**, **12**, **20**, **22** and **24**. See http://www.rsc.org/suppdata/ob/b4/b407555b/

DOI: 10.1039/b407555b

Table 1 Trifluoromethylated cyclic amides prepared according to Scheme 1 (after desilylation with TBAF)

Entry	Imide	Reaction conditions	Product	Yield (%)
1	 **3**	CF_3SiMe_3 (2 eq.), CsF (10 mol%), THF, 0 °C → rt, 4 h	 **4**	99
2	 **5**	CF_3SiMe_3 (2 eq.), CsF (10 mol%), THF, 0 °C → rt, 5 h	 **6**	91
3	 **7**	CF_3SiMe_3 (2 eq.), TBAF (10 mol%), THF, 0 °C → rt, 4 h	 **8**	86
4	 **9**	CF_3SiMe_3 (2 eq.), CsF (10 mol%), THF, rt, 5 h	 **10**	94
5	 **11**	CF_3SiMe_3 (4 eq.), CsF (20 mol%), THF, rt, 16 h	 **12**	79
6	 **13**	CF_3SiMe_3 (2 eq.), CsF (20 mol%), THF, rt, 4 h	 **14**	traces[a]
7	 **15**	CF_3SiMe_3 (3 eq.), TBAF (20 mol%), THF, rt, 6 h	 **16**	none[b]
8	 **17**	CF_3SiMe_3 (2 eq.), CsF (10 mol%), THF, 0 °C → rt, 5 h	 **18**	88
9	 **19**	CF_3SiMe_3 (2 eq.), TMAF (20 mol%), THF, rt, 12 h	 **20**	28[c]

[a] 79% recovery of starting material (s. m.). [b] 50% recov. of s. m. [c] 54% recov. of s. m.

ing single diastereoisomeric trifluoromethylated products, as can be seen from NMR spectra and from the crystal structure of lactam **12** (Fig. 2), which reveals the expected *trans*-configuration between the CF_3-group and the annelated four-membered ring.§

Having established a valuable access to CF_3-substituted bicyclic amides, we then applied this method to the conversion of unsymmetrically functionalised bi- and tricyclic imides to trifluoromethylated lactams which could possibly serve as precursors for novel fluorinated thrombin inhibitors.[12] Thus, treatment of the *endo*-configurated bicyclic imide scaffold **21**[13c,15] under CsF catalysis with four equivalents of CF_3SiMe_3 at 0 °C in THF and subsequent acid hydrolysis furnished trifluoromethylated lactam **22** with a good chemical yield of 59% (Scheme 2).

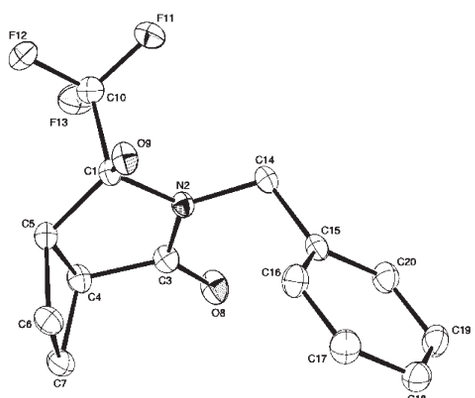
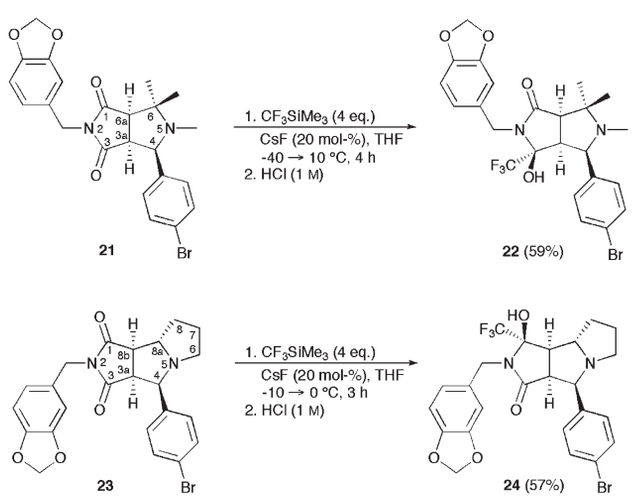


Fig. 2 ORTEP representation of the structure of trifluoromethylated amide **12** (arbitrary atom numbering) with vibrational ellipsoids obtained at 193 K and shown at the 30% probability level.



Scheme 2 Nucleophilic trifluoromethylation of functionalised cyclic imides **21** and **23** with CF_3SiMe_3.

Interestingly, also in this case, a smaller excess of CF_3SiMe_3 such as two equivalents did not lead to complete conversion of the starting amide. Moreover, desilylation of the intermediate silyl ether took place smoothly under acidic conditions with aqueous HCl (1 M), while the use of TBAF led to the formation of additional by-products, presumably again due to ring-opening of the lactam under basic conditions. As it was the case before, nucleophilic attack of the trifluoromethylating agent took place regio- and diastereoselectively at the less hindered position resulting in the incorporation of the CF_3-substituent from the convex *exo*-face of the bicycle and at its lower carbonyl group.

The corresponding trifluoromethylation reaction of the *endo*,*trans*-configurated tricyclic scaffold **23**[13,15] was also accomplished in a regio- and diastereoselective fashion from the *exo*-face, albeit in this case at the upper carbonyl group, furnishing lactam **24** in 57% chemical yield after hydrolysis.

In conclusion, we have developed a reliable protocol for the nucleophilic trifluoromethylation of cyclic five-membered imides using CF_3SiMe_3 in the presence of $TBAF{\cdot}3H_2O$, TMAF or CsF in THF. Application of this method to functionalised bi- and tricyclic imides resulted in the regio- and diastereoselective formation of lactams **22** and **24** in good chemical yields, which could serve as precursors for the synthesis of novel trifluoromethylated thrombin inhibitors. Work towards the extension of this method to the synthesis of other perfluoroalkylated lactams is currently under progress in our laboratories.

This work was supported by the ETH research council. A. H.-R. thanks the Deutsche Forschungsgemeinschaft DFG, for a post-doctoral fellowship (Emmy Noether-Programm).

Notes and references

‡ *Typical experimental protocol for the nucleophilic trifluoromethylation using CF_3SiMe_3:* To a solution of the imide (1.00 mmol) in dry THF (10 cm^3) under N_2 at 0 °C, CF_3SiMe_3 (2.00 mmol) and an appropriate F^- source ($TBAF{\cdot}3H_2O$, CsF or TMAF, 10–20 mol%) were sequentially added. The resulting suspension was stirred for 2–4 h at 0 °C and was slowly warmed to room temperature. A solution of TBAF (1 M in THF, 2.0 cm^3, 2.00 mmol) was added and after 30 min of additional stirring, the mixture was hydrolysed with 2 M HCl (15 cm^3) and extracted with EtOAc (3 × 10 cm^3). The organic layers were washed with 1 M HCl (10 cm^3) and saturated aqueous NaCl solution (10 cm^3), dried ($MgSO_4$) and concentrated *in vacuo.* Purification of the resulting residue by flash column chromatography (SiO_2; hexanes/EtOAc 3 : 1) afforded the desired trifluoromethylated compounds.

§ *Crystal data.* Compound **12**, $C_{14}H_{14}F_3NO_2$ (M_r = 285.26), triclinic, space group $P\bar{1}$, D_c = 1.466 g cm^{-3}, Z = 2, a = 6.4271(3), b = 7.7669(4), c = 14.1095(8) Å, α = 95.290(2)°, β = 94.206(2)°, γ = 111.866(2)°, V = 646.44(6) $Å^3$, T = 193 K, μ = 0.126 mm^{-1}. Approximate crystal size 0.22 × 0.03 × 0.02 mm, 2530 unique reflections collected, R_I = 0.0467 based on 1820 reflections with $I > 2\sigma(I)$, $wR(F^2)$ = 0.1270. CCDC reference number 239185. See http://www.rsc.org/suppdata/ob/b4/b407555b/ for crystallographic data in .cif or other electronic format.

1 (*a*) *Fluorine in Bioorganic Chemistry*, eds. J. T. Welch and S. Eshwarakrishnan, Wiley, New York, 1991; (*b*) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, eds. R. Filler, Y. Kobayashi and L. M. Yagupolskii, Elsevier, Amsterdam, 1993; (*c*) *Organofluorine Chemistry—Principles and Commercial Applications*, eds. R. E. Banks, B. E. Smart and J. C. Tatlow, Plenum Press, New York, 1994; (*d*) T. Hiyama, *Organofluorine Compounds, Chemistry and Applications*, Springer, Berlin, 2000; (*e*) For a recent special issue on "Fluorine in the Life Sciences", see: *ChemBioChem*, 2004, **5**, 557–728.

2 A. Leo, C. Hansch and D. Elkins, *Chem. Rev.*, 1971, **71**, 525–616.

3 (*a*) M. Schlosser and D. Michel, *Tetrahedron*, 1996, **52**, 99–108; (*b*) D. O'Hagan and H. S. Rzepa, *Chem. Commun.*, 1997, 645–652; (*c*) B. E. Smart, *J. Fluorine Chem.*, 2001, **109**, 3–11; (*d*) B. K. Park, N. R. Kitteringham and P. M. O'Neill, *Annu. Rev. Pharmacol. Toxicol.*, 2001, **41**, 443–470.

4 (*a*) M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555–6666; (*b*) P. Lin and J. Jiang, *Tetrahedron*, 2000, **56**, 3635–3671; (*c*) B. R. Langlois and T. Billard, *Synthesis*, 2003, 185–194.

5 I. Ruppert, K. Schlich and W. Volbach, *Tetrahedron Lett.*, 1984, **25**, 2195–2198.

6 (*a*) G. K. S. Prakash and A. K. Yudin, *Chem. Rev.*, 1997, **97**, 757–786; (*b*) R. P. Singh and J. M. Shreeve, *Tetrahedron*, 2000, **56**, 7613–7632; (*c*) G. K. S. Prakash and M. Mandal, *J. Fluorine Chem.*, 2001, **112**, 123–131.

7 Some selected examples: (*a*) T. Brigaud, O. Lefebvre, R. Plantier-Royon and C. Portella, *Tetrahedron Lett.*, 1996, **37**, 6115–6116; (*b*) R. P. Singh, G. Cao, R. L. Kirchmeier and J. M. Shreeve, *J. Org. Chem.*, 1999, **64**, 2873–2876; (*c*) J.-C. Blazejewski, E. Anselmi and M. P. Wilmshurst, *Tetrahedron Lett.*, 1999, **40**, 5475–5478; (*d*) G. K. S. Prakash, M. Mandal and G. A. Olah, *Angew. Chem., Int. Ed.*, 2001, **40**, 589–590; (*e*) D. V. Sevenard, P. Kirsch, G.-V. Röschenthaler, V. N. Movchun and A. A. Kolomeitsev, *Synlett*, 2001, 379–381; (*f*) D. V. Sevenard, V. Ya. Sosnovskikh, A. A. Kolomeitsev, M. H. Königsmann and G. V. Röschenthaler, *Tetrahedron Lett*, 2003, **44**, 7623–7627.

8 Recent examples: (*a*) Z. Mincheva, M. Courtois, J. Crèche, M. Rideau and M.-C. Viaud-Massuard, *Bioorg. Med. Chem.*, 2004, **12**, 191–197; (*b*) S. M. Capitosti, T. P. Hansen and M. L. Brown, *Bioorg. Med. Chem.*, 2004, **12**, 327–336; (*c*) A. Leonardi, D. Barlocco, F. Montesano, G. Cignarella, G. Motta, R. Testa, E. Poggesi, M. Seeber, P. G. De Benedetti and F. Fanelli, *J. Med. Chem.*, 2004, **47**, 1900–1918; (*d*) M. L. López-Rodríguez, D. Ayala, A. Viso, B. Benhamú, R. Fernández de la Pradilla, F. Zarza and J. A. Ramos, *Bioorg. Med. Chem.*, 2004, **12**, 1551–1557; (*e*) K. Kuramochi, Y. Mizushina, S. Nagata, F. Sugawara, K. Sakaguchi and S. Kobayashi, *Bioorg. Med. Chem.*, 2004, **12**, 1983–1989.

9 R. P. Singh, R. L. Kirchmeier and J. M. Shreeve, *J. Org. Chem.*, 1999, **64**, 2579–2581.

10 V. Broicher and D. Geffken, *Arch. Pharm. (Weinheim)*, 1990, **323**, 929–931.

11 S. Kantamneni, PhD Thesis, University of South Carolina, 1993.

12 (*a*) J. A. Olsen, D. W. Banner, P. Seiler, U. Obst-Sander, A. D'Arcy, M. Stihle, K. Müller and F. Diederich, *Angew. Chem., Int. Ed.*, 2003, **42**, 2507–2511; (*b*) J. A. Olsen, D. W. Banner, P. Seiler, B. Wagner, T. Tschopp, U. Obst-Sander, M. Kansy, K. Müller and F. Diederich, *ChemBioChem*, 2004, **5**, 666–675; (*c*) J. Olsen, P. Seiler, B. Wagner, H. Fischer, T. Tschopp, U. Obst-Sander, D. W. Banner, M. Kansy, K. Müller and F. Diederich, *Org. Biomol. Chem.*, 2004, **2**, 1339–1352.

13 (*a*) U. Obst, V. Gramlich, F. Diederich, L. Weber and D. W. Banner, *Angew. Chem., Int. Ed.*, 1995, **34**, 1739–1742; (*b*) U. Obst, D. W. Banner, L. Weber and F. Diederich, *Chem. Biol.*, 1997, **4**, 287–295; (*c*) U. Obst, P. Betschmann, C. Lerner, P. Seiler, F. Diederich, V. Gramlich, L. Weber, D. W. Banner and P. Schönholzer, *Helv. Chim. Acta*, 2000, **83**, 855–909; (*d*) P. Betschmann, S. Sahli, F. Diederich, U. Obst and V. Gramlich, *Helv. Chim. Acta*, 2002, **85**, 1210–1245.

14 M. Ostendorf, R. Romagnoli, I. Cabeza Pereiro, E. C. Roos, M. J. Moolenaar, W. N. Speckamp and H. Hiemstra, *Tetrahedron: Asymmetry*, 1997, **8**, 1773–1789 and cited refs.

15 *Endo*, *exo* refer to the orientation of the 4-bromophenyl ring at C(4) with respect to the bicyclic perhydropyrrolo[3,4-*c*]pyrrole scaffold, and *cis*, *trans* to the position of this ring with respect to the configuration of C(8a) at the fusion of the two pentagons in the perhydropyrrolizidine bicycle; for the synthesis of this scaffold, see ref. 13.