Intramolecular Fluorocyclizations of Unsaturated Carboxylic Acids with a Stable Hypervalent Fluoroiodane Reagent

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Abstract: A new class of fluorinated lactones was prepared by the intramolecular fluorocyclizations of unsaturated carboxylic acids by using the stable fluoroiodane reagent in combination with $AgBF_4$. This unique reaction incorporates a cyclization, an aryl migration, and a fluorination all in one step. The fluoroiodane reagent, prepared easily from fluoride, can also be used without a metal catalyst to give moderate yields within just 1 hour, thus demonstrating that it is a suitable reagent for developing new ¹⁸F-labelled radiotracers for PET imaging.

F luorinated heterocycles, which are highly sought after building blocks for the pharmaceutical and agrochemical industries, can be accessed in a single step by the intramolecular fluorocyclization of alkenes.^[11] γ-Butyrolactones are common structural motifs found in a variety of natural products which exhibit a wide range of biological properties (Figure 1).^[2] Since the benzyl-substituted γ-lactones **3** have



Figure 1. Examples of naturally occurring benzyl-substituted $\gamma\text{-butyro-lactones.}^{[2]}$

shown anticancer and anti-inflammatory activities,^[3e] new synthetic strategies have been developed for their construction,^[3] but as far as we are aware, no one has prepared any fluorinated analogues.

To date, work on the fluorolactonizations of unsaturated carboxylic acids has focused on using fluoraza reagents in combination with a base.^[4] These electrophilic fluorinating reagents have also been used successfully for the preparation of fluorinated cyclic ethers and amines by fluoroetherifica-

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tion^[5] and aminofluorinations.^[6] However, these reagents are normally made from elemental fluorine making them prohibitively expensive for large-scale applications.^[7] Nucleophilic fluoride sources are much more attractive in terms of cost and for the preparation of ¹⁸F-labelled radiotracers for medical diagnostics. Surprisingly, there has only been one report of a nucleophilic fluorolactonization. Difluoroiodotoluene, in the presence of pyridine-6HF, gave fluorinated γ lactones in moderate yields (40–50%).^[8] In contrast, the intramolecular aminofluorinations of alkenes using nucleophilic sources of fluoride have been well-studied for the synthesis of 3-fluoropyrrolidines, 3-fluoropiperidines, and 3fluoroazepanes.^[9] The disadvantage is that most of these reactions used HF-pyridine, which is highly corrosive and has to be handled in specialized Teflon reaction vessels.

As part of our research program on designing new fluorination synthetic strategies,^[10,11] we reported the synthesis of the novel fluorinating reagent 4 based on the cyclic hypervalent iodine(III) skeleton (see Figure 2). The key feature of **4** is that it is easily prepared by nucleophilic fluorinations,^[11a,12b] but it can simulate electrophilic fluorinations with 1,3-dicarbonyl substrates and styrenes to create new C-F bonds.^[11,13] The chelate sidearm makes 4 a much more stable and easy to handle powder compared to the difluoroiodoarenes,^[8,14] and it can be used in standard laboratory glassware.^[15] Earlier this year, Szabó and coworkers demonstrated that 4 can be used for the intramolecular fluorocyclizations of unsaturated amines, alcohols, and malonates in the presence of transition-metal catalysts.^[13b] Herein, we report an unusual reaction which combines an intramolecular fluorocyclization with an arvl migration to deliver novel lactones containing a tertiary alkyl fluoride using 4 and AgBF₄ (Figure 2). In contrast, the fluorolactonizations of unsaturated carboxylic acids with fluoraza reagents are reported to give y-lactones containing a primary alkyl fluoride.^[4a,d] The fluoroiodane 4 therefore provides the unique opportunity to prepare fluorinated analogues of benzyl-substituted y-lactones, which are currently inaccessible with fluoraza reagents.



Figure 2. Overview of fluorolactonizations. Tf = trifluoromethane-sulfonyl.

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Table 1: Optimization of fluorocyclization conditions.[a]



[a] Reaction conditions: **5a** (0.36 mmol), fluoroiodane **4**, and the additive were stirred in CH₂Cl₂ (0.2 mL). No solvent was used in entry 2. 4 Å molecular sieves (0.09 g) were added to the reaction in entries 7–10. [b] Yield determined by ¹H NMR spectroscopy with naphthalene (1.0 equiv) as an internal standard. [c] Reaction conducted in CH₃CN. [d] The reaction was scaled up to 0.71 mmol of **5a**. [e] Yield of isolated product given within parentheses.

To probe the feasibility of an intramolecular fluorocyclization, the preliminary investigation and optimization studies were carried out with 5a (Table 1). Treatment of 5a with 4 and TREAT-HF at 60 °C for 24 hours resulted in an encouraging 35 % yield of 5-benzyl-5-fluorodihydrofuran-2(3H)-one (6a; entry 2). However, 6a was not produced when the fluoroiodane was used without an additive (entry 1) and the addition of KF inhibited the reaction completely (entry 3). In contrast, the introduction of Lewis acids, [Cu(MeCN)₄]PF₆ and AgBF₄ catalytically (entries 4 and 5) or stoichiometrically (entry 6), generated increasing amounts of 4-oxo-5-phenylpentanoic acid (7; up to 75%). We were encouraged by the latter result because 7 was probably formed by the hydrolysis of the competing hydroxy-substituted lactone, 5-benzyl-5hydroxydihydrofuran-2(3H)-one. The addition of 4 Å molecular sieves (entry 7) prevented water competing with fluoride as the nucleophile and changed the reaction completely, thus affording a 76% yield of 6a. When 1.5 equivalents of fluoroiodane were used, the yield increased to 93%, but it dropped slightly to 86% with 0.4 equivalents of AgBF₄. As expected, the fluorocyclization of 5a did not proceed without 4 (entry 10). The reaction proceeded well within just 1 hour at 40°C, thus delivering **6a** in an 81% yield by using 1 equivalent of $AgBF_4$ and 1.5 equivalents of 4 in the presence of 4 Å molecular sieves (entry 11).

The scope of the reaction was probed with a series of unsaturated carboxylic acids and the results are presented in Table 2. The mild reaction conditions were compatible with a number of functional groups on the aromatic ring, including alkoxy (entry 2), alkyl (entry 3), halide (entries 4 and 5), and trifluoromethyl (entry 6) substituents. The fluorinated lactones **6b–f** were each isolated in high yields (65–79%), thus





[a] Reaction conditions: Substrate **5** (0.7 mmol), **4** (1.1 mmol), AgBF₄ (0.7 mmol), and 4 Å molecular sieves (0.18 g) were stirred in CH_2Cl_2 (0.4 mL) at 40 °C for 1 h. [b] Yield determined by ¹H NMR spectroscopy with naphthalene (1.0 equiv) as an internal standard. [c] Yield of isolated product within parentheses.

showing that the reaction was unaffected by the introduction of either electron-donating or electron-withdrawing substituents onto the aromatic ring. The fluorocyclization of 5phenyl-5-hexenoic acid (entry 7) was also studied to investigate if δ -lactones could be accessed using this methodology, but **6g** was isolated in only a moderate yield (38%). Isobenzofuranones are privileged structures which appear in numerous natural products and can have useful biological properties.^[16] On changing the substrate structure to 2-(1phenylvinyl)-benzoic acid (5h) (entry 8), the more electronrich terminal phenyl group underwent the phenyl migration, rather than the aromatic backbone, and the fluorinated isobenzofuranone 6h was isolated in 86% yield. Substitution at the 4-position of the terminal aromatic ring was tolerated well with halides (entries 10 and 11), thus giving high yields (69-76%), but a slightly lower yield was obtained with the methyl substituent (entry 9). In entry 12, however, the aromatic backbone underwent the phenyl migration, thus resulting in a δ -lactone fused to an aromatic ring (61). The low 32% yield was due to elimination problems and formation of the alkene in conjugation with the aromatic ring, thus giving 3-methyl-1H-isochromen-1-one (81) in 12% yield (see the Supporting Information). The novel products generated with 4 are different to those reported from the fluorolactonizations of 5a and 5h with electrophilic fluorinating reagents; these reactions afforded y-lactones containing a primary alkyl fluoride (Figure 3).^[4a,d]

The proposed mechanism for the fluorolactonizations is shown in Figure 4. In the first step the metal catalyst activates the fluoroiodane to form 11 which undergoes an electrophilic addition to the alkene in 5a to give the cyclic iodonium intermediate 12. An intramolecular nucleophilic attack of the



Figure 3. Fluorocyclizations with fluoraza reagents.^[4a,d]



Figure 4. Proposed mechanism for the intramolecular fluorocyclizations.

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hydroxy group occurs at the more-substituted carbon atom because it is better able to stabilize the partial positive charge and is therefore more electrophilic. The π donation of the aromatic ring results in the phenonium ion intermediate **14** with the iodoaryl group acting as an excellent leaving group. Finally, **14** is ring opened by fluoride, thus resulting in **6a** with fluorination at the quaternary center. A similar aryl migration has also been reported in the difluorination of styrenes using **4**, and in the intramolecular lactonization of **5a** with (diacetoxyiodo)benzene.^[13a,17] The same mechanism can be used to rationalize all of the results in Table 2. In compounds **5h–k** the more-electron-rich terminal aromatic ring underwent the aryl migration, whereas in **51** the aromatic backbone underwent the aryl migration to form the δ -lactone **61**.

Since **4** is easily prepared from simple anionic fluoride salts, it is an attractive reagent for preparing ¹⁸F-labelled radiotracers for PET imaging. To explore its potential application for synthesizing ¹⁸F-labelled lactones, we further investigated the fluorocyclization of **5a** using molecular sieves as the only additive (see Table S1 in the Supporting Information). This protocol would ensure that the fluoride could only be provided by **4** and was not coming from the tetrafluoroborate anion of the silver catalyst, as reported by Szabó and co-workers in the difluorination of styrenes.^[13a] Without any metal catalyst we obtained a 63 % yield of **6a** (Scheme 1). A short reaction time is essential in view of the short half-life of ¹⁸F (110 min) and on reducing the reaction time from 18 to



Scheme 1. Fluorocyclization with fluoroiodane 4 and molecular sieves.

1 hours, the yield of **6a** fell from 63 to 46% yield (see Table S1). After further optimization (see Table S1), **6a** was produced in a good 58% yield within just 1 hour at 40 °C in acetonitrile by using 1.5 equivalents of **4**.

This new fluorination protocol was applied to a small series of unsaturated carboxylic acids (Table 3). These promising results suggest that **4** holds great potential for preparing novel ¹⁸F-labelled heterocycles and developing new PET tracers, which are currently inaccessible with conventional nucleophilic fluorination chemistry.

In conclusion, we have developed a new and mild method for the synthesis of fluorinated lactones using the air- and moisture-stable **4** in combination with $AgBF_4$. This unusual reaction combines an intramolecular fluorocyclization with an aryl migration to deliver novel lactones, which contain a tertiary alkyl fluoride. In contrast, the same reactions with fluoraza reagents provide lactones containing a primary alkyl fluoride. Furthermore, the fluorination can also proceed without a metal catalyst in 1 hour, thus demonstrating clearly that **4** is suitable for the production of new ¹⁸F-labelled radiotracers for PET imaging.



Table 3: Fluorocyclizations with 4 and molecular sieves.^[a]



[a] Reaction conditions: Substrate 5 (0.7 mmol), fluoroiodane 4 (1.1 mmol), and 4 Å molecular sieves (0.18 g) were stirred in CH_3CN (0.4 mL) at 40 °C for 1 h. [b] Yield determined by ¹H NMR spectroscopy with naphthalene (1.0 equiv) as an internal standard. [c] Yield of isolated product within parentheses.

Experimental Section

General procedure with metal catalyst: The substrate **5** (0.71 mmol), fluoroiodane **4** (0.30 g, 1.07 mmol), AgBF₄ (0.14 g, 0.71 mmol), and 4 Å molecular sieves (0.18 g) were stirred in dichloromethane (0.4 mL) at 40 °C for 1 h. The solvent was then removed and product **6** was purified by column chromatography.

General procedure without metal catalyst: The substrate 5 (0.71 mmol), fluoroiodane 4 (0.30 g, 1.07 mmol), and 4 Å molecular sieves (0.18 g) were stirred in acetonitrile (0.4 mL) at 40 °C for 1 h. The solvent was then removed and product 6 was purified by column chromatography.

Keywords: cyclizations \cdot fluorine \cdot hypervalent compounds \cdot lactones \cdot silver

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- a) J. R. Wolstenhulme, V. Gouverneur, Acc. Chem. Res. 2014, 47, 3560; b) G. Liu, Org. Biomol. Chem. 2012, 10, 6243; c) S. C. Wilkinson, R. Salmon, V. Gouverneur, Future Med. Chem. 2009, 1, 847.
- [2] a) A. Sari, *Nat. Prod. Res.* 2010, 24, 56; b) C. Zidorn, S. Grass, E. P. Ellmerer, K.-H. Ongania, H. Stuppner, *Phytochemistry* 2006, 67, 2182; c) F. O. Shode, A. S. Mahomed, C. B. Rogers, *Phytochemistry* 2002, 61, 955; d) R. Mali, K. N. Babu, P. G. Jagtap, *J. Chem. Soc. Perkin Trans.* 1 2001, 3017.
- [3] a) M. Peña-López, H. Neumann, M. Beller, *Chem. Commun.* 2015, *51*, 13082; b) C. C. Oliveira, M. V. Marques, M. N. Godoi, T. Regiani, V. G. Santos, E. A. F. dos Santos, M. N. Eberlin, M. M. Sa, C. R. D. Correira, *Org. Lett.* 2014, *16*, 5180; c) H. Qrareya, C. Raviola, S. Protti, M. Fagnoni, A. Albini, *J. Org. Chem.* 2013, *78*, 6016; d) S. Protti, M. Fagnoni, A. Albini, *J. Am. Chem. Soc.* 2006, *128*, 10670; e) J. D. Lambert, J. E. Rice, J. Hong, Z. Hou, C. S. Yang, *Bioorg. Med. Chem. Lett.* 2005, *15*, 873.

- [4] a) D. Parmar, M. S. Maji, M. Rueping, *Chem. Eur. J.* 2014, 20, 83; b) Y. A. Serguchev, L. F. Lourie, M. V. Ponomarenko, E. B. Rusanov, N. V. Ignat'ev, *Tetrahedron Lett.* 2011, 52, 5166; c) L. F. Lourie, Y. A. Serguchev, G. V. Shevchenko, M. V. Ponomarenko, A. N. Chernega, E. B. Rusanov, J. A. K. Howard, *J. Fluorine Chem.* 2006, 127, 377; d) M. Okada, Y. Nakamura, H. Horikawa, T. Inoue, T. Taguchi, *J. Fluorine Chem.* 1997, 82, 157.
- [5] a) D. Parmar, M. Rueping, *Chem. Commun.* 2014, *50*, 13928;
 b) L. F. Lourie, Y. A. Serguchev, M. V. Ponomarenko, E. B. Rusanov, M. V. Vovk, N. V. Ignat'ev, *Tetrahedron* 2013, *69*, 833;
 c) S. C. Wilkinson, O. Lozano, M. Schuler, M. C. Pacheco, R. Salmon, V. Gouverneur, *Angew. Chem. Int. Ed.* 2009, *48*, 7083; *Angew. Chem.* 2009, *121*, 7217.
- [6] a) T. Fujiwara, T. Seki, T. Yakura, Y. Takeuchi, J. Fluorine Chem.
 2014, 165, 7; b) L. E. Combettes, O. Lozano, V. Gouverneur, J. Fluorine Chem. 2012, 143, 167.
- [7] a) P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent, C.-H. Wong, Angew. Chem. Int. Ed. 2005, 44, 192; Angew. Chem. 2005, 117, 196; b) G. S. Lal, G. P. Pez, R. G. Syvret, Chem. Rev. 1996, 96, 1737.
- [8] M. Sawaguchi, S. Hara, T. Fukuhara, N. Yoneda, J. Fluorine Chem. 2000, 104, 277.
- [9] a) J. Cui, Q. Jia, R.-Z. Feng, S.-S. Liu, T. He, C. Zhang, Org. Lett.
 2014, 16, 1442; b) S. Suzuki, T. Kamo, K. Fukushi, T. Hiramatsu, E. Tokunaga, T. Dohi, Y. Kita, N. Shibata, Chem. Sci. 2014, 5, 2754; c) W. Kong, P. Feige, T. de Haro, C. Nevado, Angew. Chem. Int. Ed. 2013, 52, 2469; Angew. Chem. 2013, 125, 2529; d) Q. Wang, W. Zhong, X. Wei, M. Ning, X. Meng, Z. Li, Org. Biomol. Chem. 2012, 10, 8566.
- [10] a) M. Fornalczyk, K. Singh, A. M. Stuart, *Chem. Commun.* 2012, 48, 3500; b) M. Fornalczyk, K. Singh, A. M. Stuart, *Org. Biomol. Chem.* 2012, 10, 3332.
- [11] a) G. C. Geary, E. G. Hope, K. Singh, A. M. Stuart, *Chem. Commun.* 2013, 49, 9263; b) G. C. Geary, E. G. Hope, K. Singh, A. M. Stuart, *RSC Adv.* 2015, 5, 16501.
- [12] a) C. Y. Legault, J. Prevost, *Acta Crystallogr. Sect. E* 2012, 68, 01238; b) V. Matoušek, E. Pietrasiak, R. Schwenk, A. Togni, *J. Org. Chem.* 2013, 78, 6763.
- [13] a) N. O. Ilchenko, B. O. A. Tasch, K. J. Szabó, Angew. Chem. Int. Ed. 2014, 53, 12897; Angew. Chem. 2014, 126, 13111; b) W. Yuan,
 K. J. Szabó, Angew. Chem. Int. Ed. 2015, 54, 8533; Angew. Chem. 2015, 127, 8653.
- [14] a) T. Kitamura, S. Kuriki, M. H. Morshed, Y. Hori, Org. Lett.
 2011, 13, 2392; b) M. A. Arrica, T. Wirth, Eur. J. Org. Chem.
 2005, 395; c) M. Sawaguchi, S. Ayuba, S. Hara, Synthesis 2002, 1802.
- [15] The thermal stability of fluoroiodane 4 and some of its precursors were investigated using differential scanning calorimetry (see Table S2 in the Supporting Information) and the results show that it is safe to use 4 up to 100 °C.
- [16] R. Karmakar, P. Pahari, D. Mal, Chem. Rev. 2014, 114, 6213.
- [17] A. C. Boye, D. Meyer, C. K. Ingison, A. N. French, T. Wirth, Org. Lett. 2003, 5, 2157.

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