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Use of Fluoroalkyl as a Latent Group for Internal Alkylation: Application to the Synthesis of Bridged Tetrahydrofluorenones

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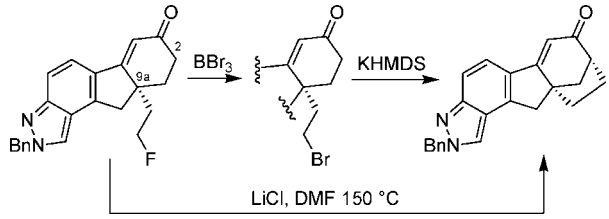
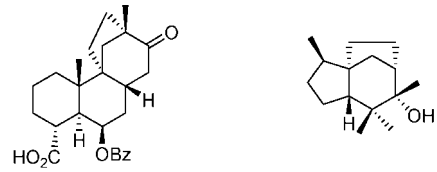
ABSTRACT



Tetrahydrofluorenones which possess a C9a-fluoroalkyl substituent were efficiently converted to tetrahydrofluorenones which contain a ring bridging C9a−C2. Conditions include a stepwise sequence of conversion to an alkyl bromide followed by treatment with base, and a direct cyclization by treatment with lithium chloride in DMF heated to 150 °C.

Natural product syntheses often feature the use of an intramolecular alkylation α to a ketone to form a bridging ring. Internal alkylations are featured in the syntheses of the skeleton of Scopadulcic Acid B **1**,[1] and of (−)-prezizanol **2** and related compounds[2] (Figure 1). In both of these cases, a sulfonate, ultimately derived from ozonolysis and subsequent reduction of an allyl substituent, was used as the leaving group.

Generally regarded as unreactive, alkyl fluorides are rarely used as alkylating agents in organic synthesis. However, recent reports describe the use of *tert*-alkyl and allyl fluorides for intermolecular alkylation mediated by boron trifluoride or organoaluminums.[3] These powerful reactions occur by abstraction of fluoride to generate a carbocation. An important limitation of these methods is that primary alkyl fluorides were found to be unreactive. However, primary alkyl fluorides have been successfully coupled with β-phenylethyl Grignard reagents in Zr-catalyzed reactions and with vinyl Grignard reagents in Ni-catalyzed alkylative dimerization reactions.[4] Additionally, magnesium enamides have been efficiently alkylated with primary alkyl fluorides and cyclohexyl fluoride to provide α-alkylated ketones upon hydroly-



1 Scopadulcic acid B **2** (-)-Prezizanol

Figure 1. Natural product syntheses which feature an intramolecular alkylation.

(1) Tagat, J. R.; Puar, M. S.; McCombie, S. W. *Tetrahedron Lett.* **1996**, *37*, 8463–8466.
(2) Sakurai, K.; Kitahara, T.; Mori, K. *Tetrahedron.* **1990**, 761–774.
(3) (a) Ooi, T.; Uraguchi, D.; Kagoshima, N.; Maruoka, K. *Tetrahedron Lett.* **1997**, *32*, 5679–5682. (b) Hirano, K.; Fujita, K.; Yormitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2004**, *45*, 2555–2557. (c) Hirano, K.; Hideki, Y.; Oshima, K. *Org. Lett.* **2004**, *26*, 4873–4875.

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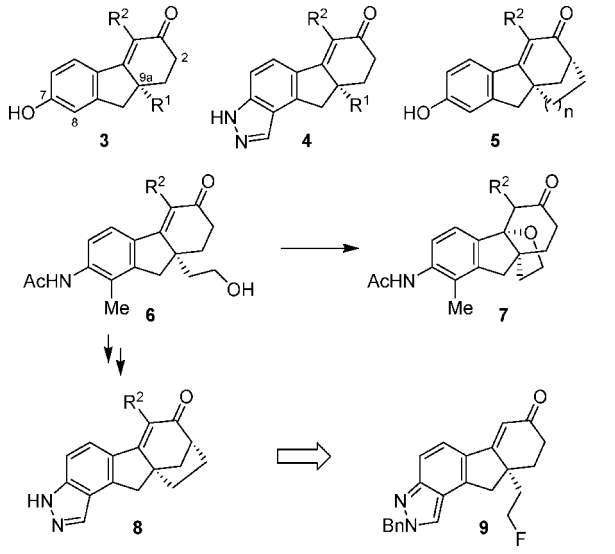
sis; however, there were no examples of enamides derived from enones.[5]

Halogen exchange of alkyl fluorides is also known.[6] Boron trihalides are particularly effective for this reaction, owing in part to the strength of the resulting boron−fluoride bond.[6c] However, this reaction has seen limited use in synthesis.[7] One potential novel application of this reaction would be to use an alkyl fluoride appended to a synthetic intermediate so that it can be later activated for intramolecular alkylation. In this way the fluoride would represent a valuable alternative to a protected alkoxide with several important advantages: alkyl fluorides are relatively stable to a variety of conditions, they are often more easily introduced than their alkoxy counterparts, and they can be directly activated to a better leaving group without the need for a deprotection step. Furthermore this tactic would be particularly useful in cases where a free hydroxyl group would not be tolerated, e.g., due to incompatible functionality.

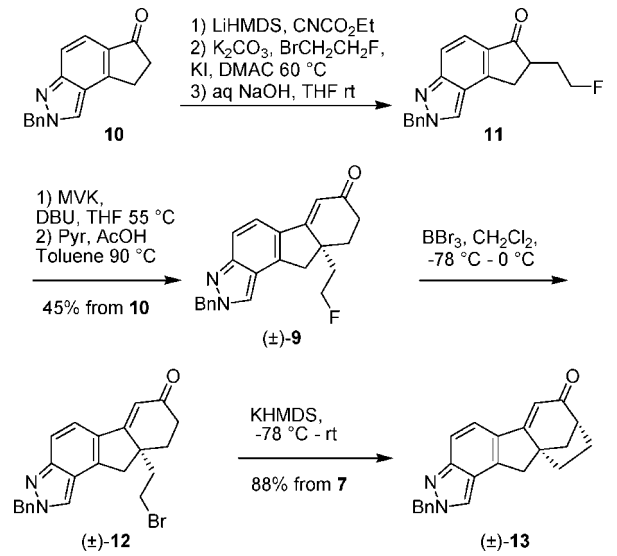
Scheme 1



Phenolic tetrahydrofluorenones **3** and fused pyrazolotetrahydrofluorenones **4** are potent selective classes of ligands for the estrogen receptor β (ERβ) (Scheme 1.[8] We have recently reported an important subclass of the phenolic tetrahydrofluorenones in which an alkyl bridge connects C9a and C2 **5**.[9,10] In the course of our efforts to make bridged analogues in the fused-pyrazolo-class **8**, we encountered difficulties that forced us to improve their synthesis. Initially, we had successfully prepared compounds represented by **8** from a C9a-alkoxy intermediate **6** which often required protection as an acetate or benzyl ether. To undergo an intramolecular alkylation reaction the C9a-alkoxy substituent was converted to a mesylate or a triflate to obtain the desired bridged compound. In some cases, this route was complicated by the formation of a cyclic ether **7** by intramolecular Michael reaction of carbinol **6**.[11] Often, but not always, the resulting ether could be opened and thus remain synthetically useful. However, this undesired reaction prompted us to explore a route to **8** that would feature the use of a tetrahydrofluorenone intermediate **9** substituted with a C9a-alkyl fluoride, which would serve as the latent bridging ring.

We demonstrated the effectiveness of this strategy by the synthesis of **13**, an important intermediate in the preparation of C9a−C2 ethyl-bridged pyrazolotetrahydrofluorenones (Scheme 2).

Scheme 2



Pyrazoloindanone **10**,[12] was alkylated with fluoroethyl bromide to give **11**, which was converted to the tetrahydrof-

(4) (a) Terao, J.; Watabe, H.; Kambe, N. *J. Am. Chem. Soc.* **2005**, *127*, 3656–3657. (b) Terao, J.; Kambe, N. *Bull. Chem. Soc.* **2006**, *79*, 663–672.

(5) Hatakeyama, T.; Ito, S.; Yamane, H.; Nakamura, M.; Nakamura, E. *Tetrahedron.* **2007**, *63*, 8440–8448.

(6) (a) Olah, G. A.; Narang, S. C.; Field, L. D. *J. Org. Chem.* **1981**, *46*, 3727–3728. (b) Rozov, L. A.; Lessor, R. A.; Kudzma, L. V.; Ramig, K. *J. Fluorine Chem.* **1998**, *88*, 51–54. (c) Namavari, M.; Satyamurthy, N.; Barrio, J. R. *J. Fluorine Chem.* **1995**, *72* (1), 89–93.

(7) Theodoridis, G. *Tetrahedron Lett.* **1998**, *39*, 9365–9368.

(8) (a) Wilkening, R. R.; Ratcliffe, R. W.; Tynebor, E. C.; Wildonger, K. J.; Fried, A. K.; Hammond, M. L.; Mosley, R. T.; Fitzgerald, P. M. D.; Sharma, N.; McKeever; Nilsson, S.; Carlquist, M.; Thorsell, A.; Locco, L.; Katz, R.; Frisch, K.; Birzin, E. T.; Wilkinson, H. A.; Mitra, S.; Cai, S.; Hayes, E. C.; Schaeffer, J. M.; Rohrer, S. P *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3489–3494. (b) Wilkening, R. R.; Ratcliffe, R. W.; Fried, A. K.; Meng, D.; Sun, W.; Colwell, L.; Lambert, S.; Greenlee, M.; Nilsson, S.; Thorsell, A.; Mojena, M.; Tudela, C.; Frisch, K.; Chan, W.; Birzin, E. T.; Rohrer, S.; Hammond, M. L *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3896–3901.

(9) Wildonger, K. J.; Ratcliffe, R. W.; Mosley, R. T.; Hammond, M. L.; Birzin, E. T.; Rohrer, S. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4462–4466.

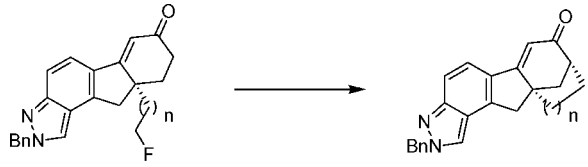
(10) We have referred to compounds in this paper as substituted derivatives of 1,2,9,9a-tetrahydro-3*H*-fluoren-3-ones. The IUPAC name for the ring system represented by **9** is 8,9,9a,10-tetrahydroindeno[2,1-*e*]indazol-7(3*H*)-one; the ring system of **13** is 3,9,10,11-tetrahydro-8,10a-methanoazuleno[2,1-*e*]indazol-7(8*H*)-one; **15** is a 2,8,9,10,11,12-hexahydro-7*H*-8,11a-methanocycloocta[3,4]cyclopenta[1,2-*e*]indazol-7-one; **18a** is a gibba-1,3,4a(10a),4b-tetraen-6-one−methane (1:2); **18c** is a 7,8,9,10-tetrahydro-7,10a-methanocycloocta[*a*]inden-6(11*H*)-one.

(11) Mori et al. observed a similar result. See ref 2.

(12) Experimental details for the preparation of **10** are included in the Supporting Information.

luorenone **9** by Robinson annulation in 45% yield from **10**. Treatment of **9** with boron tribromide gave **12**, which was treated with potassium hexamethyldisilylamide to give **13** in 88% yield. Compound **13** can then be functionalized to give biologically interesting analogues such as those represented by **8**. Additional examples of this novel strategy are shown in Tables 1 and 2.

Table 1. Cyclization of Fluoroalkyl Pyrazolotetrahydrofluorenones



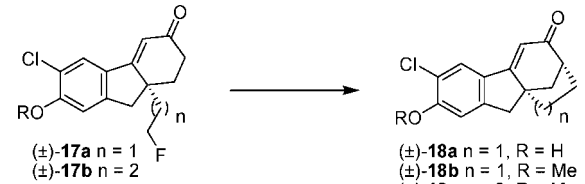
(±)-**9** n = 1
(±)-**14** n = 2

(±)-**13** n = 1
(±)-**15** n = 2

entry	substrate	conditions	yield	product
1	**9**	LiCl, DMF, 150 °C	80−90%	**13**
2	**9**	KHMDS, THF −78 °C to rt	30%	**13**
3	**9**	K_2CO_3, KI, DMAc	N.R.[a]	
4	**9**	DBU, THF 70 °C	N.R.[a]	
5	**14**	(1) BBr_3; (2) KHMDS	74%	**15**

[a] Isolated starting material.

Table 2. Cyclization of Anisolic Fluoroalkyl Tetrahydrofluorenones



(±)-**17a** n = 1
(±)-**17b** n = 2

(±)-**18a** n = 1, R = H
(±)-**18b** n = 1, R = Me
(±)-**18c** n = 2, R = Me

entry	substrate	conditions	yield	product
1	**17a**	LiCl, DMF, 150 °C	67−90%	**18a**
2	**17a**	KHMDS, THF −78 °C to rt	73%[a]	**18b**
3	**17b**	LiCl, DMF, 150 °C	N.R.[b]	
4	**17b**	KHMDS, THF rt	N.R.[c]	
5	**17b**	(1)BBr_3; (2) KHMDS	67%	**18c**

[a] 93:7 product:s.m. by ^{1}H NMR. [b] Major product in a complex reaction mixture is the alkyl chloride. [c] Isolated starting material.

An alternative to the stepwise cyclization of fluoroethyl compound **9** to the ethyl-bridged compound **13** was found. Treatment of **9** with lithium chloride at 150 °C cleanly afforded **13** (presumably through an intermediate alkyl chloride) in 80−90% yield (Table 1, entry 1). In a rare example of alkylation by direct displacement of a primary alkyl fluoride, KHMDS affected cyclization of **9** in modest yield (entry 2). However, other bases such as potassium carbonate or DBU (which works for the cyclization of **12**) gave no reaction.

This method was also useful in the preparation of phenolic bridged tetrahydrofluorenones **5**.[13] In the case of the construction of a phenolic tetrahydrofluorenone, the lithium chloride cyclization is a particularly powerful reaction (Table 2). Applying the chemistry from Scheme 2, 4-chloro-5-methoxyindanone **16** was converted to 9a-fluoroethyl **17a** and 9a-fluoropropyl **17b** tetrahydrofluorenones.[14] When treated with lithium chloride in DMF at 150 °C, compound **17a** undergoes cyclization and demethylation[15] of the anisole to give compound **18a**. Due to the competing demethylation, the bidged, anisolic tetrahydrofluorenone, **18b**, could not be obtained by this method.[16] However, **18b** was accessible in useful yield by treatment of **17a** with KHMDS (entry 2). Propyl-bridged **18c** could only be obtained by the original stepwise manner (entries 3, 4, and 5).

In summary, we have developed a strategy for the construction of bridged tetrahydrofluorenones that features the use of a fluoroalkyl substituent as the latent bridging ring. We believe this strategy to be novel for the construction of bridged cycloalkenone compounds. Several conditions were successful to affect the cyclization. While the stepwise conversion with boron tribromide followed by base was more general, the lithium chloride cyclization has been a powerful reaction in our laboratories, particularly when phenolic analogues are desired. Further discussion of the ERβ activity of these bridged tetrahydrofluorenones will follow in due course.

Acknowledgment. The authors thank Amanda Makarewicz (Department of Preparative Chemistry and Separations, Merck and Co., Inc.) for a large-scale preparation of **10**.

Supporting Information Available: Experimental procedures and spectral data, including a procedure for the preparation of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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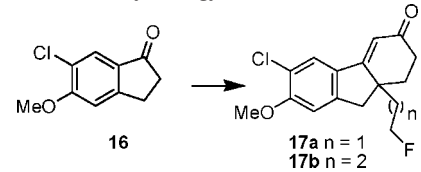
(13) For a related report, see: Scott, J. P.; Ashwood, K. M.; Brands, K. M. J.; Brewer, S. E.; Cowden, C. J.; Dolling, U. H.; Emerson, K. M.; Gibb, A. D. ; Goodyear, A. ; Oliver, S. F. ; Stewart, G. W. ; Wallace, D. J. *Org. Process Res. Devel.* Published to the Web Nov. 10, 2007; DOI 10.1021/op700178q.

(14) 4-Chloro-5-methoxyindanone **16** (Di Stefano, A.; Sozio, P.; Grazia, L.; Cacciatore, I.; Moscaiatti, B.; Costa, B.; Pinnen, F. *Farmaco* **2002,** *57*, 303–313.) was converted by analogy to Scheme 2 to **17a** and **17b**.



16 **17a** n = 1
17b n = 2

(15) Bernard, A. M.; Ghiani, M. R.; Piras, P. P.; Rivoldini, A. *Synthesis* **1989**, 287–289.

(16) On the basis of LC-MS and ^{1}H NMR we suspect that the cyclization proceeds through the C9a-ethyl chloride intermediate, which went to approximately 5% upon heating at 100 °C overnight. Trace cyclization, but also trace demethylation, is observed at 120 °C. At temperatures required to make the cyclization reaction practical (>130 °C), demethylation of both **17a** and **18b** is competitive. Thus, we were unable to use these conditions to cleanly obtain **18b**.