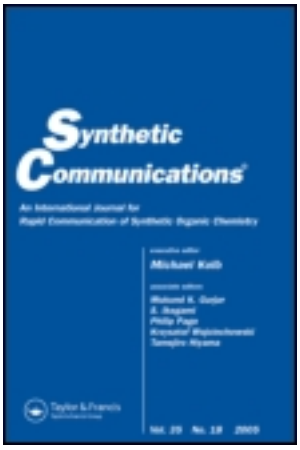

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New Methodology for the Synthesis of α,α-difluoroketones

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New Methodology for the Synthesis of α,α-Difluoroketones

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Abstract: A new methodology is described for the synthesis of α,α-difluorinated ketones by the addition of organolithium reagents to α,α-difluoro-N-methoxy-N-methyl amides (Weinreb amides).

Keywords: α,α-Difluoroketones; α,α-Difluoro-N-methoxy-N-methyl amides; Pyruvic acid

The growing importance of fluorinated compounds in pharmaceutical[1] and agrochemical[2] industry emphasizes the need for the development of new methodologies for the synthesis of fluorinated compounds. In medicinal chemistry, fluorine is often introduced at metabolically labile sites[1c] to improve the metabolic stability of the drug candidates. Fluorine can also be used to improve the physicochemical properties of drug molecules,[1e] such as lipophilicity or basicity. Increasingly, in medicinal chemistry, fluorine has been used to enhance the binding affinity[1c,f] of the drug candidate to the target proteins. Our own involvement in the design and synthesis of a very potent class of fluorine containing CXCR2-CXCR1 dual antagonists[3] for treating various inflammatory diseases required the synthesis of various α,α-difluoroketones **1**. The unsuccessful α-fluorination (Figure 1) of the furylethylketone **3** using the standard enolate fluorination[4] and attempts of various unsuccessful Friedel–Crafts acylations[5] of substituted furans with α,α-difluoroacid chlorides led to the exploration of an alternate route for the synthesis of α,α-difluoroketones.

Although other cumbersome methods are available for the α-fluorination[6] of ketones, we were interested in developing a simple

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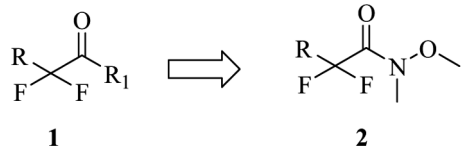


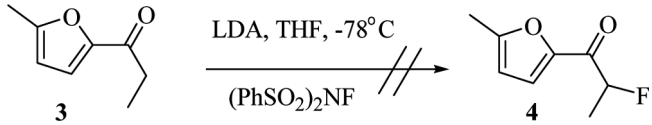
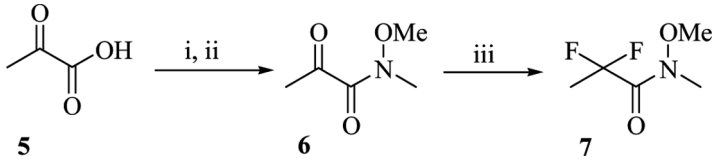


Figure 1. Unsuccessful electrophilic fluorination.

and general synthesis of difluoroketones from the readily available β-keto acids or from the commercially available α,α-difluoro-carboxylic acids. Herein, we report a simple and general route for the synthesis of α,α-difluoroketones **1** from the corresponding Weinreb amides **2** by the addition of aryl and hetero aryllithium reagents.

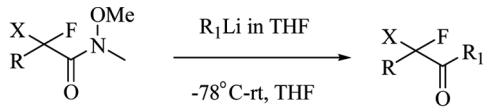
The commercially available pyruvic acid **5** was converted to the corresponding acid chloride by treatment with oxalyl choride, and subsequent treatment with N,O-dimethylhydroxylamine hydrochloride and triethylamine afforded the Weinreb amide **6**. The amide **6** was converted to the corresponding difluoroamide **7** by treatment with diethylaminosulfurtrifluoride[7] (DAST) in dichloromethane in good yield (Scheme 1). The amides **8** and **9** were prepared from the corresponding α,α-difluoro and α-fluoro phenyl acetic acids through their acid chlorides and further treatment with N,O-dimethylhydroxylamine hydrochloride and triethylamine.

Having obtained the difluoroamide **7**, the addition of in situ prepared 2-lithiofuran[8] afforded the desired ketone **10** in 82% yield. Similarly, ketones **11–14** were obtained in very good yield by the addition of the corresponding lithiofurans to difluoroamides **7** and **8**. The lithiofurans



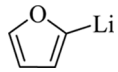
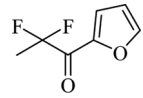
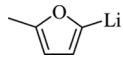
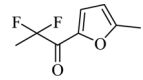
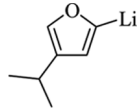
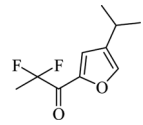
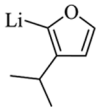
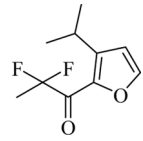
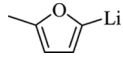
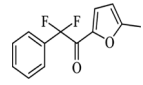
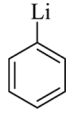
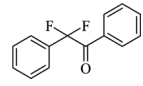
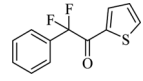
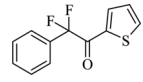
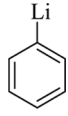
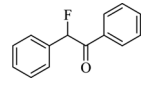
Scheme 1. Reagents and conditions: i) Oxalylchloride, CH_2Cl_2, rt, 3 h, 80%, ii) $CH_3ONHCH_3 \cdot HCl$, Et_3N, CH_2Cl_2, 0 °C–rt, 82%, iii) DAST, CH_2Cl_2, reflux, 24 h; 70%.

Table 1. Addition of R_1Li to the fluoro Weinreb amides



7, R = CH_3, X = F
8, R = Ph, X = F
9, R = Ph, X = H

Ketones; **10-18**

Entry	R_1Li	Amide	Product (ketone)	Yield (%)	Purity (%)
1		7	 **10**	82	97
2		7	 **11**	85	91
3	(a) 	7	 **12**	55	88
	(b) 	7	 **13**	32	90
4		8	 **14**	89	91
5		8	 **15**	90	97
6		8	 **16**	86	96
7		9	 **17**	85	98
8		9	 **18**	82	96

were prepared in situ from 2-methylfuran and 3-isopropylfuran[9] by treatment with n-butyl lithium at −78 °C. In the case of 3-isopropyl furan, treatment of n-butyllithium generated a mixture of regioisomeric lithiofurans, which in turn produced regioisomeric ketones **12** and **13** as the major and minor products respectively (Table 1). Phenyl lithium and thienyl lithium addition to the amides **8** and **9** produced the corresponding ketones (**15–18)** in excellent yields.

In conclusion, we have developed a new simple methodology for the convenient synthesis of various α,α-difluoro-aryl and hetero-aryl ketones from the readily available difluoro Weinreb amides. These ketones can be further converted to the corresponding difluoroalcohols or amines. This methodology is very simple and straightforward compared to the existing enolate fluorination to make difluorinated compounds.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Inova spectrometer (500 MHz for ^{1}H NMR; 125 MHz for ^{13}C NMR, 470 MHz for ^{19}F NMR) using TMS as an internal standard for ^{1}H NMR and ^{13}C NMR and $FCCl_3$ for ^{19}F NMR). Infrared spectra were obtained on an ATI Mattson genesis series FTIR. LCMS was recorded on a PE SCIEX API 150 EX single-stage quadrupole mass spectrometer. Thin-layer chromatography (TLC) analysis was performed on silica-gel plates (Analtech silica-gel GF plates). All products were purified by flash-column chromatography using Whatman purasil 60 A silica gel (230–400 mesh).

General Procedure for the Synthesis of Difluorinated Amide 7

DAST (7.36 g, 0.0456 mol) was added to a solution of the keto-amide **6** (3.0 g, 0.0228 mol) in CH_2Cl_2 at 0 °C under an N_2 atmosphere. The reaction mixture was brought to room temperature during an hour and heated at 50 °C for 24 h. The reaction mixture was cooled to 0 °C, carefully treated with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2(100 mL). The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The solution was filtered over anhydrous sodium sulfate, and removal of the solvent under reduced pressure gave the crude product, which was purified by column chromatography using dichloromethane and n-pentane (1:10) to afford the difluoro-amide **7**(2.6 g; 74%) as a colorless liquid.

Compound **7**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.72 (3H, s), 3.24 (3H, s), 1.81 (3H, t, $J = 19$ z); ^{13}C NMR (125 MHz, $CDCl_3$): 164.1, 117.0 (t, $J_{C\text{-}F} = 249$ Hz), 61.8, 32.8, 21.55 (t, $J_{C\text{-}F} = 25$ Hz); ^{19}F NMR

(470 MHz, $FCCl_3$ in $CDCl_3$): −97.33 (s); LCMS (m/z): 154.0 $(M+H)^+$, 134. purity = 96%.

General Procedure for the Synthesis of Difluorinated Ketones (10–18)

n-BuLi in hexane (5.2 mL, 0.01339 mol) was added dropwise to a solution of the 2-methyl furan (1 g, 0.0122 mol) in anhydrous ether (15 mL) at −78 °C. The reaction mixture was warmed to room temperature, than heated at 40 °C for 45 min. The reaction mixture was cooled to −78 °C and a solution of the difluorinated amide **7** (2.23 g, 0.0146 mol) in anhydrous ether was added. The reaction mixture was stirred at −78 °C for 4 h, slowly warmed to room temperature, and stirred continuously for 2 h. The reaction mixture was then cooled to 0 °C and carefully treated with saturated aqueous NH_4Cl solution. The reaction mixture was extracted with ether (50 mL); the combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The solution was filtered, and the solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography using ethyl acetate and hexane (1:10) to afford the difluoro-ketone **11** (1.7 g, 80%) as a colorless liquid.

Compound **11**: IR ν_{max} (film) cm^{-1}: 2950, 1765, 1512, 1462, 1286; ^1H NMR (500 MHz, $CDCl_3$): δ 7.4 (1H, m), 6.24 (1H, $J = 3.5$ Hz, 0.8 Hz;d of q), 2.41 (3H, s); 1.82 (3H, t, $J = 19$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 177.0 (t, $J_{C\text{-}F} = 31.7$ Hz), 160.7, 146.7, 125.1, 118.5 (t, $J_{CF} = 249$ Hz), 109.7, 20.8 (t, $J_{CF} = 25.3$ Hz), 14.1; ^{19}F NMR (470 MHz, $FCCl_3$, in $CDCl_3$): −95.97 (2F, q, J = 19.2 Hz). Purity = 91%.

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REFERENCES

1. (a) Isanbor, C.; O'Hagan, D. Fluorine in medicinal chemistry: A review of anticancer agents. *J. Fluorine Chem.* **2006**, *127*, 303–319; (b) Ismail, F. Important fluorinated drugs in experimental and clinical use. *J. Fluorine Chem.* **2002**, *118*, 27–33; (c) Park, B. K.; Kitteringham, N. R.; O'Neill, P. M. Metabolism of fluorine containing drugs. *Ann. Rev. Pharmacol. Toxicol.* **2001**, *41*, 443–470; (d) Reiss, J. G. Fluorine in our arteries. *New J. Chem.* **1995**, *19*, 891–909; (e) Park, B. K.; Kitteringham, N. R. Effects of fluorine on drug metabolism.

Drug Metabolism Rev. **1994**, *26*, 605–643; (f) Shengguo, S.; Adeboye, A. Fluorinated molecules as drugs and imaging agents in the CNS. *Curr. Top Med. Chem.* **2006**, *6*, 1457–1464; (g) Kirk, K. L. Fluorine in medicinal chemistry: Recent therapeutic applications of fluorinated small molecules. *J. Fluorine Chem.* **2006**, *127*, 1013–1029.

2. Dicciani, N. K. Fluorine. *Chem. Engin. News* **2003**, *58*, 48.
3. (a) Dwyer, M. P.; Yu, Y.; Chao, J.; Aki, C.; Chao, J.; Biju, P.; Girijavallabhan, V.; Rindgen, D.; Bond, R.; Mayor-Ezel, R.; Jakway, J.; Hipkin, R. W.; Fossetta, J.; Gonsiorek, W.; Bian, H.; Fan, X.; Terminelli, C.; Fine, J.; Lundell, D.; Merritt, J. R.; Rokoz, L. L.; Kaiser, B.; Li, G.; Wang, W.; Stauffer, T.; Ozgur, L.; Baldwin, J.; Taveras, A. G. Discovery of 2-hydroxy-N,N-dimethyl-3-{2-[[(R)-1-(5-methylfuran-2-yl)propyl]amino]-3,4-dioxocyclobut-1-enylamino}benzamide (SCH 527123): A potent, orally bioavailable CXCR2/CXCR1 receptor antagonist. *J. Med. Chem.* **2006**, *49*, 7603–7606; (b) Widdowson, K. L.; Elliot, J. D.; Veber, D. F.; Nie, H.; Rutledge, M. C.; McCleland, B. W.; Xiang, J.-N.; Jurewicz, A.; White, J. R.; Sarau, H. M. Evaluation of potent and selective small molecule antagonist for the CXCR2 chemokine receptor. *J. Med. Chem.* **2004**, *47*, 1319–1321.
4. Hill, B.; Liu, Y.; Taylor, S. D. Synthesis of α-fluorosulfonamides by electrophilic fluorination. *Org. Lett.* **2004**, *6*, 4285–4288, and references cited therein.
5. Fritz-Lanhals, E. Synthesis of optically active (2-fluoroacyl) benzenes. *Synlett* **1999**, *11*, 1805–1807.
6. (a) Ayuba, S.; Yoneda, N.; Fukuhara, T.; Hara, S. Fluorination of sulfides using IF_5-$Et_3N.3HF$. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1597–1604; (b) Stavber, G.; Zupan, M.; Jereb, M.; Stavber, S. Selective and effective fluorination of organic compounds in water using selectfluor F-TEDA-BF_4. *Org. Lett.* **2004**, *6*, 4973–4976; (c) Ridge, D. N.; Hanifin, J. W.; Harten, L. A.; Johnson, B. D.; Menschick, J.; Nicolau, G.; Sloboda, A. E.; Watts, D. E. Potential anti-arthritic agents, 2: Benzoylacetonitriles and *β*-amino cinnamonitrile. *J. Med. Chem.* **1979**, *22*, 1385–1389.
7. (a) Koch, G.; Loiseleur, O.; Altmann, K. H. Total synthesis of 26-fluoroepothilone B. *Synlett* **2004**, *4*, 693–697; (b) Golubev, A. S.; Schedel, H.; Radics, G.; Fioroni, M.; Thust, S.; Burger, K. Hexafluoroacetone as a protecting and activating reagent 5,5-difluoro- and trans-5-fluoropipecolic acids from glutamic acid. *Tetrahedron Lett.* **2004**, *45*, 1445–1447; (c) Singh, R. P.; Shreeve, J. M. Recent advances in nucleophilic fluorination reactions of organic compounds with Deoxofluor and DAST. *Synthesis* **2002**, *17*, 2561–2578.
8. Jen, K. Y.; Cava, M. P. Improved synthesis of aromatic diselenides. *J. Org. Chem.* **1983**, *48*, 1449–1451.
9. (a) Chadwick, D. J.; Chambers, J; Hargraves, H. E.; Meakins, G. D.; Snowden, R L. Preparation of substituted furan- and thiophene-2-carboxaldehydes and -2-[2H]carboxaldehydes, and of 2-furyl ketones. *J. Chem. Soc., Perkin Trans.* **1973**, *20*, 2327–2332; (b) Gilman, H.; Calloway, N. O.; Burtner, R. R. Orientation in the furan series, IX: The Friedel–Crafts reaction with 2-furfural. *J. Am. Chem. Soc.* **1935**, *57*, 906–907.