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Aromatic N-N Exchange Reactions of N,N-Dimethylamino *gem*-Difluorinated Heterocycles. A Convenient Synthesis of New 5-Imidazol-1-yl α,α-Difluoroketones.

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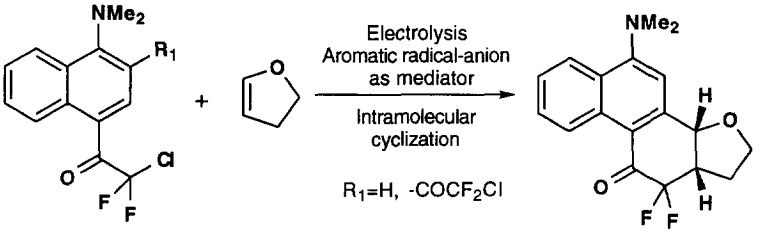
Abstract: Aromatic nucleophilic substitution reaction of N,N-dimethylamino α,α-difluoroketones **2** and **3** in anhydrous dimethylsulfoxide, with several tetramethylammonium salts of imidazole as nucleophiles including imidazole, benzimidazole, imidazole-2-carboxaldehyde, 2-(4'-methoxyphenyl)imidazole and 2-methyl-5-nitro imidazole proceeds under mild conditions to give the corresponding nitrogen-nitrogen exchanged products **4-12** in moderate to good yields. Copyright © 1996 Elsevier Science Ltd

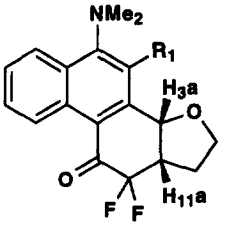
An increasing interest has been paid for several years to the chemistry of various fluorine-containing heterocycles due to their unique physical properties, specific chemical reactivity, and their remarkable potential bilogical activity[1]. Many selectively fluorinated analogues of biologically important compounds have demonstrated dramatic enhancement in their biological activity[2]. Important efforts have been made toward the synthesis of compounds containing a difluoromethylene group adjacent to a carbonyl group[3], because α,α-difluoroketones have been successfully used as inhibitors of hydrolytic enzymes, and greatly enhanced biological activity has been reported compared with their nonfluorinated analogues[2]. Methods for the preparation of *gem*-difluorocyclic compounds through the reactions of the corresponding carbonyl compounds with fluorinating reagents such as DAST[4] have some limitations due to low yield and lack of functional group selectivity. A new method for the preparation of *gem*-difluorocyclic compounds is thus highly desirable[5].

Recently we found a novel and practical method for the synthesis of heterocyclic α,α-difluoroketones involving free-radical electrochemical addition of 2-chloro-1-(4-dimethylamino-naphthalen-1-yl)-2,2-difluoro-ethanone and of 2-chloro-1-[3-(chloro-difluoro-acetyl)-4-dimethylamino-napthalen-1-yl]-2,2-difluoro-ethanone (which are easily prepared from *N,N*-dimethyl-1-naphthylamine and chlorodifluoroacetic anhydride) on olefinic substrates such as 2,3-dihydrofuran, n-butyl vinyl ether and N-vinyl imidazole followed by intramolecular cyclization of the resulting γ,γ-difluoroalkyl radical[6]:

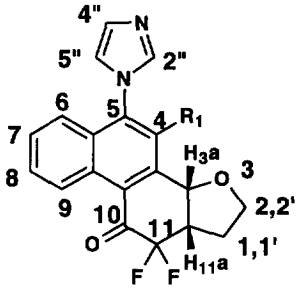


N,N-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine was found to undergo various nitrogen-nitrogen, nitrogen-sulfur and nitrogen-oxygen exchange reactions to give interesting trifluoromethylated heterocycles[7]. We wish herein to report a facile synthetic method based on the methodology of M. Hojo et al[7]. for preparing some new substituted *gem*-difluoro heterocycles **4-12** of significant interest, by reaction of the heterocyclic α,α-

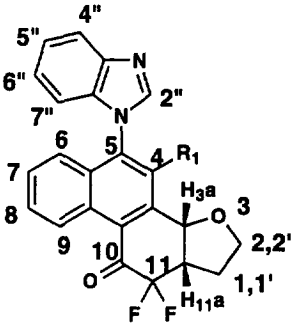
difluoroketones **2** and **3** with imidazole nucleophiles such as imidazole, benzimidazole, 2-(4'-methoxyphenyl)imidazole, imidazole-2-carboxaldehyde and 2-methyl-5-nitro imidazole:



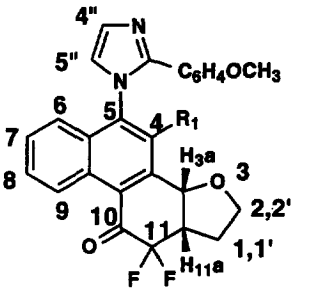
R_1=H, **1**
R_1=-$COCF_2Cl$, **2**
R_1=-$COCF_2H$, **3**



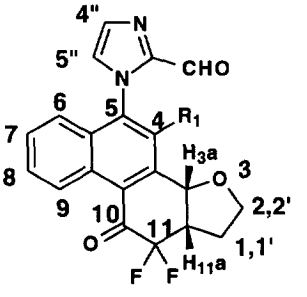
R_1=-$COCF_2Cl$, **4**
R_1=-$COCF_2H$, **5**



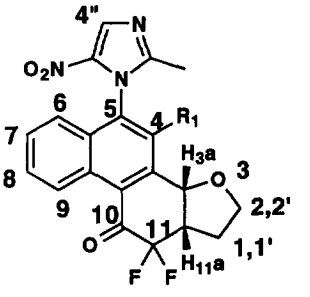
R_1=-$COCF_2Cl$, **6**
R_1=-$COCF_2H$, **7**



R_1=-$COCF_2Cl$, **8**



R_1=-$COCF_2Cl$, **9**
R_1=-$COCF_2H$, **10**



R_1=-$COCF_2Cl$, **11**
R_1=-$COCF_2H$, **12**

In first attempts, the *gem*-difluoro ketones 4-(chloro-difluoro-acetyl)-5-dimethylamino-11, 11-difluoro-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one **2** and 4-difluoroacetyl-5-dimethylamino-11, 11-difluoro-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one **3**[6] were mixed with free -NH imidazole and heated in refluxing acetonitrile for 24 hours; the corresponding exchanged products **4** and **5** were obtained in 35% and 25% isolated yields, after nucleophilic displacement of the -NMe_2 group. Besides the desired substituted products, other fluorinated products (not isolated) were observed by ^{19}F NMR analysis of the crude

reaction mixture. However, milder conditions using dried tetramethylammonium salt of imidazole ([$NuNMe_4$]/[Substrate]=3) in anhydrous DMSO, at 50°C for 10 hours, were found to be more effective for the synthesis of the exchanged products **4** (65%) and **5** (55%); probably the better yields could be explained by a higher nucleophilicity of the anion of imidazole. Imidazole-2-carboxaldehyde and 2-methyl-5-nitro imidazole anions, less reactive nucleophiles, gave exchanged products in moderate yields with increasing the concentration of the nucleophiles ([$NuNMe_4$]/[Substrate]=10) (Table 1). 2-(4'-methoxyphenyl)imidazole, despite the increasing electron density on the imidazole ring reacts poorly as compare to imidazole anion. This unsatisfactory result maybe explained by a repulsive effect between the chloro or difluoroacetyl group and the methoxyphenyl ring. The products which represent the remaining balance material were the unreacted starting material (major compound) and other yet unidentified products (as observed by HPLC and ^{19}F NMR of the raw solution). Longer reaction time and/or higher temperatures resulted in the decomposition of the exchanged products into the unidentified products observed by HPLC and ^{19}F NMR. The nucleophilic substitution reaction was found to be regiospecific as the -N(1) isomer was isolated as the sole product. The presence of the electro-withdrawing groups, $-COCF_2Cl$ and $-COCF_2H$ on the phenanthren ring, is necessary so as to activate the substitution of the dimethylamino group and it was found that the yields are generally higher with the chloro-difluoroacetyl substituent. Attempts to react the α,α-difluoroketone **1** with imidazole anion resulted in recovery of the starting material. Formation of the substituted products was monitored by HPLC and the yields are moderate to good. The structures of compounds **4-12** obtained after column chromatography, were confirmed by their spectral and analytical data[8].

Table 1: Synthesis of the 5-Imidazol-1-yl α,α-Difluoroketones

Substrate[a]	Nucleophile[b]	Product (%)[c]
4-(chloro-difluoroacetyl)-5-dimethylamino-11,11-difluoro-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one **2**	Imidazole	**4** (65)
	Benzimidazole	**6** (71)
	2-(4'-Metoxyphenyl)imidazole	**8** (32)
	Imidazole-2-carboxaldehyde[d]	**9** (45)
	2-Methyl-5-nitro imidazole[d]	**11** (40)
4-difluoroacetyl-5-dimethylamino-11,11-difluoro-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one **3**	Imidazole	**5** (55)
	Benzimidazole	**7** (48)
	Imidazole-2-carboxaldehyde[d]	**10** (32)
	2-Methyl-5-nitro imidazole[d]	**12** (25)

a: C_{sub}= $1.58x10^{-3}$ mol + C_{NuNMe_4}= $4.73.0x10^{-3}$ mol in anhydrous DMSO at 50°C for 10 hours. b: used as the tetramethylammonium salt. c: isolated yield. d: C_{sub}= $1.58x10^{-3}$ mol + C_{NuNMe_4}= $15.8x10^{-3}$ mol in anhydrous DMSO at 50°C for 10 hours.

The *gem*-difluoroketones **3** as well as **5**, **7**, **10** and **12** can also be synthesized from the chloro-difluoroacetylated ketones **2**, **4**, **6**, **9** and **11** by reductive dechlorination either by constant potential electrolysis in DMSO + 0.1M Et_4NBF_4 at - 1.60V vs SCE (on a carbon felt cathode) in the presence of large excess of acetic acid (2.5F/mole, isolated yields close to 45%) or under milder conditions (refluxing EtOH, 3-5 hours, isolated yields close to 70%) using sodium formaldehyde sulfoxylate (Rongalit)[9].

The present procedure may be utilized as a facile and convenient synthetic method for fluorine-containing naphthalen-fused heterocycles which are difficulty accessible by other methods. The present reaction can be

extended to bifunctional reagents as nucleophiles and is applicable to the syntheses of various fluorine containing heterocycles. We are now extending such reactions (including other nitrogen bases as nucleophiles) to the substrates presented in this letter as well as to other aromatic α,α-difluoroketones prepared by our free-radical electrochemical approach. Evaluation of biological activities for **1-3** as well as **4-12** will be done in a due course.

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7. Some interesting syntheses of fluorine heterocycles were achieved by various aromatic nucleophilic N-N, N-S and N-O exchange reactions followed by cyclizations using N,N-dimethyl-2,4-bis(trifluoroacetyl)-1-napthylamine as substrate: Okada, E.; Masuda, R.; Hojo, M.; Imazaki, N. *Heterocycles*. **1995**, *40*, 905-911 and references cited therein.

8. A typical procedure for the reaction between α,α-difluoroketone **2** and the anion of imidazole is as follows: Into a three-necked flask equipped with a drying tube, a dropping funnel and a nitrogen inlet were added 0.5g (1.58 mmol) of the α,α-difluoroketone **2** in 20mL of anhydrous DMSO. The solution is stirred vigorously until complete dissolution. Then a 20mL DMSO solution of 0.66g (4.73 mmol) of the tetramethylammonium salt of the imidazole (carefully dried under high vacuum) were added dropwise over 20 minutes. When the addition was complete the solution was heated at 50°C for 10 hours when the yield of the desired product remain constant (as checked by HPLC). The solution was diluted with brine (100mL) and extracted with EtOAc (3x100mL); the combined organic solutions were washed with brine (2x100mL), water (2x100mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure gave a yellow solid as crude product. Column chromatography on silica gel using EtOAc/hexane (1:2, v/v, as eluent), evaporation of the appropriate fractions and recrystallization from $CHCl_3$/hexane gave 0.35g (1.03 mmol, 65%) of the **4-(chloro-difluoro-acetyl)-11,11-difluoro-5-imidazolyl-1-yl-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one 4**. m.p= 122-124°C (yellowish powder). TLC (EtOAc/hexane, 1:1, v/v): R_F= 0.4. UV (CH_3CN) λ_{max}: 268 and 386 nm. ^{1}H NMR ($CDCl_3$): δ_H 2.06-2.13 (m, 1H, H_1 or $H_{1'}$), 2.28-2.35 (m, 1H, $H_{1'}$ or H_1), 3.41-3.44 (m, 1H, H_{11a}), 3.85-4.00 (m, 2H, H_2 and $H_{2'}$), 5.32-5.35 (d, 1H, H_{3a}, J=7Hz), 7.28 (s, 1H, $H_{2''}$), 7.49-7.69 (m, 2H, H_7 and H_8), 7.72 (s, 1H, $H_{4''}$ or $H_{5''}$), 8.11-8.15 (d, 1H, H_6), 9.29-9.34 (d, 1H, H_9). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F -56.7 (s, 2F), -101.2 (1F, dd, J_{F-F}=272Hz, $^{3}J_{F-H_{11a}}$= 13.5Hz), -112.40 (1F, dd, J_{F-F}=272Hz, $^{3}J_{F-H_{11a}}$= 12.5Hz). Mass (CI/CH_4): m/e= 341 ($M+H^+$). Analysis: Calcd. C 67.06, H 4.11, N 8.23. Found. C 67.28, H 4.24, N 8.32.

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