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Synthesis of α-(heteroarylthio)-α,α-difluoroacetophenone derivatives via the $S_{RN}1$ methodology

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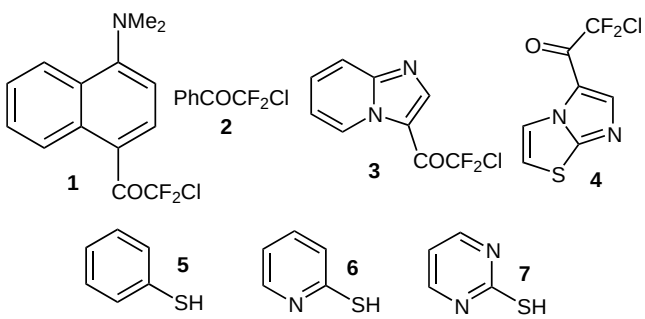
Abstract—New α-(heteroarylthio)-α,α-difluoroacetophenone Ar^1-$COCF_2S$-Ar^2 derivatives **8**–**15** were synthesized in moderate to good yields via the $S_{RN}1$ methodology, from the reaction of a series of chlorodifluoromethylated ketones **1**–**4** with aromatic and heterocyclic thiols **5**–**7**. The corresponding Ar^1-$CHOHCF_2S$-Ar^2 **16**–**23** were also prepared in moderate yields, using sodium borohydride in absolute ethanol. The compounds may find some biological applications as potent anti-HIV-1 as well as useful synthons for agrochemicals.

There continues to be an interest in the synthesis of new *gem*-difluorinated compounds because of the potential biological properties of such molecules.[1] Electrophilic carbonyl derivatives, such as α,α-difluoroketones, are compounds of great interest because they have the capability to form hydrates and hemiketals.[1] It is believed that this property allows some fluorinated ketones to mimic the transition states involved in the hydrolytic action of many enzymes.[1] As part of our ongoing efforts in the search for new methodologies for the synthesis of fluorinated compounds with biological applications, we recently synthesized a series of Het-CF_2SAr derivatives[2] via the $S_{RN}1$ methodology[3] with bromodifluoromethylated heterocycles as starting materials and commercially available aromatic (phenyl) and heterocyclic (pyridine, pyrimidine, imidazole, triazole, tetrazole) sulfur nucleophiles. Some of the compounds prepared by this approach were found to possess some interesting anti-HIV-1 activity as new non-nucleoside reverse transcriptase (RT) inhibitors (NNRTIs).[4]

Methods to prepare R^1-$COCF_2S$-R^2 derivatives are limited; α-(alkylthio)-α,α-difluoroacetophenone analogs have been prepared by electrochemical fluorination of α-(phenylthio)acetophenone,[5] oxidative desulfurization–fluorination of orthothioesters[6] and electrophilic *gem*-difluorination of α-(alkylthio)acetophenone derivatives with *N*-fluoropyridinium salts.[7a] However, these methods suffer from the use of excess oxidizing agent,[6] lack of wide applications or relatively high cost of the fluorinated agent.[7a] Eto et al.,[7b] recently extended their fluorination reactions of $ArCOCH_2SCH_3$ derivatives,[7a] to an alternative methodology that consisted of the addition of phenyllithiums to $RSCF_2CO_2Et$ derivatives (prepared by substitution reactions of $BrCF_2COOEt$ of $S_{RN}1$ type, as Burton et al. similarly reported[8]); as an application such $ArCOCF_2SR$ derivatives were transformed into new antifungal 1,2,4-triazoles. Unfortunately in this report, only one example of substitution reactions of $PhCOCF_2Cl$ was successfully reported with methanethiolate as nucleophile. Our recent studies on the single electron transfer (SET) reactions of a series of chlorodifluoromethylated ketones[9] demonstrated that these ketones were good electron-acceptors and there-



Scheme 1.

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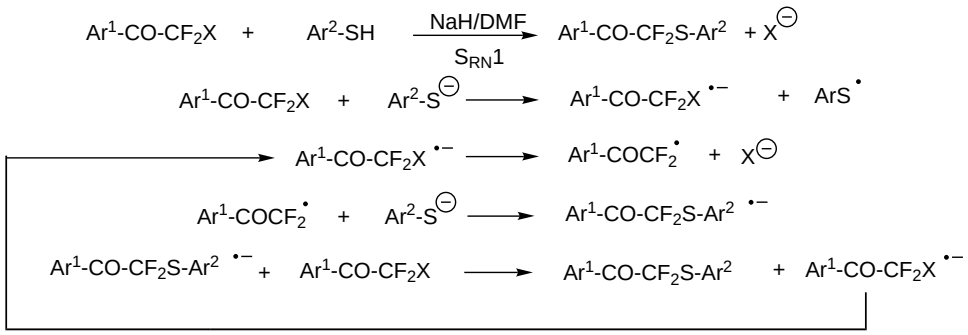
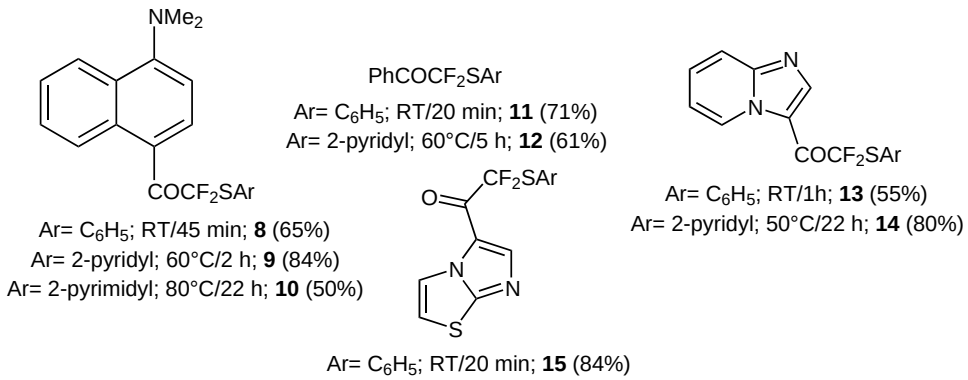
fore prompted us to engage such substrates **1**–**4** in valuable potential $S_{RN}1$ reactions with aromatic and heterocyclic thiols **5**–**7** (Scheme 1).

In such a way novel Het-$COCF_2S$-Ar derivatives **8**–**15** were obtained from the corresponding α,α-difluoroacetyl radicals and subsequent trapping with aromatic and heterocyclic thiolates (Scheme 2). In this mechanism the nucleophile acts as the electron-transfer reagent (initiation step) to generate an electrophilic α,α-difluoroacetyl radical that could react with the nucleophile. The mechanism is a typical catalytic chain reaction as the radical-anion of the starting ketone is regenerated (propagation step). Initial experimentation with **1** and sodium phenyl thiolate **5** lead to the observation that the reaction giving **8** was rapid and exothermic, being complete in only 45 minutes. It was soon discovered that other mercapto-substituted heterocycles, Ar^2-SH, were able to be successfully reacted with **1** to give **9** and **10**, as can be seen by looking at Scheme 3. The anions were conveniently generated in anhydrous DMF using dry NaH, which was weighed out rapidly in the air and transferred to the reaction apparatus as quickly as possible. The isolated yields of these reactions vary from 50 to 84%, and no significant optimization of the yields was performed other than using a two-fold excess of the anion and following the reaction by TLC until the starting material was gone. By looking at Scheme 3, it can be seen that substitution of an aromatic CH with a nitrogen leads to lowered reactivity with all the ketones. Thus, the anions of 2-mercaptopyridine and 2-mercaptopyrimidine are much less reactive than benzenethiolate. Multiple nitrogen substitution in the heterocyclic ring of the anion results in greatly reduced reactivity, as the ketones were usually consumed under more vigorous conditions (60°C/2 h for **9**; 80°C/22 h for **10**; 60°C/5 h for **12**; 50°C/20 h for **14**). This is consistent with an electronic effect where electron-withdrawing substitution of the anion slows down the reaction (decreasing nucleophilicity). Attempts to increase the yields, with these mercapto-heterocycles, at higher temperatures and longer reaction times, resulted in significant loss of the desired product with the formation of colored decomposed products, especially with the 2-mercaptopyrimidine. All the products were obtained as viscous oils or crystals after silica gel chromatography.[10] None of the yields have been optimized and room for improvement certainly exists.

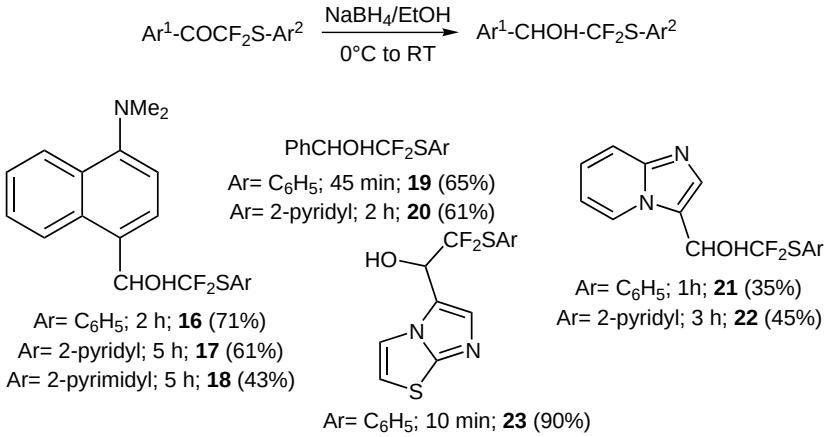
From a mechanistic point of view, the observation that the presence of 1,4-dinitrobenzene strongly inhibits the reaction of **1** with **6** is a good indication for the $S_{RN}1$ mechanism. However, further experiments are needed (such as trapping the intermediate radical with an electron-rich olefin or a spin trap) to confirm the mechanism. The only side-products which represent the remaining balance material were the hydrogenolysis compounds $RCOCF_2H$ resulting from hydrogen atom abstraction from the solvent of the α,α-difluoroacetyl radical. With the 2-mercaptopyrimidine as nucleophile, appreciable amounts of unidentified products were usually observed by TLC (fluorescent spots) when reactions were run at 60 or 80°C; as a consequence, the



Scheme 2.



Scheme 3.



Scheme 4.

yield of substituted product **10** is only moderate. At room temperature, these impurities are in less amount but conversion is low.

In order to get additional compounds for our screening program, the Ar^1-$COCF_2S$-Ar^2 derivatives were conveniently subjected to sodium borohydride reduction, in ethanol, to give the corresponding Ar^1-CHOH-CF_2S-Ar^2 derivatives **16**–**23** in good yields (Scheme 4).

In conclusion, to the best of our knowledge, this is the first report of the substitution reactions of aromatic and heterocyclic chlorodifluoromethylated ketones with sulfur nucleophiles[11] and the application to the facile synthesis of α-(heteroarylthio)-α,α-difluoroacetophenone derivatives. The products are good candidates for further chemical elaboration and will be tested as potential HIV-1 inhibitors. From the recent literature,[7b] these derivatives could also find some application as agrochemicals. Further experiments are currently under way to confirm the $S_{RN}1$ mechanism. The electrochemical induction of the $S_{RN}1$ substitution will also be performed to check if some of the yields could be improved under less vigorous conditions, especially for nucleophiles derived from pyridine, pyrimidine and other nitrogen heterocycles.

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10. A typical representative procedure for the $S_{RN}1$ reactions is as follows: In a 25-ml, three-necked round-bottom flask equipped with a magnetic stirrer, a reflux condenser and a nitrogen inlet, anhydrous DMF (10 ml/mmol) by syringe followed by 2 equivalents of NaH (95% dry) were added under nitrogen. To the rapidly stirred gray suspension was added 2 equivalents of the nucleophile. Gas was evolved and the NaH dissolved giving a clear solution after 20 min of stirring. After stirring for 20 min, the starting chlorodifluoromethylated ketone was added all at once. The reaction was monitored by TLC and after total consumption of the starting material, the solution was hydrolyzed with an aqueous NaCl solution and the solution was extracted with dichloromethane (3×). The combined organic extracts were washed with an aqueous NaCl solution (5×) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography. Selected examples: **1-(4-Dimethylamino-naphthalen-1-yl)-2,2-difluoro-2-(pyridin-2-ylsulfanyl)-ethanone 9**: viscous

yellow oil. ^{1}H NMR ($CDCl_3$): δ_H 8.83 (d, 1H, $J=9.41$ Hz), 8.47 (m, 1H), 8.35 (dt, 1H, $J=1.89$, 3.85, 8.31 Hz), 8.17 (d, 1H, $J=7.48$ Hz), 7.60 (m, 3H), 7.50 (m, 1H), 7.20 (m, 1H), 6.93 (d, 1H, $J=8.38$ Hz), 3.04 (s, 6H). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −73.4 (2F, s). HRMS (70 eV): calcd for $C_{19}H_{16}F_2N_2OS$ 358.0951, found 358.0962. **1-(4-Dimethylamino-naphthalen-1-yl)-2,2-difluoro-2-(pyrimidin-2-ylsulfanyl)-ethanone 10**: viscous greenish oil. ^{1}H NMR ($CDCl_3$): δ_H 8.60 (m, 1H), 8.37 (d, 2H, $J=4.98$ Hz), 8.19 (m, 2H), 7.52 (m, 2H), 6.96 (m, 2H), 3.02 (s, 6H). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −78.4 (2F, s). HRMS (70 eV): calcd for $C_{18}H_{15}F_2N_3OS$ 359.0904, found 359.0912. **2,2-Difluoro-2-(phenylthio)acetophenone 11**:[5,7b] clear colorless liquid. ^{1}H NMR ($CDCl_3$) δ_H 8.12 (m, 2H), 7.68–7.58 (m, 3H), 7.52–7.35 (m, 5H); ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −77.7 (2F, s); HRMS (70 eV): calcd for $C_{14}H_{10}F_2OS$ 264.0420, found 264.0411. Anal. calcd for $C_{14}H_{10}F_2OS$: C, 63.62; H, 3.81. Found C, 63.88; H, 3.90. **2,2-Difluoro-1-imidazo[1,2-*a*]pyridine-3-yl-2-(pyridin-2-ylsulfanyl)-ethanone 14**: white crystals (mp 84°C). ^{1}H NMR ($CDCl_3$): δ_H 9.61 (d, 1H, $J=6.82$ Hz), 8.66 (brs, 1H), 8.52 (d, 1H, $J=4.46$ Hz), 7.85 (d, 1H, $J=8.89$ Hz), 7.67 (m, 3H), 7.26 (m, 1H), 7.21 (d, 1H, $J=6.86$ Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −77.48 (2F, s). HRMS (70 eV): calcd for $C_{14}H_9F_2N_3OS$ 305.0434, found 305.0445. **2,2-Difluoro-1-imidazo[2,1-*b*]thiazole-5-yl-2-phenylsulfanyl-ethanone 15**: white solid (mp 86.2–87.8°C). ^{1}H NMR ($CDCl_3$): δ_H 8.36 (d, 1H, $J=4.42$ Hz), 8.20 (brs, 1H), 7.64 (d, 1H, $J=7.17$ Hz), 7.36–7.50 (m, 5H, H-arom.), 7.14 (d, 1H, $J=4.27$), 7.26 (m, 1H), 7.21 (d, 1H, $J=6.86$ Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −79.72 (2F, s). HRMS (70 eV): calcd for $C_{13}H_8F_2N_2OS_2$ 310.0046, found 310.0055.

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