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Synthesis and electron-transfer reactions of some 3-difluoroacetylated imidazo[1,2-*a*]pyridine derivatives

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Abstract—The synthesis of new 3-chlorodifluoroacetylated imidazo[1,2-*a*]pyridines **1**–**6** and their difluoroacetyl derivatives is presented. The reductive cleavage of the halogenated ketones was investigated by cyclic voltammetry, and tetrakis(dimethylamino)ethylene (TDAE) was found to be an effective reductant for the generation of the corresponding α,α-difluoroacetyl anions and for the synthesis of new *gem*-difluoromethylated imidazo[1,2-*a*]pyridine derivatives **7**–**12**.

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] Azaindolizine and particularly imidazo[1,2-*a*]pyridine derivatives are important heterocycles that have received a great deal of attention because of their significant and potential biological activities [benzodiazepine receptor ligands (Zolpidem; Fig. 1),[2] antiviral molecules,[3] antibacterial agents[4] and anti-ulcer agents[5]]. Even recently, bicyclic imidazo derivatives (imidazo[1,2-*a*]pyridine, imidazo[2,1-*b*]thiazole) have been screened as new anti-HIV-1 compounds (Fig. 1) such as non-nucleoside reverse transcriptase (RT) inhibitors (NNRTIs)[6] and HIV-1 protease inhibitors.[7]

As part of our ongoing efforts in the search of new methodologies for the synthesis of fluorinated compounds with potential biological applications,[8] we wish to report the synthesis of new chloro- and difluoroacetylated imidazo[1,2-*a*]pyridine derivatives **1**–**6** and their single electron-transfer reactions, using the tetrakis(dimethylamino)ethylene (TDAE) as an electron donor.[8d,8e,9] In such a way novel *gem*-difluorinated imidazo[1,2-*a*]pyridine derivatives **7**–**12** were obtained from the corresponding α,α-difluoroacetyl anions and subsequent in situ nucleophilic addition to aromatic and heterocyclic aldehydes. Imidazo[1,2-*a*]pyridine derivatives **2**–**6** were synthesized in moderate to good yields, according to Tschitschibabin, by condensation of 2-aminopyridine with the appropriate α-bromoke-

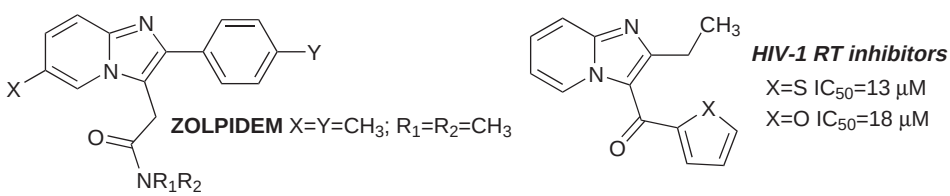

Figure 1.

Keywords: imidazo[1,2-*a*]pyridine; cyclic voltammetry; tetrakis(dimethylamino)ethylene; fluorine and compounds.

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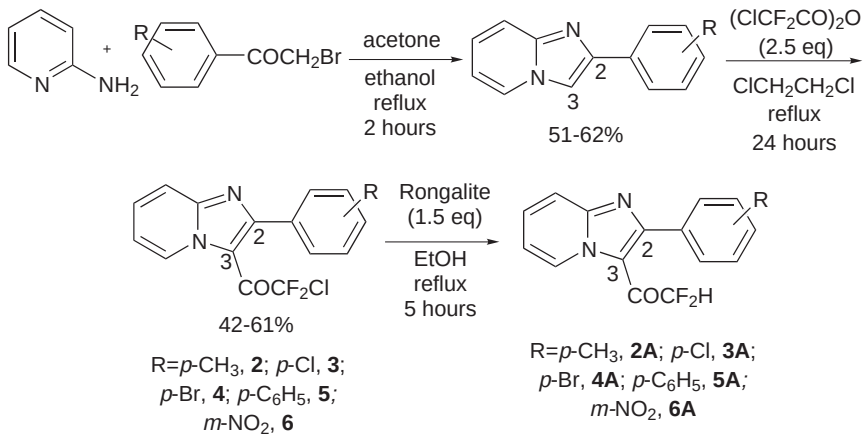
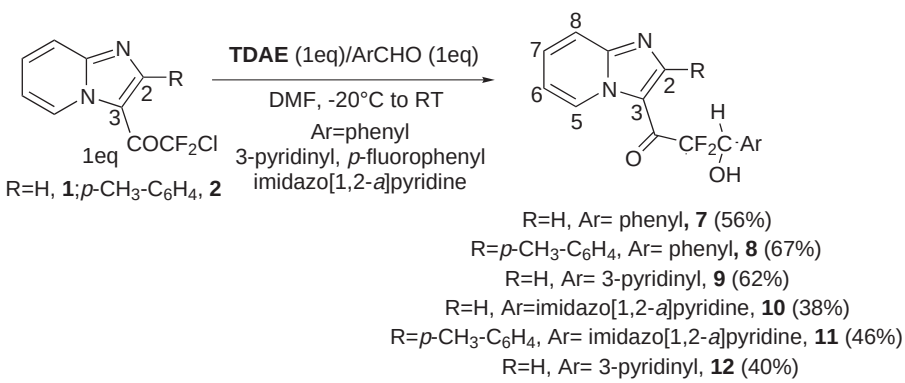
tone.[10] Introduction of the $COCF_2Cl$ moiety at the C-3 position was achieved using 2.5 equiv. of chlorodifluoroacetic anhydride in refluxing anhydrous 1,2-dichloroethane for 24 h. Imidazo[1,2-*a*]pyridine-3-$COCF_2Cl$ **1**, was obtained in a similar manner from commercially available imidazo[1,2-*a*]pyridine. The products can be purified by simple recrystallization from the crude product or by silica gel chromatography. The corresponding difluoroacetyl derivatives **1A**–**6A** were obtained under mild conditions, by reductive dechlorination using sodium formaldehyde sulfoxylate (Rongalite)[11] in refluxing absolute ethanol (Scheme 1).

Cyclic voltammetry of **1**, chosen as a model substrate (in anhydrous DMF+0.1 M NBu_4PF_6), shows that the first two-electron reduction wave (as compared with the one-electron oxidation wave of the ferrocene) located at −1.25 V versus SCE (first peak potential E_{pc1} at 0.2 V/s on a glassy carbon electrode) is irreversible (up to 500 V/s) and corresponds to the cleavage of the C–Cl bond and to the formation of the corresponding difluoroacetyl derivative **1A** ($E_{pc2}=-1.58$ V versus SCE at 0.2 V/s) as the reduction product, as was shown by comparison with an authentic sample. The cleavage of the radical anion is very fast (stepwise mechanism) and, therefore, the major pathway of the α,α-difluoroacetyl radical is a further reduction to the hydrogenolysis product, probably at a close potential to **1**. At this point, our studies on the cyclic voltammetry of TDAE,[8e] as well as on the chlorodifluoromethylated ketones **2**–**6** (first peak potential varies from −1.15 to −1.28 V versus SCE in DMF+0.1 M NBu_4PF_6 at 0.2 V/s), prompted us to try TDAE as a mild and conceptually different synthetic electron-transfer reagent (as compared to the classical Reformatsky reaction[1]) for the generation of difluoroacetyl anions, and subsequent reactions with aromatic and imidazo[1,2-*a*]pyridine-3-carbaldehyde derivatives as trapping agents. In a typical experiment, 1 equiv. of ketone **1** was condensed, in anhydrous DMF at −20°C, with 1 equiv. of benzaldehyde in the presence of TDAE; as we have reported for the reactions involving aromatic chlorodifluoromethylated ketones,[8d] an equimolar amount of TDAE was necessary for complete reduction of the starting ketone **1**, with the reaction being almost complete after 2 h (TLC). After the usual work-up, fluorine NMR of the crude product revealed the presence of the desired alcohol **7** characterized by two doublets of doublets (δ_F −110.8 and −121.7 ppm/$CFCl_3$ with $J_{F-F}=261$ Hz and $^3J_{H-F}=18.12$ and 6.82 Hz) and the difluoroacetylated ketone **1A** (δ_F −126.3 ppm/$CFCl_3$; doublet with $^2J_{H-F}=$ 55 Hz) in a 2:1 ratio. The alcohol adduct was isolated as a white solid in 56% yield after purification by silica gel chromatography and preparative TLC.[12] Similarly, in the presence of benzaldehyde (1 equiv.) and TDAE (1 equiv.), ketone **2** gave the desired alcohol **8** in 67%



Scheme 1.



Scheme 2.

yield. Imidazo[1,2-*a*]pyridine-3-carbaldehyde[13] was also found to be a good electrophile and the corresponding alcohols were obtained in reasonable yields. Formation of the products was monitored by TLC and the yields were moderate (Scheme 2).

The only side-products, which represent the remaining balance material, were the hydrogenolysis compounds $RCOCF_2H$ resulting from protonation of the α,α-difluoroacetyl anion. None of the yields have been optimized and room for improvement certainly exists.

In conclusion, to the best of our knowledge, this is the first report of a facile synthesis of *gem*-difluorinated imidazo[1,2-*a*]pyridine derivatives.[14] Based on the cyclic voltammetric experiments, TDAE has been found (as in our previous studies) to be effective for the generation of stable α,α-difluoroacetyl anions. The addition products are good candidates for further chemical elaboration and are potentially useful for biological applications. Work is in progress to use these chlorodifluoroacetylated ketones, as well as new bicyclic imidazo halogenodifluoromethyl ketone derivatives (imidazo[1,2-*a*]pyrimidine, imidazo[2,1-*b*]thiazole and imidazo[2,1-*b*]oxazole), in various single electron-transfer (TDAE and $S_{RN}1$[15]) reactions of synthetic utility.

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12. A typical procedure for the reaction between **1**, TDAE and benzaldehyde is as follows: Into a two-necked flask equipped with a silica gel drying tube and a nitrogen inlet were added, under nitrogen at −20°C, a 5 ml anhydrous DMF solution of **1** (0.35 g, 1.52 mmol) and benzaldehyde (0.16 g, 1.52 mmol; 0.15 ml). The solution was stirred and maintained at this temperature for 30 min and then the TDAE (0.30 g, 1.52 mmol, 0.15 ml) was added dropwise (via a syringe). A red color immediately developed with the formation of a fine, white precipitate. The solution was vigorously stirred at −20°C for 1 h and then warmed up to room temperature for 2 h. After this time, TLC analysis (EtOAc–hexane, 90:10) clearly showed that the ketone **1** was totally consumed. The orange-red turbid solution was filtered (to remove the octamethyloxamidinium dichloride) and hydrolyzed with 30 ml of H_2O. The aqueous solution was extracted with $CHCl_3$ (3×30 ml), the combined organic solutions were washed with brine (3×30 ml), H_2O (3×30 ml) and then dried over $MgSO_4$. Evaporation of the solvent left an orange viscous liquid as crude product. Purification by silica gel chromatography (EtOAc–hexane, 90:10 as eluent) and preparative TLC (hexane–CH_2Cl_2, 98:2) gave 0.256 g (0.85 mmol, 56%) of the alcohol **7** as a white solid. **2,2-Difluoro-3-hydroxy-1-imidazo[1,2-*a*]pyridin-3-yl-3-phenyl-propan-1-one**. ^{1}H NMR ($CDCl_3$): δ_H 5.37–5.43 (1H, dd, J=17.5, 6.44 Hz, -C*H*OH), 7.18–7.22 (1H, m, H-6), 7.37–7.39 (3H, m, H-arom.), 7.51–7.53 (2H, m, H-arom.), 7.59–7.64 (1H, m, H-2), 7.79–7.82 (1H, m, H-7), 8.50–8.52 (1H, m, H-8), 9.66–9.68 (1H, H-5, dd, J=4.25, 1.08 Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −106.96 (1F, dd, J=273, 7.52 Hz), −117.62 (1F, dd, J=273, 17.18 Hz). Anal. calcd for $C_{16}H_{12}F_2N_2O_2$: C, 63.57; H, 4.00; N, 9.27. Found: C, 63.64; H, 4.03; N, 9.33.

13. Prepared in good yields by formylation (with $POCl_3$ in DMF at 80°C) of the corresponding imidazo[1,2-*a*]pyridine derivatives.
14. The synthesis of imidazo[2,1-*b*]thiazole-5-$COCF_3$ has been reported: Hopkinson, C. P.; Meakins, G. D.; Purcell, R. J. *J. Chem. Res., S.* **1993**, *161*, 201.
15. Recently $S_{RN}1$ reactions (nitronate anions as nucleophiles) with bicyclic imidazo derivatives (imidazo[1,2-*a*]pyridine and pyrimidine, imidazo[2,1-*b*]thiazole) have been published: (a) Roubaud, C.; Vanelle, P.; Maldonado, J.; Crozet, M. P. *Tetrahedron* **1995**, *51*, 9643–9656; (b) Vanelle, P.; Madadi, N.; Roubaud, C.; Maldonado, J.; Crozet, M. P. *Tetrahedron* **1991**, *47*, 5173–5184. We recently synthesized the 5-chlorodifluoroacetyl imidazo[2,1-*b*]thiazole and applied the $S_{RN}1$ reaction with phenyl thiolate as nucleophile; the desired substituted product was obtained in 80% yield and subsequent reduction of the carbonyl with $NaBH_4$ gave the alcohol product in 76% yield. The compound is regarded as an analogue of known HIV-1 protease inhibitors (Ref. 7). Its activity as a potent HIV-1 RT (see Ref. 6) and protease (see Ref. 7) inhibitors will be checked, as well as the activity of the imidazo[2,1-*b*]thiazole-5-$COCF_2SPh$.