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Stereodivergent formation of fluorine-containing enamides

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ABSTRACT

2-Chloro-1,1,1,2-tetrafluoroethane **1** (HCFC-124) obtained as one of the major byproducts of tetrafluoroethylene synthesis were successfully employed for the stereodivergent construction of tetrafluorinated enamides **4** just by selection of a base for affecting the removal of HCl.

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1. Introduction

In recent years, we have been interested in utilization of hydrochlorofluorocarbons (HCFC) as the convenient as well as versatile starting materials for construction of a variety of fluorinated compounds [1], and focused our attention to 2-chloro-1,1,1,2-tetrafluoroethane **1** (HCFC-124) obtained as one of the major byproducts during the course of the tetrafluoroethylene synthesis. Its utilization was reported by us [2] for the ready construction of α-fluoro-α,β-unsaturated acids with a variety of substituents at the β-position, usually with a high level of (*Z*)-stereoselectivity which were initiated by the condensation of the carbanion from **1** and appropriate carbonyl compounds. During our ongoing study in this area, successful employment of imines as electrophiles was realized and these products further led to stereodivergent conversion to fluorine-containing enamides as possible intermediates with pharmaceutical interests. In this article are reported synthetic details of these processes.

2. Results and discussion

First of all, with reference to the previous study [2], HCFC-124 was treated with small excess of *n*-BuLi at −80 °C for 0.5 h to generate the corresponding carbanion which was further mixed with the imine from benzaldehyde and benzylamine (Table 1, Entry 1). However, only a complex mixture was obtained whose ^{19}F NMR analysis did not show any significant amounts of fluorinated products. Then, for the purpose of effective activation of the imine function, electron-withdrawing groups were introduced as R^2 (Entries 2 and 3), and both *p*-toluenesulfonyl (Ts) and *t*-butoxycarbonyl (Boc) moieties were found to work properly to furnish the desired adducts **1ba** and **1ca** in excellent yields, respectively. The latter Boc group easier to be removed was selected for further investigation on the scope of R^1. In the case of aromatic imines with electron-donating substituents like *p*-methoxy (Entry 4) and *p*-methyl (Entry 5), nucleophilic addition occurred efficiently and the adducts **1cb** and **1cc** were successfully obtained, respectively. On the other hand, electron-withdrawing bromo and trifluoromethyl groups at the *para* position were not suitable at all in spite of their electrophilically activating nature of the C=N bond (entries 6 and 7). This phenomenon is in quite sharp contrast to the previous reaction[2)] of the same anionic species with *p*-(trifluoromethyl)benzaldehyde, attaining only slightly lower chemical yield of 72% than the ones of *p*-tolyl- (90%) and *p*-anisaldehydes (89%). In spite of no clear proof, increase of the pK_a values of the benzylic proton by these substituents would affect this tendency, leading to smooth conversion of the initial anion on nitrogen to the one at the benzylic position [3], and the following elimination of chloride would furnish enamine which might cause further undesired reactions under the conditions employed. Moderate yield was recorded by the imine with the 2-furyl moiety (Entry 8), but the one with the β-phenethyl group was not a good substrate at all. This discrepancy clearly indicated the requirement of the appropriate imine activation by R^1 for attainment of good results (Entry 9). This is also the case for the imine with a *c*-C_6H_{11} group, only 16% of the product being isolated. Although we have

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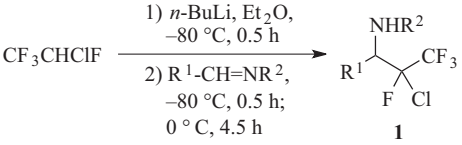
Table 1
Reaction of HCFC-124 with a variety of imines.



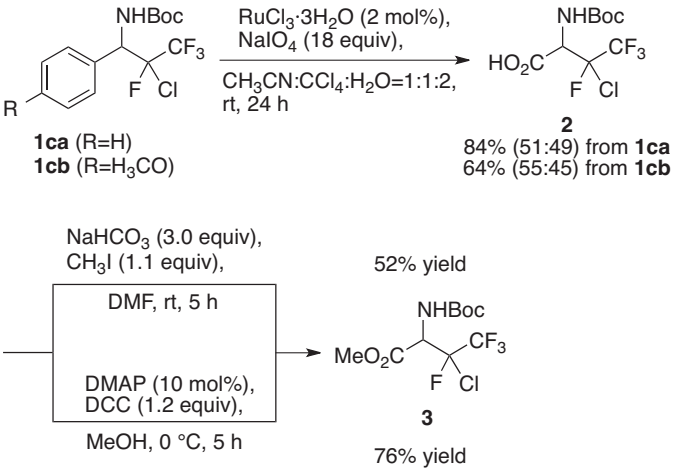
Entry	R^1	R^2	Product	Yield (%)	DR[a]
1	Ph–	$PhCH_2$–	**1aa**	Complex	–
2	Ph–	*p*-H_3C–$C_6H_4SO_2$–	**1ba**	80	53:47
3	Ph–	*t*-BuOC(O)–	**1ca**	82	52:48
4	*p*-H_3CO–C_6H_4–	*t*-BuOC(O)–	**1cb**	76	57:43
5	*p*-H_3C–C_6H_4–	*t*-BuOC(O)–	**1cc**	59	55:45
6	*p*-Br–C_6H_4–	*t*-BuOC(O)–	**1cd**	14	50:50
7	*p*-F_3C–C_6H_4–	*t*-BuOC(O)–	**1ce**	0	–
8	2-Furyl	*t*-BuOC(O)–	**1cf**	33	57:43
9	$PhCH_2CH_2$–	*t*-BuOC(O)–	**1cg**	Trace	–
10	*c*-C_6H_{11}–	*t*-BuOC(O)–	**1ch**	16	51:49
11[b]	Ph–	*t*-BuOC(O)–	**1ca**	(11)[c]	ND

[a] Diastereomeric ratios determined by ^{19}F NMR.
[b] Following to our previous report [2], to a *t*-BuOK solution of the imine in Et2O was added HCFC-124 (3 equiv.) at −20 °C and after stirring for 0.5 h, and reaction was continued at 0 °C for 4.5 h.
[c] In the parenthesis was shown the yield determined by ^{19}F NMR.

not tried yet, employment of a Lewis acids might open the way to obtain such products.

In the previous report [2], we described that *t*-BuOK was employed as the convenient alternative base specifically for aromatic electrophiles without α-proton to the carbonyl group. This protocol, direct addition of gaseous HCFC-124 to a premixed solution containing this base and a carbonyl compound, enabled acceptance of the nucleophilic attack of the CF_3CFCl anion as quickly as possible when it was generated. However, this method was unfortunately proved to be inapplicable to the present imine system, only producing the desired material in 11% yield (Entry 11). This might be attributed to the stability of the anionic species CF_3CClFK: although this modified method previously worked well for condensation with aromatic aldehydes, but its lifetime under the reaction conditions would not be long enough to react with the less reactive imine, leading to possible decomposition to KF and CF_2=CFCl due to strong intramolecular interaction of K···F [4].

It is well-known that aromatic rings can be oxidatively converted to a carboxyl group by the action of the $RuCl_3$–$NaIO_4$ combined system [5], and the selected adducts, **1ca** and **1cb** obtained above, were subjected to the reported condition (Scheme 1). Their smooth



Scheme 1. Conversion of **1ca** and **1cb** to **2** and **3**.

transformation into the desired carboxylic acid **2** was realized in good to excellent yields with complete retention of the Boc group for protection of the amino moiety. The lower yield of **2** from **1cb** might stem from other processes proceeding at the same moment, giving rise to formation of unidentified byproducts.

The carboxylic acid **2** thus obtained was then converted to the corresponding methyl ester **3** whose preparation was conveniently carried out in two different routes: the $NaHCO_3$-mediated methylation afforded 52% of the ester **3** which was also obtained in better yield by way of the standard DCC condensation in the presence of a catalytic amount of DMAP [6].

We have also investigated dehydrochlorination of the amino ester **3** as the promising precursor for a variety of fluorine-containing amino acids [7]. Results were summarized in Table 2. First of all, pyridine [8] was proved not to possess sufficient basicity for abstraction of the proton α to the carbonyl group and increase of the temperature to reflux affected this process only slightly (Entries 1 and 2). On the other hand, triethylamine with higher basicity worked efficiently to furnish the desired enamide **4** in a *Z* specific manner whose stereochemistry was unambiguously clarified by its ^1H–^{19}F HOESY spectrum, showing a clear cross peak between the N–*H* proton and vinylic F. It is interesting to note that change of a base to the representative lithium amide, LDA, totally altered the stereoselectivity of the product **4**, and *E* selectivity as high as 80–90% was attained. Incomplete conversion by treatment with an approximately equimolar amount of LDA (Entries 4–6) was improved by two equivalent of this base, realizing almost quantitative conversion of **3** and constructing 95% yield of **4** after 5 h stirring at −80 °C (Entry 9). Moreover, raising the reaction temperature from −80 to −40 °C recorded almost the same yield but apparently deteriorated the *E* selectivity from 87 to 63%, respectively (Entries 7 vs 8). This formal elimination of HCl was also affected by the more favorable base *t*-BuOK in terms of its handling. In this instance, in contrast to the instance of LDA, −40 °C seemed to be more suitable, and 5 h stirring at this temperature was found to be suffice to attain a similar level of chemical yield as well as stereoselectivity to LDA (Entry 11). The corresponding lithium salt formed *in situ* from *t*-BuOH and *n*-BuLi also worked quite nicely (Entry 12).

This interesting reversal of the stereoselectivity would be elucidated by the mechanism shown in Scheme 2. Circumstance at the deprotonation of **3** by LDA would be understood on the basis of

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