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Mitsunobu synthesis of symmetrical alkyl and polyfluoroalkyl secondary amines

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Abstract

Trifluoromethanesulfonamides (triflamides) having the structure $CF_3SO_2N[(CH_2)_3R]_2$ (R = C_nF_{2n+1} or C_nH_{2n+1}, n = 4, 6, 8, 10) are obtained in high yields, when $CF_3SO_2NH_2$ is reacted with 3-perfluoroalkyl-1-propanols or the parent aliphatic alcohols in a Mitsunobu reaction (Ph_3P/[*i*-$PrO_2CN{=}NCO_2$-*i*-Pr]/ether). Products are isolated easily by fluorous extraction, fluorous solid–organic liquid filtration or *n*-heptane/CH_3OH extraction. Consecutive deprotection of triflamides with $LiAlH_4$ in boiling ether or dioxane solution affords the title amines in good overall yields. Fluorous partition coefficients of the *F*-tagged amides and amines are determined and qualitatively analyzed.

Keywords: Amines; Fluorophilicity; Ideal separation; Mitsunobu reaction; Trifluoromethanesulfonamide

1. Introduction

Fluorous amines are important compounds that have been used as scavengers or precursors for the synthesis of fluorous reagents and catalysts [1]. Their synthesis usually involves several steps starting from perfluoroalkyl iodides [2]. The Mitsunobu reaction is a useful tool for the alkylation of an acidic pronucleophile (NuH) with a primary or secondary alcohol (ROH) to afford the coupled products (NuR) [3]. When NuH has a pK_a < 11, the use of Ph_3P/diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) reagent pairs resulted in good yields, while for alkylation of less acidic partners other mediators were introduced [4]. Due to the wide scope of the Mitsunobu reaction, several strategies were elaborated which provide quicker work-up procedures instead of using the time demanding 'classical' chromatographic methods for the separation of products and spent reagents (e.g. Ph_3PO, *i*-$PrO_2CNHNHCO_2$-*i*-Pr [$DIADH_2$]). Some of these methods rely on the application of orthogonal phases and of reagents with tuned phase affinities, thus providing ideal separations [5]. Fluorous Mitsunobu reactions have increasing scope since the introduction of novel fluorous azodicarboxylates (^{F}DEAD) and phosphines ($^F Ph_3P$) [6]. In its *reverse* fluorous versions, however, using fluorous substrates (^{F}NuH/ROH, NuH/^{F}ROH or ^{F}NuH/^{F}ROH) with the classical Ph_3P/DIAD couple, the fluorous products (^{F}NuR, NuR^F or ^{F}NuR^F) are easily separable from all other reaction components [7].

A series of long chain fluorous primary and secondary amines has been synthesized by reductive alkylation of $PhCH_2NH_2$ using one or two equivalents of perfluoroalkylalkanals and an excess of $NaBH(OAc)_3$, respectively, followed by the removal of the protecting benzyl-group [2a] or by the ammonolysis of perfluoroalkylpropyl iodides [2b]. Some syntheses of secondary amines that can be easily scaled up to the hundred gram scale rely on the alkylation of $ArSO_2NHR'$ and CF_3CONH_2 substrates and the consecutive deprotection of $ArSO_2NRR'$ (R, R' = alkyl) and CF_3CONR_2 (R = alkyl) intermediates formed, respectively [8].

2. Results and discussion

To devise more effective synthetic processes that can furnish easily secondary fluorous amines on the gram scale, we

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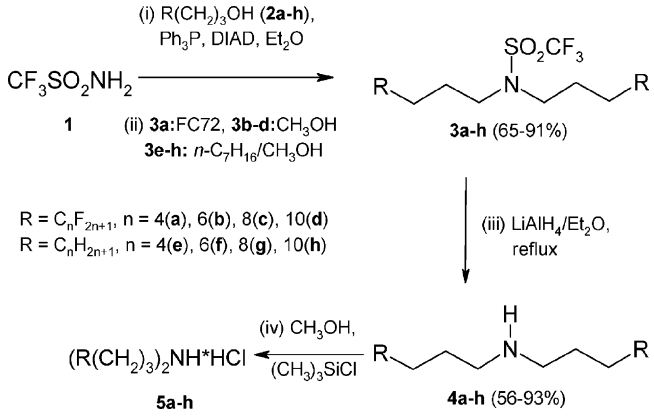

Scheme 1. Synthesis of symmetrical secondary amines.

considered using two-basic QSO_2NH_2 type NH-acids (Q = Ar, perfluoroalkyl) of appropriate pK_a [9] and fluorous alcohols under classical Mitsunobu conditions. We have found that the reaction of triflamide (**1**) and fluorous (**2a–d**) or fatty alcohols (**2e–h**) with slight excess of Ph_3P/DIAD in ether affords fluorophilic or lipophilic triflamides (**3a–h**, Scheme 1) in good yields.

These results are in accordance with literature precedents where CF_3SO_2NHR triflamides had been alkylated with alcohols using Ph_3P/DIAD or DEAD reagent pairs and the intermediates formed deprotected to afford *N*-alkyl benzylamines or some biologically active polyamines [9,10].

Our attempts to extend the scope of this reaction to secondary alcohols failed when (±)-2-octanol was tested. The use of $C_nF_{2n+1}(CH_2)_mOH$ ($m \geq 3$) as fluorous alcohols is justified by the fact, that the presence of at least an $(CH_2)_3$ spacer between the C_nF_{2n+1} and OH groups is necessary to mitigate the strong electron withdrawing effect of fluorine atoms on the reaction centers [7a]. Since triflamides **3** have non-polar character, they are easily separated from the reagent derived polar compounds (Ph_3PO, $DIADH_2$). Fluorous amides (**3a–d**) were isolated using fluorous extraction (**3a**) or fluorous solid (**3b–d**)–organic liquid filtration, while the lipophilic ones (**3e–h**) were isolated with *n*-heptane/CH_3OH extraction.

Consecutive deprotection [10] of triflamides **3** with an excess of $LiAlH_4$ in boiling ether or dioxane solutions afforded the secondary amines **4** in crystalline or liquid state following an extractive work-up procedure. The solids were obtained in high purity (≥98%), while most of the liquids can be purified further by precipitation of their crystalline hydrochlorides **5** from a methanol solution with an excess of HCl generated in situ (Scheme 1 and Section 4).

The amides **3** and amines **4** were assayed by GC and characterized by microanalysis (**e–h**) or HRMS (**a–d**) and ^1H, ^{13}C and ^{19}F NMR spectroscopy (**a–h**), as described in Section 4. The NMR properties showed numerous patterns, but usually of a routine nature. For example, the NCH_2CH_2 ^{13}C signals were grouped in ranges (triflamides **3a–h**, $\delta = 48.3$–48.6; secondary amines **4a–h**, $\delta = 48.1$–50.3; amine hydrochlorides **5a–h**, $\delta = 48.3$–48.6), always downfield of the $CH_2C_nF_{2n+1}$ signals (**3a–d**, **4a–d**, **5a–d**, $\delta = 26.9$–29.6).

Quantitative data on the fluorous phase affinities of the above polyfluoroalkyl amides and amines were sought.

Table 1
Fluorophilicities of some triflamides and amines

Entry	ln *P*
3a	0.77
4a	0.71
3b	2.25
4b	1.98
3c	3.56
4c	3.40[a]
3d	4.47
4d	4.08

[a] cf. Ref. [2a,b].

Accordingly, the perfluoro(methylcyclohexane) [$CF_3C_6F_{11}$]/toluene partition coefficients (*P*) were determined by GC as described in Section 4. Then, these values were converted to a free energy scale by taking their natural logarithm, and displayed as, $f = \ln P$, fluorophilicities (Table 1).

The results obtained are in agreement with predictable trends [7c,11], since compounds with larger calculated molar volume and lower estimated vaporization energy should have higher ln *P* values. Thus, the substitution of NH for NSO_2CF_3 (**3** → **4**) resulted in a decrease for each pairs (**4a** < **3a**, **4b** < **3b**, **4c** < **3c**, **4d** < **3d**), while the lengthening of fluorous ponytails increased the fluorophilicities in both series (**3**, **4**) in the **a** < **b** < **c** < **d** sequence.

3. Conclusions

Symmetrical secondary amides were synthesized effectively under Mitsunobu conditions using triflamide as a precursor. Their reductive deprotection afforded a series of novel polyfluoroalkyl amines and alkyl ones known in Refs. [15–19]. Workup procedures involved only simple separation processes and furnished the crude target products in relatively high purity. The *n*-heptane/CH_3OH liquid–liquid biphasic system was introduced for the ideal separation of lipophilic reaction products from classical Mitsunobu reaction mixtures (Section 4).

4. Experimental details

4.1. Solvents and reagents

Diethyl ether and dichloromethane (A.R. grade) were purchased from Reanal and distilled from P_2O_5 before use. Dioxane (A.R. grade) was purchased from Reanal, and distilled from sodium/benzophenone before use. Methanol, *n*-heptane and *iso*-octane (A.R. grades) were purchased from Reanal and used as received. FC-72 (mixture of perfluorohexanes) was purchased from Fluorochem Ltd. and used as received. Triflamide (**1**) [12] and fluorous alcohols **2a** [13] and **2b–d** [14] were prepared as reported and purified by fractional distillation under reduced pressure to afford **2a** (bp 64 °C/20 mmHg, GC: 98.0%), **2b** (bp 84–86 °C/20 mmHg, GC: 99.0%), **2c** (bp 82–83 °C/0.1 mmHg, mp 42 °C, GC: 99.1%) and **2d** (bp 110 °C/0.1 mmHg, mp 86–89 °C, GC: 98.1%). Alcohols **2e–h** (GC ≥ 98%, 98%, 99% and 97%) were