A New Practical and Convenient Access to the Synthesis of *N,N*-Dialkyl-3,3,3-trifluoropropanamides

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N,N-Dialkyl-3,3,3-trifluoropropanamides were readily synthesized in good to excellent yields through *N,N*-dialkyl(3,3,3-trifluoro-1-propynyl)amines, which were generated by the reaction of *N,N*-dialkyl(2,2,3,3,3-pentafluoropropyl)- or -(2,3,3,3-tetrafluoro-1-propenyl)amines with lithium diisopropylamide in the presence or absence of *N,N'*-dimethylpropyleneurea at room temperature or 0 °C.

3,3,3-Trifluoropropanoic acid and its derivatives are important and fundamental compounds in organic fluorine chemistry. In spite of their high utility as a synthetic block, there have been found merely limited applications of them to organic synthesis.[1] Major reasons for this are considered to lie in the paucity of facile and practical methods for the synthesis of such compounds. In recent years, several methods have been reported[2] for preparing 3,3,3-trifluoropropanoic acid derivatives, but some of them still suffer from defects, such as low yields, use of reagents which are hazardous or difficult in handling, and multistage manipulations. Therefore, it is of great value to develop a more effective route to the synthesis of this sort of compounds.

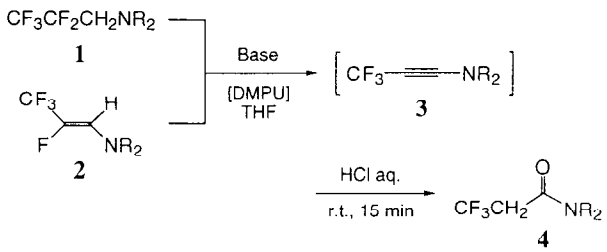
In close connection with our studies on the preparations and applications of polyfluorinated enamines and ammonium salts,[3] we set up a research program to extend the chemistry of fluoroalkynylamines,[4] particularly those formulated as Rf-C≡C-NR_2, and have now succeeded for the first time in the facile preparation of *N,N*-dialkyl-(3,3,3-trifluoro-1-propynyl)amines (**3**)[5] and their transformation into *N,N*-dialkyl-3,3,3-trifluoropropanamides (**4**). This communication describes the results of these reactions, providing a new efficient and convenient method for the synthesis of such amides starting from 2,2,3,3,3-pentafluoropropanol.

$$CF_3CF_2CH_2OH + (CF_3SO_2)_2O \xrightarrow[3\ h]{reflux} CF_3SO_3CH_2CF_2CF_3 \quad (84\%)$$

$$CF_3SO_3CH_2CF_2CF_3 + R_2NH \xrightarrow[60\ °C\text{-}reflux,\ 1\text{-}24\ h]{no\ solvent} \underset{\mathbf{1}}{CF_3CF_2CH_2NR_2} \quad (45\text{-}93\%)$$

N,N-Dialkyl(2,2,3,3,3-pentafluoropropyl)amines (**1**) were prepared in two steps from commercially available 2,2,3,3,3-pentafluoropropanol by a slight modification of the literature method,[6] as shown above.

When amine **1c** (R = *n*-Bu) thus obtained was allowed to react with 2.2 equiv. of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at room temperature for 2 h, *N,N*-dibutyl-(3,3,3-trifluoro-1-propynyl)amine (**3c**) was formed in 47% yield, the starting amine being left unchanged in 41% yield, as shown in Table 1 (Entry 3). This alkynylamine **3c** was found to be readily converted into *N,N*-dibutyl-3,3,3-trifluoropropanamide (**4c**) by simple treatment with 5% aqueous HCl at room temperature for 15 min. Such bases as *n*-butyllithium and potassium *t*-butoxide were much less efficient than LDA (Entries 4 and 5) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was ineffective for the reaction (Entry 6). The addition of *N,N'*-dimethyl propyleneurea (DMPU) to the reaction mixture was quite crucial



a: R = Me, **b**: R = *n*-Pr, **c**: R = *n*-Bu,
d: R = -$(CH_2)_5$-, **e**: R = -$(CH_2)_2O(CH_2)_2$-,
f: R = Ph; Me, **g**: R = *i*-Pr, **h**: R = $PhCH_2$

for completion of the reaction (Entries 7 and 8). Eventually, the reaction was carried out in the following manner. To a THF solution of LDA (2.2 equiv.) were successively added DMPU (2.2 equiv.) and a THF solution of **1c** at 0 °C. The whole mixture was stirred at ambient temperature for 2 h. After the consumption of **1c** was confirmed by ^{19}F NMR, the reaction mixture was poured into 5% aqueous HCl.[7] The resultant mixture was stirred at room temperature for 15 min, and then extracted with dichloromethane. The extracts were dried over Na_2SO_4, followed by filtration and concentration *in vacuo*. The residue was purified by silica-gel column chromatography to give analytically pure *N,N*-dibutyl-3,3,3-trifluoropropanamide (**4c**)[8] in 88% yield (Entry 8).

The amines **1a** (R = Me)[9] and **1d** (R = -$(CH_2)_5$-) also underwent the reactions to afford the corresponding 3,3,3-trifluoropropanamides **4a** and **4d** in almost quantitative yields (Entries 1 and 10). The reaction of **1g** (R = *i*-Pr) with LDA under similar conditions proceeded sluggishly to result in a decrease in the yield of **4g** (Entry 11). Meanwhile, the reaction of **1h** (R = $PhCH_2$) did not take place at all, the starting amine being recovered quantitatively (Entry 12). This result probably comes from preferential deprotonation of the benzylic hydrogens in **1h** with LDA.

Of much significance is that no formation of *N,N*-dialkyl-(2,3,3,3-tetrafluoro-1-propenyl)amines (**2**) was observed in these reactions and even in the reaction using 1.1 equiv. of LDA. In the latter reaction nearly half an amount of **1c** remained unreacted (Entry 9). Such observations clearly suggest that the enamines **2** are more readily deprotonated with the base than the amines **1**. Then, a variety of enamines **2** were prepared according to the procedure reported recently by us[3d] and were subjected to the synthesis of the amides **4**. On treating **2** with LDA (1.1 equiv.) in the absence of DMPU in THF at 0 °C for 1 h, the reaction very cleanly occurred to lead to the quantitative forma-

Table 1. Synthesis of the amides **4** from **1** or **2**

Entry	1 or 2	Base	DMPU /eq.	Temp /°C	Time /h	Yield/% 3[a] (1 or 2)[a]	4[b]
1	**1a**	LDA	2.2	0	2	92 (tr)	86
2	**1c**	LDA	0	0	2	14 (75)	14
3	**1c**	LDA	0	r.t.	2	47 (41)	45
4	**1c**	*n*-BuLi	0	r.t.	2	5 (43)	tr
5	**1c**	*t*-BuOK	0	r.t.	24	23 (44)	22
6	**1c**	DBU	0	r.t.	24	0 (100)	0
7	**1c**	LDA	2.2	0	2	84 (9)	83
8	**1c**	LDA	2.2	r.t.	2	94 (tr)	88
9	**1c**	LDA[c]	1.1	r.t.	2	44 (48)	44
10	**1d**	LDA	2.2	r.t.	2	97 (tr)	90
11	**1g**	LDA	2.2	r.t.	24	66 (21)	65
12	**1h**	LDA	2.2	r.t.	24	0 (100)	0
13	**2a**	LDA[c]	0	0	1	92 (tr)	81
14	**2b**	LDA[c]	0	0	1	97 (tr)	90
15	**2c**	LDA[c]	0	0	1	96 (tr)	89
16	**2d**	LDA[c]	0	0	1	95 (tr)	85
17	**2e**	LDA[c]	0	0	1	94 (tr)	88
18	**2f**	LDA[c]	0	0	1	95 (tr)	88

[a] Determined by ^{19}F NMR of the crude mixture. [b] Isolated yields.
[c] The amounts of LDA employed were 1.1 equivalents.

tion of the corresponding alkynylamines **3**, which gave rise to the amides **4**[8] in excellent yields by the action of 5% aqueous HCl (Entries 13-18).

It is worth mentioning that the present protocol can be applied to the access of higher carbon homologues of **4**, though the reaction conditions are slighly modified. For instance, *N*,*N*-dibutyl(2,2,3,3,4,4,4-heptafluorobutyl)amine, prepared from the corresponding polyfluorinated butanol, was allowed to react with lithium diethylamide[10] (3.3 equiv.) and DMPU (3.3 equiv.) in THF at 0 ℃ for 2 h to form *N*,*N*-dibutyl(3,3,4,4,4-pentafluoro-1-butynyl)amine quantitatively. Successive treatment of it with HCl afforded *N*,*N*-dibutyl-3,3,4,4,4-pentafluorobutanamide[8] in 85% yield.

In summary, we have demonstrated that the present reactions serve as a quite convenient and practical means for synthesizing *N*,*N*-dialkyl-3,3,3-trifluoropropanamides **4** as well as higher carbon homologues, which are otherwise accessible with much difficulty. Further synthetic applications of **4** and a unique type of alkynylamines **3** are now in progress.

References and Notes

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7 *N*,*N*-Dibutyl(3,3,3-trifluoro-1-propynyl)amine (**3c**) was isolated if no acidic treatment was performed. Yield 48%; Bp 36 ℃/15 mmHg (1 mmHg = 133.322 Pa); IR (cm^{-1}) 2361 (C≡C); ^{1}H NMR ($CDCl_3$, Me_4Si, 300 MHz) δ = 0.94 (t, *J* = 7.2 Hz, 3H×2), 1.31-1.43 (m, 2H×2), 1.55-1.65 (m, 2H×2), 2.98 (t, *J* = 7.2 Hz, 2H×2); ^{19}F NMR ($CDCl_3$, $CFCl_3$, 84.2 MHz) δ = -45.3 (s, 3F); HRMS Found: *m/z* 221.1378. Calcd for $C_{11}H_{18}F_3N$: M, 221.1391.

8 All products gave satisfactory spectral and analytical data.

9 The amine **1a** was prepared according to our previously reported method. See: H. Yamanaka, H. Ganbayashi, M. Kuwabara, K. Fukunishi, and M. Nomura, *Nippon Kagaku Kaishi*, **1988**, 1036.

10 The use of LDA appreciably lowered the yields (33-35%) of the alkynylamine and amide.