

New Efficient Method for the Stereoselective Synthesis of α -(Trifluoromethyl)- α , β -unsaturated Amides.

Lewis Acid-Catalyzed Reaction of 3,3,3-Trifluoro-1-propynylamine with Carbonyl Compounds

Toshiya Mantani, Keisuke Shiomi, Takashi Ishihara,* and Hiroki Yamanaka

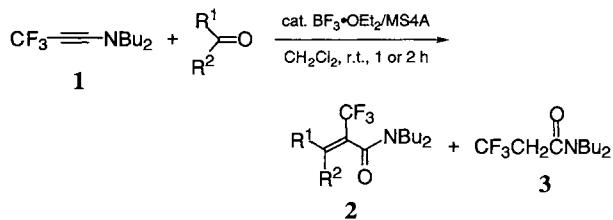
Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585

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N,N-Dibutyl-(3,3,3-trifluoro-1-propynyl)amine, prepared readily by the dehydrofluorination of *N,N*-dibutyl-(2,2,3,3,3-pentafluoropropyl)amine with lithium diisopropylamide at room temperature, smoothly reacted with a variety of aldehydes and ketones in the presence of a catalytic amount of Lewis acid and molecular sieves 4A at ambient temperature to give the corresponding α -(trifluoromethyl)- α , β -unsaturated amides in good to excellent yields with high *Z* stereoselectivity.

α, β -Unsaturated carbonyl compounds have widely been used as potent synthetic blocks in organic synthesis, particularly as Michael acceptors for conjugate addition reactions¹ or dienophiles and dipolarophiles for cycloaddition reactions.^{2,3} The counterparts carrying the trifluoromethyl substituent at the α position are likewise of great value as synthetic blocks for the construction of a variety of selectively trifluoromethylated compounds, which attract much attention in biological or material chemistry. In the literature, to our best knowledge, merely three types of methods are found for the preparation of α -(trifluoromethyl)- α, β -unsaturated carbonyl compounds, namely, the pyrolysis of *O*-acetate of trifluoroacetone cyanohydrin or α -hydroxy- α -(trifluoromethyl)propanoate,⁴ the direct or Pd(II)-catalyzed carbonylation of 3,3,3-trifluoro-1-propen-2-yllithium derived from 2-bromo-3,3,3-trifluoro-1-propene,^{5,6} and the Reformatsky reaction of 2,2-dichloro-3,3,3-trifluoropropanoate with aldehydes followed by reductive elimination.⁷ However, these methods suffer from serious drawbacks, such as extremely limited scope of the reaction, lack of the stereoselectivity of the reaction, and/or the difficult availability of the starting propanoate. Therefore, the development of a more general and efficient means for preparing such α -trifluoromethylated compounds is strongly demanded.

During the course of our studies on the preparations and applications of polyfluoroalkenyl- or alkynylamines,^{8,9} we found that *N,N*-dibutyl-(3,3,3-trifluoro-1-propynyl)amine (1) very readily underwent unique reactions with carbonyl compounds in the presence of Lewis acid.¹⁰ Herein, we would like to report the preliminary results of these reactions, especially demonstrating that the present reactions can serve as a highly effective and versatile method for the stereoselective synthesis of α -trifluoromethylated α, β -unsaturated amides 2.



First, the reaction of **1**, readily prepared from *N,N*-dibutyl-

(2,2,3,3,3-pentafluoropropyl)amine and lithium diisopropylamide,⁹ with benzaldehyde was carried out in dichloromethane (CH_2Cl_2) in the presence of molecular sieves 4A (MS4A) at room temperature for 24 h. ^{19}F NMR of the reaction mixture showed that only a trace quantity of **2a** was formed and **1** remained mostly unchanged. An acidic workup of the mixture gave *N,N*-dibutyl-3,3,3-trifluoropropanamide (**3**) in 79% yield. When 5 mol% of $\text{BF}_3\text{-OEt}_2$ was applied to the reaction, the amides **2a** and **3** were obtained in 28% and 67% yields, respectively (Entry 1). An increase (10 mol%) in the amount of $\text{BF}_3\text{-OEt}_2$ allowed the reaction to proceed very efficiently, resulting in the formation of **2a** in 92% yield (Entry 2). The presence of MS4A was requisite to suppress the formation of **3**, which may come from the acidic hydration with a slight amount of water contaminating the starting crude amine **1**; the reaction in the absence of MS4A produced 28% of **3** along with 66% of **2a**, and the reaction using lanthanum(III) triflate, known to be resistant to hydrolysis,¹¹ gave a satisfactory result even in the absence of MS4A, though the reaction time had to be extended to 24 h (Entry 6). Lewis acids other than $\text{BF}_3\text{-OEt}_2$, such as zinc bromide, titanium(IV) chloride, and tin(IV) chloride, were also effective for the reaction (Entries 3-5). Toluene, diethyl ether, and tetrahydrofuran were employed as the solvents comparable to CH_2Cl_2 (Entries 7-9).

Thus, the general procedure for the reaction is as follows. To a mixture of aldehyde or ketone (1.1 equiv.) in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ (10 mol%) and MS4A (1 g to 1 mmol of 1) in CH_2Cl_2 was dropwise added 1-propynylamine 1 (1.0 equiv.) under argon. The whole mixture was stirred at room temperature for 1 h. In the case of ketone, the reaction period was 2 h. MS4A was removed by filtration and the filtrate was washed successively with 3% HCl and brine, followed by drying over anhydrous Na_2SO_4 . Evaporation of the solvent and column chromatography on silica gel using benzene and AcOEt gave analytically pure product 2.¹²

As summarized in Table 1, a variety of aromatic and aliphatic aldehydes, including α,β -unsaturated aldehydes, smoothly underwent the reaction with **1** leading to the corresponding α -(trifluoromethyl)- α,β -unsaturated amides **2** in high yields. Of much importance is that these reactions took place in a highly stereoselective manner, except for the reaction of 2,2-dimethylpropanal, to afford the (*Z*)-isomers of **2** exclusively (Entries 2, 10-20). The reaction of 2,2-dimethylpropanal gave an isomeric mixture of the *E* : *Z* ratio of 44 : 56 (Entry 21).¹³ The decrease in the stereoselectivity seems to be attributed to the steric bulk of the *tert*-butyl group of the aldehyde. Ketones also participated nicely in the reaction, giving rise to good yields of **2** (Entries 22-25), but the *Z* stereoselectivity was not so high.

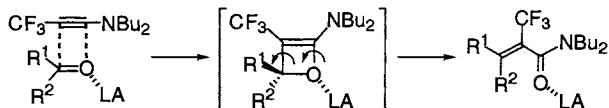
Although the mechanism of this reaction awaits further investigation, the following reaction scheme can be drawn at the present time. Thus, the amine **1** may attack a Lewis acid-

Table 1. Lewis acid-catalyzed reaction of 3,3,3-trifluoro-1-propynylamine (1) with various carbonyl compounds

Entry	Carbonyl compd	R ¹	R ²	Lewis acid ^a	Solvent	Time /h	Yield ^b % of 2	Isomer ratio ^c E : Z	Yield ^b % of 3
1	Ph		H	BF ₃ •OEt ₂ ^d	CH ₂ Cl ₂	1	2a 28	<3 : >97	67
2	Ph		H	BF ₃ •OEt ₂	CH ₂ Cl ₂	1	2a 92	<3 : >97	tr
3	Ph		H	ZnBr ₂	CH ₂ Cl ₂	1	2a 90	<3 : >97	5
4	Ph		H	TiCl ₄	CH ₂ Cl ₂	1	2a 80	<3 : >97	12
5	Ph		H	SnCl ₄	CH ₂ Cl ₂	1	2a 81	<3 : >97	5
6	Ph		H	La(OTf) ₃ ^e	CH ₂ Cl ₂	24	2a 71	<3 : >97	8
7	Ph		H	BF ₃ •OEt ₂	PhCH ₃	1	2a 84	<3 : >97	3
8	Ph		H	BF ₃ •OEt ₂	Et ₂ O	1	2a 82	<3 : >97	6
9	Ph		H	BF ₃ •OEt ₂	THF	1	2a 82	<3 : >97	7
10	p-MeC ₆ H ₄		H	BF ₃ •OEt ₂	CH ₂ Cl ₂	1	2b 95	<3 : >97	2
11	p-MeOC ₆ H ₄		H	BF ₃ •OEt ₂	CH ₂ Cl ₂	1	2c 81	<3 : >97	6
12	p-ClC ₆ H ₄		H	BF ₃ •OEt ₂	CH ₂ Cl ₂	1	2d 87	<3 : >97	4
13	2-Thienyl		H	BF ₃ •OEt ₂	CH ₂ Cl ₂	1	2f 81	4 : 96	tr
14	(E)-PhCH=CH		H	BF ₃ •OEt ₂	CH ₂ Cl ₂	1	2g 82	<3 : >97	tr
15	(Z)-PhCH=CF ^f		H	BF ₃ •OEt ₂	CH ₂ Cl ₂	1	2h 97	<3 : >97	tr
16	(E)-MeCH=CH		H	BF ₃ •OEt ₂	CH ₂ Cl ₂	1	2j 95	4 : 96	3
17	CH ₂ =C(Me)		H	BF ₃ •OEt ₂	CH ₂ Cl ₂	1	2k 88	<3 : >97	6
18	Pr		H	BF ₃ •OEt ₂	CH ₂ Cl ₂	1	2l 83	<3 : >97	5
19	c-Hex		H	BF ₃ •OEt ₂	CH ₂ Cl ₂	1	2m 82	<3 : >97	11
20	i-Pr		H	BF ₃ •OEt ₂	CH ₂ Cl ₂	1	2n 89	4 : 96	3
21	t-Bu		H	BF ₃ •OEt ₂ ^g	CH ₂ Cl ₂	2	2o 68	44 : 56	23
22	Me		Me	BF ₃ •OEt ₂	CH ₂ Cl ₂	2	2p 85	—	6
23	-(CH ₂) ₅ -			BF ₃ •OEt ₂	CH ₂ Cl ₂	2	2r 77	—	8
24	Ph		Me	BF ₃ •OEt ₂	CH ₂ Cl ₂	2	2s 72	29 : 71	9
25	CH ₂ =CH		Me	BF ₃ •OEt ₂	CH ₂ Cl ₂	2	2t 71	28 : 72	13

^a Unless otherwise noted, 10 mol% of Lewis acid was used. ^b The yields refer to pure products isolated by column chromatography on silica gel. ^c Measured by ¹⁹F NMR of the crude products prior to isolation. ^d Carried out by using 5 mol% of Lewis acid. ^e The reaction was carried out in the absence of MS4A by using 30 mol% of Lewis acid. ^f Prepared from β -fluorovinamidinium salt and phenylmagnesium bromide.¹⁵ ^g Carried out by using 20 mol% of Lewis acid.

coordinated carbonyl compound to form an oxetene intermediate. This intermediate would be subject to ring-opening in such a way that the Lewis acid part and the substituent R¹ or R² (R¹ > R²) exert the least possible repulsive interaction, leading preferentially to the product 2.



In summary, we have developed an efficient and stereo-selective access to the (Z)-isomers of α -(trifluoromethyl)- α , β -unsaturated amides 2, which are otherwise very difficult to prepare, through the Lewis acid-catalyzed reaction of poly-fluorinated 1-alkynylamine 1 with various carbonyl compounds. Further studies on the synthetic application of 1 are in progress.

References and Notes

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- All isolated compounds exhibited satisfactory spectral (IR, HRMS, ¹H (300 MHz) and ¹⁹F (84 MHz) NMR) and analytical data.
- The stereochemical assignments of 2 were tentatively made on the basis both of the relative magnitudes of long-range ⁴J(CF₃—vinyl H) or ⁵J(CF₃— β -CH) values and of the relative ¹⁹F chemical shifts for the CF₃ group. Thus, the long-range couplings for the (Z)-isomers are smaller than those for the (E)-isomers, and the chemical shifts for the former are consistently lower than those for the latter. Similar tendencies are observed for trifluoromethylated olefinic compounds.¹⁴
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