New Synthetic Protocol with Trifluoro-1-propynylamines. An Efficient Access to α-(Trifluoromethyl)-δ-keto Amides *via* Hetero Diels-Alder Reaction

Toshiya Mantani, Tsutomu Konno, Takashi Ishihara,* and Hiroki Yamanaka
Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585

(Received March 27, 2000; CL-000282)

N,*N*-Dibutyl(3,3,3-trifluoro-1-propynyl)amine readily reacts with α,β-unsaturated ketones or aldehydes in refluxing benzene for 3–36 h to form the corresponding Diels-Alder adducts, 2-(dibutylamino)-3-(trifluoromethyl)-4*H*-pyrans, of which the successive treatment with alumina at ambient temperature for 1 h leads to the ring-opening products, α-trifluoromethylated δ-keto amides in fairly good to excellent yields.

Carboxylic acid derivatives bearing the trifluoromethyl group at the α position are extremely useful intermediates for the preparation of various sorts of trifluoromethyl-incorporated compounds, especially those of biological and material interest. Although the literature includes several reports dealing with the synthetic methods for α-trifluoromethyl carboxylic acid derivatives,[1,2] they are not necessarily sufficient to the diversity of demands in organic synthesis. Therefore, it is of much synthetic value to develop a new method for preparing such carboxylic acid derivatives.

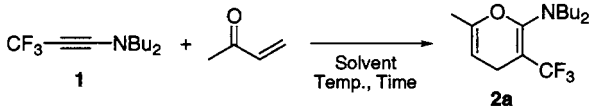


Table 1. Cycloaddition reaction of **1** with MVK

Entry	Solvent	Temp.	Time/h	Yield[a]/% of **2a**	Recovery[a]/% of **1**
1	CH_2Cl_2	r.t.	3	71	28
2	CH_2Cl_2	r.t.	24	85	tr
3	CH_2Cl_2	refl.	3	97	tr
4	benzene	refl.	3	>99 (99)	0
5	toluene	refl.	3	82	0

[a]Determined by ^{19}F NMR. Value in parentheses is of isolated yield.

During the course of our studies to extend the chemistry and applications of fluorine-containing 1-alkenylamines (enamines)[3] and 1-alkynylamines (ynamines),[4,5] we have found that *N*,*N*-dibutyl(3,3,3-trifluoro-1-propynyl)amine (**1**) readily undergoes hetero Diels-Alder reaction with α,β-unsaturated ketones or aldehydes yielding the corresponding cycloadducts **2**,[6] followed by simple treatment with alumina to lead to α-trifluoromethylated δ-keto amides **3**. This communication discloses the preliminary results demonstrating that the present reactions can serve as a novel efficient and convenient route to the synthesis of such amides, which are difficult to prepare by other methods.

When the ynamine **1**, prepared in three steps from commercially available pentafluoropropanol,[4] was allowed to react with 1.5 equiv of 3-buten-2-one (methyl vinyl ketone, MVK) in dichloromethane at room temperature for 3 h, 2-(dibutylamino)-6-methyl-3-(trifluoromethyl)-4*H*-pyran (**2a**)[7] was formed in 71% yield, the starting amine being left unchanged in 28% yield, as shown in Table 1 (Entry 1). Either prolonged reaction period or higher reaction temperature induced the formation of **2a** in excellent yields (Entries 2,3). The best result was obtained from the reaction in refluxing benzene for 3 h, where **2a** was provided quantitatively (Entry 4). The reaction at the reflux temperature of toluene resulted in a lowering of the yield of **2a**, due to its thermal decomposition (Entry 5). It is worthwhile to note that the present [4+2] cycloaddition of **1** makes a sharp contrast to the previously reported [2+2]-type reaction[5] with α,β-unsaturated carbonyl compounds, facilitated by a Lewis acid catalyst, leading exclusively to (*Z*)-α-(trifluoromethyl)-α,β-unsaturated amides.

More significantly, the resultant cycloadduct **2a** was found to be readily converted into *N*,*N*-dibutyl-2-(trifluoromethyl)-5-oxohexanamide (**3a**)[8] by the action of basic or acidic reagents, as summarized in Table 2. Thus, on treating **2a** with 20% NaOH, silica gel (1 g/mmol of **2a**), or alumina (1 g/mmol of **2a**) at room temperature for 1 h, the corresponding amide **3a** was obtained in 91%, 82%, and 99% yields, respectively (Entries 4–6). The similar treatment with 3–10% HCl gave rise to **3a** in 46–70% yields, along with the formation of 2-(trifluoromethyl)-4-hexen-5-olide (**4a**)[9] (30-50%) (Entries 2,3). Exposure of **2a** to H_2O did not cause any chemical changes (Entry 1).

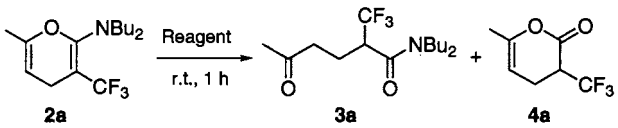
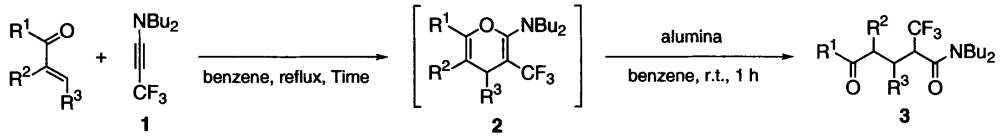


Table 2. Transformation of cycloadduct **2a**

Entry	Reagent	Ratio[a] of **3a** : **4a**	Yield[b]/% of **3a**	Yield[b]/% of **4a**
1[c]	H_2O	—	0	0
2	10% HCl	46 : 54	46	50
3	3% HCl	70 : 30	70	30
4	20% NaOH	>99 : <1	91	0
5	Silica gel	83 : 17	82	tr
6	Alumina	>99 : <1	99	0

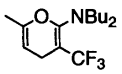
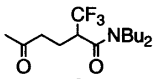
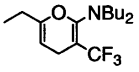
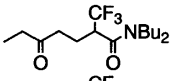
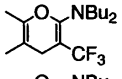
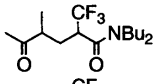
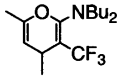
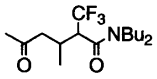
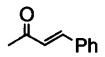
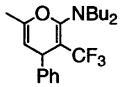
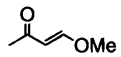
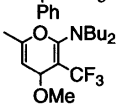
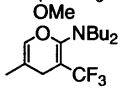
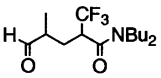
[a]Determined by ^{19}F NMR. [b]Isolated yields. [c]Carried out for 24 h.

Eventually, these reactions are recommended to be carried out in the following typical manner. A solution of **1** (1 mmol) and 3-buten-2-one (1.5 mmol) in benzene (3 mL) was gently refluxed with stirring under an atmosphere of argon for 3 h. After cooling, alumina (1 g, ICN Alumina N, Act. 1) was added to the reaction mixture and the whole was stirred at ambient temperature for 1 h. Filtration and concentration under vacuum followed by silica-gel column chromatography afforded analytically pure α-trifluoromethylated amide **3a** in 98% overall yield.



1 2 3

Table 3. Preparation of α-(trifluoromethyl)-δ-keto amides **3** from the ynamine **1** and α,β-unsaturated carbonyl compounds

Entry	Carbonyl compd	Time/h	Cycloadduct **2**	Yield[a]/% of **2**	Keto amide **3**	Yield[b]/% of **3**	Diastereo ratio[c]
1		3	**2a** 	99	**3a** 	99	—
2		3	**2b** 	94	**3b** 	93	—
3		36	**2c** 	85	**3c** 	96	70 : 30
4		36	**2d** 	54	**3d** 	99	80 : 20
5		36	**2e** 	tr		0	—
6		36	**2f** 	0		—	—
7		36	**2g** 	58	**3g** 	55	70 : 30

[a]Determined by ^{19}F NMR. [b]Values are of isolated product and are based on **2**. [c]Measured by ^{19}F NMR. The stereochemistry is not assigned.

Table 3 summarizes the results of these reactions. Various α,β-unsaturated ketones and aldehyde participated nicely in the hetero Diels-Alder reaction with **1**, giving the corresponding 2-(dibutylamino)-3-(trifluoromethyl)-4*H*-pyrans **2**[9] in fairly good to excellent yields. It should be mentioned that the cycloaddition reactions of β-substituted α,β-unsaturated ketones (Entries 4-6) or α,β-unsaturated aldehyde (Entry 7) occurred very reluctantly and hence required longer reaction time. Particularly the reactions of β-phenyl- and β-methoxy-substituted ones did not take place at all, the starting ynamine **1** being recovered quantitatively. Thus obtained cycloadducts **2** were readily transformed into the corresponding amides **3**[9] by the action of alumina.

In short, we have demonstrated that the fluorinated ynamine **1** reacts as a dienophile with α,β-unsaturated ketones or aldehydes to produce the cycloadducts **2**, whose successive treatment with alumina provides α-(trifluoromethyl)-δ-keto amides **3**. This sequence of the reactions can constitute a novel convenient means for the synthesis of such a unique type of compounds, which are otherwise accessible with difficulty.

References and Notes

1 For the methods with trifluoromethylated building blocks, see: T. Yokozawa, T. Nakai, and N. Ishikawa, *Tetrahedron Lett.*, **25**, 3987 (1984); T. S. Everett, S. T. Purrington, and C. L. Bumgardner, *J. Org. Chem.*, **49**, 3702 (1984); T. Yokozawa, T. Nakai, and N. Ishikawa, *Chem. Lett.*, **1987**, 1971; G. Shi and Y. Xu, *J. Org. Chem.*, **55**, 3383 (1990).

2 For the methods via trifluoromethylation, see: K. Iseki, T. Nagai, and Y. Kobayashi, *Tetrahedron: Asymmetry*, **5**, 961 (1994); Y. Dan-oh and K. Uneyama, *Bull. Chem. Soc. Jpn.*, **68**, 2993 (1995).

3 H. Yamanaka, K. Shiomi, and T. Ishihara, *Tetrahedron Lett.*, **36**, 7267 (1995); H. M. Park, T. Uegaki, T. Konno, T. Ishihara, and H. Yamanaka, *Tetrahedron Lett.*, **40**, 2985 (1999).

4 H. Yamanaka, T. Mantani, K. Shiomi, and T. Ishihara, *Chem. Lett.*, **1998**, 615.

5 T. Mantani, K. Shiomi, T. Ishihara, and H. Yamanaka, *Chem. Lett.*, **1999**, 855.

6 For the [4+2] cycloaddition of fluorine-free 1-alkynylamines, see: J. Ficini, J. Besseyre, and A. Krief, *Bull. Chim. Soc. Fr.*, **1976**, 987; J. Ficini, *Tetrahedron*, **32**, 1449 (1976); J. Collard-Motte and Z. Janousek, *Top. Curr. Chem.*, **130**, 89 (1986); A. Padwa, Y. Gareau, B. Harrison, and A. Rodriguez, *J. Org. Chem.*, **57**, 3540 (1992).

7 **2a**: IR (cm^{-1}) 1720 (C=C), 1655 (C=C); ^{1}H NMR ($CDCl_3$, Me_4Si, 300 MHz) δ = 0.90 (t, *J* = 7.2 Hz, 6H), 1.23–1.50 (m, 8H), 1.74 (dt, *J* = 1.5, 1.2 Hz, 3H), 2.80 (dd, *J* = 3.0, 1.2 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 4H), 4.62 (t, *J* = 1.5, 3.0 Hz, 1H); ^{19}F NMR ($CDCl_3$, $CFCl_3$, 84.2 MHz) δ = -60.67 (s, 3F); MS *m/z* (rel. intensity) 291 (M^+, 13), 57 (100).

8 **3a**: IR (cm^{-1}) 1717 (C=O), 1651 (C=O); ^{1}H NMR ($CDCl_3$, Me_4Si, 300 MHz) δ = 0.93 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H), 1.22-1.60 (m, 8H), 2.07–2.18 (m, 1H), 2.14 (s, 3H), 2.60 (dt, *J* = 6.5, 18.3 Hz, 1H), 2.43 (dt, *J* = 6.6, 18.3 Hz, 1H), 3.19–3.65 (m, 6H); ^{19}F NMR ($CDCl_3$, $CFCl_3$, 84.2 MHz) δ = -67.29 (d, *J* = 8.8 Hz, 3F); HRMS Found: *m/z* 309.1915. Calcd for $C_{15}H_{26}F_3NO_2$: M, 309.1915.

9 All products gave satisfactory spectral and analytical data.