Pergamon

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Tetrahedron 59 (2003) 2899–2905

TETRAHEDRON

Cycloaddition reactions of β-trifluoroacetylvinyl ethers

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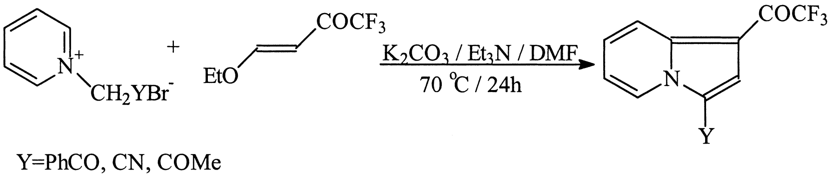
Received 6 November 2002; revised 3 February 2003; accepted 27 February 2003

Abstract—β-Trifluoroacetyl vinyl ethers ROCH═CHCOCF$_3$ react smoothly as dienophiles with α,β-unsaturated carbonyl compounds to give the unexpected 2-alkoxyl-5-trifluoroacetyl-3,4-dihydro-2*H* pyrans. These products are formed by elimination and addition of the alcohol to the products of the normal hetero Diels–Alder reaction (2-alkoxyl-3-trifluoroacetyl-2,3-dihydro-2*H* pyrans). In contrast, 1,3-dipolar cycloaddition of ROCH═CHCOCF$_3$ with ArCH═N(O)Me proceeds via a *Z-endo* transition state to give regio- and stereospecific 4-trifluoroacetyl substituted isoxazolidines and their derivatives. © 2003 Elsevier Science Ltd. All rights reserved.

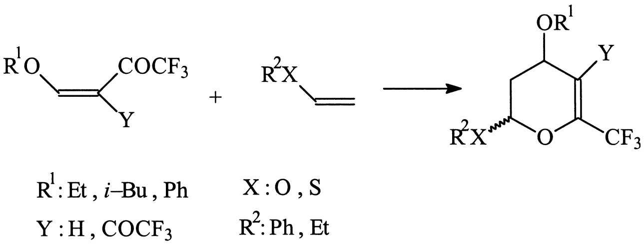
1. Introduction

β-Trifluoroacetyl vinyl ethers ROCH═CHCOCF$_3$ **1** are potential fluorinated 1,3-dicarbonyl compounds and were first prepared in 1967. Since then, their preparation and chemical transformations have been extensively investigated.[1] However, their cycloaddition reactions have not been extensively studied. During our investigations on pull–push olefins,[2] we found that **1** reacted readily as a dipolarophile with pyridinium or isoquinolinium *N*-ylides to give the corresponding 1-trifluoroacetyl substituted indolizines and their derivatives (Scheme 1).



Scheme 1.

Recently, Hojo et al.[3] reported reactions of β-(trifluoroacetyl)vinyl ether or β,β-bis(trifluoroacetyl)vinyl ether with electron-rich alkenes such as vinyl ether, or ethyl vinyl sulfide. Several 6-trifluoromethylated 3,4-dihydro-2*H* pyrans were prepared (Scheme 2).



Scheme 2.

However, the Diels–Alder reaction of compound **1** using as the dienophiles with the heterodienes has not been studied until now.

In order to develop the application of compound **1** in the construction of fluorine containing five and six membered heterocycles, we recently investigated the cycloaddition reactions of compound **1** such as the hetero Diels–Alder and the 1,3-dipolar cycloaddition reactions. Herein we report our results.

2. Results and discussion

The [2+4] cycloadditions of **1** with a little excess α,β-unsaturated aldehydes R^{1}CH═C(R^2)CHO **2** (R^1,R^2=H, CH$_3$) were carried out in a sealed glass tube at 140°C without solvent. A small amount of 2,4-di-*tert*-butyl-4-

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Keywords: β-trifluoroacetyl vinyl ethers; hetero Diels–Alder reaction; 1,3-dipolar cycloaddition; nitrones; trifluoroacetylated isoxazolidines.

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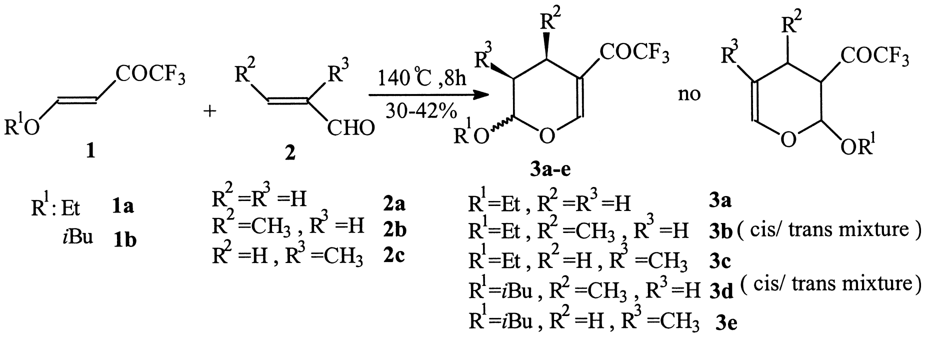
doi:10.1016/S0040-4020(03)00344-2



Scheme 3.

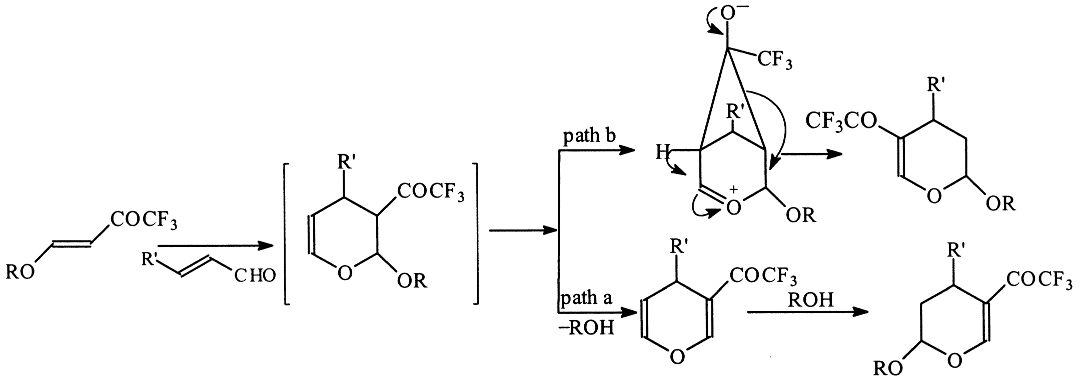
methylphenol (1 mol%) was added to avoid polymerization of **2**. After stirring for 8 h, TLC analysis showed that the reaction was finished. Separation and purification of the reaction products were accomplished by fractional distillation and column chromatography. The pure products were obtained as yellow oils.

It was surprising that according to the NMR and IR spectra, the product was not the expected 2-alkoxyl-3-trifluoroacetyl-3,4-dihydro-2*H* pyran. For example, the ^{1}H NMR spectrum of the product **3a** has only one alkene proton, which is a single peak at 7.71 ppm. The chemical shift of the CF_3 group in the ^{19}F NMR spectrum of **3a** is −68.5 ppm indicating that the CF_3CO group is bonded to an unsaturated carbon atom. In the ^{13}C NMR spectrum of **3a**, the chemical shift of double bond carbon atoms are 159.5 ppm (q, $^4J_{C-F}$=5.3 Hz) and 111.87 ppm(s), which are very close to the spectrum of 5-trifluoroacetyl-3,4-dihydron-2*H* pyran [(162.2 ppm (q), $^4J_{C-F}$=5.3 Hz), 111.2 ppm (s)].[4] The IR spectrum of **3a** shows strong absorptions at 1613 cm^{-1} and 1683 cm^{-1}, which indicate that there is a conjugated carbonyl group. The other products (**3b**–**e**) have similar NMR and IR spectra. According to these data, we assigned the products as 2-alkoxyl-5-trifluoroacetyl-3,4-dihydron pyrans (Scheme 3).

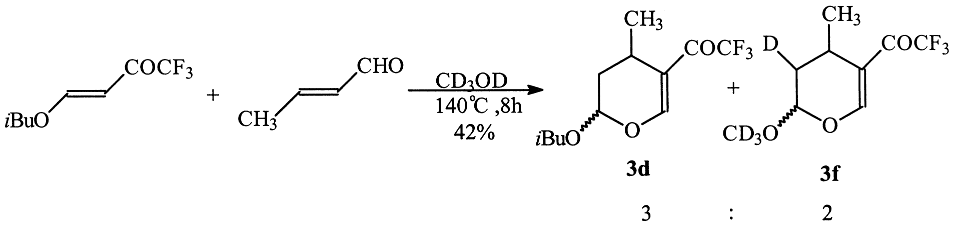
For the formation of the products **3**, there are two possible reaction pathways (Scheme 4).

In order to verify the above proposed possibilities, we carried out the reaction of $Bu^iOCH{=}CHCOCF_3$ (**1b**) with $CH_3CH{=}CHCHO$ (**2b**) in CD_3OD solvent. After similar treatment, 2-methoxyl-d$_3$-3-deuterium-4-methyl-5-trifluoroacetyl 3,4-dihydro-2*H*-pyran **3f** as well as the normal product (2-isobutoxyl-4-methyl-5-trifluoroacetyl 3,4-dihydro-2*H*-pyran **3d**) were obtained. The ratio of **3d**/**3f** is about 3:2 (Scheme 5).

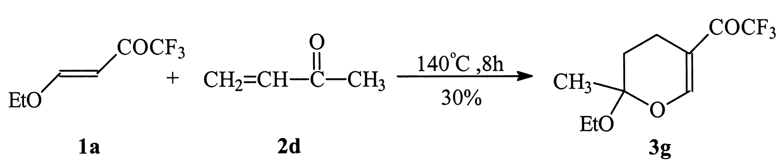
From this result it is clear that the products **3** should come from an elimination-addition process of the normal Diels–Alder cycloaddition product. It was noticed that the reaction of **1a** with crotonaldehyde **2b** gave a mixture of *cis*- and *trans*-adducts of 2-ethyl-4-methyl-5-trifluoroacetyl-3,4-dihydro-2*H* pyran **3b** in a ratio of 55:45, according to the ^{1}H NMR spectrum. It was not possible to separate the *cis*- and *trans*-mixtures by preparative TLC. However, when **1**



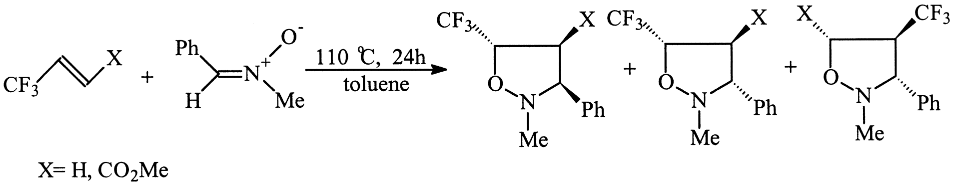
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

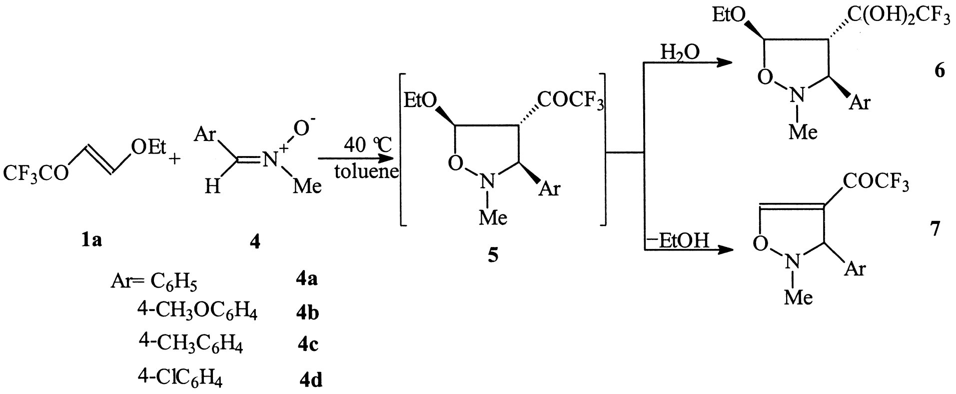
was treated with **2c**, only one product was obtained. Similar results were also obtained when **1b** was reacted with **2b** and **2c**. The product **3d** is a *cis/trans* isomer mixture, while **3e** is not (Scheme 3). Methyl vinyl ketone **2d** reacted similarly with **1a** to give 2-ethoxyl-2-methyl-5-trifluoroacetyl-dihydro-2*H*-pyran **3g** as the sole product (Scheme 6).

Utilization of **1** and **3** as synthetic intermediates for the preparation of various CF_3 containing compounds with potential biological activity is now under investigation.

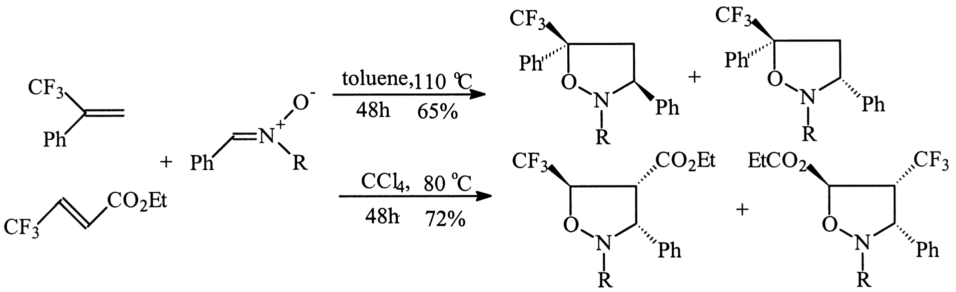
Next, we tried to investigate the 1,3-dipolar cycloaddition of **1** with nitrones. Amongst the 1,3-dipolar reagents, nitrones have been widely applied in the preparation of isoxazolidines.

In the past decades, several research groups[5] reported the preparation of trifluoromethylated isoxazolidines and their derivatives by the [2+3] cycloaddition of trifluoremethylated alkenes with nitrones. However, in many cases these reactions gave the mixtures of regio- and stereoisomeric cycloaddition products. An example is shown in Scheme 7.[6]

The 1,3-dipolar cycloaddition of *C*-arylnitrones ArCH=N(O)Me **4** (Ar=Ph, 4-$CH_3C_6H_4$, 4-ClC_6H_4) with $EtOCH{=}CHCOCF_3$ were carried out in toluene at 40°C which is a lower reaction temperature compared to other similar reactions.[7] For example, reaction of ethyl-3-trifloromethyl cinnamate or 1-trifluormethyl styrene with **4a** was reported in refluxing toluene (140°C). The observed difference in the reactivity between **1** and the above mentioned dipolarophiles can be attributed to the presence of the powerful electron-withdrawing CF_3CO group. After stirring for 4 days, TLC analysis showed that the reaction had finished and only one product was formed. It was found that the 4-trifluoroacetyl isoxazolidines **5** were easy to



Scheme 8.



Scheme 9.

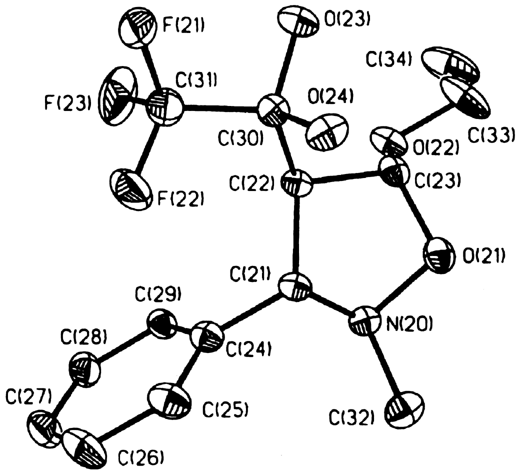
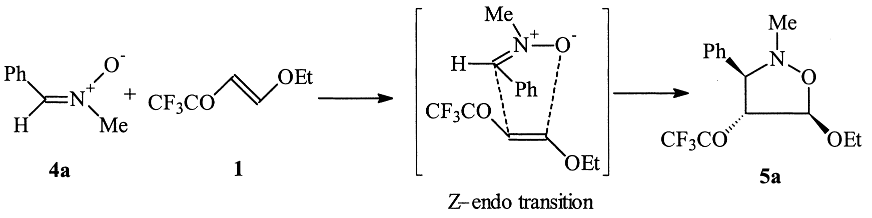
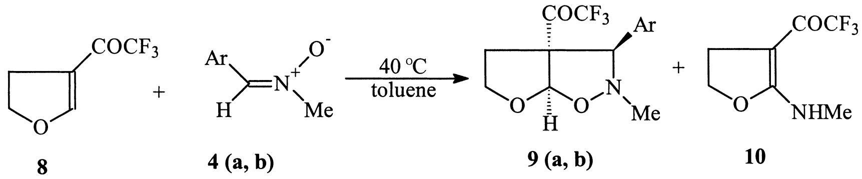


Figure 1. The structure of compound **6a**.



Scheme 10.



Scheme 11.

hydrate or eliminate to give compounds **6** and **7** during the purification process by column chromatography on a silica gel (Scheme 8).

Eguchi and Depons[7] reported that 2-trifluoromethyl styrene reacted with *N*-methyl *C*-phenylnitrone to give two stereoisomeric cycloaddition products, while 1-ethoxycarbonyl-3,3,3-trifluoro-propene gave two regioisomers (Scheme 9).

However, in our case the [2+3] cycloaddition gave only one product (presumed to be **5**) according to the TLC analysis of the reaction mixture. The ^{1}H NMR spectra of **6** have a value of the coupling constant (8 Hz) between 3-H and 4-H indicates their *trans* relationship which was similar to examples in the literatures.[5a,7b] The structure of compound **6** was also confirmed by X-ray diffraction analysis of **6a** (Fig. 1).

It is known that aldonitrones generally exist in the more stable *Z* configuration.[8] Bjorgo[9] also reported that the *N*-methyl *C*-phenylnitrone **4a** exists as a mixture of *Z* and *E* isomers at 147°C. Under our reaction conditions (40°C), however, nitrones **4** should react with **1** in their *Z* form. Since an electron-withdrawn group (CF_3CO) is present in dipolarophile **1**, the *endo* transition state should be more favorable, because of the secondary orbital interaction between a p-orbital of the nitrogen atom and the π-orbital of the C═O group.[10] Hence, we believe that the [2+3] dipolar cycloaddition of **1** with nitrones **4** proceeds via a *Z-endo* transition, which minimizes the steric interaction to give exclusively the 3,4-*trans*, 4,5-*trans* product **5** (Scheme 10).

It was noteworthy that when cyclic 3-trifluoroacetyl 2,3-dihydro-2*H* furan **8** was reacted with nitrones, a similar regio- and stereospecific cycloaddition product bicyclo-isoxazolidine **9** was obtained, accompanied by a small amount of 4-trifluoroacetyl-5-(*N*-methylamino)-2,3-dihydro-2*H* furan **10** as by-product. Compound **10** could arise from the nucleophlic reaction of **8** with MeNHOH, which could come from the decomposition of **4** (Scheme 11).

The bicycle isoxazodilidine **9** is stable and did not hydrate during the chromatographic process. In the ^{19}F NMR spectra of **9**, the chemical shift of the CF_3CO group is −71.5 ppm which is more downfield compared with the products **6** (−84.5 ppm) in which the CF_3CO group was hydrated and **7** (−74.5 ppm) in which the CF_3CO group was conjugated with a carbon–carbon double bond.

Under similar reaction conditions when **4c** was reacted with **8**, the only isolated product was **10** and no corresponding [2+3] cycloaddition product **9c** formed. We repeated this reaction three times in different solvents ($CH_3C_6H_5$, C_6H_6, CCl_4) and different temperatures (40–80°C) but all failed to give **9c**. It is difficult to explain why **4c** was all decomposed to HN(Me)OH under these reaction conditions.

Table 1. The reaction of the nitrones **4** with the pull–push alkenes **1** or **8**

Entry	Reactant		Products and yield (%)[a]	
	(**1** or **8**)	**4**	**6** and **7**	Or **9** and **10**
1	**1**	**4a**	**6a** (38)	**7a** (16)
2	**1**	**4b**	**6b** (40)	**7b** (17)
3	**1**	**4c**	**6c** (43)	**7c** (13)
4	**1**	**4d**	**6d** (18)	**7d** (6)
5	**8**	**4a**	**9a** (36)	**10** (5)
6	**8**	**4b**	**9b** (28)	**10** (15)
7	**8**	**4c**		**10** (30)

[a] Isolated yield based on **1** or **8**.

A summary of all the reaction results of the nitrones with the pull–push alkenes (**1** or **8**) are listed in Table 1.

In summary, some new cycloaddition reaction of β-trifluoroacetyvinyl ethers with alkene and vinyl nitrones have been developed.

3. Experimental

3.1. General

Solvents were purified and dried before use. Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR and ^{19}F NMR spectra were recorded on Varian-360 or Bruker AM-300 instruments with Me_4Si and $CFCl_3$ (with upfield negative) as internal and external standards respectively; NMR spectra were recorded in chloroform-*d* unless otherwise stated. IR spectra were obtained with a Perkin–Elmer 983G, spectrophotometer using KBr disks of the compound. Low and high-resolution mass spectra were obtained on HP 5989a and Finnigan MAT instruments, respectively. Elemental analyses were performed by this institute. The X-ray structure analysis was performed with a Rigaku/AFC 7R Diffractometer

4-(Ethoxy)-1,1,1-trifluoromethyl-3-en-2-one **1**,[11a] aryl-*N*-methyl nitrones **4**,[11b] and 4-trifluoroacetyl-2,3-dihydron-2*H* furan **8**[2b] were prepared according to the literature methods.

3.1.1. General reaction procedure for the Diels–Alder reaction of 1 with α,β-unsaturated carbonyl compounds. A mixture of **1a** (1.96 g, 10 mmol), **2b** (1.05 g, 15 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (0.44 g) in a sealed glass tube was heated at 140°C and stirred for 8 h. The crude product was distilled out under vacuum, then purified by column chromatography using ethyl acetate and pentane (1:60) as eluent to give 2-ethoxyl-4-methyl-5-trifluoroacetyl-3,4-dihydro-2H pyran **3b** (0.9 g, 40%) which is a *trans* and *cis* mixture (3:4); yellow oil, [Found: C, 50.28; H, 5.30 $C_{10}H_{13}F_3O_3$ requires C, 50.42; H, 5.50%]; δ_H (300 MHz, $CDCl_3$) 1.16 (3H, d, J=7.2 Hz, 4-CH_3), 1.22 (3H, t, J=7.2 Hz, $\mathit{CH_3}CH_2O$), 1.28 (3H, d, J=7.2 Hz, 4-CH_3), 1.88 (2H, m, 3-H), 1.95 (2H, m, 3-H), 2.76 (1H, m, 4-H), 2.90 (1H, m, 4-H), 3.66 (1H, dq, J=12.0, 7.2 Hz, $CH_3\mathit{CH_2}O$), 3.90 (1H, dq, J=12.0, 7.2 Hz $CH_3\mathit{CH_2}O$), 5.17 (1H, t, J=5.7 Hz, 2-H), 5.27 (1H, t, J=3.0 Hz, 2-H), 7.69 (1H, s, 6-H); δ_F (282 MHz, $CDCl_3$) −68.3 (3F, s, CF_3); δ_C (75.3 MHz, $CDCl_3$) 15.0 ($\mathit{CH_3}CH_2O$), 19.5, 20.1 (4-CH_3), 22.2, 23.5 (3-C), 32.7, 33.8 (4-C), 65.1, 65.2 ($CH_3\mathit{CH_2}O$), 99.3, 99.5 (2-C), 116.1, 116.7 (5-C), 116.8 (q, $^1J_{C-F}$=282 Hz, CF_3), 158.9, 159.8 (q, $^1J_{C-F}$=5.5 Hz, 6-C), 178.8 (q, $^2J_{C-F}$=32 Hz, C=O); IR (KBr) ν_{max}=1683, 1611, 1191, 1142 cm^{-1}; MS (*m/z*, %): 238 (M^+, 8.36), 220 (M^+H-F, 36.10), 205 ($M^+H-F-CH_3$, 99.84), 192 (M^+-EtOH, 29.63), 123 ($M^+-EtOH-CF_3$, 72.92), 97 (CF_3CO^+, 19.85), 69 (CF_3^+, 24.10), 57 ($C_3H_5O^+$, 100.00).

3.1.2. 2-Ethoxyl-5-trifluoroacetyl-3,4-dihydro-2*H* pyran 3a. Yield 46%. Yellow oil, [Found: C, 48.17; H, 4.88 $C_9H_{11}F_3O_3$ requires C, 48.22; H, 4.95%]; δ_H (300 MHz, $CDCl_3$) 1.22 (3H, t, J=7.1 Hz, CH_3), 1.85, 2.01 (2H, m, 3-H), 2.36 (2H, dd, J=8.0, 5.4 Hz, 4-H), 3.66 (2H, dq, J=12.0, 7.2 Hz, $CH_3\mathit{CH_2}O$), 3.89 (1H, dq, J=12.0, 7.2 Hz, $CH_3\mathit{CH_2}O$), 5.23 (1H, dd, J=4, 2.6 Hz, 2-H), 7.71 (1H, s, 6-H); δ_F (282 MHz, $CDCl_3$) −69.0 (3F, s, CF_3); δ_C (75.3 MHz, $CDCl_3$) 14.5 ($\mathit{CH_3}CH_2O$), 14.8 (3-C), 25.4 (4-C), 64.9 ($CH_3\mathit{CH_2}O$), 99.1 (2-C), 111.9 (5-C), 116.7 (q, J_{C-F}=282 Hz, CF_3), 159.5 (q, $^4J_{C-F}$=5.7 Hz, 6-C),178.8 (q, $^2J_{C-F}$=34.2 Hz, C=O); IR (KBr) ν_{max}=1683, 1613, 1190, 1143 cm^{-1}; MS (*m/z*, %): 224 (M^+, 7.16), 205 (M^+-F, 8.70), 179 (M^+-OEt, 57.78), 178 (M^+-EtOH, 35.29), 127 (M^+-COCF_3, 7.67), 72 ($C_3H_4O_2^+$, 63.16), 69 (CF_3^+, 25.75), 44 (CO_2^+, 100.00).

3.1.3. 2-Ethoxyl-3-methyl-5-trifluoroacetyl-3,4-dihydro-2*H* pyran 3c. Yield 35%. Yellow oil; δ_H (300 MHz, $CDCl_3$) 1.00 (3H, d, J=7.0 Hz, 3-CH_3), 1.08 (3H, t, J=7.2 Hz, $\mathit{CH_3}CH_2O$), 1.23 (3H, d, J=7.0 Hz, 3-CH_3), 1.70–2.49 (3H, m, 3-H and 4-H), 3.65 (1H, dq, J=12.0, 7.2 Hz $CH_3\mathit{CH_2}O$), 3.83 (1H, dq, J=12.0, 7.2 Hz, $CH_3\mathit{CH_2}O$), 4.78 (1H, d, J=5.6 Hz, 2-H), 5.03 (1H, d, 2-H), 7.63 (1H, s, 6-H); δ_F (282 MHz, $CDCl_3$) −69.3 (3F, s, CF_3); IR (KBr) ν_{max}=1683, 1613, 1141, 1100 cm^{-1}; MS (*m/z*, %): 239 (M^+H, 3.13), 238 (M^+, 3.75), 220 (M^+H-F, 23.11), 192 (M^+-OEt, 44.84), 123 ($M^+-EtOH-CF_3$, 30.77), 97 (CF_3CO^+, 21.73), 69 (CF_3^+, 27.89), 58 ($C_3H_6O_2^+$, 100.00); HRMS (EI): M^+, found 238.0838. $C_{10}H_{13}F_3O_3$ requires 238.08361.

3.1.4. 2-(3-Methylbutoxyl)-4-methyl-5-trifluoroacetyl-3,4-dihydro-2H pyran 3d. Yield 39%. Yellow oil, [Found: C: 54.16; H: 6.36 $C_{12}H_{17}F_3O_3$ requires C, 54.14; H, 6.39%]; δ_H (300 MHz, $CDCl_3$) 0.91 (3H, d, J=7.0 Hz, $(\mathit{CH_3})_2CH$), 0.93 (3H, d, J=7.0 Hz, $(\mathit{CH_3})_2CH$), 1.15 (3H, d, J=7.0 Hz, 4-CH_3 *cis*), 1.24 (3H, d, J=7.0 Hz, 4-CH_3 *trans*), 1.86–1.95 (2H, m, 3-H), 1.92 (1H, m, $(CH_3)_2\mathit{CH}$), 2.75 (m, 4-H, *cis*), 2.89 (m, 4-H, *trans*), 3.36 (1H, dd, J=9.2, 6.9 Hz, $\mathit{CH_2}O$), 3.71 (1H, dd, J=9.2, 6.8 Hz, $\mathit{CH_2}O$), 5.14 (1H, d, J=5.8 Hz, 2-H, *cis*), 5.24 (1H, d, J=7.2 Hz, 2-H *trans*), 7.68 (1H, s, 6-H); δ_F (282 MHz, $CDCl_3$) −69.8 (3F, s, CF_3); IR (KBr) ν_{max}=1686, 1607, 1191, 1141 cm^{-1}; MS (*m/z*, %): 266 (M^+, 2.43), 197 (M^+-CF_3, 1.86), 193 (M^+-iBuO, 25.73), 192 (M^+-iBuOH, 36.49), 123 (M^+-iBuOH$-CF_3$, 21.43), 95 (M^+-iBuOH$-CF_3CO$, 8.43), 57 ($C_4H_9^+$, 100.00).

3.1.5. 2-(3-Methylbutoxyl)-3-methyl-5-trifluoroacetyl-3,4-dihydro-2*H* pyran 3e. Yield 36%. Yellow oil; δ_H (300 MHz, $CDCl_3$) 0.89 (6H, d, J=6.4 Hz, 2-CH_3), 1.09 (3H, d, J=6.6 Hz, 3-CH_3), 1.89 (1H, m, $(CH_3)_2CH$), 1.91–2.07 (1H, m, 3-H), 2.10 (1H, m, 4-H), 2.40 (1H, m, 4-H), 3.34 (1H, d, J=6.9 Hz, CH_2O), 3.68 (1H, d, J=6.6 Hz, CH_2O), 5.04 (1H, s, 2-H), 7.68 (1H, s, 6-H); δ_F (282 MHz, $CDCl_3$) −69.3 (3F, s, CF_3); δ_C (75.3 MHz, $CDCl_3$) 15.7 (3-CH_3), 19.1 ($(\mathit{CH_3})_2CH$), 22.0 ($(CH_3)_2\mathit{CH}$), 28.5 (3-C), 30.3 (4-C), 76.1 ($\mathit{CH_2}O$), 101.9 (2-C), 112.4 (5-C), 113.9 (q, $^1J_{C-F}$=280 Hz, CF_3), 159.0 (q, $^4J_{C-F}$=5.7 Hz, 6-C), 179.2 (q, $^2J_{C-F}$=32 Hz, C=O); IR (KBr) ν_{max}=1683, 1614, 1101, 1064 cm^{-1}; MS (*m/z*, %): 266 (M^+, 2.43), 197 (M^+-CF_3, 1.86), 193 (M^+-iBuO, 25.73), 192 (M^+-iBuOH, 36.49), 123 (M^+-iBuO$-CF_3$, 21.43), 96 (M^+-iBuOH$-$ $COCF_3$, 4.95), 57 ($C_4H_9^+$, 100.00); HRMS (EI): M^+, found 266.11298. $C_{12}H_{17}F_3O_3$ requires 266.11162.

3.1.6. 2-Ethoxyl-2-methyl-5-trifluoroacetyl-3,4-dihydro-2*H* pyran 3g. Yield 30%. Yellow oil; δ_H (300 MHz, $CDCl_3$) 1.35 (3H, t, J=7.1 Hz, CH_3CH_2O), 2.14 (3H, s, 2-CH_3), 2.21–2.58 (4H, m, 3-H and 4-H), 4.20 (2H, q, J=7.1 Hz, CH_3CH_2O), 7.52 (1H, s, 6-H); δ_F (282 MHz, $CDCl_3$) −70.3 (3F, s, CF_3); IR (KBr) ν_{max}=1680, 1605, 1195, 1140 cm^{-1}; MS (m/z, %): 239 (M^++1, 100.00), 193 (M^+−OEt, 39.01), 123 (M^+−EtOH−CF_3, 4.75), 69 (CF_3^+, 4.47), 43 ($C_2H_3O^+$, 24.99); HRMS (EI): M^+, found 238.08228. $C_{10}H_{13}F_3O_4$ requires 238.08168.

3.1.7. 2-Methoxyl-d$_3$-3-deuterium-4-methyl-3,4-dihydro-2*H* pyran 3f. Yield 16%. Yellow oil; δ_H (300 MHz, $CDCl_3$) 1.15 (3H, d, J=5.7 Hz, 4-CH_3, *cis*), 1.22 (3H, d, J=7.2 Hz, 4-CH_3, *trans*), 1.85–1.97 (1H, m, 3-H), 2.76 (1H, q, J=4.8 Hz, 4-H, *cis*), 2.91 (1H, q, J=6.0 Hz, 4-H, *trans*), 5.08 (1H, d, J=5.4 Hz, 2-H, *cis*), 5.14 (1H, d, J=5.7 Hz, 2-H, *trans*), 7.69 (1H, s, 6-H); δ_F (282 MHz, $CDCl_3$) −69.1 (s, CF_3); IR (KBr) ν=1680, 1615, 1183, 1141 cm^{-1}; MS (m/z, %): 209 (M^+−F, 83.73), 194 (M^+−CD_3O, 22.29), 159 (M^+−CF_3, 1.81), 131 (M^+−$COCF_3$, 1.82), 97 ($COCF_3$, 24.10), 69 (CF_3, 100.00); HRMS (EI): M^+−F, found 209.09273. $C_9H_7D_4F_2O_3$ requires 209.09440.

3.2. General procedure for the reaction of the nitrone with 1

4-(Ethoxy)-1,1,1-trifluoromethyl-3-en-2-one **1** (0.5 g, 3 mmol) was added into a 25 mL flask containing a solution of phenyl-*N*-methyl nitrone **4a** (0.41 g, 3 mmol) and toluene (10 mL). This reaction mixture was stirred at 40°C for 4 days, TLC analysis showed that the reaction finished. After removal of solvent, the residue obtained was separated and purified by column chromatography using ethyl acetate and pentane (1:10) as elute to give the two pure products **6a** (0.35 g, solid) and **7a** (0.15 g, oil).

3.2.1. 2-(*N*-Methyl)-3-phenyl-4-(1,1-dihydroxyl-2,2,2-trifluoroethyl)-5-ethoxyl-isoxazolidine 6a. White solid mp 95–97°C, [Found: C, 52.39; H, 5.67; N, 4.23 $C_{14}H_{18}F_3O_4N$ requires C, 52.34; H, 5.65; N, 4.36%]; δ_H (300 MHz, $CDCl_3$) 1.16 (3H, t, J=7.1 Hz, CH_3CH_2O), 2.40 (3H, s, NCH_3), 3.06 (1H, d, J=8.0 Hz, 3-H), 3.11 (2H, s, 2OH), 3.46 (1H, dd, J=8.0, 2.1 Hz, 4-H), 3.75 (2H, q, J=7.2 Hz, CH_3CH_2O), 5.24 (1H, d, J=2.1 Hz, 5-H), 7.0 (5H, m, C_6H_5); δ_F (282 MHz, $CDCl_3$) −85.0 (s, CF_3); IR (KBr) ν_{max}=3286, 2974, 1605, 1200–1000 cm^{-1}; MS (m/z, %): 321 (M^+, 1.57), 303 (M^+−H_2O, 8.33), 257 (M^+−EtOH−H_2O, 11.54), 160 (M^+−EtOH−H_2O−CF_3CO, 7.41), 135 (C_6H_5CH=N^+(Me)O, 60.13), 134 ($C_6H_5C^+$=N(Me)O, 100.00), 77 ($C_6H_5^+$, 10.55).

3.3. Crystal structure data of compound 6a

$C_{14}H_{18}NO_4F_3$ MW=321.3, monoclinic, space group *Cc*, a=20.754(3), b=10.690(1), c=14.243(2) Å, β=90.93(1)°, V=3159.5(7) Å^3, Z=8 (two molecules in asymmetric unit), D_c=1.351 g/cm^3. F(000)=1344.0, λ (Mo K_α)=0.71369, crystal size=0.1×0.4×0.3 mm^3. Intensity data were collected at 20°C with a Sciemens P4 diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-1\leq h\leq 26$, $-13\leq k\leq 1$, $-18\leq l\leq 18$. Three standard reflections were monitored after every 100 reflections, but no significant decay was found. The structure was solved by a direct method. All non-hydrogen atoms were positioned and anisotropic thermal parameters refine from 4639 reflections by a full-matrix least-squares technique to R=0.055 (for 3930 observed reflections with $F>4\sigma(F)$) and R=0.087 (for all). The calculations were performed on a PC computer with SHELXS 97 programs. Atomic scattering factors were taken from the International Tables for X-ray Crystallography (1974, vol. IV). Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 202097.

3.3.1. 2-(*N*-Methyl)-3-phenyl-4-(trifluoroacetyl) isoxazole 7a. Yellow oil; δ_H (300 MHz, $CDCl_3$) 2.63 (3H, s, NCH_3), 4.53 (1H, s, 3-H), 6.93 (5H, s, C_6H_5), 7.43 (1H, s, 5-H); δ_F (282 MHz, $CDCl_3$) −74.0 (3F, s, CF_3); IR (KBr) ν_{max}=3066, 1672, 1595, 1195–1120 cm^{-1}; MS (m/z, %): 257 (M^+, 33.08), 188 (M^+−CF_3, 8.10), 180 (M^+−Ph, 100.00), 160 (M^+−$COCF_3$, 42.68), 77 ($C_6H_5^+$, 25.19); HRMS (EI): M^+, found 257.06255. $C_{12}H_{10}F_3O_2N$ requires 257.06636.

3.3.2. 2-(*N*-Methyl)-3-(4-methoxylphenyl)-4-(1,1-dihydroxyl-2,2,2-trifluoroethyl)-5-ethoxyl-isoxazolidine 6b. White solid; mp 97–98°C, [Found: C, 51.43; H, 5.67; N, 3.91 $C_{15}H_{20}F_3O_5N$ requires C, 51.28; H, 5.74; N, 3.99%]; δ_H (300 MHz, $CDCl_3$) 1.19 (3H, t, J=7.0 Hz, CH_3CH_2O), 2.42 (3H, s, N−CH_3), 3.04 (1H, d, J=8.0 Hz, 3-H), 3.26 (2H, s, 2OH), 3.47 (1H, m, 4-H), 3.74 (2H, q, J=7.0 Hz, CH_3CH_2O), 3.76 (3H, s, OCH_3), 5.24 (1H, d, J=1.5 Hz, 5-H), 6.85 (2H, AB, J=8.0 Hz, ArH), 7.34 (2H, AB, J=8.0 Hz, ArH); δ_F (282 MHz, $CDCl_3$) −84.8 (3F, s, CF_3); IR (KBr) ν_{max}=3342, 2938, 1612, 1349–1300, 1200–1000 cm^{-1}; MS (m/z, %): 333 (M^+−H_2O, 16.27), 287 (M^+−H_2O−OEt, 6.33), 164 ($CH_3OC_6H_4C$=N(Me)O^+, 100.00), 77 ($C_6H_5^+$, 9.91).

3.3.3. 2-(*N*-Methyl)-3-(methoxylphenyl)-4-(trifluoroacetyl)-isoxazole 7b. Yellow oil; δ_H (300 MHz, $CDCl_3$) 2.43 (3H, s, NCH_3), 3.70 (3H, s, OCH_3), 4.60 (1H, s, 3-H), 6.93 (2H, AB, J=8.0 Hz, ArH), 7.34 (2H, AB, J=8.0 Hz, ArH), 7.46 (1H, s, 5-H); δ_F (282 MHz, $CDCl_3$) −74.5 (3F, s, CF_3); IR (KBr) ν_{max}=2481, 1680, 1598, 1190–1120 cm^{-1}; MS (m/z, %): 287 (M^+, 17.51), 190 (M^+−CF_3CO, 12.03), 180 (M^+−Ar, 39.42), 135 (M^+−Ar−NOMe, 100.00); HRMS (EI): M^+, found 287.07463. $C_{13}H_{12}F_3O_3N$ requires 287.07693.

3.3.4. 2-(*N*-Methyl)-3-phenyl-4-(1,1-dihydroxyl-2,2,2-trifluoroethyl)-5-ethoxyl-isoxazolidine 6c. White solid mp 97–100°C, [Found: C, 53.59; H, 6.02; N, 3.89 $C_{15}H_{20}F_3O_4N$ requires C, 53.73; H, 6.01; N, 4.18%]; δ_H (300 MHz, $(CD)_2CO$) 1.19 (3H, t, J=8.0 Hz, CH_3CH_2O), 2.28 (3H, s, Ar-CH_3), 2.43 (3H, s, N−CH_3), 3.06 (1H, d, J=7.0 Hz, 3-H), 3.38 (2H, s, 2OH), 3.44 (1H, m, 4-H), 3.76 (2H, q, J=8.0 Hz, CH_3CH_2O), 5.25 (1H, d, J=1.0 Hz, 5-H), 7.10 (2H, AB, J=8.0 Hz, ArH),7.31 (2H, AB, J=8.0 Hz, ArH); δ_F (282 MHz, $(CD)_2CO$) −84.5 (s, CF_3); IR (KBr) ν_{max}=3256, 2976, 1519, 1200–1136, 1075–974, 809 cm^{-1}; MS (m/z, %): 335 (M^+, 2.91), 317 (M^+−H_2O, 10.99), 226 ($M^+ - C_7H_7^{+} - H_2O$, 4.86), 148 ($ArC{=}N(Me)O^+$, 100.00), 91 ($C_7H_7^{+}$, 37.60), 77 ($C_6H_5^{+}$, 4.79).

3.3.5. 2-(*N*-Methyl)-3-benzyl-4-(trifluoroacetyl)-isoxazole 7c. Yellow oil; δ_H (300 MHz, $CDCl_3$) 2.05 (3H, s, $CH_3C_6H_4$), 2.46 (3H, s, N*CH*$_3$), 4.63 (1H, s, 3-H), 6.90 (4H, m, ArH), 7.43 (1H, s, 5-H); δ_F (282 MHz, $CDCl_3$) −74.0 (3F, s, CF_3); IR (KBr) ν_{max}=1672, 1594, 1190–1120 cm^{-1}; MS (*m*/*z*, %): 272 ($M^+ + 1$, 57.53), 271 (M^+, 50.79), 180 ($M^+ - C_7H_7$, 100.00), 174 ($M^+ - COCF_3$, 16.23), 91 ($C_7H_7^{+}$, 16.73); HRMS (EI): M^+, found 271.08101. $C_{13}H_{12}F_3O_2N$ requires 271.08201.

3.3.6. 2-(*N*-Methyl)-3-(4-chlorophenyl)-4-(1,1-dihydroxyl-2,2,2-trifluoroethyl)-5-ethoxyl-isoxazolidine 6d. White solid mp 97–99°C; δ_H (300 MHz, $CDCl_3$) 1.23 (3H, t, *J*=8.0 Hz, *CH*$_3$CH$_2$O), 1.60 (2H, broad, 2OH), 2.60 (3H, s, N–CH_3), 3.58 (1H, dd, *J*=8.0 Hz, 4-H), 3.80 (1H, d, *J*=7.0 Hz, 3-H), 3.85 (2H, q, *J*=8.0 Hz, CH$_3$*CH*$_2$O), 5.23 (1H, d, *J*=1.5 Hz, 5-H), 7.35 (4H, AB, ArH); δ_F (282 MHz, $CDCl_3$) −78.8 (3F, s, CF_3); IR (KBr) ν_{max}=3250, 1590, 1490, 1200–1090, 1050 cm^{-1}; MS (*m*/*z*, %): 339/337 ($M^+ - H_2O$, 12.40/33.80), 293/291 ($M^+ - H_2O - EtOH$, 4.04/10.21), 226/264 ($M^+ - EtOH - N(Me)O$, 7.67/22.66), 248/246 ($M^+ - EtOH - N(Me)O - H_2O$, 2.26/6.55), 168 ($M^+ - H_2O - C_7H_8ClNO$, 100.00); HRMS (EI): M^+, found 337.07074. $C_{14}H_{17}F_3O_4NCl$ requires 337.07194.

3.3.7. 2-(*N*-Methyl)-3-(4-chlorophenyl)-4-(trifluoroacetyl)-isoxazole 7d. Yellow oil; δ_H (300 MHz, $CDCl_3$) 3.00 (3H, s, N*CH*$_3$), 5.05 (1H, s, 3-H), 7.35 (4H, m, ArH), 7.83 (1H, s, 5-H); δ_F (282 MHz, $CDCl_3$) −74.5 (3F, s, CF_3); IR (KBr) ν_{max}=3069, 1675, 1598, 1190–1110 cm^{-1}; MS (*m*/*z*, %): 293/291 (M^+, 5.42/16.20), 224/222 ($M^+ - CF_3$, 3.45/12.32), 196/194 ($M^+ - COCF_3$, 15.68/48.42), 180 ($M^+ - C_6H_4Cl$, 100.00); HRMS (EI): M^+, found 291.06457. $C_{12}H_9F_3O_2ClN$ requires 291.06836.

3.3.8. Tetrahydrofurano-[4,5-*d*]-2-methyl-3-phenyl-8-trifluoroacetyl-isoxazolidine 9a. White solid mp 110–112°C, [Found: C, 55.74; H, 7.67; N, 4.44 $C_{14}H_{14}F_3O_3N$ requires C, 55.82; H, 4.68; N, 4.65 %]; δ_H (300 MHz, $CDCl_3$) 1.93 (1H, m, 4-H), 2.25 (1H, m, 4-H), 2.65 (3H, s, N–*CH*$_3$), 4.20 (1H, m, 5-H), 4.23 (1H, s, 3-H), 4.43 (1H, dd, 5-H), 5.93 (1H, s, 7-H), 7.40 (5H, m, C_6H_5); δ_F (282 MHz, $CDCl_3$) −72.0 (3F, s, CF_3); IR (KBr) ν_{max}=1741, 1582–1491, 1230–1125, 1018 cm^{-1}; MS (*m*/*z*, %): 301 (M^+, 13.77), 256 ($M^+ - N(Me)O$, 1.51), 135 ($C_6H_5CH{=}N(Me)O^+$, 57.47), 134 ($C_6H_5C^+ - N(Me)O^+$, 100.00), 77 ($C_6H_5^{+}$, 0.75).

3.3.9. Tetrahydrofurano-[4,5-*d*]-2-methyl-3-(4-methoxylphenyl)-8-trifluoroacetyl-isoxazolidine 9b. Oil. δ_H (300 MHz, $CDCl_3$) 1.93 (1H, m, 4-H), 2.15 (1H, m, 4-H), 2.63 (3H, s, N–*CH*$_3$), 3.80 (3H, s, OCH_3), 4.20 (2H, s, *CH*$_2$O), 4.33 (1H, s, 3-H), 5.90 (1H, s, 7-H), 7.34 (5H, m, C_6H_5); δ_F (282 MHz, $CDCl_3$) −71.5 (3F, s, CF_3); IR (KBr) ν_{max}=1740, 1580, 1250–1167, 1091 cm^{-1}; MS (*m*/*z*, %): 312 (M^+H, 5.92), 311 (M^+, 9.31), 266 ($M^+H - OCH_3 - CH_3$, 3.26), 165 ($CH_3OC_6H_4CH{=}N(Me)O$, 100.00), 164 ($CH_3OC_6H_4C{=}N(Me)O^+$, 99.89), 97 (CF_3CO^+, 9.26); HRMS (EI): $M^+ - OCH_3 - CH_3$, found 285.06339. $C_{13}H_{10}F_3O_3N$: 285.05993.

3.3.10. 2-Methylamino-3-trifluoroacetyl-4,5-dihydrofuran 10. [Found: C, 43.00; H, 4.09; N, 7.02 $C_7H_8F_3O_2N$ requires C, 43.08; H, 4.10; N, 7.18%]; δ_H (300 MHz, $CDCl_3$) 3.03 (3H, d, *J*=5.0 Hz, NH*CH*$_3$), 3.12 (2H, t, *J*=8.0 Hz, *CH*$_2$CH$_2$O), 4.60 (2H, t, *J*=8.0 Hz, CH$_2$*CH*$_2$O), 9.35 (1H, s, NH); δ_F (282 MHz, $CDCl_3$) −74.8 (3F, s, CF_3); IR (KBr) ν_{max}=3200, 2970, 1672, 1599 cm^{-1}; MS (*m*/*z*, %): 195 (M^+, 75.78), 126 ($M^+ - CF_3$, 100.00), 97 (CF_3CO^+, 13.48), 69 (CF_3, 54.84).

Acknowledgements

This work was supported by the National Natural Science Foundation of China (NNSFC) (No. 20032010, 20072049) and the Innovation Foundation of Chinese Academy of Sciences for financial support.

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