



# 1,3-Dipolar cycloaddition reactions of ethyl 2-hydropoly(per)fluoroalk-2-enoates with nitrones

Jin-Tao Liu,\* Qi-Hui Jin, He-Jun Lü and Wei-Yuan Huang

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China

Received 8 May 2001; revised 20 June 2001; accepted 28 June 2001

**Abstract**—Ethyl 2-hydropoly(per)fluoroalk-2-enoates react readily with nitrones under mild conditions to give 5-fluoroalkyl substituted isoxazolidines as a mixture of two diastereoisomers (*trans* and *cis*) in high yields. © 2001 Elsevier Science Ltd. All rights reserved.

Recently, fluorine-containing heterocyclic compounds have received increasing attention due to their potential biological properties, and there has been considerable effort to broaden synthetic methods for the incorporation of fluorine.<sup>1–5</sup> As useful fluorine-containing building blocks, ethyl 2-hydropoly(per)fluoroalk-2-enoates,  $R_FCF=CHCO_2Et$  ( $R_F$ =polyfluoroalkyl or perfluoro-

alkyl), have been under research in our laboratory for the past few years to synthesize fluoroalkyl substituted heterocycles.<sup>6,7</sup> Previous studies showed that  $R_FCF=CHCO_2Et$  generated in situ from  $R_FCF_2CH_2CO_2Et$  with base can be employed as dipolarophiles for reactions with various *N*-ylides.<sup>8–11</sup> In this paper, we report the 1,3-dipolar cycloaddition reaction of

**Table 1.** 1,3-Dipolar cycloaddition reactions of nitrones with esters **2**

Entry	Nitrones	$R_F$	Conditions	Products (yield %) <sup>a</sup>
			Nitrone: <b>2</b> /time/temp.	
1	<b>1</b>	$CICF_2CF_2CF_2$	1:1/0.5 h/rt	<b>3a</b> (40)
				<b>4a</b> (60)
2	<b>1</b>	$CF_3(CF_2)_3CF_2$	1:1/0.5 h/rt	<b>3b</b> (33)
				<b>4b</b> (56)
3	<b>1</b>	$BrCF_2$	1:1/0.5 h/rt	<b>3c</b> (59)
				<b>4c</b> (40)
4	<b>1</b>	$CICF_2(CF_2)_3CF_2$	1:1/0.5 h/rt	<b>3d</b> (45)
				<b>4d</b> (45)
5	<b>5</b>	$CICF_2CF_2CF_2$	2:1/3 days/rt	<b>6a</b> (48)
				<b>7a</b> (48)
6	<b>5</b>	$CF_3(CF_2)_3CF_2$	2:1/3 days/rt	<b>6b</b> (48)
				<b>7b</b> (35)
7	<b>8</b>	$CICF_2CF_2CF_2$	2:1/3 days/rt	<b>9a + 10a</b> (78)
				<b>9a:10a</b> (1:4) <sup>b</sup>
8	<b>11</b>	$CICF_2CF_2CF_2$	1:1/6 days/reflux	<b>12a</b> (27)
				<b>13a</b> (68)
9	<b>11</b>	$CICF_2(CF_2)_3CF_2$	1:1/6 days/reflux	<b>12d</b> (23)
				<b>13d</b> (64)

<sup>a</sup> Isolated yield based on **2**.

<sup>b</sup> Determined by GC.

**Keywords:** ethyl 2-hydropoly(per)fluoroalk-2-enoate; 5-fluoroalkylisoxazolidine; nitrone.

\* Corresponding author. Fax: +86-021-64166128; e-mail: jtliu@pub.sioc.ac.cn

ethyl 2-hydropoly(per)fluoroalk-2-enoates with nitrones.

The reactions are very simple and convenient. In a typical procedure, a mixture of 1 mmol of 3,4-dihydroisoquinoline *N*-oxide **1**, 1 mmol of ethyl 2-hydrodo-decafluorohept-2-enoate **2b** and 3 mL of CH<sub>2</sub>Cl<sub>2</sub> was stirred at ambient temperature until the completion of the reaction (monitored by <sup>19</sup>F NMR). After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel. The results are summarized in Table 1.

The reaction is regioselective, resulting in the formation of isoxazolidines with the CO<sub>2</sub>Et and R<sub>F</sub> groups in C-4 and C-5 positions, respectively. This is caused mainly by the electronic factor. The more electron-deficient end (C-2) of the dipolarophile added to the nitron oxygen atom. As illustrated in Scheme 1, all reactions gave two diastereoisomeric cycloadducts (*cis* and *trans*). In the case of **1**, *N*-propylidene propanamine *N*-oxide **5** and nitron **11**, the two diastereoisomeric products were separated by column chromatography. The structure of compound **3a** was confirmed by X-ray crystallography (Fig. 1). The two isomers obtained from the reaction of nitron **8** and **2** could not be separated by column

chromatography, and so the ratio of the two isomers were evaluated by GC and <sup>19</sup>F NMR. The reaction of nitron **1** and ester **2** was very fast at room temperature. With other nitrones, longer reaction times were required under similar conditions and a reflux temperature was necessary in the case of nitron **11** for the reaction to take place.

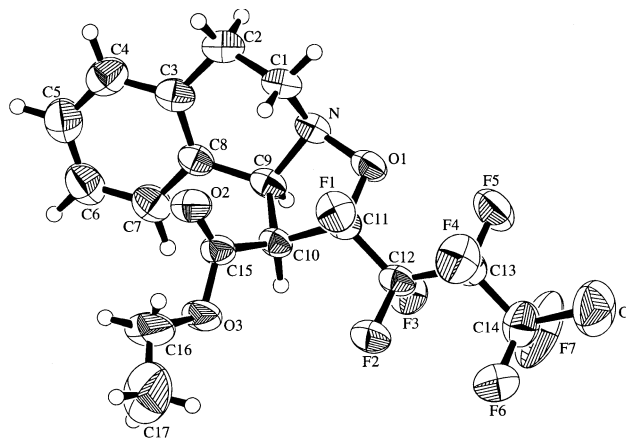
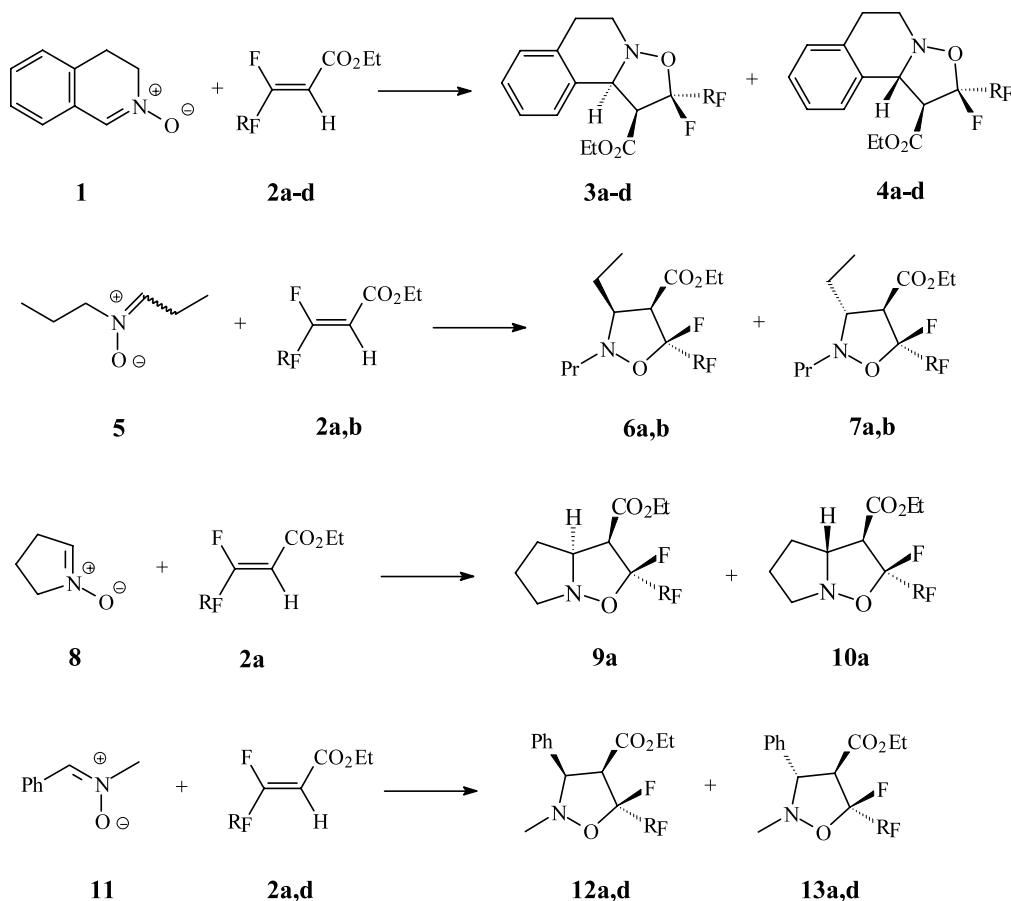
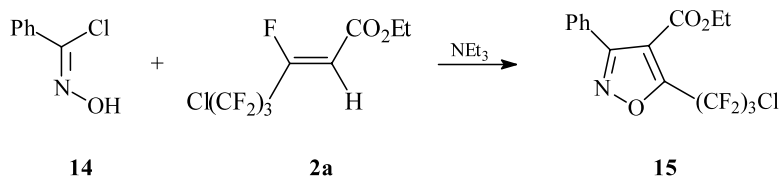


Figure 1. The crystal structure of **3a**.

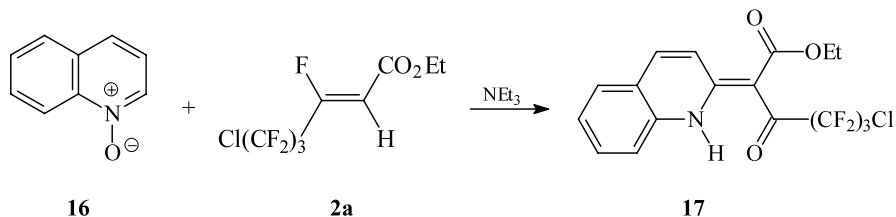


R<sub>F</sub> = Cl(CF<sub>2</sub>)<sub>3</sub>, a; F(CF<sub>2</sub>)<sub>5</sub>, b; BrCF<sub>2</sub>, c; Cl(CF<sub>2</sub>)<sub>5</sub>, d

Scheme 1.



Scheme 2.



Scheme 3.

Similarly, ester **2a** reacts with benzonitrile oxide prepared in situ to give the corresponding 5-fluoroalkylisoxazole **15** (Scheme 2). The same result was obtained from the reaction of benzonitrile oxide with  $\beta$ -fluoroalkyl- $\beta$ -keto esters.<sup>12</sup>

When quinoline *N*-oxide **16** was allowed to react with ester **2**, no cycloadduct was obtained. Instead the ring-opening product **17** was formed, as shown by elemental analysis, <sup>1</sup>H NMR, <sup>19</sup>F NMR and MS spectra (Scheme 3). This is consistent with reported results.<sup>13</sup>

The fluorine-containing isoxazolidines obtained above are quite stable, and no elimination of HF was observed during reaction and subsequent workup procedures. The relative configuration of all the diastereoisomers at the C-3 position was determined by means of X-ray crystallography and NMR spectra. In the case of isoxazolidines **3** and **4**, the structure of the *trans* isomer **3** was confirmed by X-ray crystallography. The *trans* isomers showed higher chemical shifts for H-3 due to the deshielding effect of the neighboring ester group, and lower chemical shifts for H-4, than their *cis* counterparts (**4**). This guide was applied to other fluorine-containing isoxazolidines, the compounds with higher chemical shifts for H-3 being assigned as the *trans* isomers. This was proven by NOESY experiments with compound **6a**.

### Acknowledgements

We thank the National Natural Science Foundation of China for financial support.

### References

1. *Biomedical Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y., Eds.; Kodansha: Tokyo, 1982.
2. *Preparation, Properties and Industrial Application of Organofluorine Compounds*; Banks, R. E., Ed.; Ellis Horwood: Chichester, 1982.
3. Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.
4. Chambers, R. D.; Sargent, C. R. *Adv. Heterocyclic Chem.* **1981**, *28*, 1.
5. Silvester, M. J. *Aldrichimica Acta* **1991**, *24*, 31.
6. Huang, W.-Y.; Lu, L.; Zhang, Y.-F. *Chin. J. Chem.* **1990**, *281*.
7. Liu, Y.-S.; Huang, W.-Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 982.
8. Zhang, X.-C.; Huang, W.-Y. *J. Fluorine Chem.* **1998**, *92*, 13.
9. Zhang, X.-C.; Huang, W.-Y. *J. Fluorine Chem.* **1998**, *87*, 57.
10. Zhang, X.-C.; Huang, W.-Y. *Tetrahedron Lett.* **1997**, *27*, 4827.
11. Zhang, X.-C.; Huang, W.-Y. *Tetrahedron* **1998**, *54*, 12465.
12. Bravo, P.; Diliddo, D.; Resnati, G. *Tetrahedron* **1994**, *50*, 8827.
13. Iwao, M.; Kuraishi, T. *J. Heterocyclic Chem.* **1978**, *15*, 1425.