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Microwave assisted Diels-Alder cycloaddition of 2-fluoro-3-methoxy-1,3-butadiene

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Abstract

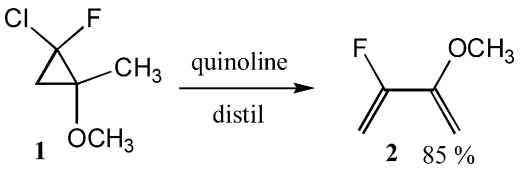
The title fluorodiene (**2**) reacts with several dienophiles in moderate yields (20–65%, 0.5 h to 3d) when thermal activation is used. When 100 W microwave radiation is used the reaction yields (70–90%, 5–25 min) are greatly improved and the reaction times are much shorter. A microwave procedure is also used for the hydrolysis of vinyl ether cycloadducts to alpha-fluoroketones.

Keywords: Fluorodiene; Diels-Alder cycloaddition; Microwaves

1. Introduction

Building blocks for the construction of fluorinated molecules by Diels-Alder chemistry are relatively unavailable [1]. Only four monofluoro butadienes [2–5] and two difluoro butadienes have been used in cycloaddition reactions [6,7]. The list of mono and difluorodienophiles is also low but is on the rise [8–13].

In an earlier note [5] we described the preparation of 2-fluoro-3-methoxy-1,3-butadiene (**2**) from Schlosser's fluorochlorocyclopropane (**1**) [14] and briefly described its cycloaddition characteristics. In this paper we provide more experimental details on the reaction of **2** with a variety of dienophiles, and we show that the reactions are greatly enhanced by the use of microwave radiation.



1 **2** 85 %

2. Results and discussion

The diene **2** reacts with various dienophiles as shown in Table 1 in moderate yields (20–65%) under thermal activation except for the very reactive *N*-phenyltriazolidone. The reactions are conducted in acetonitrile solution in a closed vacuum hydrolysis tube for the times shown, 0.5 h to 3 d. When the cycloadditions are performed in closed vacuum hydrolysis tubes under 100 W microwave radiation the yields are greatly improved (70–90%) and the reaction times (5–25 min) are much shorter.

Initially the question about the cycloaddition reactivity of **2** with dienophiles is focused on what effect fluorine might have on the reaction. It is calculated that the fluorine should not have much effect on the pi electron energy levels [15], but the electronegativity of the fluorine atom could deactivate the diene through sigma induction [16]. The results of the Diels-Alder reactions indicate that the fluorine has no hinderance to the reaction.

The use of microwave radiation has thus far shown little beneficial effect on Diels-Alder reactions [17–21]. Narsaiah reports that some fluorinated 2(1*H*)pyridones would not undergo cyclization with microwave radiation [20]. In our present study the use of microwave radiation greatly enhances the yield of the cycloaddition reactions of **2** as shown in Table 1. In general the effect of microwaves is to cause a dramatic rapid increase in the temperature of a reaction. The results here would substantiate that the rapid temperature increase greatly

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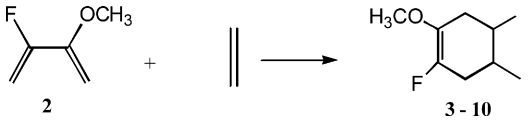
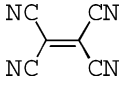
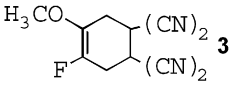
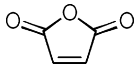
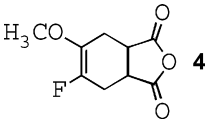
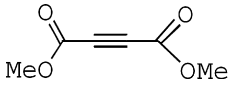
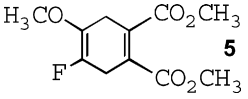
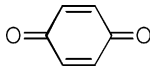
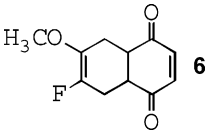
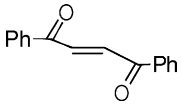
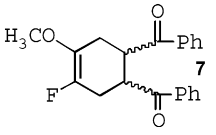
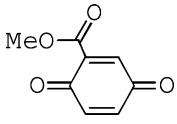
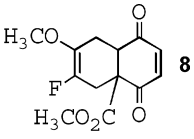
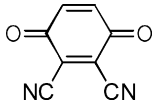
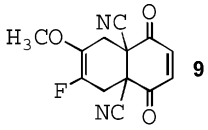
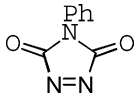
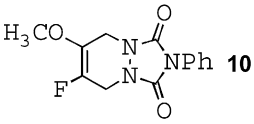
Table 1
Cycloaddition of 2 with dienophiles



Dienophile	Product	Thermal, % yield, °C, time	Microwave, % yield, time, m
	 **3**	55%, 30, 0.5 h	90%, 2
	 **4**	65%, 30, 0.5 h	88%, 2
	 **5**	50%, 70, 8 h	75%, 10
	 **6**	20%, 80, 20 h	65%, 25
	 **7**	20%, 80, 3 d	75%, 25
	 **8**	55%, 60, 8 h	87%, 15
	 **9**	50%, 60, 12 h	74%, 14
	 **10**	95%, rt, 5 min	NA

improves the reaction yield. Compound **8** is formed with complete regioselectivity in both the thermal and microwave experiments.

The vinyl ether cycloaddition products **3–10** were subjected to hydrolysis to alpha-fluoroketones. Alpha-fluoroketones are somewhat difficult to prepare because of the lability of the fluorine atom towards elimination. In our studies on the hydrolysis of **3–10** we found that alpha-fluoroketones could be detected in every reaction, but that only three compounds, **11**, **12**, **13** could be isolated without loss of the fluorine atom. The experimental conditions for the hydrolysis of the fluoro vinyl ethers requires that acetonitrile–water solutions undergo microwave irradiation for 20–30 min. Conventional catalysis, HCl, *p*-toluenesulfonic acid and Dowex, caused extensive decomposition to occur. Thus compounds **11**, **12** and **13** could be obtained only by hydrolysis in acetonitrile and water under microwave irradiation. The stereochemistry of the fluorine atom relative to the other ring substituents in **11** and **12** is as yet undetermined.