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Journal of Fluorine Chemistry 128 (2007) 710–713
JOURNAL OF FLUORINE CHEMISTRY
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Microwave assisted Diels-Alder cycloaddition of 2-fluoro-3-methoxy-1,3-butadiene

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Received 24 January 2007; received in revised form 10 March 2007; accepted 10 March 2007
Available online 15 March 2007

Abstract

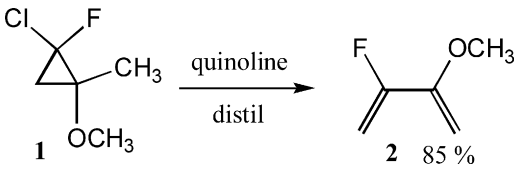
The title fluorodiene (**2**) reacts with several dienophiles in moderate yields (20–65%, 0.5 h to 3d) when thermal activation is used. When 100 W microwave radiation is used the reaction yields (70–90%, 5–25 min) are greatly improved and the reaction times are much shorter. A microwave procedure is 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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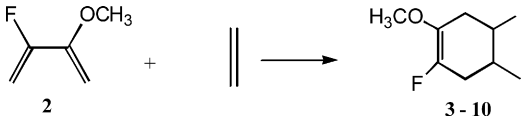
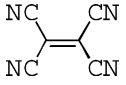
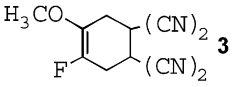
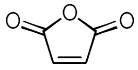
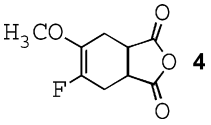
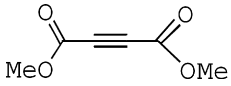
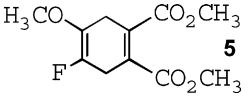
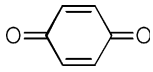
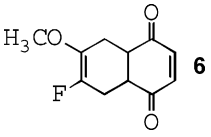
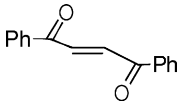
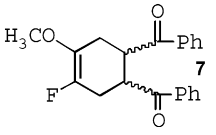
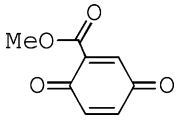
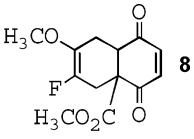
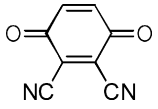
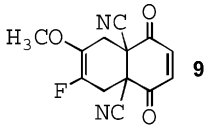
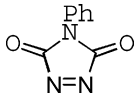
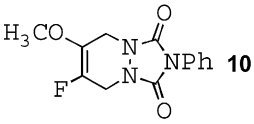
doi:10.1016/j.jfluchem.2007.03.010

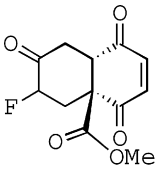
Table 1
Cycloaddition of 2 with dienophiles



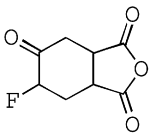
Dienophile	Product	Thermal, % yield, °C, time	Microwave, % yield, time, m
	 **3**	55%, 30, 0.5 h	90%, 2
	 **4**	65%, 30, 0.5 h	88%, 2
	 **5**	50%, 70, 8 h	75%, 10
	 **6**	20%, 80, 20 h	65%, 25
	 **7**	20%, 80, 3 d	75%, 25
	 **8**	55%, 60, 8 h	87%, 15
	 **9**	50%, 60, 12 h	74%, 14
	 **10**	95%, rt, 5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

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

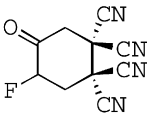
The vinyl ether cycloaddition products **3–10** were subjected to hydrolysis to alpha-fluoroketones. Alpha-fluoroketones are somewhat difficult to prepare because of the lability of the fluorine atom towards elimination. In our studies on the hydrolysis of **3–10** we found that alpha-fluoroketones could 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.



11 45%



12 20%



13 60%

3. Experimental procedure

3.1. Preparation of 2-fluoro-3-methoxybuta-1,3-diene (2)

Distilled quinoline (30 mL) was transferred to a 100 mL round-bottom flask quipped with magnetic stirring. Hydroquinone (20 mg) was added, along with 1-chloro-1-fluoro-2-methoxy-2-methylcyclopropane (**1**) (12.0 g, 0.087 mol). The reaction was heated to 90 °C in a silicon oil bath and allowed to reflux 10–14 h using a water-jacketed condenser topped with a calcium chloride ($CaCl_2$) drying tube. The $CaCl_2$ drying tube was replaced with a vacuum jacketed short path Vigreux column. The colorless product was distilled from 45 to 70 °C (bath temp. 90 °C) using 60 to 90 mm Hg vacuum, to give (**2**) (7.6 g) in 85% yield. ^{1}H NMR ($CDCl_3$, TMS) δ 3.63 (s, CH_3), 4.28 (m, CH_2), 4.64 (m, CH_2), 4.69 (m, CH_2), 4.75 (m, CH_2), 4.83 (m, CH_2), 4.84 (m, CH_2), 4.99–5.00 (m, CH_2); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −111.2 (dd, CF); ^{13}C NMR δ 55.0 (s, OCH_3), 84.0 (d, C4, J = 0.5 Hz), 90.2 (d, C1, J = 2 Hz), 153.7 (d, C3, J = 3 Hz), 157.2, 160.5 (d, C2, J = 188 Hz). Anal. Calcd for C_5H_7FO: *m/e* 102. Found: 102.

3.2. General procedure for thermal cycloadditions of 2

A solution of dienophile (200 mg) and an equivalent amount of 2 in 3 mL of dry acetonitrile was added to a vacuum hydrolysis tube. The pressure cap was tightened and the mixture was heated for the temperature and time noted in Table 1. The amber solutions were concentrated under dry nitrogen and subjected to either flash column chromatography or HPLC.

3.3. General procedure for microwave cycloadditions of 2

Solutions of the dienophiles and **2** were prepared as described for the thermal cycloaddition above. The capped vacuum hydrolysis tube was placed into a commercial (Walmart) microwave oven operating at 100 W. A hole was drilled in the back of the oven so that the hydrolysis tube could be place in the oven without exposing the plastic cap to the microwave radiation otherwise the cap melts. The reaction mixtures were usually yellow and were worked up as described above.

3.4. Analytical data for cycloaddition products 3–10

Spectral data were obtained on samples in $CDCl_3$ solution. TMS was the standard for ^{1}H NMR and ^{13}C NMR spectra. $CFCl_3$ was the standard for ^{19}F NMR spectra.

3.4.1. 4-Fluoro-5-methoxycyclohex-4-ene-1,1,2,2-tetracarbonitrile (3)

(oil) ^{1}H NMR δ 2.62 (m, CH_2, 2H), 3.50 (s, CH_3, 2H); ^{19}F NMR δ −150.4 (m, CF). ^{13}C NMR δ 21.7 (s, C6) 22.8 (d, C3), 53.3 (s, OCH_3), 105.0, 106.2 (s, C1, C2), 111.4 (m, CN), 120.4 (d, C4, J = 118 Hz) 126.8 (d, C5, J = 2 Hz). Anal. Calcd for $C_{11}H_7FN_4O$: C, 57.39, H, 3.07. Found: C, 57.10, H, 2.99.

3.4.2. 5-Fluoro-3a,4,7,7a-tetrahydro-6-methoxyisobenzofuran-1,3-dione (4)

mp 106–108, ^{1}H NMR δ 2.40–2.80 (m, CH_2, 2H), 3.40 (m, CH, 1H), 3.60 (s, CH_3, 3H); ^{19}F NMR δ −133.2 (m, CF); ^{13}C NMR δ 25.1 (m, C4, J = 3 Hz), 25.8 (s, C7),39.8, 40.0 (m, 3a,7a), 58.5 (s, OCH_3), 128.3 (d, C5, J = 122 Hz), 129.1 (C6), 136.4 (m, CO). Mass spectrum: Calcd *m/e* 200. Found *m/e* 200.

3.4.3. 4-Fluoro-5-methoxycyclohexa-1,4-diene-1,2-dicarboxylate (5)

(oil) ^{1}H NMR δ 2.63 (m, CH_2, 2H), 3.50 (m, CH_3, 2H), 3.76 (s, CH_3, 3H); ^{19}F NMR δ −146.7 (m, CF); ^{13}C NMR δ 29.5 (s, C6), 30.5 (d, C3, J = 2 Hz), 52.3–53.3 (s, OCH_3 of ester), 77.5 (OCH_3), 130.2 (d, C4, J = 126 Hz), 134.06 (m, C5), 152.0 (C1, C2), 167.2 (CO). Anal. Calcd for $C_{11}H_{13}FO_5$: C, 54.1%, H, 5.37%. Found: C, 54.3%, H, 5.22%.

3.4.4. 6-Fluoro-4a,5,8,8a-tetrahydro-7-methoxynaphthalene-1,4-dione (6)

mp 38–39, ^{1}H NMR δ 1.90 (m, CH_2, 2H) 2.15 (m, CH_2, 2H), 3.3 (m, CH, 1H), 3.50 (s, CH_3, 3H), 7.05 (d, CH, 2H); ^{19}F NMR δ −134.3 (m, CF). ^{13}C NMR δ 22.9 (C8), 25.8 (d, C5, J = 3 Hz), 39.9 (s, 8aC), 53.1 (s, OCH_3 of ether) 40.5 (s, 4aC), 116.8 (d, 6C, J = 122 Hz), 119.1 (s, C7), 137.10, 140.0 (s, 2,3-C), 203.1, 204.2 (CO). Anal. Calcd for $C_{11}H_{11}FO_3$: C, 62.85, H, 5.27. Found: C, 63.02, H, 5.36.

3.4.5. 4,5-Dibenzoyl-1-fluoro-2-methoxycyclohex-1-ene (7)

mp 97–99, ^{1}H NMR δ 1.98–2.23 (m, 3-CH_2, 2H), 2.60 (d, 6-CH_2, 2H), 4.2 (m, 4CH and 5CH, 2H), 7.34–7.44 (10H aromatic); ^{19}F NMR δ −134.1 (m). ^{13}C NMR δ 23.3 (C3), 26.7 (d, C6, J = 2 Hz), 45.2, 46.7 (C4, C5), 122.1 (d, C1, J = 122 Hz), 126.7 (C2), 120–135 (aromatic), 199.1, 201.0 (CO). Anal. Calcd for $C_{21}H_{19}FO_3$: C, 74.54, H, 5.68. Found: C, 74.56, H, 5.54. The *cis/trans* configuration of the benzoyl substituents is not known.

3.4.6. Methyl 6-fluoro-1,4,4a,5,8,8a-hexahydro-7-methoxy-1,4-dioxonaphthalene-4a-carboxylate (8)

(oil) ^{1}H NMR δ 2.1, 2.2 (m, 8-CH_2, 2H), 2.6, 2.8 (m, 5-CH_2, 2H), 3.78 (s, 7-OCH_3, 3H), 3.9 (s, OCH_3 of ester, 3H), 6.62, 6.82 (d, 2,3-CH, 2H); ^{19}F NMR δ −134.4 (m); ^{13}C NMR δ 22.9 (s, C8), 28.1 (d, C5, J = 3 Hz), 48.8 (s, 8a-C), 52.4 (s, OCH_3 of ester), 52.6 (s, OCH_3 of ether) 58.5 (s, 4a-C), 114.2 (d, C7, J = 3 Hz), 116.8 (d, C6, J = 122 Hz), 137.10 (s, C2), 140.0 (s, C3), 171.2 (s, CO of ester), 197.8 (d, CO), 200.8 (d, CO). Anal. Calcd for $C_{13}H_{13}FO_5$: C, 58.2, H, 4.88. Found: C, 57.98, H, 4.68.

The regioselectivity observed for **8** was proven by COSY measurements that the protons on C5 were only coupled with each other, but the protons on C8 were coupled with each other and the proton on C7a.

*3.4.7. 6-Fluoro-1,4,4a,5,8,8a-hexahydro-7-methoxy-1,4-dioxonaphthalene-4a,8a-dicarbonitrile (**9**)*

mp 116–119, ^{1}H NMR δ 2.23 (m, CH_2, 2H), 2.48 (m, CH_2, 2H), 3.50 (s, CH_3, 3H), 7.05 (d, CH, 1H); ^{19}F NMR δ −135.4 (m, CF), 78 (s, 7-OCH_3, 3H), 3.9 (s, OCH_3 of ester, 3H), 6.62, 6.82 (d, 2,3-CH, 2H); ^{19}F NMR δ −134.4 (m); ^{13}C NMR δ 20.6 (C6), 21.4 (d, C5, J = 3 Hz), 41.6 (s, 8a-C), 44.3 (4aC), 53.2 (s, OCH_3), 120.3 (d, C7), 126.9 (d, C6, J = 132 Hz), 119.3, 119.5 (CN), 137.1, 137.4 (s, C2, C3), 197.8 (CO), 200.8 (CO). Anal. Calcd for $C_{13}H_9FN_2O_3$: C, 60.00, H, 3.49. Found: C, 60.12, H, 3.50.

*3.4.8. N-Phenyl-6-fluoro-7-methoxy-2H-[1,2,4]triazolo[1.2a]pyridazine-1,3(5H, 8H)-dione (**10**)*

mp 149–151, ^{1}H NMR δ 3.82 (s, OCH_3, 3H), 4.03 (m, 5-CH_2, 2H), 4.17 (s, 8-CH_2, 2H), 7.25–7.5 (m, aromatic, 5H); ^{19}F NMR δ −147.6; ^{13}C NMR δ 43.7, 43.9 (5 and 8-C), 59.9 (OCH_3), 122.1 (6-C, d, J = 116 HZ), 128.5, 136 (aromatic), 152.3, 154 (C=O). Anal. Calcd for $C_{13}H_{12}FN_3O_3$: C, 56.3, H, 4.36. Found: C, 56.0, H, 4.46.

3.5. General procedure for the preparation of alpha-fluoroketones and their analytical data

A solution of 1:1 acetonitrile:water containing 50 mg of the vinyl ether was placed in a closed vacuum hydrolysis tube and subjected to microwave radiation for 20 min. The solution was cooled quickly and the solvents were removed under vacuum. The spectral data were obtained and indicated a purity for the sample of around 90%, but satisfactory C, H analysis were not obtained and no parent ion was observed in the mass spectrum.

*3.5.1. Methyl 6-fluoro-1,4,4a,5,6,7,8,8a-octahydro-1,4,7-trioxonaphthalene-4a-carboxylate (**11**)*

^{1}H NMR δ 1.8–2.1 (m, CH_2, 2H), 3.6 m (CH, 1H), 3.9 (s, CH_3, 3H), 4.0 (d, CHF, J = 45 Hz, 1H), 6.85, 7.05 (dd, CH1 and CH2, 2H), ^{19}F NMR δ −194.4 (m, CF).

*3.5.2. 6-Fluoro-tetrahydroisobenzofuran-1,3,5(6H)-trione (**12**)*

^{1}H NMR δ 2.0–3.8 (m CH_2 and CH, 4H), 3.9 (d of m, CHF, J = 47 Hz, 1H). ^{19}F NMR δ −193.8 (m, CF); ^{13}C NMR δ 25.7–27.3 (m, 7C), 34.7 (4C) 37.3–39.8 (m, 3a, 7a C), 90.1 (d, CF J = 385 Hz), 170.1 (CO) 175.0 (CO), 206.2 (CO).

*3.5.3. 4-Fluoro-5-oxocyclohexane-1,1,2,2-tetracarbonitrile (**13**)*

^{1}H NMR δ 2.80–3.00 (m, CH_2, 2H), 4.00 (m, CFH, J = 47 Hz, 1H); ^{19}F NMR δ −197.2 (m, CF).

Acknowledgment

This research was funded by the National Science Foundation, Research in Undergraduate Institutions.

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