Fumaroyl Chloride: An Acetylene Synthon for the Diels-Alder Synthesis of Specifically Deuteriated Cyclohexenes

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There is a continuing interest in reagents that can function as acetylene synthons in [4+2] cycloaddition reactions[1]. The most recent demonstration of this interest[1] prompts us to report upon an approach to this problem, which was developed some years ago[2], in the course of work with selectively deuteriated cyclohexenes[3-7] and 3,3,6,6-tetradeuteriocyclohexa-1,4-diene[8,9,10].

Our work, like that of Anet[5], Zefirov[6], and Bodot[7], is based upon the well-known lead tetraacetate bis-decarboxylation procedure[11], first discussed by Doering[12] and by Grob[13]. In the work of Anet[5] and Zefirov[6], the *cis*-1,2-cyclohexanedicarboxylic acids **5a, d** were subjected to bis-decarboxylation. In the work of Bodot[7], both the *cis*-dicarboxylic acid **5a** and its *trans* isomer **7b** were converted to cyclohexene. The latter reaction proceeded without scrambling of deuterium;

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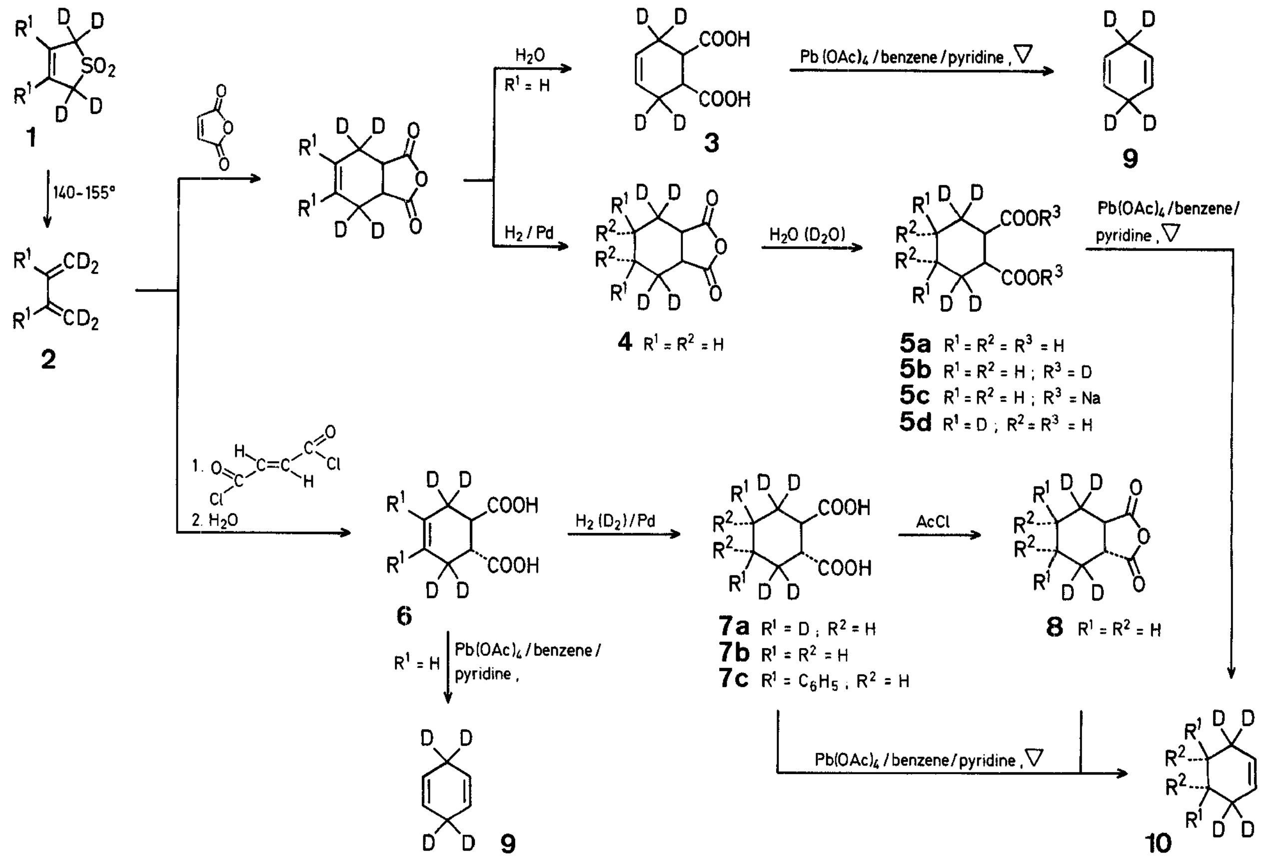

however, the location of deuterium in the cyclohexene prepared from the *cis*-dicarboxylic acids has not been commented upon.

Substrates **3–8** were prepared in 75–80% overall yield by reaction of butadiene-1,1,4,4-d_4[6,7,14] (**2**, $R^1 = H$), perdeuteriobutadiene[15] (**2**, $R^1 = D$), or 2,3-diphenylbutadiene-1,1,4,4-d_4 (**2**, $R^1 = C_6H_5$) with maleic anhydride or fumaroyl chloride, followed by hydrolysis and hydrogenation (or deuterogenation) of the double bond. The oxidation procedure consisted of addition of the substrate to anhydrous pyridine (12 ml/g), to which freshly prepared lead(IV) acetate had been added under nitrogen. The temperature was raised to 35–45°, at which point vigorous evolution of carbon dioxide commenced, and volatile products were swept out of the mixture in a stream of nitrogen. The temperature was maintained between 45–55° for 2 h to complete the reaction, and the product was then isolated[5,7,16]. With the exception of **3** and **6**, G.L.C. analysis revealed the olefinic product to have greater than 95% purity in each case.

The present results, and those of the previous workers[5–7] are summarized in the Table.

The efficiency of the bis-decarboxylation is seen to be *trans*-diacid ~ *cis*-diacid > sodium salt > anhydride. However, the more important observations are those in the last column of the Table which reveal that the bis-decarboxylation of the *cis*-diacids **3** and **5a–d** is accompanied by significant scrambling of deuterium. This is not reduced significantly by prior exchange of the carboxy hydrogens. In contrast, the bis-decarboxylation of the *trans*-diacids **6**, **7**, **8** proceeds without evidence of deuterium scrambling. These results suggest that stereoelectronic effects are operative in the bis-decarboxylation of cyclohexene- and cyclohexane-1,2-dicarboxylic acids[17]. This is also evident from the composition of the unsaturated products obtained from **3** and **6**. The product from **6** ($R^1 = H$)[18] consists of benzene (10%) and 1,4-cyclohexadiene (**9**; 90%), whereas that from **3** ($R^1 = H$) consists of benzene (50%), 1,4-cyclohexadiene (**9**; 48%) and 1,3-cyclohexadiene (2%).

In view of the simplicity of the operations and the absence of deuterium scrambling in the bis-decarboxylation of the *trans*-diacids, it can be concluded that fumaroyl chloride is superior to maleic anhydride as an acetylene synthon for the Diels-Alder synthesis of specifically deuteriated cyclohexenes. Although the yields of olefin are less than 50% when the oxidation is performed under the standard conditions described above, the higher yield obtained with **7c**, in benzene solvent, should be noted.

Boiling points are uncorrected. Melting points were determined on a Kofler hot-stage melting-point apparatus or in capillary tubes in a Thomas-Hoover capillary melting-point apparatus, and are uncorrected. Analytical G.L.C. determinations were performed on a Beckman GC-2 chromatograph. The column packing was 15% butanediol succinate on Embacel or 30% SE-30 on Chromosorb W. A Fisher Preparative Partitioner or a Varian Aerograph Autoprep 700 gas chromatograph was employed for preparative separations. The column used in preparative G.L.C. was 0.82 cm × 61 cm aluminium tubing with the same packings as in the analytical columns. Analytical separations were conducted at 130°, the presence of known compounds being confirmed by enrichment with authentic material. Areas under the peaks were calculated by the method of triangulation[19]. I.R. spectra were recorded on a Beckman IR5A instrument. ^{1}H-N.M.R. spectra were obtained on a Varian A60 spectrometer; chemical shifts are reported relative to internal TMS. The I.R. and ^{1}H-N.M.R. spectra and boiling points of the cyclohexene and 1,4-cyclohexadiene obtained from the hydrogen analogs of **4**, **5a–d**, **7a**, **b**, **8** were in accord with those of the authentic materials. Commercial pyridine was purified by refluxing over barium oxide (0.25 g/10 ml) followed by distillation, the fraction boiling at 115.0–115.5° being retained.

Table. Formation of Deuteriated Cyclohexenes (**10**) and 1,4-Cyclohexadiene (**9**) by Lead (IV) Acetate Decarboxylation

Substrate	Reactant [mmol]		Product	Yield	Hydrogen [%]
	Substrate	$Pb(OAc)_4$		[%]	at positions 3 and 6 each
3	11.3	13.6	**9**	32[a]	12
4 ($R^1=R^2=H$)	6.3	7.5	**10** ($R^1=R^2=H$)	9[a]	9
5a	11.3	11.5	**10** ($R^1=R^2=H$)	35[a]	10
	54.0	64.3	**10** ($R^1=R^2=H$)	42[a]	10
			10 ($R^1=R^2=H$)	33–40[a,b]	[c]
			10 ($R^1=R^2=H$)	69[d]	[c]
5b	11.2	13.5	**10** ($R^1=R^2=H$)	41[a]	8
5c	11.3	13.6	**10** ($R^1=R^2=H$)	14[a]	9
5d	28.7	33.8	**10** ($R^1=D$, $R^2=H$)	38[a]	9
			10 ($R^1=D$, $R^2=H$)	20[e,f]	[c]
6 ($R^1=H$)	28.7	33.7	**9**	40[a]	[g]
7a	45.5	54.2	**10** ($R^1=D$, $R^2=H$)	43[a]	[g]
7b	45.5	54.2	**10** ($R^1=R^2=H$)	46[a]	[g]
			10 ($R^1=R^2=H$)	41[d,f]	[g]
7c	3.0	3.9	**10** ($R^1=C_6H_5$, $R^2=H$)	69[h,i]	[g]
8 ($R^1=R^2=H$)	9.5	11.3	**10** ($R^1=R^2=H$)	9[a]	[g]

[a] Characterized by b.p., refractive index, I.R.-, and ^{1}H-N.M.R. spectra.
[b] see Ref. [6]
[c] Not reported.
[d] see Ref. [7].
[e] see Ref. [5].
[f] Characterized by b.p., I.R.-, and ^{1}H-N.M.R. spectra.
[g] None detectable by ^{1}H-N.M.R. analysis.
[h] Experiment performed in benzene (6.1 ml) containing pyridine (4.5 mmol).
[i] New compound.

Cyclohexene-3,3,6,6-d_4 (10, $R^1=R^2=H$):

*3,3,6,6-Tetradeuteriocyclohexene-*trans*-4,5-dicarboxylic Acid* (**6**, $R^1=H$): 2,2,5,5-Tetradeuteriothiophene 1,1-dioxide[14] (**1**, $R^1=H$; 35.16 g, 0.288 mol) is heated at 140–155° for 90 min and the gases produced are passed through two wash bottles containing 10% aqueous sodium hydroxide and then into a pressure bottle containing chloroform (150 ml) cooled to −78°. Fumaroyl chloride (39.77 g, 0.26 mol) is added at this temperature to form a light green solution, and the bottle is sealed. The solution is warmed to 0°, whereupon a vigorous reaction ensues, which is moderated by cooling the pressure bottle in a Dry Ice/acetone bath. After 15 min, the colorless solution is warmed to room temperature and allowed to stand for 12 h. The solution is then concentrated to an oil, which is dissolved in boiling water. Cooling of this solution affords **6** ($R^1=H$) as colorless crystals; yield: 41.0 g (81%); m.p. 171.5–172.0° (Ref. [20], m.p. 172°).

^{1}H-N.M.R. (pyridine-d_5): $\delta=5.80$ (s, 2H); 3.28 ppm (s, 2H).

*3,3,6,6-Tetradeuteriocyclohexane-*trans*-1,2-dicarboxylic Acid* (**7b**): The *trans*-diacid **6** ($R^1=H$; 9.00 g, 51.7 mmol) is dissolved in dioxane (50 ml), 10% palladium on charcoal (1.0 g) is added, and the mixture is hydrogenated at ~2 atm for 45 min at room temperature. The resultant mixture is filtered, the filtrate evaporated, and the residual product recrystallized from ethanol; yield: 8.5 g (94%); m.p. 222–223° (Ref. [20], m.p. 221°).

^{1}H-N.M.R. (pyridine-d_5): $\delta=3.03$ (s, 2H); 1.50 ppm (octet, 4H).

Cyclohexene-3,3,6,6-d_4 (**10**, $R^1=R^2=H$): The *trans*-diacid **7b** (8.00 g, 45.6 mmol) is added, under nitrogen, to a stirred to a solution of freshly prepared lead(IV) acetate (24.0 g, 54.2 mmol) in dry pyridine (96 ml). The temperature is raised to 35–45°, at which point a vigorous evolution of gas commences; nitrogen is then passed through the reaction mixture, and volatile products are collected at −78°. The temperature of the mixture is then raised to 45–55° for 2 h, and then to 105° for 12 h. The collected distillate is washed with 6 normal hydrochloric acid (10 ml) and water (2 × 10 ml), and dried with sodium sulfate. The product is at least 95% pure, according to G.L.C. analysis. It is purified by distillation at ambient pressure; yield: 1.8 g (46%); b.p. 83°; n_D^{23}: 1.4468.

***cis*-4,5-Diphenylcyclohexene-3,3,6,6-d_4 (10, $R^1=C_6H_5$, $R^2=H$):**

3,4-Diphenyl-2,5-dihydrothiophene 1,1-Dioxide: Sulfur dioxide (20.1 g, 0.313 mol) is condensed into a pressure bottle containing 2,3-diphenylbutadiene[21] (19.5 g, 95 mmol), dioxane (70 ml), and hydroquinone (100 mg) at −78° to give a bright yellow solution. The bottle is sealed and heated at 90–100° for 3 h. It is then cooled, opened, and the contents concentrated to 50 ml. Absolute ethanol (50 ml) is added, and the resultant precipitate is redissolved by heating. Cooling affords the crystalline sulfone; yield: 19.8 g (78%); m.p. 186–187° (Ref. [22], m.p. 183–184°).

3,4-Diphenyl-2,2,5,5-tetradeuteriothiophene 1,1-Dioxide (**1**, $R^1=C_6H_5$): 3,4-Diphenyl-2,5-dihydrothiophene 1,1-dioxide (9.8 g, 36.3 mmol) is added to dioxane (30 ml) containing D_2O (10 ml, 0.5 mol). Sodium deuteroxide (0.3 g) is added, and the mixture is refluxed for 70 h. It is then cooled and extracted with chloroform (2 × 50 ml). These extracts are dried with sodium sulfate and evaporated. The exchange is repeated to give the deuteriated sulfone **1** ($R^1=C_6H_5$); yield: 5.65 g (57%); m.p. 187–187.5° (from chloroform/petroleum ether).

^{1}H-N.M.R. ($CDCl_3$): only phenyl absorption at $\delta=7.3$ ppm.

2,3-Diphenyl-1,1,4,4-tetradeuteriobutadiene (**2**, $R^1=C_6H_5$): The sulfone **1** ($R^1=C_6H_5$; 4.55 g, 16.9 mmol) is distilled at 190–210°/13 torr to give a light yellow oil which crystallizes on cooling; yield: 3.15 g (90%); m.p. 49.5–50.5° (Ref. [21], m.p. 50°).

*1,2-Diphenyl-3,3,6,6-tetradeuteriocyclohexene-*trans*-4,5-dicarboxylic Acid* (**6**, $R^1=C_6H_5$): The diene **2** ($R^1=C_6H_5$) (3.10 g, 14.8 mmol) is dissolved in dry benzene (10 ml) and fumaroyl chloride (2.25 g, 14.8 mmol) is added to form a bright yellowish-green solution. This solution is refluxed for 20 h and then concentrated to give a beige oil, which is dissolved in a mixture of water (25 ml) and dioxane (20 ml), and refluxed for 45 min. The cooled mixture is extracted with ethyl acetate (2 × 75 ml), and the organic extract is dried and evaporated. The residual solid is recrystallized from ethyl acetate; yield: 4.4 g (91%); m.p. 225–226°.

Hydrogen Analog:	$C_{20}H_{18}O_4$	calc.	C 74.52	H 5.63
	(322.3)	found	74.36	5.48
		found	74.40	5.50

4,5-Diphenyl-3,3,6,6-tetradeuteriocyclohexane-trans-*1,2-dicarboxylic Acid* (**7c**): The diacid **6** ($R^1=C_6H_5$; 2.8 g, 8.57 mmol) is dissolved in a mixture of acetic acid (10 ml) and dioxane (15 ml). Palladium on carbon (0.1 g of 30% catalyst) is added, and the mixture is stirred vigorously in a hydrogen atmosphere at 90° for 75 min. A second portion of catalyst (0.4 g) is then added, and stirring is continued for 18 h. After filtration and washing with hot dioxane, evaporation affords an oil which is crystallized from benzene/ethyl acetate to give colorless crystals; yield: 2.4 g (86%); m.p. 222–224°.

Hydrogen Analog:	$C_{20}H_{20}O_4$	calc.	C 74.05	H 6.22
	(324.4)	found	74.20	6.30
		found	74.15	6.35

I.R. (KBr): $\nu_{max}=2380$–3510, 1695–1724, 1602, 1504 cm^{-1}.

^{1}H-N.M.R. (D_2O/K_2CO_3): $\delta=7.10$ (s, 5H); 6.99 (s, 5H); 3.40 (br s, 2H); 3.08, 2.78 ppm (q, 2H, $J=11.5$ Hz).

4,5-Diphenyl-3,3,6,6-tetradeuteriocyclohexene (**10**, $R^1=C_6H_5$, $R^2=H$): The diacid **7c** (1.00 g, 3.05 mmol) is added to a mixture of freshly prepared lead(IV) acetate (1.43 g, 3.86 mmol), anhydrous benzene (6.1 ml), and dry pyridine (366 mg, 4.48 mmol) to form a green solution. The solution is heated to 65°, at which point gas evolution commences. After 15 min at 65°, the solution is brought to reflux for 3 h. The mixture is then cooled, diluted with benzene (20 ml), and filtered. The gummy solid is washed with chloroform (30 ml). The combined filtrate and washings are washed successively with 10% aqueous sodium hydroxide (20 ml), 6 normal hydrochloric acid (20 ml), and water (30 ml). The organic layer is dried with sodium sulfate and concentrated to a yellow oil which crystallizes. Recrystallization from methanol affords colorless crystals; yield: 501 mg (69%); m.p. 62.0–62.5°.

Hydrogen Analog:	$C_{18}H_{18}$	calc.	C 92.96	H 7.74
	(234.2)	found	92.47	7.90
		found	92.40	7.91

I.R. (KBr): $\nu_{max}=1605$, 1582, 1499, 749–758 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta=6.67$ (br, 10H); 5.92 (s, 2H); 3.23 ppm (s, 2H).

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