Ionics (2010) 16:137–144
DOI 10.1007/s11581-009-0366-9

ORIGINAL PAPER

Electrochemical fluorination of dimethyl glutarate and its characterization

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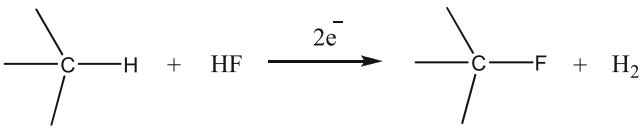
Received: 2 April 2009 / Revised: 9 June 2009 / Accepted: 29 June 2009 / Published online: 21 July 2009

Abstract Monofluoro dimethyl glutarate has been successfully synthesized for the first time by electrochemical fluorination. It is done in an undivided polypropylene cell with platinum electrodes. Initially at three different current densities, dimethyl glutarate is subjected to electrofluorination. Maximum yield of monofluoro product is obtained at 15 mA cm^{-2}. Selecting this current density, electrosynthesis is done at three different charges. Maximum yield of 71.5% of the monofluoro product is obtained with a conversion efficiency of 95.2% when the charge of 6 F/mol is passed. The synthesized product is characterized using Fourier transform infrared (FTIR), gas chromatography/mass spectrometry (GC/MS), and nuclear magnetic resonance (NMR). The product purity and composition are ascertained using GC/MS. The attachment of fluorine to methylene group is indicated using FTIR data. From NMR studies, the environment of fluorine in the neighborhood of carbon and hydrogen has been established. Results are discussed in the paper.

Keywords Selective electrochemical fluorination · Solvent-free system · Homogeneity · Ionic liquid

Introduction

Dimethyl glutarate is used in paints, enamel, varnish, lacquer, thinner, paint stripper, remover, polyamide, polyester, resins, and plasticizers. In view of this importance of these enormous applications, its synthesis becomes essential. Electrochemical fluorination of dimethyl glutarate and its fluorine derivative has not been done so far. But, electrochemical fluorination is a foundational organofluorine chemistry method for the preparation of fluorocarbon-based organofluorine compounds. The general approach represents an application of electrosynthesis. The fluorinated chemical compounds produced by electrofluorination are useful because of their distinctive solvating properties and the relative inertness of carbon–fluorine bonds. The three principal methods by which fluorine is introduced into organic compounds via the formation of new carbon to fluorine bond using electrochemical techniques, a process which, in principle, can be represented as



Electrolysis in molten fluoride salts or solutions containing fluoride ions, at noble metal or graphite anodes, is one of the methods for selective electrochemical fluorination, which are of our current interest. The principal characteristic of this method is the electrolysis of solutions of organic compounds using electrodes of platinum or graphite. This is done at high anodic potentials. Care is taken to see that such anodic potentials are below the potential where the fluorine is evolved. Typically, these reactions yield only partially fluorinated products, introducing one, two, or a maximum of four fluorine atoms into the organic substrate. Electrochemical fluorination method is in stark contrast to the other methods described later, which readily yield perfluorinated products.

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Table 1 Selective electrochemical fluorination of dimethyl glutarate at different current density

Expt. no.	Current density (mA/cm^2)	Selectivity[a] (mol%)			
		2	3	4	1
1	10	30.3	7.6	5.8	56.3
2	15	43.2	5.4	6.7	44.7
3	20	37.5	9.8	7.5	45.2

Reactant = 0.3 mol, ELECTRIC charge = 2 F/mol, cell voltage = 2.83–3.01 V

[a] Conversion based on GC data

Table 2 Selective electrochemical fluorination of dimethyl glutarate at different electric charge

Expt. no.	Electric charge (F/mol)	Selectivity[a] (mol%)			
		2	**3**	**4**	**1**
1	2	43.2	5.4	6.7	44.7
2	4	59.4	7.6	11.1	21.9
3	6	71.5	8.5	15.2	4.8

Reactant = 0.3 mol, current density = 15 mA/cm^2, cell voltage = 2.83–2.97 V

[a] Conversion based on GC data

α-Fluorine is used to modify the biological activity [1–4] in the complex drug molecules. To synthesize these α-fluoro carbonyl derivatives, multistep chemical methods are available. But, efforts to synthesize these molecules are being undertaken through single-step electrochemical partial fluorination.

Partial fluorination of aromatic compounds by electrochemical method in fluoride containing solvent-free electrolyte systems has been extensively studied and reviewed [5–8]. These studies indicate high selectivity toward fluorination of active methylene group attached to sulfur atom [5–8].

Electrolysis in molten potassium/hydrogen fluoride at a porous carbon anode (the Phillips or CAVE Process) and electrolysis in anhydrous hydrogen fluoride at nickel anodes (the Simons or ECF Process) are the other two processes for electrochemical fluorination. These two processes result in only perfluorinated products. In this laboratory, lots of efforts have been put into synthesize the fluorinated product (and not perfluorinated product) by selective electrofluorination method.

In view of the importance of fluorination of dimethyl glutarate, the synthesis of this compound has been done by selective electrochemical fluorination. Monofluoro dimethyl glutarate has been synthesized for the first time through electrochemical fluorination, and this method is specific toward the attachment of fluorine to the methylene group and not carbonyl carbon. The characterization of the compound synthesized has been done using Fourier transform infrared (FTIR), gas chromatography/mass spectrometry (GC/MS), and nuclear magnetic resonance (NMR). The results are presented in this communication.

Experimental

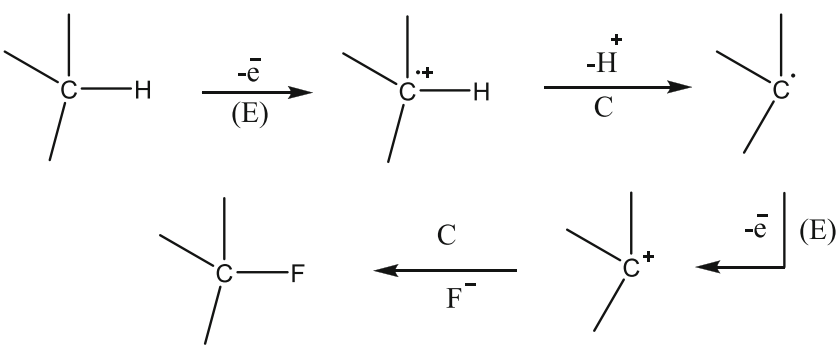
Synthetic grade (>98%) dimethyl glutarate was purchased from M/s Merck, Germany and used without further purification. High pure (>99%) triethylamine was purchased from Sisco Research Laboratory, India. Anhydrous hydrogen fluoride (AHF) >99.9% was obtained from M/s TANFAC, Cudalore, Tamilnadu, India. Preparation of $Et_3N.4HF$ has been reported elsewhere [9].

Electrochemical fluorination

The electrolyte utilized for selective fluorination of dimethyl glutarate was prepared by the some procedure described in the previous publication of selective electrochemical fluorination of alkyl phenyl acetate [9].

$Et_3N.4HF$ was used for electrochemical fluorination of dimethyl glutarate without the use of the solvent. Undivided polypropylene tube (5 ml) was served as a preparative cell for

Scheme 1 EC_BEC_N mechanism of selective fluorination



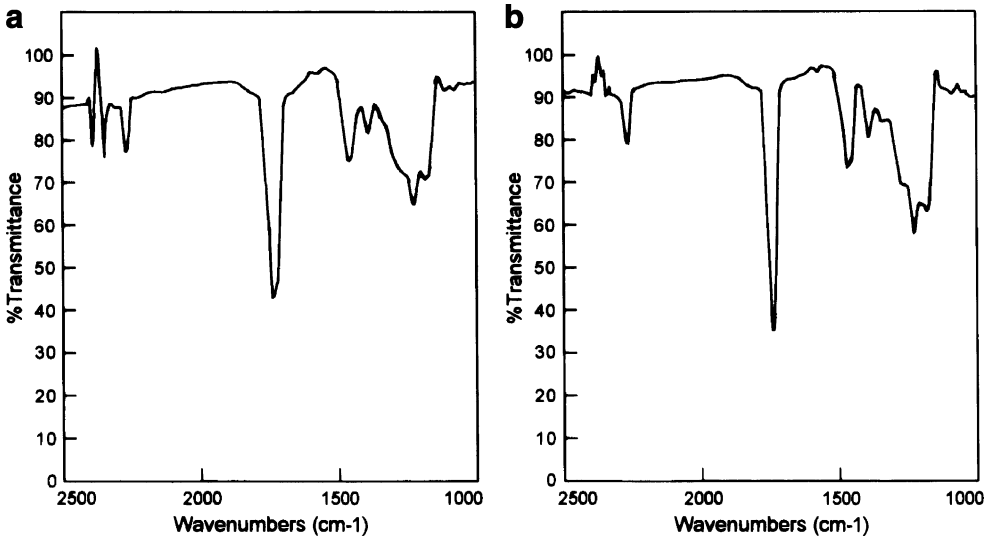


Fig. 1 **a** FTIR data of monofluoro dimethyl glutarate (**2**). **b** FTIR data of dimethyl glutarate (**1**)

the anodic fluorination of dimethyl glutarate. The anode and cathode were a rectangular platinum foil (1×3 cm^2). Pre-electrolysis of 5 ml of $Et_3N.4HF$ solution was carried out at a constant cell voltage of 2.5 V under nitrogen atmosphere. The corresponding current density was around 1.5 mA/cm^2 at the start of pre-electrolysis and dropped to 20% of initial value (0.3 mA/cm^2) after 90 min. The reactant dimethyl glutarate (0.3 mol) was added subsequently, and the electrolysis was carried out galvanostatically using an in-house fabricated galvanostat at 25±2 °C. After completion of electrolysis, the electrolyte was mixed with 50 ml of cold water and extracted using diethyl ether. The extract was washed with brine solution and dried over anhydrous magnesium sulfate. The ether solution was distilled out to get crude product.

The crude product was purified column chromatography on silica gel eluting with 70:30 mixture of hexane and ethyl acetate to give pure compound, and the products were characterized using ^1H NMR, ^{19}F NMR, and GC/MS.

Equipment

^1H NMR spectra were recorded with 400 MHz Bruker NMR Spectrometer with $CDCl_3$ and TMS as solvent and reference, respectively. ^{19}F NMR (376.5 MHz) of the products was recorded using $CFCl_3$ as internal reference. The products dissolved in chloroform were subjected to GC/MS analysis using Agilent 5975C GC/MSD with Triple-Axis HED-EM detector and 7890A GC.

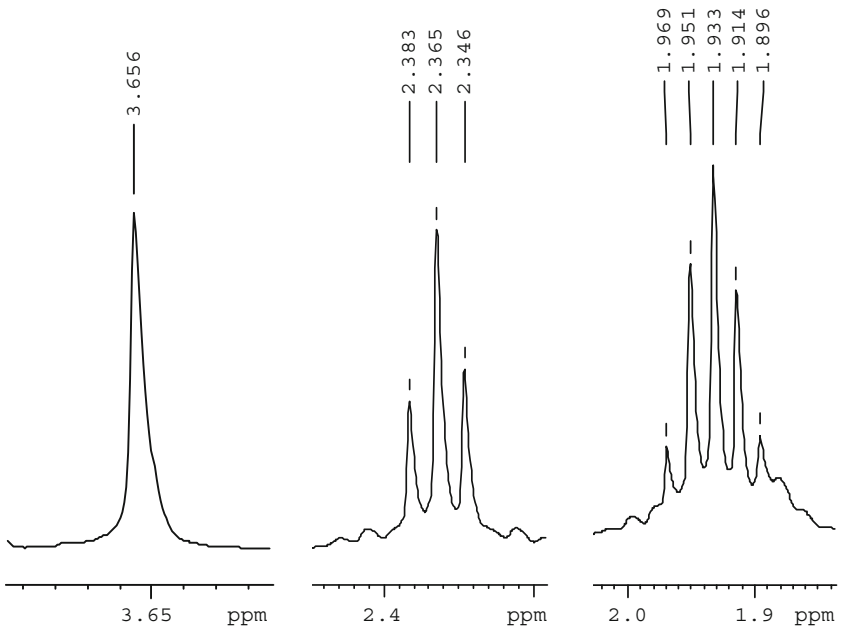


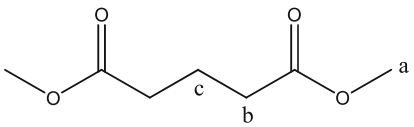
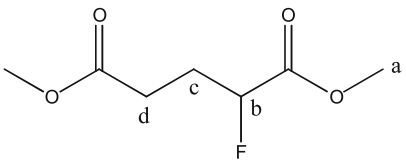
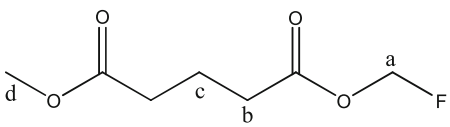
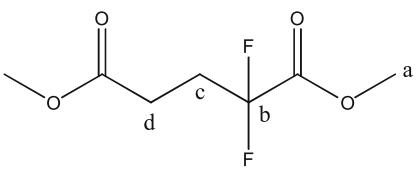
Fig. 2 The ^1H NMR spectra for the starting material (dimethyl glutarate **1**)

Results and discussion

Electrochemical fluorination of dimethyl glutarate

Dimethyl glutarate (**1**) was electrochemically fluorinated at three different current densities as indicated in Table 1. At the current density of 15 mA/cm^2, a maximum yield of monofluorinated product (compound **2**, Scheme 1) of 43.2% was obtained. Selecting the current density at 15 mA/cm^2, electrosynthesis was done at three different electric charges as indicated in Table 2. In this, a maximum yield of 71.5% for compound **2** was obtained with conversion efficiency of 95.2%. The reason for this maximum yield and high conversion efficiency may be due to the formation via EC_BEC_N mechanism. In this process, the first is an electrochemical step. This involves abstraction of electron. This is followed by abstraction of proton by conjugate base. At this stage, the compound is facile of nucleophilic fluoride attack. So, the yield and conversion efficiencies are high. Further passage of electric charge in these experiments leads to compound **4** (Scheme 1), which is not of our current interest. By the passage of excess electric charges, the fluorination of the compound occurs without the cleavage of the ester group. This results into a new mechanistic pathway, which leads to difluoro compound, which is not wanted in the present study. The product distribution pattern obtained at different current densities and electric charges passed are also shown in Tables 1 and 2, respectively.

Table 3 ^{1}H and ^{19}F NMR data of the reactant and product [11–13]

Compound	Structure	Chemical shifts (δ, ppm)
1		*a* = 3.65 (s, 6H) *b* = 2.38 (t, 4H) *c* = 1.89 (m, 2H)
2		*a* = 3.68 (s, 6H) *b* = 5.36 (dm, 1H) $^2J_{HF}$ = 47.8 Hz $^3J_{HH}$ = 7.0 Hz −179.07 (d, 1F) $^2J_{HF}$ = 48.9 Hz *c* = 1.99 (m, 2H) *d* = 2.39 (t, 2H)
3		*a* = 5.70 (dt, 2H) $^2J_{HF}$ = 47.8 Hz −157.71 (t, 1F) $^2J_{HF}$ = 52.7 Hz *b* = 2.41 (s, 4H) *c* = 1.93 (m, 2H) *d* = 3.68 (s, 3H)
4		*a* = 3.73 (s, 6H) *b* = -97.30 (s, 2F) *c* = 2.43 (t, 2H) *d* = 2.41 (t, 2H)

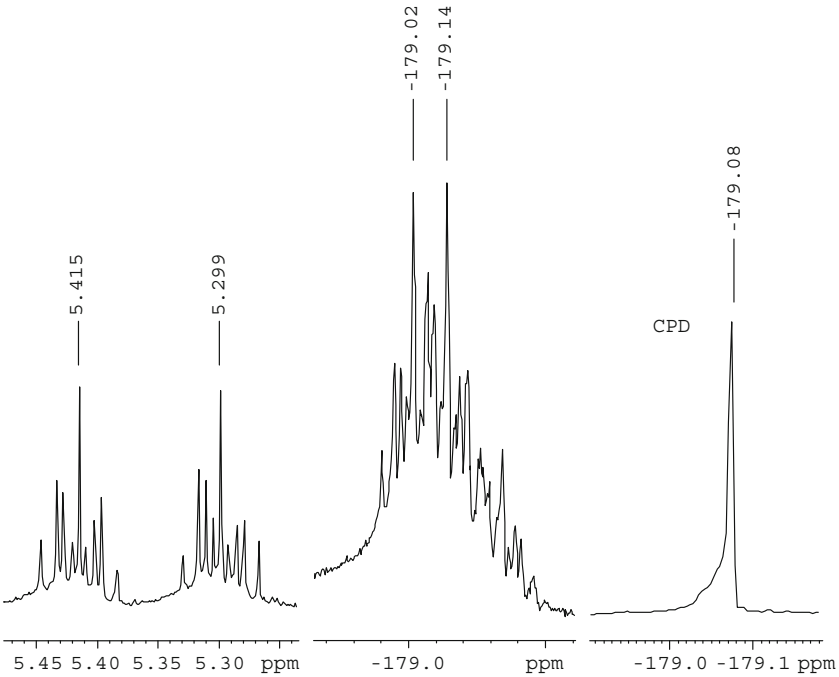


Fig. 3 The ^{1}H, ^{19}F, and ^{19}F (CPD) NMR spectra for the compound **2**

Mechanism for the formation of monofluoro dimethyl glutarate

Mechanism for the formation of **2** is indicated in Scheme 1. Formation of 2 probably occurs through the conventional EC_BEC_N mechanism (Scheme 1) proposed for selective electrochemical fluorination, where E was the electrochemical step which involves removal of an electron, then C_B refers to abstraction of proton by conjugate base, and C_N refers to nucleophilic fluoride attack [4–7]. Further fluorination without the cleavage of the ester group may also follow similar mechanistic pathway leading to difluoro compound (**4**), which has been already discussed in the previous section.

Product characterization and T_1 measurements

Figure 1a and b depicts the FTIR spectra for the synthesized product (**2**) and the starting material (**1**) in which the present investigation is interested. The variations

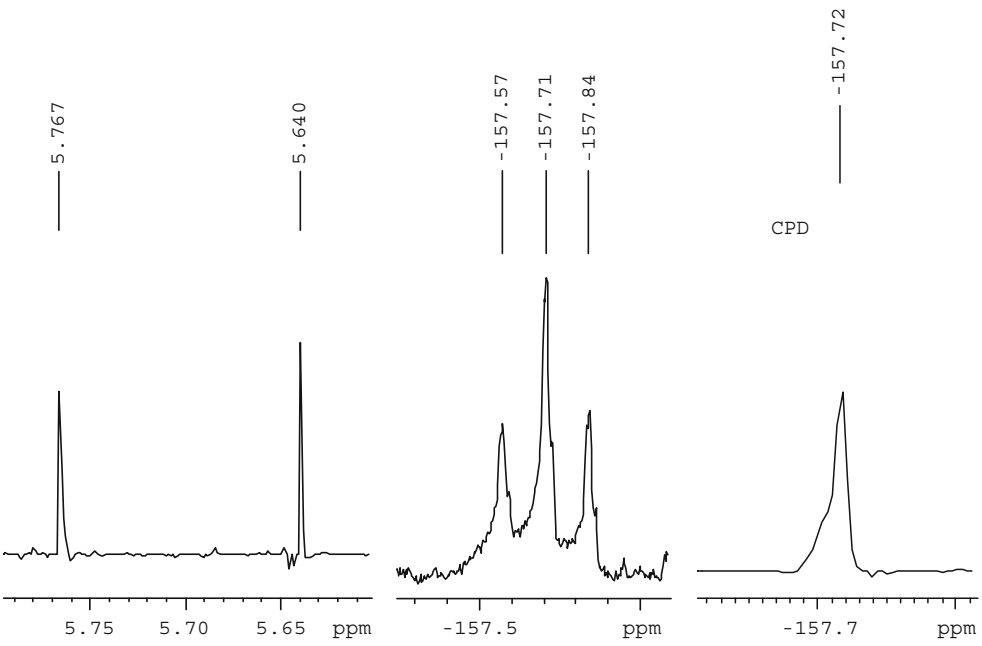


Fig. 4 The ^{1}H, ^{19}F, and ^{19}F (CPD) NMR spectra for the compound **3**

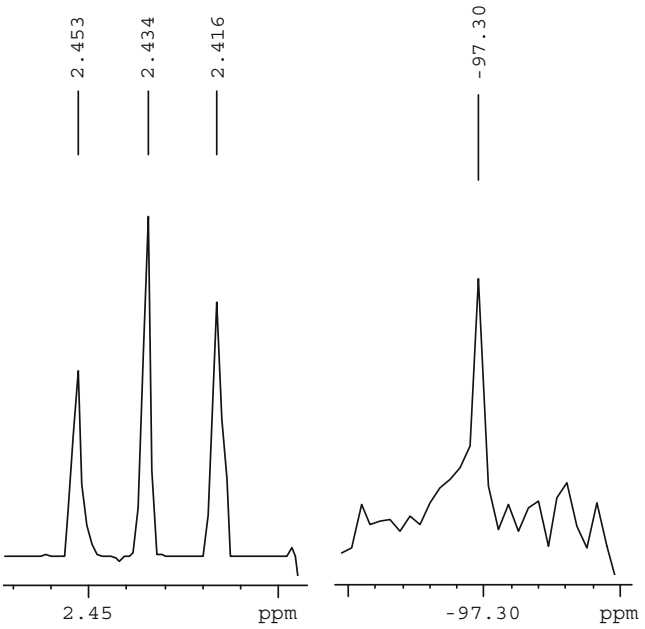


Fig. 5 The ^{1}H and ^{19}F NMR spectra for the compound **4**

Table 5 T_1 data of ^{1}H NMR for the starting material at five different temperatures

Temp. (K)	T_1 (s)		
	3.65ppm	2.38ppm	1.89ppm
Before curve fitting			
313	1.470	2.670	2.623
293	0.972	1.294	1.365
273	0.635	0.900	1.738
263	1.130	1.500	1.649
253	0.432	0.940	0.885
After curve fitting			
313	1.220	2.580	2.615
293	0.645	1.110	1.357
273	0.707	01.089	1.734
263	0.646	1.135	1.640
253	0.349	0.961	0.880

in these two are highlighted. In general, dimethyl glutarate is a compound with odd number of carbon atoms in a molecule. Normally, it can create infinite chains of associated molecules in the crystal. The peaks which represent –C═O stretching of carboxylate anion around 1,700 cm^{-1} is to be affected by the incoming anion F^{-}. This is well reflected from the FTIR spectra. In Fig. 1a (**2**), the peak intensity diminishes from 42.18 to 34.63 compared to spectra depicted in Fig. 1b (**1**). Again, around 1,400 to 1,600 cm^{-1} aliphatic –C–H bending signatures are affected (Fig. 1a) by the formation of monofluoro dimethyl glutarate (**2**) compared to the reactant (**1**) in Fig. 1b. Also, the peak around 1,200 cm^{-1},which is due to –C–O– stretching of the carboxylate anion in the reactant (**1**) and the intensity of the peaks around 1,200–1250 cm^{-1}, are diminished in the synthesized product (**2**) in Fig. 1a. All these indicate that the fluorine gets attached to carbon replacing hydrogen adjacent to the carbonyl carbon. Normally, it is expected that electron density near to –C═O is more, and fluorine is expected to attach this carbonyl carbon, whereas by electrochemical fluorination, it is attached to its nearest carbon of the –C═O group.

^{1}H NMR spectroscopy is of great utility in understanding the receptor–substrate interaction. In compound **1** (Fig. 2, Table 3) in which protons attached to carbon atom (a) appear at 3.65 ppm as singlet, this methyl group was attached to oxygen atom of the ester group, and it appears in the downfield region due to electronegative nature of oxygen atom. The methylene group (b) attached to carbonyl carbon exhibits as triplet at 2.38 ppm by coupling with adjacent methylene group (c), and the latter appears as quintet at 1.93 ppm by coupling with two adjacent methylene groups (b).

In compound **2** (Fig. 3, Table 3)—In ^{19}F NMR spectra, peak at −179.07 ppm appears as doublet with coupling constant 48.9 Hz. This shows the presence of –CHF– group. This is confirmed by decoupling of proton in fluorine NMR, which is indicated as a single peak at −179.08 ppm. In ^{1}H

Table 4 GC/MS data of fluorinated compounds **2**, **3**, and **4**

Compound	GC/MS: m/z:
2	178 ($[M].^{+}$, $C_7H_{11}O_4$, 13.5%); 163 ($[M\text{-}CH_3]^{+}$, $C_6H_8FO_4$,6.2%); 159 ($[M\text{-}F]^{+}$, $C_7H_{11}O_4$, 8.0%); 147 ($[M\text{-}O\text{-}CH_3]^{+}$, $C_6H_8FO_3$,14.3%); 119 ($[M\text{-}C(O)O\text{-}CH_3]^{+}$, $C_5H_8FO_2$,10.7%); 105 ($[C_4H_6FO_2]^{+}$, 18.8%); 91 ($[C_3H_4FO_2]^{+}$, 58.1%); 87 ($[C_4H_7O_2]^{+}$,100%); 73 ($[C_3H_5O_2]^{+}$, 63.5%); 59 ($[C_2H_3O_2]^{+}$, 47.4%); 32 ($[CHF]^{+}$, 30.4%); 31 ($[CH_3O]^{+}$, 27.7%)
3	178 ($[M].^{+}$, $C_7H_{11}FO_4$, 8.9%); 163($[M\text{-}CH_3]^{+}$, $C_6H_8FO_4$, 14.3%); 159 ($[M\text{-}F]^{+}$, $C_7H_{11}O_4$, 8.9%); 147 ($[M\text{-}OCH_3]^{+}$, $C_6H_8FO_3$, 53.6%); 129 ($[M\text{-}OCFH_2]^{+}$, $C_6H_9O_3$, 21.4%); 119 ($[M\text{-}(O)OCH_3]^{+}$, $C_5H_8FO_2$, 24.9%); 105 ($[C_4H_6FO_2]^{+}$, 28.5%); 87 ($[C_4H_7O_2]^{+}$, 100%); 77 ($[C_2H_2FO_2]^{+}$, 48.2%); 59 ($[C_2H_3O_2]^{+}$, 69.8%); 33 ($[CH_2F]^{+}$, 10.7%)
4	196 ($[M].^{+}$, $C_7H_{10}F_2O_4$, 12.3%); 181 ($[M\text{-}CH_3]^{+}$, $C_6H_7F_2O_4$, 9.3%); 177 ($[M\text{-}F]^{+}$, $C_7H_{10}FO_4$, 36.1%); 165 ($[M\text{-}OCH_3]^{+}$, $C_6H_7F_2O_3$, 14.1%); 137 ($[M\text{-}C(O)OCH_3]^{+}$, $C_5H_7F_2O_2$, 9.3%); 123 ($[C_4H_5F_2O_2]^{+}$, 7.0%); 87 ($[C_4H_7O_2]^{+}$, 100%); 73 ($[C_3H_5O_2]^{+}$, 29.7%); 59 ($[C_2H_3O_2]^{+}$, 80.7%); 50 ($[CF_2]^{+}$, 30.1%); 31 ($[CH_3O]^{+}$, 33.5%)

Table 6 T_1 data of ^{1}H NMR for monofluoro dimethyl glutarate (3.65 ppm) at five different temperatures

Temp. (K)	T_1 (s)
Before curve fitting	
313	3.447
293	2.966
273	2.148
263	1.446
253	1.388
After curve fitting	
313	3.401
293	2.962
273	1.975
263	1.527
253	1.245

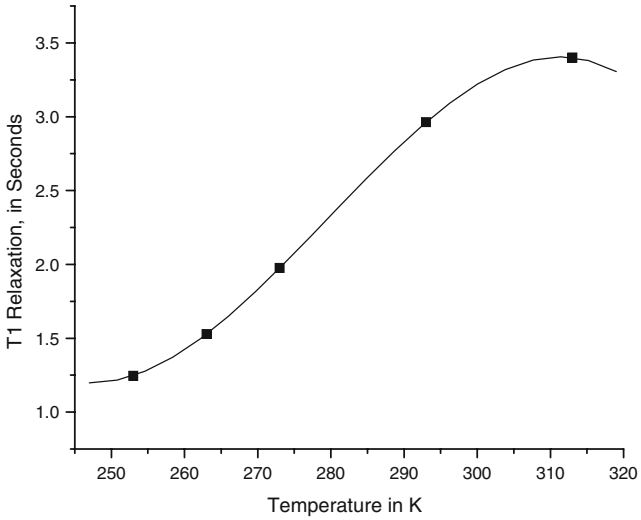


Fig. 7 T_1 data of ^{1}H NMR for monofluoro dimethyl glutarate (3.65 ppm) at five different temperatures after curve fitting

NMR spectra, peak at 5.36 ppm with doublet of multiplet found in the downfield region is due to presence of highly electronegative fluorine atom attached to carbon (b). This doublet is due to the coupling of fluorine with hydrogen in the same carbon (b), and it is confirmed by measuring coupling constant (47.8 Hz) due to $^2J_{HF}$. The multiplet is by coupling of hydrogen in carbon (b) with hydrogen in carbon (c). The proton in carbon (c) appears at 1.99 ppm slightly in the downfield region under the influence of α fluorine atom.

Compound **3** (Fig. 4, Table 3) exhibits triplet in ^{19}F NMR spectra at −157.71 ppm. The triplet is due to the coupling of fluorine with two hydrogen atoms ($^2J_{HF}$= 52.7 Hz) in the same carbon (a). We observe a single peak at −157.71 ppm when the proton was decoupled, confirming the above observation. The rest proton signals appear near in the range of compound **1**. In compound **4** (Fig. 5, Table 3), ^{19}F NMR shows single peak at −97.30 ppm that corresponds to $-CF_2-$ group, which is present in the carbon (b), and it is confirmed by the presence of two peaks appearing as triplet in the region 2.43 and 2.41 ppm for proton present in the carbon (c) and (d). If $-CF_2-$ is present in carbon (c), the proton signals for carbon (b) and (d) would appear as singlet but in the present case it is not so. Downfield shift was observed for protons in carbon (c) because of the presence of α $-CF_2-$ group. Further structural confirmation of these compounds **2**, **3**, and **4** was done with GC/MS data. The fragmentation pattern (Table 4) observed for the above said compounds clearly

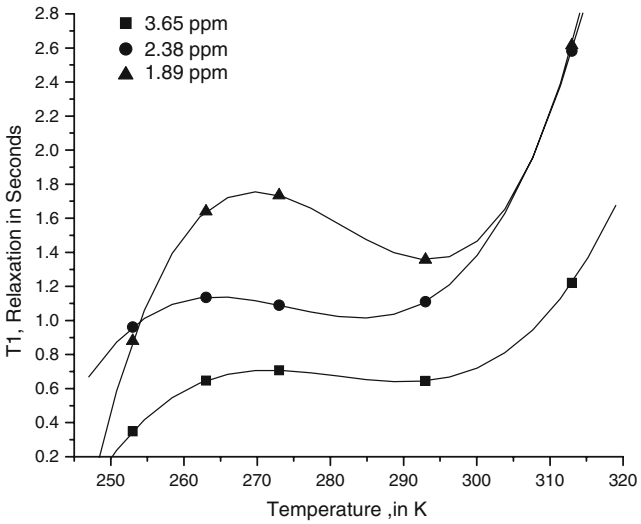


Fig. 6 T_1 data of ^{1}H NMR for the starting material at five different temperatures after curve fitting

Table 7 T_1 data for ^{19}F NMR for the compounds **2**, **3**, and **4** at five different temperatures

Temp. (K)	T_1 (s)		
	−179.07ppm	−157.71ppm	−97.30ppm
Before curve fitting			
313	3.700	2.780	2.500
293	2.520	1.500	1.730
273	1.701	0.921	1.408
263	1.249	0.539	0.857
253	0.824	0.464	0.671
After curve fitting			
313	3.925	2.497	2.819
293	2.726	1.282	2.060
273	1.849	0.631	1.527
263	1.434	0.426	1.227
253	0.982	0.256	0.841

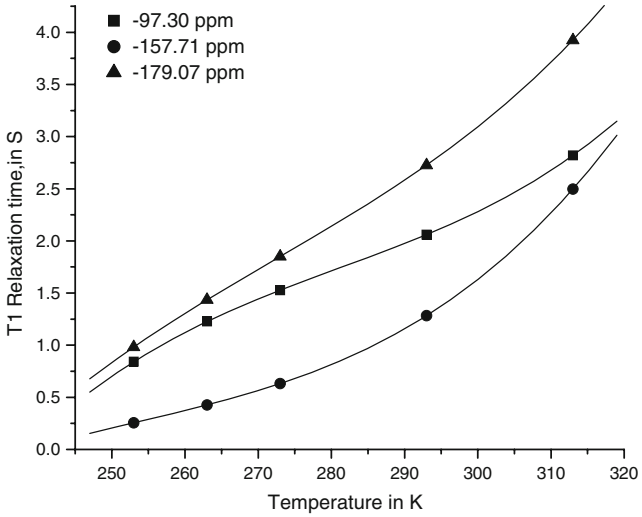


Fig. 8 T_1 data for ^{19}F NMR for the compounds **2**, **3**, and **4** at five different temperatures after curve fitting

confirms the structure and the exact location of the fluorine atom in it.

Peak splitting may be due to the carbonyl carbons at the two ends of the glutarate ligand. These have different chemical shifts due to their crystallographically different locations in the crystal. Another way to interpret the result is that carbonyl carbons at the two ends happen to have same crystallographical sites. This possibility may not be likely as it is discussed by Kim et al. [10] since it is difficult to have the same crystallographic sites for carbonyl carbons at both ends when all methylene carbons in the glutarate ligand show crystallographic splitting.

T_1 data of ^1H NMR for starting material (**1**) and monofluoro dimethyl glutarate (**2**) at five different temperatures after curve fitting are given in Tables 5 and 6, and their plot is shown in Figs. 6 and 7. From these relaxation data, it is clear that at 3.65 ppm, on comparison with the two data (Figs. 6 and 7), relaxation time is increased at all temperatures. Maximum occurs at 275 K (3.65 ppm, Fig. 6) for the reactant (**1**), whereas maximum occurs at 310 K (3.65 ppm, Fig. 7) for the monofluoro dimethyl glutarate (**2**). This shows that the carbon (b) attached to the adjacent carbonyl carbon (a) gets fluorinated.

T_1 data of ^{19}F NMR for compounds **2**, **3**, and **4** at five different temperatures after curve fitting are given in Table 7 and their plot is shown in Fig. 8. From the relaxation versus temperature data, it is clear that monofluoro dimethyl glutarate (**2**) has got high relaxation time compared to other two namely difluoro (**4**) and fluorine attached to the –O–CH_3 group (**3**). Even though one cannot categorically say, from these data, anything about the product formation, one can always speculate that higher relaxation time of the desired product of synthesis at all temperature is desirable from the point of view of crystal homogeneity and purity. In this aspect, the monofluoro compound occurs at −179.07 ppm stands better in crystal quality.

Conclusions

Dimethyl monofluoro glutarate has been successfully synthesized for the first time by electrochemical fluorination. Maximum yield of monofluoro product is obtained at 15 mA cm^{-2}. Maximum yield of 71.5% of the monofluoro product is obtained with a conversion efficiency of 95.2% when the charge of 6 F/mol is passed. The synthesized product is characterized using FTIR, GC/MS, and NMR. The product purity and composition are ascertained using GC/MS. The attachment of fluorine to methylene group is indicated using FTIR data. From NMR studies, the environment of fluorine in the neighborhood of carbon and hydrogen has been established. From the relaxation time data, it is clear that the crystal obtained is pure and homogenous.

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