Chapter 3-Section II

3.II.1 Introduction

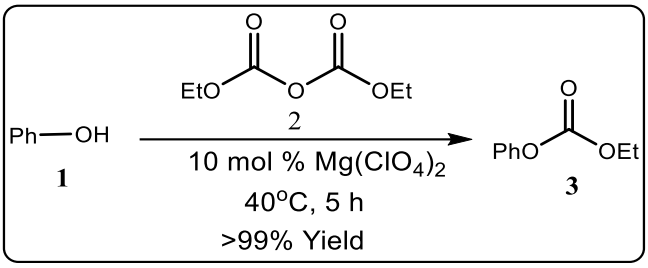
Development of various methods for the synthesis of optically pure compounds is an important subject in chemistry. Enzyme mediated Kinetic Resolution or Dynamic Kinetic Resolution along with innumerable methods of asymmetric synthesis have acquired prominent proportion in recent decades. Although Kinetic Resolution is more general method to access optically pure compounds, a certain structural requirement is necessary. The Dynamic Kinetic Resolution appears to be more attractive and atom economical option as the maximum yields of optically pure compounds can be as high as quantitative. Both the methods are extensively explored in organic synthesis. Another approach to access more quantity of optically pure material can be envisaged, where the less reactive isomer in enzyme mediated biotransformation, can be converted to the same product by inversion of configuration. In this endeavour, recently we have reported [1] one-pot synthesis of optically pure aryl carbinols from corresponding racemic alcohols involving enzyme mediated KR and Mitsunobu reaction, where the slow reacting isomer is converted to acetate using metal acetates. Mitsunobu reaction is often explored as a preferred method for converting less reactive alcohols to other functional molecules. This reaction activated the less reactive alcohol to moderately good leaving groups, for subsequent nucleophilic substitution reactions with inversion of configuration. The Mitsunobu reaction component was conducted with diethyl azodicarboxylate (DEAD) and triphenyl phosphine (Ph3P) as per the standard condition. The protocol was effective with very high chemical conversion and enantioselectivity. The best results were obtained with silver acetate as source of nucleophile. The Mitsunobu approach has already been widely explored and established as a major tool for synthetic modifications. In this effort we wish to further explore the one-pot combination of enzyme mediated reaction and Mitsunobu reaction for wider possibilities. The scope of the reaction was extended using other nucleophiles like azides, where the less reactive isomer was expected to be converted to azido derivatives.

3.II.2 Synthesis of Organic carbonates

Conversion of alcohols to other functional groups from the point of view of synthetic manipulations is critical. The alcohol group also needs to be protected for specific reasons to prevent them from participating in unwanted reactions. One of the methods to protect

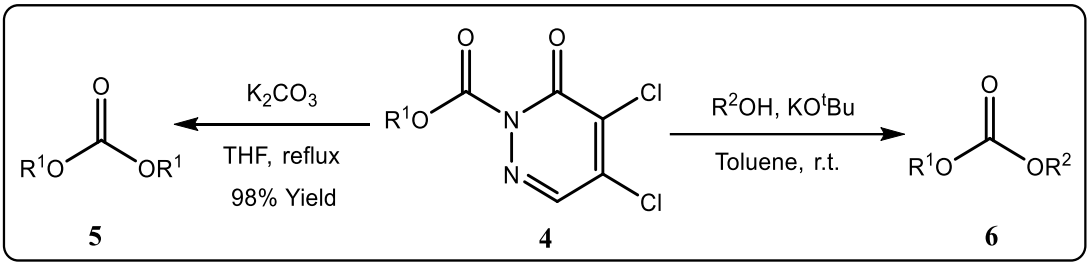
the alcohols is by converting to their carbonates. Usually, the alcohols are converted to corresponding carbonates by various methods, few of them can be summarized here.

The conventional techniques for making organic carbonates call for the utilisation of basic conditions and hazardous chemicals, such as phosgene, pyridine, and carbon monoxide.[2,3] As a result, there has recently been a lot of work put into creating methods for synthesising organic carbonate that are more environmentally friendly.[4] The organic carbonate interchange [2] has likely been the strategy that has received the most attention and has led to the creation of numerous protocols, the most of which are protected by patents.[5]



Scheme 1: Synthesis of organic Carbonates developed by Sambri et-al

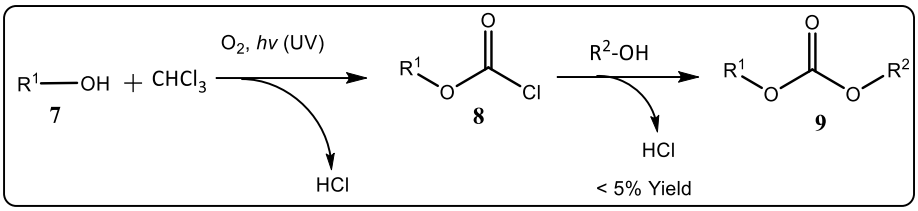
Alkoxy- or aryloxycarbonyl moieties can be obtained from alkyl and aryl chloroformates ClC(=O)OR, which are crucial sources for a variety of synthetic applications.[6] Chloroformates are frequently used in the generation of carbonates.[7] However, acyl-transfer reactions involving chloroformates have a number of drawbacks. For instance, chloroformate derivatives are frequently moisture-sensitive, gaseous compounds in ambient conditions, and they produce hydrochloric acid as a poisonous and highly acidic by-product of the reaction.



Scheme 2: Synthesis of organic Carbonates developed by Hyo Jae Yoon et-al

The main ingredients in the synthesis of carbonates and carbamates are chloroformates. As per the literature, a primary alkyl alcohol solution and a unique photo-on-demand *in situ* generation of chloroformates are described. Additionally, it enabled the one-pot

synthesis of carbonates and carbamates by adding alcohols later. Because no reagents are added during the *in situ* photo-on-demand generation of chloroformate in chloroform solvent, which make this process unique and valuable.



Scheme 3: Synthesis of organic Carbonates developed by Tsuda et-al.

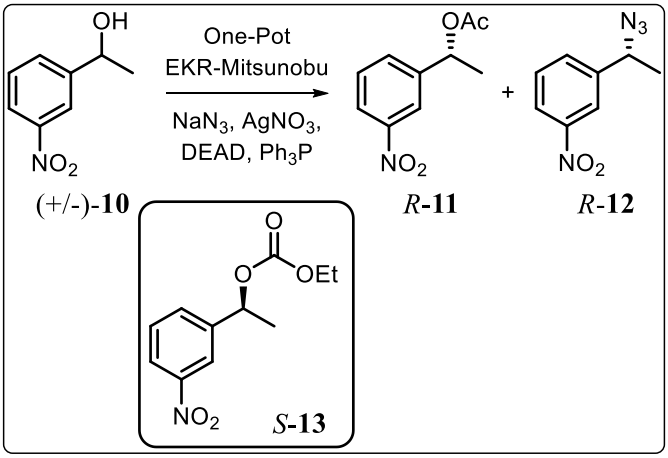
3.II.3 Result and Discussion

In this Chapter we share our observations on the unexpected formation of alkyl carbonate during the one-pot enzyme mediated Kinetic Resolution and Mitsunobu reaction with less reactive nucleophiles. To widen the scope of our approach we investigated second step of Mitsunobu reaction with sodium azide as nucleophile, assisted by the presence of silver salts. During this investigation we observed formation of ethyl carbonate as an impurity. The Mitsunobu reagent, DEAD, provides the source of ethyl carbonate in this silver mediated conversion. We further investigate this unexpected observation with more examples and offer a plausible explanation.

3.II.4 Mitsunobu reaction with azide Nucleophile

Reaction of secondary aryl carbinol was investigated for one-pot enzyme mediated Kinetic Resolution and Mitsunobu reaction. The efficacy of enzyme to discriminate the optical isomers has been established in our earlier work. The one-pot reactions are often challenging to understand due to the interactions of different components in the medium. The standard reaction was optimized with 1-(3-nitrophenyl)ethan-1-ol (*R*/*S*-**10**) (**Scheme 4**). The optically enriched acetate *R*-**11** and azide *R*-**12** were obtained in high selectivity. In order to explore utility of this approach we were keen to use different nucleophiles in the second step of Mitsunobu reaction. Initial experiments with sodium azide furnished poor yield of azide *R*-**12** (12%), hence, silver nitrate was added to *in situ* convert it to more reactive silver azide. We have already established the efficiency of silver salts in such reactions.[1] As expected there was marked improvement in the formation of the

azide *R*-**12** in presence of silver nitrate (41%). In the best conditions the combined yield of both these isolated materials was about 86%. Careful observation of the reaction mixture revealed formation of another byproduct, which was confirmed to be the ethyl carbonate **13**. Analysis of this product on chiral stationary phase HPLC indicated that it was formed almost as a single enantiomer (9% Yield, 99% ee).



Scheme 4: One-Pot EKR-Mitsunobu reaction

3.II.5 Synthesis of Organic Carbonates.

This unexpected formation of the ethyl carbonate in presence of silver nitrate prompted us to further explore this one-pot reaction. Several practical methods are available for the preparation of carbonates from corresponding alcohols, such as using sodium borohydride in dialkyl carbonate solvents,[8,,9] catalyst CsF supported on α-alumina,[10] Organotin-oxomolybdate coordination polymer.[11] Although the present reaction was not designed to prepare carbonates from alcohols, its serendipitous formation merits more investigation. Furthermore, the high optical purity of this ethyl carbonate **13** was an encouraging observation and the scope of this stereospecific reaction is attractive.

3.II.5.1 Optimisation condition for the carbonate formation

The reaction of carbonate formation was examined with 1-(3-nitrophenyl)ethan-1-ol (**10**) to determine the role of each reagents (Table 1). The reaction with DEAD in the absence of Ph_3P and silver salt did not proceed at all. The same reaction with DEAD and Ph_3P, under the well established Mitsunobu condition furnished only traces of carbonate **13**. However, in presence of silver nitrate (1.0 eq.) along with DEAD/Ph_3P, the reaction

proceeded smoothly to give a good yield of carbonate **13**. Interestingly, the reaction with DEAD and silver nitrate in absence of Ph_3P, also resulted in the formation of **13** in good isolated yield. This observation is interesting as the smooth conversion without triphenylphosphine may indicate deviation from Mitsunobu type reaction pathway. As expected, the reaction did not proceed without DEAD, hence, eliminating the possibility of contamination of any other source of carbonate during the reaction. All the reactions were performed under the inert atmosphere of nitrogen gas.

Scheme 5: Mitsunobu reaction with **$AgNO_3$**

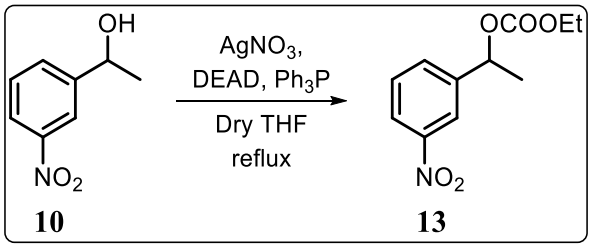


Table 1. Screening of conditions for carbonate formation[a]

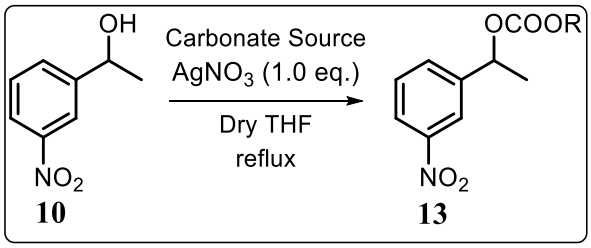
No	$AgNO_3$ (eq.)	DEAD (eq.)	Ph_3P (eq.)	Time (h)	Yield (%)
1	--	2.0	--	72	NR
2	--	--	2.0	72	NR
3	--	2.0	2.0	72	< 2
4	1.0	2.0	2.0	24	74
5	1.0	2.0	--	48	85
6	1.0	--	2.0	72	NR

[a]Isolated Yield; Ratio, with respect to **10**; NR = No Reaction on TLC.

3.II.5.2 Modified Conditions for Carbonate formation

As stated above the source of carbonate must be DEAD, which was further established by performing the reaction with diisopropylazodicarboxylate (DIPAD), where the corresponding iso-propyl carbonate was formed (entry 2; Table 2). The other two esters, ethyl benzoate and ethyl acetate, did not result in the formation of **13** in the presence of silver nitrate.

Scheme 6: Synthesis of carbonate with different carbonate source



10 **13**

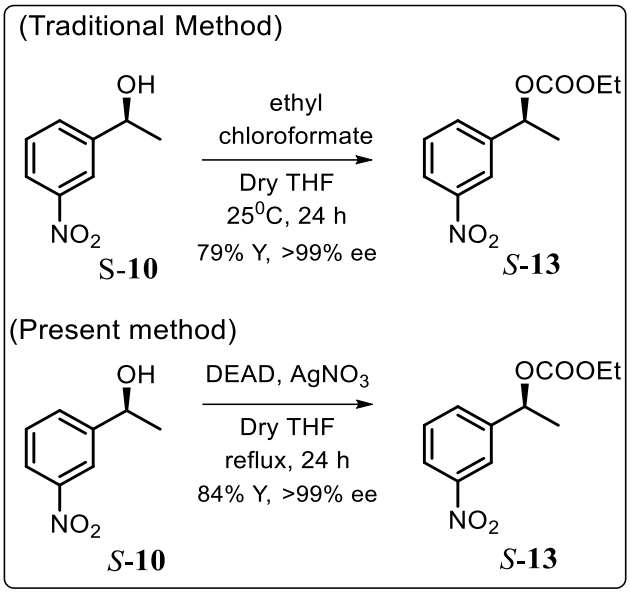
Table 2. Screening different sources of carbonate moiety[a]

No	Source of alkyl (eq)	Compound (R in ether)	Time (h)	Yield (%)
1	DEAD (2.0)	10 (Et)	48	85
2	DIPAD (2.0)	23 (i-Pr)	72	63
3	PhCOOEt	10	78	Not observed
4	EtOAc	10	78	Not observed

[a]Isolated Yield; Ratio, with respect to **10**.

3.II.5.3 Study of Absolute Configuration for carbonate formation.

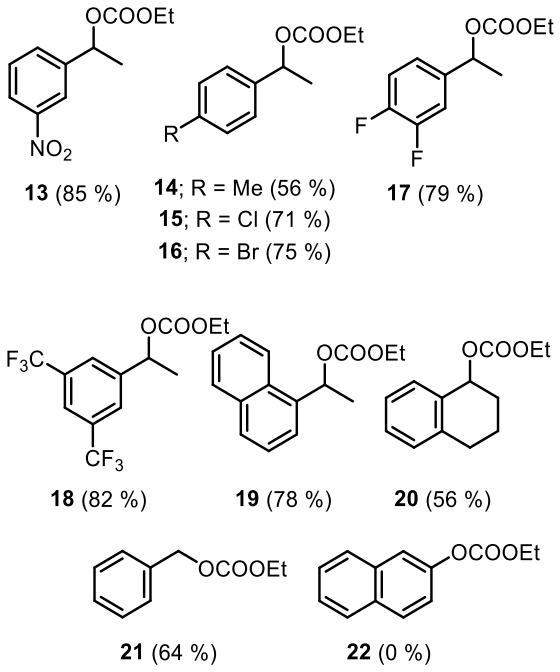
The main feature of Mitsunobu reaction is the stereochemical consideration as the substitution takes place with inversion of configuration.[12] Further reactions were performed to ascertain this aspect (**Scheme 2**). Reaction with optically pure *S*-**10** with ethyl chloroformate as electrophile in a dry THF resulted in the formation of *S*-**13**, indicating the retention of configuration. Reaction of *S*-**13** with the help of DEAD/$AgNO_3$ gave *S*-**13** in marginally better yield. Both the experiments confirmed the retention of configuration at the chiral center of the alcohol. The stereospecific conversion of secondary chiral alcohol to alkyl carbonate is critical consideration for possible applications of this methodology.



Scheme 7: Stereochemical considerations

3.II.5.4 Substrate study for the carbonate synthesis.

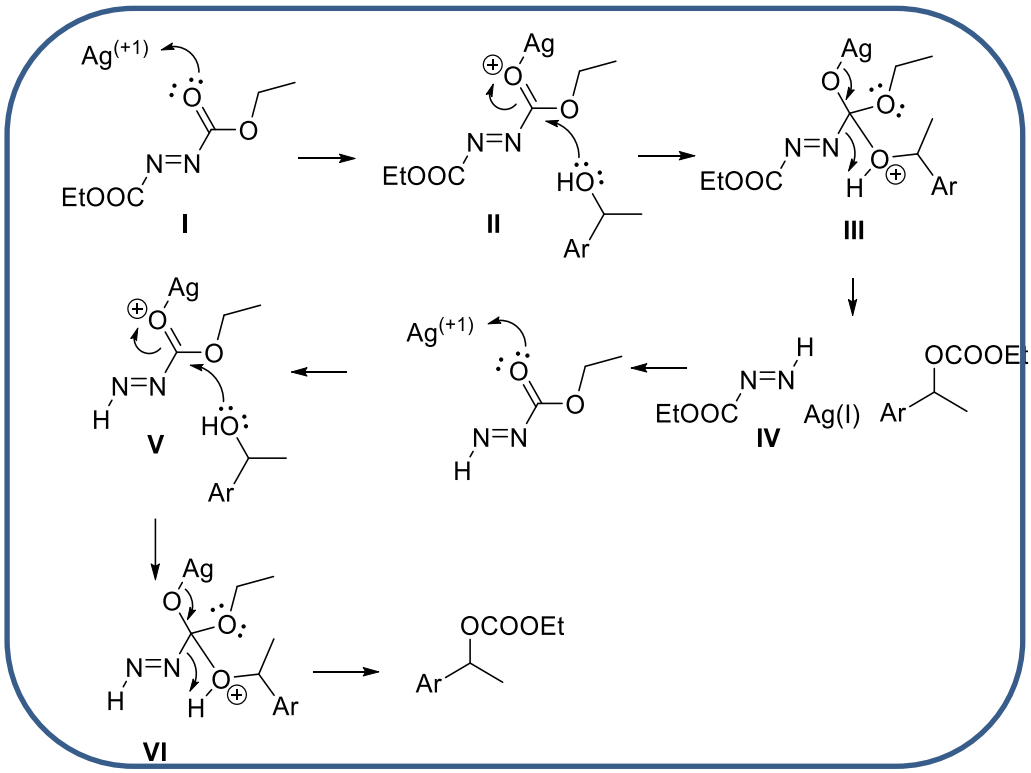
The method is then extended for a few more substrates to confirm the generality of the reaction (**Scheme 8**). Reaction seems to be working well, better for the aryl carbinols with electron withdrawing substituent on the aromatic ring. It's worth mentioning that the carbonate formation did not proceed for phenols, as in the case of 2-naphthol.



Scheme 8: Examples of ethyl carbonate formation with the present method. DEAD (2.0 eq.), $AgNO_3$ (1.0 eq.) in dry THF, reflux (48 h); isolated yields in parenthesis

3.II.5.5 Plausible Mechanism of the reaction

This type of carbonate formation under Mitsunobu reaction in presence of silver salt is not known. The role of silver ion in many organic reactions is well established.[13] Having established the required condition for the formation of ethyl carbonate, we propose a possible explanation of this reaction (**Scheme 9**). We have established that the presence of silver salt for the reaction is necessary, with silver sulphate in place of silver nitrate, **13** was obtained in 63% yield. The reaction of carbonate formation proceeds in the absence of Ph_3P, which may indicate that there may not be playing active role in the mechanism. The $Ag^{(+1)}$ may activate the carbonyl of **I** by binding with the lone pair forming **II**. The alcohol will attack on this activated carbonyl to form **III**, which will give carbonate and the imide I**V**. A molecule of ethyl diazenecarboxylate can be liberated from **III**, which is attacked by the second molecule of alcohol on carbinal carbon in **V**,. There is a possibility of repetition of the same on both ester groups of **I**, resulting in the formation of **VI**. The same reaction was performed with more classical Lewis acid, copper(II)triflate and DEAD, where **13** was obtained, under unoptimized conditions in around 30% yield.



Scheme 9: Proposed mechanism of ether formation

The proposed mechanism supports all the observations, including the fact that it doesn't work with phenolic hydroxyl group, probably due to its low nucleophilicity. This explanation is also in agreement with stereochemical considerations.

3.II.6 Conclusion

In conclusion, we have investigated an unexpected formation of alkyl carbonates from aryl carbinols under modified Mitsunobu conditions with dialylazodicarboxylate and silver salt. The reaction proceeds in stereospecific manner, with retention of configuration at the chiral center, reaction doesn't work with phenols.

3.II.7 Standard Experimental Procedures:

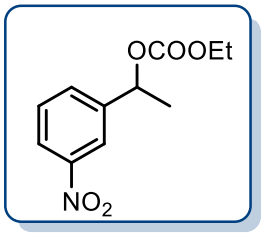
General procedure for Carbonate formation with $AgNO_3$:

To an oven dried two neck round bottom flask racemic alcohol **10** (0.3 g, 1.8 mmol) and $AgNO_3$ (0.301 g, 1.8 mmol) was added in dry THF (10 mL) and cool the reaction mixture to 0 ^{0}C in an ice bath with stirring. Then slow addition of solution of DEAD (0.657 mL, 3.60 mmol) in dry THF (5 mL) at 0^{o}C to the reaction mixture. The reaction mixture was stirred on a reflux condition and followed by TLC. After the completion of reaction solvent was removed under reduced pressure the residue was taken in ethyl acetate and washed with water and brine then extracted with Ethyl acetate (3X25 mL). The organic layer was dried over sodium sulphate and the crude product was purified by silica-gel column chromatography (2% Ethyl acetate- Petroleum ether). Colourless liquid **13** was obtained. Yield obtained (0.297 g, 85%).

Procedure for carbonate formation by ethyl chloroformate:

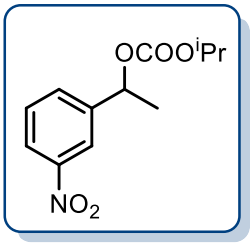
To an oven dried two neck round bottom flask racemic alcohol **10** (0.1 g, 0.59 mmol), was dissolve in dry THF (5 mL) and cool the reaction flask to 0 ^{0}C in an ice bath with stirring, then slowly add NaH (0.05 g, 2.4 mmol) in a portion wise to the reaction mixture. Stirred the reaction mixture for 15 minutes then add ethyl chloroformate (0.07 mL, 0.72 mmol) dropwise to the reaction mixture. The reaction mixture was stirred at room temperature and followed by TLC. . After the completion of reaction mixture is quenched by ammonium chloride and extracted with Ethyl acetate (3X25 mL). The organic layer was dried over sodium sulphate and the crude product was purified by silica-gel column chromatography (2% Ethyl acetate- Petroleum ether). Colorless liquid **13** was obtained. Yield obtained Yield obtained (0.113 g, 79%).

Ethyl (1-(3-nitrophenyl)ethyl) carbonate 13



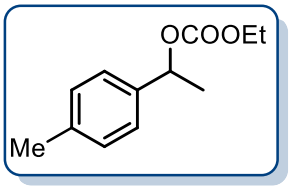
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.22 (m, 1H), 7.72 (m, 1H), 7.56 (m, 1H), 5.70 (q, *J* = 6.4 Hz,1H), 4.19 (m, 2H), 1.64 (d, *J* = 6.4 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 154.31, 148.41, 143.34, 132.17, 129.69, 123.12, 121.09, 74.85, 64.34, 22.34, 14.21. **IR (KBr)** υ 3092, 2986, 1744, 1533, 1449, 1352, 1257, 1171, 1095, 1059, 898, 790 cm^{-1}. **HRMS** (ESI-MS) m/z: Calculated for $[M]^+$ 239.0794 Found 239.0788.

Isopropyl (1-(3-nitrophenyl)ethyl) carbonate 23



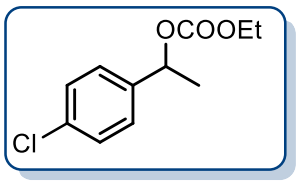
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.22 (m, 1H), 7.73 (m, 1H), 7.56 (m, 1H), 5.79 (q, *J* = 6.4 Hz, 1H), 4.86 (m, 1H), 1.64 (d, *J* = 6.4 Hz, 3H), 1.33 (d, *J* = 6.4 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 153.81, 148.40, 143.47, 132.14, 129.67, 123.07, 121.08, 74.66, 72.46, 22.36, 21.75. **IR(KBr)** υ 3091, 2985, 1748, 1618, 1583, 1534, 1352, 1258,1215, 1093, 911,790, 687 cm^{-1}. **HRMS** (ESI-MS) m/z: Calculated for $[M+Na]^+$ 276.0848 Found 276.0860.

Ethyl (1-(p-tolyl)ethyl) carbonate 14



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J*=8.4 Hz, 2H), 7.19 (d, *J*= 8.4 Hz, 2H), 5.71 (q, *J*=6.4 Hz, 1H), 4.16 (m, 2H), 2.36 (s, 3H), 1.60 (d, *J*=6.4 Hz, 3H), 1.30 (t, *J*=7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 154.57, 138.18, 137.90, 129.21, 126.07, 76.18, 63.83, 22.29, 21.16, 14.25. **IR(KBr)** υ 2984, 2933, 1744, 1615, 1451, 1372, 1257, 1210, 1056, 1008, 858, 817, 791 cm^{-1}. **HRMS** (ESI-MS) m/z: Calculated for $[M+Na]^+$ 231.0997 Found 231.0989.

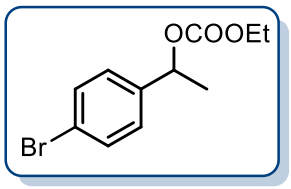
1-(4-chlorophenyl)ethyl ethyl carbonate 15



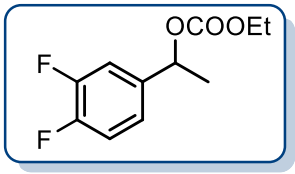
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J*= 6.4 Hz, 4H), 5.69 (q, *J* = 6.4 Hz, 1H), 4.19 (m, 2H), 1.58 (d, *J* = 6.4 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H).**^{13}C-NMR (100**

MHz, $CDCl_3$) δ 154.44, 139.71, 133.90, 128.76, 127.49, 75.41, 64.01, 22.27, 14.23. **IR(KBr)** υ: 2984, 2931, 1744, 1598, 1493, 1259, 1209, 1056, 1009, 858, 790 cm^{-1}. **HRMS** (ESI-MS) m/z: Calculated for $[M+Na]^+$ 251.0451 Found 251.04454.

1-(4-bromophenyl)ethyl ethyl carbonate 16



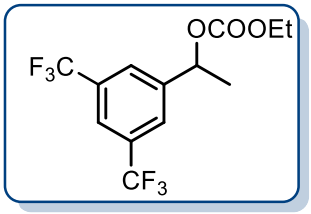
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 5.68 (q, *J* = 7.2 Hz, 1H), 4.18 (t, *J* = *6.8* Hz, 2H), 1.58 (d, *J* = 6.8 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 154.41, 140.22, 131.70, 127.79, 122.02, 75.43, 64.02, 22.24, 14.24. **IR(KBr)** υ: 2983, 1744, 1488, 1372, 1259, 1055, 1007, 825, 761 cm^{-1}. **HRMS** (ESI-MS) m/z: Calculated for $[M+Na]^+$ 294.9946 Found 254.9941, 294.9922, 295.9984, 299.0621



1-(3,4-difluorophenyl)ethyl ethyl carbonate 17

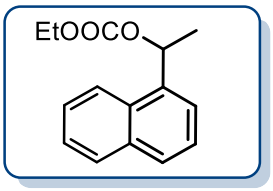
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 3H), 5.69 (q, *J* = 6.4 Hz, 1H), 4.19 (m, 2H), 1.58 (d, *J* = 6.4 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 154.35, 151.36-150.96 (dd, 20 Hz, 10 Hz, 1 C-F), 149.39-148.99 (dd, 20 Hz, 10 Hz, 1 C-F), 138.24, 122.26 -122.18 (d, 3 Hz, 1 C-F), 117.40-117.27 (d, 13 Hz, 1 C-F), 115.28-115.14 (d, 13 Hz, 1 C-F), 74.86, 64.11, 22.20, 14.17. **IR(KBr)** υ 2987, 1746, 1613, 1521, 1439, 1260, 1159, 1119, 1058, 934, 820, 779 cm^{-1}. **HRMS** (ESI-MS) m/z: Calculated for $[M]^+$ 230.0755 Found 231.1000

1-(3,5-bis(trifluoromethyl)phenyl)ethyl ethyl carbonate 18



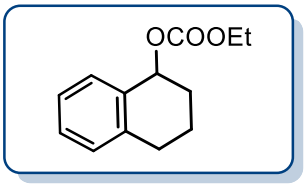
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 3H), 5.82 (q, *J*=6.8 Hz, 1H), 4.21 (m, 2H), 1.64 (d, *J*=6.8 Hz, 3H), 1.33 (t, *J*=7.2 Hz, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 154.91, 144.39-144.33 (d, 16 Hz, 1 C-F), 132.86-131.92 (q, 15 Hz, 3 C-F), 126.91-126.06 (d, 15 Hz, C-F), 124.93, 122.82-122.45 (d, 37 Hz, C-F), 75.27, 65.14, 23.06, 14.86. **IR(KBr)** υ: 2988, 1747, 1466, 1279, 1179, 1139, 1013, 760 cm^{-1}. **HRMS** (ESI-MS) m/z: Calculated for $[M]^+$ 230.0755 Found 231.1000

Ethyl (1-(naphthalen-1-yl)ethyl) carbonate 19



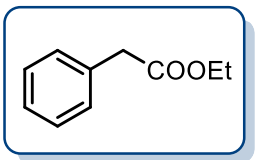
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J*=8.4 Hz, 1H), 8.90 (d, *J*=8.4 Hz, 1H), 8.83 (d, *J*=8.4 Hz, 1H), 7.65 (d, *J*=6.8 Hz, 1H), 7.53 (m, 3H), 6.52 (q, *J*=6.4 Hz, 1H), 4.20 (m, 2H), 1.77 (d, *J*=6.4 Hz, 3H), 1.32 (t, *J*=6.8 Hz, 3H).**^{13}C-NMR (100 MHz, $CDCl_3$)** δ 154.64, 137.12, 133.80, 130.06, 128.94, 128.55, 126.37, 125.69, 125.43 ,123.12, 122.98, 73.33, 64.02, 22.04, 14.26. **IR(KBr)** υ 2984,1744, 1597, 1512, 1449, 1371, 1263, 1172, 1090, 1005, 866, 778 cm^{-1}. **HRMS** (ESI-MS) m/z: Calculated for $[M+Na]^+$ 267.0997 Found 267.0992.

Ethyl (1,2,3,4-tetrahydronaphthalen-1-yl) carbonate 20



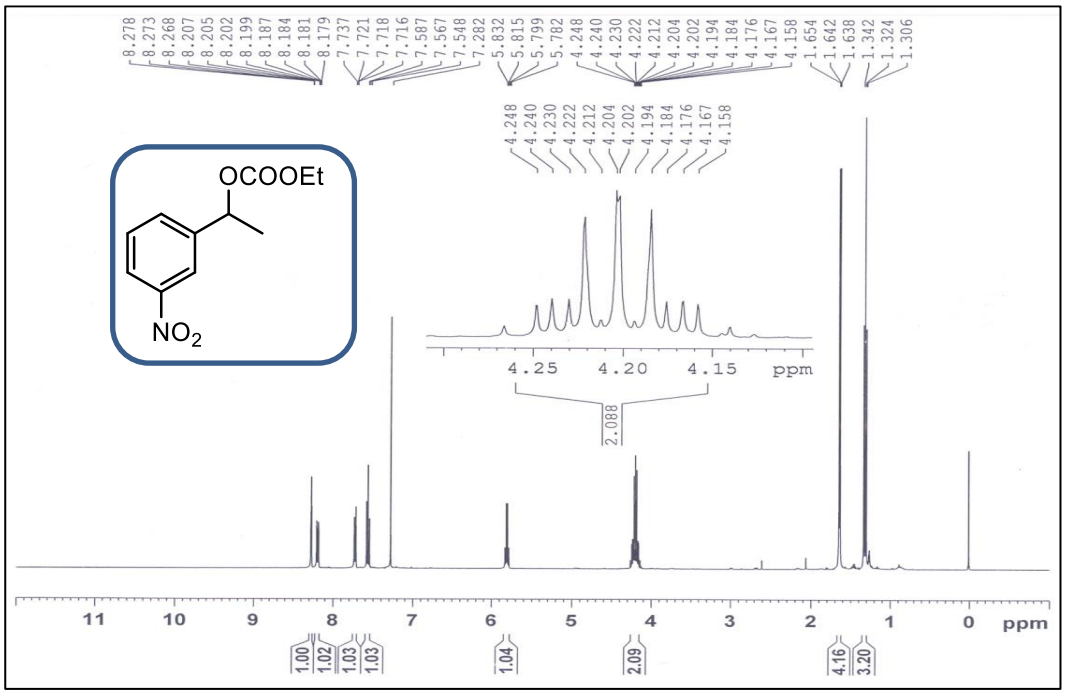
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J*=7.2 Hz, 1H), 7.26 (m, 1H), 7.22 (m, 1H), 7.14 (m, 1H), 5.87 (t, *J*=7.2 Hz, 1H), 4.25 (m, 2H), 2.88 (m, 1H), 2.78 (m, 1H), 2.15 (m, 1H), 2.05 (m, 2H), 2.02 (m, 1H), 1.34 (d, *J*=7.2 Hz, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** 155.13, 137.91, 133.79, 129.70, 129.10, 128.41, 126.13, 73.93, 63.91, 29.00, 28.88, 18.53, 14.32. **IR(KBr)**υ 3023, 2990, 1737, 1493, 1453, 1335, 1261, 1195, 1059, 1002, 941, 884, 748 cm^{-1}.

benzyl ethyl carbonate 21

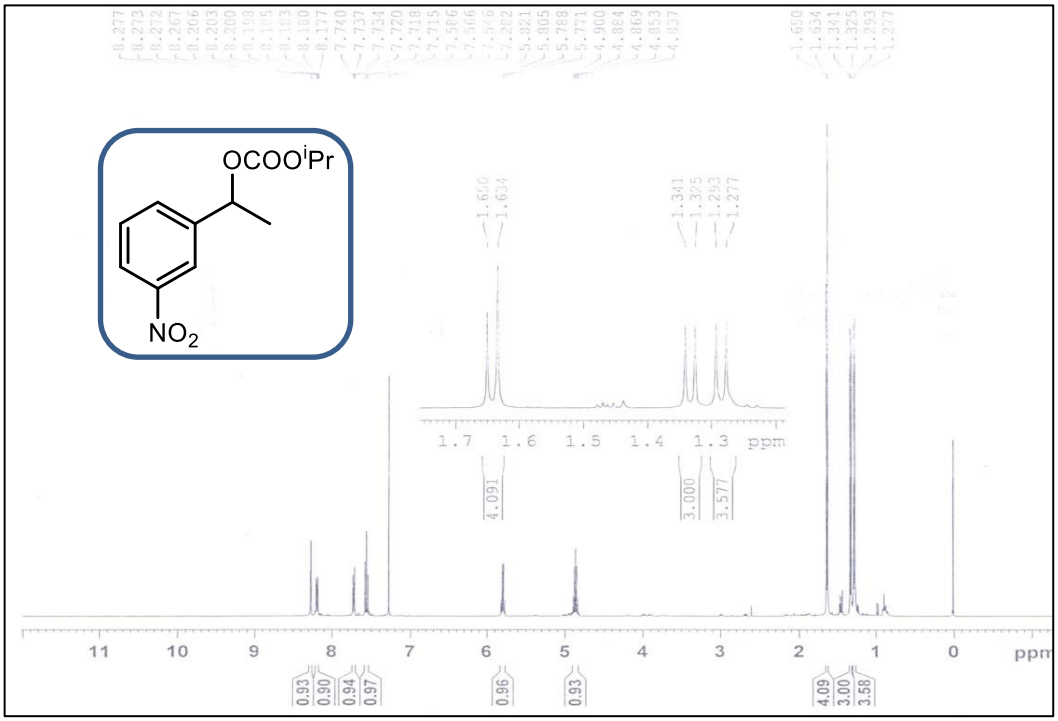


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 5H), 5.18 (s, 2H), 4.23 (q, *J*=6.8 Hz, 2H), 1.33 (t, *J*=7.2 Hz, 3H).**^{13}C-NMR (100 MHz, $CDCl_3$)** δ 155.14, 135.32, 128.60, 128.51, 128.34, 69.45, 64.16, 14.28. **IR(KBr)** υ 3034, 2983, 1745, 1584, 1497, 1385, 1260, 1085, 1006, 909, 876, 749, 698 cm^{-1}. **HRMS** (ESI-MS) m/z: Calculated for $[M+H]^+$ 181.0865 Found 181.1004.

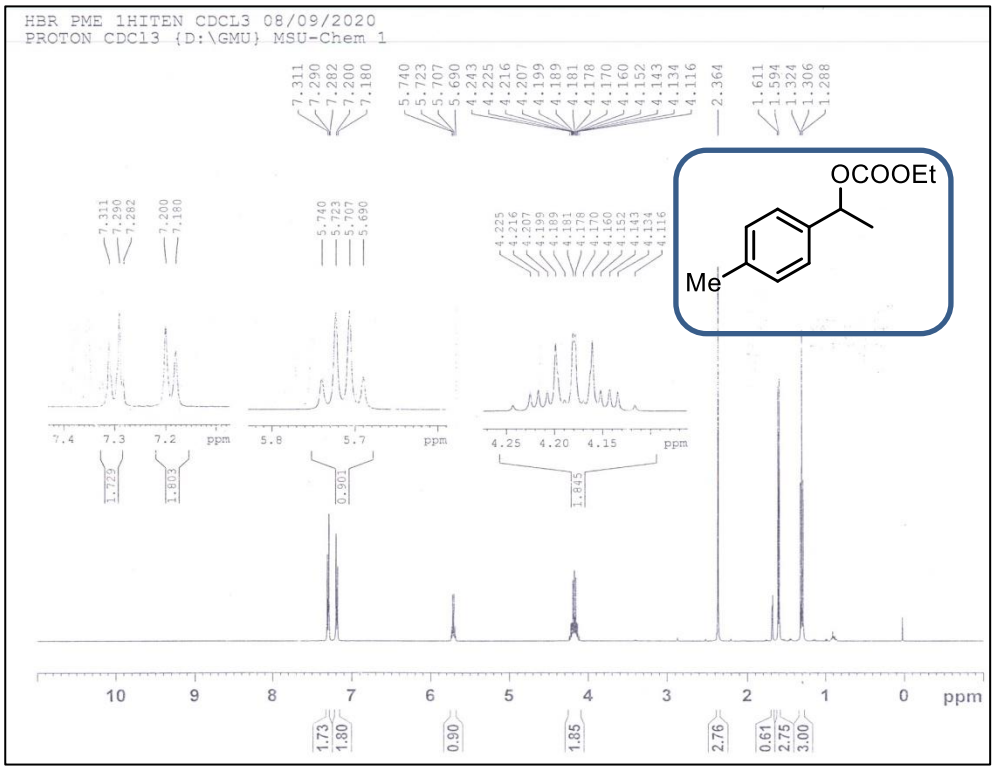
3.II.8 Spectral Data



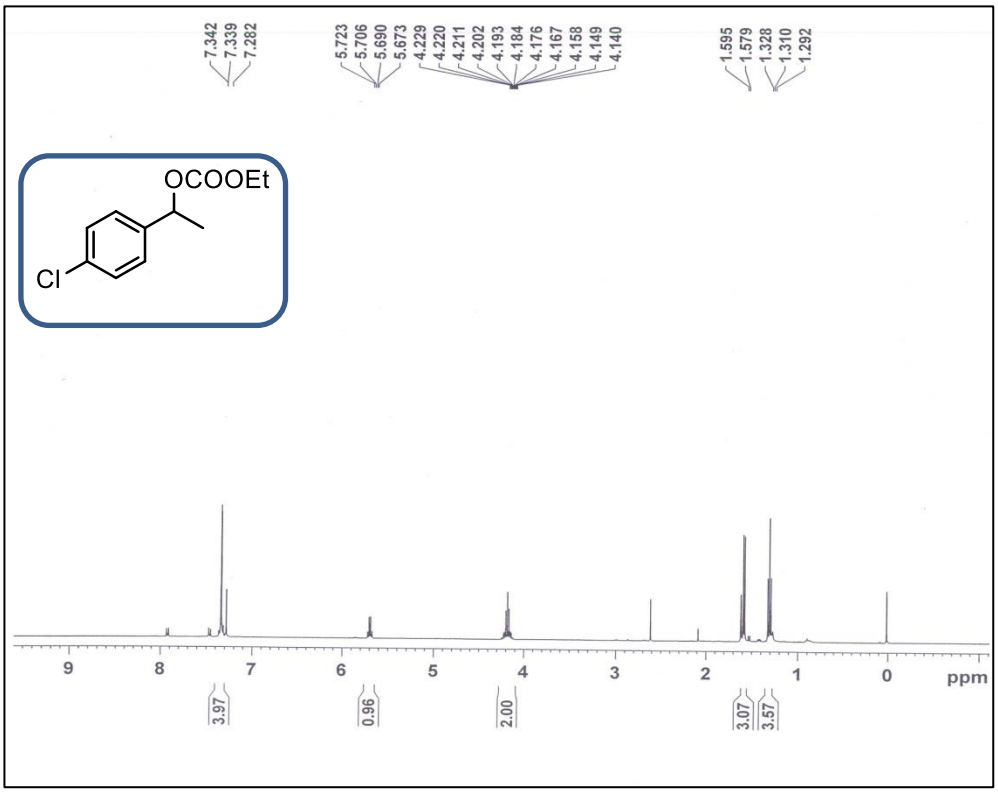
^{1}H NMR of ethyl (1-(3-nitrophenyl)ethyl) carbonate **13**



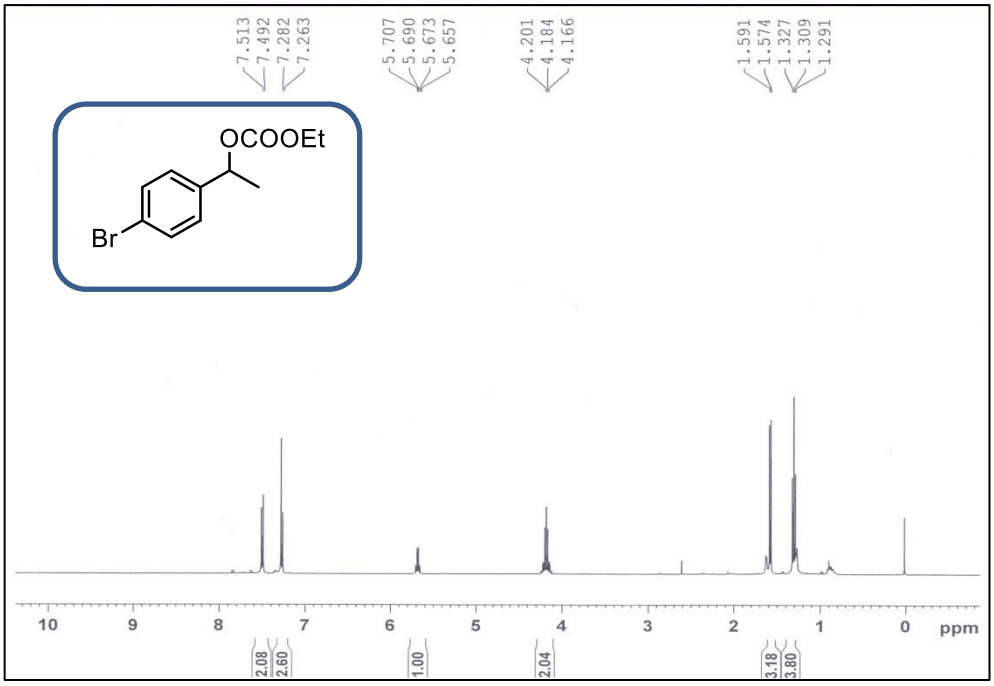
^{1}H NMR of isopropyl (1-(3-nitrophenyl)ethyl) carbonate **23**



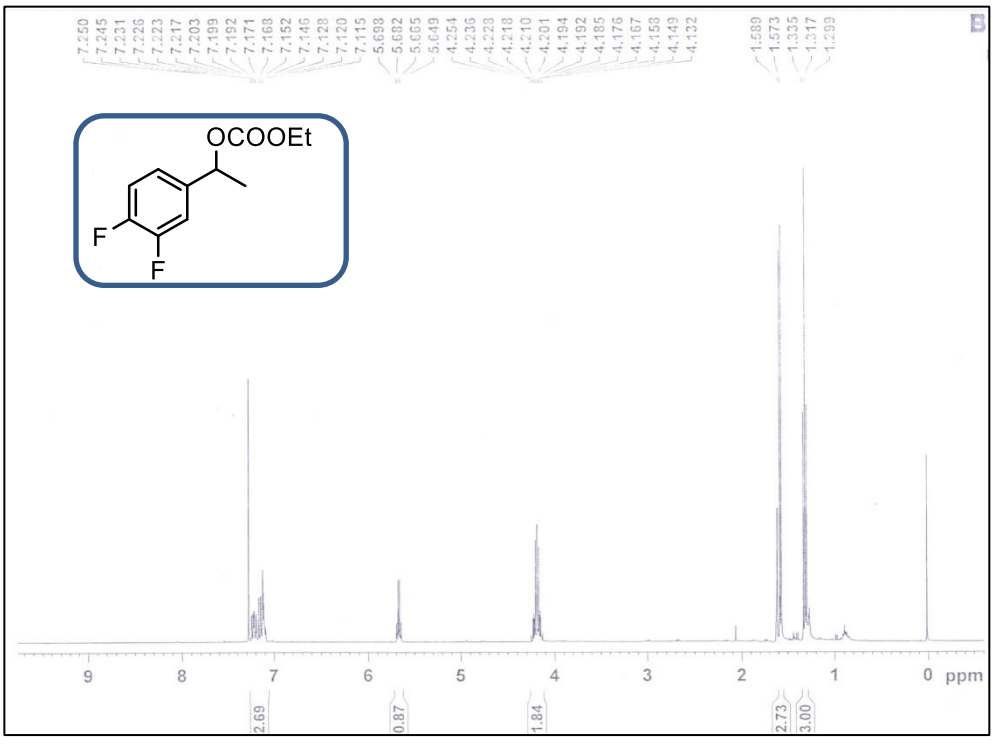
^{1}H NMR of ethyl (1-(p-tolyl)ethyl) carbonate **14**



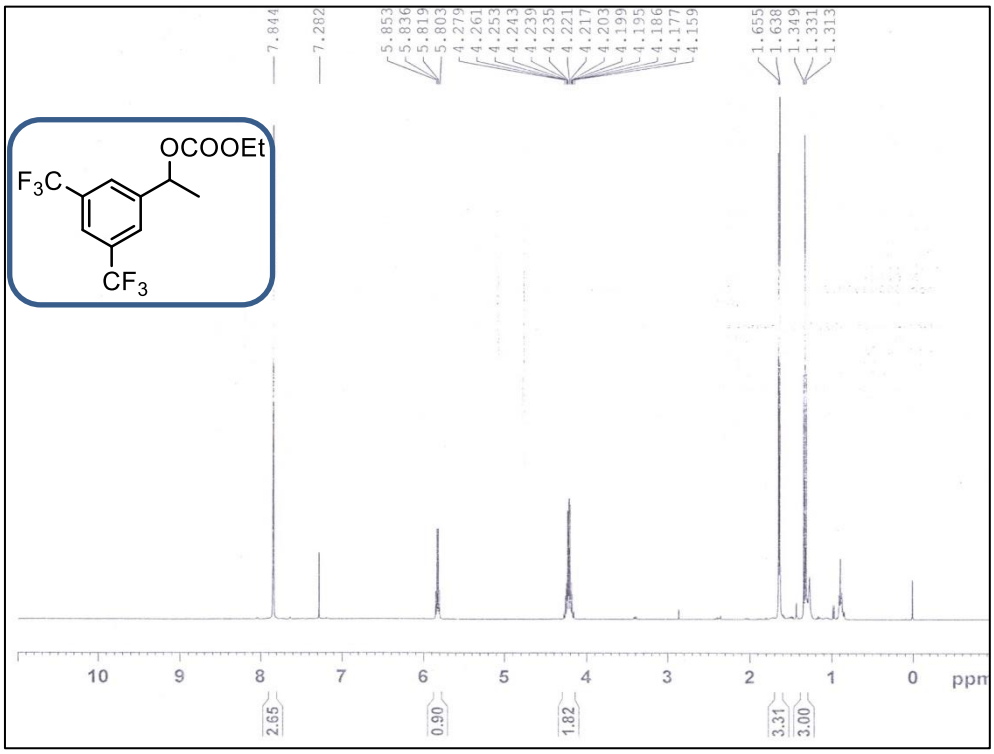
^{1}H NMR of 1-(4-chlorophenyl)ethyl ethyl carbonate **15**



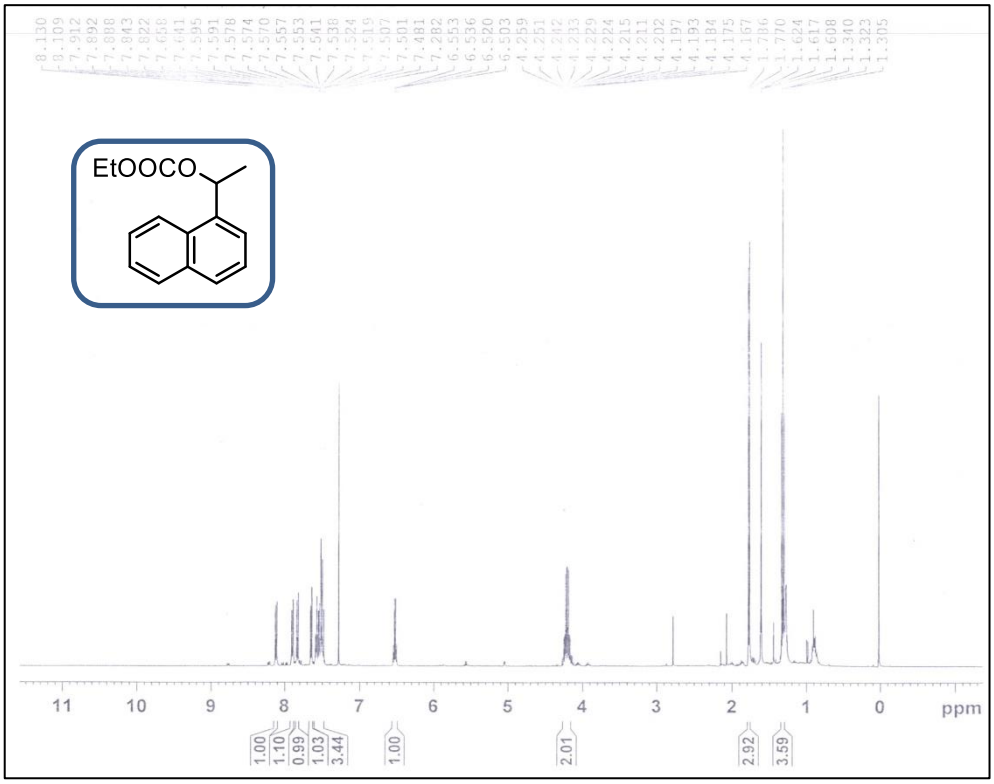
^{1}H NMR of 1-(4-bromophenyl)ethyl ethyl carbonate **16**



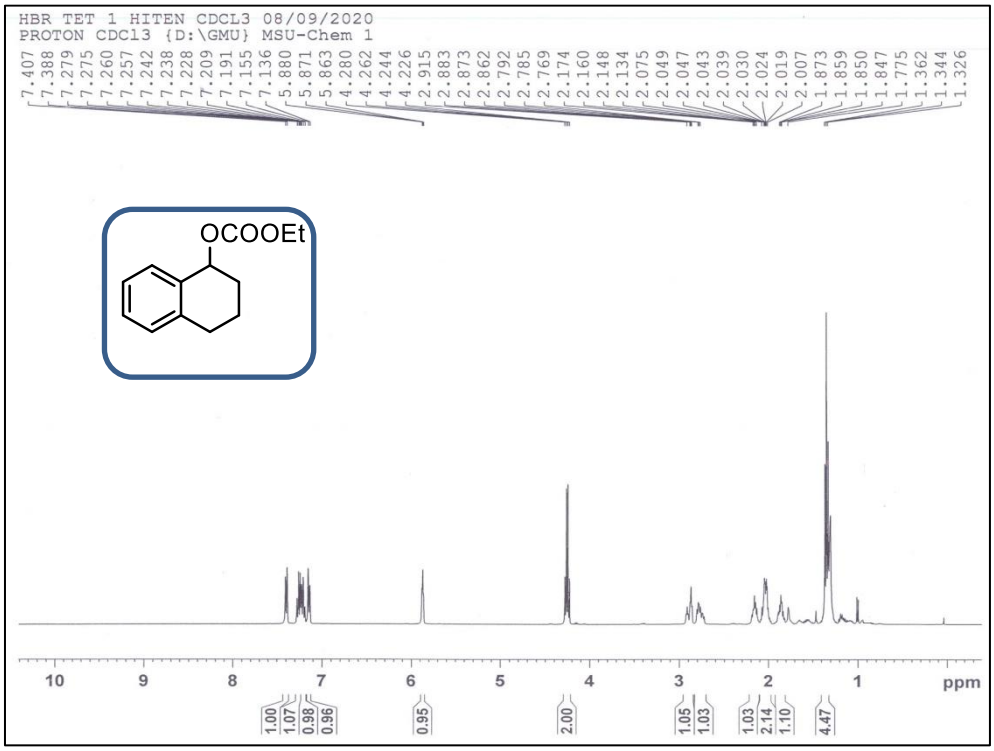
^{1}H NMR of 1-(3,4-difluorophenyl)ethyl ethyl carbonate **17**



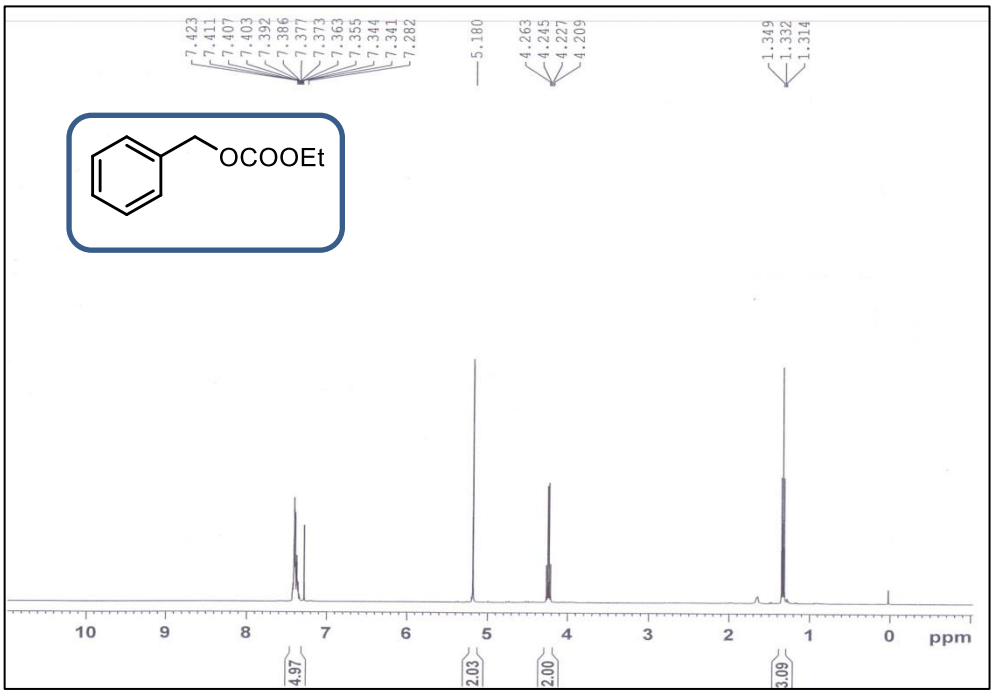
^{1}H NMR of 1-(3,5-bis(trifluoromethyl)phenyl)ethyl ethyl carbonate **18**



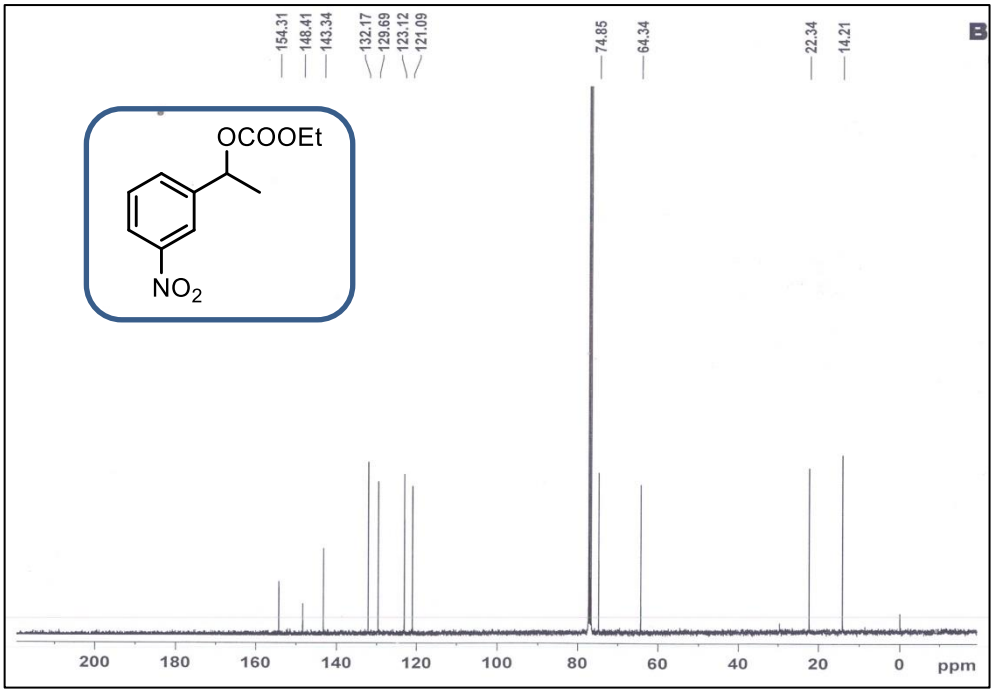
^{1}H NMR of ethyl (1-(naphthalen-1-yl)ethyl) carbonate **19**



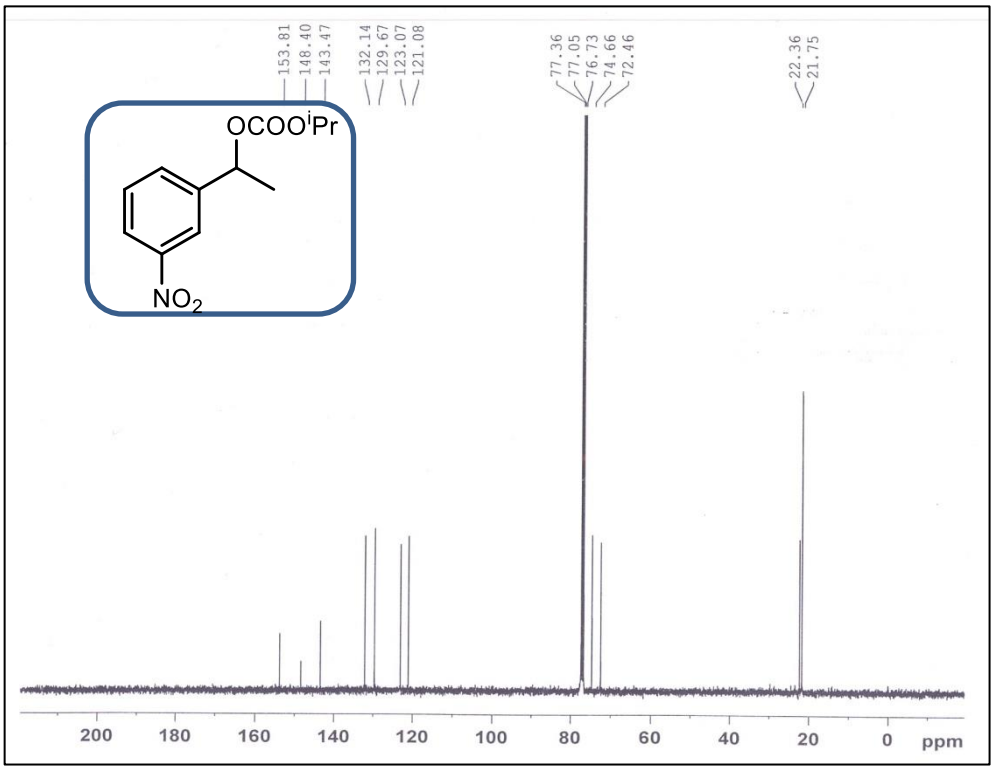
^{1}H NMR of ethyl (1,2,3,4-tetrahydronaphthalen-1-yl) carbonate **20**



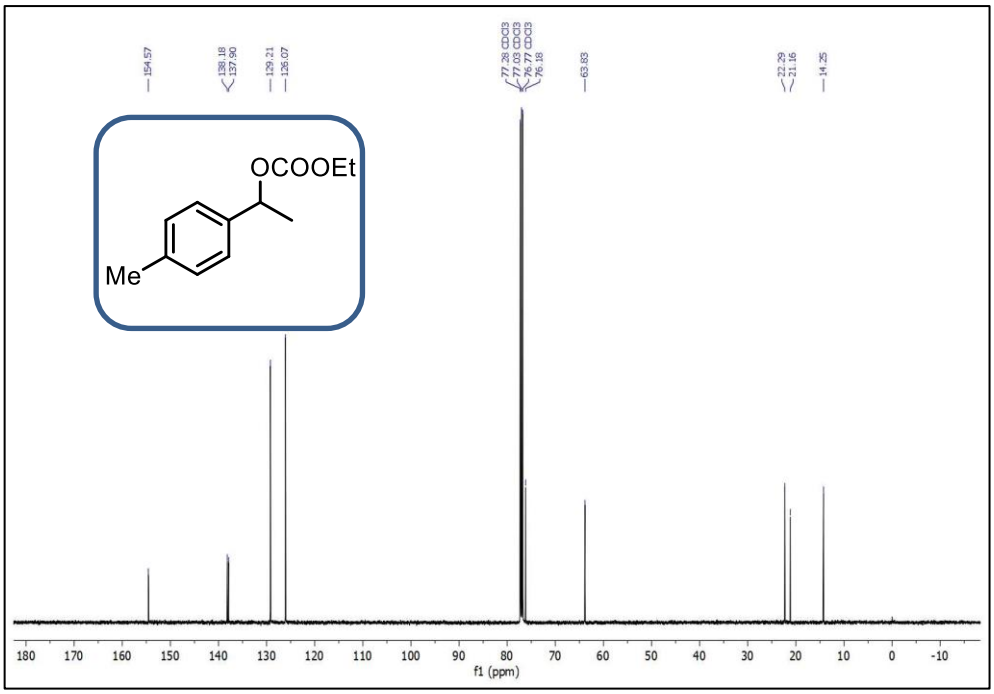
^{1}H NMR of benzyl ethyl carbonate **21**



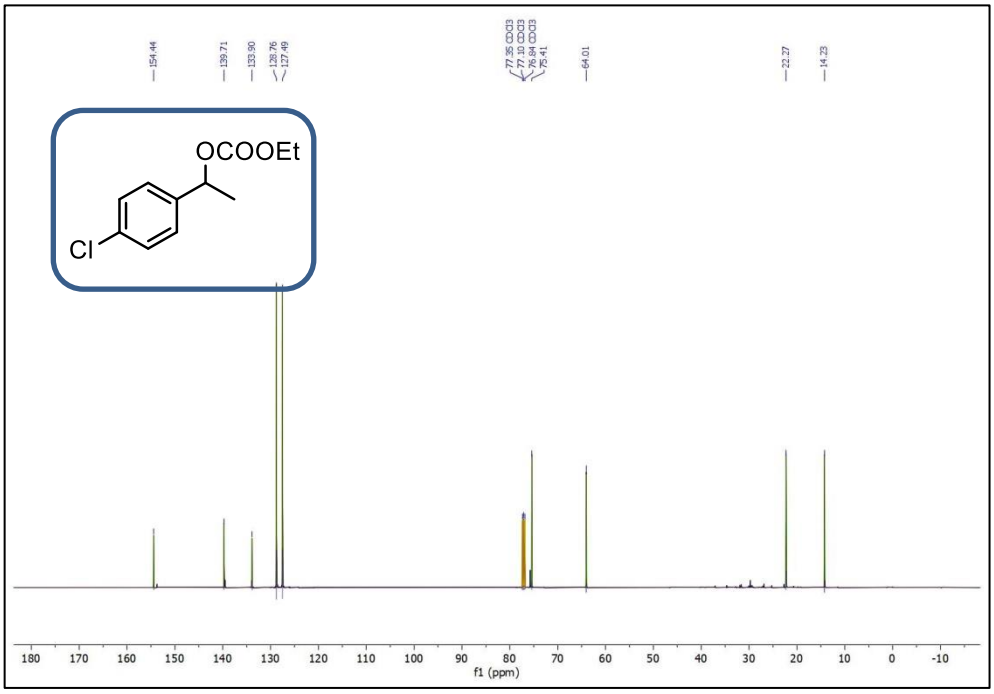
^{13}C NMR of ethyl (1-(3-nitrophenyl)ethyl) carbonate **13**



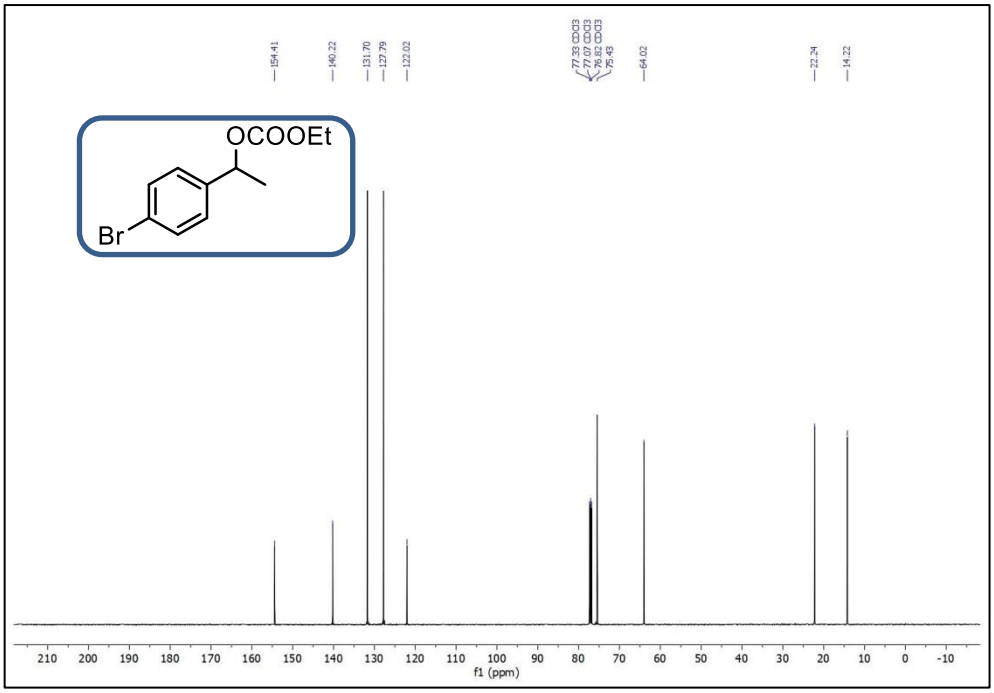
^{13}C NMR of isopropyl (1-(3-nitrophenyl)ethyl) carbonate **23**



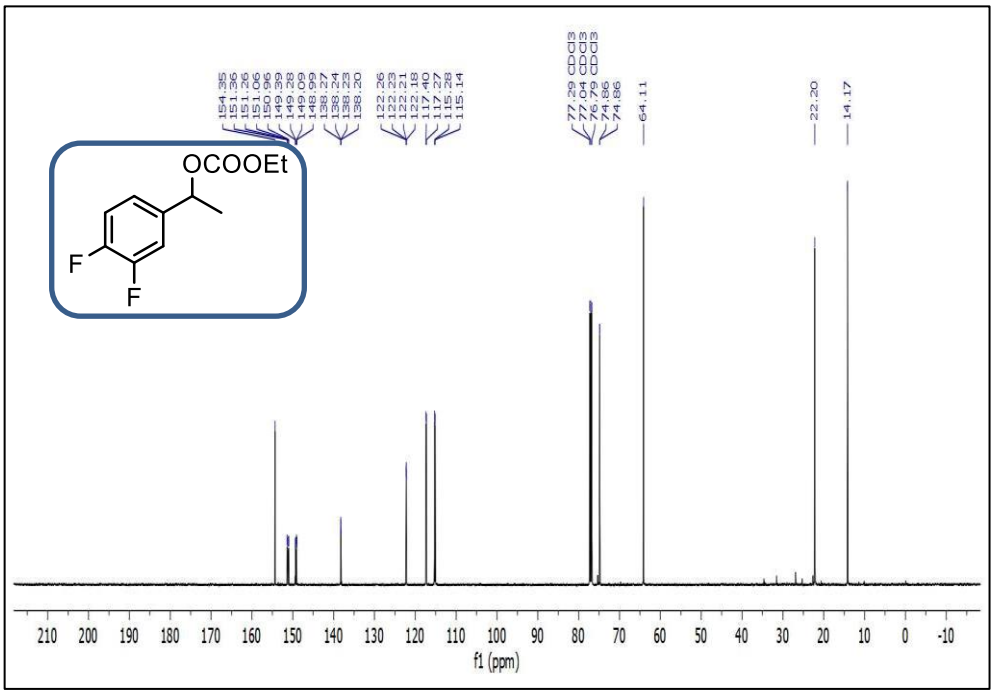
^{13}C NMR of ethyl (1-(p-tolyl)ethyl) carbonate **14**



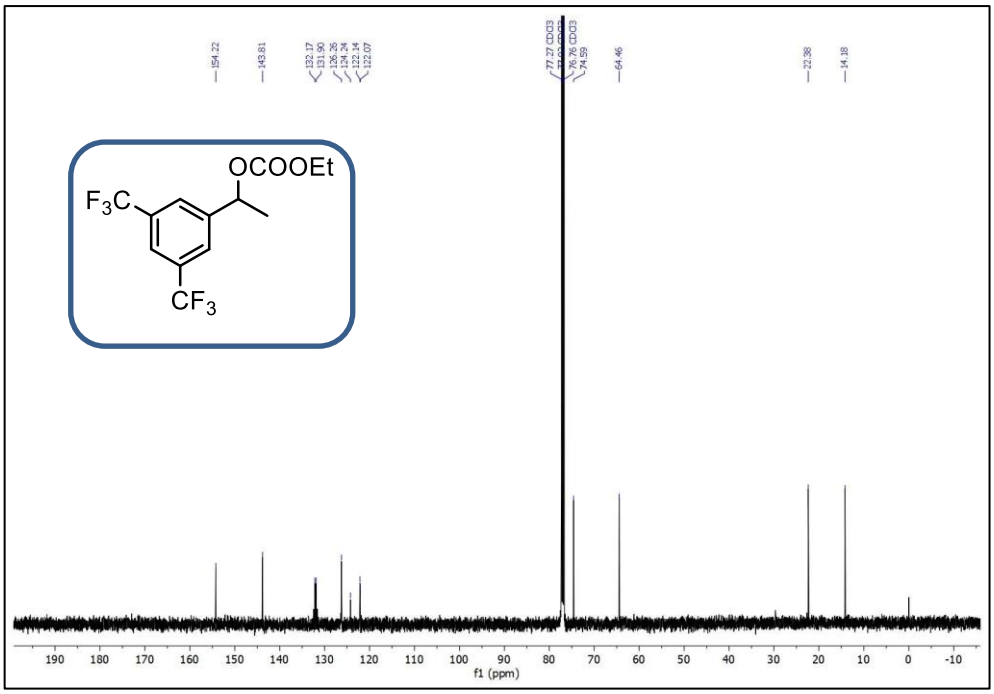
^{13}C NMR of 1-(4-chlorophenyl)ethyl ethyl carbonate **15**



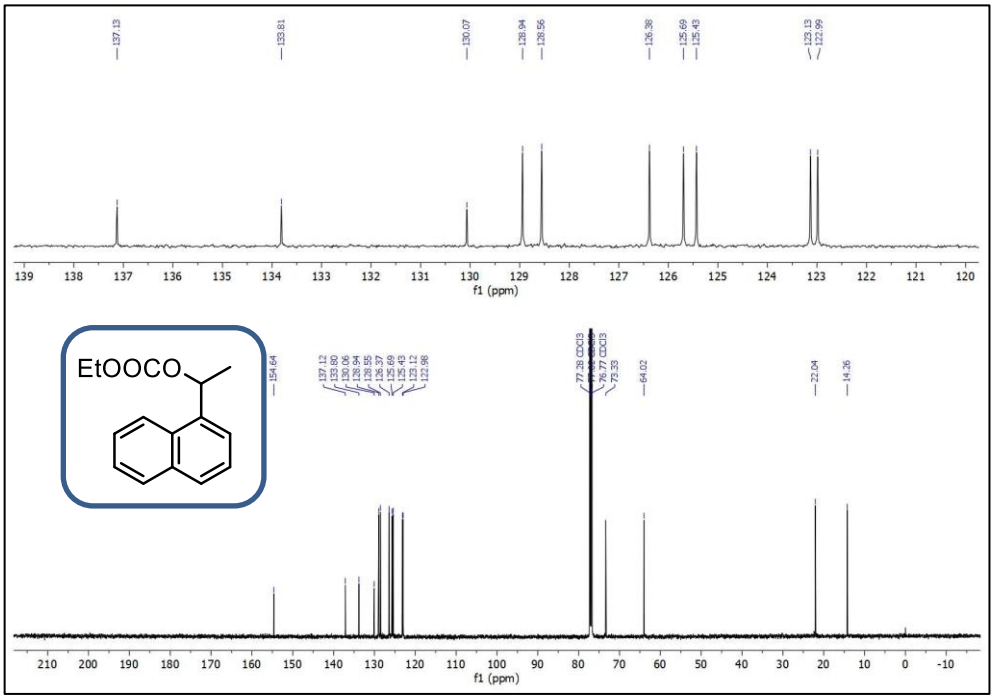
^{13}C NMR of 1-(4-bromophenyl)ethyl ethyl carbonate **16**



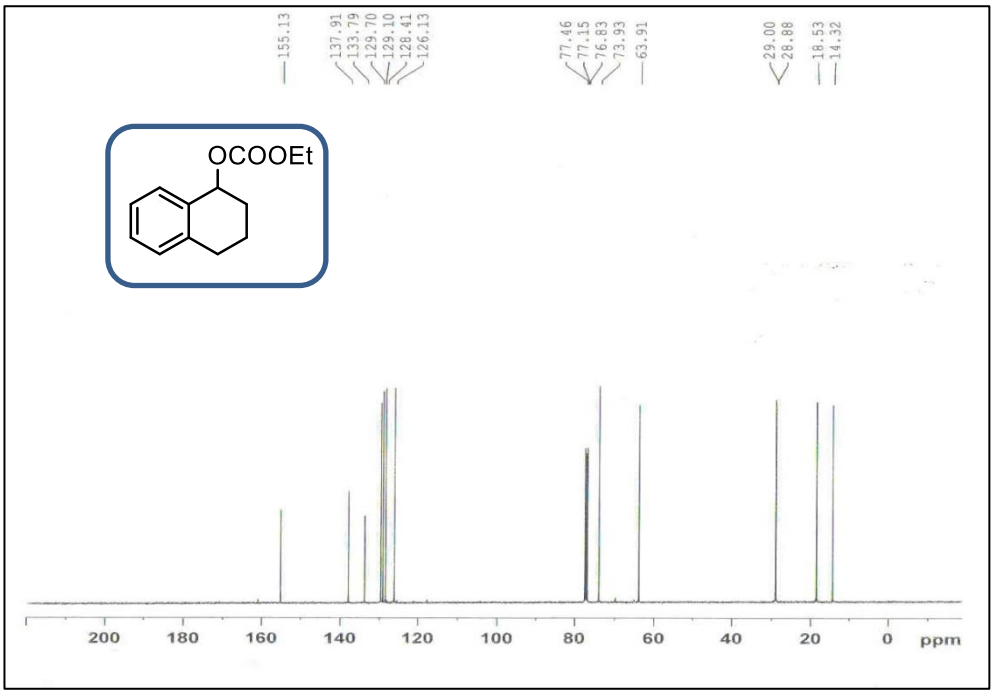
^{13}C NMR of 1-(3,4-difluorophenyl)ethyl ethyl carbonate **17**



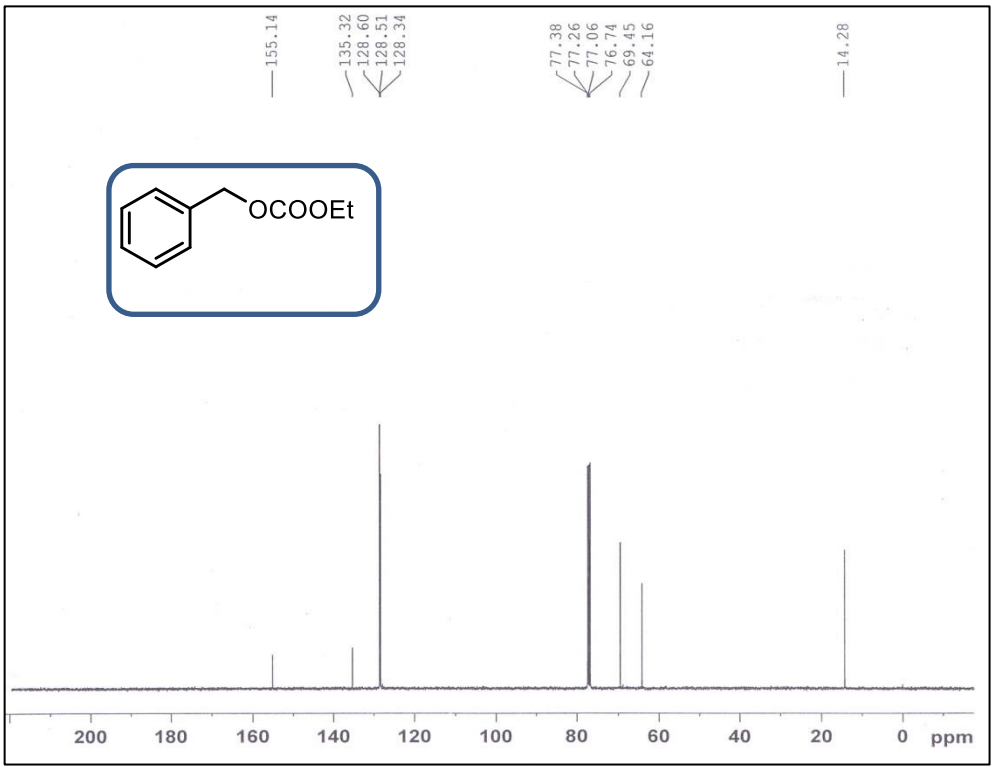
^{13}C NMR of 1-(3,5-bis(trifluoromethyl)phenyl)ethyl ethyl carbonate **18**



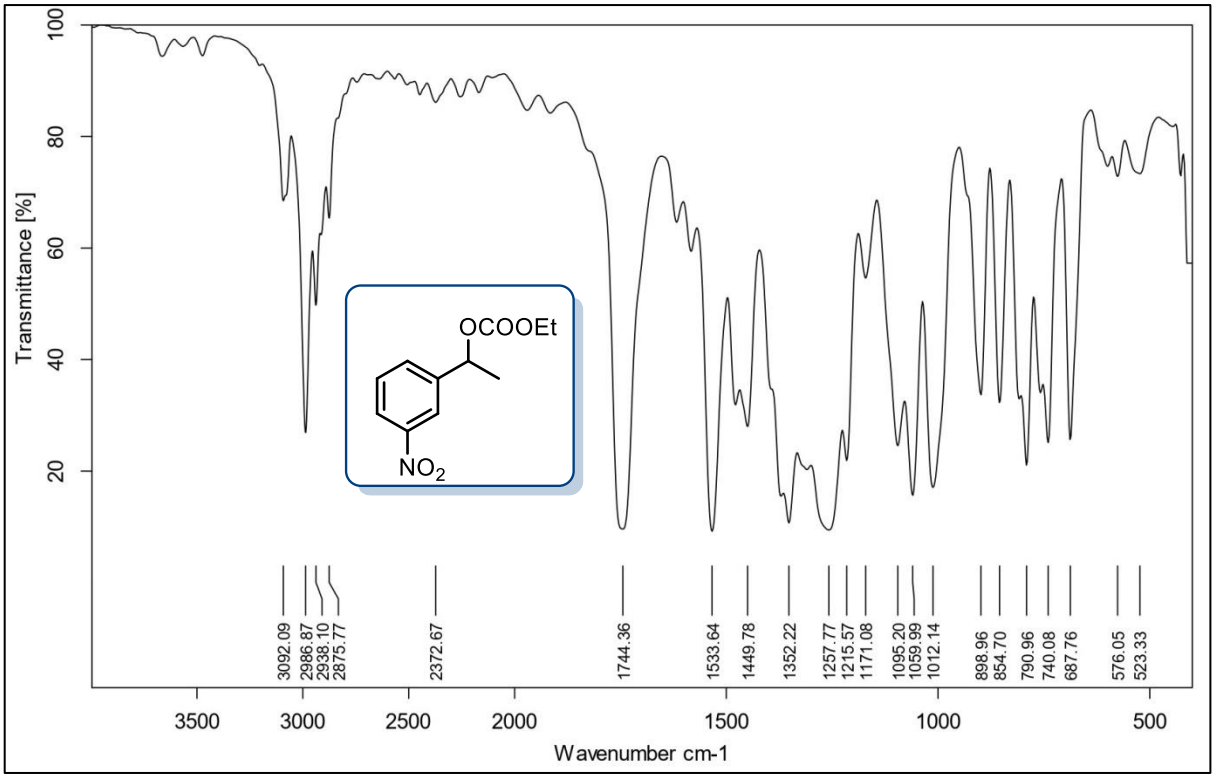
^{13}C NMR of ethyl (1-(naphthalen-1-yl)ethyl) carbonate **19**



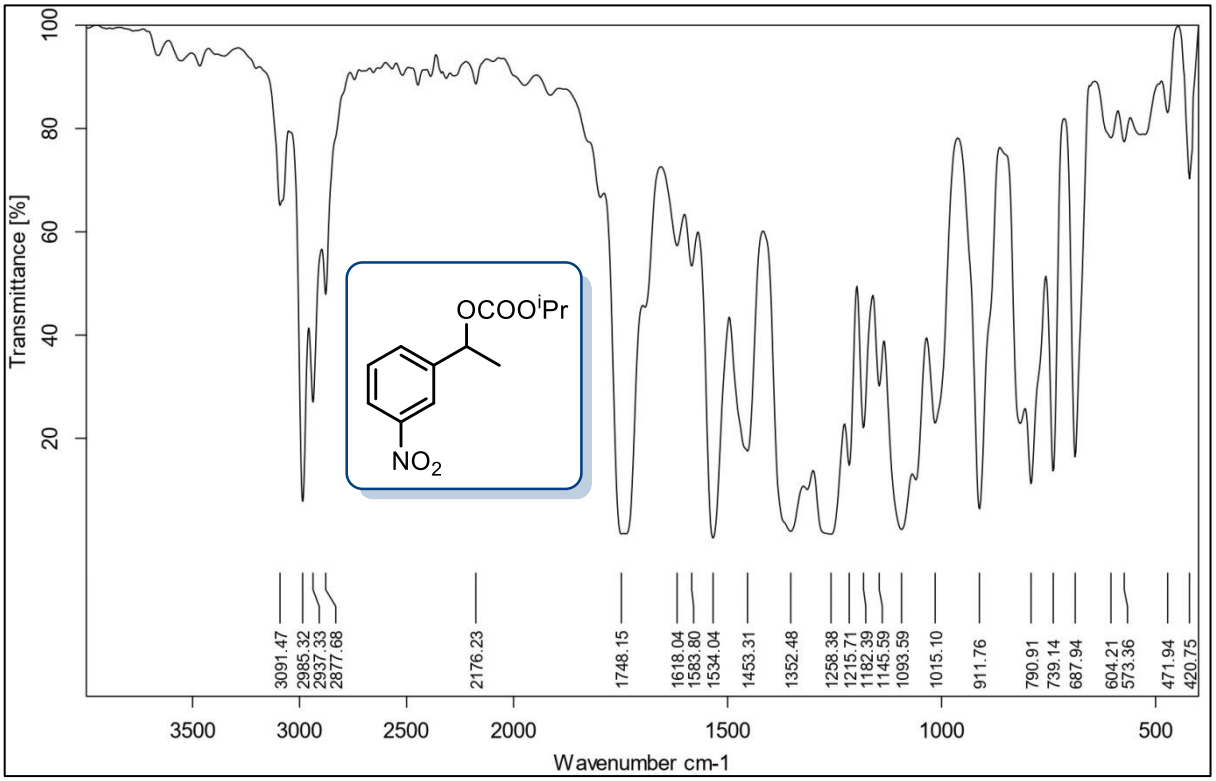
^{1}H NMR of ethyl (1,2,3,4-tetrahydronaphthalen-1-yl) carbonate **20**



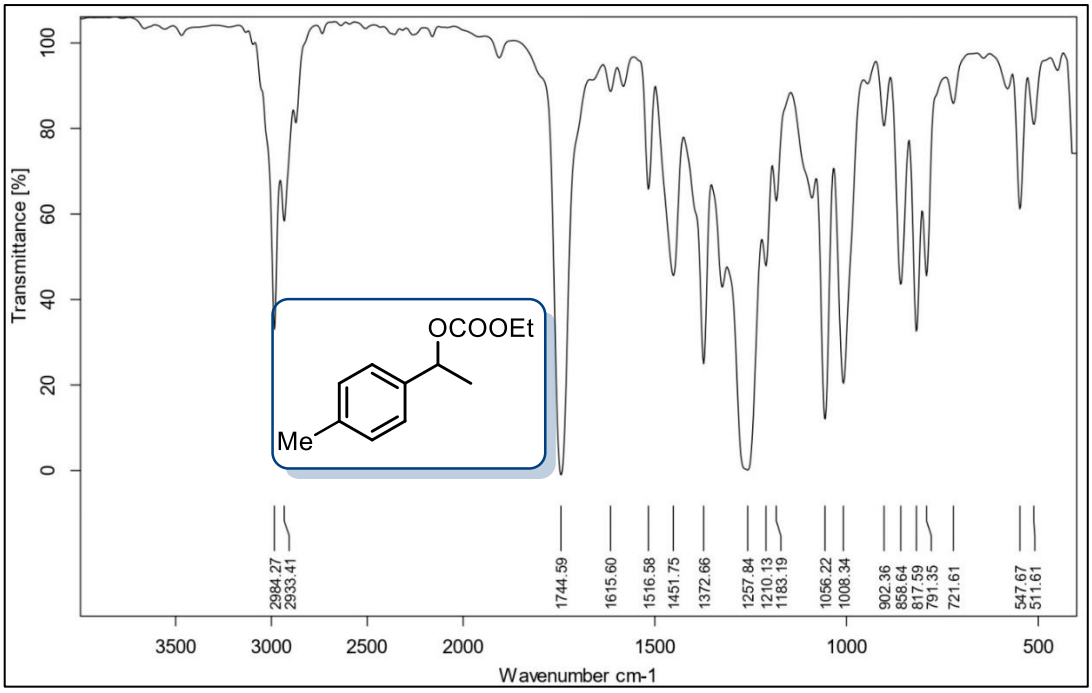
^{13}C NMR of benzyl ethyl carbonate **21**



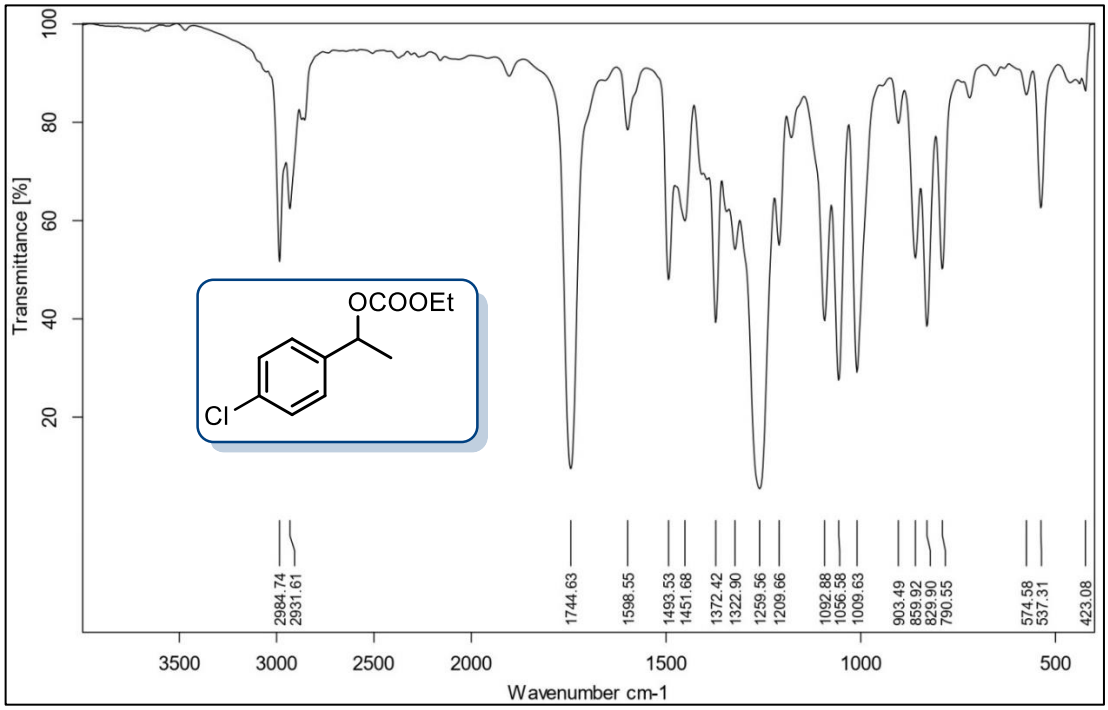
IR of ethyl (1-(3-nitrophenyl)ethyl) carbonate **13**



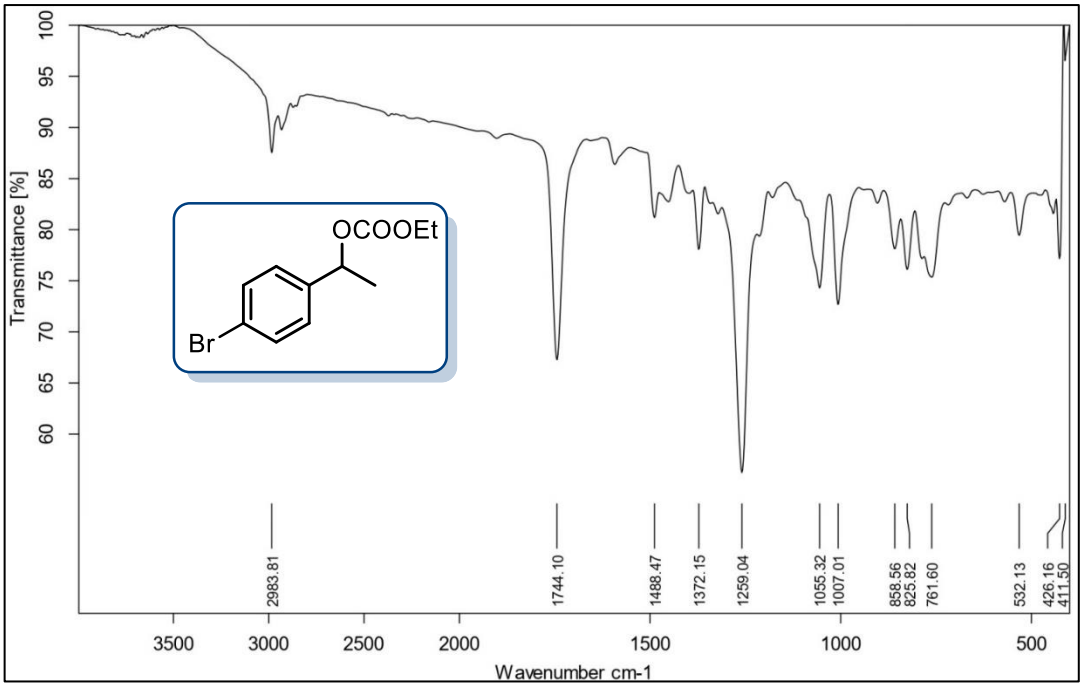
IR of ethyl (1-(3-nitrophenyl)ethyl) carbonate **23**



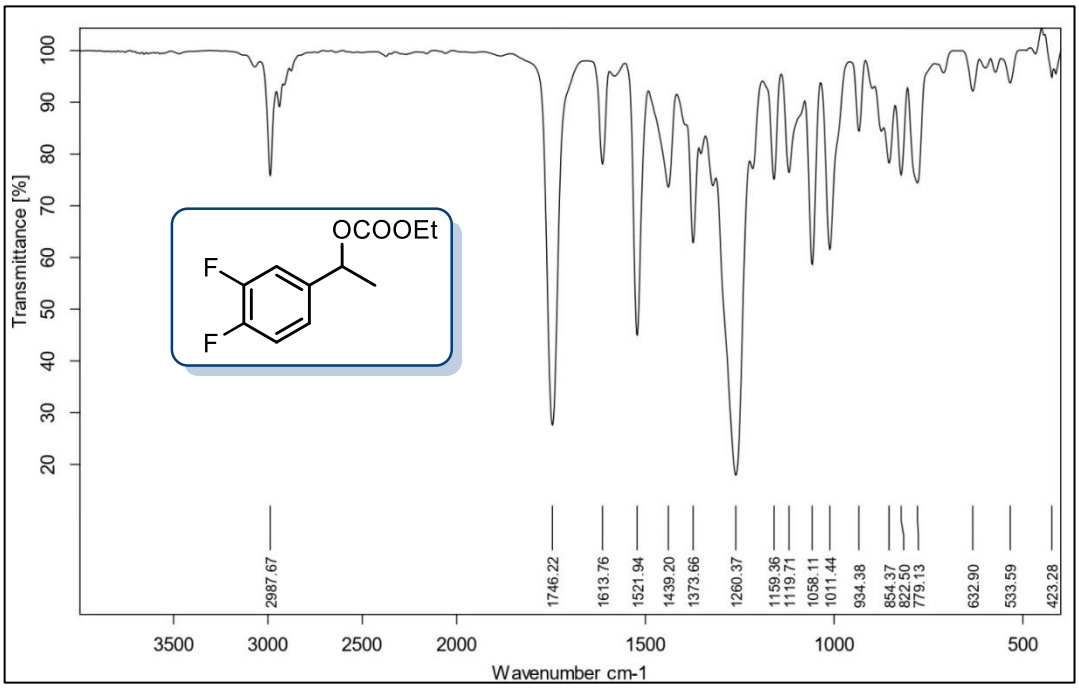
IR of ethyl (1-(p-tolyl)ethyl) carbonate **14**



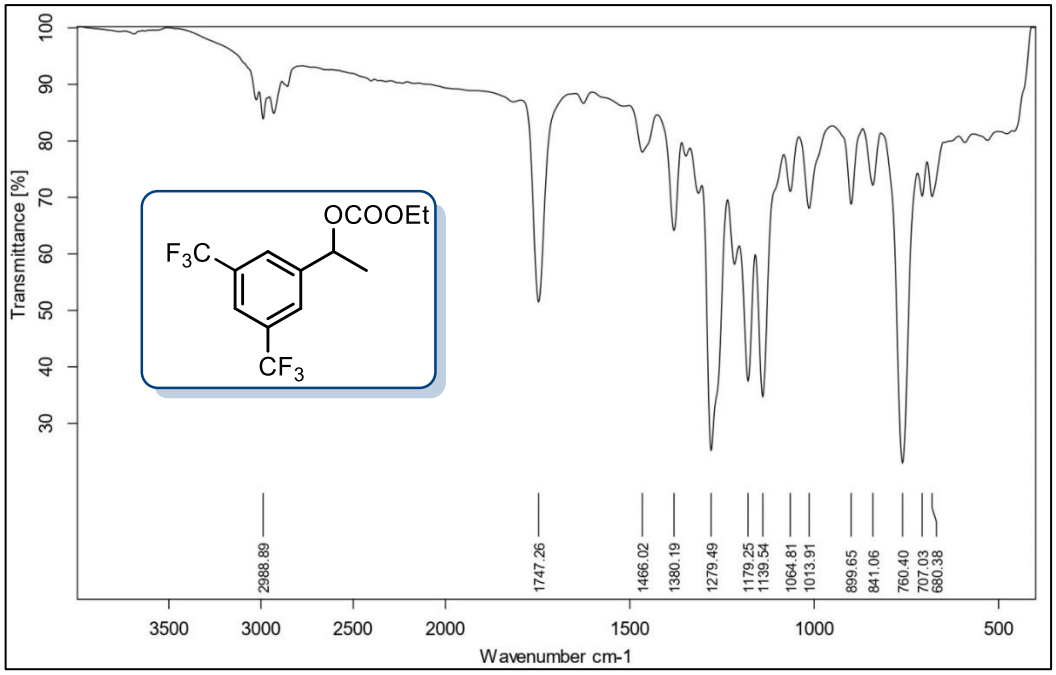
IR of 1-(4-chlorophenyl)ethyl ethyl carbonate **15**



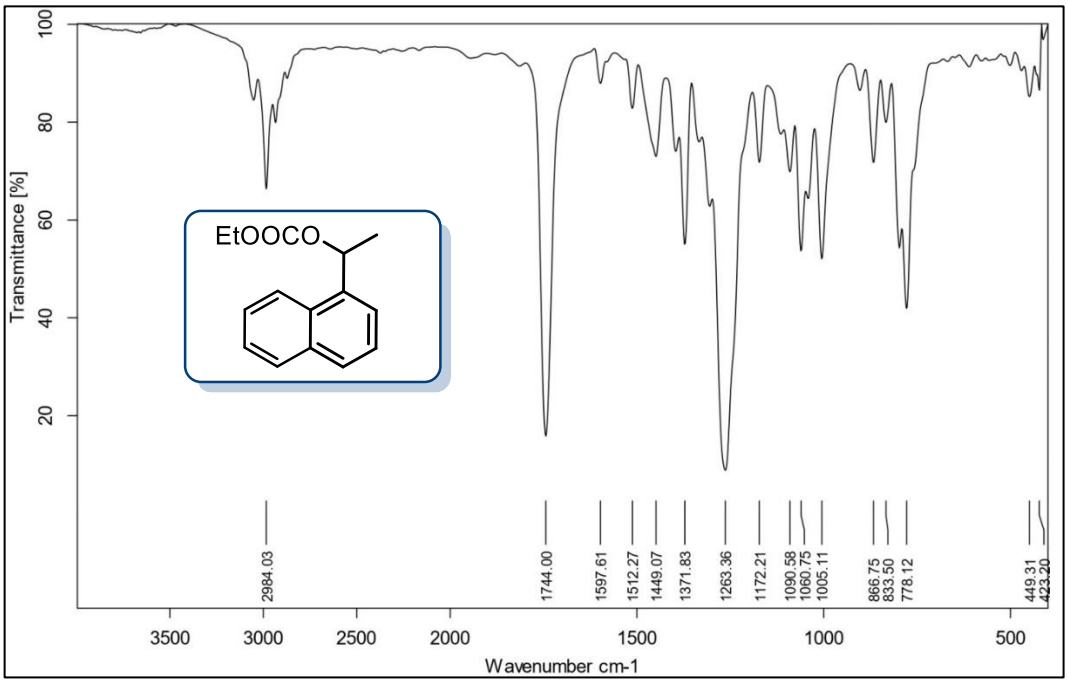
IR of 1-(4-bromophenyl)ethyl ethyl carbonate **16**



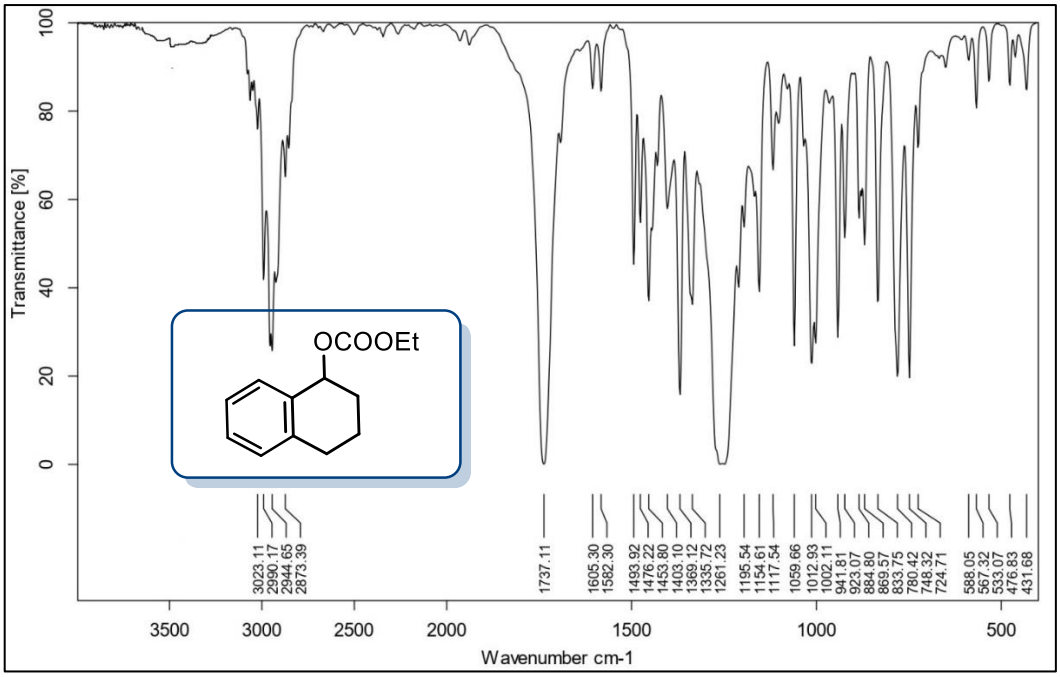
IR of 1-(3,4-difluorophenyl)ethyl ethyl carbonate **17**



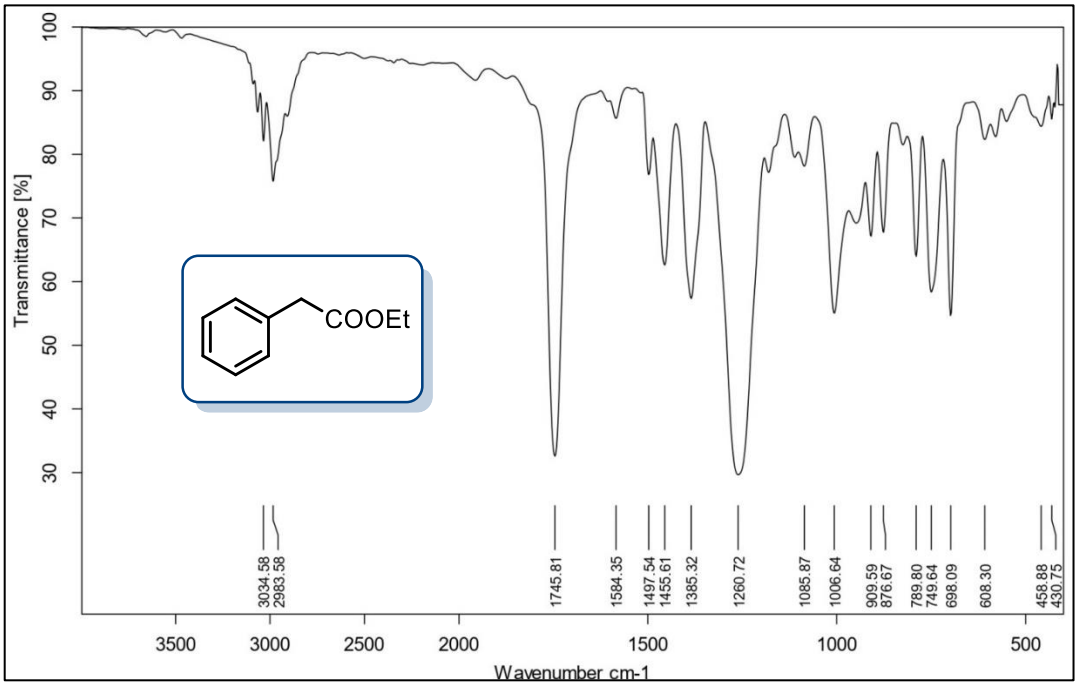
IR of 1-(3,5-bis(trifluoromethyl)phenyl)ethyl ethyl carbonate **18**



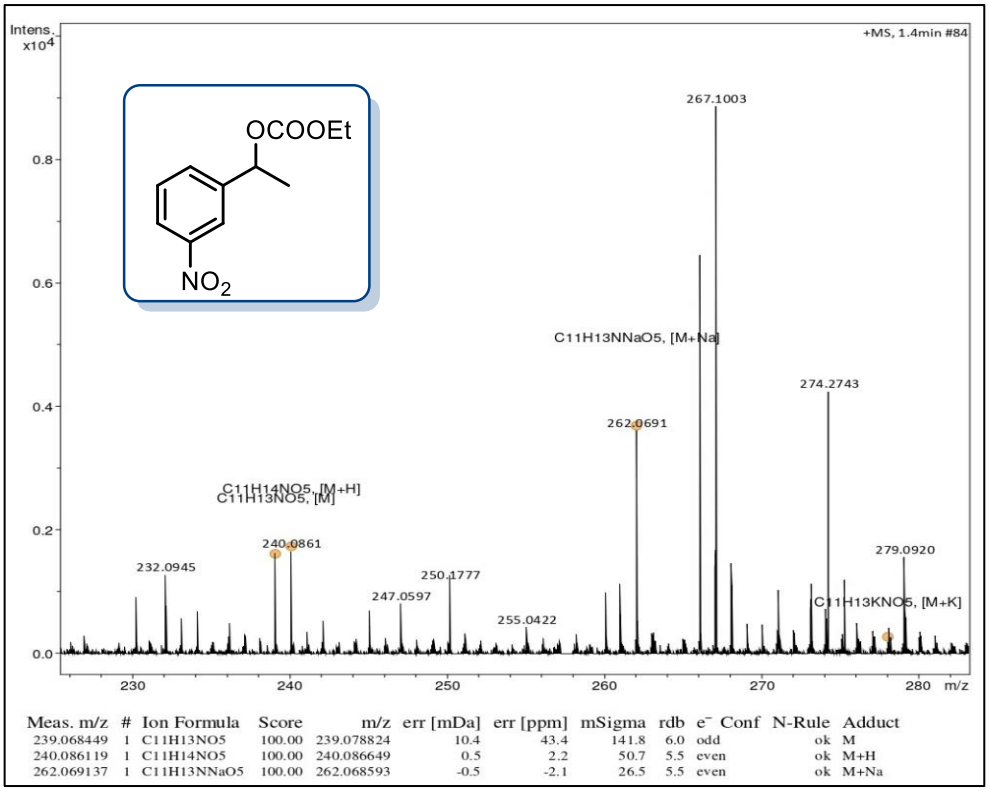
IR of ethyl (1-(naphthalen-1-yl)ethyl) carbonate **19**



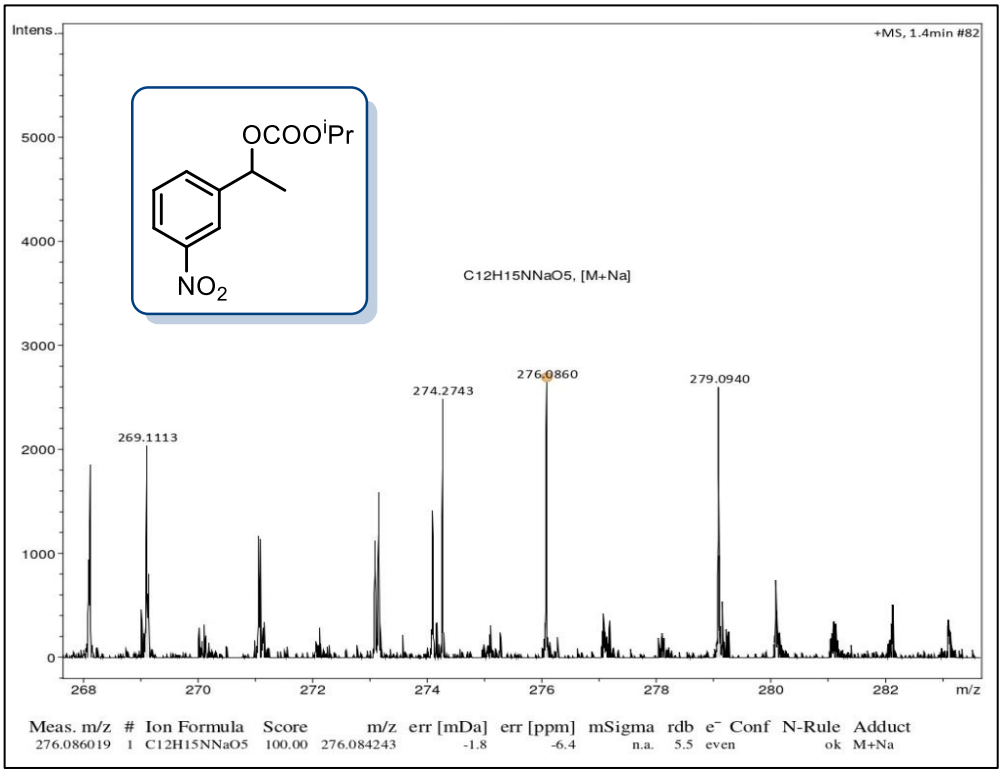
IR of ethyl (1,2,3,4-tetrahydronaphthalen-1-yl) carbonate **20**



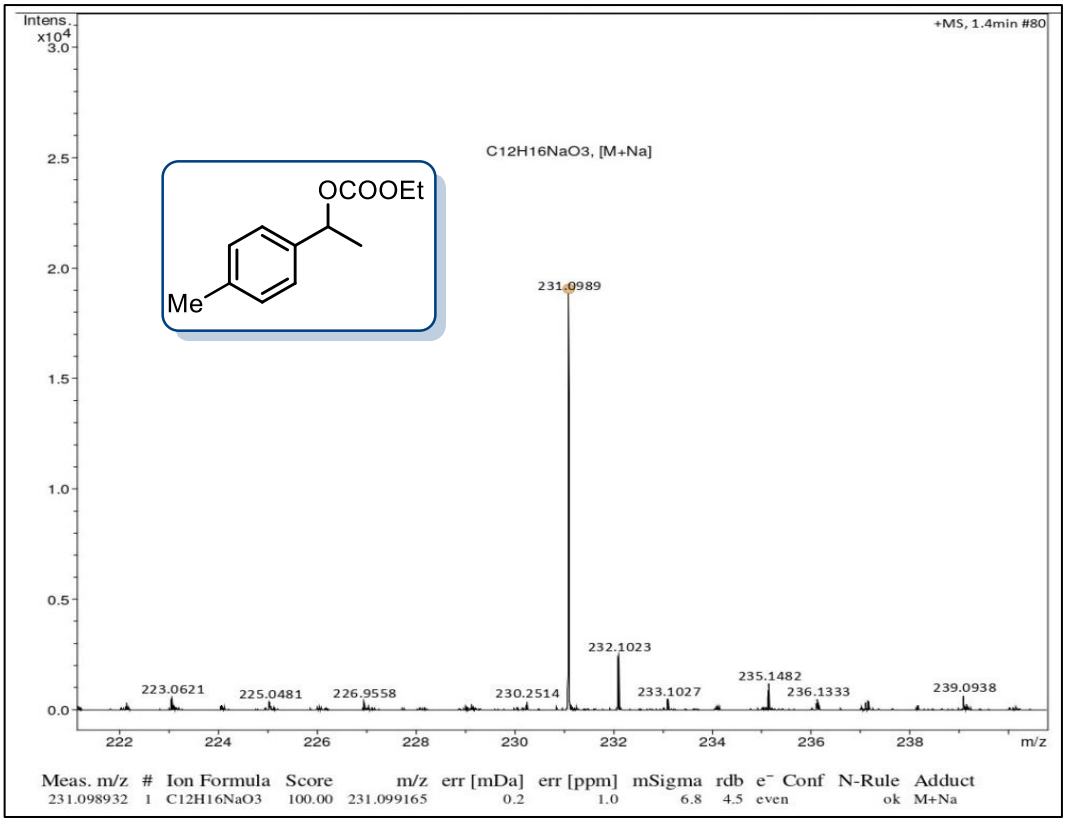
IR of benzyl ethyl carbonate **21**



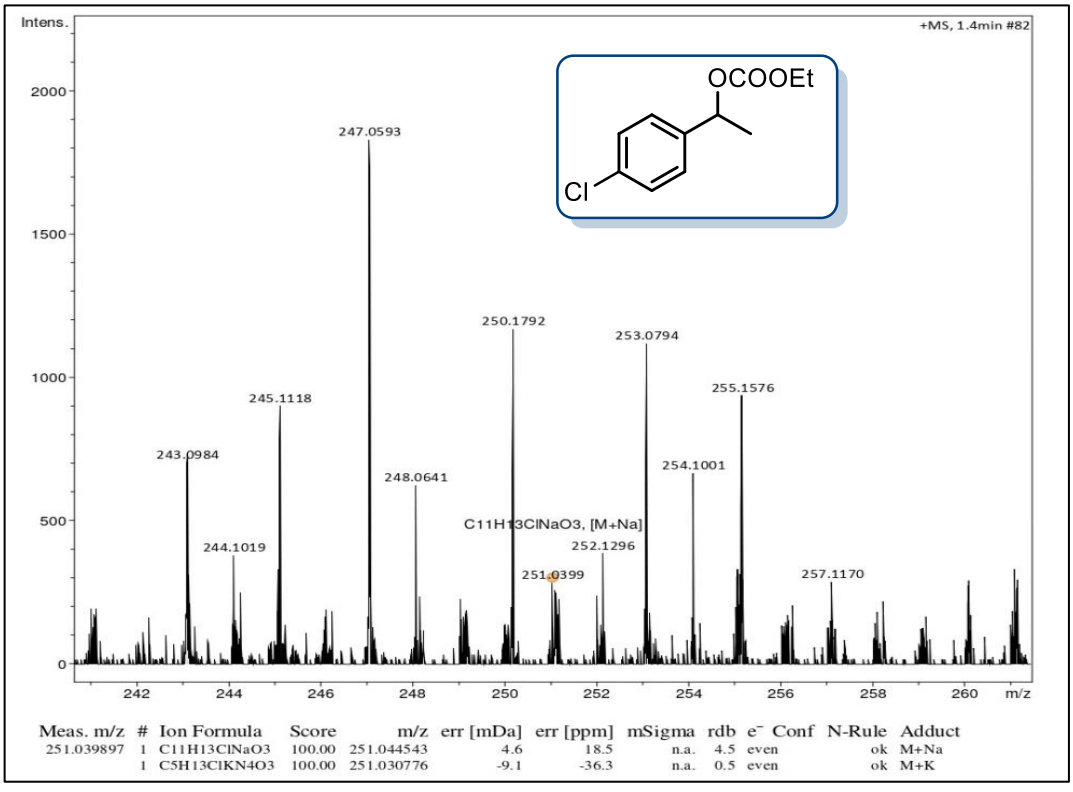
HRMS of ethyl (1-(3-nitrophenyl)ethyl) carbonate **13**



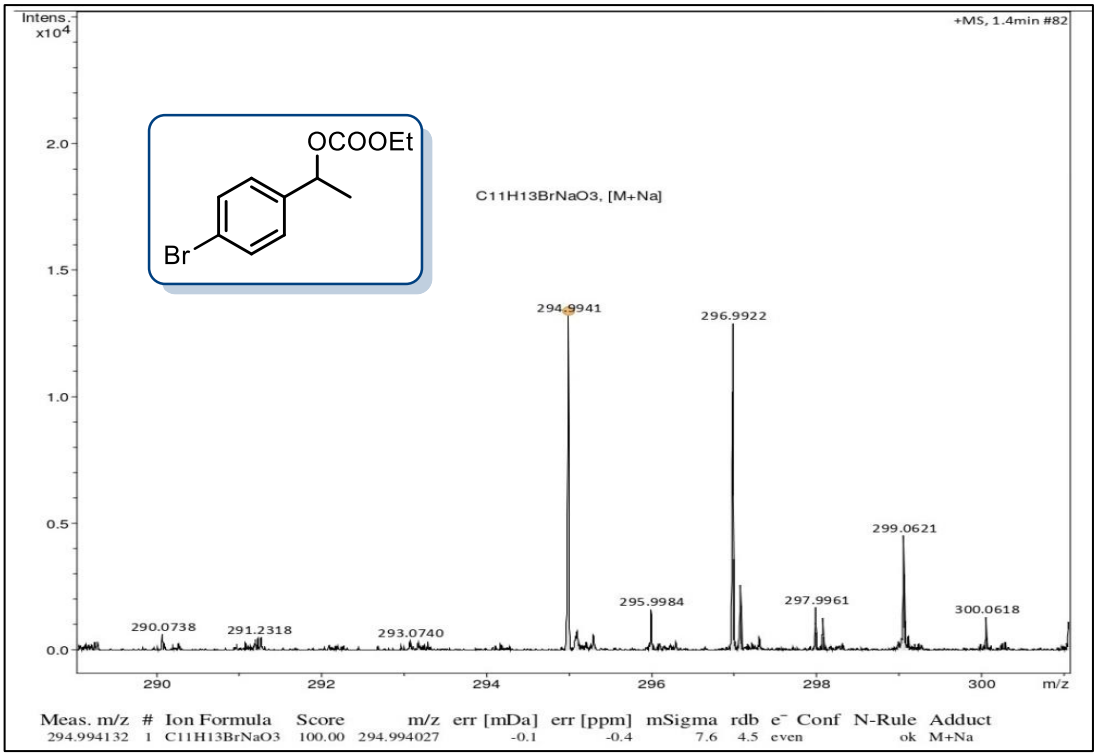
IR of isopropyl (1-(3-nitrophenyl)ethyl) carbonate **23**



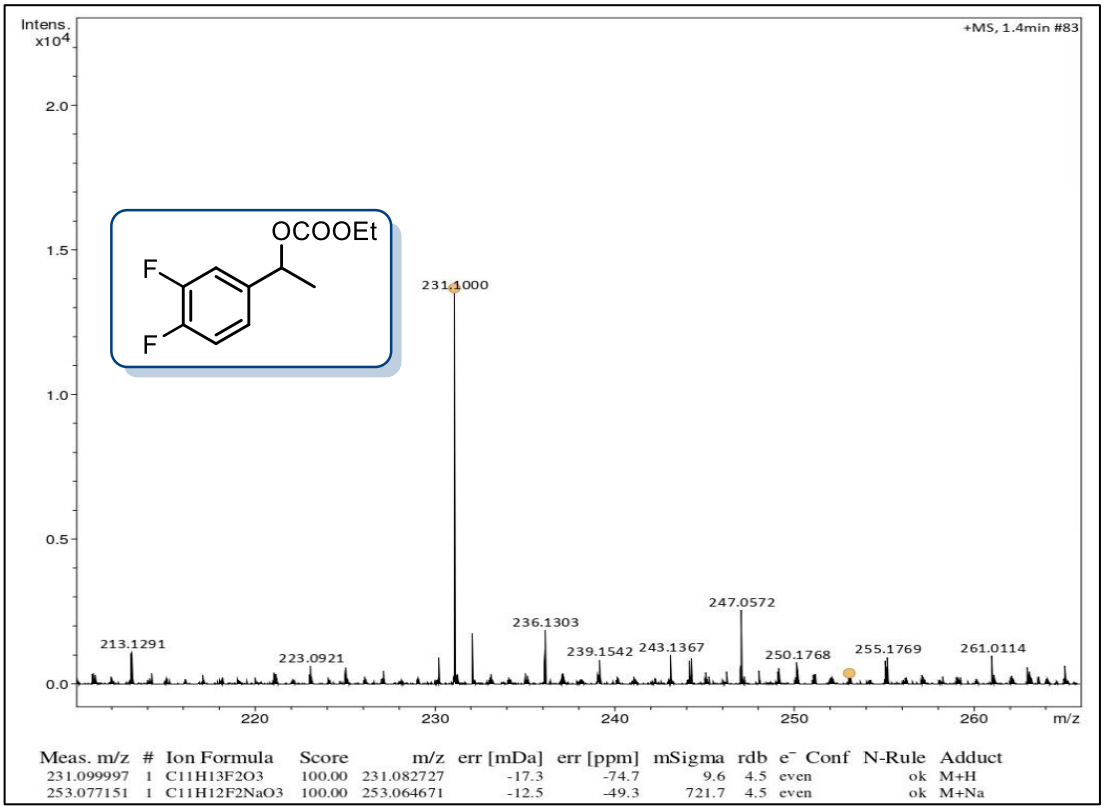
HRMS of ethyl (1-(p-tolyl)ethyl) carbonate **14**



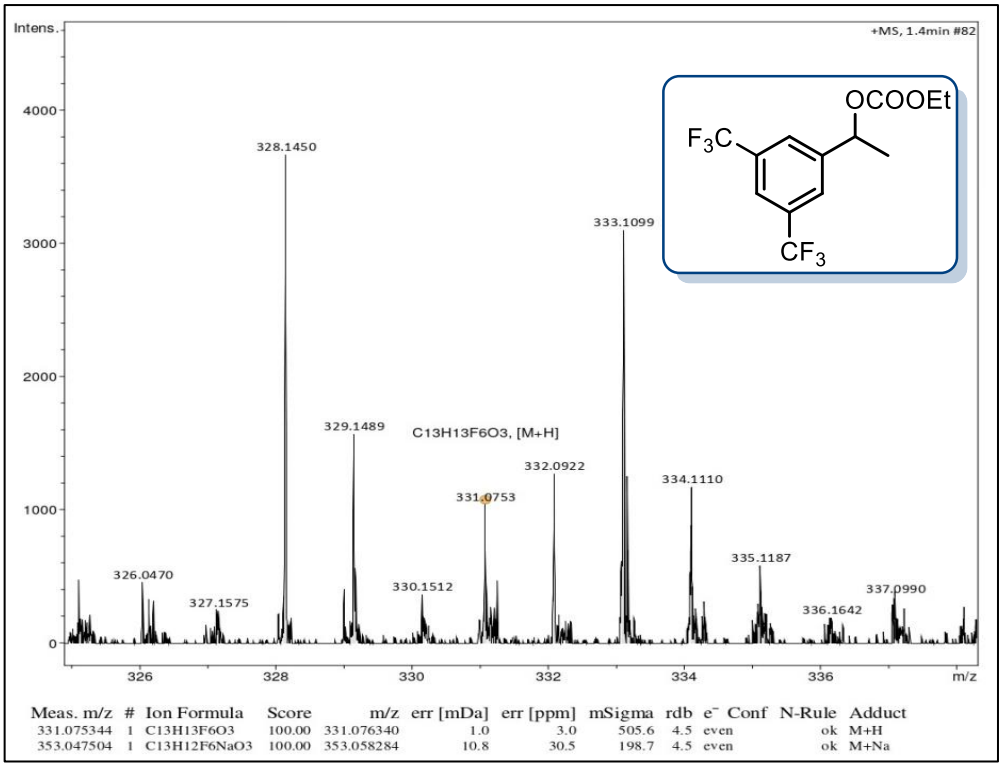
HRMS of 1-(4-chlorophenyl)ethyl ethyl carbonate **15**



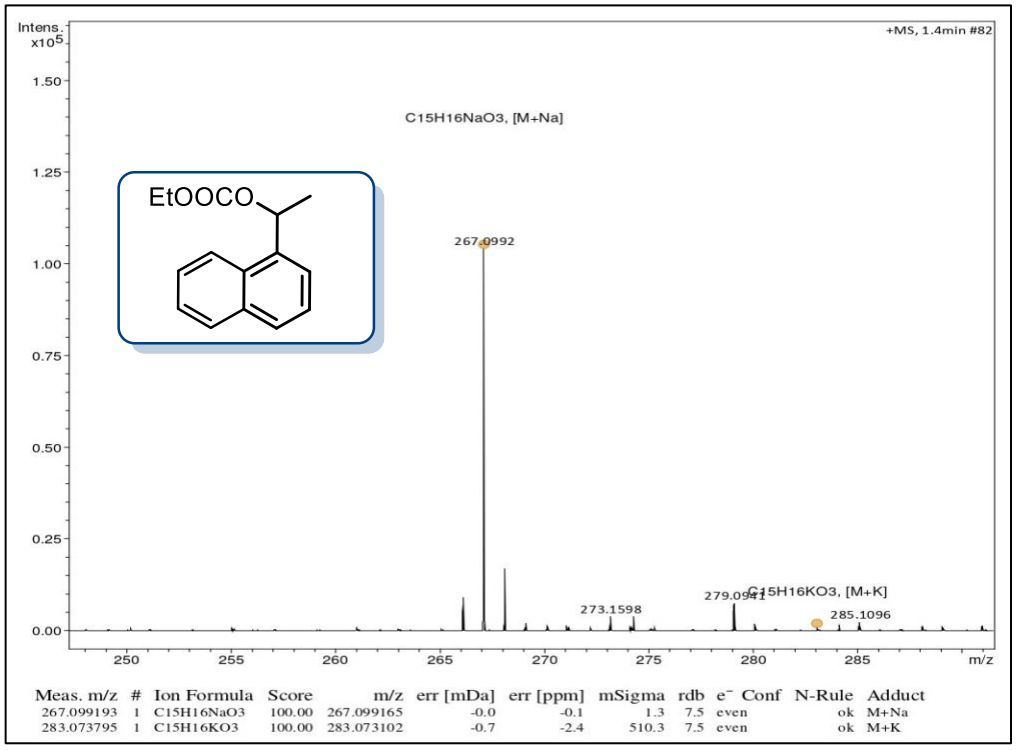
HRMS of 1-(4-bromophenyl)ethyl ethyl carbonate **16**



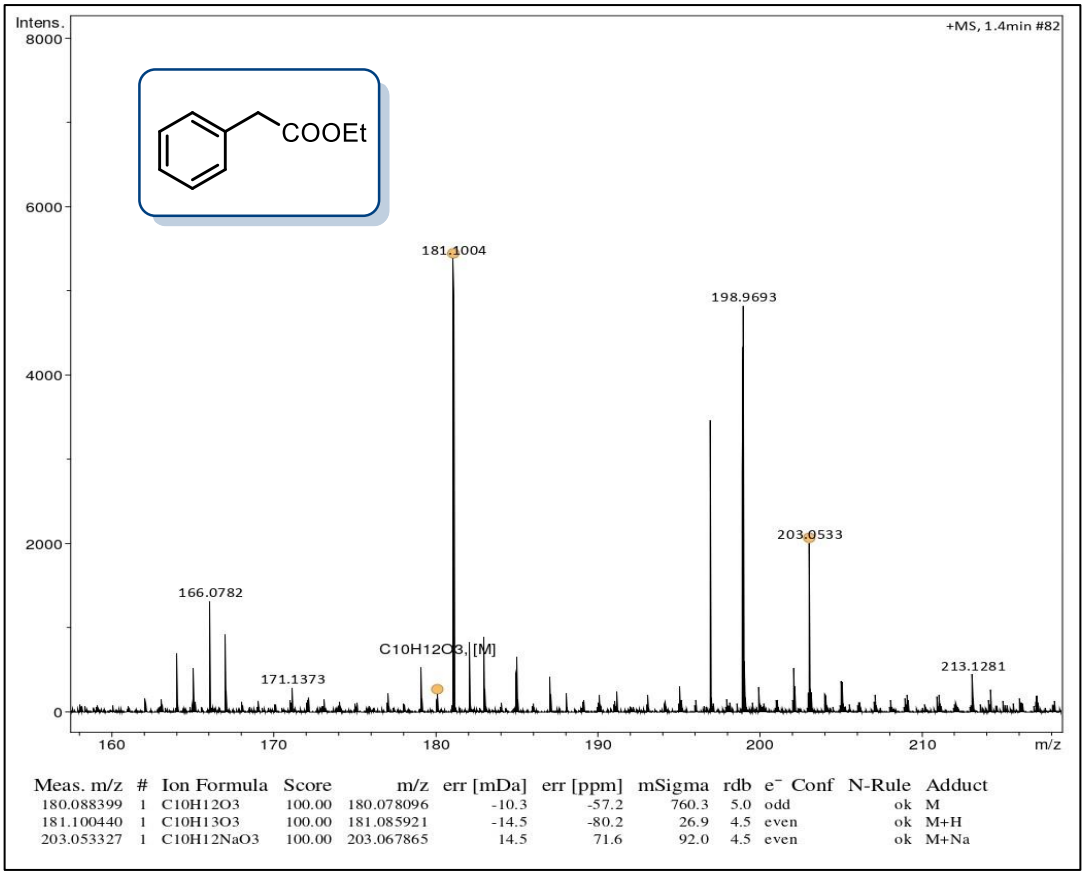
HRMS of 1-(3,4-difluorophenyl)ethyl ethyl carbonate **17**



HRMS of 1-(3,5-bis(trifluoromethyl)phenyl)ethyl ethyl carbonate **18**



HRMS of ethyl (1-(naphthalen-1-yl)ethyl) carbonate **19**

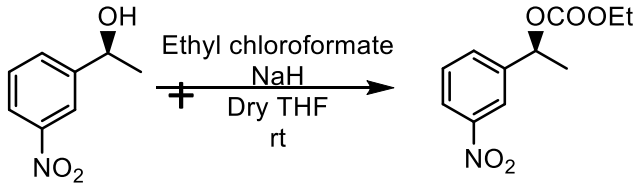


Meas. m/z	#	Ion Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule	Adduct
180.088399	1	C10H12O3	100.00	180.078096	-10.3	-57.2	760.3	5.0	odd	ok	M
181.100440	1	C10H13O3	100.00	181.085921	-14.5	-80.2	26.9	4.5	even	ok	M+H
203.053327	1	C10H12NaO3	100.00	203.067865	14.5	71.6	92.0	4.5	even	ok	M+Na

HRMS of benzyl ethyl carbonate **21**

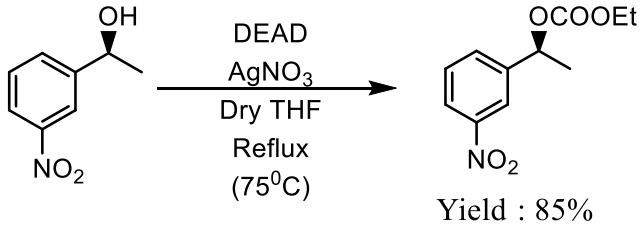
Proof of absolute Configuration

Traditional approach

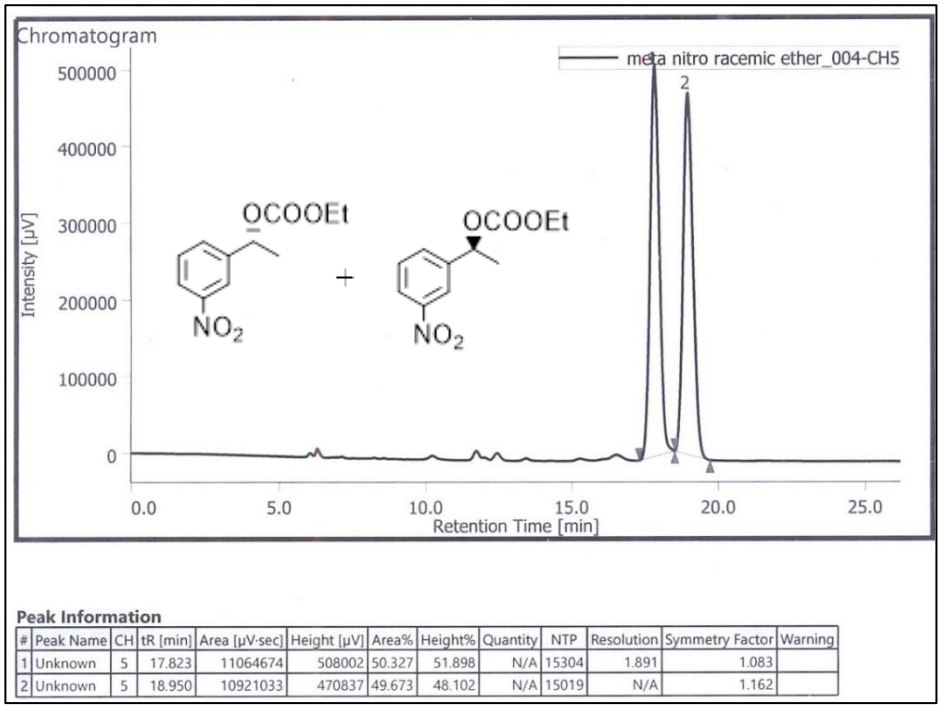


Yield : 63%

Present Approach



Yield : 85%

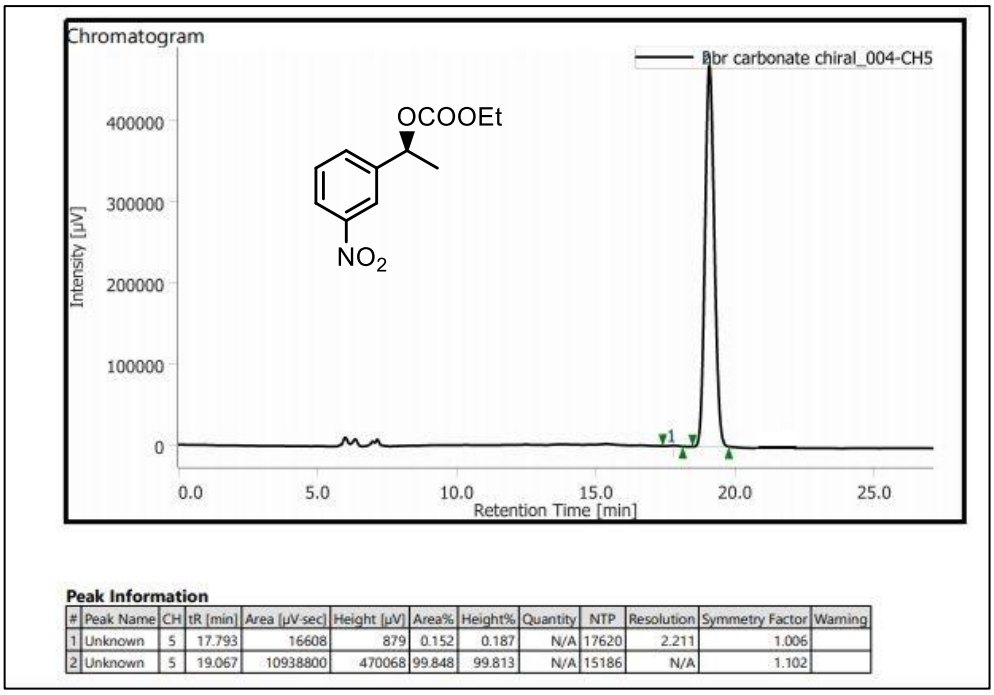


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	17.823	11064674	508002	50.327	51.898	N/A	15304	1.891	1.083	
2	Unknown	5	18.950	10921033	470837	49.673	48.102	N/A	15019	N/A	1.162	

HPLC of Racemic ethyl (1-(3-nitrophenyl)ethyl) carbonate

Traditional approach

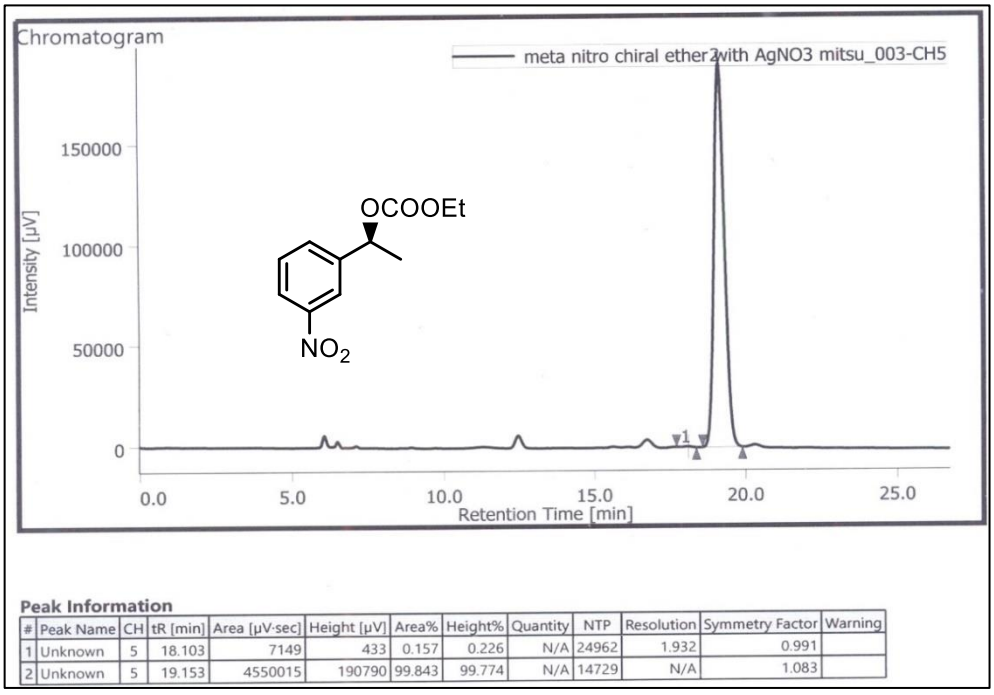


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	17.793	16608	879	0.152	0.187	N/A	17620	2.211	1.006	
2	Unknown	5	19.067	10938800	470068	99.848	99.813	N/A	15186	N/A	1.102	

HPLC of (S) ethyl (1-(3-nitrophenyl)ethyl) carbonate

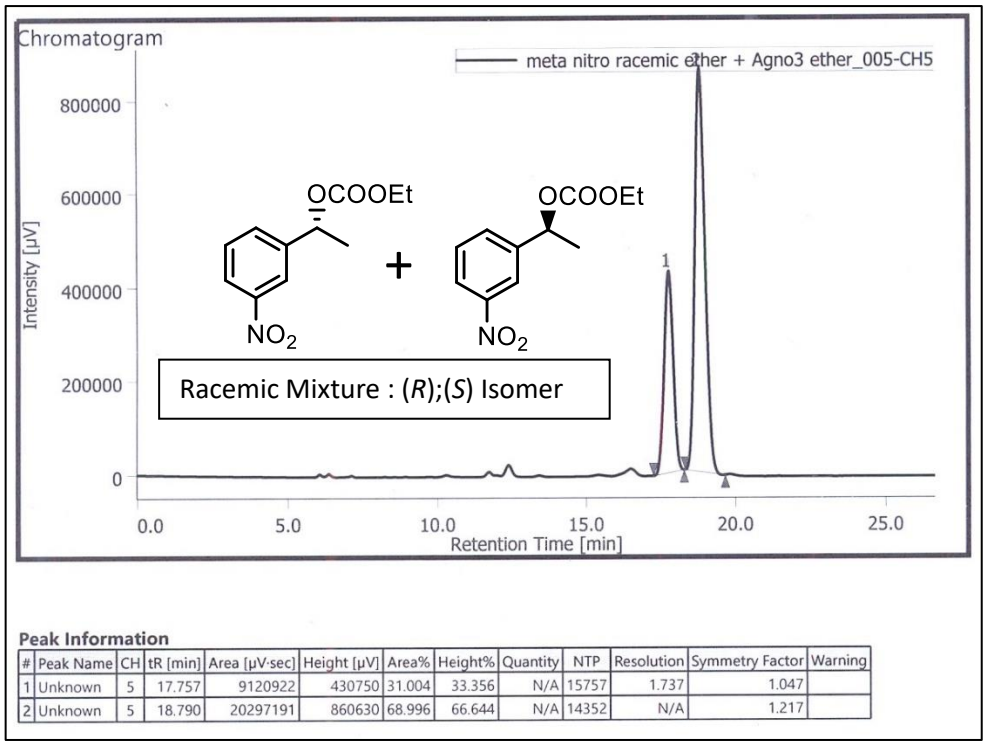
Present Approach



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.103	7149	433	0.157	0.226	N/A	24962	1.932	0.991	
2	Unknown	5	19.153	4550015	190790	99.843	99.774	N/A	14729	N/A	1.083	

HPLC of (S) ethyl (1-(3-nitrophenyl)ethyl) carbonate with Only $AgNO_3$



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	17.757	9120922	430750	31.004	33.356	N/A	15757	1.737	1.047	
2	Unknown	5	18.790	20297191	860630	68.996	66.644	N/A	14352	N/A	1.217	

HPLC of ethyl (1-(3-nitrophenyl)ethyl) carbonate
(Racemic Mixture + (S) Isomer)

3.II.9 References

1. Raval, H. B.; Bedekar, A.V. *New J. Chem.* **2020**; *44*, 21238-21243.
2. Shaikh, A.-A. G.; Siviram, S. *Chem. Rev.* **1996**, *96*, 951
3. Hegarty A. F. *Comprehensive Organic Chemistry (Ed.: I. O. Sutherland), Pergamon, London*, **1979**, *2*, 1067
4. Tundo, P. ; Selva, M. *Acc. Chem. Res.* **2002**, *35*, 706–716.
5. Fukuoka, S.; Tojo, M.; Kawamura, M. (Asahi Chemical Industry Co.) WO **1991**. 9109832
6. (a) Gymer, G. E.; Narayanaswami, S. In Comprehensive Organic Functional Group Transformations; Vol. 6, Part 4; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds.; Chap. 6.14; Pergamon: Oxford, **1995**, 407. (b) Hua, R.; Shimada, S.; Tanaka, M. *J. Am. Chem. Soc.* **1998**, *120*, 12365.
7. (a) Kreutzberger, C. B. *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley: New York, **2001**, (b) Sammet, B. *Synlett* **2009**, 3050. (c) Cotarca, L.; Eckert, H. *Phosgenations*: *A Handbook;* Wiley-VCH: Weinheim, **2003**.
8. (a) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Palazzi, P.; Sambri, L. *Eur. J. Org. Chem.* **2006**, 4429-4434. (b) Moon, H. K,; Sung, G. H.; Yoon, Y-J.; Yoon, H. J. *Synlett* **2016**, *27*, 1577-1581. (c) Liang, F.; Yanai, M.; Suzuki, Y.; Tsuda, A. *Org. Lett*. **2020**, *22*, 3566-3569. (d) Belokon, Y. N.; Blacker, A. J.; Clutterbuck, L. A,; North, M. *Org*. *Lett*. **2003**, *5*, 4505-4507.
9. Osumah, A.; Magolan, J.; Waynant, K. V. *Tetrahedron Lett.* **2019,** *60*, 151203.
10. Clacens, J.; Genuit, D.; Veldurthy, B.; Bergeret, G.; Delmotte, L.; Garcia-ruiz, A.; Figueras, F. *Appl Catal B Environ*. **2004**, *53*, 95–100.
11. Song, J.; Zhang, B.; Wu, T.; Yang, G.; Han, B. *Green Chem*. **2011**, 922–927.
12. (a) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev*. **2009**, *109*, 2551–2651.(b) Overman, L. E.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 9465. (c) Lawton, G. R.; Ji, H.; Silverman, R. B. *Tetrahedron Lett.* **2006**, *47*, 6113-6115. (d) Yasuda, N.; Hsiao, Y.; Jensen, M. S.; Rivera, N. R.; Yang, C.; Wells, K. M.; Yau, J.; Palucki, M.; Tan, L.; Dormer, P. G.; Volante, R. P.; Hughes, D. L.; Reider, P. J. *J. Org. Chem*. **2004**, *69*, 1959-1966. (e) Zuccarello, G.; Bouzide, A.; Kvarnstro¨m, I.; Niklasson, G.; Svensson, S. C. T.; Brisander, M.; Danielsson, H.; Nillroth, U.; Karle,´N. A.; Hallberg, A.; Classon, B.; Samuelsson, B. *J. Org. Chem*. **1998**, *63*, 4898-4906.

13. (a) Swamy, K. C. K.; Kumar N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev*. **2009**, *109*, 2551–2651. (b) Chong, Q.; Xin, X.; Wang, C.; Wu, F.; Wan, B. *Tetrahedron*. **2014**, *70*, 490–494. (c) Berkessa, S. C.; Clarke, Z. J. F.; Fotie, J.; Bohle, D. S.; Grimm, C. C. *Tetrahedron Lett.* **2016**, *57*, 1613–1618. (d) Wang, S. S.; Fu, H.; Shen, Y.; Sun, M.; Li, Y. M. *J Org Chem*. **2016**, *81*, 2920–2929. (e) Dong, W.; Qi, L.; Song, J. Y.; Chen, J. M.; Guo, J. X.; Shen, S.; Li, L. J.; Li, W.; Wang, L. J. *Org Lett*. **2020**, *22*, 1830–1835. (f) Shu, C.; Feng, J.; Zheng, H.; Cheng, C.; Yuan, Z.; Zhang, Z.; Xue, X. S.; Zhu, G. *Org Lett.* **2020**, *22*, 9398–9403. (g) Zheng, J.; Zhang, Y.; Wang, D.; Cui, S. *Org Lett.* **2016**, *18*, 1768–1771. (h) Sun, J.; Qiu, J. K.; Wu, Y. N.; Hao, W. J.; Guo, C.; Li, G.; Tu, S. J.; Jiang, B. *Org Lett*. **2017**, *19*, 754–757. (i) Lo, V. K. Y.; Chan, Y. M.; Zhou, D.; Toy, P. H.; Che, C. M. *Org Lett*. **2019**, *21*, 7717–7721. (j) Daru, J.; Benda, Z.; Póti, Á.; Novák, Z.; Stirling, A. *Chem – A Eur J.* **2014**, *20*, 15395–15400. (k) He, C.; Guo, S.; Ke. J.; Hao, J.; Xu, H.; Chen, H.; Lei, A. *J Am Chem Soc*. **2012**, *134*, 5766–5769. (l) Zhao, Y. H.; Li, Y.; Luo, M.; Tang, Z.; Deng, K. *Synlett*. **2016**, *27*, 2597–2600. ,14