

The azide-alkyne cycloaddition catalysed by metal acetates

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ABSTRACT

Azide-alkyne cycloadditions were performed in mild conditions in the presence of metal acetates, namely silver (I)-, nickel (II)- and cadmium (II) acetate as heterogeneous catalysts. The cycloaddition behaviour was dependent upon the metal acetate, the solvent and the azide moiety. With Ag (I) and Ni (II) acetates, mixtures of 4- and 5-substituted 1,2,3-triazoles were obtained with fair yields, while in the presence of Cd (II) acetate, regioselective cycloadditions to 4-substituted 1,2,3-triazoles occurred with high yields. Two concurrent intermediates were proposed in order to account all the experimental findings. The catalyst recovery was always easy to perform, and their reuse was also taken into account.

KEYWORDS: azide, metal acetates, heterogeneous catalysis, alkyne, 1,3-Dipolar cycloaddition, regioselectivity.

INTRODUCTION

One of the main interests of regioselective cycloadditions between azides and monosubstituted alkynes lie upon the widespread biomedical activity of the resulting 1,2,3-triazoles [1]. Some of their derivatives are effective drugs against epilepsy [2], diabetes [3], HIV virus [4] and Alzheimer's disease [5], thus representing a valuable tool in organic synthesis as well as in the field of drug discovery [6]. In the last few years there has been a flowering of metal-catalysed methodologies devoted to the improvement of the thermal azide-alkyne cycloaddition. It should be recalled that the classic, uncatalysed Huisgen cycloaddition is usually

carried out in refluxing solvents and is a scarcely regioselective reaction [7, 8]. The celebrated "click" cycloaddition occurs in mild conditions in the presence of simple copper (I) salts [9, 10], affording only 4-substituted 1,2,3-triazoles. The same regioselectivity was observed in the presence of silver (I) complexes [11]. Ruthenium (II) [12-14], iridium (I) [15] and nickel (II) [16] complexes were then highlighted as homogeneous catalysts giving selectively 5-substituted 1,2,3-triazoles.

Some authors pointed out the need for silver (I) [11] or nickel (II) [15] complexes as homogeneous catalysts to achieve the azide-alkyne cycloaddition, since no reaction occurred in the presence of simple silver (I) or nickel (II) salts. The rationale for this failure, as well as the apparent discrepancy with the "click" cycloaddition, was not explained. In a further study, the occurrence of the azide-alkyne cycloaddition in the presence of AgCl/Et₃N in refluxing tetrahydrofuran was pointed out [17]. But the use of the silver acetate/Et₃N catalyst was there limited to the single example of the benzylazide/phenylacetylene reaction that occurred with moderate yield [17]. On the other hand, it was stated that several nickel salts including nickel acetate were able to catalyse the azide-alkyne cycloaddition in moderate yields only in the presence of an appropriate reducing agent, namely hydrazine or sodium ascorbate [18]. In the light of all the above findings, the present paper is devoted to describe the feasibility of the azide-alkyne cycloaddition in the presence of metal acetates alone, namely silver (I)-, nickel (II)- and cadmium (II) acetate as heterogeneous catalysts. Scope and limitations of this protocol will be taken into account. Known azides **1a-d**, mono- and disubstituted acetylenes **2a-d** and **3** were chosen as suitable reactants (Figure 1).

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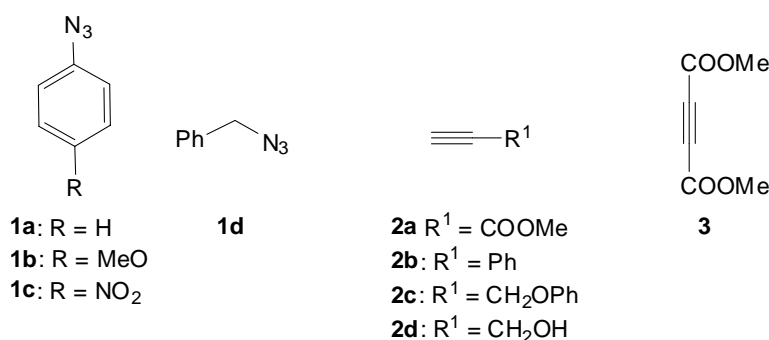


Figure 1. Reagents for the azide-alkyne cycloaddition.

MATERIALS AND METHODS

General

¹H-NMR (300 MHz) and ¹³C-NMR (75 MHz) spectra were taken with a Bruker AMX 300 instrument (in CDCl₃ solutions at room temperature). Chemical shifts are given as parts per million from tetramethylsilane. Coupling constants (*J*) values are given in hertz and are quoted to ±0.1 Hz consistently with NMR machine accuracy. Reagent chemicals were used as purchased from Aldrich Chemical Company Ltd. Solvents were dried and stored over 4Å molecular sieves prior to use.

All products **4**, **5** and **6** are known in the literature [18-27].

Uncatalysed cycloaddition between phenylazide **1a** and methyl propiolate **2a**

General procedure: A solution of phenylazide **1a** (200 mg, 1.68 mmol) and methyl propiolate **2a** (155 mg, 1.85 mmol) in the appropriate solvent (6.7 mL) was stirred for the time and at the temperature indicated in Table 1. Evaporation of the solvent gave a residue.

In the case of entries 1 and 4 the residue was dissolved in EtOAc (10 mL). The organic layer was dried over Na₂SO₄, and subsequent evaporation gave the mixture of cycloadducts **4aa** and **5aa**.

In the case of entries 7, 10 and 15 the residue contained the mixture of cycloadducts **4aa** and **5aa**.

In the case of entry 11 the residue was chromatographed on a silica gel column with hexane/EtOAc 7:3. First fractions contained the 5-substituted-1,2,3-triazole **5aa** (12 mg, 3.6%), and subsequent elution afforded the 4-substituted-1,2,3-triazole **4aa** (53 mg, 15.5%).

1-Phenyl-5-methoxycarbonyl-1,2,3-triazole **5aa**.

¹H-NMR: 3.85 (3H, s, CH₃-), 7.50-7.57 (5H, m, aromatics), 8.26 (1H, s, triazole C₄-H); ¹³C-NMR: 53.4 (q, -CH₃), 120.8 (d, aromatic), 125.6 (d, aromatic), 129.5 (d, aromatic), 130.1 (d, triazole-C₄), 137.0 (s, aromatic), 140.9 (s, triazole-C₅), 161.5 (s, ester >C=O).

1-Phenyl-4-methoxycarbonyl-1,2,3-triazole **4aa**.

¹H-NMR: 4.00 (3H, s, CH₃-), 7.47-7.77 (5H, m, aromatics), 8.51 (1H, s, triazole C₅-H); ¹³C-NMR: 52.3 (q, -CH₃), 120.8 (d, aromatic), 125.6 (d, aromatic), 128.9 (s, triazole-C₅), 129.9 (d, aromatic), 136.3 (s, aromatic), 140.5 (s, triazole-C₄), 161.0 (s, ester >C=O).

Cycloaddition between phenylazide **1a** and methyl propiolate **2a** catalysed by silver (I) acetate

General procedure: For entries 2, 5, 8, 12, 13, 16, 17 and 18, Table 1, a suspension of phenylazide **1a** (200 mg, 1.68 mmol), methyl propiolate **2a** (155 mg, 1.85 mmol) and silver (I) acetate (70 mg, 0.42 mmol) in the appropriate solvent (6.7 mL) was stirred in the dark for the time and at the temperature listed in Table 1.

For entries 3, 6, 9 and 14, Table 1, a suspension of phenylazide **1a** (200 mg, 1.68 mmol), methyl propiolate **2a** (155 mg, 1.85 mmol), silver (I) acetate (70 mg, 0.42 mmol) and caesium carbonate (68 mg, 0.21 mmol) in the appropriate solvent (6.7 mL) was stirred in the dark for the time and at the temperature listed in Table 1.

The undissolved material was filtered off, and evaporation of the solvent gave a residue that was chromatographed on a silica gel column with hexane/EtOAc 7:3. First fractions contained the 5-substituted-1,2,3-triazole **5aa** and subsequent elution afforded the 4-substituted-1,2,3-triazole **4aa**.

Table 1. Cycloaddition between phenylazide **1a** and methyl propiolate **2a** in the presence of silver (I) acetate.

Entry	Acetate/additive	Solvent	T (°C)	Time (h)	4aa + 5aa (%)	4aa:5aa ^a
1	– / –	aq. acetone ^a	20	24	6	85:15
2	AcOAg / –	aq. acetone ^b	20	24	17	89:11
3	AcOAg/Cs ₂ CO ₃	aq. acetone ^b	20	24	30	87:13
4	– / –	aq. acetone ^b	50	6	11	79:21
5	AcOAg / –	aq. acetone ^b	50	6	31	86:14
6	AcOAg/Cs ₂ CO ₃	aq. acetone ^b	50	6	32	88:12
7	– / –	acetone	20	24	3	86:14
8	AcOAg / –	acetone	20	24	18	89:11
9	AcOAg/Cs ₂ CO ₃	acetone	20	24	28	86:14
10	– / –	acetone	50	6	9	81:19
11	– / –	acetone	50	24	19	81:19
12	AcOAg / –	acetone	50	6	49	92:8
13	AcOAg / –	acetone	50	24	65	91:9
14	AcOAg/Cs ₂ CO ₃	acetone	50	6	51	86:14
15	– / –	toluene	50	6	5	81:19
16	AcOAg / –	toluene	50	6	37	80:20
17	AcOAg / –	1,4-dioxane	50	6	44	76:24
18	AcOAg / –	isopropanol	50	6	40	79:21

^aAs deduced by ¹H-NMR analysis. ^b80% v./v.

Cycloaddition between phenylazide **1a** and methyl propiolate **2a** catalysed by nickel (II) acetate

General procedure: For entries 1, 3, 4, 5, 8 and 9, Table 2, a suspension of phenylazide **1a** (200 mg, 1.68 mmol), methyl propiolate **2a** (155 mg, 1.85 mmol) and nickel (II) acetate (74 mg, 0.42 mmol) in the appropriate solvent (6.7 mL) was stirred for the time and at the temperature listed in Table 2.

For entries 2 and 6, Table 2, a suspension of phenylazide **1a** (200 mg, 1.68 mmol), methyl propiolate **2a** (155 mg, 1.85 mmol), nickel (II) acetate (74 mg, 0.42 mmol) and caesium carbonate (68 mg, 0.21 mmol) in the appropriate solvent (6.7 mL) was stirred for the time and at the temperature indicated in the Table 2.

For entry 7, Table 2, a suspension of phenylazide **1a** (200 mg, 1.68 mmol), methyl propiolate **2a** (155 mg, 1.85 mmol), nickel (II) acetate (74 mg, 0.42 mmol) and triphenylphosphine (110 mg, 0.42 mmol) in dry acetone (6.7 mL) was stirred at 50 °C for 6h.

The undissolved material was filtered off, and evaporation of the solvent gave a residue that was chromatographed on a silica gel column with hexane/EtOAc 7:3. First fractions contained the 5-substituted-1,2,3-triazole **5aa** and subsequent elution afforded the 4-substituted-1,2,3-triazole **4aa**.

Cycloaddition between phenylazides **1** and methyl propiolate **2a** catalysed by cadmium (II) acetate

General procedure: A suspension of azide **1** (2.0 mmol), methyl propiolate **2a** (185 mg, 2.2 mmol) and cadmium (II) acetate (95 mg, 0.5 mmol) in dry acetone (6 mL) was stirred at 50 °C for the time indicated in Table 3. The undissolved material was filtered off, and evaporation of the solvent gave a residue that was chromatographed on a silica gel column with hexane/EtOAc 7:3. First fractions contained the 5-substituted-1,2,3-triazole **5** and subsequent elution afforded the 4-substituted-1,2,3-triazole **4**.

1-(4-Methoxy)phenyl-5-methoxycarbonyl-1,2,3-triazole 5ba. ¹H-NMR: 3.87 (3H, s, CH₃), 3.90 (3H,

Table 2. Cycloaddition between phenylazide **1a** and methyl propiolate **2a** in the presence of nickel (II) acetate.

Entry	Acetate/additive	Solvent	T (°C)	Time (h)	4aa + 5aa (%)	4aa:5aa ^a
1	(AcO) ₂ Ni/—	aq. acetone ^b	20	24	6	85:15
2	(AcO) ₂ Ni/Cs ₂ CO ₃	aq. acetone ^b	20	24	17	89:11
3	(AcO) ₂ Ni/—	aq. acetone ^b	20	24	30	87:13
4	(AcO) ₂ Ni/—	aq. acetone ^b	50	6	11	79:21
5	(AcO) ₂ Ni/—	acetone	50	6	31	86:14
6	(AcO) ₂ Ni/Cs ₂ CO ₃	acetone	50	6	32	88:12
7	(AcO) ₂ Ni/Ph ₃ P	acetone	20	24	3	86:14
8	(AcO) ₂ Ni/—	isopropanol	20	24	18	89:11
9	(AcO) ₂ Ni/—	isopropanol	20	24	28	86:14

^aAs deduced by ¹H-NMR analysis. ^b80% v/v.

Table 3. Cycloaddition between arylazides **1a-c** and methyl propiolate **2a** in the presence of cadmium (II) acetate.

Entry	Ar	Time (h)	4 + 5 (%)	4:5
1	Ph	5	73	85:15
2	4-MeO-C ₆ H ₄	5	81	79:21
3	4-NO ₂ -C ₆ H ₄	6	47	55:45

s, CH₃-), 7.03-7.07 (2H, m, aromatics), 7.41-7.43 (2H, m aromatics), 8.27 (1H, s, triazole C₄-H); ¹³C-NMR: 52.4 (q, -CH₃), 55.6 (q, -CH₃), 114.1 (d, aromatic), 127.1 (d, aromatic), 128.6 (s, aromatic), 129.3 (s, triazole-C₅), 138.1 (d, triazole-C₄), 158.3 (s, aromatic), 161.5 (s, ester >C=O).

1-(4-Methoxy)phenyl-4-methoxycarbonyl-1,2,3-triazole 4ba. ¹H-NMR: 4.00 (3H, s, CH₃-), 4.01 (3H, s, CH₃-), 7.05-7.08 (2H, m, aromatics), 7.66-7.69 (2H, m, aromatics), 8.47 (1H, s, triazole C₅-H); ¹³C-NMR: 52.4 (q, -CH₃), 55.7 (q, -CH₃), 115.0 (d, aromatic), 122.5 (d, aromatic), 125.6 (d, triazole-C₅), 129.6 (s, aromatic), 140.3 (s, triazole-C₄), 160.5 (s, aromatic), 161.2 (s, ester >C=O).

1-(4-Nitro)phenyl-5-methoxycarbonyl-1,2,3-triazole 5ca. ¹H-NMR: 3.93 (3H, s, CH₃-), 7.75-7.77 (2H, m, aromatics), 8.32 (1H, s, triazole C₄-H), 8.43-8.45 (2H, m aromatics); ¹³C-NMR: 52.7 (q, -CH₃), 120.9 (d, aromatic), 128.3 (d, aromatic), 132.0 (s, triazole-C₅), 138.2 (d, triazole-C₄), 140.8 (s, aromatic), 160.5 (s, aromatic), 167.6 (s, ester >C=O).

1-(4-Nitro)phenyl-4-methoxycarbonyl-1,2,3-triazole 4ca. ¹H-NMR: 4.04 (3H, s, CH₃-), 8.03-8.06 (2H, m, aromatics), 8.47-8.50 (2H, m, aromatics), 8.65 (1H, s, triazole C₅-H); ¹³C-NMR: 52.2 (q, -CH₃), 115.2 (d, aromatic), 130.8 (d, aromatic), 132.2 (s, triazole-C₄), 138.4 (d, triazole-C₅), 140.4 (s, aromatic), 157.8 (s, aromatic), 167.34 (s, ester >C=O).

Cycloaddition between benzylazide **1d** and acetylenes **2** and **3** catalysed by metal acetates

General procedure: A suspension of benzylazide **1d** (300 mg, 2.26 mmol), the appropriate alkyne **2** (2.5 mmol) and the appropriate metal acetate (0.57 mmol) in dry acetone (9 mL) was stirred (in the dark in the case of silver (I) acetate) at 50 °C for the time indicated in Table 4. The undissolved material was filtered off, and rotary evaporation of the solvent gave a residue.

In the case of entries 1, 2, 5 and 6 the residue was chromatographed on a silica gel column with hexane/EtOAc 7:3. First fractions contained the 5-substituted-1,2,3-triazole **5**, and subsequent elution afforded the 4-substituted-1,2,3-triazole **4**.

Table 4. Cycloaddition between benzylazide **1d** and monosubstituted acetylenes **2a-d** in the presence of metal acetates.

Entry	R	Acetate	Time (h)	4 + 5 (%)	4:5
1	COOMe	(AcO)Ag	6	78	88:12
2	COOMe	(AcO) ₂ Ni	6	68	84:16
3	COOMe	(AcO) ₂ Cd	2.5	95	100:0
4	Ph	(AcO) ₂ Cd	6	88	100:0
5	CH ₂ OPh	(AcO) ₂ Cd	12	67	85:15
6	CH ₂ OH	(AcO) ₂ Cd	16	55	69:31

1-Benzyl-5-methoxycarbonyl-1,2,3-triazole 5da.

¹H-NMR: 3.89 (3H, s, CH₃-), 5.92 (2H, s, -CH₂-), 7.32 (5H, m, aromatics), 8.13 (1H, s, triazole C₄-H); ¹³C-NMR: 52.4 (q, -CH₃), 53.4 (t, -CH₂-), 127.4 (s, aromatic), 128.0-128.7 (aromatics), 134.9 (s, triazole-C₅), 138.2 (d, triazole-C₄), 158.8 (s, ester >C=O).

1-Benzyl-4-methoxycarbonyl-1,2,3-triazole 4da.

¹H-NMR: 3.94 (3H, s, CH₃-), 5.60 (2H, s, -CH₂-), 7.31-7.40 (5H, m, aromatics), 8.00 (1H, s, triazole C₅-H); ¹³C-NMR: 52.1 (q, -CH₃), 54.5 (t, -CH₂-), 127.3 (d, triazole-C₅), 128.3-129.3 (aromatics), 133.7 (s, aromatic), 140.3 (s, triazole-C₄), 161.1 (s, ester >C=O).

1-Benzyl-5-phoxymethyl-1,2,3-triazole 5dc.

¹H-NMR: 4.91 (2H, s, -CH₂-), 5.67 (2H, s, -CH₂-), 6.91-7.32 (11H, m, aromatics + triazole C₄-H); ¹³C-NMR: 52.6 (t, -CH₂-), 58.1 (t, -CH₂-), 114.4-129.1 (aromatics), 135.1 (s, triazole-C₅), 143.7 (d, triazole-C₄), 158.7 (s, ether >C-O).

1-Benzyl-4-phoxymethyl-1,2,3-triazole 4dc.

¹H-NMR: 5.21 (2H, s, -CH₂-), 5.54 (2H, s, -CH₂-), 6.98-7.38 (10H, m, aromatics), 7.55 (1H, s, triazole C₅-H); ¹³C-NMR: 54.2 (t, -CH₂-), 62.0 (t, -CH₂-), 114.8-129.5 (aromatics), 134.5 (s, aromatic), 144.6 (s, triazole-C₄), 158.2 (s, ether >C-O).

1-Benzyl-5-hydroxymethyl-1,2,3-triazole 5dd.

¹H-NMR: 3.10 (1H, br s, -OH), 4.58 (2H, s, -CH₂-), 5.62 (2H, s, -CH₂-), 7.23-7.38 (5H, m, aromatics), 7.58 (1H, s, triazole C₄-H); ¹³C-NMR: 51.9 (t, -CH₂-), 52.6 (t, -CH₂-), 127.4 (d, aromatic), 127.9 (d, aromatic), 129.0 (d, aromatic), 133.0 (d, triazole-C₄), 134.7 (s, triazole-C₅), 137.0 (s, aromatic).

1-Benzyl-4-hydroxymethyl-1,2,3-triazole 4dd.

¹H-NMR: 2.00 (1H, br s, -OH), 4.73 (2H, s, -CH₂-), 5.50 (2H, s, -CH₂-), 7.28-7.37 (5H, m, aromatics), 7.49 (1H, s, triazole C₄-H); ¹³C-NMR: 54.0 (t, -CH₂-), 55.8 (t, -CH₂-), 122.4 (d, triazole-C₄), 128.0 (d, aromatic), 128.8 (d, aromatic), 129.0 (d, aromatic), 137.0 (s, triazole-C₅), 148.4 (s, aromatic).

In the case of entries 3 and 4 the residue was crystallised with *i*Pr₂O affording 4-substituted-1,2,3-triazoles **4da** and **4db**.

1-Benzyl-4-phenyl-1,2,3-triazole 4db.

¹H-NMR: 5.60 (2H, s, CH₂-), 7.33-7.42 (8H, m, aromatics), 7.68 (1H, s, triazole C₅-H), 7.80-7.83 (2H, m, aromatics); ¹³C-NMR: 54.2 (t, -CH₂-), 119.6-129.2 (aromatics), 130.6 (s, aromatic), 134.7 (s, aromatic), 148.2 (d, triazole-C₄).

In the case of dimethylacetylene dicarboxylate (DMAD), a suspension of benzylazide **1d** (0.30 g, 2.26 mmol), DMAD **3** (0.36 g, 2.5 mmol) and cadmium acetate (107 mg, 0.57 mmol) in dry acetone (9 mL) was stirred at 50 °C for 40 min. The undissolved material was filtered off, and evaporation of the solvent gave a residue that was crystallised with *i*Pr₂O affording the 1,2,3-triazole **6** (0.60 g, 96%).

1-Benzyl-4,5-dimethoxycarbonyl-1,2,3-triazole 6.

¹H-NMR: 3.84 (3H, s, CH₃-), 3.92 (3H, s, CH₃-), 5.77 (2H, s, CH₂-), 7.21-7.31 (5H, m, aromatics); ¹³C-NMR: 52.7 (q, -CH₃), 53.3 (q, -CH₃), 53.9 (t, -CH₂-), 128.0 (d, aromatic), 128.9 (d, aromatic), 129.2 (d, aromatic), 129.8 (s, aromatic), 133.9 (s, triazole-C₅), 140.1 (s, triazole-C₄), 158.8 (s, ester >C=O), 160.4 (s, ester >C=O).

Cycloaddition between phenylazides **1** and methyl propiolate **2a** catalysed by copper (I) iodide

General procedure: A suspension of azide **1** (2.0 mmol), the appropriate alkyne **2** (2.2 mmol) and copper (I) iodide (0.19 g, 1.0 mmol) in dry toluene (8 mL) was stirred at 50 °C for 7h. The undissolved material was filtered off, and evaporation of the solvent gave a residue that was crystallised with *i*Pr₂O affording 4-substituted-1,2,3-triazoles **4**.

RESULTS AND DISCUSSION

The behaviour of phenylazide **1a** towards methyl propiolate **2a** in the presence of 0.25 mol/equiv of the metal acetate was investigated as the reference reaction (Scheme 1, Tables 1 and 2). For the sake of clarity, the results were grouped according to the metal acetate. Data concerning the cycloadditions carried out in the presence of silver (I) acetate are listed in Table 1 and deserve some comments.

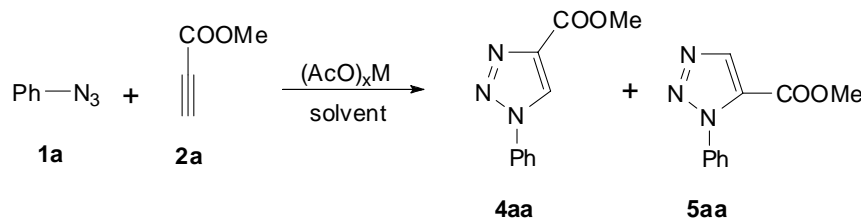
At 20 °C (entries 1-3 and 7-9), sizeable amounts of the starting phenylazide were recovered by interrupting the reaction after 6 and 24 h. Consequently, low yields of the isomeric 1,2,3-triazole cycloadducts **4aa** and **5aa** were observed. Despite this drawback, the standard reaction **1a** + **2a** was not driven to completion since prolonged reaction times would be uncompetitive compared to the above-mentioned metal-catalysed azide-alkyne cycloadditions [9-16]. Furthermore, the presence of caesium carbonate as additive did not enhance these disappointing reaction yields. By raising the temperature to 50 °C (entries 4-6 and 10-14), a general improvement of the cycloaddition yield was observed. Close inspection of these data revealed that yield enhancements were only slightly due to thermal effects. The worst behaviour of the reactions carried out in aqueous acetone was

ascribed to the partial hydration of methyl propiolate, since methyl 2-oxopropionate was recovered as a trivial side-product. Consistently to the concerted nature of the azide-alkyne reaction [28], little solvent effect was experienced (entries 5, 12 and 15-18). It is known that the regiochemistry course of the thermal cycloaddition between phenylazide and methyl propiolate is the result of a delicate balance of both the HOMO and the LUMO orbitals of the azide [29, 30]. Despite the 4-substituted 1,2,3-triazole **4aa** results as the major isomer [31], the variation of the regiochemical ratio **4aa**:**5aa** from 76:24 to 92:8 is difficult to rationalize on the grounds of simple frontier molecular orbital theory (FMO).

This regiochemical behaviour may be the result of an interplay of factors due to catalyst, solvent and temperature effects. Because of the close similarity of the ¹H-NMR spectra of the isomeric cycloadducts **4** and **5** [31], the independent synthesis of the 4-substituted 1,2,3-triazoles **4** were performed in the presence of copper (I) iodide in toluene (see Supporting Information).

The standard reaction **1a** + **2a** was performed in the presence of nickel (II) acetate. The results are listed in Table 2 and resemble that obtained with silver (I) acetate, such that the same considerations can be applied.

In the presence of cadmium (II) acetate (Scheme 2 and Table 3), the standard reaction **1a** + **2a** was complete after 5 h with better cycloadduct yield compared to that obtained with other metal acetates (see Table 1, entry 12 and Table 2, entry 5). This result is also much better than that obtained in the thermal conditions (36h in refluxing carbon tetrachloride) [21]. By varying the electronic nature of the aryl pendant, a reactivity decrease was



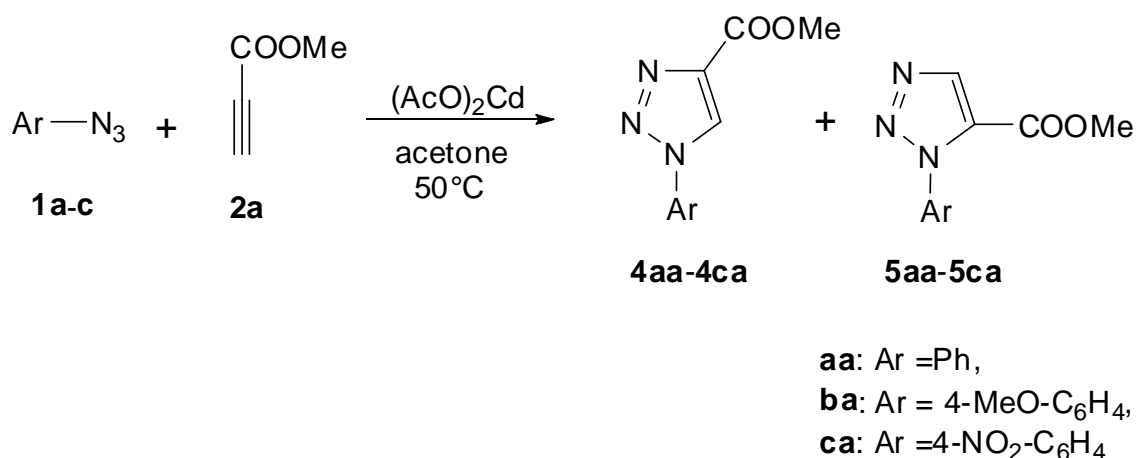
Scheme 1. Cycloaddition between phenylazide **1a** and methyl propiolate **2a** in the presence of silver (I) acetate.

paralleled by substituent's σ -Hammett increase, while the regioselectivity was quite superimposable to that observed in the case of the corresponding thermal processes.

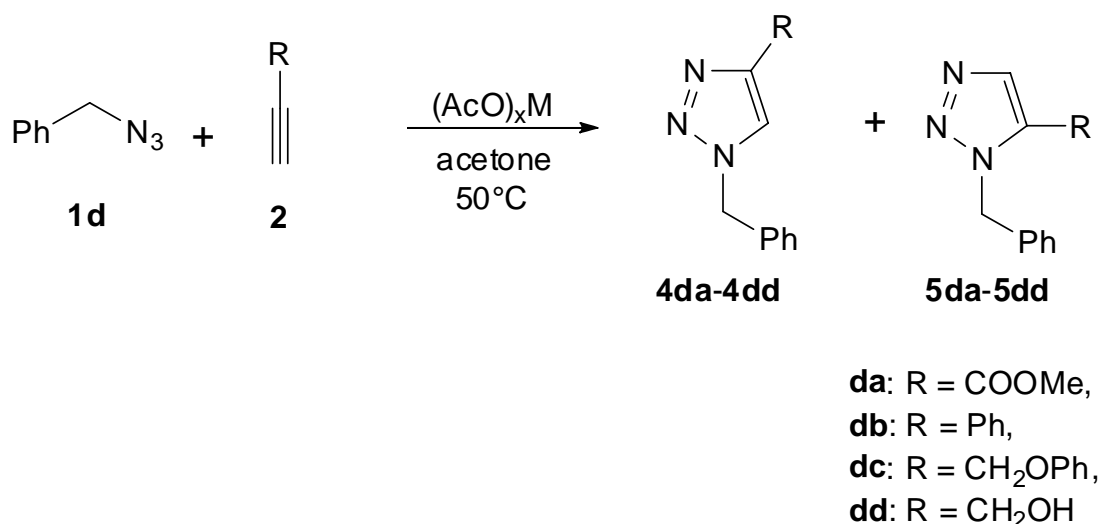
The behaviour of benzylazide **1d** towards monosubstituted acetylenes **2a-d** is depicted in Scheme 3 and Table 4. A further enhancement of both reactivity and cycloaddition yields was observed with respect to the corresponding arylazides **1a-c** (entries 1-3). The most striking feature of the reactions **1d** + **2** relies upon the complete

regioselectivity displayed in the case of the non-complexating acetylenes **2a,b** (entries 3,4), while the more complexating the dipolarophile, the less effective is cycloaddition regioselectivity (entries 5,6).

Due to the slight solubility of the metal acetates in acetone, recovery of the catalysts was achieved by simple filtration. In the case of the reaction between benzylazide and methyl propiolate, it was possible to reuse cadmium acetate three times without loss of catalytic activity. However, a decrease in the catalyst activity was observed since the fourth run.



Scheme 2. Cycloaddition between arylazides **1a-c** and methyl propiolate **2a** in the presence of cadmium (II) acetate.



Scheme 3. Cycloaddition between benzylazide **1d** and monosubstituted acetylenes **2a-d** in the presence of metal acetates.

Finally, the reaction between benzylazide and dimethylacetylene dicarboxylate **3** (DMAD) was performed as a representative of disubstituted acetylenes. In the presence of cadmium (II) acetate at 50 °C the reaction was complete in 40 minutes giving the corresponding 1,2,3-triazole **6** (Figure 2) with quantitative yield.

All the above findings may be rationalised provided the two competing reaction intermediates **7** and **8** does work in non-aqueous solvents (Figure 3). The main difference between these labile complexes and the key intermediate involved in the copper (I) catalysed "click" cycloaddition [32] is that no σ bond is operating between the metal M and the carbon-carbon triple bond. Due to their d^{10} electronic configuration, silver (I) and cadmium (II) should

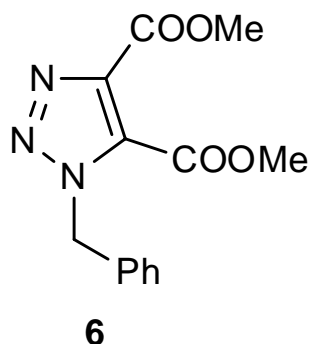


Figure 2. 1-Benzyl-5,6-dimethoxycarbonyl-1H-1,2,3-triazole **6**.

provide 16 and 18 electron complexes, while the d^9 nickel (II) acetate should generate a couple of 17 electron intermediates.

The proposal of the two labile intermediates **7** and **8** was conceived in the light of the known π -complexing ability of silver (I), nickel (II) and cadmium (II) towards the carbon-carbon triple bond [33-36] and azides [16, 37, 38]. As far as cadmium (II) acetate is concerned, no data are available about its complexation with organic azides but only with the azido anion [39]. The tetrahedral structure of both intermediates **7** and **8** is consistent to that of the above-mentioned literature complexes and allows the approach of the cycloaddends into parallel planes, as is required for concerted processes [28]. The regiochemical preference of the cycloadditions towards 4-substituted 1,2,3-triazoles **4** should be dictated by the more favourable steric requirements of intermediate **7** compared to **8** (R-M repulsion). The better reactivity displayed by benzylazide **1d** may also be ascribed to steric factors, the alkylaromatic pendant being more flexible than the phenyl ring of azidobenzene **1a** (Ar-M interactions). The electronic features of the azide dictate the cycloaddition outcome; the worse reactivity of electron-poor 4-nitrophenylazide **1c** should be related to its reduced ability to act as a ligand compared to azides **1a,b** and **1d**. Thus, it is reasonable to believe that the formation of both intermediates **7** and **8** should be more difficult with azide **1c**; low product yields and poor regioselectivity indicate a cycloaddition course close

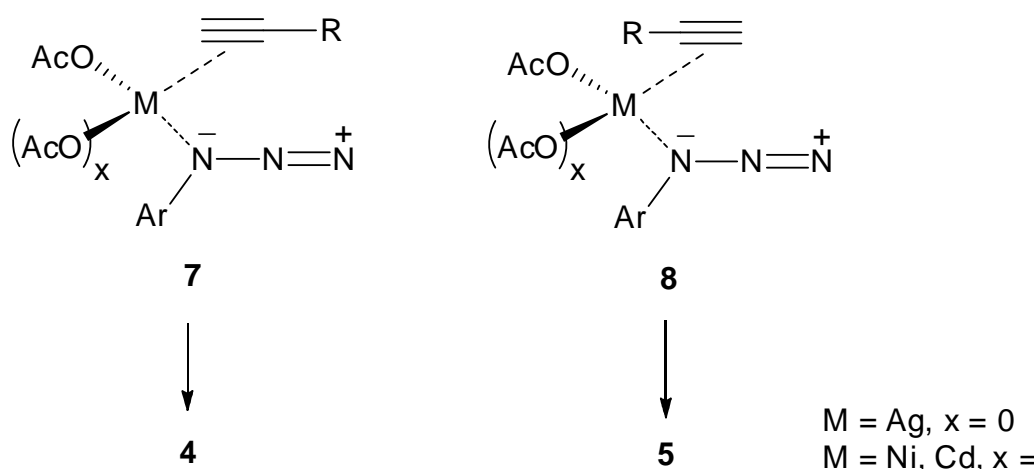


Figure 3. Intermediates **7** and **8** proposed to rationalise the experimental findings.

to that of the thermal process [21]. The lesser reactivity and regioselectivity observed with acetylenes **2c,d** may be related to the presence of the potentially complexating $-\text{CH}_2\text{OH}$ and $-\text{CH}_2\text{OPh}$ groups that could be able to partially replace the acetylenic bond as the π -ligand in both the intermediates **7** and **8**. As a further relevant remark, the lack of a metal-alkyne σ -bond accounts for the high reactivity of DMAD **3**. This latter point represents an improvement of the “click” reactions whereby the $\text{M}-\text{C}\equiv$ bond precludes the cycloaddition to disubstituted acetylenes.

CONCLUSIONS

As a concluding remark, the feasibility of the azide-alkyne cycloaddition in the presence of metal acetates as heterogeneous catalysts was verified and it was possible to rationalise all the experimental findings upon the intervention of two novel labile intermediates. The simple metal salts used here are commercially available and considerably cheaper than the metal complexes used as homogeneous catalysts for the same cycloaddition. The behaviour of silver (I) and nickel (II) acetate displayed marked similarities, namely moderate cycloadduct yield and a regioselectivity course similar to that

of thermal reactions. Instead, cadmium acetate gave much better results affording in some cases the 4-substituted 1,2,3-triazole as the single regioisomer with high yield. However, the depicted heterogeneous catalysis by metal acetates cannot be described as a general method in the azide-alkyne cycloadditions since it was dependent on both electronic and steric features of the reactants. As positive statements, it should be pointed out that reactions occur in short times and mild conditions, and the workup and the catalyst recovery are very easy due to the poor solubility of the metal acetates in the reaction medium.

ACKNOWLEDGEMENTS

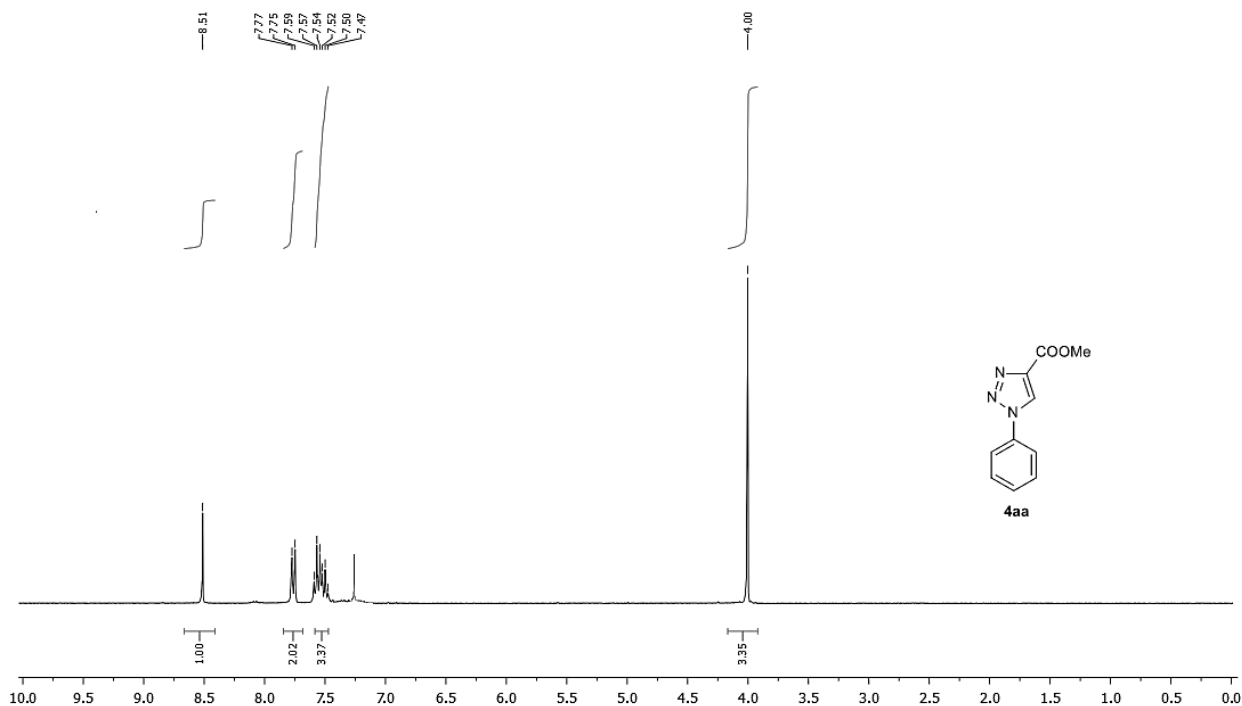
Thanks are due to the student Luca Pietro Carati who carried out part of the experiments and to Dr. Lara de Benassuti, University of Milan, who accomplished NMR spectra.

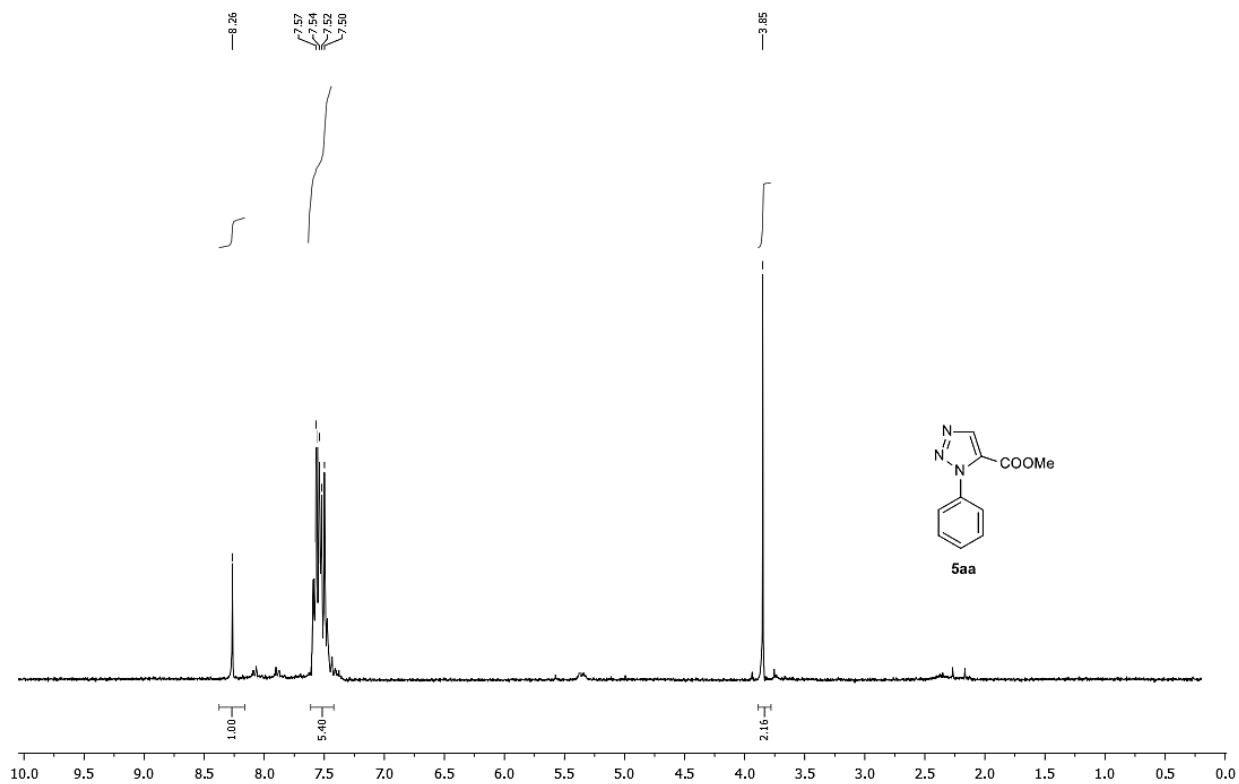
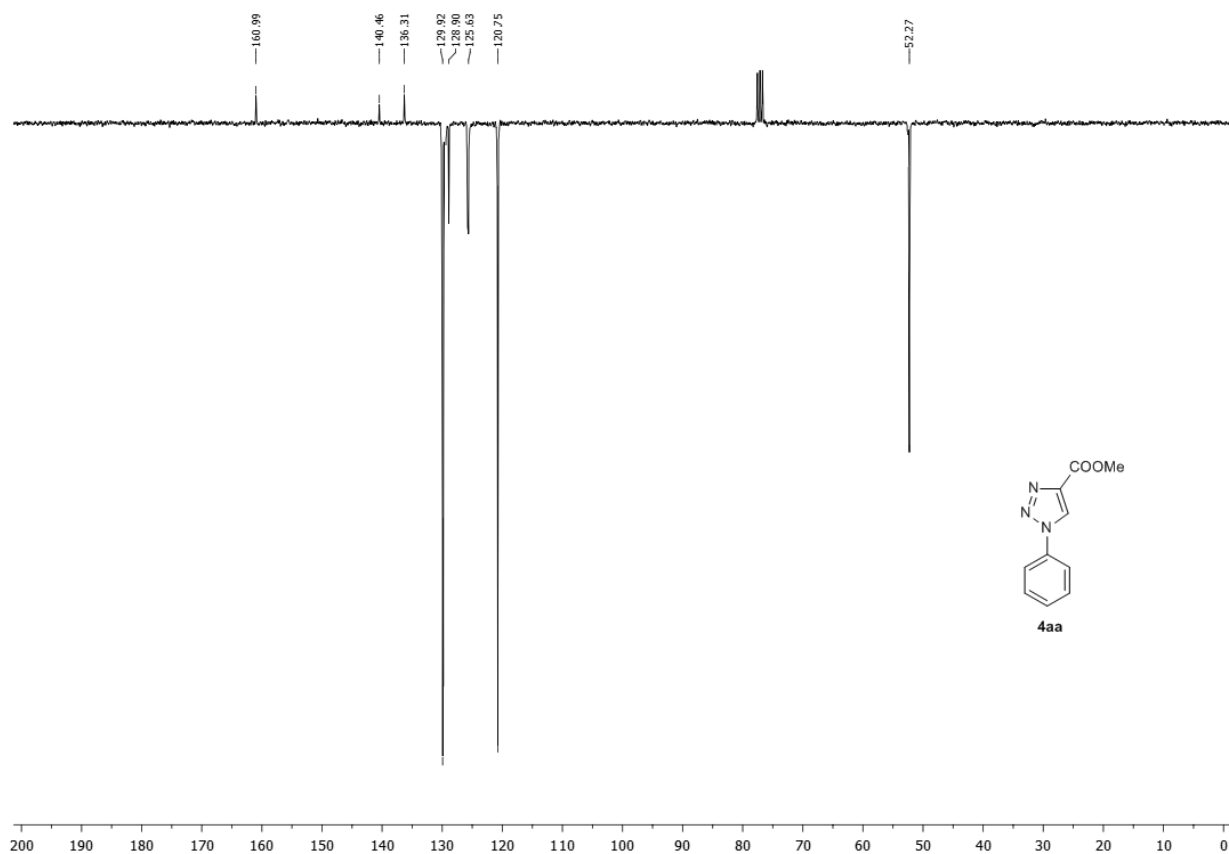
CONFLICT OF INTEREST STATEMENT

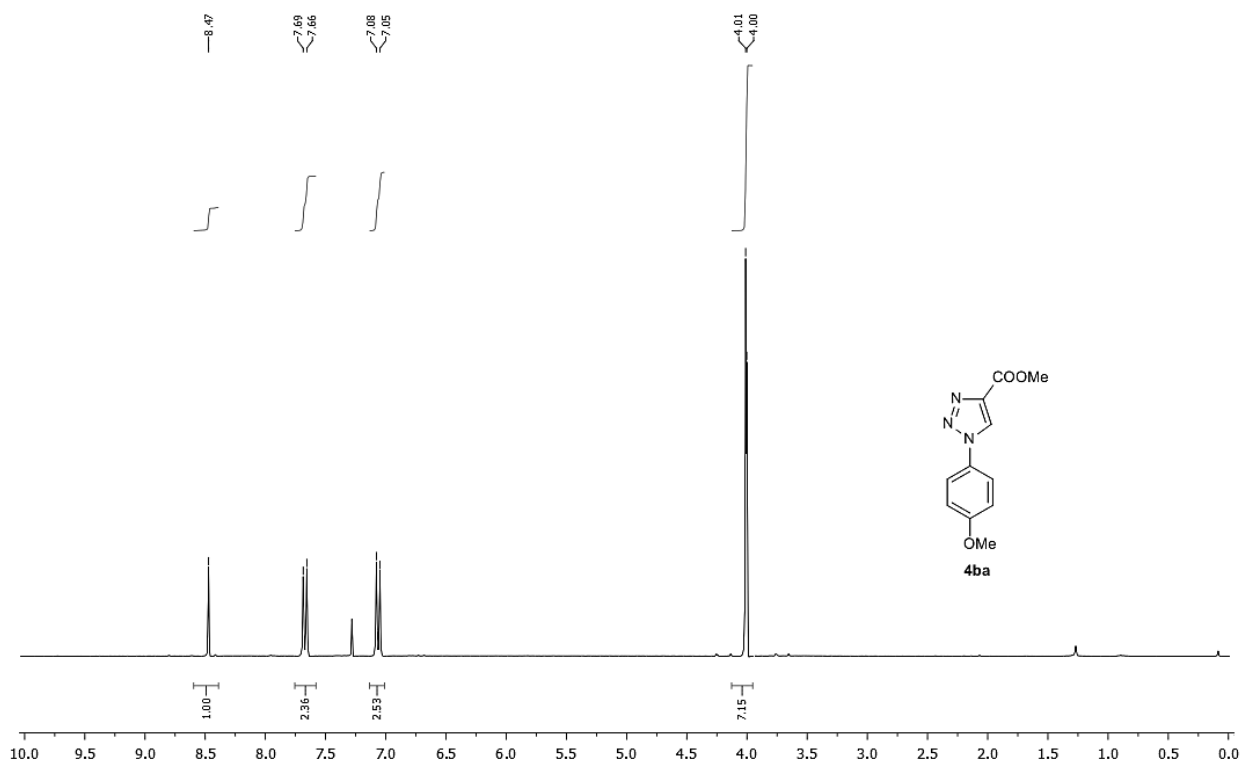
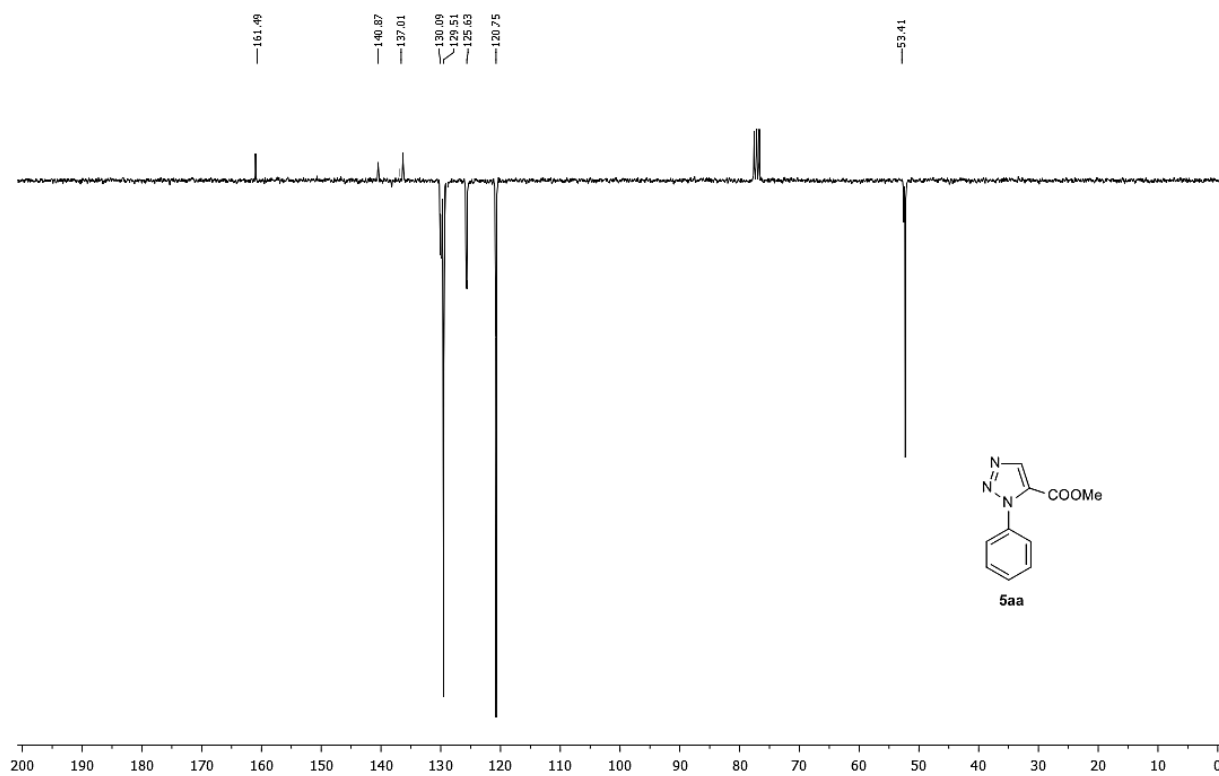
The authors declare no conflict of interest, financial or otherwise.

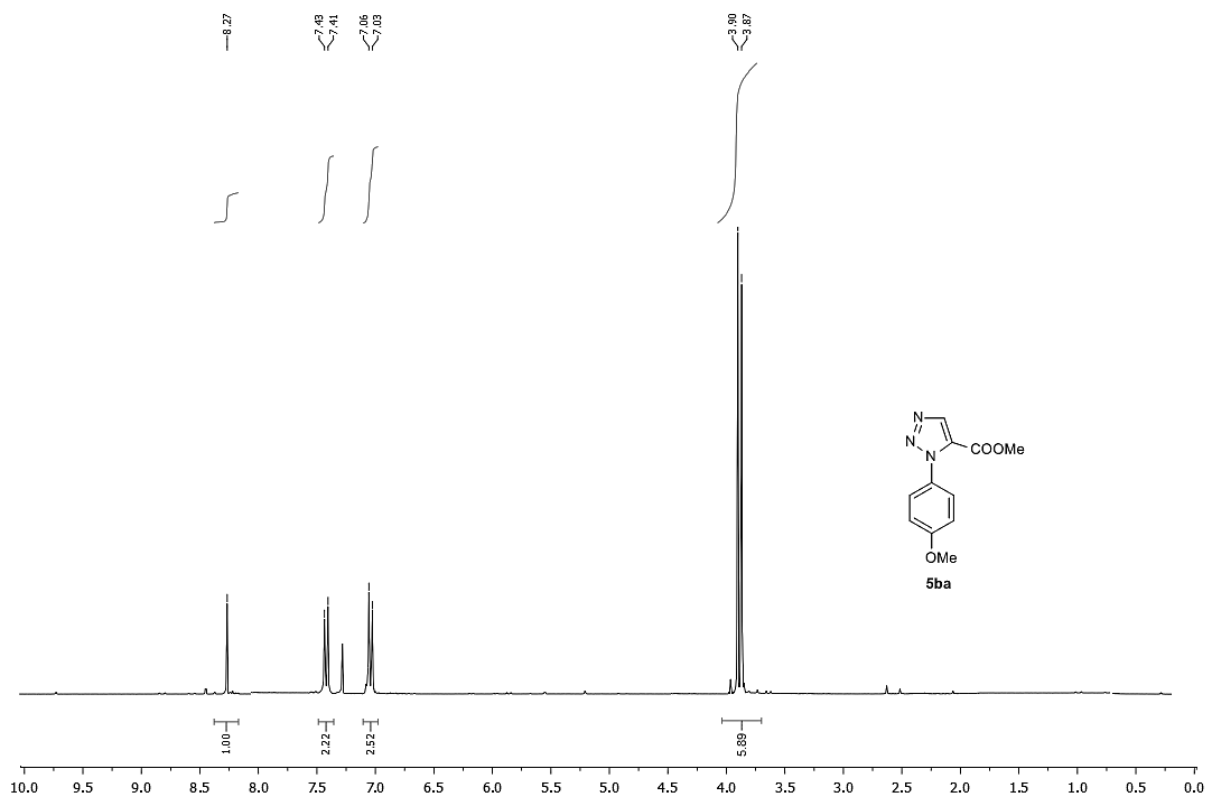
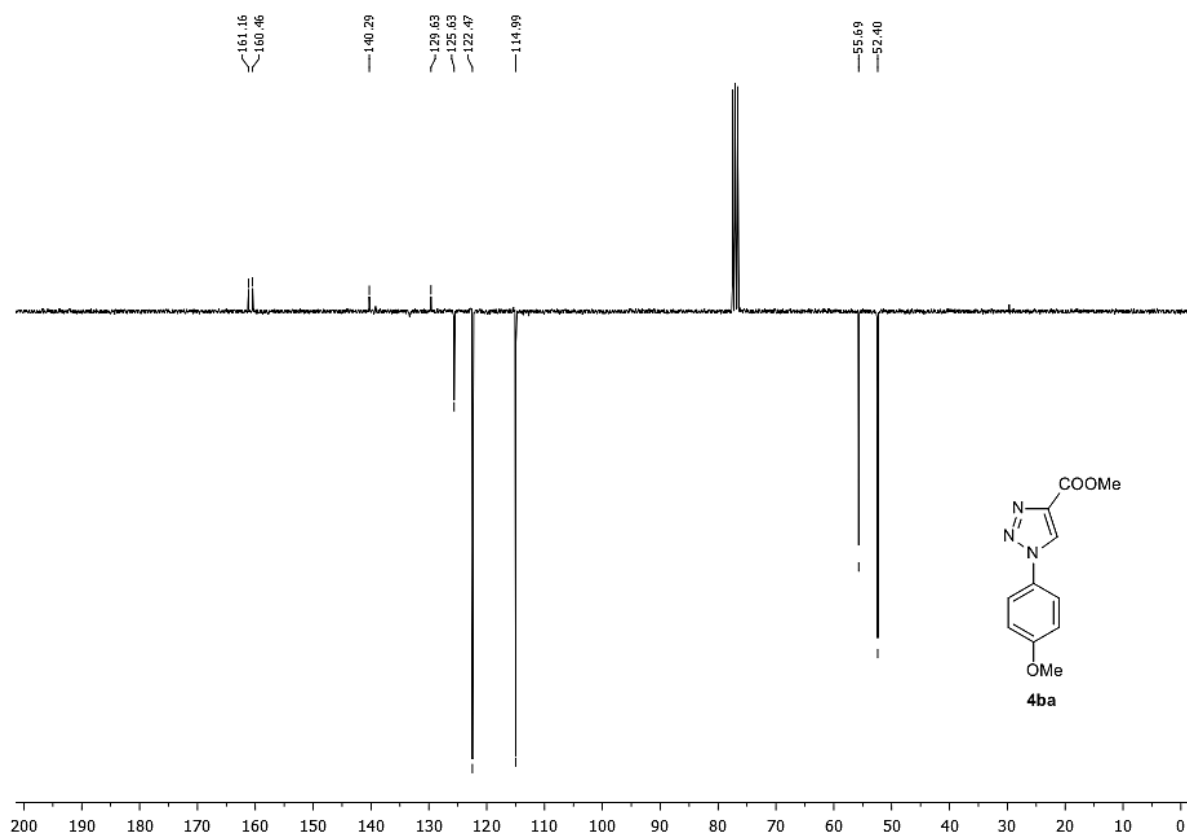
SUPPORTING INFORMATION

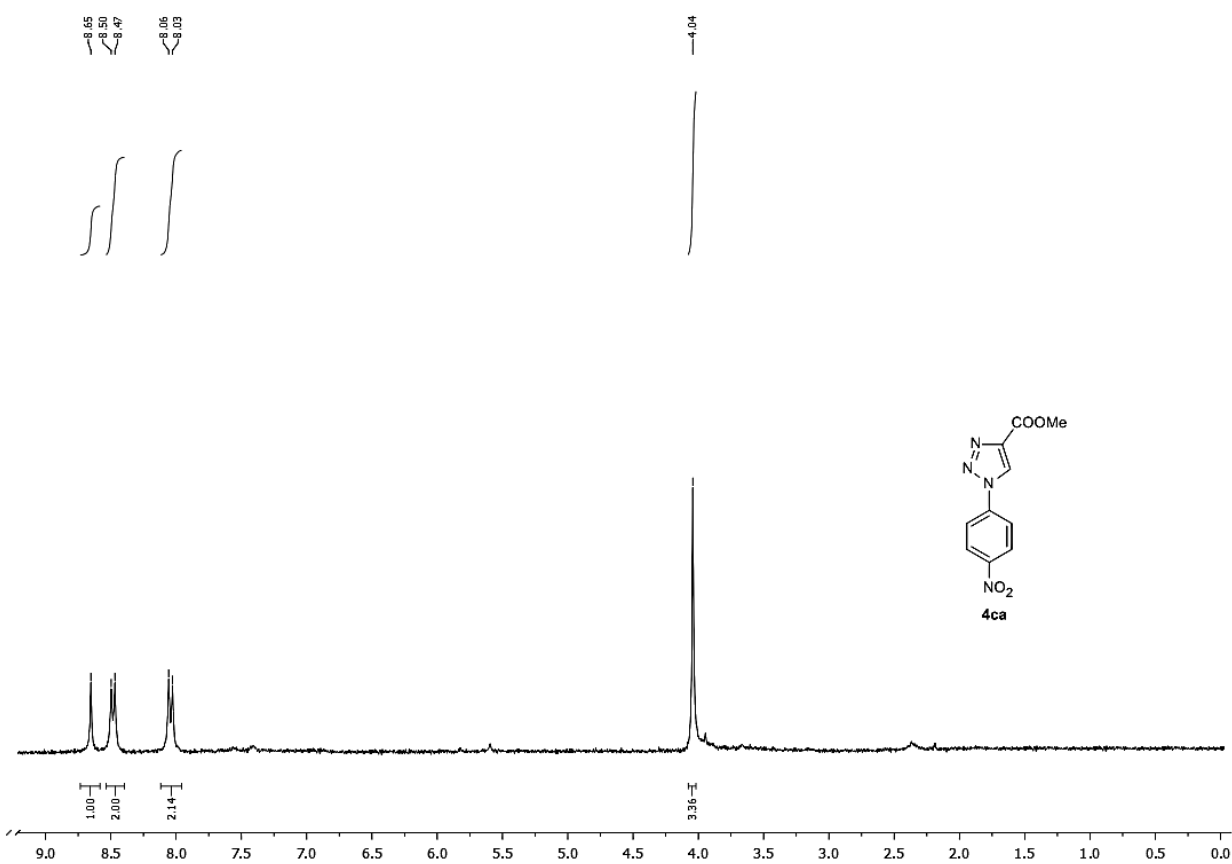
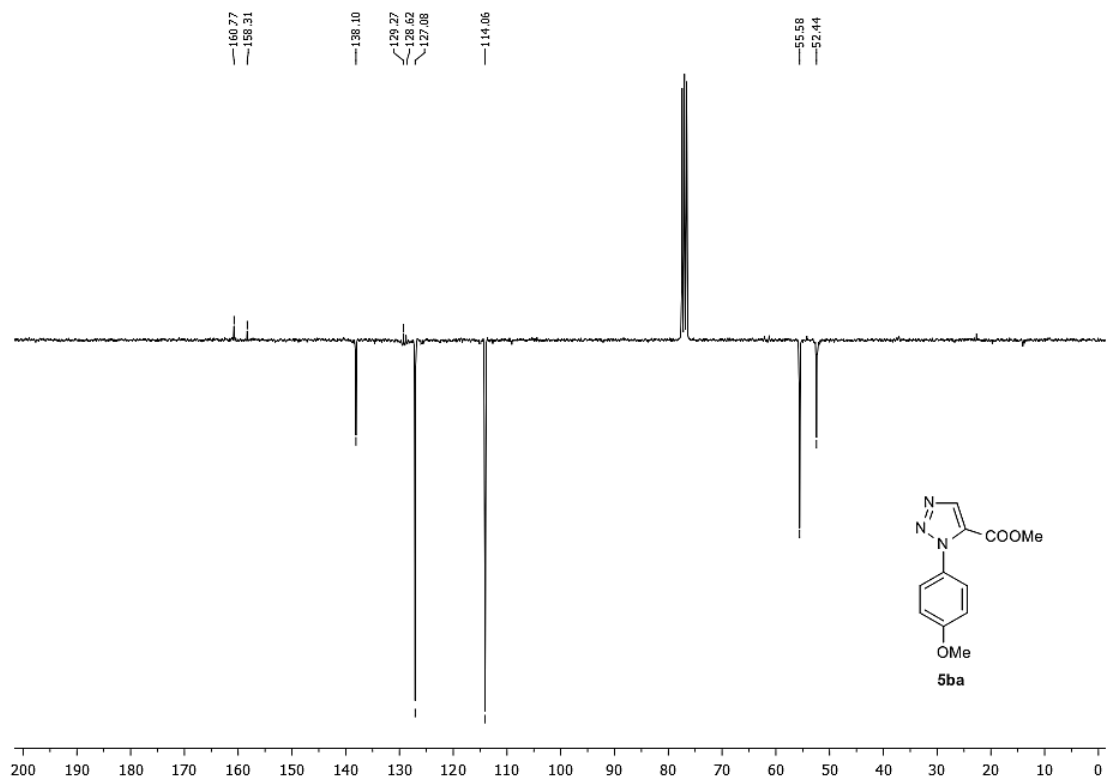
^1H and ^{13}C NMR spectra of products **4**, **5** and **6**.

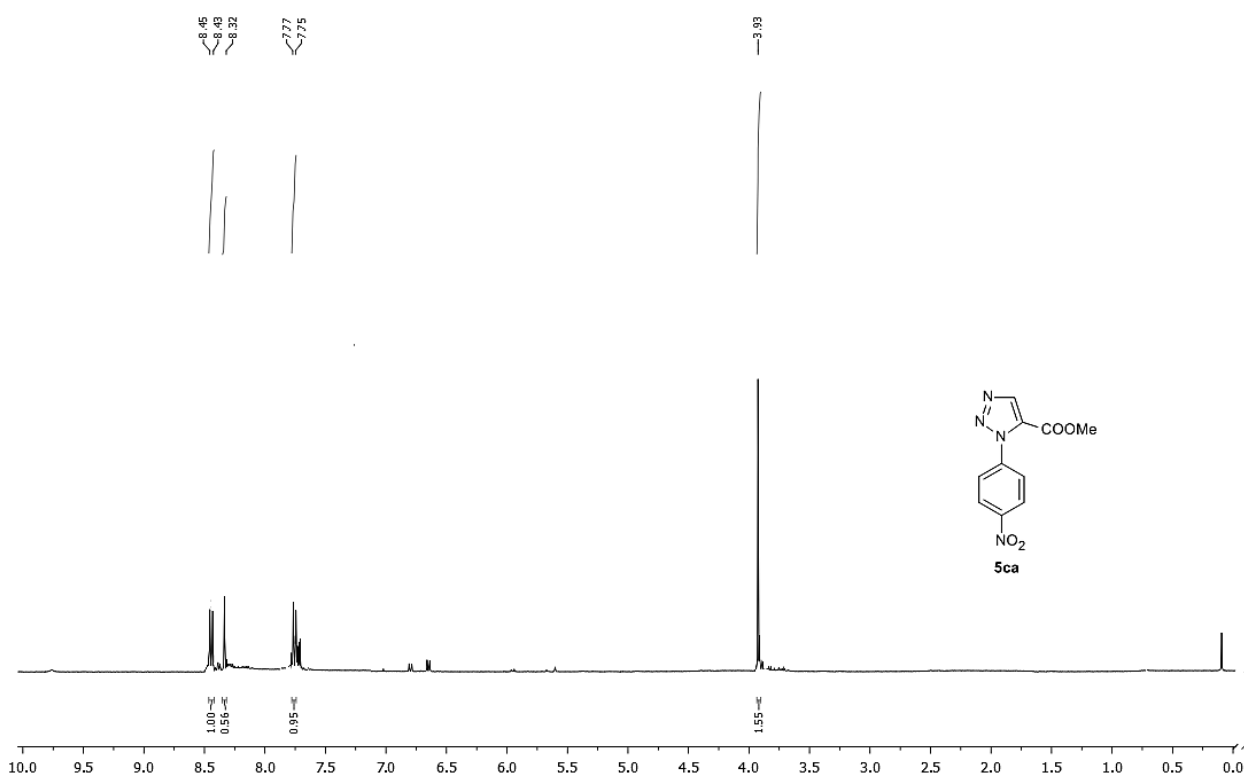
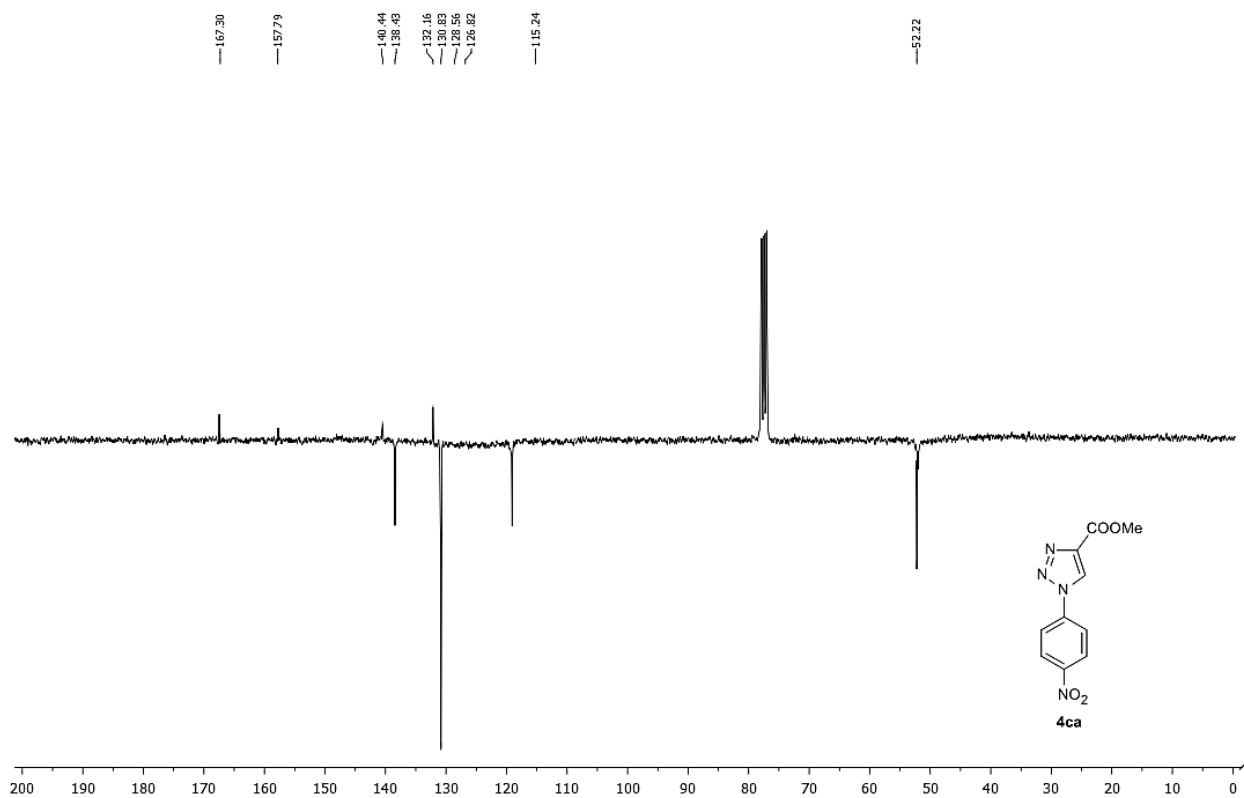


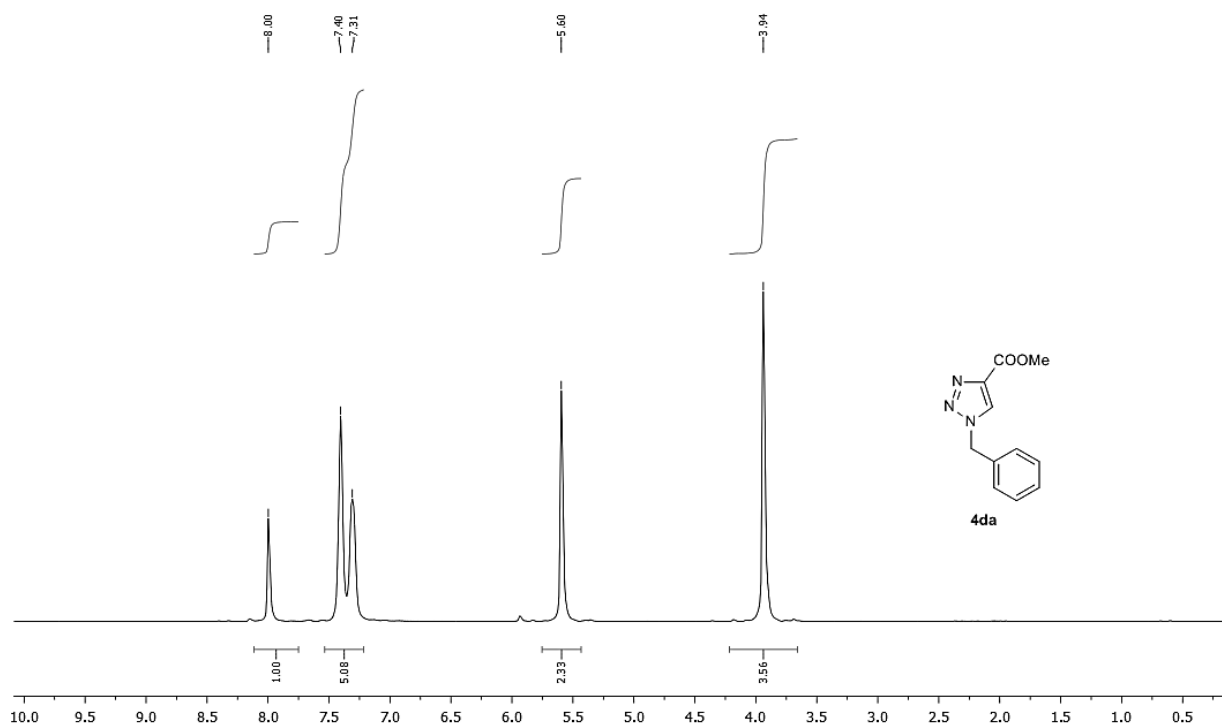
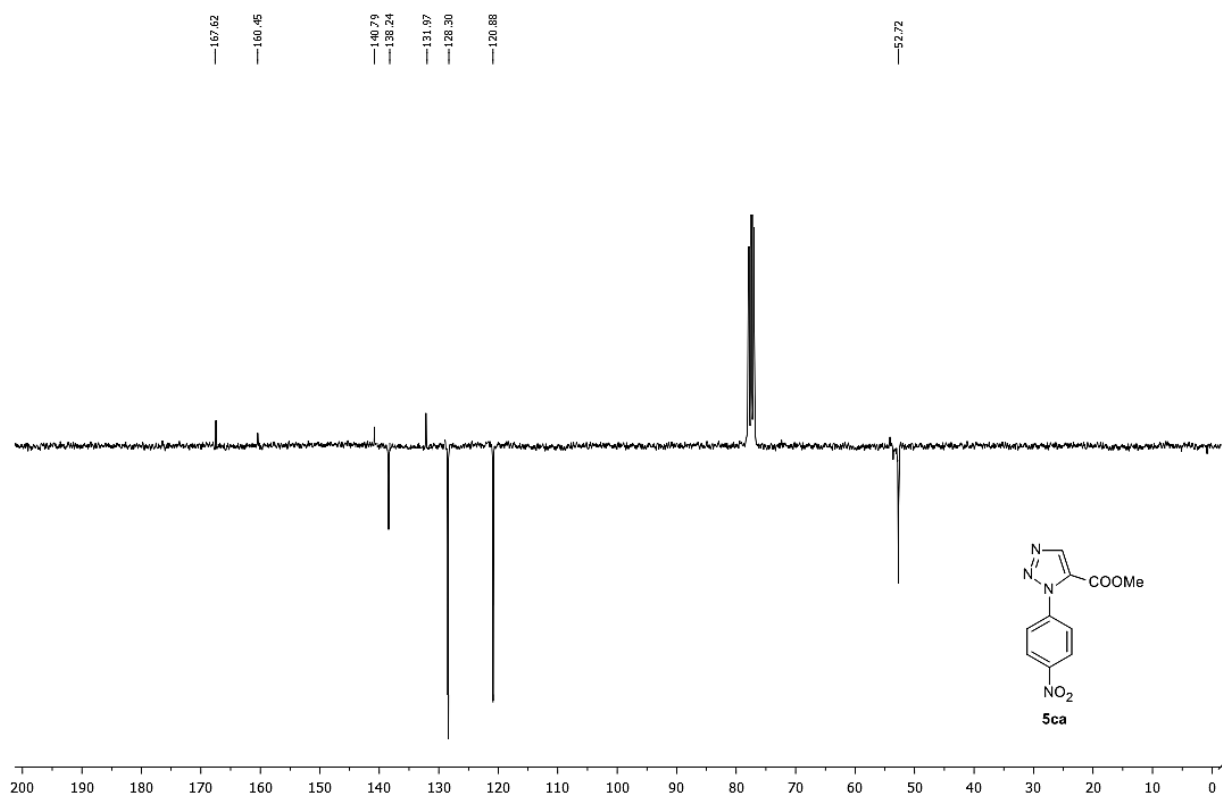


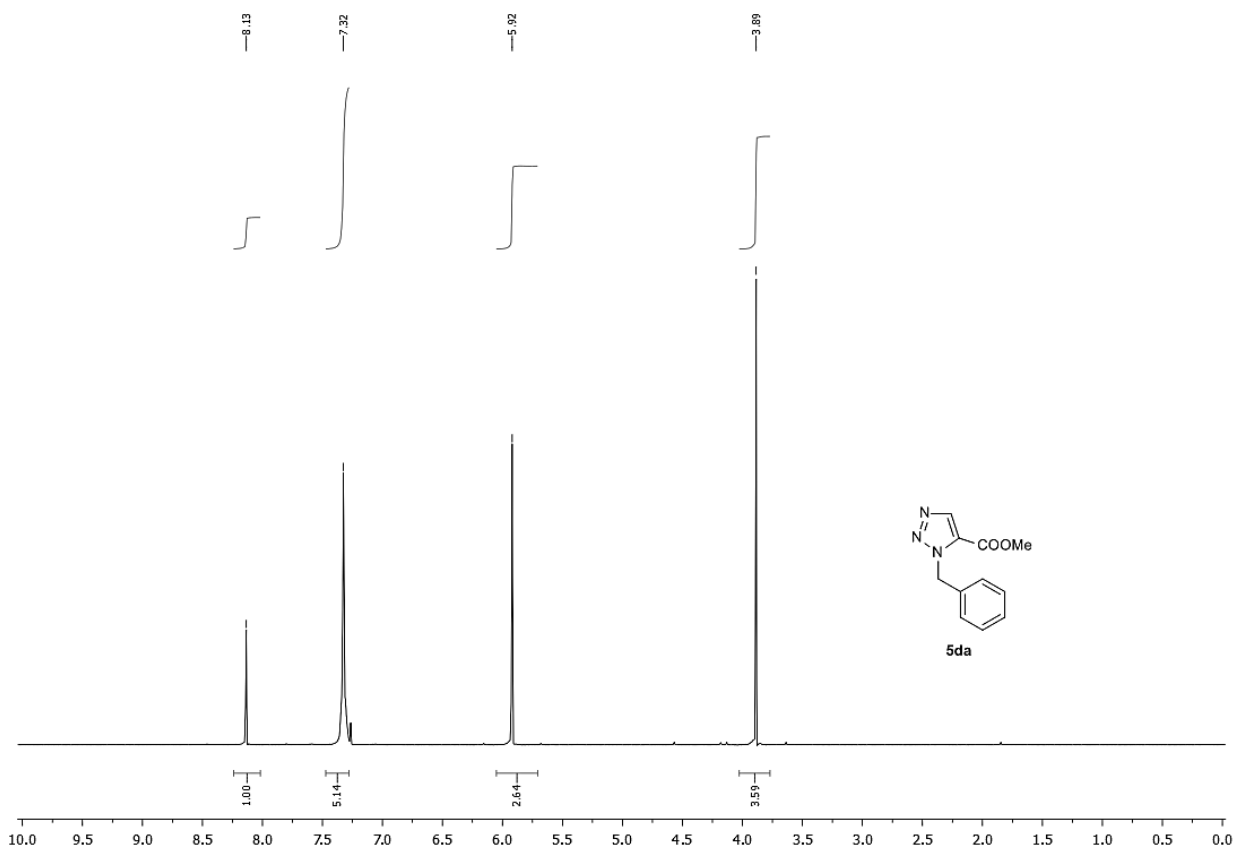
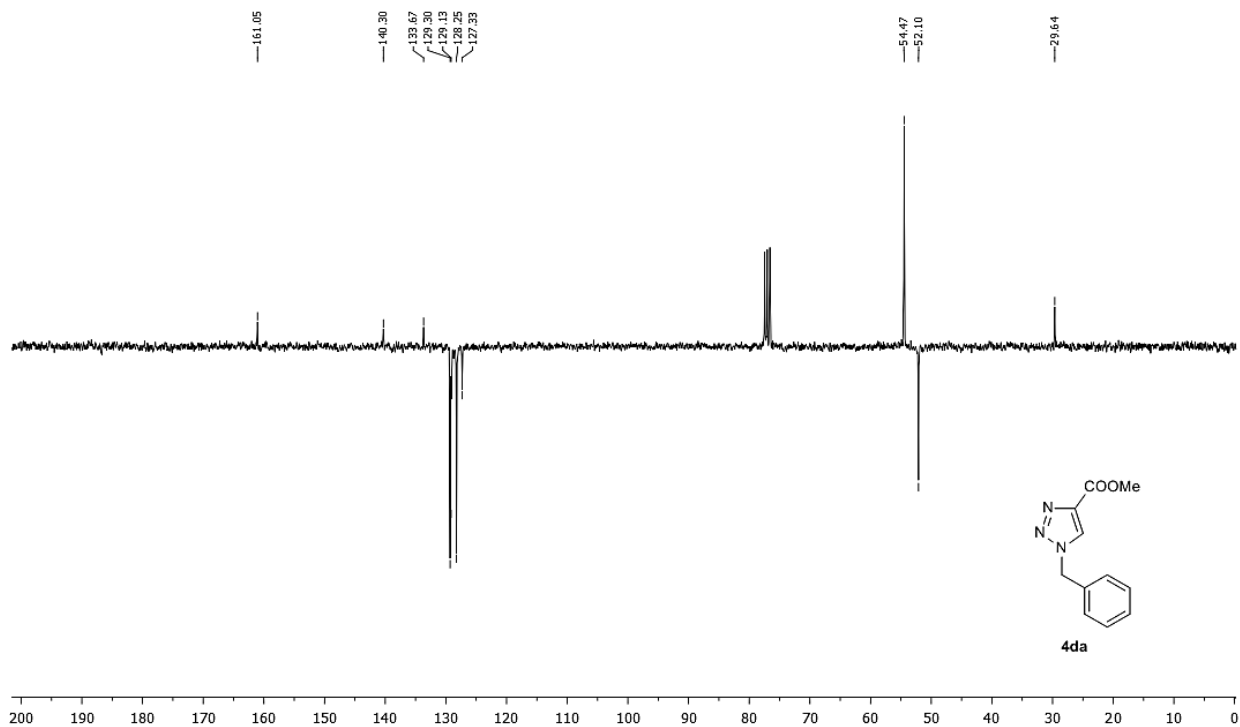


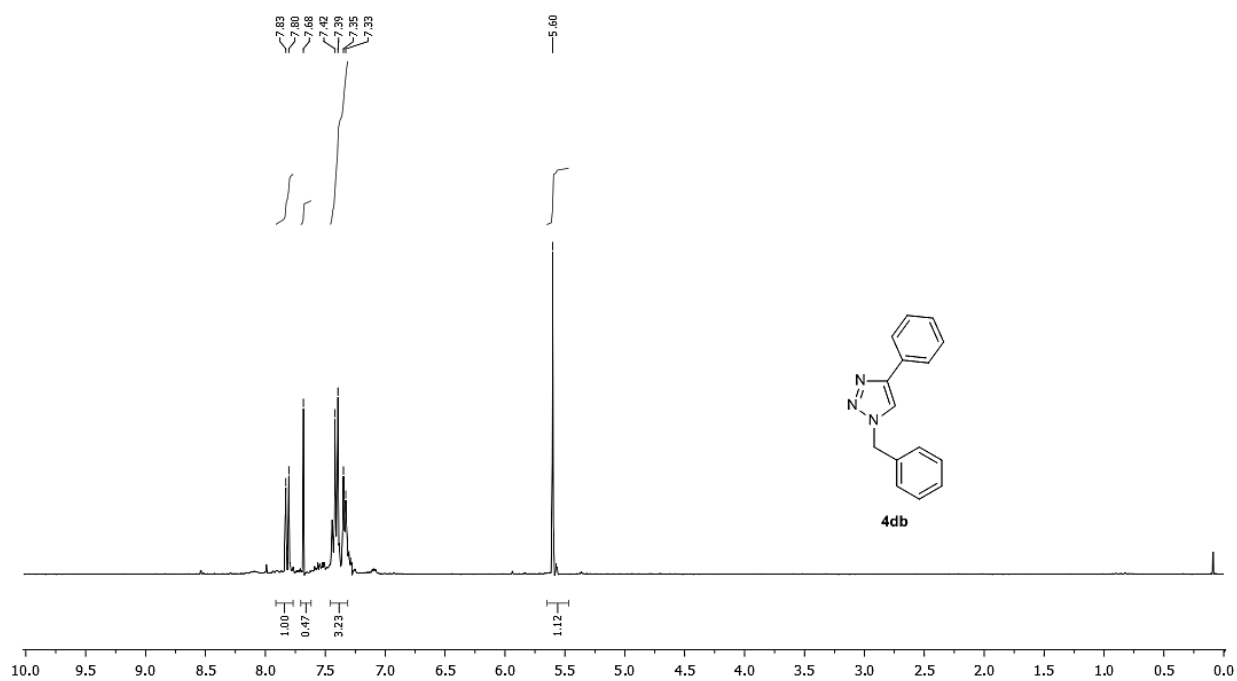
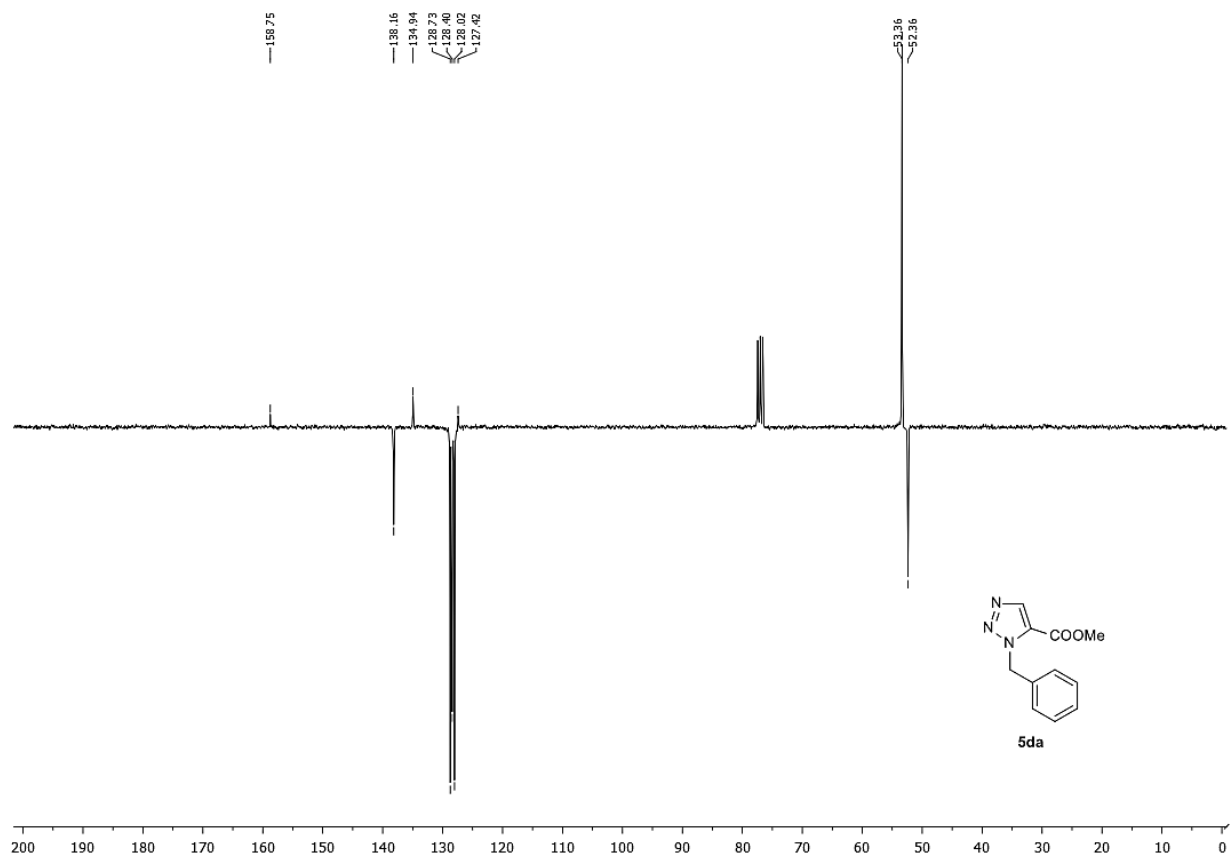


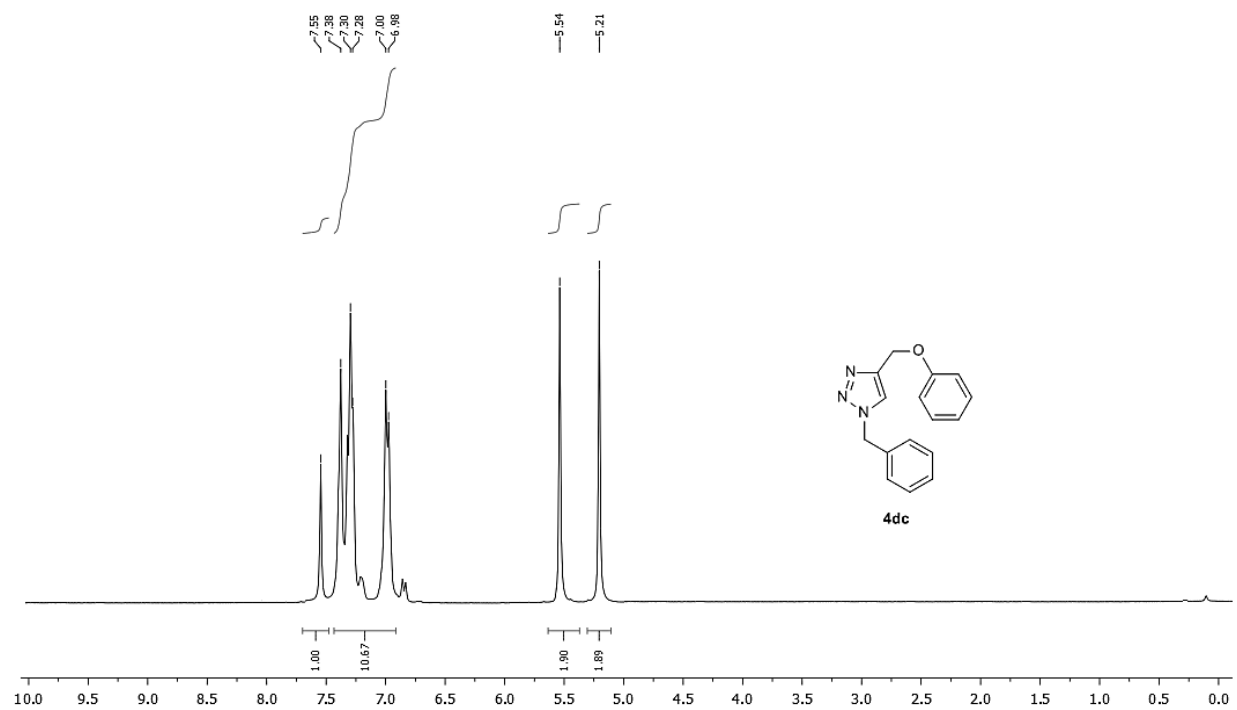
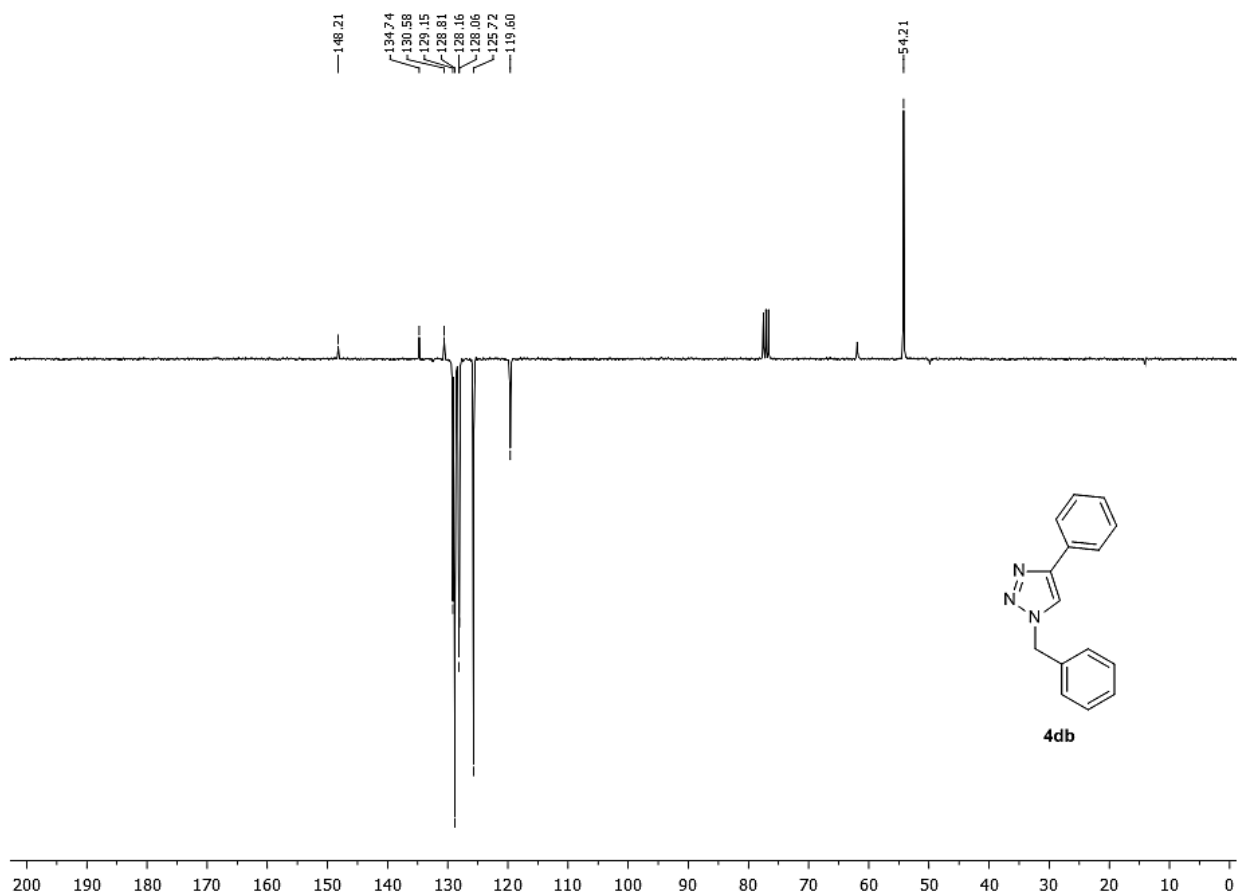


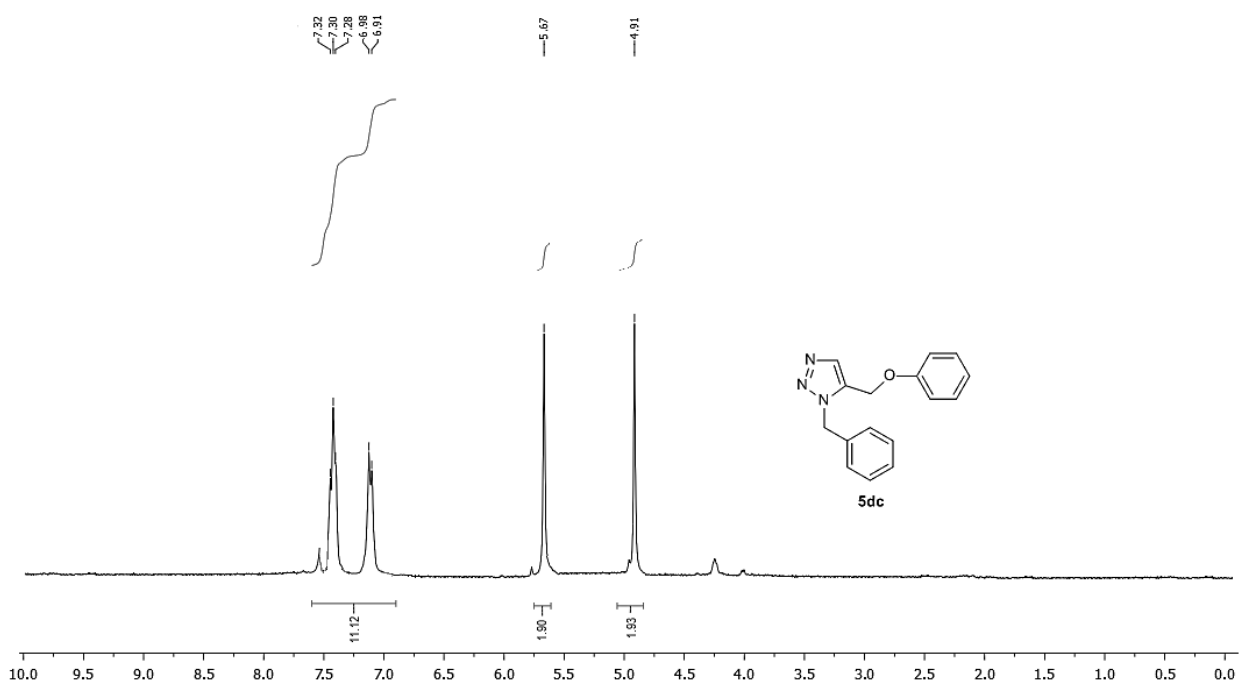
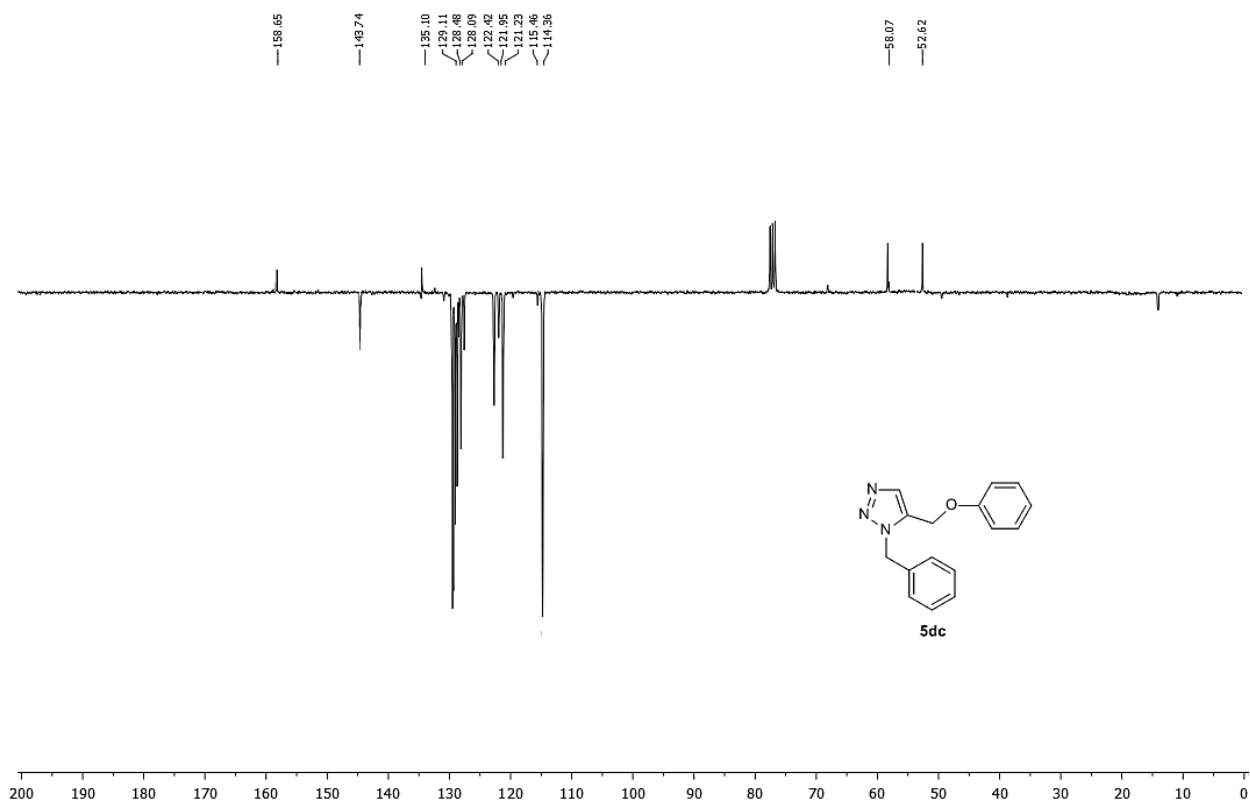


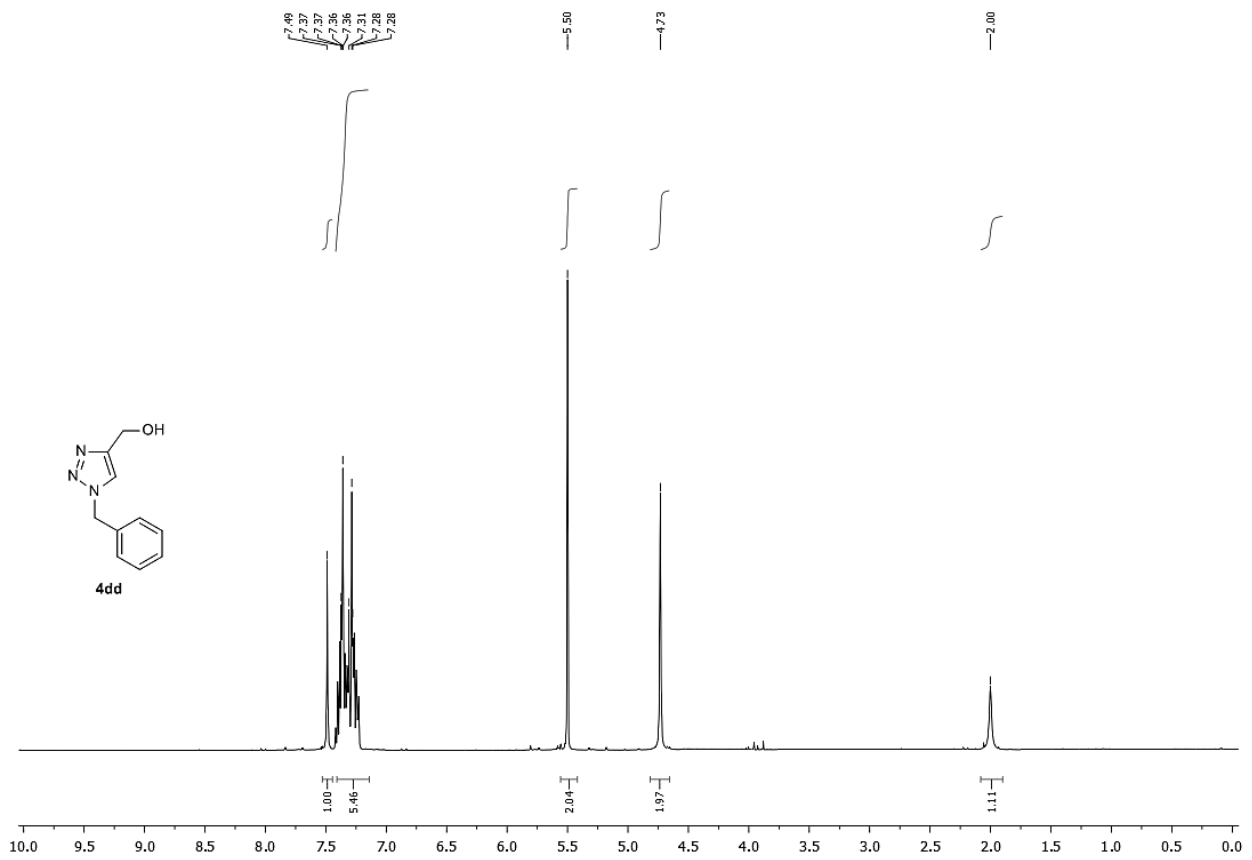
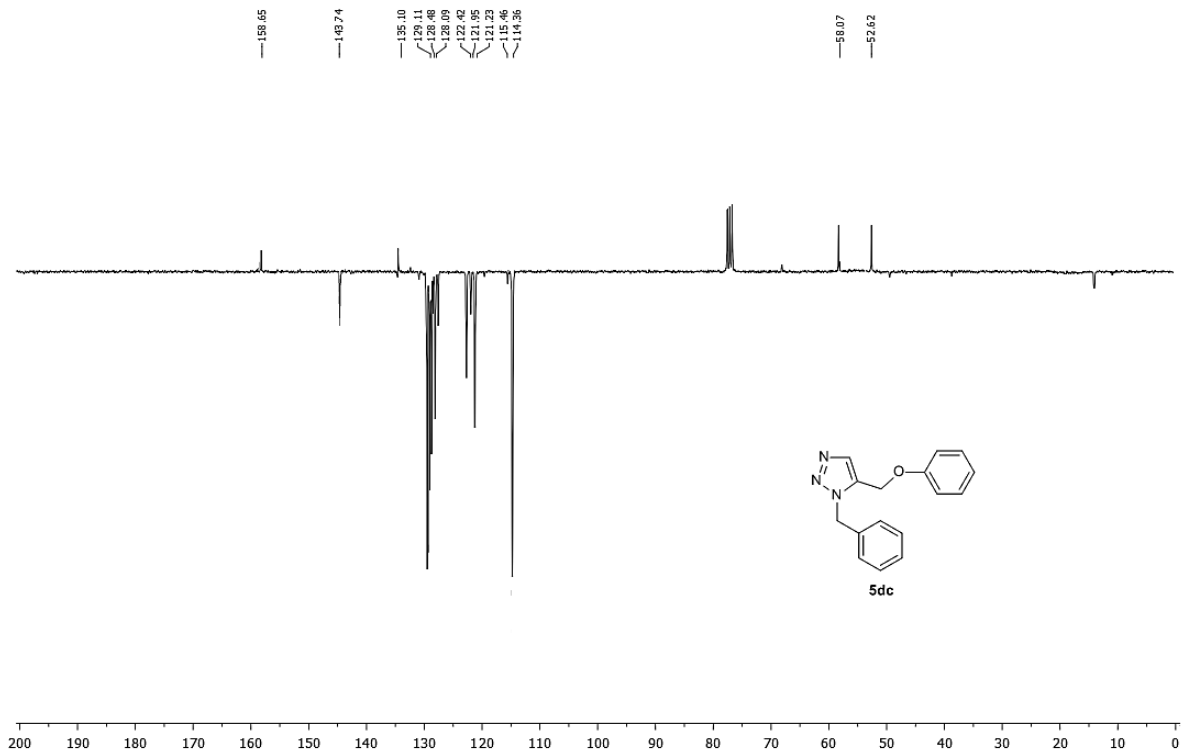


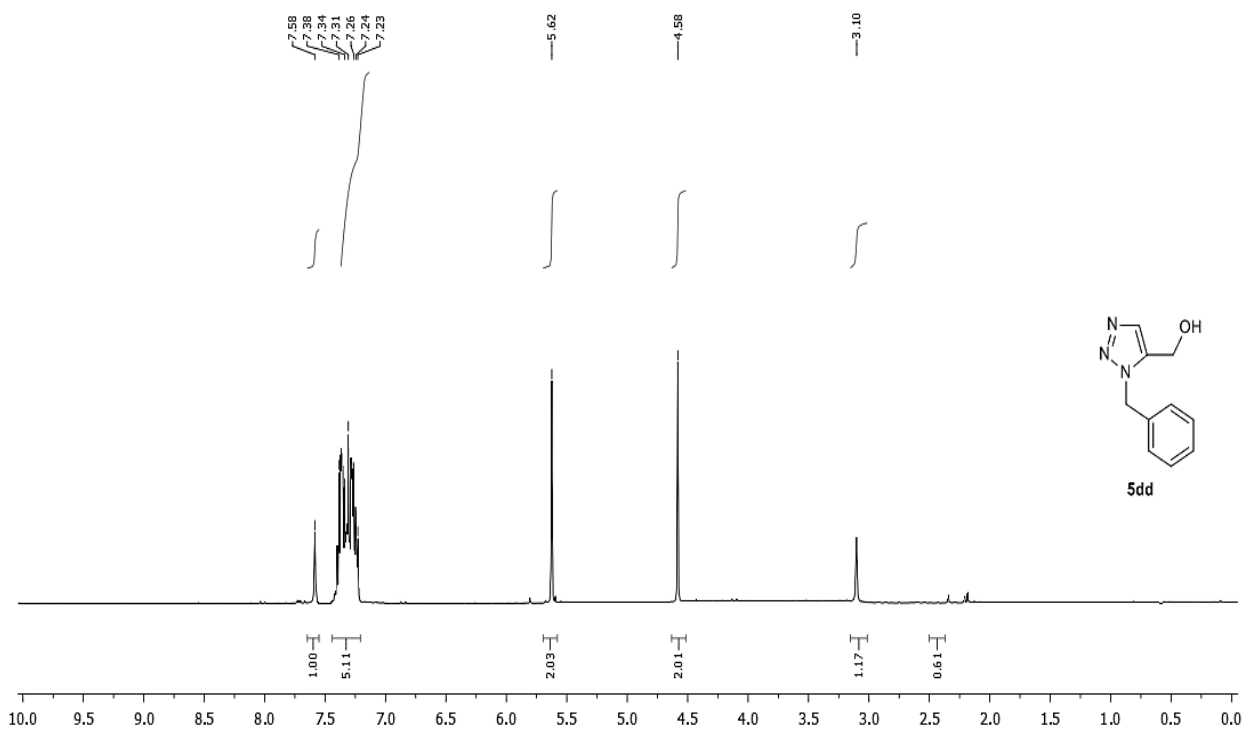
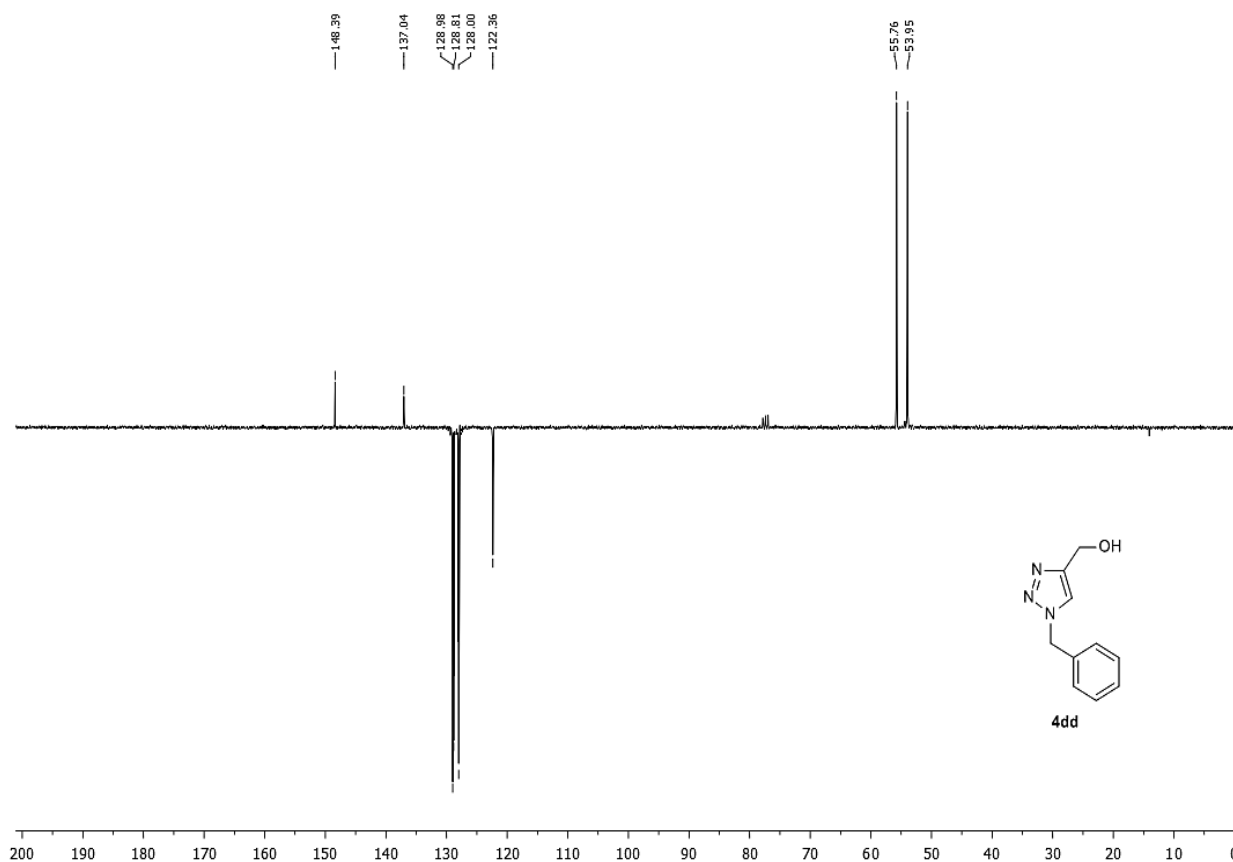


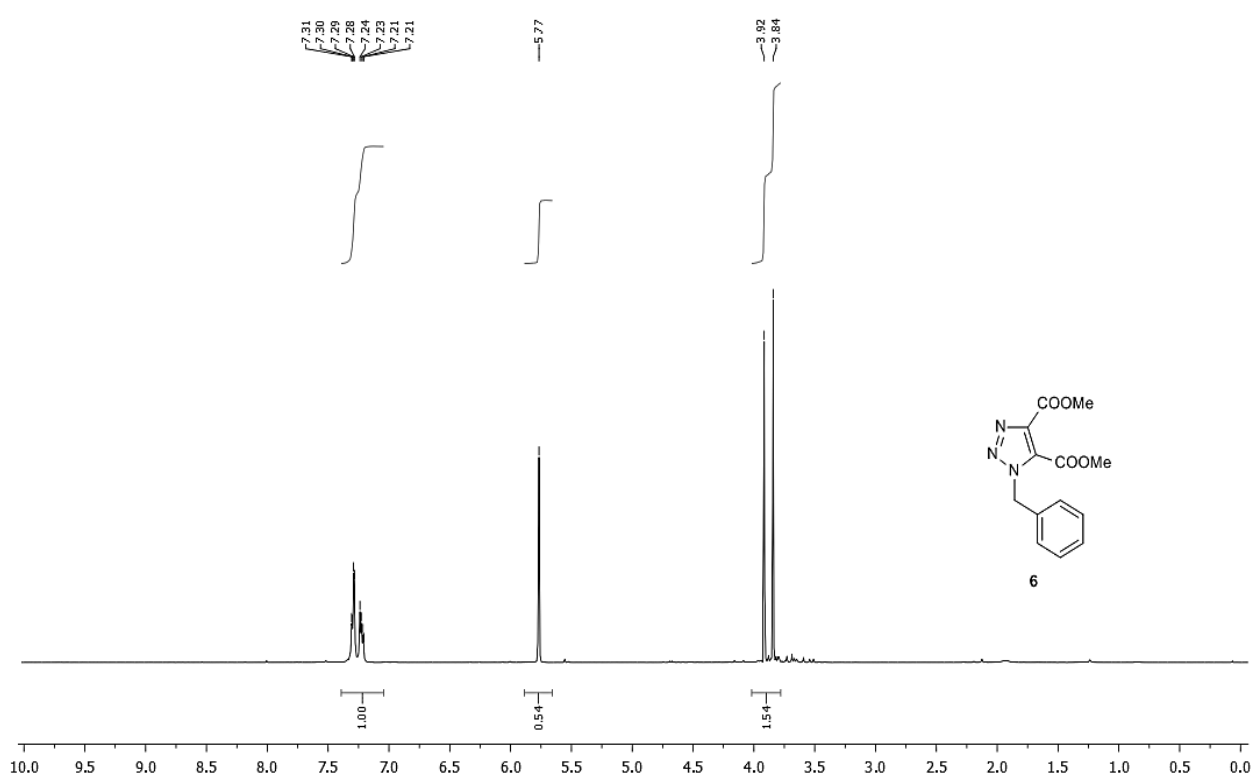
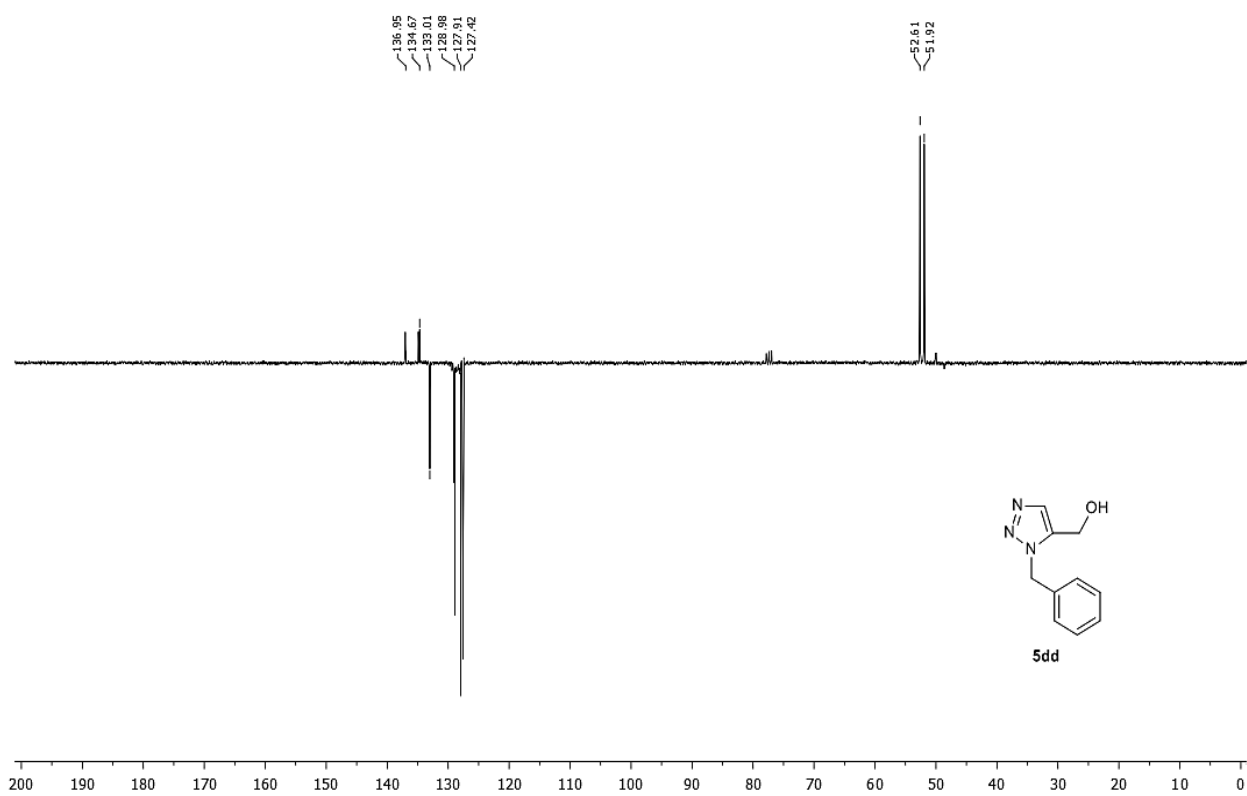


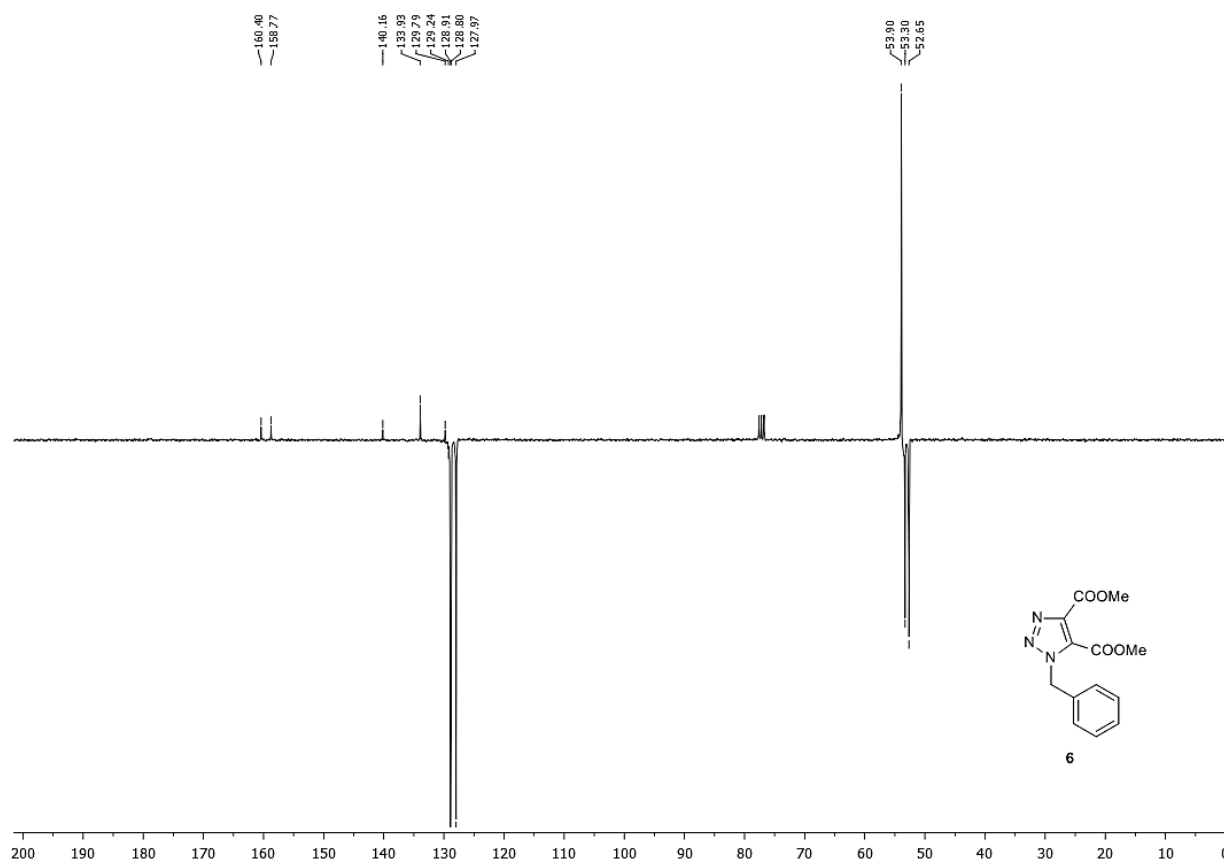












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