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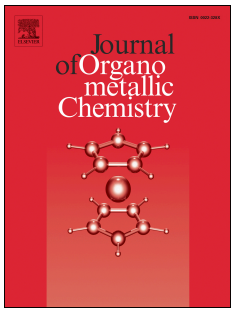

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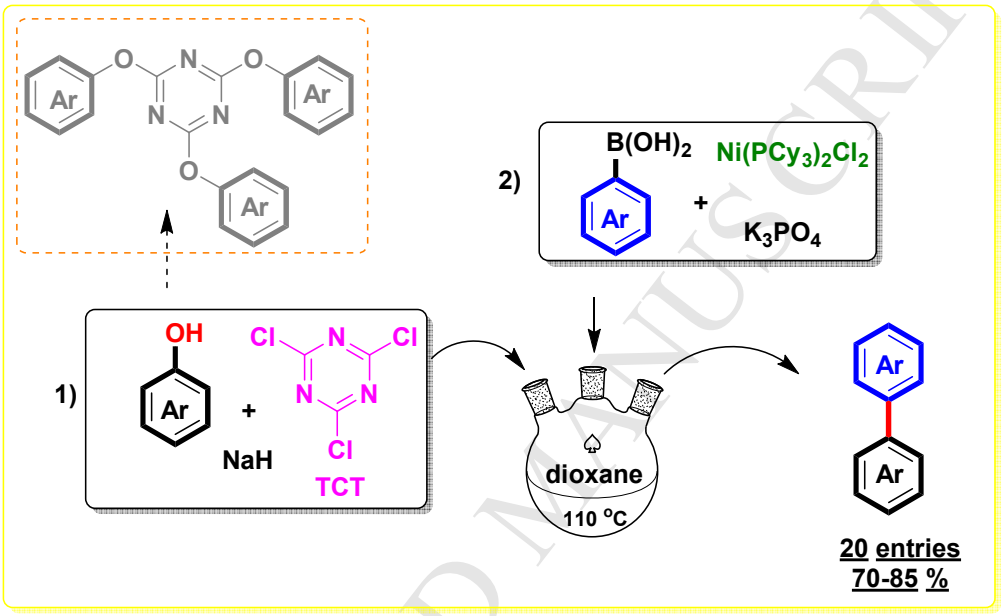

Nickel-catalyzed one-pot synthesis of biaryls from phenols and arylboronic acids *via* C-O activation using TCT reagent

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Abstract

In this study, the direct Nickel-catalyzed Suzuki-Miyaura coupling reaction of phenols and arylboronic acids via C-O bond activation using 2,4,6-trichloro-1,3,5-triazine (TCT) is described. Initially, phenols were reacted with TCT to give the corresponding 2,4,6-triaryloxy-1,3,5-triazine (TAT) products. Subsequently, arylboronic acid, base and Ni-catalyst were added to the generated aryl C-O electrophile to obtain the final biaryl product. This study represents a simple and direct method for the synthesis of biaryls from phenolic compounds using sub-stoichiometric amounts of TCT as a cheap and readily available C-O activating reagent.

Keywords: Suzuki-Miyaura reaction, Biaryl, Phenol, 2,4,6-Trichloro-1,3,5-triazine, Nickel

Introduction

Biaryls have an imperative structural motif, which exist extensively in pharmaceutical, advanced materials and natural compounds with a wide range of chemical, biological and physical applications [1]. Transition metal-catalyzed Suzuki−Miyaura reactions have been known as a potent and essential method for the synthesis of this class of compounds [2]. At the

present, the Suzuki–Miyaura coupling has been well developed and is currently one of the efficient methodologies for the synthesis of biaryls in both laboratory and industry [3].

In the recent years, remarkable progress has also been developed to use phenolic compounds in the cross-coupling reactions instead of aryl halides due to the higher diversity, abundance, and availability of these materials [4]. The most used aryl C-O electrophiles are ethers,[5] carboxylates,[6] carbamates,[7] carbonate,[8,7c] phosphoramides,[9] phosphonium salts,[10] phosphates,[11] pivalates,[6b] sulfamates,[12,7c] tosylates,[13] mesylates[14,12b] and heteroaryl ethers [15].

In the most cases, phenolic compounds were first converted to the corresponding aryl C-O electrophiles and then used in metal-catalyzed reaction. Recently, the *in situ* activation of phenols has emerged as an attractive approach for Ni-catalyzed cross-coupling reactions (Scheme 1) [16].

Scheme 1

Scheme 1. Activation of phenolic compounds for the *in situ* generation of aryl C-O electrophiles to use in metal-catalyzed C-C bond formation reactions

The *in situ* phenol activation strategy provides important advantages over previous methods including, single step operation, efficiency, economy, and environmental impact [16]. Considering the aforementioned points, we decided to use an efficient reagent which can easily react with phenols to convert them into an active aryl C-O electrophile for participation in metal-catalyzed coupling reactions.

In our previous studies, we reported that 2,4,6-trichloro-1,3,5-triazine (TCT) is an efficient C-O activating reagent and by the use of this reagent, phenolic compounds were converted directly to their corresponding amines, arenes, and symmetrical biphenyls [17]. In continuation of this study, we would like to introduce an efficient method for direct Ni-catalyzed Suzuki-Miyaura coupling of phenols using TCT regent. In the course of our study, we found that Li *et al*. has used 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT, **B**) for the activation of phenolic compounds in the synthesis of biaryls (Scheme 2) [15].

Scheme 2

Scheme 2. The use of heteroaryl ethers (**C**) for synthesis of biaryls starting from TCT in a three-step process

As shown in Scheme 2, TCT reagent is the starting material for activation of phenolic compounds, but this method is a three step process. First, TCT was converted to CDMT and then reacted with phenol in order to generate aryl C-O electrophile (**C**). Finally, C reacts with aryl boronic acid to give biaryl. On the other hand, activation of one equivalent of phenol is achieved by one equivalent of TCT. Herein, we disclose a direct Ni-catalyzed Suzuki–Miyaura coupling of phenols and arylboronic acids via C–O activation using TCT reagent. In this method, activation of phenols using TCT is a one-pot process and one equivalent of TCT is used for activation of three equivalents of phenol, avoiding pre-activation steps and using sub-stoichiometric amounts of TCT.

Results and Discussion

The applied conditions for the synthesis of 2,4,6-tris(*p*-aryloxy)-1,3,5-triazine (TAT) are based on our previous method [17]. The *in situ* generated TAT was used in the cross-coupling with

arylboronic acids for the synthesis of biaryls. To survey the possibility of direct Suzuki–Miyaura coupling reaction via C-O bond activation using TCT reagent, *p*-cresol (**1a**) and phenylboronic acid (**2a**) was selected as model substrates for optimization study. The obtained results are summarized in Table 1.

Table 1

Table 1. Optimization of the conditions for the coupling of *p*-cresol and phenylboronic acid using TCT as a C-O activating agent [a]

The reaction of *p*-cresol and phenylboronic acid in 1,4-dioxane using $NiCl_2.5H_2O$ as catalyst and K_3PO_4 as a base resulted no product (Table 1, entry 1). The reactivity of $Ni(PPh_3)_2Cl_2$ as catalyst having a monodentate ligand was evaluated and only 40% of the product was obtained (Table 1, entry 2). The yield was enhanced to 85% when $Ni(PCy_3)_2Cl_2$ was used as catalyst (Table 1, entry 3). Catalysts having bidentate ligands such as $NiCl_2$(dppe), $NiCl_2$(dppp), and $NiCl_2$(dppf) were also tested, but no superiority was observed (Table 1, entries 4-6) [18].

Among the used bases and solvents, K_3PO_4 was found as the most suitable base [19] and 1,4-dioxane as the preferred solvent (Table 1, entries 7-12). Also, 7.5 mol% of $Ni(PCy_3)_2Cl_2$, 4 equiv. of K_3PO_4 and 3 equiv. of phenylboronic were found to be the optimum amounts of the catalyst, base and coupling partner respectively (Table 1, entries 13-17).

Consequently, we selected the optimum conditions for the preparation of other biaryl compounds starting from commercially accessible phenols and arylboronic acids (Scheme 3).

Scheme 3

Scheme 3. Cross-coupling of different phenolic derivatives with arylboronic acids. Reaction conditions: Phenol (1 mmol), boronic acid (3 mmol), K_3PO_4 (4 mmol), 1,4-dioxane (5 mL), under argon gas and reaction time = 24h. All yields are isolated products.

As shown in Scheme 3, various phenols and boronic acids were surveyed. Both electron-rich (**3a** & **3b**) and electron-poor phenols (**3c** & **3d**) furnished excellent yields of the corresponding products. Isovanilline as a naturally occurring phenol with two functional groups (OMe and CHO) was also used as a phenolic partner and compound **3e** was obtained in 82% yield. 4-Fluorophenol was used as substrate and 4-fluoro-1,1'-biphenyl compound (**3f**) was obtained in 84% yield, demonstrating that carbon-fluorine bond is robust under our optimized conditions [3c]. Due to the interaction of heteroatoms in heteroaryl compounds with metal catalysts and the low reported yields in many catalytic systems,[20] we decided to synthesize compounds **3g-l** from phenolic substrates in order to show the merit and applicability of our synthetic approach in synthesis of this category of compounds. Since, naphthalene structural units are widely used in designing of the advanced material for application in organic electronic devices,[21] we also synthesized compounds **3m-o** from naphthols in good yields. The functional group compatibility of the reaction was highlighted by the synthesis of compound **3p** as a xanthene product (Scheme 4) [22].

Scheme 4

Scheme 4. Synthesis of a xanthene-based biaryl. Reaction conditions: phenolic compound (1 mmol), thiophen-2-ylboronic acid (3 mmol), K_3PO_4 (4 mmol), 1,4-dioxane (5 mL), under argon gas, reaction time = 24h. Yields are isolated products.

The structural diversity of this process was further established using estrone leading to the formation of the steroid derivative **3r** (Scheme 5).

Scheme 5

Scheme 5. Synthesis of a steroid derivative from estrone and phenyl boronic acid. Reaction conditions: phenolic compound (1 mmol), phenyl boronic acid (3 mmol), K_3PO_4 (4 mmol), 1,4-dioxane (5 mL), under argon gas, reaction time = 24h. Yields are isolated product.

We also proposed a plausible mechanism for this reaction as shown in Scheme 6. Some experiments were conducted to obtain a deeper insight into the reaction mechanism (Scheme 7). In an experiment, under the optimized conditions, **4a** was converted to **3a**, demonstrating that the generated TAT during the reaction process acts as aryl C-O electrophile (Scheme 7). When 1,3,5-tris(*p*-tolyloxy)benzene (**5a**) was used instead of 2,4,6-tris(*p*-tolyloxy)-1,3,5-triazine (**4a**) no product was obtained (Scheme 7). This experiment clarifies that the *ortho* nitrogen atom in the structure of TCT has important role in the activation of C-O bond. Accordingly, it seems that Ni catalyst coordinates first with the *ortho* nitrogen atom of TAT and this action facilities the oxidative addition of Ni to C-O bond (steps **I-III**). After transmetalation (step **IV**), and reductive elimination (step **V**), the desired product is obtained (Scheme 2). The catalytic reaction cycle is essentially similar to the general Ni-catalyzed cross-coupling mechanism for aryl halides and boronic acids [23].

Scheme 6

Scheme 6. The proposed mechanism for direct Ni-catalyzed cross-coupling of phenols with arylboronic acids using TCT reagent

Scheme 7

Scheme 7. An experiment to show the role of *ortho* nitrogen atom in the structure of TCT in activation of C-O bond. Reaction conditions: **4a** or **5a** (0.34 mmol), phenylboronic acid (3 mmol), K_3PO_4 (4 mmol), 1,4-dioxane (5 mL), under argon gas, reaction time = 24h and isolated yield.

Conclusions

In conclusion, we have exposed the direct Nickel-catalyzed cross-coupling reaction of phenol derivatives with arylboronic acids mediated by TCT reagent. The protocol carried out efficiently with a variety of substrates to give the corresponding products in high yields. This study suggests that TCT as a cheap, readily available and efficient reagent could find valuable synthetic applications for other coupling reactions in the future.

Experimental Section

General Experimental Details

Chemicals were purchased from Fluka and Aldrich chemical companies and used without further purification. The known products were characterized by comparison of their spectral and physical data with those reported in the literature. ^{1}H (250 MHz) and ^{13}C NMR (62.9 MHz) spectra were recorded on a Bruker Advance spectrometer in $CDCl_3$ solutions with tetramethylsilane (TMS) as the internal standard. FT-IR spectroscopy (Shimadzu FT-IR 8300 spectrophotometer) was employed for characterization of the products. Melting points were determined in open capillary tubes in a Barnstead electro-thermal 9100 BZ circulating oil melting point apparatus. The reaction monitoring was accomplished by TLC on silica gel

PolyGram SILG/UV254 plates. Column chromatography was carried out on columns of silica gel 60 (70-230 mesh).

General procedure for direct Ni-catalyzed cross-coupling of phenols and arylboronic acids mediated by TCT reagent

Into a conical three-necked flask (50 mL), a mixture of phenol (1 mmol), and NaH (1.5 mmol) were stirred in dry 1,4-dioxane (10 mL) for 1h at room temperature. Then 0.37 mmol of TCT was added to the reaction media and let stirring continue for another hour. Afterward the reaction mixture was stirred at 110 °C for 10h. Then arylboronic acid (3 mmol), $Ni(PCy_3)_2Cl_2$ (7.5 mol%), and K_3PO_4 (4.0 mmol) was added to the reaction mixture under argon gas. The mixture was stirred for another 24h. After completion of the reaction confirmed by TLC the reaction mixture was cooled down to room temperature and 50 mL of CH_2Cl_2 and 50 mL of water were added. After the extraction of dichloromethane from water, the organic extract was dried over Na_2SO_4. The products were purified by column chromatography (hexane/ethyl acetate) to obtain the desired purity.

Acknowledgements

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Electronic Supplementary Information (ESI) available: Experimental procedures, spectral data and copies of ^{1}H, ^{13}C NMR for all synthesized compounds.

References and notes

[1] (a) P. Lloyd-Williams, E. Giralt, Chem. Soc. Rev. 30 (2001) 145-157;

(b) L. Pu, Chem. Rev. 98 (1998) 2405-2494;

(c) A. Khalafi-Nezhad, F. Panahi, J. Organomet. Chem. 717 (2012) 141-146;

(d) O. A. Akrawi, M. Hussain, P. Langer, Tetrahedron Lett. 52 (2011) 1093-1095.

[2] (a) T. Welton Chem. Rev. 99 (1999) 2071-2083;

(b) A. F. Littke, G. C. Fu, Angew. Chem. Int. Ed. 41 (2002) 4176-4211;

(c) N. Iranpoor, H. Firouzabadi, A. Safavi, S. Motevalli, M. M. Doroodmand, Appl. Organometal. Chem. 26 (2012) 417-422;

(d) H. Firouzabadi, N. Iranpoor, M. Gholinejad, J. Organomet. Chem. 695 (2010) 2093-2097;

(e) A. Safavi, N. Maleki, N. Iranpoor, H. Firouzabadi, A. R. Banazadeh, R. Azadi, F. Sedaghati, Chem. Commun. (2008) 6155-6157;

(f) J. Yamaguchi, K. Muto, K. Itami, Eur. J. Org. Chem. (2013) 19-30.

[3] (a) F. Schneider, A. Stolle, B. Ondruschka, H. Hopf, Org. Process Res. Dev. 13 (2009) 44-48;

(b) R. Martin, S. L. Buchwald, Acc. Chem. Res. 41 (2008) 1461-1473;

(c) M. Tobisu, T. Xu, T. Shimasaki, N. Chatani, J. Am. Chem. Soc. 133 (2011) 19505-19511;

(d) V. Pandarus, D. Desplantier-Giscard, G. Gingras, F. Béland, R. Ciriminna, M. Pagliaro, Org. Process Res. Dev. 17 (2013) 1492-1497;

(e) C. Valente, S. Calimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, Angew. Chem. Int. Ed. 51 (2012) 3314-3332;

(f) V. Polshettiwar, A. Decottignes, C. Len, A. Fihri, ChemSusChem 3 (2010) 502-522;

(g) H. Bonin, E. Fouquet, F.-X. Felpin, Adv. Synth. Catal. 353 (2011) 3063-3084;

(h) E. J.-G. Anctil, V. Snieckus, J. Organomet. Chem. 653 (2002) 150-160;

(i) H. Groger, J. Prakt. Chem. 342 (2000) 334-339.

[4] (a) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A. Resmerita, N. K. Garg, V. Percec, Chem. Rev. 111 (2011) 1346-1416;

(b) D.-G. Yu, B.-J. Li, Z.-J. Shi, Acc. Chem. Res. 43 (2010) 1486-1495;

(c) T. Mesganaw, N. K. Garg, Org. Process Res. Dev. 17 (2013) 29-39.

[5] M. Tobisu, T. Shimasaki, N. Chatani, Angew. Chem. Int. Ed. 47 (2008) 4866-4869.

[6] (a) B.-T. Guan, Y. Wang, B.-J. Li, D.-G. Yu, Z.-J. Shi, J. Am. Chem. Soc. 130 (2008) 14468-14470;

(b) K. W. Quasdorf, X. Tian, N. K. Garg, J. Am. Chem. Soc. 130 (2008) 14422-14423.

[7] (a) K. W. Quasdorf, A. Antoft-Finch, P. Liu, A. L. Silberstein, A. Komaromi, T. Blackburn, S. D. Ramgren, K. N. Houk, V. Snieckus, N. K. Garg, J. Am. Chem. Soc. 133 (2011) 6352-6363;

(b) M. Baghbanzadeh, C. Pilger, C. O. Kappe, J. Org. Chem. 76 (2011) 1507-1510;

(c) K. W. Quasdorf, M. Riener, K. V. Petrova, N. K. Garg, J. Am. Chem. Soc. 131 (2009) 17748-17749.

[8] (a) P. Leowanawat, N. Zhang, V. Percec, J. Org. Chem. 77 (2012) 1018-1025;

(b) R. Kuwano, R. Shimizu, Chem. Lett. 40 (2011) 913-915.

[9] Y. -L. Zhao, Y. Li, Y. Li, L.-X. Gao, F.-S. Han, Chem. Eur. J. 16 (2010) 4991-4994.

[10] S.-M. Li, J. Huang, G.-J. Chen, F.-S. Han, Chem. Commun. 47 (2011) 12840-12842.

[11] H. Chen, Z. Huang, X. Hu, G. Tang, P. Xu, Y. Zhao, C. -H. Cheng, J. Org. Chem. 76 (2011) 2338-2344.

[12] (a) G. –J. Chen, F. –S. Han, Eur. J. Org. Chem. (2012) 3575-3579;

(b) N. Zhang, D. J. Hoffman, N. Gutsche, J. Gupta, V. Percec, J. Org. Chem. 77 (2012) 5956-5964.

[13] (a) C.-H. Xing, J.-R. Lee, Z.-Y. Tang, J. R. Zheng, Q. S. Hu, Adv. Synth. Catal. 353 (2011) 2051-2059;

(b) H. Gao, Y. Li, Y.-G. Zhou, F.-S. Han, Y.-J. Lin, Adv. Synth. Catal. 353 (2011) 309-314.

[14] V. Percec, J.-Y. Bae, D. H. Hill, J. Org. Chem. 60 (1995) 1060-1065.

[15] X.–J. Li, J.–L. Zhang, Y. Geng, Z. Jin, J. Org. Chem. 78 (2013) 5078-5084.

[16] (a) D. -G. Yu, B. -J. Li, S. -F. Zheng, B. -T. Guan, B. -Q. Wang, Z. -J. Shi, Angew. Chem. Int. Ed. 49 (2010) 4566-4570;

(b) F.-A. Kang, Z. Sui, W. V. Murray, Eur. J. Org. Chem. (2009) 461-479;

(c) G. –J. Chen, J. Huang, L. –X. Gao, F. –S. Han, Chem. Eur. J. 17 (2011) 4038-4042;

(d) F.-A. Kang, Z. Sui, W. V. Murray, J. Am. Chem. Soc. 130 (2008) 11300-11302;

(e) C. Shi, C. C. Aldrich, Org. Lett. 12 (2010) 2286-2289;

(f) F.-A. Kang, J. C. Lanter, C. Cai, Z. Sui, W. V. Murray, Chem. Commun. 46 (2010) 1347-1349;

(g) V. P. Mehta, S. G. Modha, E. V. Van der Eycken, J. Org. Chem. 75 (2010) 976-979;

(h) K. W. Quasdorf, X. Tian, N. K. Garg, J. Am. Chem. Soc. 130 (2008) 14422-14423;

(i) A. Sharma, D. Vachhani, E. Van der Eycken, Org. Lett. 14 (2012) 1854-1857;

(j) D.–G. Yu, Z.–J. Shi, Angew. Chem., Int. Ed., 50 (2011) 7097-7100;

(k) Y. –L. Zhao, G. –J. Wub, F.–S. Han, Chem. Commun., 48 (2012) 5868-5870;

(l) L. Chen, H. Lang, L. Fang, M. Zhu, J. Liu, J. Yu, L. Wang, Eur. J. Org. Chem. (2014) 4953-4957.

[17] a) N. Iranpoor, F. Panahi, Adv. Synth. Catal. 356 (2014) 3067. b) N. Iranpoor, F. Panahi, *Org. Lett.* 2014, DOI: 10.1021/ol503560e.

[18] a) $NiCl_2$(dppf) was prepared from $NiCl_2 \cdot 6H_2O$ and bisphosphine ligand (dppf) according to a literature procedure: A.W. Rudie, D. W. Lichtenberg, M. L. Katcher, A. Davison, Inorg. Chem. 17 (1978) 2859. b) The $NiCl_2$(dppp) complexe was synthesized from $NiCl_2 \cdot 6H_2O$ and the corresponding bisphosphine ligand according to a literature procedure: G. R. Van Hecke, W. D. Horrocks, Inorg. Chem. 5 (1966) 1968. c) $NiCl_2(PCy_3)_2$ was prepared from $NiCl_2 \cdot 6H_2O$ and PCy_3 ligand according to a literature procedure: T. Saito, H. Munakata, H. Imoto, Inorg. Synth. 17 (1977) 84.

[19] L. Liu, S. Zhang, H. Chen, Y. Lv, J. Zhu, Y. Zhao, Chem. Asian J. 8 (2013) 2592-2595.

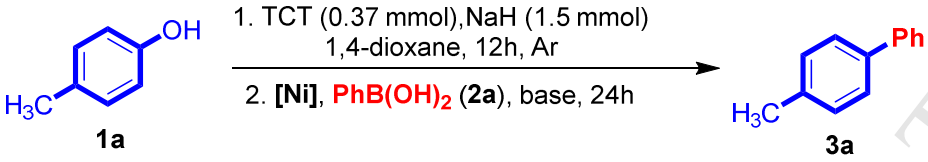
[20] X. Chen, L. Zhou, Y. Li, T. Xie, S. Zhou, J. Org. Chem., 79 (2014) 230-239.

[21] Y. Zou, D. D. Young, A. Cruz-Montanez, A. Deiters, Org. Lett. 10 (2008) 4661-4664.

[22] K. Niknam, F. Panahi, D. Saberi, M. Mohagheghnejad, J. Heterocyclic Chem., 47 (2010) 292-300.

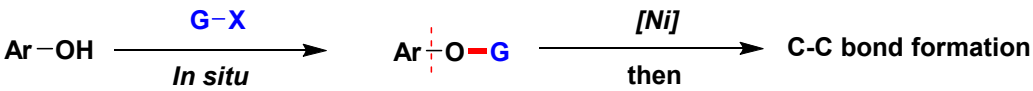
[23] F.-S. Han, Chem. Soc. Rev., 42 (2013) 5270-5298.

Table 1. Optimization of the reaction conditions for the synthesis of biaryl from *p*-cresol and arylboronic acids using TCT as a C-O activator reagent[a]

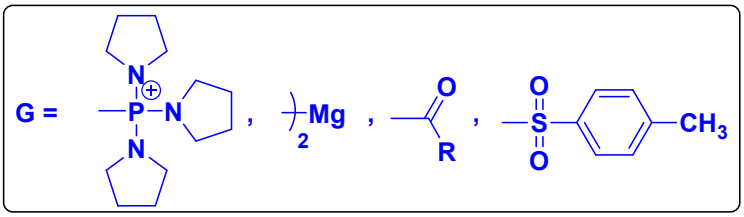


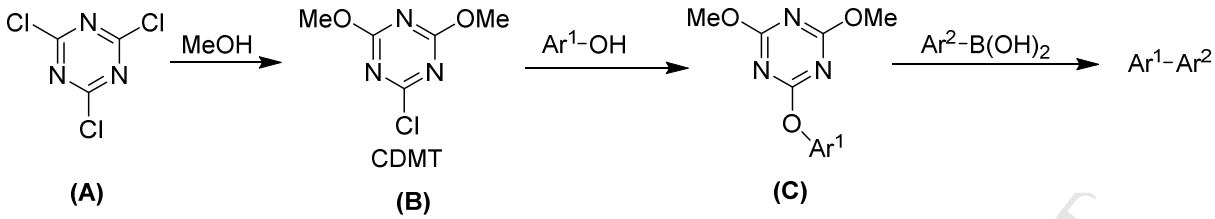
Entry	Ni-catalyst (mol%)	Solvent (T/°C)	Base	Yield (%)[b]
1	$NiCl_2$ (10)	1,4-dioxane (110)	K_3PO_4	0
2	$Ni(PPh_3)_2Cl_2$ (5)	1,4-dioxane (110)	K_3PO_4	40
3	$Ni(PCy_3)_2Cl_2$ (5)	1,4-dioxane (110)	K_3PO_4	85
4	$Ni(dppe)Cl_2$ (5)	1,4-dioxane (110)	K_3PO_4	60
5	$Ni(dppp)Cl_2$ (5)	1,4-dioxane (110)	K_3PO_4	82
6	$Ni(dppf)Cl_2$ (5)	1,4-dioxane (110)	K_3PO_4	85
7	$Ni(PCy_3)_2Cl_2$ (5)	toluene (110)	K_3PO_4	75
8	$Ni(PCy_3)_2Cl_2$ (5)	xylene (110)	K_3PO_4	75
9	$Ni(PCy_3)_2Cl_2$ (5)	THF (80)	K_3PO_4	60
10	$Ni(PCy_3)_2Cl_2$ (5)	1,4-dioxane (110)	K_2CO_3	68
11	$Ni(PCy_3)_2Cl_2$ (5)	1,4-dioxane (110)	KO*t*-Bu	65
12	$Ni(PCy_3)_2Cl_2$ (5)	1,4-dioxane (110)	-	0
13	$Ni(PCy_3)_2Cl_2$ (2.5)	1,4-dioxane (110)	K_3PO_4	53
14	$Ni(PCy_3)_2Cl_2$ (7.5)	1,4-dioxane (110)	K_3PO_4	86
15	$Ni(PCy_3)_2Cl_2$ (10)	1,4-dioxane (110)	K_3PO_4	87
16	$Ni(PCy_3)_2Cl_2$ (7.5)	1,4-dioxane (110)	K_3PO_4	84[c]
17	$Ni(PCy_3)_2Cl_2$ (7.5)	1,4-dioxane (110)	K_3PO_4	76[d]

[a] Reaction conditions: **1a** (1 mmol), **2a** (3 mmol), base (4 mmol), solvent (5 mL), time = 24h. [b] Isolated yield. [c] 3 mmol of base was used. [d] 2 mmol of phenylboronic acid was used.

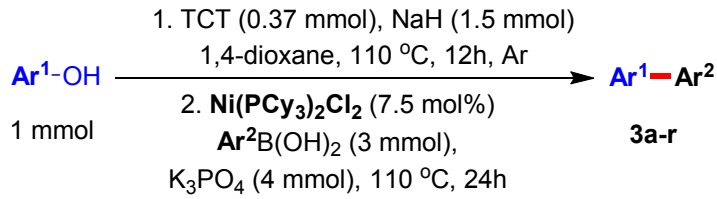


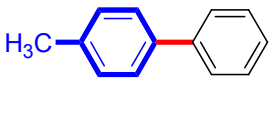
Aryl C-O electrophile



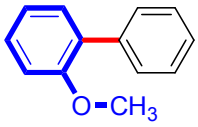


(A) **(B)** **(C)**

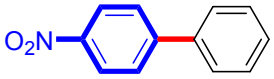




3a: 87%

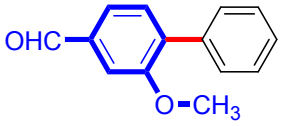


3b: 84%

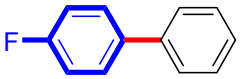


3c: 86%

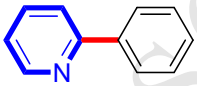
3d: 82%



3e: 82%



3f: 84%



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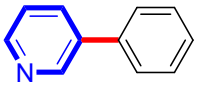
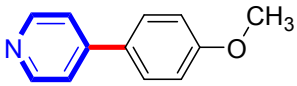
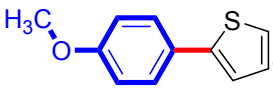


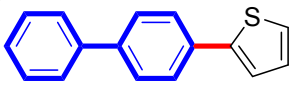
3h: 82%



3i: 77%



3j: 81%



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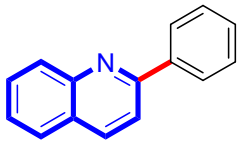
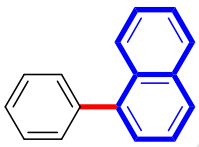
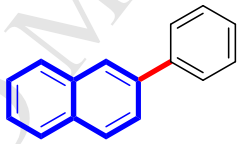


3l: 78%



3m: 82%



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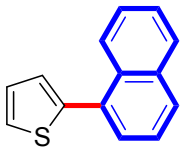
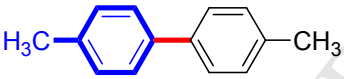


3o: 82%



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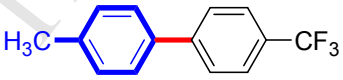
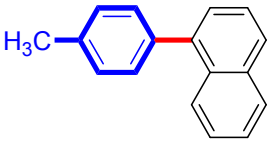
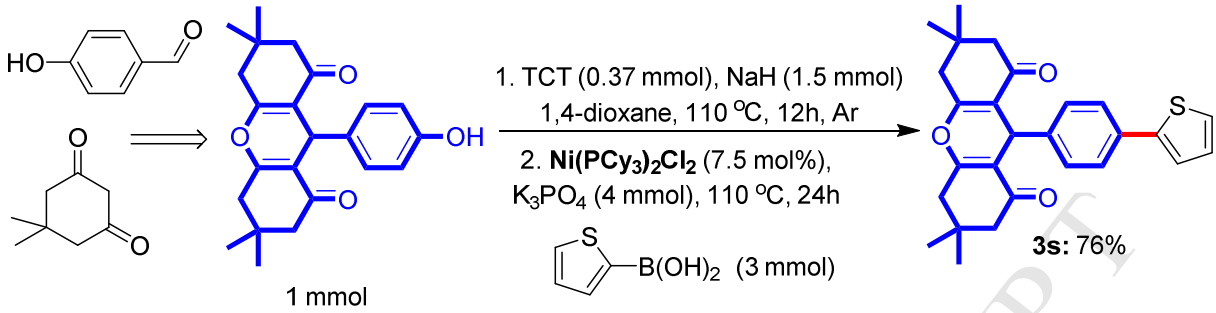
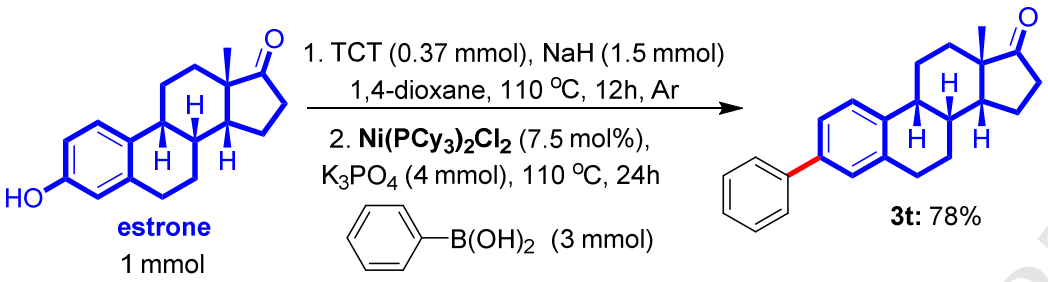


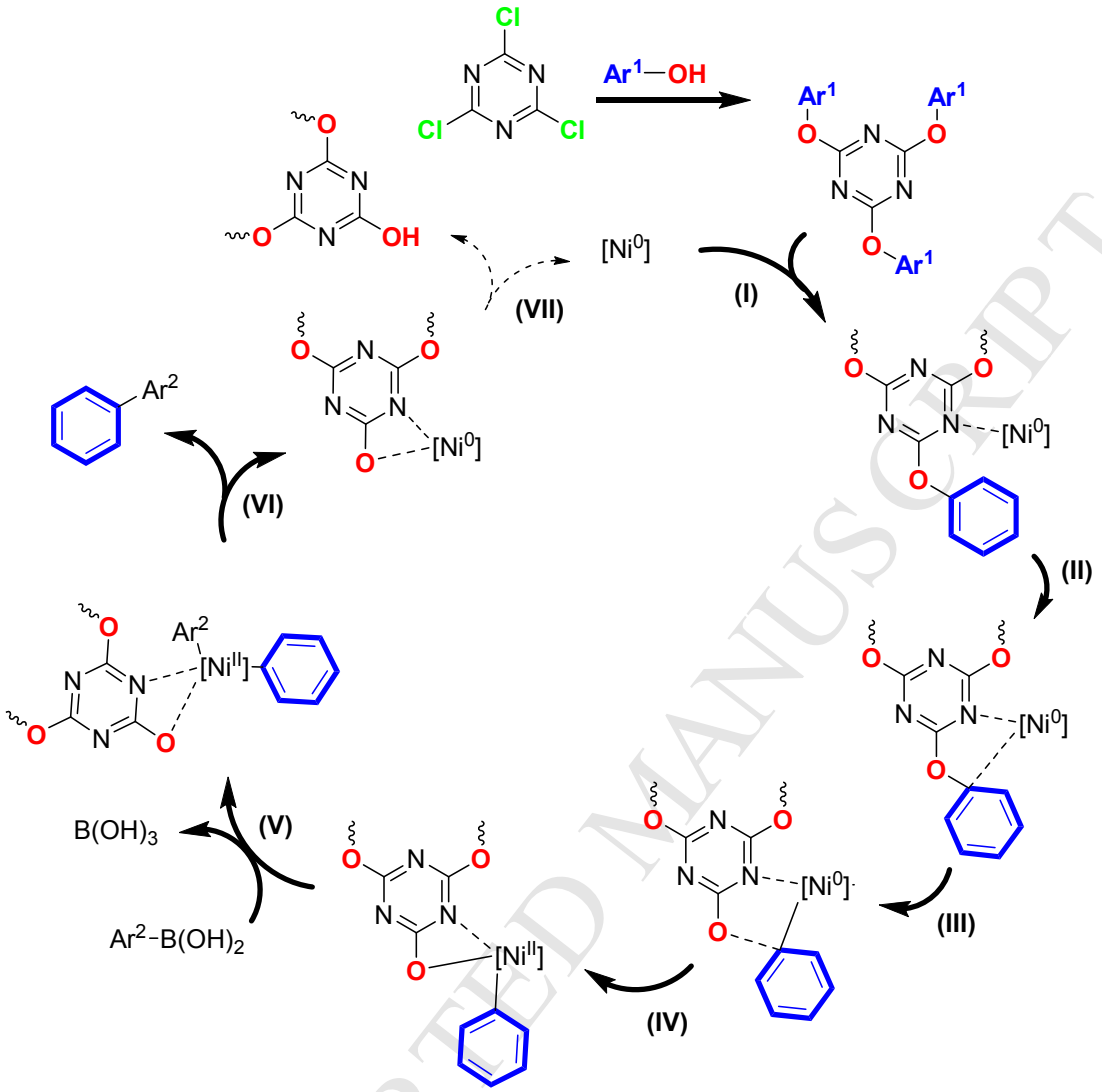
3q: 83%



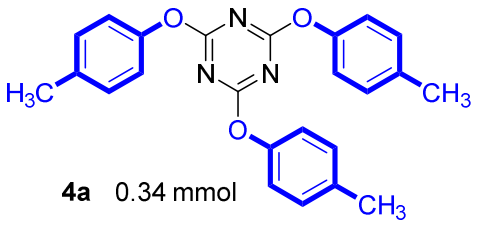
3r: 80%





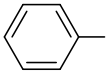


1)



4a 0.34 mmol

Ni(PCy$_3$)$_2$Cl$_2$ (7.5 mol%),
K_3PO_4 (4 mmol), 110 °C

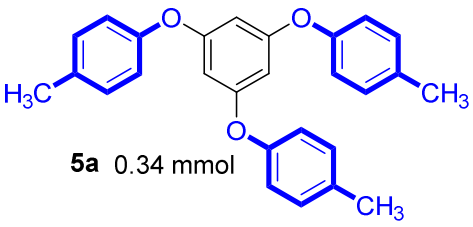


(3 mmol)

24h, 89%

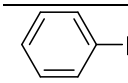
3a

2)



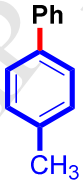
5a 0.34 mmol

Ni(PCy$_3$)$_2$Cl$_2$ (7.5 mol%),
K_3PO_4 (4 mmol), 110 °C



(3 mmol)

24h



3a

► Nickel-catalyzed cross-coupling reactions of phenol derivatives with arylboronic acids
► In situ activation of phenols using TCT for utilization in C-C coupling reactions
► TCT as a cheap, readily available reagent for C-O bond activation of phenolic compounds
► Direct synthesis of biaryls from phenols using TCT as C-O bond activator

Nickel-catalyzed one-pot synthesis of biaryls from phenols and arylboronic acids *via* C-O activation using TCT reagent

Nasser Iranpoor,* Farhad Panahi, and Fereshteh Jamedi

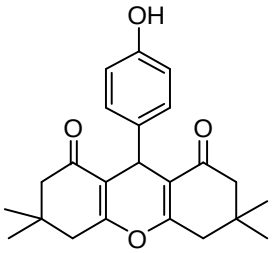
Department of Chemistry, College of Sciences, Shiraz University, Shiraz, 71454, Iran

Email: iranpoor@chem.susc.ac.ir

Outline

1. Experimental procedures

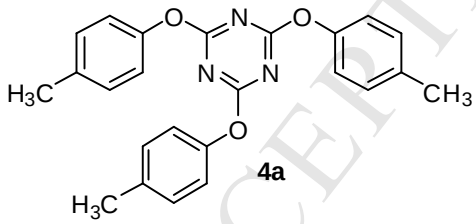
1.2. Procedure for the synthesis of 9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (1p)[1]



1p

To a solution of 4-hydroxybenzaldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexane-dione (2 mmol) and aryl amine (1 mmol) in ethanol (2 mL) in ethanol (2 mL) in a round-bottom flask, SBSSA (0.03 g) was added. The mixture was heated under reflux conditions and the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the remaining was washed with warm ethanol in order to separate catalyst. Then, water (20 mL) was added to the filtrate and was allowed to stand at room temperature for 1 h. During this time, crystals of the pure product were formed, which were collected by filtration and dried. For further purification, the product recrystalized from hot ethanol (85%, 0.31g). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.97 (s, 6H), 1.08 (s, 6H), 2.09-2.26 (m, 4H), 2.45 (s, 4H), 4.65 (s, 1H), 6.51 (d, *J* = 7.4 Hz, 2H), 7.04 (d, *J* = 7.4 Hz, 2H), 7.17 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 27.4, 29.3, 30.9, 32.4, 41.0, 50.7, 115.4, 116.0, 129.3, 135.5, 154.8, 162.6, 197.3.

1.3. Synthesis of 2,4,6-tris(*p*-tolyloxy)-1,3,5-triazine (4a)



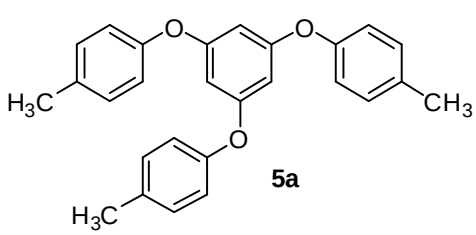
4a

Into a canonical flask (50 mL), a mixture of *p*-cresol (3.1 mmol), and NaH (5 mmol) were stirred in dry 1,4-dioxane (10 mL) for 1h at room temperature. Then 1 mmol of TCT was added to the reaction media and let stirring continue for another hour. Afterward the raction mixture was stirred at 110 °C for 10h. After completion of the reaction, as indicated by TLC, the mixture was cooled down to room temperature and the solvent was removed under vacum. Then, 50 mL of $CHCl_3$ and 100 mL of water was added to the crude prduct and $CHCl_3$ was extracted from water. The organic extract was dried over Na_2SO_4. The product was purified by recrystalization in $CHCl_3$ to afforded pure product. ^{1}H NMR (250 MHz,

1) K. Niknam, F. Panahi, D. Saberi, and M. Mohagheghnejad, *J. Heterocyclic Chem.*, 2010, **47**, 292

$CDCl_3$): δ (ppm) = 2.35 (s, 9H), 7.05 (d, *J* = 8.1 Hz, 6H), 7.16 (d, *J* = 8.0 Hz, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 21.0, 121.0, 130.2, 135.1, 149.9, 174.6. Anal. Calcd. for $C_{24}H_{21}N_3O_3$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.02; H, 5.21; N, 10.41.

1.4. Synthesis of 1,3,5-tris(p-tolyloxy)benzene (5a)[2]



5a

Into a 100-mL, three-necked, round-bottom flask equipped with a magnetic stirrer, a reflux condenser, a Dean-Stark trap and a nitrogen inlet, 1,3,5-tribromobenzene (0.40 g, 1.27 mmol), *p*-cresol (0.46g, 4.25 mmol), sodium carbonate (0.5 g, 4.72 mol), and copper(I) iodide (0.04g) were placed. Dimethyl acetamide (DMAc) (5mL) and Toluene (1 mL) were then carefully poured in the flask. The mixture was then heated to 160 °C. The water generated during the reaction was removed by toluene azeotropic distillation for 4-5 h. After completion of dehydration, the mixture was further stirred under reflux for 90h and poured into distilled water containing 1 mL of conc. hydrochloric acid. The precipitate that formed was collected by filtration and air-dried. For further purification, the product was purified by column chromatography to afford product as yellow solid: ^1H NMR (250 MHz, DMSO-d_6): δ (ppm) = 2.32 (s, 9H), 6.25 (s, 3H), 7.03 (d, *J* = 7.9 Hz, 6H), 7.13 (d, *J* = 8.1 Hz, 6H). ^{13}C NMR (62.5 MHz, DMSO-d_6): 19.9, 101.8, 118.9, 129.1, 130.4, 154.8, 158.9. Anal. Calcd. for $C_{27}H_{24}O_3$: C, 81.79; H, 6.10. Found: C, 81.68; H, 6.01.

2. Spectral data for synthesized compounds

2.1. 4-Methyl-1,1'-biphenyl (3a)[3]

^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.53 (s, 3H), 7.37-7.47 (m, 2H), 7.51-7.57 (m, 5H), 7.62-7.74 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 21.6, 127.4, 127.5, 127.8, 128.8, 129.4, 130.1, 131.4, 132.1, 138.1.

2) I. Y. Jeon, L. –S. Tan and J. –B. Baek, *Polymer Preprints* 2008, **49**, 89.
3) D. Zim, V. R. Lando, J. Dupont, A. L. Monteiro, *Org. Lett.* **2001**, *3*, 3049.

2.2. 2-Methoxy-1,1'-biphenyl (3b)[4]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 3. 79 (s, 3H), 6.98-7.05 (m, 2H), 7.29-7.42 (m, 5H), 7.54 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 55.6, 111.5, 121.1, 127.0, 128.1, 128.9, 129.6, 131.2, 138.9, 157.0.

2.3. 4-Nitro-1,1'-biphenyl (3c)[5]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.45-7.76 (m, 7H), (d, *J* = 8.9 Hz, 2H), 8.31 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 124.9, 127.6, 127.9, 128.9, 129.5, 129.7, 141.1, 147.8.

2.4. [1,1'-Biphenyl]-4-carbonitrile (3d)[6]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.41-7.48 (m, 3H), 7.58-76 (m, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 110.8, 118.6, 127.3, 127.5, 128.7, 128.9, 129.3, 129.5, 129.9, 130.5, 132.1, 139.8, 146.2.

2.5. 2-Methoxy-[1,1'-biphenyl]-4-carbaldehyde (3e)[4]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 3.93 (s, 3H), 7.28-7.45 (m, 5H), 7.52-7.60 (m, 3H), 10.05 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 55.8, 109.6, 125.3, 127.4, 127.5, 128.3, 128.4, 129.4, 131.6, 136.5, 137.2, 157.1, 191.9. Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.19; H, 5.61.

2.6. 4-Fluoro-1,1'-biphenyl (3f)[7]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.13 (t, *J* = 9.0 Hz, 2H), 7.34-7.44 (m, 3H) 7.53-7.58 (m, 4H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 115.3, 127.4, 127.5, 128.8, 137.1, 139.9, 161.1, 163.7. Anal. Calcd. for $C_{12}H_9F$: C, 83.70; H, 5.27 Found: C, 83.62; H, 5.19.

2.7. 2-Phenylpyridine (3g)[8]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.23 (d, *J* = 9.0 Hz, 1H) 7.43-7.99 (m, 7H), 8.71 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 120.3, 122.4, 126.3, 127.7, 137.0, 139.5, 149.3, 157.1. Anal. Calcd. for $C_{11}H_9N$: C, 85.13; H, 5.85; N, 9.03 Found: C, 85.02; H, 5.78; N, 8.96.

4) N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553.
5) Iranpoor, N.; Firouzabadi, H.; Safavi, A.; Motevalli, S.; Doroodmand, M. M. *Appl. Organometal. Chem.* **2012**, *26*, 417.
6) Li, X. –J.; Zhang, J. –L.; Geng, Y.; Jin, Z. *J. Org. Chem.* **2013**, *78*, 5078.
7) J.-H. Li, W.-J. Liu, Y.-X. Xie, *J. Org. Chem.*, **2005**, *70*, 5409.
8) N. Kudo, M. Perseghini, G. C. Fu, *Angew. Chem., Int. Ed.* 2006, **45**, 1282.

2.8. 3-Phenylpyridine (3h)[6]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.32-7.58 (m, 6H), 7.86-7.88 (m, 1H), 8.59 (d, *J* = 4Hz, 1H), 8.86 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 123.4, 127.1, 128.3, 129.1, 134.5, 136.7, 137.8, 149.3, 149.4. Anal. Calcd. for $C_{11}H_9N$: C, 85.13; H, 5.85; N, 9.03 Found: C, 85.00; H, 5.76; N, 8.97.

2.9. 4-(4-Methoxyphenyl)pyridine (3i)[9]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 3.87 (s, 3H), 7.00 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 5.4 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 8.62 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 55.4, 114.5, 121.2, 128.0, 130.4, 147.8, 150.1, 150.7, 160.8. Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56 Found: C, 77.75; H, 5.91; N, 7.49.

2.10. 2-(4-Methoxyphenyl)thiophene (3j)[10]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 3.83 (s, 3H), 6.91 (d, *J* = 5.2 Hz, 2H), 6.97-7.06 (m, 1H), 7.20-7.26 (m, 2H), 7.53 (d, *J* = 4.7 Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 55.4, 114.1, 122.0, 123.8, 127.2, 127.4, 127.8, 143.9, 159.1. Anal. Calcd. for $C_{11}H_{10}OS$: C, 69.44; H, 5.30 Found: C, 69.38; H, 5.22.

2.11. 2-([1,1'-biphenyl]-4-yl)thiophene (3k)

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.32-7.49 (m, 7H), 7.54-7.59 (m, 5H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 127.5, 127.8, 128.0, 128.3, 128.8, 129.6, 133.1, 141.3, 142.4, 150.1. Anal. Calcd. for $C_{16}H_{12}S$: C, 81.32; H, 5.12 Found: C, 81.25; H, 5.06.

2.12. 3-(Thiophen-2-yl)quinoline (3l)[8]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.17-7.26 (m, 1H), 7.40-7.56 (m, 4H), 7.81-8.08 (m, 3H), 9.2 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 123.9, 125.4, 127.0, 127.4, 127.5, 128.3, 128.7, 128.8, 131.2, 139.9, 146.8, 148.2. Anal. Calcd. for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63 Found: C, 73.81; H, 4.20; N, 6.54.

2.13. 1-Phenylnaphthalene (3m)[11]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.24-7.52 (m, 5H), 7.82-7.99 (m, 7H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 125.0, 125.9, 126.0, 126.2, 126.8, 128.4, 128.6, 129.2, 131.2, 133.5, 137.3, 140.6, 141.7. Anal. Calcd. for $C_{16}H_{12}$: C, 94.08; H, 5.92 Found: C, 94.01; H, 5.85.

9) O. Kobayashi, D. Uraguchi, T. Yamakawa, *Org. Lett.* 2009, **11**, 2679.
10) X. Chen, L. Zhou, Y. Li, T. Xie, S. Zhou, *J. Org. Chem.* 2014, **79**, 230.
11) D. –G. Yu and Z. –J. Shi, *Angew. Chem. Int. Ed.* 2011, **50**, 7097.

2.14. 2-Phenylnaphthalene (3n)[9]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.36 (d, *J* = 9.7 Hz, 2H), 7.41-7.49 (m, 3H), 7.68-7.79 (m, 2H), 7.87-7.90 (m, 4H), 8.02 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 125.8, 125.9, 126.9, 127.0, 127.1, 128.7, 132.2, 132.9, 133.9, 134.2, 138.6, 141.3. Anal. Calcd. for $C_{16}H_{12}$: C, 94.08; H, 5.92 Found: C, 93.98; H, 5.83.

2.15. 2-(Naphthalen-1-yl)thiophene (3o)[8]

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.19-7.32 (m, 4H), 7.44-7.58 (m, 3H), 7.84-7.97 (m, 2H), 8.22-8.25 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 125.1, 125.2, 125.3, 125.8, 126.7, 126.8, 127.2, 127.4, 127.5, 128.6, 128.7, 129.3, 131.5, 132.0, 133.25, 141.1. Anal. Calcd. for $C_{14}H_{10}S$: C, 94.08; H, 5.92 Found: C, 94.01; H, 5.87.

2.16. 4,4'-Dimethyl-1,1'-biphenyl (3p)[12]

^{1}H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 2.06 (s, 6H), 7.18-7.30 (m, 8H). ^{13}CNMR (62.5 MHz, $CDCl_3$/TMS): δ (ppm) = 19.8, 126.5, 127.0, 129.3, 129.8, 136.7, 141.6. Anal. Calcd. for $C_{14}H_{14}$: C, 92.26; H, 7.74 Found: C, 92.18; H, 7.65.

2.17. 4-Methyl-4'-(trifluoromethyl)-1,1'-biphenyl (3q)

^{1}H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 2.40 (s, 3H), 7.27 (d, *J* = 9.2 Hz, 2H), 7.48 (d, *J* = 6.5 Hz, 2H), 7.70 (s, 4H). ^{13}CNMR (62.5 MHz, $CDCl_3$/TMS): δ (ppm) = 21.1, 120.2, 120.2, 123.0, 125.6, 127.1, 128.6 (q, 31.5 Hz), 129.6, 136.8, 138.0, 144.6. Anal. Calcd. for $C_{14}H_{11}F_3$: C, 71.18; H, 4.69. Found: C, 71.04; H, 4.58.

2.18. 1-(*p*-Tolyl)naphthalene (3r)

^{1}H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 2.46 (s, 3H), 2.29-2.53 (m, 8H), 7.84-7.93 (m, 3H). ^{13}CNMR (62.5 MHz, $CDCl_3$/TMS): δ (ppm) = 21.2, 125.3, 125.7, 125.9, 126.1, 126.8, 127.3, 128.2, 129.0, 129.9, 131.7, 133.7, 136.9, 137.8, 140.2. Anal. Calcd. for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.48; H, 6.38.

2.19. 3,3,6,6-Tetramethyl-9-(4-(thiophen-2-yl)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3s)

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.98 (s, 6H), 1.10 (s, 6H), 2.12-2.28 (m, 4H), 2.47 (s, 4H), 4.70 (s, 1H), 7.14-7.18 (m, 2H), 7.25-7.29 (m, 1H), 7.41-7.44 (m, 2H), 7.65-7.79 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 27.1, 29.6, 32.2, 32.7, 41.6, 50.3,

12) Toummini, D.; Ouazzani, F.; Taillefer, M. *Org. Lett.* **2013**, *15*, 4690-4693.

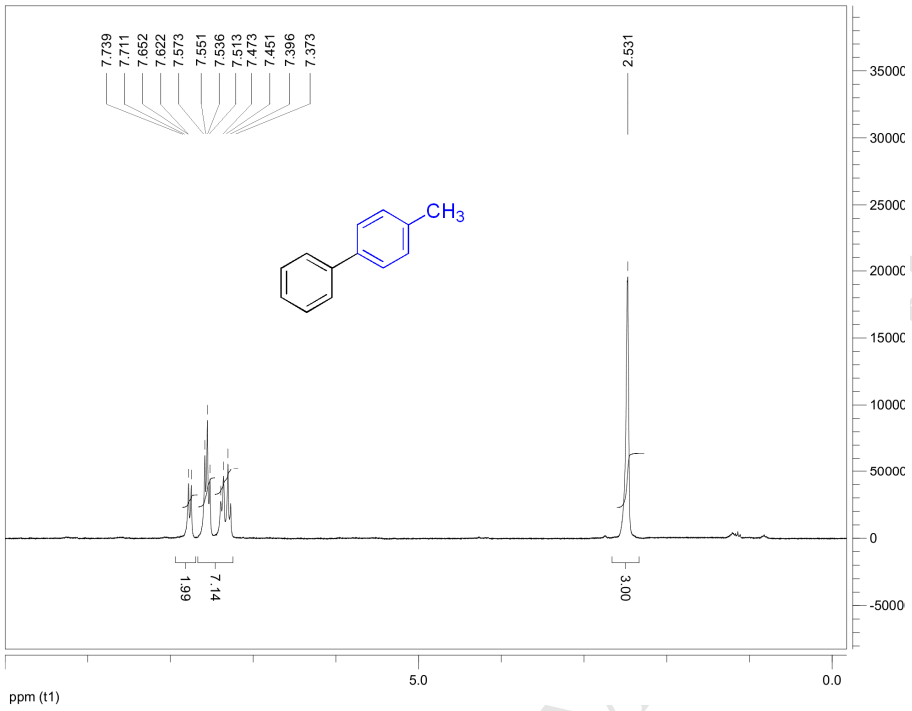
113.1, 114.1, 127.4, 128.0, 128.3, 128.8, 129.4, 143.6, 149.1, 157.1, 196.6. Anal. Calcd. for $C_{27}H_{28}O_3S$: C, 74.97; H, 6.52, Found: C, 74.89; H, 6.55.

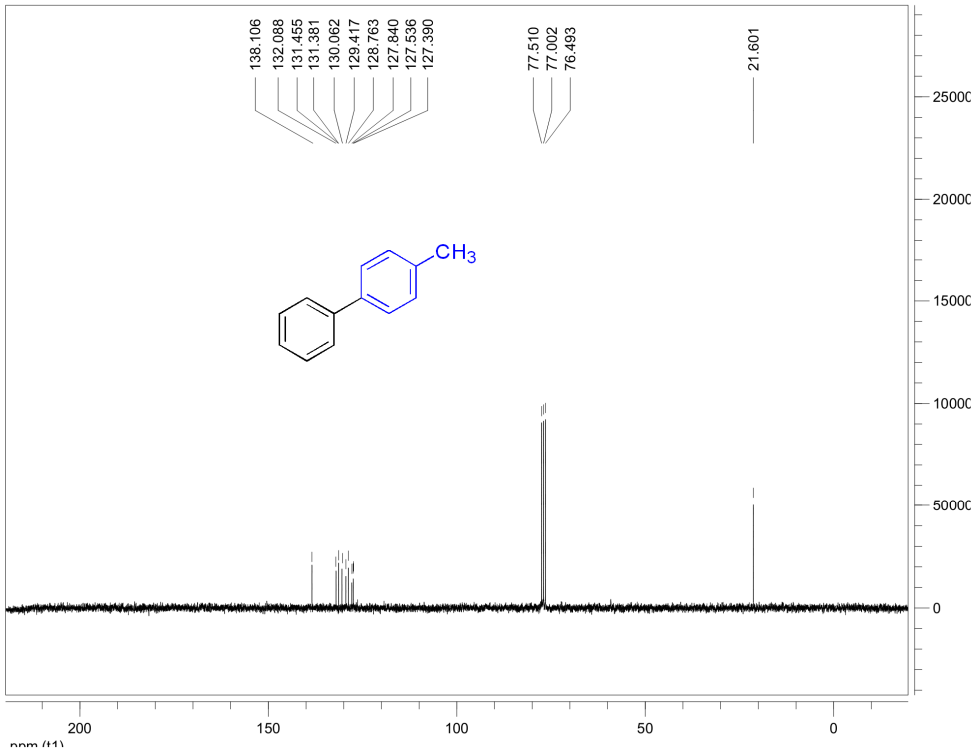
2.20. 13-methyl-3-phenyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (3t)

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.93 (s, 3H), 1.44-170 (m, 5H), 1.90-2.20 (m, 7H), 2.25-2.46 (m, 3H), 2.95 (m, 2H), 7.31-7.46 (m, 6H), 7.60-7.62 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 13.7, 21.8, 24.2, 25.7, 26.5, 26.6, 29.6, 31.7, 35.7, 38.2, 45.0, 48.1, 50.3, 124.5, 125.7, 126.9, 127.4, 127.5, 128.8, 136.9, 138.8, 138.9, 141.3. Anal. Calcd. for $C_{24}H_{26}O$: C, 87.23; H, 7.93 Found: C, 87.17; H, 7.88.

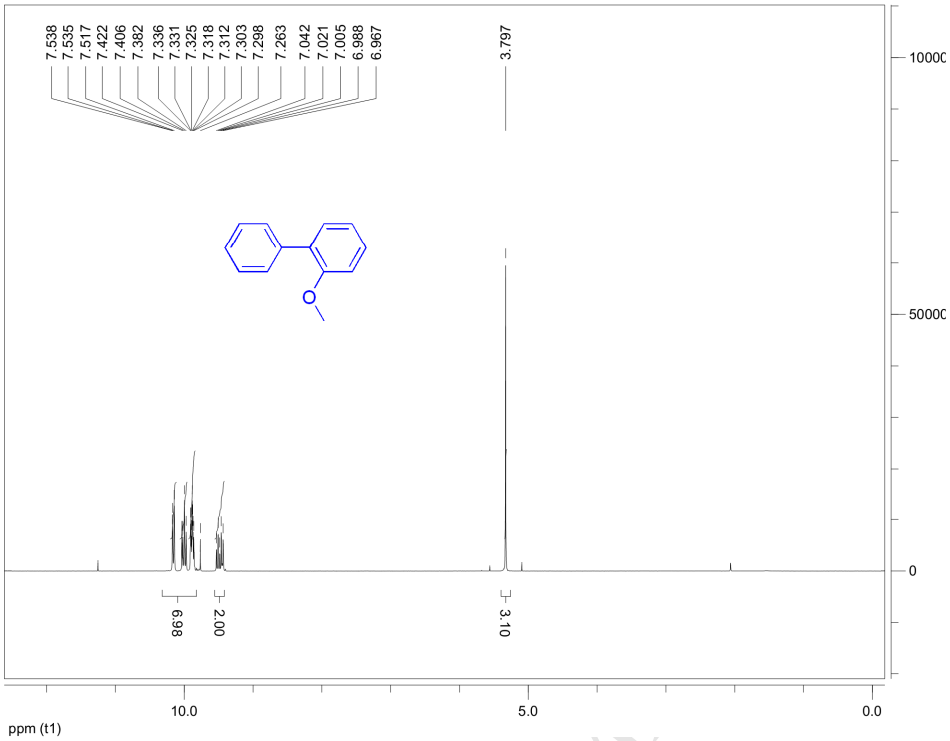
3. Copies of ^{1}H, ^{13}C NMR for all synthesized compounds

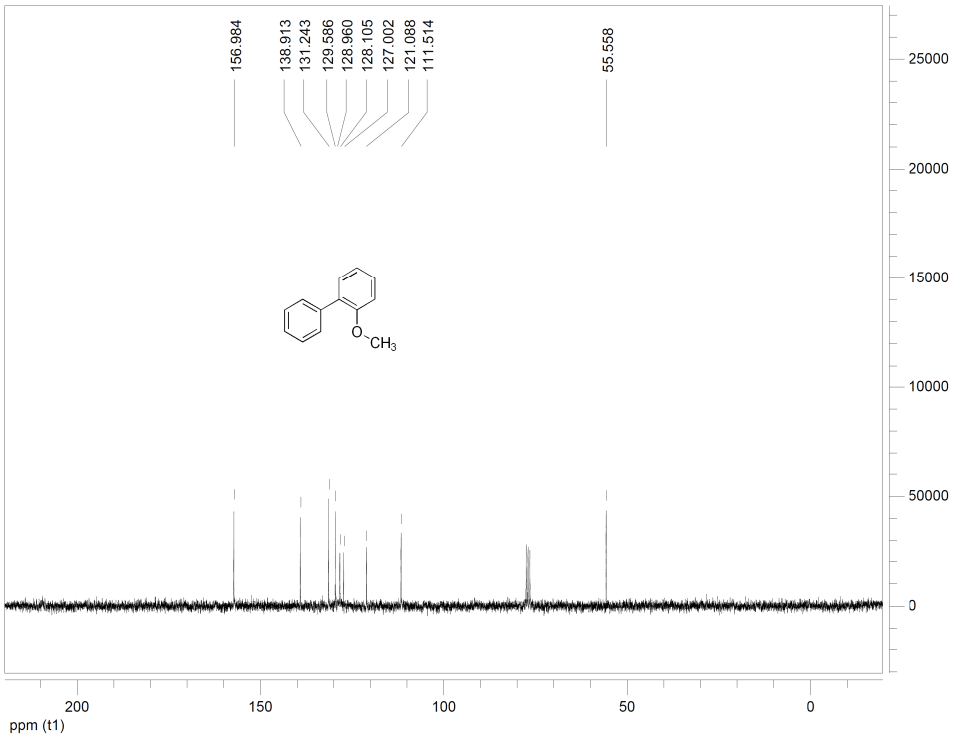
3.1. 4-Methyl-1,1'-biphenyl (3a)



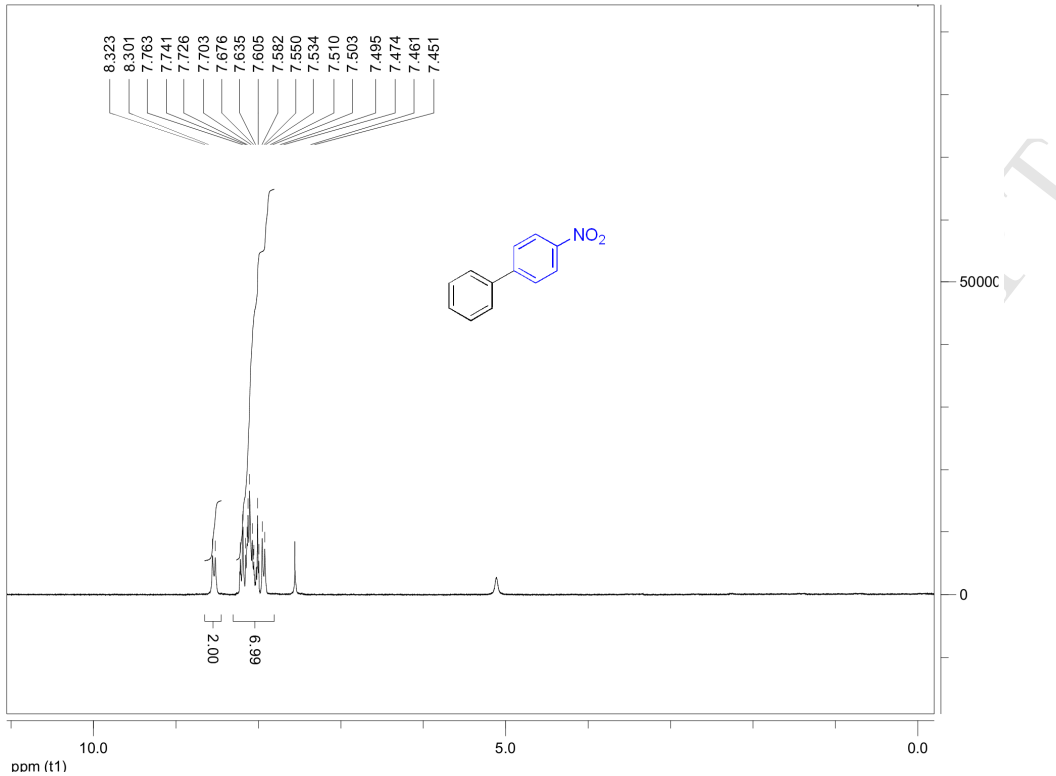


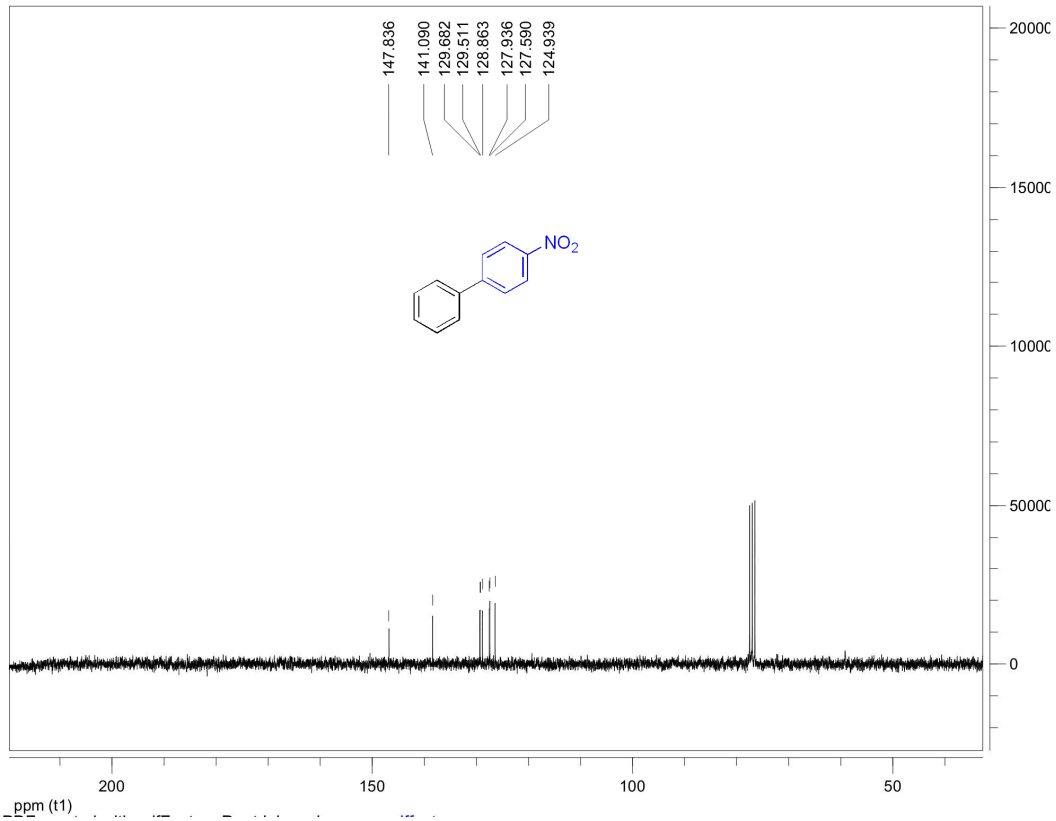
3.2. 2-Methoxy-1,1'-biphenyl (3b)



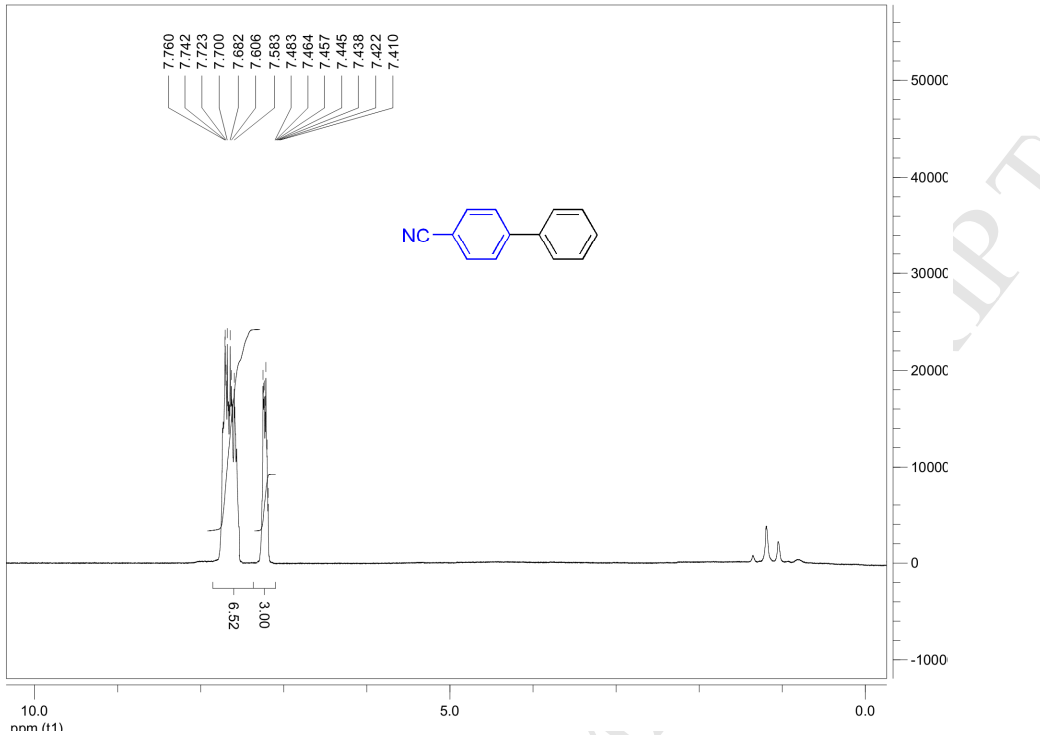


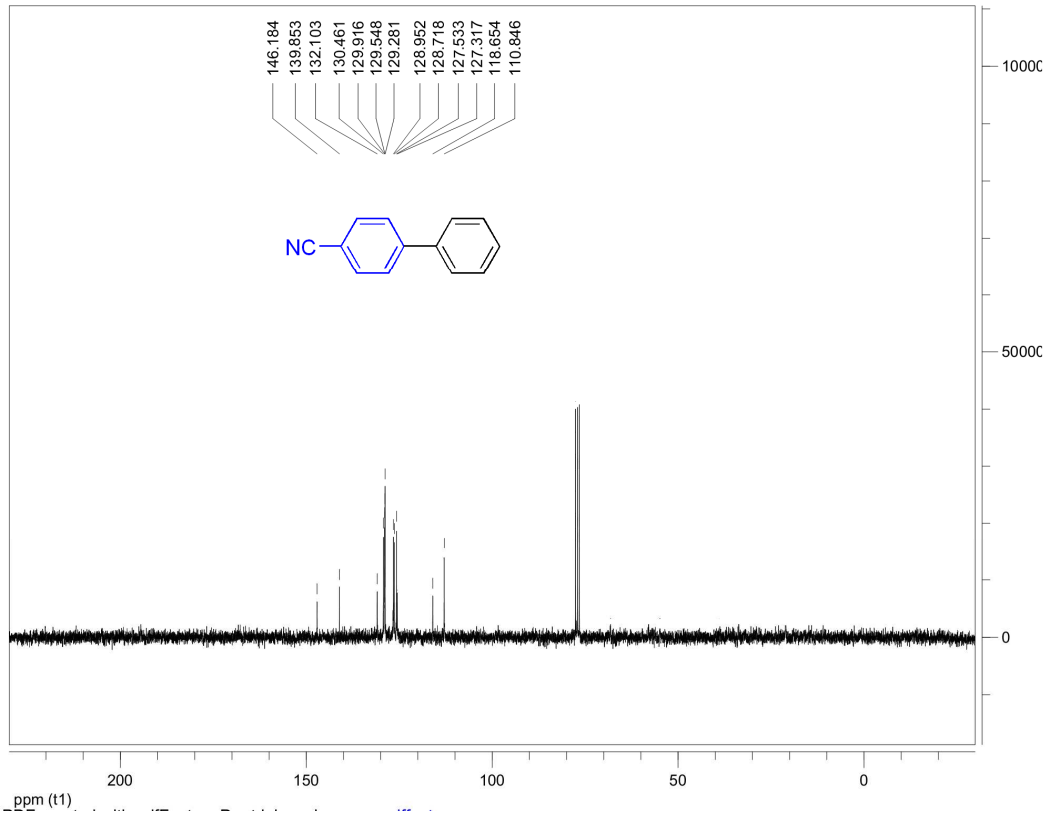
3.3. 4-Nitro-1,1'-biphenyl (3c)



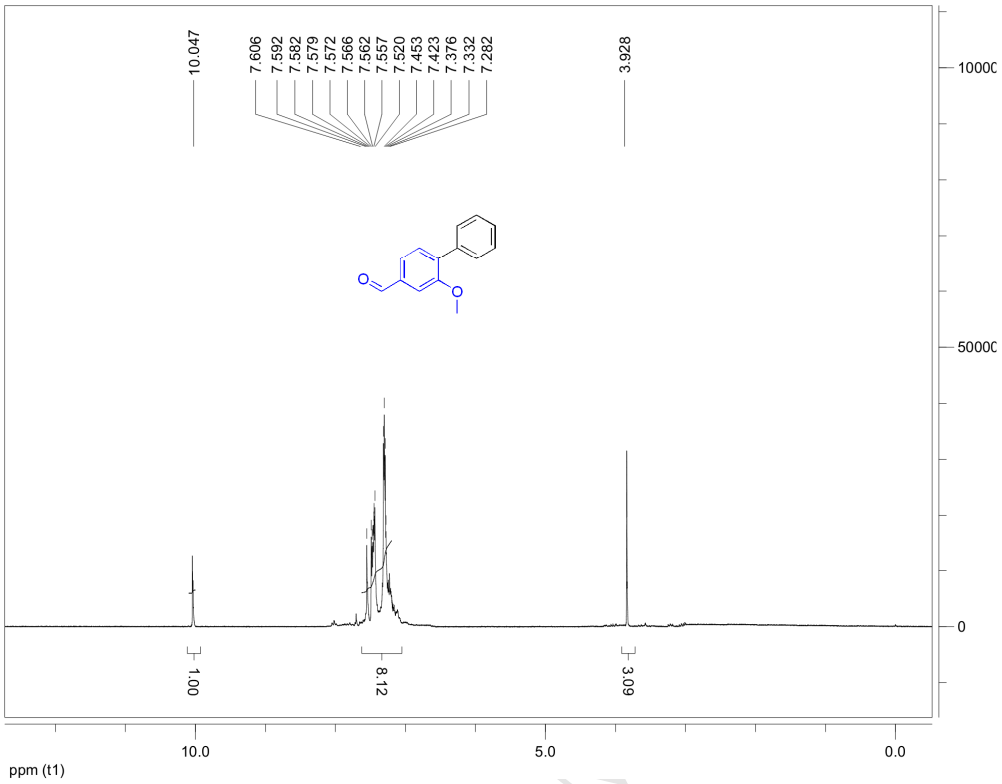


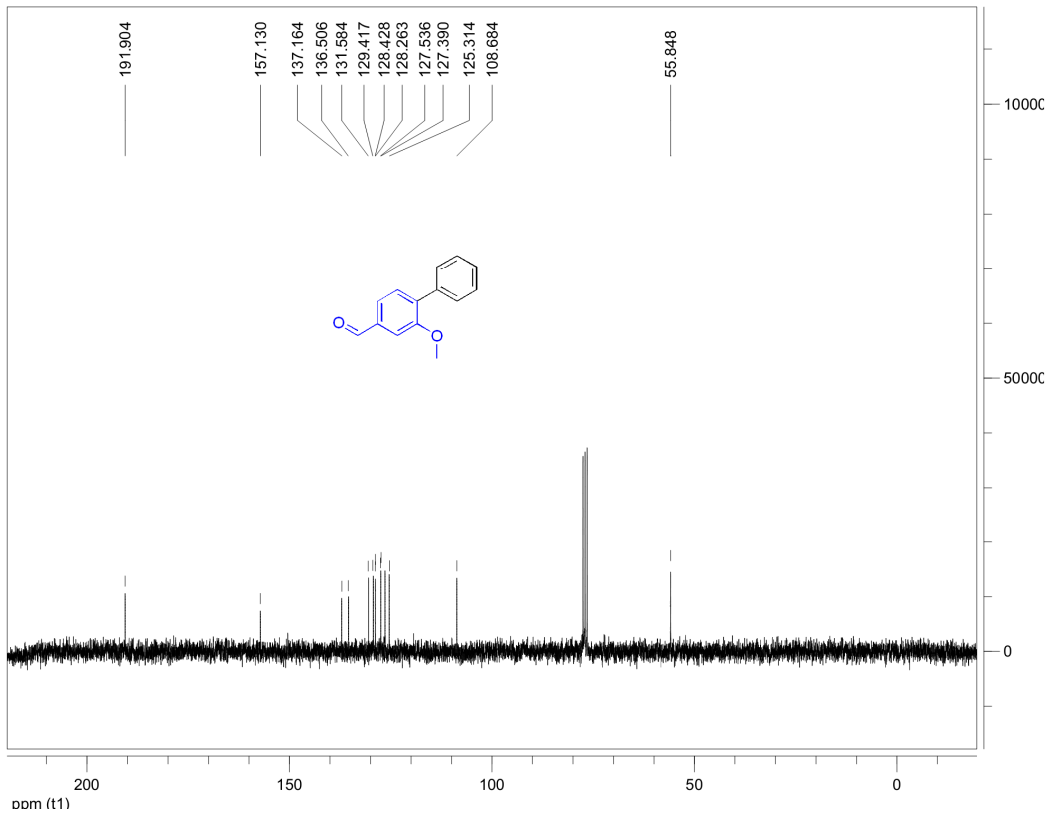
3.4. [1,1'-Biphenyl]-4-carbonitrile (3d)



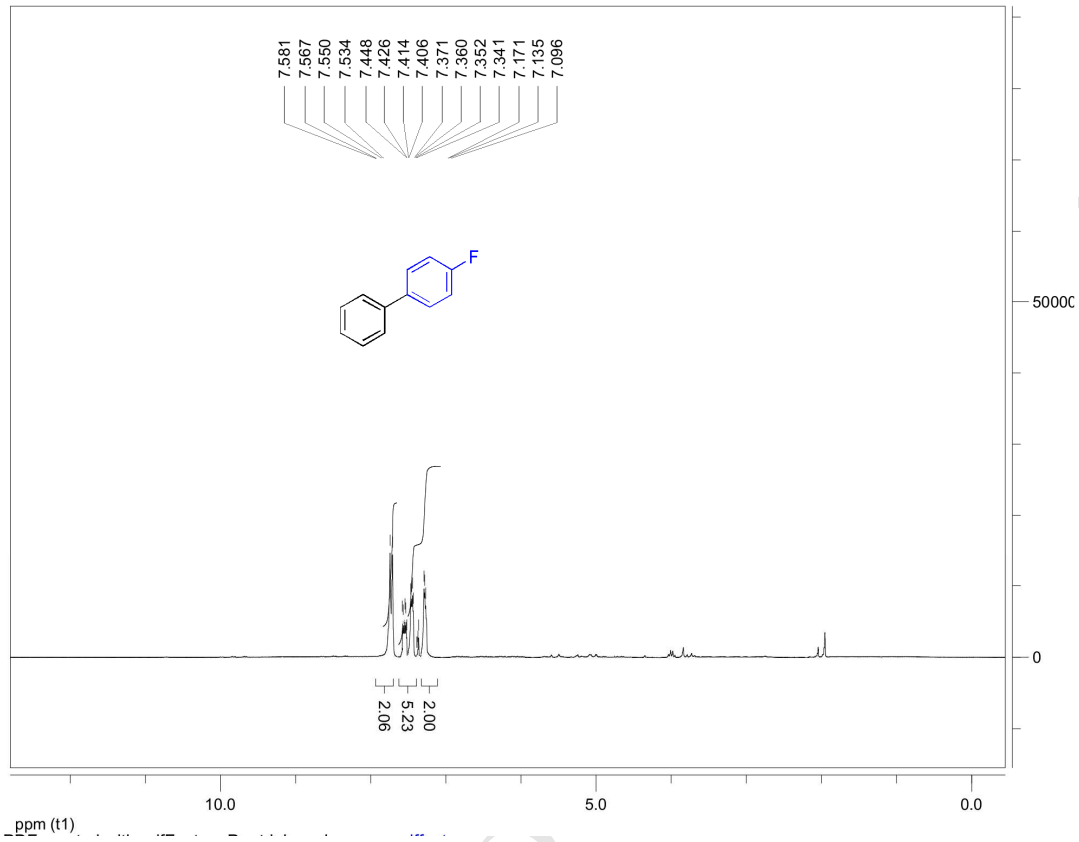


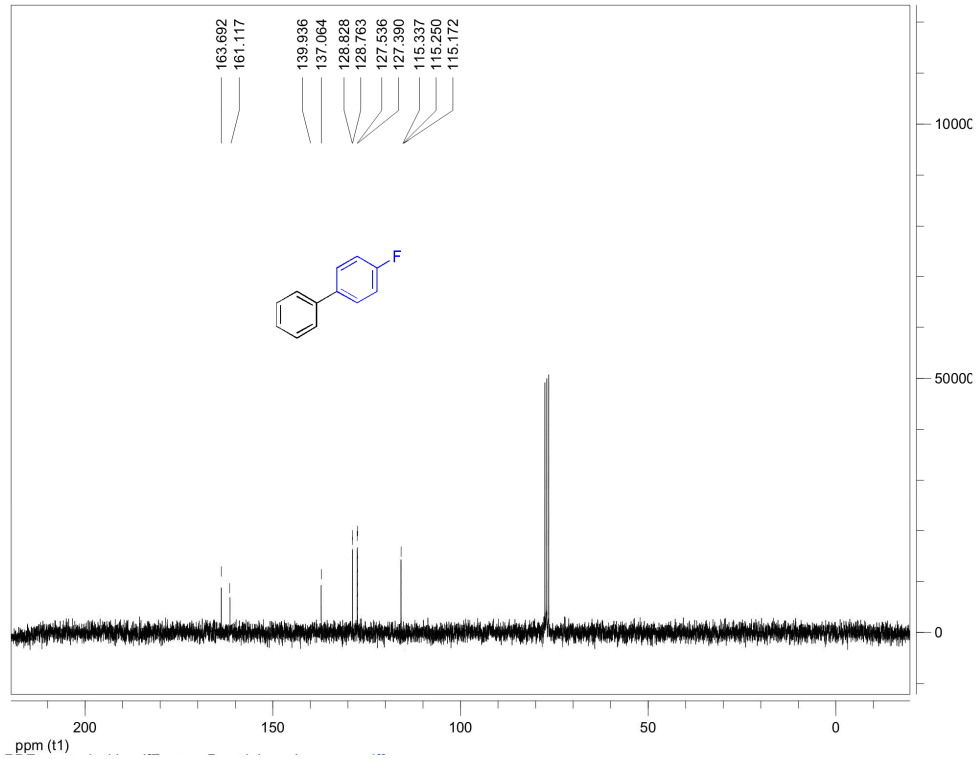
3.5. 2-Methoxy-[1,1'-biphenyl]-4-carbaldehyde (3e)



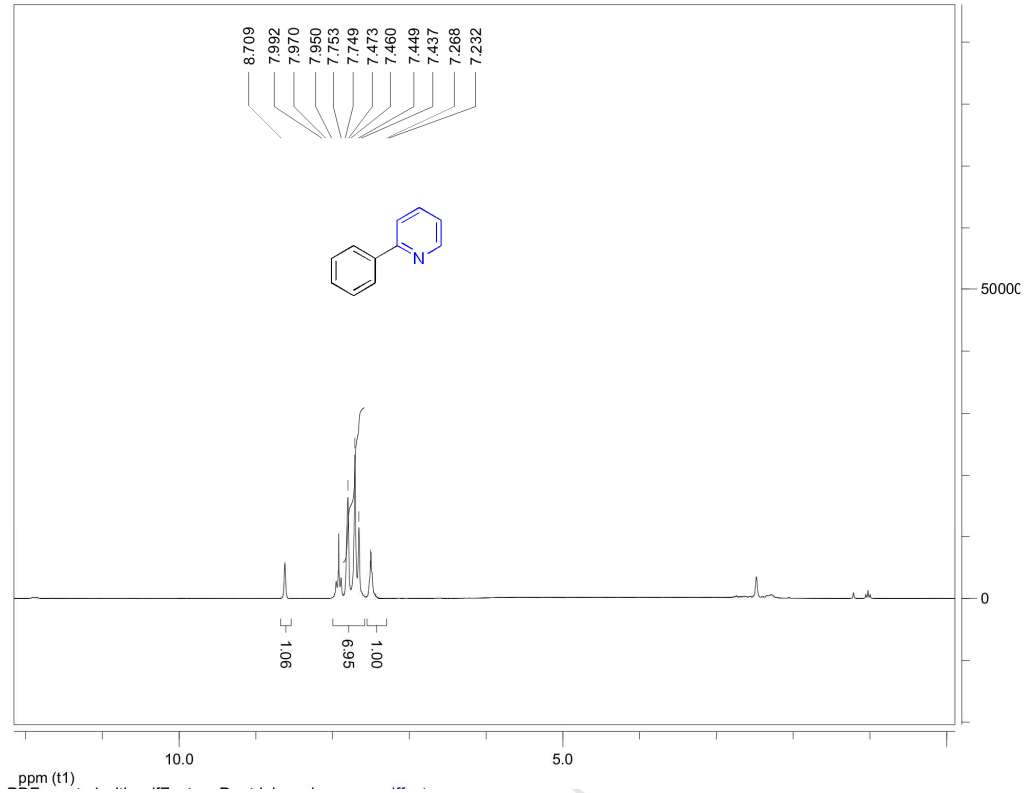


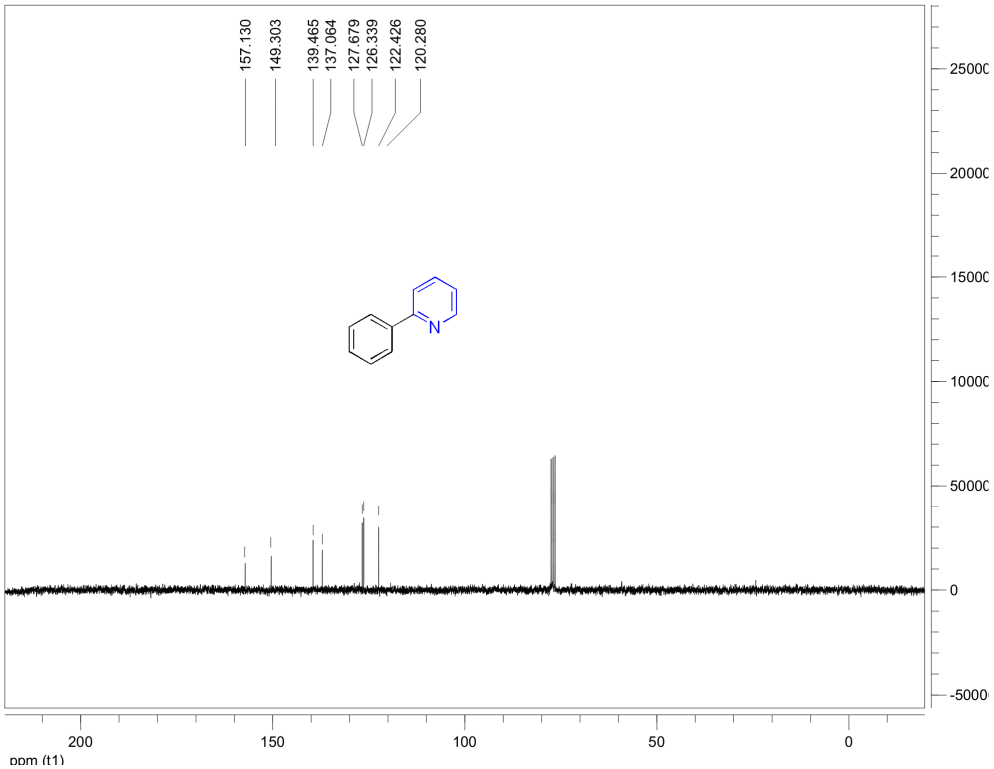
3.6. 4-Fluoro-1,1'-biphenyl (3f)



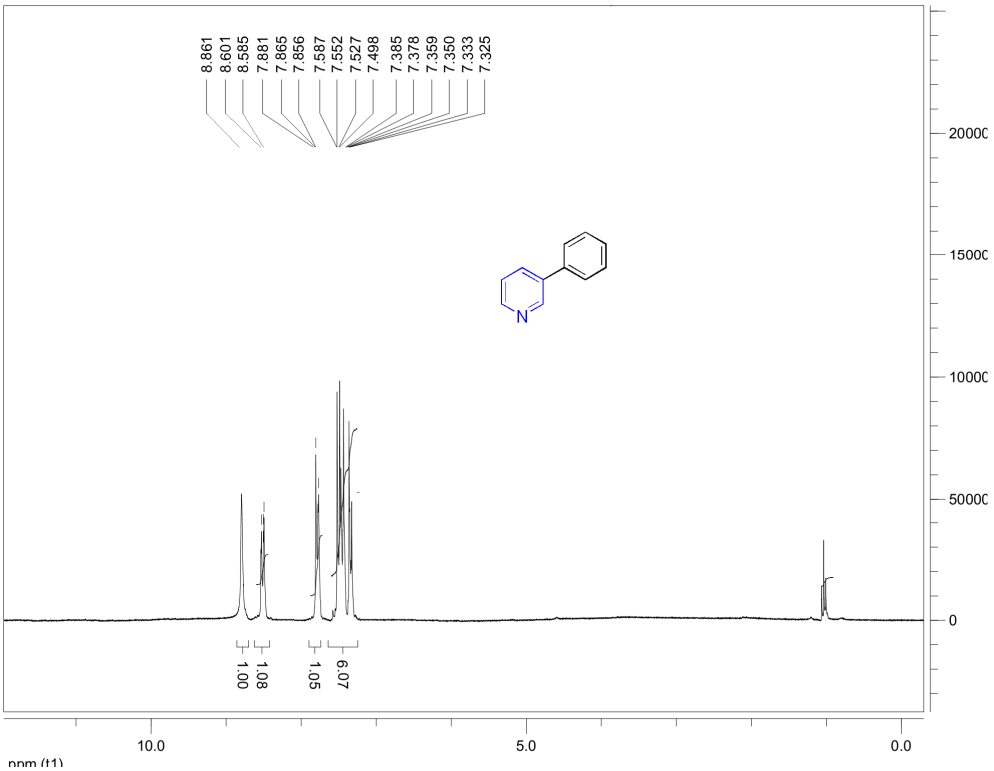


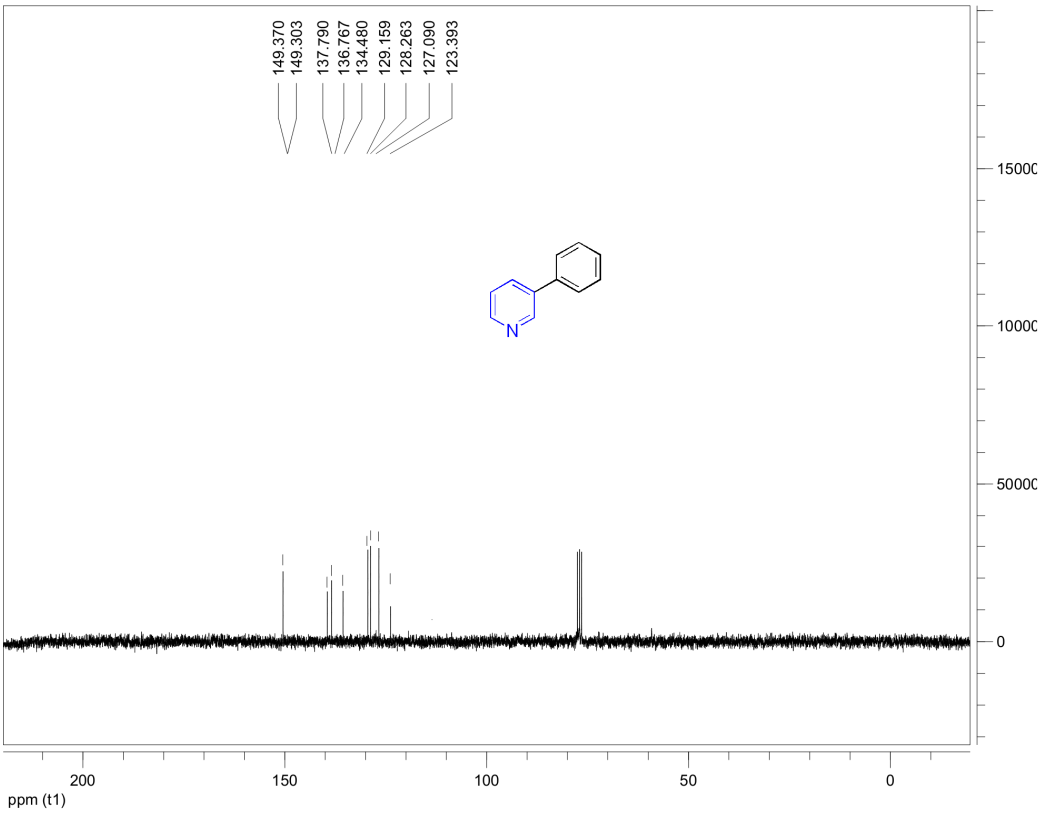
3.7. 2-Phenylpyridine (3g)



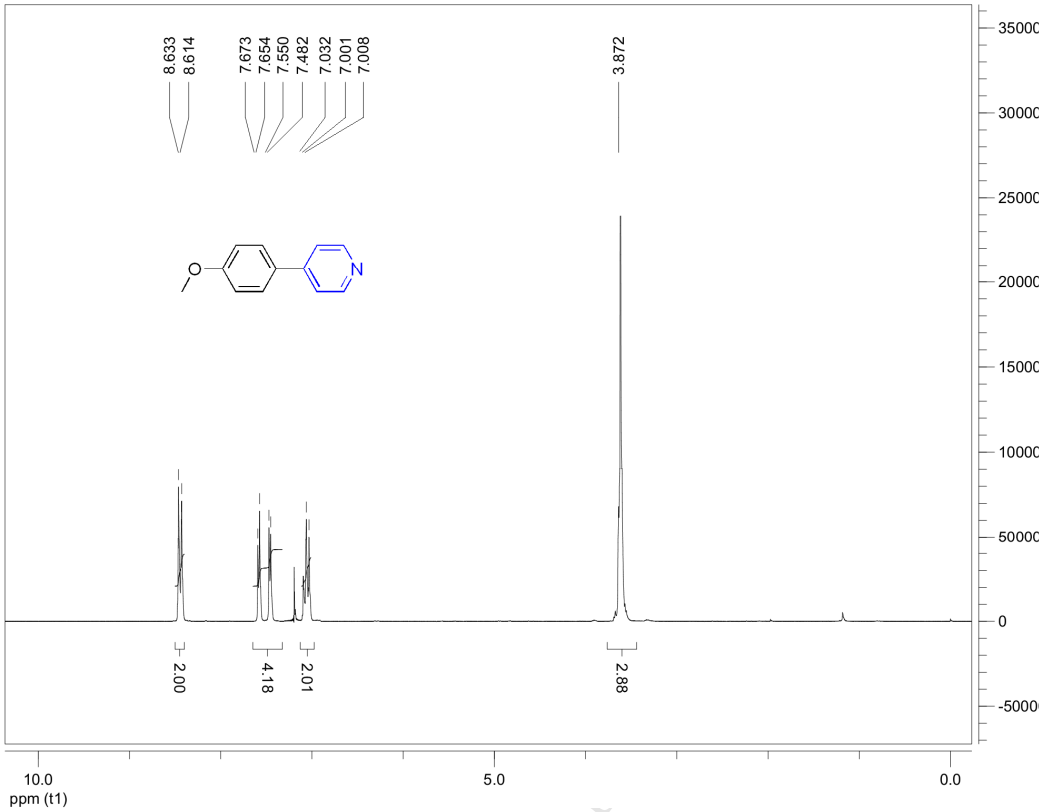


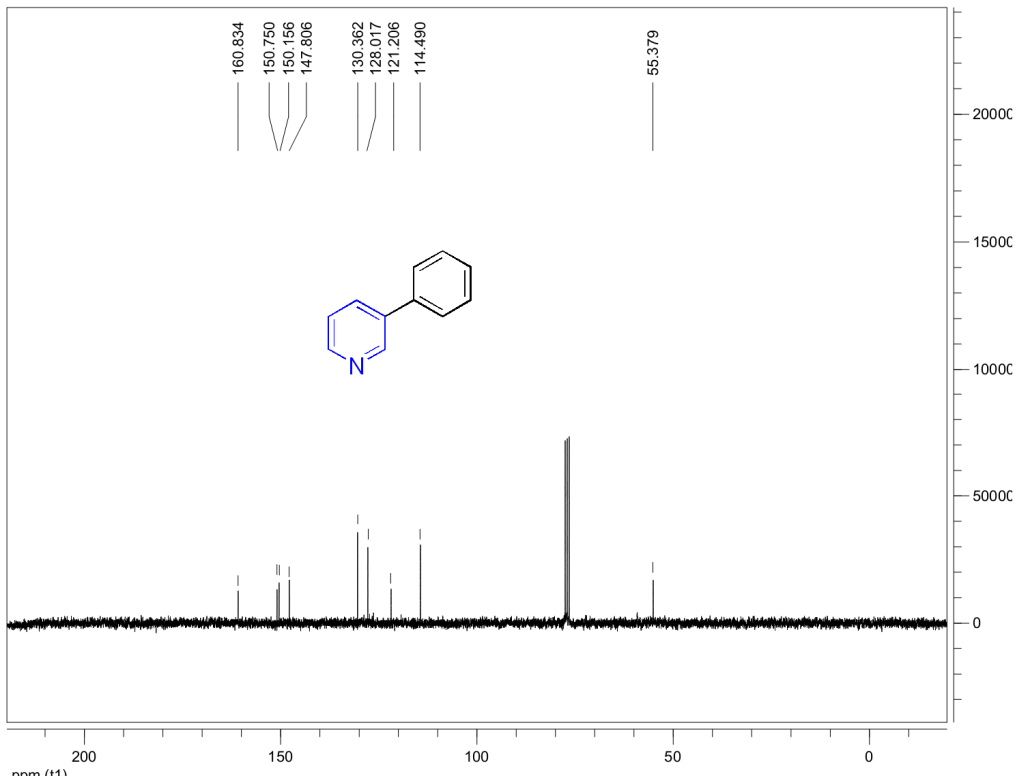
3.8. 3-Phenylpyridine (3h)



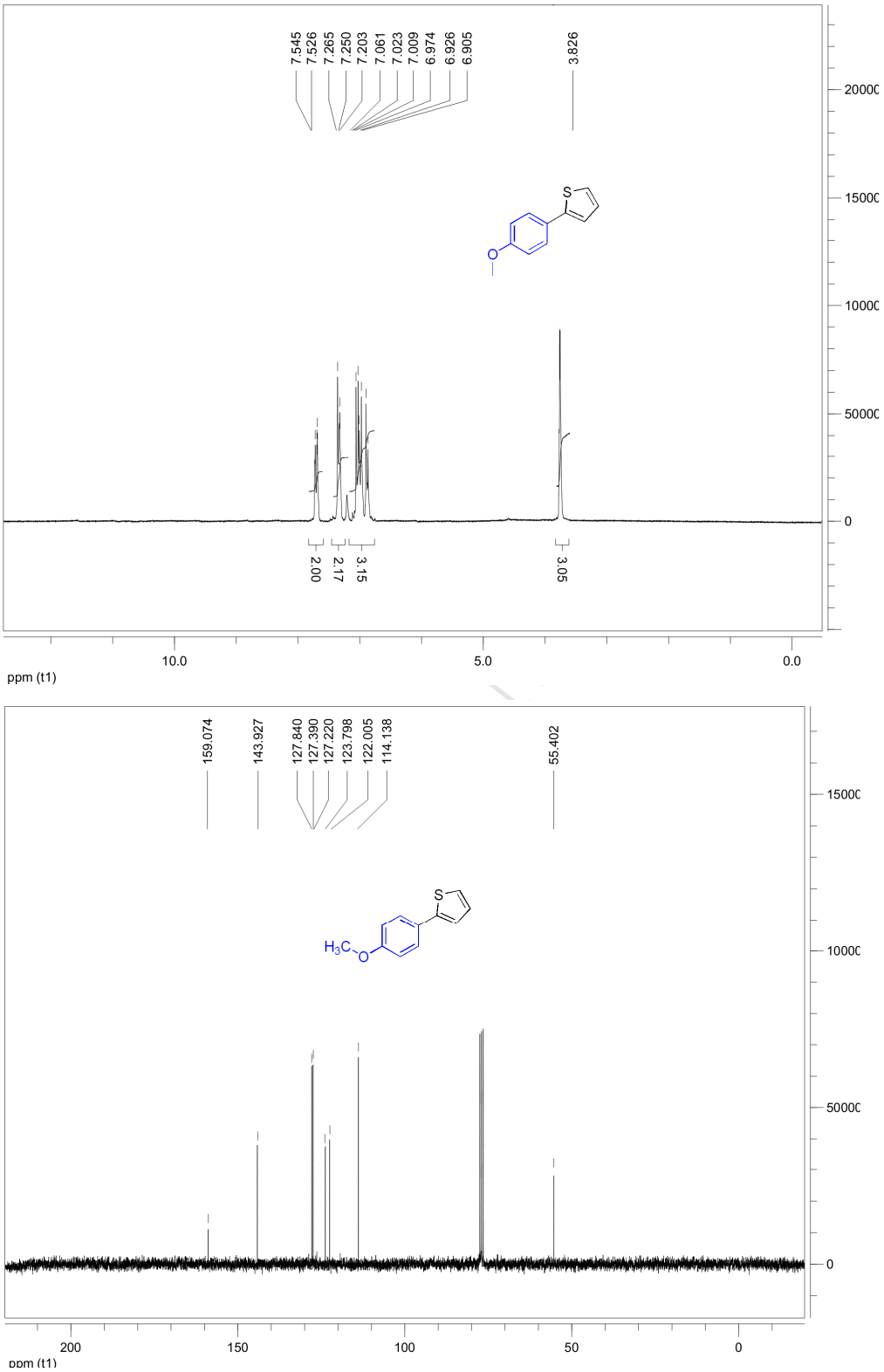


3.9. 4-(4-Methoxyphenyl)pyridine (3i)

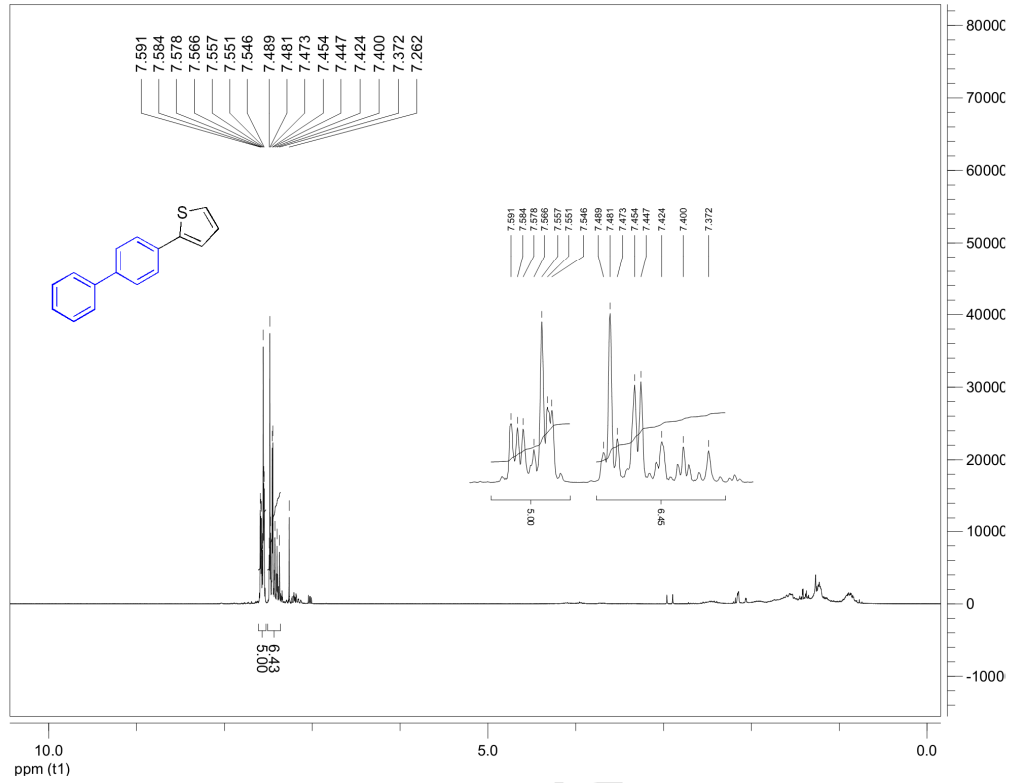


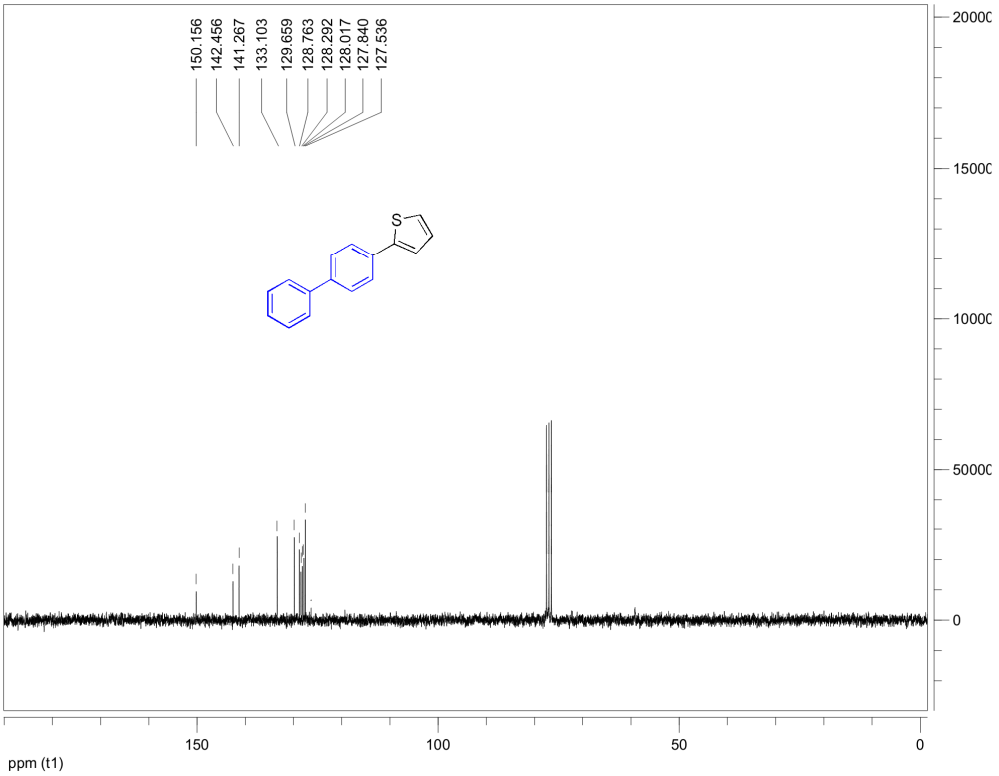


3.10. 2-(4-Methoxyphenyl)thiophene (3j)

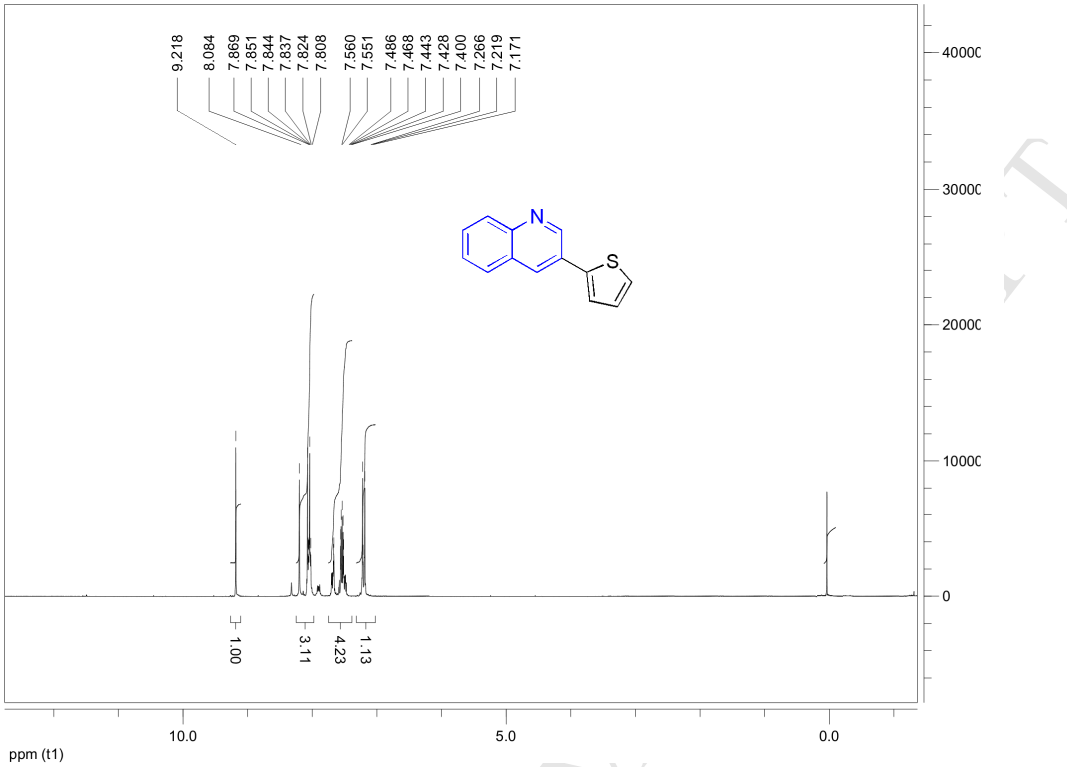


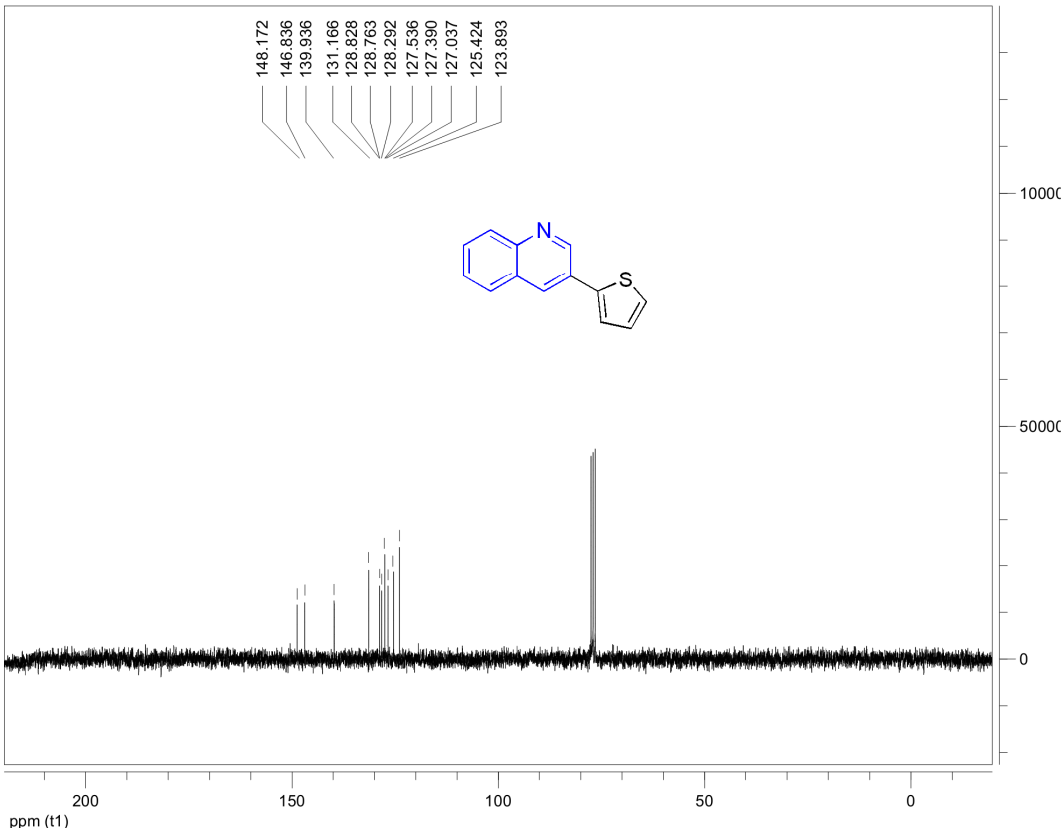
3.11. 2-([1,1'-biphenyl]-4-yl)thiophene (3k)



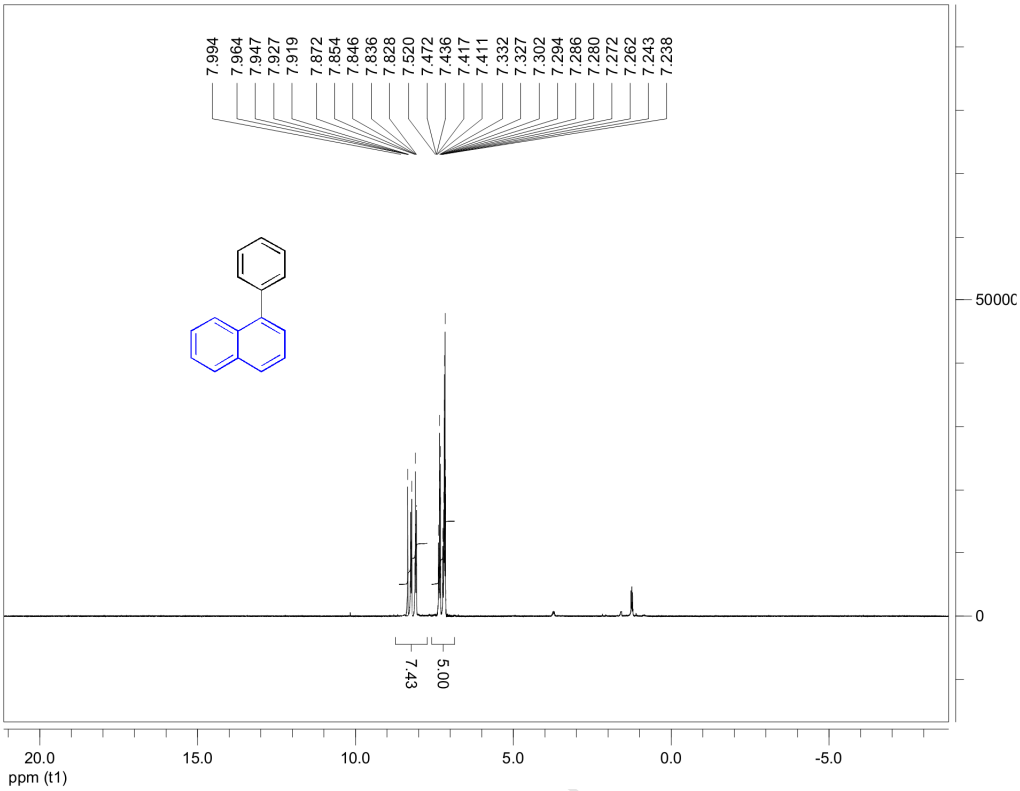


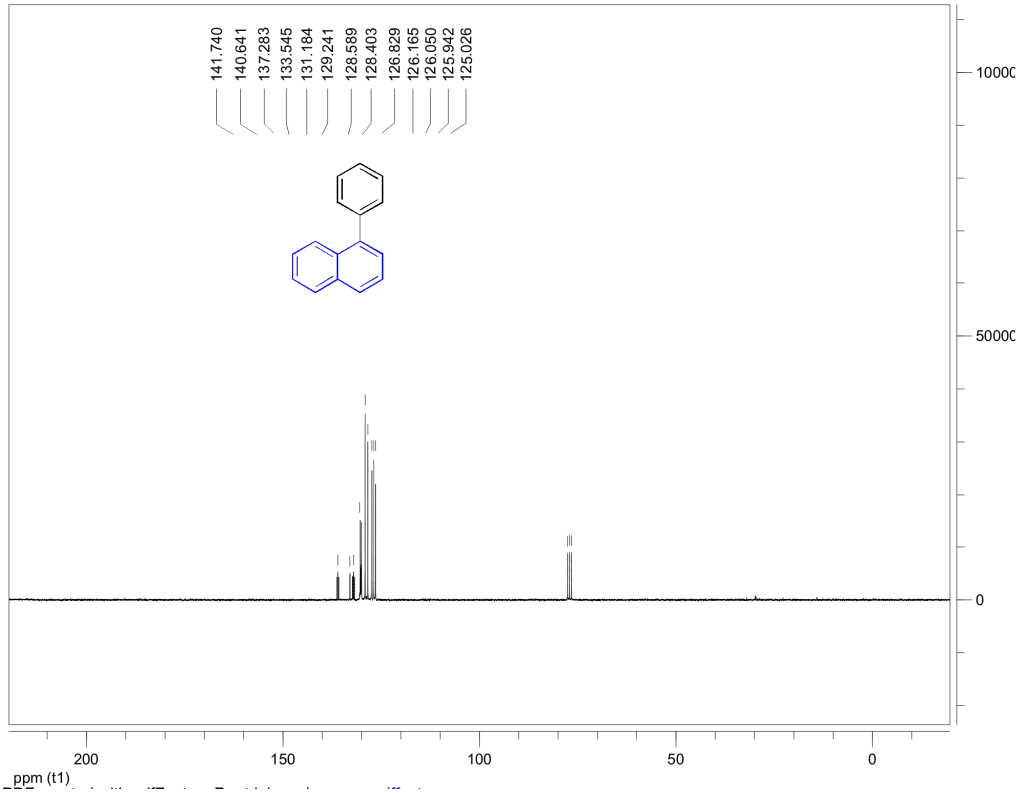
3.12. 3-(Thiophen-2-yl)quinoline (3l)



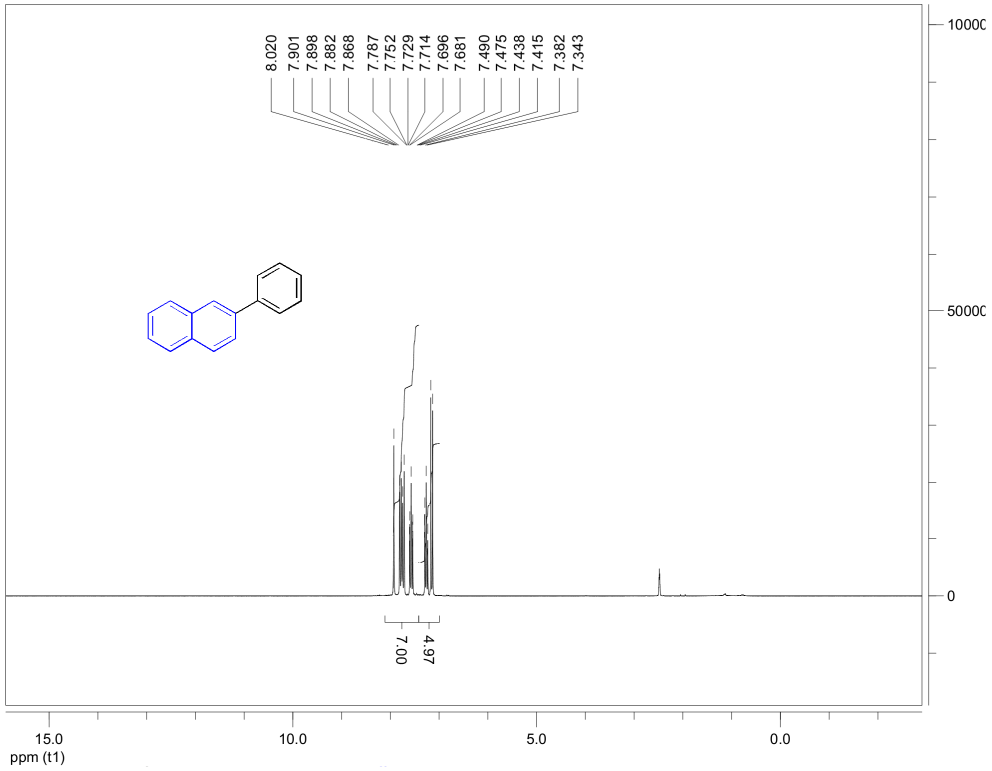


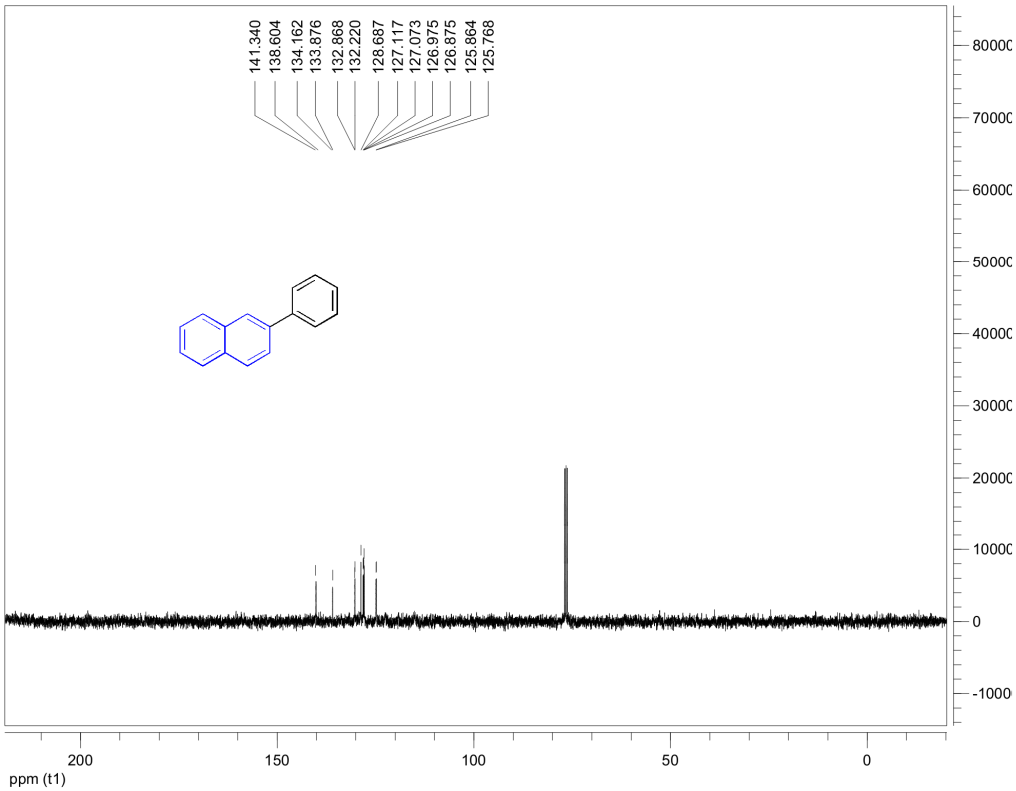
3.13. 1-Phenylnaphthalene (3m)



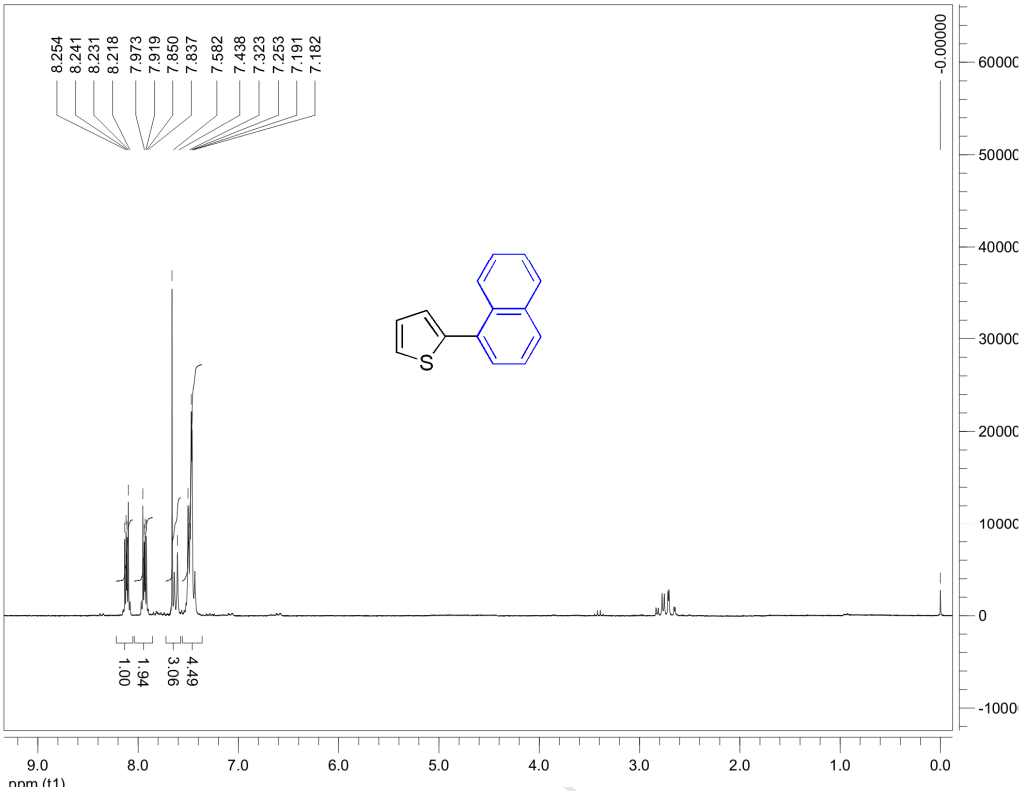


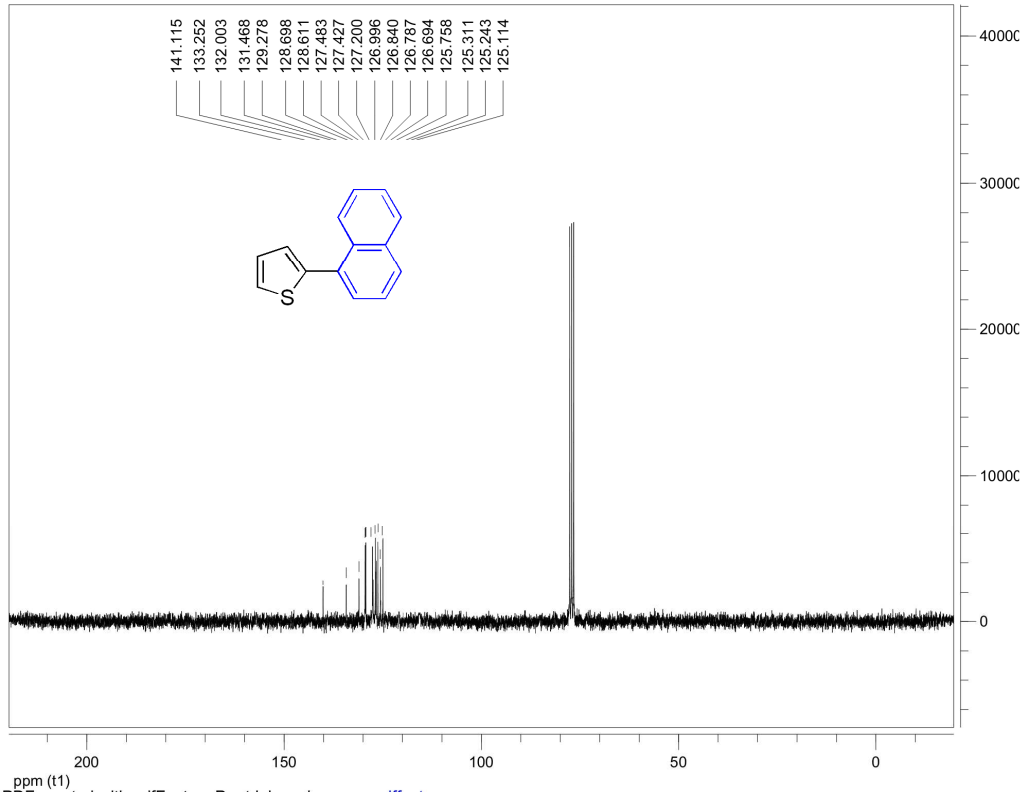
3.14. 2-Phenylnaphthalene (3n)



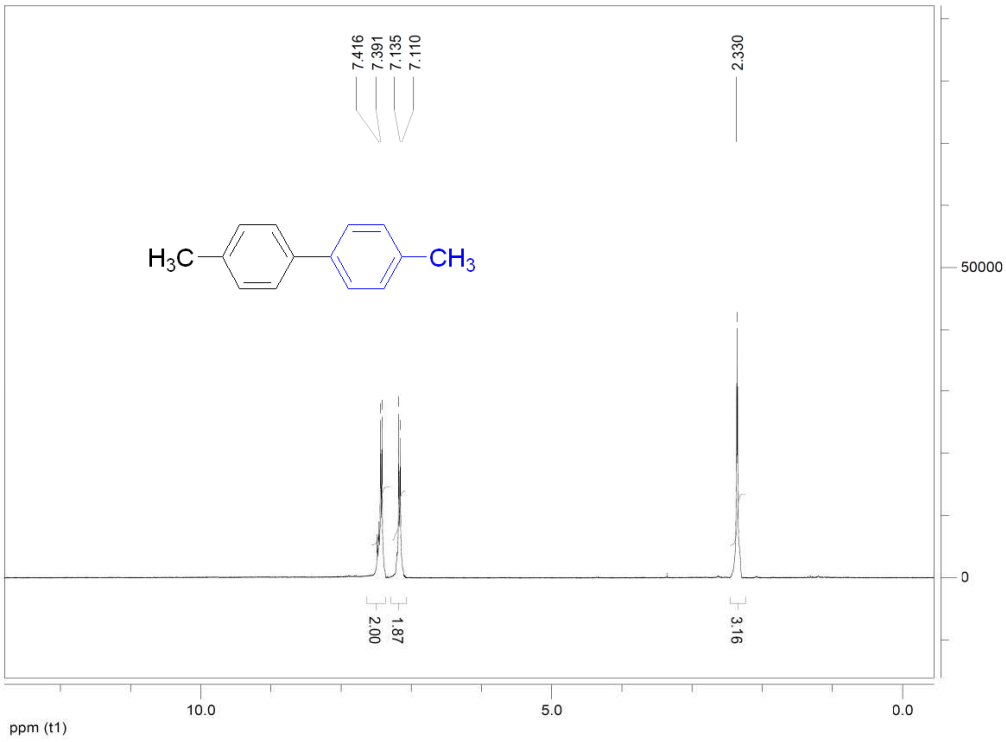


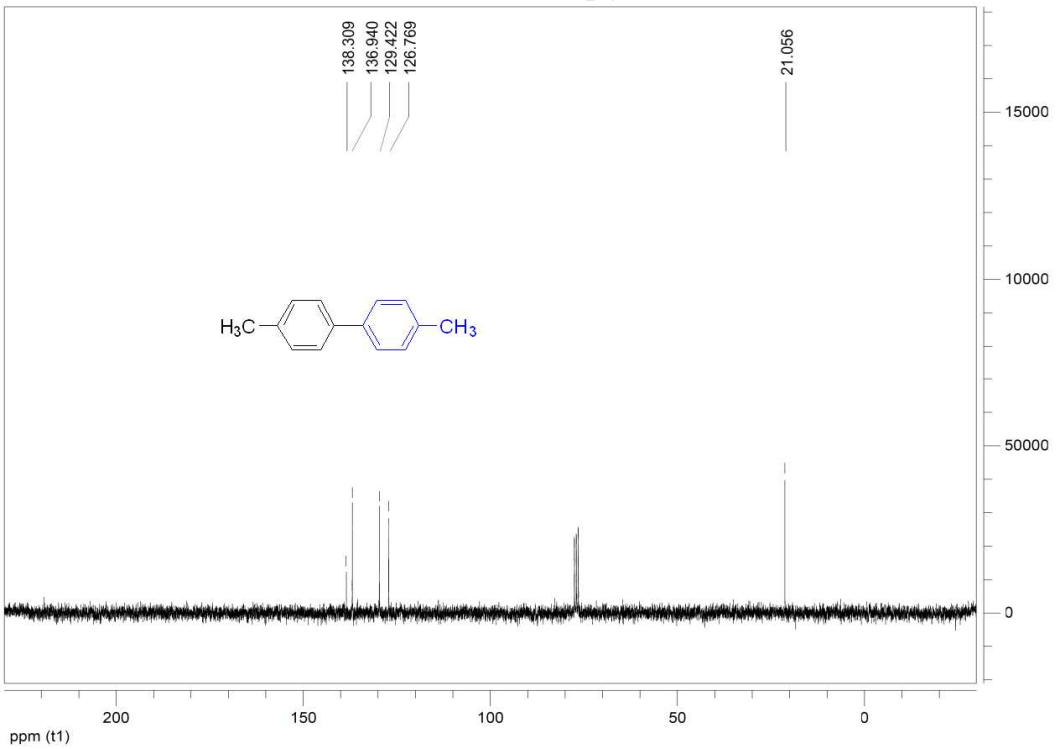
3.15. 2-(Naphthalen-1-yl)thiophene (3o)



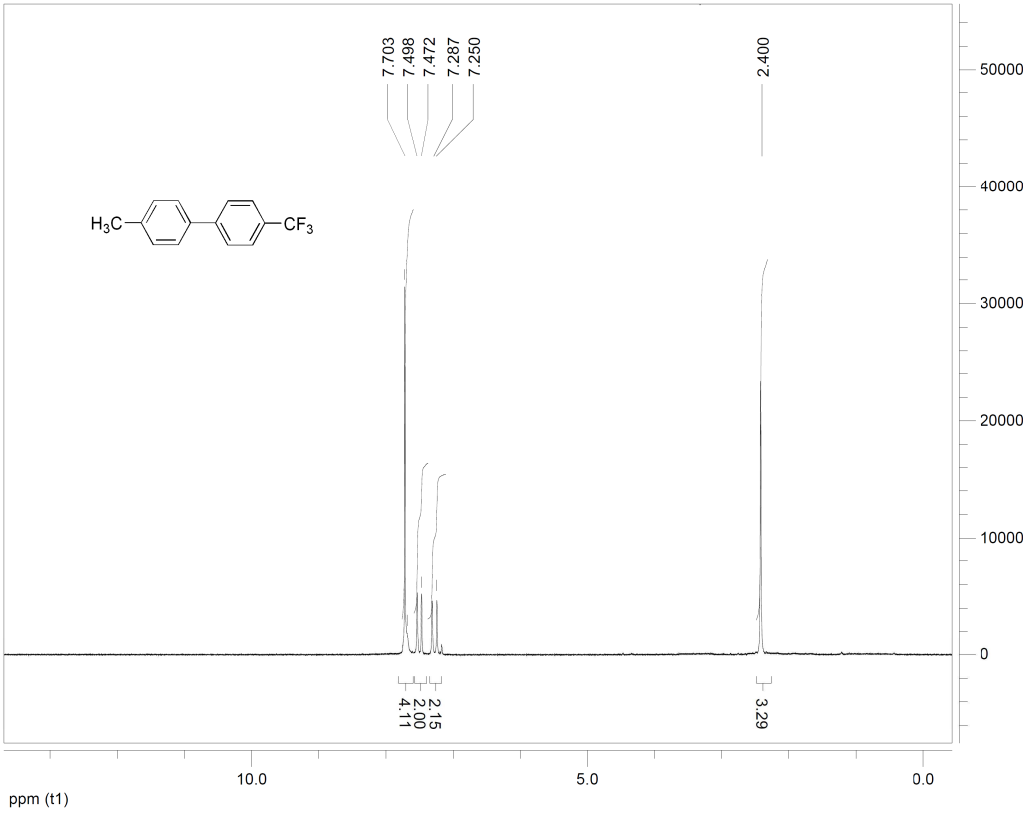


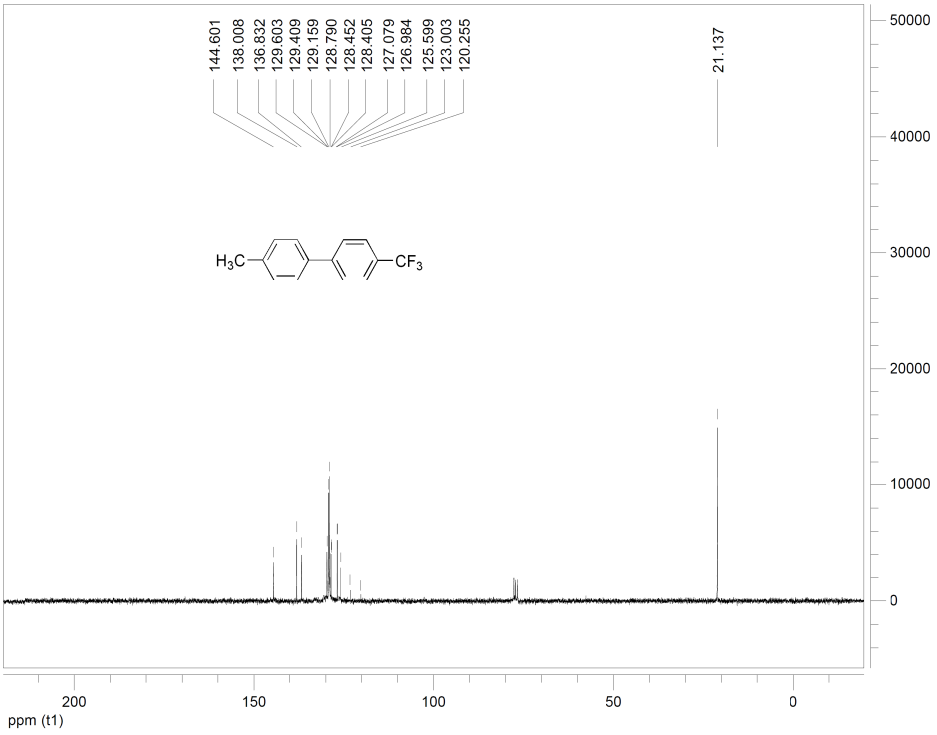
3.16. 4,4'-Dimethyl-1,1'-biphenyl (3p)



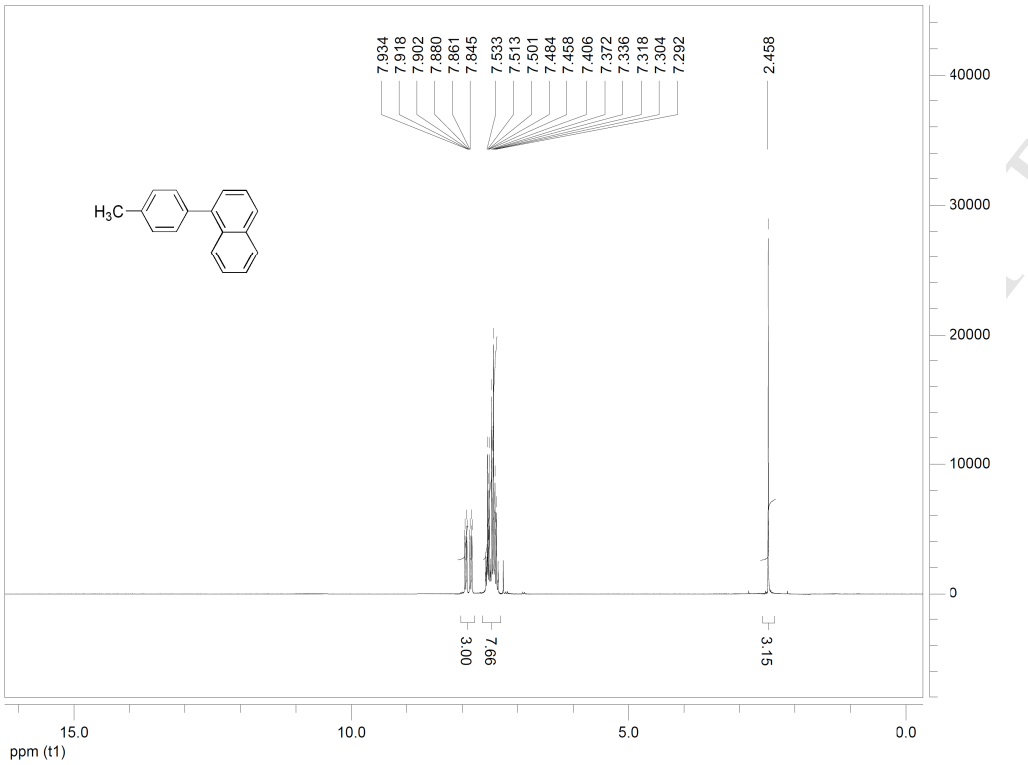


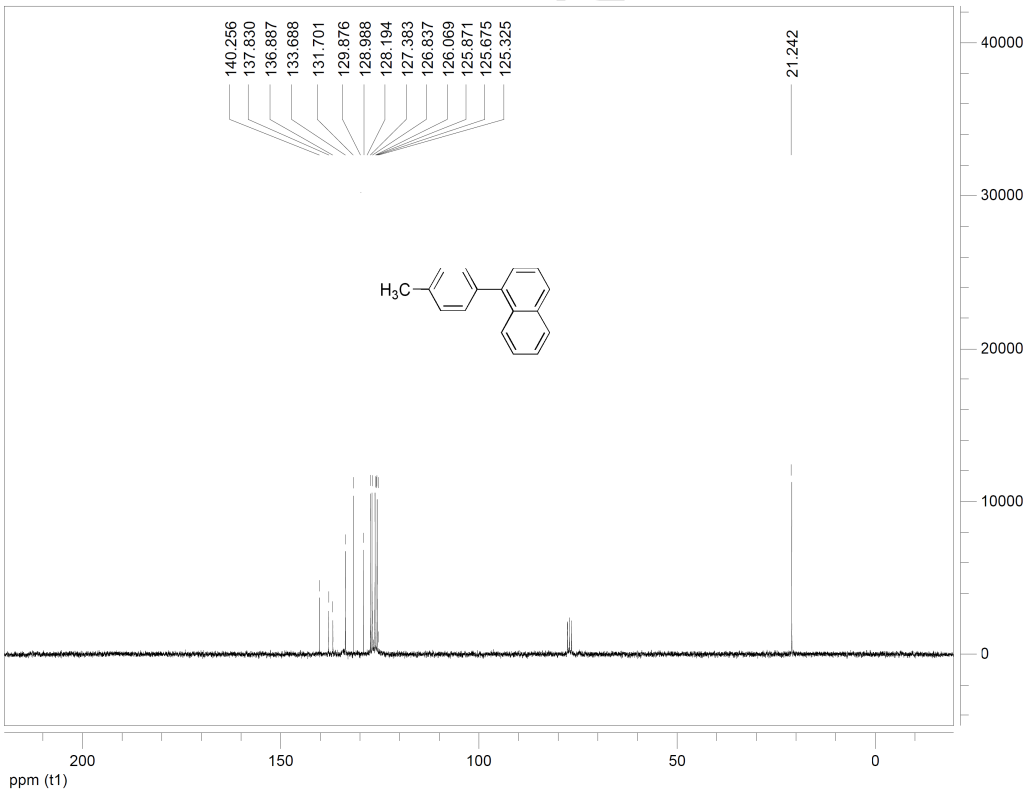
3.17. 4-Methyl-4'-(trifluoromethyl)-1,1'-biphenyl (3q)



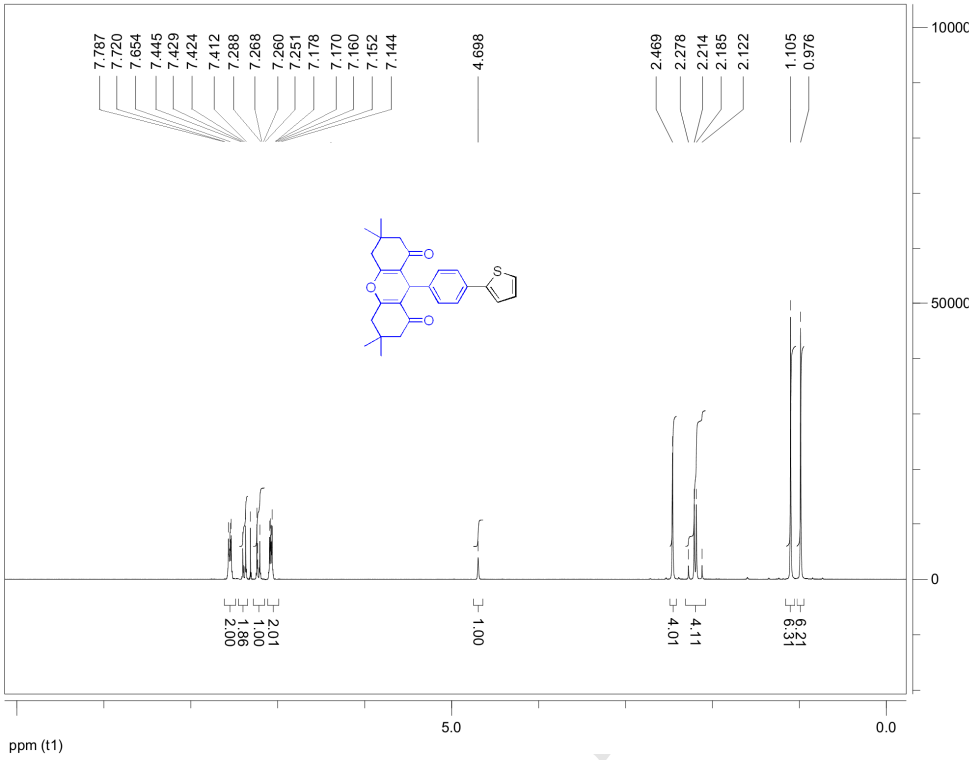


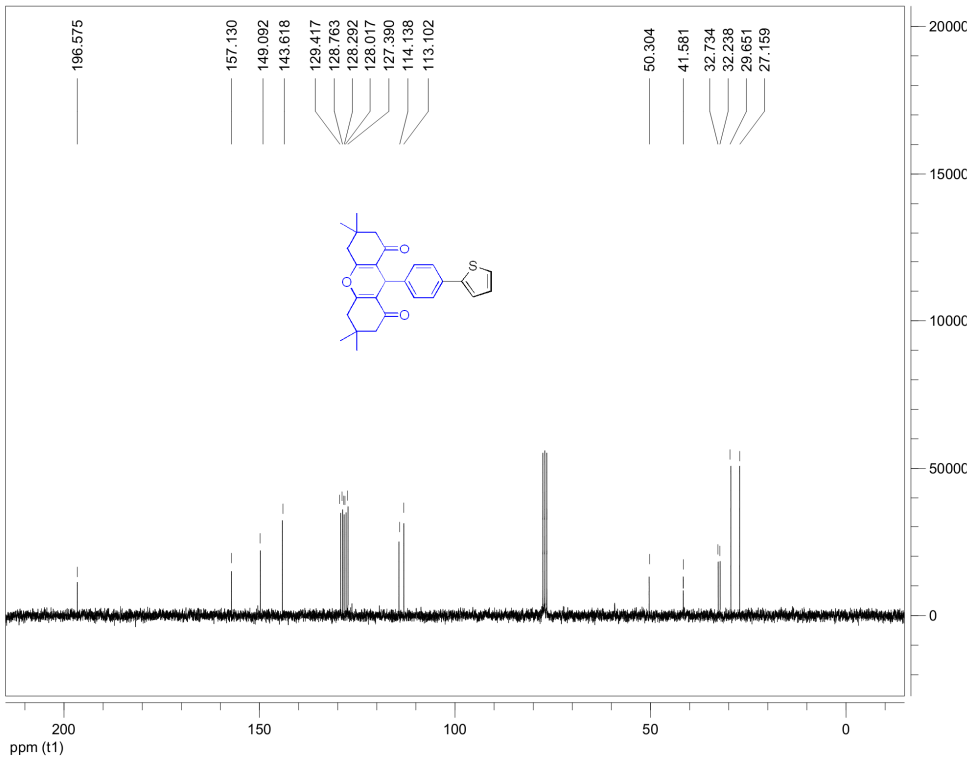
3.18. 1-(*p*-Tolyl)naphthalene (3r)





3.19. 3,3,6,6-tetramethyl-9-(4-(thiophen-2-yl)phenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3p)





3.20. 13-methyl-3-phenyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (3r)