Green Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: L. Kang, M. Luo, C. M. Lam, L. Hu, D. Little and C. Zeng, *Green Chem.*, 2016, DOI: 10.1039/C6GC00666C.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/greenchem

View Article Online
DOI: 10.1039/C6GC00666C

Electrochemical C-H functionalization and subsequent C-S and C-N bond formation: Paired electrosynthesis of 3-amino-2-thiocyanato α,β-unsaturated carbonyl derivatives mediated by bromide ion

Li-Shuo Kang, [a] Mi-Hai Luo, [a] Chiu Marco Lam, [b] Li-Ming Hu,[a] R. Daniel Little [b] and Cheng-Chu Zeng[*, a, c]

[a] College of Life Science & Bioengineering, Beijing University of Technology, Beijing 100124, P. R. China, E-mail: zengcc@bjut.edu.cn

[b] Department of Chemistry & Biochemistry, University of California, Santa Barbara, Santa Barbara 93106-9510, CA

[c] Beijing Advanced Innovation Center for Food Nutrition and Human Health, Beijing Technology and Business University, Beijing 100048, China

Abstract: An efficient paired electrosynthesis involving C-H functionalization and subsequent C-S and C-N bond formation for the assembly of valuable 3-amino-2-thiocyanato-α,β-unsaturated carbonyl derivatives has been developed. In the paired electrolysis, the amino and thiocyanato moieties originate from a single reagent or a combination of ammonium acetate and potassium isocyanate. The chemistry proceeds in a simple undivided cell employing a sub-stoichiometric amount of NH_4Br that serves both as an inner sphere type redox catalyst and a supporting electrolyte; in this manner additional conducting salt is not required. The reaction also works using catalytic amount of NH_4Br. Cyclic voltammetry and the results of control experiments demonstrate that the reaction proceeds via an anodically initiated C-H functionalization of the 1,3-dicarbonyl substrates that occurs via the electrochemical oxidation of bromide and simultaneous cathodic reduction of ammonium ion.

Keywords: electrochemical C-H functionalization; paired electrolysis; indirect electrolysis; α-thiocyanation; 3-amino-2-thiocyanato-α,β-unsaturated carbonyl derivatives

1. Introduction

Oxidative functionalization of C-H bonds to form new C-C and C-heteroatom

View Article Online
DOI: 10.1039/C6GC00666C

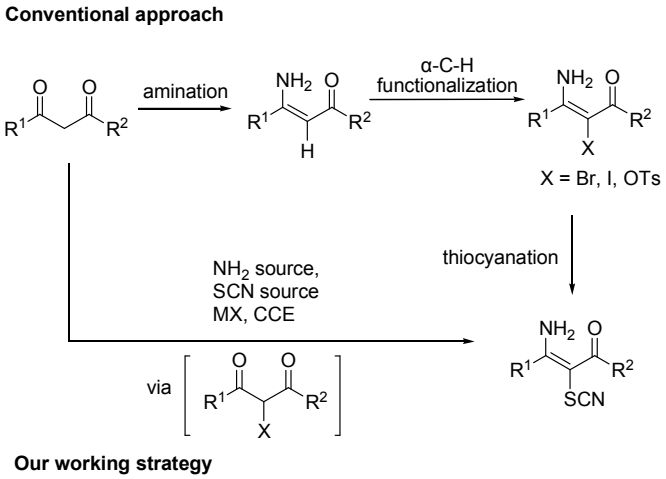
bonds has proven to be of importance in organic chemistry due to its high atom economy and responsible use of ecological resources.[1] Along with the classical methods using a chemical oxidant or photochemistry, electrochemistry provides an alternative method to achieve the C-H functionalization by heterogeneous electron transfer between an electrode and a substrate (direct electrolysis) or by using a redox catalyst (indirect electrolysis).[2] In the course of an electrolysis, paired processes have attracted much attention in both academic and industrial settings since they use both the oxidation reaction at the anode and the reduction reaction at the cathode to generate synthetically useful product(s), and (ideally) achieve a 200 % electrolysis efficiency.[3]

3-Amino-2-thiocyanato-α,β-unsaturated carboxyl compounds are useful substances that often serve in the synthesis of 4,5-disubstituted 2-aminothiazoles,[4] which in turn are invaluable intermediates for the preparation of thiazole derivatives possessing herbicidal and other important biological activities.[5] The synthesis of 3-amino-2-thiocyanato-α,β-unsaturated carboxyl compounds is generally achieved through a sequence of steps involving β-amination, introduction of an α-halo/tosyloxy substituent, and α-thiocyanation (Scheme 1).[4] This multi-step approach suffers from the use of harsh conditions, large excess of oxidizing agents, and the production of large amounts of waste.

We are interested in C-H oxidative functionalization processes induced by redox catalysts.[6] Along with the use of other mediators,[6a-6d] we have applied simple halide ions as inner sphere type redox catalysts for paired electrolysis.[6g-6i] Based on our experience in paired electrolysis and electrochemical C-H bond functionalization, we hypothesized that a constant current electrolysis (CCE) of β-dicarbonyl compounds in the presence of halide ion might initially generate α-halodicarbonyl intermediates that would further undergo α-thiocyanation and β-amination in the presence of a source of a synthetic equivalent for NH_2 and SCN (Scheme 1). We report herein a novel strategy for the synthesis of 3-amino-2-thiocyanato-α,β-unsaturated carbonyl compounds using a halide salt as a redox catalyst via paired electrolysis. The protocol features step efficiency and atom economy, avoiding pre-functionalization of the

View Article Online
DOI: 10.1039/C6GC00666C

starting β-dicarbonyl compound and tedious isolation of intermediates.

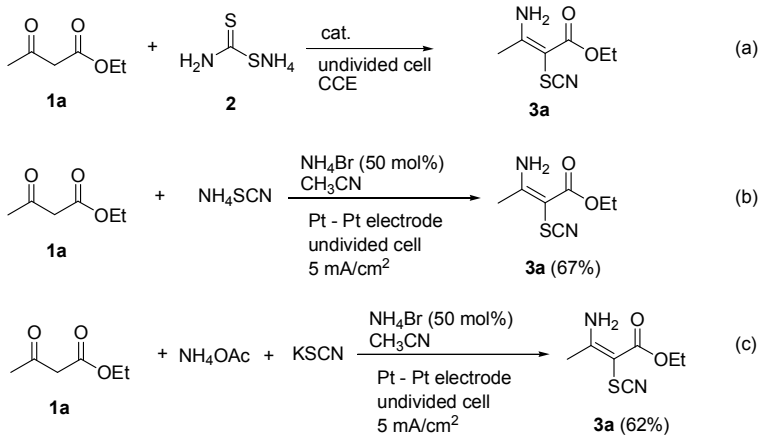


Scheme 1. Conventional approach and our working strategy for the synthesis of 3-amino-2-thiocyanato-α,β-unsaturated carbonyl compounds.

2. Results and discussion

To investigate the feasibility of the approach outlined above, we chose ethyl acetoacetate **1a** and ammonium carbamodithioate **2** as model substrates (Scheme 2a and Table 1). Attempts to optimize the reaction conditions began with a constant current electrolysis that was carried out in a simple beaker-type cell equipped with a graphite plate anode and a Ni plate cathode at room temperature. When NaI was used as a redox catalyst and methanol as a solvent, the desired adduct, (*E*)-ethyl 3-amino-2-thiocyanatobut-2-enoate (**3a**) was isolated in a 34% yield after passing 3.5 F/mol of charge (Table 1, entry 1). Encouraged by the result, redox catalyst screening was subsequently carried out in an effort to improve the yield. We observed that among all iodide and bromide salts examined (NaI, NaBr, NH_4I, NH_4Br, Et_4NBr and Bu_4NI), NH_4Br gave the best result, and a 45% yield of **3a** was achieved (Table 1, entries 2-6).

View Article Online
DOI: 10.1039/C6GC00666C

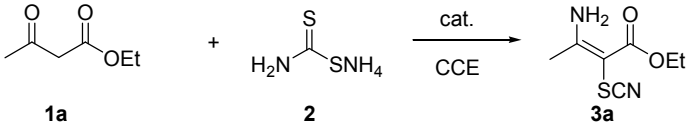


Scheme 2. Electrochemical synthesis of (E)-ethyl 3-amino-2-thiocyanatobut-2-enoate from the reaction of **1a** with different NH_2 and SCN sources.

Next, the effect of solvent was examined. It was observed that the ^1H NMR yield of **3a** increased to 73% and 79% when the electrochemical reaction was conducted in ethanol and CH_3CN, respectively (entries 7 and 8). In contrast, **3a** was not detected when DMF, DMSO, H_2O and THF were used as solvents (entries 9-12).

Further screening of electrode materials demonstrated that Pt net was preferred (entries 13 and 14). The investigation of redox catalyst loading showed that the yield of **3a** decreased from 95% to 39% when NH_4Br loading decreased from 50 to 20 mol% (compare entries 14 and 15). A further decrease of NH_4Br loading to 10 mol% decreased the yield of products significantly (entry 16). Notably, only a trace of **3a** was detected in the absence of NH_4Br, which reveals that NH_4Br is essential to the success of the one-pot electrosynthesis of **3a**.

Table 1. Optimization of the reaction conditions [a]



Entry	Anode/cathode	Mediator (equiv)	Solvent	Yield (%)[b]
1	C-Ni	NaI (0.5)	MeOH	34[c]
2	C-Ni	NaBr (0.5)	MeOH	36[c]
3	C-Ni	NH_4I (0.5)	MeOH	44[c]
4	C-Ni	NH_4Br (0.5)	MeOH	45[c]

View Article Online
DOI: 10.1039/C6GC00666C

5	C-Ni	Et_4NBr (0.5)	MeOH	43[c]
6	C-Ni	Bu_4NI (0.5)	MeOH	15[c]
7	C-Ni	NH_4Br (0.5)	EtOH	73
8	C-Ni	NH_4Br (0.5)	MeCN	79
9	C-Ni	NH_4Br (0.5)	H_2O	N. D[d]
10	C-Ni	NH_4Br (0.5)	THF	N. D[d]
11	C-Ni	NH_4Br (0.5)	DMF	N. D[d]
12	C-Ni	NH_4Br (0.5)	DMSO	N. D[d]
13	Pt-Ni	NH_4Br (0.5)	MeCN	93
14	Pt-Pt	NH_4Br (0.5)	MeCN	95, 89[c]
15	Pt-Pt	NH_4Br (0.2)	MeCN	39[e]
16	Pt-Pt	NH_4Br (0.1)	MeCN	18[e]
17	Pt-Pt	NH_4Br (0.0)	MeCN	2[e]

[a] Reaction conditions: ethyl acetoacetate **1a (**1.0 mmol**)**, **2a** (1.5 mmol) and redox mediator in 10 mL of solvent, undivided cell, room temperature, current density of 5 mA/cm^2, about 3.5 F/mol of charge.

[b] ^1H NMR yield.

[c] Isolated yield after column chromatograph.

[d] Non detected.

[e] ^1H NMR yield in the presence of 0.1 M $LiClO_4$ as supporting electrolyte.

For the reactions described above, the -NH_2 and -SCN subunits of the product **3a** both originate from **2**. For completeness, alternative sources were also explored. As shown in Scheme 2b, under the optimal reaction conditions described above, but using NH_4SCN in place of ammonium carbamodithioate, **3a** was isolated in a 67% yield. In addition, when a combination of NH_4OAc and KSCN were employed as potential sources of NH_2 and SCN, **3a** was produced in a 62% isolated yield (Scheme 2c). In each case, the yield of **3a** was lower than using **2** (entry 14, Table 1). We therefore prefer to use **2** for the paired electrolysis.

View Article Online
DOI: 10.1039/C6GC00666C

With the optimal conditions in hand, we then studied the scope and the generality of the protocol, by examining reactions of ammonium carbamodithioate **2** with a variety of 1,3-dicarbonyl compounds, **1**. As shown in Table 2, 3-oxoesters, such as methyl (**1b**) and *t*-butyl ester (**1c**), afforded the corresponding adducts **3b** and **3c** in 75% and 85% yields, respectively (entries 2 and 3, Table 2). Good yields of **3d** (80%) and **3e** (71%) were also obtained when **1d** and **1e** were employed as the 3-oxoester counterparts (entries 4 and 5, Table 2). Notably, when the hindered *t*-butyl ketone **1f** was subjected to the optimal conditions, adduct **3f** was not isolated and presumably did not form (entry 6).

The standard conditions could also be applied to 3-oxoamides, although slightly lower yields were obtained when compared to the corresponding 3-oxoesters. As shown in Table 2, use of 3-oxobutanamide derivatives, **1g**, **1h**, and **1i**, afforded the desired products in 59%, 55% and 52% yields, respectively (entries 7-9).

The electrochemical reaction of **2** with aliphatic 1,3-diketones also proceeded smoothly. For example, when pentane-2,4-dione (**1j**) was subjected to electrolysis under the standard conditions, adduct **3j** formed in an 80% yield (entry 10). Cyclic diketones such as cyclohexane-1,3-dione (**1k**), and 5,5-dimethyl cyclohexane-1,3-dione (**1l**), also worked well, leading to good yields of **3k** and **3l** (entries 11 and 12).

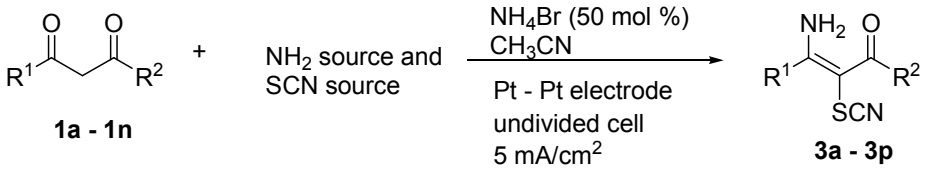
The standard conditions were also applied to aromatic 1,3-dicarbonyl compounds. It was found that the reaction of phenylbutane-1,3-dione (**1m**) with **2** proceeded sluggishly and only 11% of adduct **3m** was isolated (entry 13). By using KSCN and NH_4OAc, the yield of **3m** increased to 22% (entry 14). However, in the cases of **1n,** the product **3n** was not detected (entry 15); instead, 4-methoxybenzoic acid was isolated in a 12% yield. We note, too, that in the reactions with aromatic 1,3-dicarbonyl compounds described above, an unidentified white precipitate was formed as the main product, which is believed to be a polymer, although its exact structure is not known, since the precipitate is insoluble in MeOH, EtOH, CH_3CN, CH_2Cl_2, EtOAc, acetone and water.

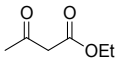
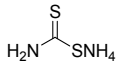
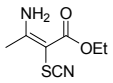
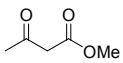
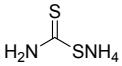
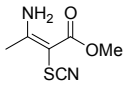
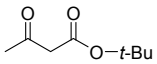
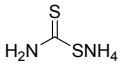
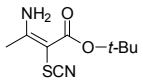
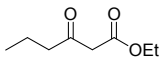
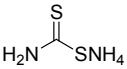
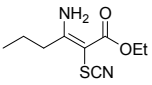
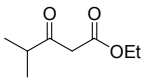
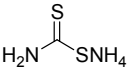
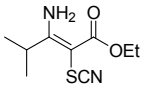
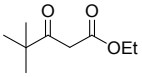
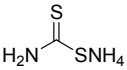
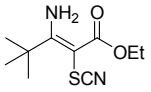
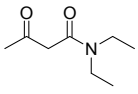
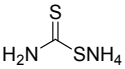
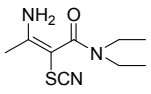
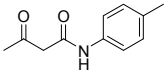
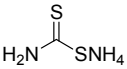
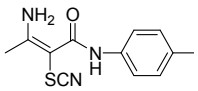
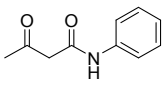
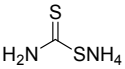
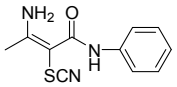
Other sources of the NH_2 functionality were also tolerated by the paired

View Article Online
DOI: 10.1039/C6GC00666C

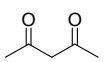
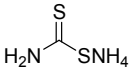
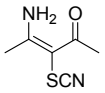
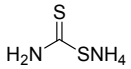
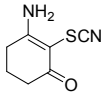
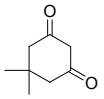
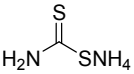
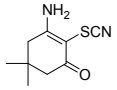
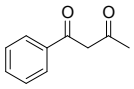
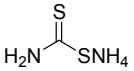
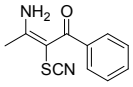
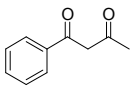
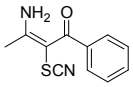
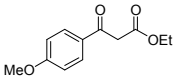
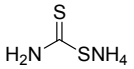
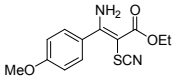
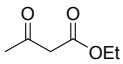
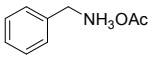
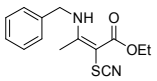
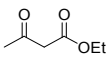
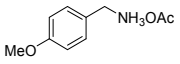
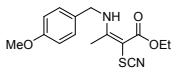
electrolysis protocol. For example, the reactions of ethyl acetoacetate **1a** with benzyl ammonium acetate under the standard conditions afforded adduct **3o** in a 39% yield (entry 16). Similarly, a 26% yield of adduct **3p** was isolated when *p*-methoxybenzyl ammonium acetate was used as the amino source (entry 17).

Table 2. Scope and generality of the electrochemical reaction.



entry	diketone		SCN source	NH_2 source	product		yield
1		**1a**				**3a**	89
2		**1b**				**3b**	75
3		**1c**				**3c**	85
4		**1d**				**3d**	80
5		**1e**				**3e**	71
6		**1f**				**3f**	-
7		**1g**				**3g**	59
8		**1h**				**3h**	55
9		**1i**				**3i**	52

View Article Online
DOI: 10.1039/C6GC00666C

10		**1j**				**3j**	80
11		**1k**				**3k**	67
12		**1l**				**3l**	49
13		**1m**				**3m**	11
14		**1m**	KSCN	NH_4OAc		**3m**	22
15		**1n**				**3n**	-[c]
16		**1a**	KSCN			**3o**	39%
17		**1a**	KSCN			**3p**	26%

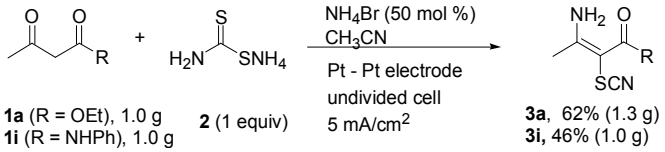
[a] Reaction conditions: diketone derivatives **1** (1.0 mmol), NH_2 and SCN source (each 1.5 mmol) and NH_4Br (0.5 equiv) in 10 mL of acetonitrile, undivided cell, platinum net (2×2.5 cm^2) as anode and cathode electrodes, 40 ^oC, constant current electrolysis at current density of 5 mA/cm^2, ~3.5 F/mol charge.

[b] Isolated yield.

[c] 4-methoxybenzoic acid was isolated as the main product.

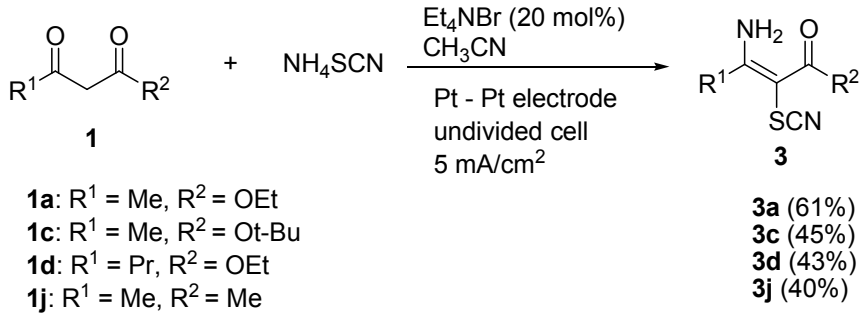
In addition to the wide range of substrates to which our protocol is applicable, we note that it can be scaled to gram quantities thus highlighting its practicality. As shown in Scheme 3, when 1.0 gram of **1a** or **1i** was allowed to react with **2** under the standard conditions, adducts **3a** (from **1a**) and **3i** (from **1i**) were isolated in 62 % and 46 % yields, respectively.

View Article Online
DOI: 10.1039/C6GC00666C

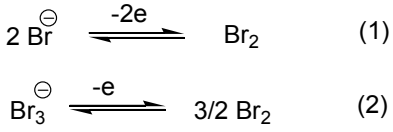


Scheme 3. Scaling up

The process can also be achieved using catalytic amounts of bromide salt. As shown in Scheme 4, when NH_4SCN was used, its reaction with 1,3-dicarbonyl compounds in the presence of 20 mol% of Et_4NBr as a redox catalyst gave moderate to good yields of the corresponding adducts.



Scheme 4. Paired electrolysis of 3-amino-2-thiocyanato-α,β-unsaturated carbonyl derivatives using a catalytic amount of bromide ion



To provide mechanistic insight, cyclic voltammetry was used as the initial tool. As shown in curve a of Figure 1, the CV of NH_4Br in acetonitrile exhibits two oxidation waves, one at 0.60 V and the other, 0.93 V vs $Ag/AgNO_3$ (0.1 M in CH_3CN). According to the literature,[7] we assign the first peak to correspond to the oxidation of bromide to form molecular bromine, Br_2 (eq. 1). Once formed, its reaction with bromide ion leads to tribromide Br_3^-. The second wave is therefore attributed to the anodic oxidation of Br_3^- to produce Br_2 (eq. 2). Curve b refers to the CV of NH_4Br in the presence of 5 equiv of ethyl acetoacetate. Here we observe that the intensity of the two oxidation peaks increases, while the reduction peak current decreases. Since ethyl acetoacetate is not oxidized in the potential range from 0.0 V to 1.5 V vs $Ag/AgNO_3$ (0.1 M in CH_3CN) that was used (curve e), the increase in the oxidative peak current

View Article Online
DOI: 10.1039/C6GC00666C

is attributed to a catalytic current, resulting from the reaction of the in situ electrochemically-generated bromine and ethyl acetoacetate, generating α-bromo ethyl acetoacetate and bromide ion that leads to an increase of oxidation peak current and the appearance of catalytic current accompanying the conversion of **1** to **5** (Scheme 5).

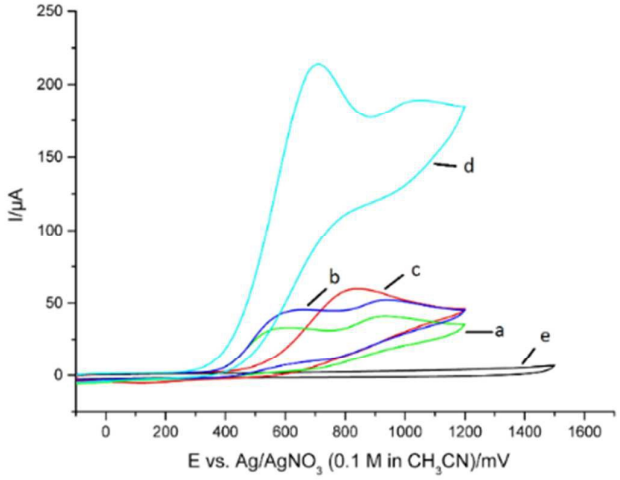


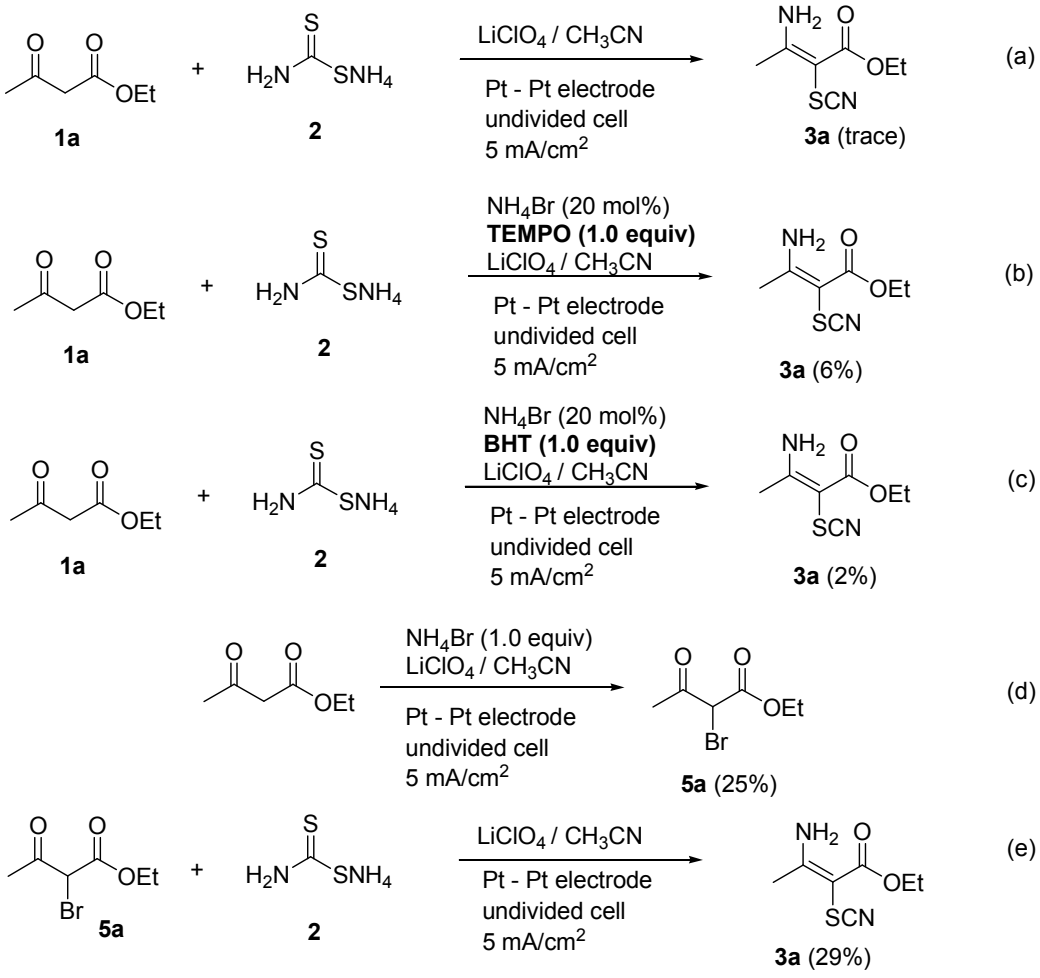
Figure 1. Cyclic voltammogram of NH_4Br, **1a** and **2** in 0.1 M $LiClO_4/CH_3CN$, using GC disk working electrode, Pt wire and $Ag/AgNO_3$ (0.1 M in CH_3CN) as counter and reference electrode at 100 mV/s scan rate. a: NH_4Br (2 mmol/L). b: NH_4Br (2 mmol/L) and **1a** (10 mmol/L). c: **2** (2 mmol/L). d: NH_4Br (2 mmol/L), **1a** (10 mmol/L) and **2** (10 mmol/L). e: **1a** (2 mmol/L).

Curve c, portraying the CV of **2**, reveals an irreversible oxidation peak at 0.83 V vs $Ag/AgNO_3$ (0.1 M in CH_3CN). It is significant to note that when **2** was added to the mixture described above, an additional dramatic increase in the catalytic current was observed (curve d). Thus, the first peak current increased from 33 to 214 μA, indicating that **2** promotes the regeneration of bromide anion (note the conversion of **5** to **6** in Scheme 5).

Several control experiments were performed in an effort to obtain additional insight into the reaction mechanism. As shown in Scheme 5a, the direct electrolysis of the mixture of **1a** and **2** using $LiClO_4$ as the conducting salt, without the presence of a halide-based salt, afforded only trace amounts of **3a**, indicating that the efficient formation of **3a** involves halide as a mediator. When the reaction was performed in

View Article Online
DOI: 10.1039/C6GC00666C

the presence of TEMPO, a radical scavenger, less than 6% yield of **3a** was detected (Scheme 5b), as was also the case in the presence of BHT (Scheme 5c). These results implicate the role of a radical intermediate. Electrolysis of the ethyl acetoacetate, **1a**, in the absence of **2** under otherwise identical conditions afforded ethyl 2-bromo-3-oxobutanoate **5a** in 25% (Scheme 5d). Moreover, an electrolysis of a mixture of the α-bromo keto ester **5a** and **2** without the addition of a bromide salt, produced **3a** in a 29% yield (Scheme 5e). These results indicate that the brominated keto ester **5a** is likely a key intermediate for the one-pot synthesis of 3-amino-2-thiocyanatobut-2-enoate, under our standardized reaction conditions.

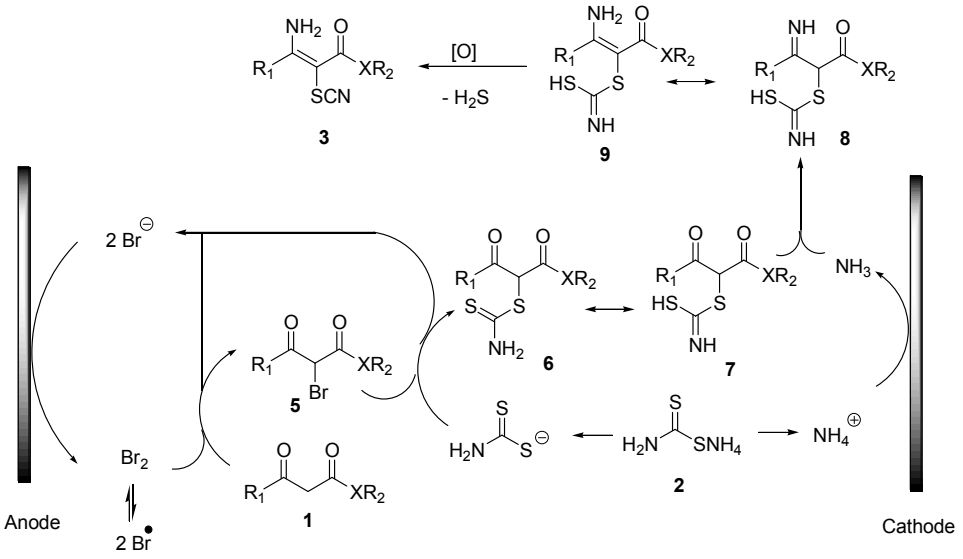


Scheme 5. Controlled experiments

Based on the CV analysis and preparative scale electrolysis results, a

View Article Online
DOI: 10.1039/C6GC00666C

plausible mechanism is proposed and shown in Scheme 5. The reaction sequence begins with the anodic oxidation of bromide ion to form molecular bromine and its subsequent reaction with substrates **1** to afford α-brominated structures **5**. During this step, bromide is regenerated. The subsequent nucleophilic substitution reaction of **5** with the carbamodithioate anion, resulting from the dissociation of the ammonium salt **2**, generates intermediate **6** or its tautomer **7**. Once again, the bromide ion is regenerated, this time in the subsequent thiocyanation (**5**→**6**) step. The generated bromide is oxidized again at the surface of the anode and enter the redox cycle. Therefore, the bromide works as an inner sphere type redox mediator.[2c] Meanwhile, the cathodic reduction of ammonium ion affords ammonia, which reacts with **7** to afford the ketoimine **8** and its tautomer **9**. Further anodic oxidation of **9** leads to the expulsion of H_2S and production of the final product **3**.[8,9]



Scheme 6. Proposed mechanism for the electrochemical synthesis of 3-amino-2-thiocyanato-α,β-unsaturated carbonyl derivatives mediated by NH_4Br.

3. Conclusion

In summary, an effective electrochemical protocol for the synthesis of 3-amino-2-thiocyanato-α,β-unsaturated carbonyl derivatives has been developed. The

View Article Online
DOI: 10.1039/C6GC00666C

chemistry proceeds via a paired electrolysis mode in a simple undivided cell, wherein bromide is oxidized anodically and ammonium ion is reduced cathodically. In the reaction, an additional conducting salt is not required and a sub-stoichiometric amount of bromide salt serves both as an inner sphere type redox catalyst and the supporting electrolyte. The reaction also works using catalytic quantities of Et_4NBr as a redox catalyst. The ability to scale up the protocol demonstrates its practicality. The paired electrolysis avoids pre-functionalization, tedious isolation of intermediates, the utilization of external oxidants, the production of large amount of waste, and therefore represents an environmentally benign means by which to achieve the transformation. Application of these ideas and results to other types of reactions is underway in our laboratory.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (No. 21272021, 21472011) and the National Key Technology R&D Program (2011BAD23B01). ZCC and RDL are grateful to the US National Science Foundation supported PIRE-ECCI Program (OISE-0968399) for fostering our international collaboration, and the Center for the Sustainable Use of Renewable Feedstocks (CenSURF), an NSF Center for Chemical Innovation (CHE-1240194).

References

1 (*a*) S. A. Girard, T. Knauber and C. J. Li, *Angew. Chem., Int. Ed*., 2014, **53**, 74; (*b*) I. B. Krylov, V. A. Vil and A. O. Terentev, *Beilstein J. Org. Chem*., 2015, **11**, 92; (*c*) C. L. Sun and Z. J. Shi, *Chem. Rev*., 2014, **114**, 9219; (*d*) R. Narayan, K. Matcha and A. P. Antonchick, *Chem. Eur. J*., 2015, **21**, 14678; (*e*) R. Samanta, K. Matcha and A. P. Antonchick, *Eur. J. Org. Chem*., 2013, **26**, 5769.

2 For some excellent reviews of organic electrochemical reactions used in synthesis, see: (*a*) J. I. Yoshida, K. Kataoka, R. Horcajada and A. Nagaki, *Chem. Rev*., 2008, **108**, 2265; (*b*) J. B. Sperry and D. L. Wright, *Chem. Soc. Rev*., 2006, **35**, 605. For reviews of indirect electrolysis, see: (*c*) R. Francke and R. D. Little, *Chem. Soc. Rev*., 2014, **43**, 2492; (*d*) Y. N. Ogibin, M. N. Elinson and G. I. Nikishin, *Russ.*

View Article Online
DOI: 10.1039/C6GC00666C

Chem. Rev., 2009, **78**, 89; (*e*) E. Steckhan, *Angew. Chem., Int. Ed*., 1986, **25**, 683. For recent examples, see: (*a*) K. J. Frankowski, R. Z. Liu, G. L. Milligan, K. D. Moeller and J. Aubé, *Angew. Chem., Int. Ed*., 2015, **54**, 10555; (*b*) H. Ding, P. L. DeRoy, C. Perreault, A. Larivée, A. Siddiqui, C. G. Caldwell, S. Harran and P. G. Harran, *Angew. Chem., Int. Ed*., 2015, **54**, 4818; (*c*) T. Morofuji, A. Shimizu and J. I. Yoshida, *J. Am. Chem. Soc*., 2014, **136**, 4496; (*d*) T. Morofuji, A. Shimizu and J. I. Yoshida, *J. Am. Chem. Soc*., 2013, *135*, 5000; (*e*) T. Morofuji, A. Shimizu and J. I. Yoshida, *Angew. Chem., Int. Ed*., 2012*,* **51**, 7259; (*f*) F. Kakiuchi, T. Kochi, H. Mutsutani, N. Kobayashi, S. Urano, M. Sato, S. Nishiyama and T. Tanabe, *J. Am. Chem. Soc*., 2009, **131**, 11310; (*g*) B. Elsler, D. Schollmeyer, K. M. Dyballa, R. Franke and S. R. Waldvogel, *Angew. Chem., Int. Ed*., 2014, **53**, 5210; *h*) Z. L. Zhang, J. H. Su, Z. G. Zha and Z. Y. Wang, *Chem. Commun*., 2013, **49**, 8982.

3 For a review, see: (*a*) N. Aust, A. Kirste, In Encyclopedia of applied electrochemistry., (Kreysa, G. et al. Eds), 1505; For recent examples on paired electrolysis, see: (*b*) R. Matthessen, J. Fransaer, K. Binnemans and D. De Vos, *ChemElectroChem*., 2015, **2**, 73; (*c*) M. F. Hartmer and S. R. Waldvogel, *Chem. Commun*., 2015, **51**, 16346; (*d*) G. Hilt, *Angew. Chem. Int. Ed*., 2003, **42**, 1720.

4 (*a*) Y. S. Park and K. Kim, *Tetrahedron Lett*., 1999, **40**, 6439; (*b*) G. Meng, M. Wang, A. Q. Zheng, J. W. Dou and Z. J. Guo, *Green. Chem. Lett. Rev*., 2014, **7**, 46; (*c*) J. M. Chen and X. Huang, *Synlett*., 2004, 552.

5 (*a*) F. E. Dayan, A. C. Vincent, J. G. Romagni, S. N. Allen, S. O. Duke, M. V. Duke, J. J. Bowling and J. K. Zjawiony, *J. Agric. Food Chem.,* 2000, **48**, 3689; (*b*) A. A. Thomas, Y. L. Huerou and J. D. Meese, *Bioorg. Med. Chem. Lett*., 2008, **18**, 2206; (*c*) D. Hisashi, M. Aya, K. Masakatsu and N. Satoshi, *J. Org. Chem*., 2015, **80**, 6250.

6 (*a*) C. C. Zeng, N. T. Zhang, C. M. Lam and R. D. Little, *Org. Lett*., 2012, **14**, 1314; (*b*) N. T. Zhang, C. C. Zeng, C. M. Lam, R. K. Gbur and R. D. Little, *J. Org. Chem*., 2013, **78**, 2104; (*c*) N. N. Lu, N. T. Zhang, C. C. Zeng, L. M. Hu, S. J. Yoo and R. D. Little, *J. Org. Chem*., 2015, **80**, 781; (*d*) N. N. Lu, S. J. Yoo, L.

View Article Online
DOI: 10.1039/C6GC00666C

J. Li, C. C. Zeng and R. D. Little, *Electrochim. Acta*., 2014, **142**, 254; (*e*) J. Chen, W. Q. Yan, C. M. Lam, C. C. Zeng, L. M. Hu and R. D. Little, *Org. Lett*., 2015, **17**, 986; (*f*) W. J. Gao, W. C. Li, C. C. Zeng, H. Y. Tian, L. M. Hu and R. D. Little, *J. Org. Chem*., 2014, **79**, 9613; (*g*) W. C. Li, C. C. Zeng, L. M. Hu, H. Y. Tian and R. D. Little, *Adv. Synth. Catal*., 2013, **355**, 2884; (*h*) W. C. Li, Z. Z. Zhang, C. C. Zeng, L. M. Hu and H. Y. Tian, *Curr. Org. Synth*., 2014, **11**, 454; (*i*) Z. Z. Zhang, N. T. Zhang, L. M. Hu, Z. Q. Wei, C. C. Zeng, R. G. Zhong and Y. B. She, *RSC Adv.*, 2011, **1**, 1383.

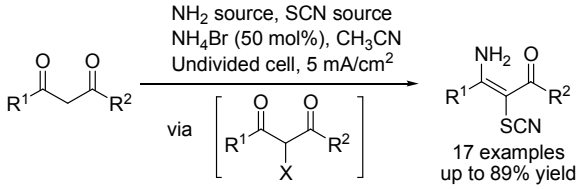
7 (*a*) G. D. Allen, M. C. Buzzeo, C. Villagrán, C. Hardacre and R. G. Compton, *J. Electroanal. Chem*., 2005, **575**, 311; (*b*) I. Damljanovic, D. Stevanovic, M. Vukicevic and R. D. Vukicevic, *Carbohydrate Res*., 2011, **346**, 2683.

8 T. Matsuki, N. X. Hu, Y. Aso, T. Otsubo and F. Ogura, *Bull. Chem. Soc. Jpn*., 1988, **61**, 2117.

9 It is really very terrible when toxic H_2S is formed. Therefore, when scaling up, we can try to use thiocyanate such as NH_4SCN, KSCN and NaSCN, instead of carbamodithioate anion for the thiocyanation.

View Article Online
DOI: 10.1039/C6GC00666C

Table of contents entry



An efficient paired electrosynthesis involving C-H functionalization and subsequent C-S and C-N bond formation for the assembly of valuable 3-amino-2-thiocyanato-α,β-unsaturated carbonyl derivatives has been developed.

View Article Online
DOI: 10.1039/C6GC00666C

Electrochemical C-H functionalization and subsequent C-S and C-N bond formation: Paired electrosynthesis of 3-amino-2-thiocyanato α,β-unsaturated carbonyl derivatives mediated by bromide ion

Li-Shuo Kang, [a] Mi-Hai Luo, [a] Chiu Marco Lam, [b] Li-Ming Hu,[a] R. Daniel Little [b] and Cheng-Chu Zeng[*, a, c]

[a] College of Life Science & Bioengineering, Beijing University of Technology, Beijing 100124, P. R. China, E-mail: zengcc@bjut.edu.cn

[b] Department of Chemistry & Biochemistry, University of California, Santa Barbara, Santa Barbara 93106-9510, CA

[c] Beijing Advanced Innovation Center for Food Nutrition and Human Health, Beijing Technology and Business University, Beijing 100048, China

Table of contents for the supporting information

View Article Online
DOI: 10.1039/C6GC00666C

1. Experimental

1.1 Instruments and reagents

All melting points are uncorrected. IR spectra were recorded as KBr pellets. All the material **1a-1n** and solvents were commercially available and used without further purification.

1.2 Typical procedure for the synthesis of 3-amino-2-thiocyanato-2-butenoate 3 by constant current electrolysis.

A 50 mL beaker-type cell was equipped with a Pt anode and a Pt plate cathode and connected to a DC regulated power supply. To the cell was added ethyl acetoacetate **1** (1 mmol), amine **2** (1.5 mmol) and NH_4Br (50 mol%) dissolved in 15 mL of CH_3CN. The mixture was electrolyzed using constant current conditions (~5 mA/cm^2) at 40 ^oC while stirring. The electrolysis was terminated when the starting material **1** was consumed as determined by TLC. After the electrolysis, the solvent was removed under reduced pressure and extraction was carried out using ethyl acetate (3×15 mL); the combined organic layers were washed with a saturated aqueous Na_2CO_3 solution, and dried over $MgSO_4$. Purified product was obtained after column chromatography on silica gel using a solvent mixture of petroleum ether and ethyl acetate.

1.3 Cyclic voltammetry experiments

Cyclic voltammograms were recorded at room temperature using a Princeton Applied Research Model 273A Potentiostat/Galvanostat equipped with electrochemical analysis software and a conventional three-electrode cell. A glassy carbon (GC) disk electrode (ca. ϕ = 3 mm) or a Pt disk electrode (ca. ϕ = 1 mm) was used as the working electrode and a Pt wire as the counter electrode. $Ag/AgNO_3$ (0.1 M in CH_3CN) was used as a reference electrode. All electrodes for CV experiments were purchased from CH Instruments, Inc. USA.

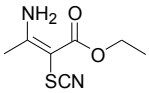
The working electrodes were carefully polished on a polishing pad before each experiment using a fine mesh alumina slurry, and then ultrasonically rinsed with

View Article Online
DOI: 10.1039/C6GC00666C

acetone. All solutions were degassed by sparging dry nitrogen through the solution for 10 min prior to conducting each electrochemical experiment; a nitrogen atmosphere was maintained throughout. In each measurement, the three electrodes were fixed in place, and were not allowed to be disturbed in any manner.

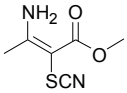
2. Spectroscopic Data

(*E*)-3-Amino-2-thiocyanato-but-2-enoic acid ethyl ester (3a)[1]



White solid; m.p. 111 - 113 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.37 (t, J = 7.2 Hz, 3H), 2.42 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 5.56 (s, 1H), 9.32 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 23.2, 60.75, 75.5, 113.7, 168.4, 168.6; **IR** (KBr) (cm^{-1}): υ 3417, 2986, 2142, 1622, 1269; **HRMS** calcd for $C_7H_9N_2O_2S$: 185.0385, found: 185.0355.

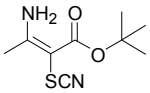
(*E*)-3-Amino-2-thiocyanato-but-2-enoic acid methyl ester (3b)[2]



White solid; m.p. 90 - 93 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.81 (s, 3H), 5.60 (s, 1H), 9.31 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.4, 52.0, 76.0, 113.3, 128.8, 168.5, 168.8; **IR** (KBr) (cm^{-1}): υ 3427, 3329, 2950, 2146, 1633, 1276; **HRMS** calcd for $C_6H_9N_2O_2S$: 173.0385, found: 173.0381.

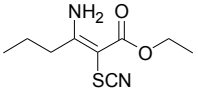
(*E*)-3-Amino-2-thiocyanato-but-2-enoic acid tert-butyl ester (3c)[3]

View Article Online
DOI: 10.1039/C6GC00666C



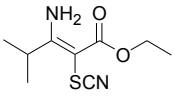
Pale yellow solid; m.p. 82 - 84 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.56 (s, 9H), 2.37 (s, 3H), 5.42 (s, 1H), 9.25 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.5, 28.3, 81.2, 113.6, 167.3, 168.0; **IR** (KBr) (cm^{-1}): υ 3292, 3101, 1597, 1527, 1430; **HRMS** calcd for $C_9H_{15}N_2O_2S$: 215.0854, found: 215.0847.

(*E*)-3-Amino-2-thiocyanato-hex-2-enoic acid ethyl ester (3d)[1]



Pale yellow solid; m.p. 121 - 123 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.07 (t, J = 7.6 Hz, 3H), 1.38 (t, J = 6.8 Hz, 3H), 1.69-1.78 (m, 2H), 2.68-2.71 (m, 2H), 4.26 (q, J = 6.8 Hz, 2H), 5.54 (s, 1H), 9.41 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.7, 14.4, 21.3, 38.1, 60.8, 75.7, 113.7, 168.7, 171.8; **IR** (KBr) (cm^{-1}): υ 3410, 3295, 2965, 2146, 1621, 1266; **HRMS** calcd for $C_9H_{13}N_2O_2S$: 213.0698, found: 213.0707.

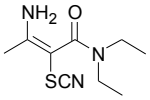
(*E*)-3-Amino-4-methyl-2-thiocyanato-pent-2-enoic acid ethyl ester (3e)



Brown oil; liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (d, J = 6.8 Hz, 6H), 1.35 (t, J = 6.8 Hz, 3H), 3.64-3.71 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 5.73 (s, 1H), 9.55 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 20.3, 32.5, 60.8, 74.3, 113.9, 168.4, 176.5; **IR** (KBr) (cm^{-1}): υ 3424, 2982, 2143, 1668, 1612, 1161; **HRMS** calcd for $C_9H_{13}N_2O_2S$: 213.0698, found: 213.0707.

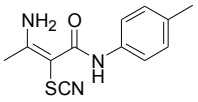
View Article Online
DOI: 10.1039/C6GC00666C

(*E*)-3-Amino-2-thiocyanato-but-2-enoic acid diethylamide (3g)



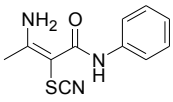
Pale yellow solid; m.p. 135 - 136 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.19 (t, J = 6.8 Hz, 6H), 2.23 (s, 3H), 3.47 (q, J = 7.2 Hz, 4H), 5.34 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6, 16.3, 41.6, 113.6, 148.7, 163.8, 167.2; **IR** (KBr) (cm^{-1}): υ 3293, 3144, 2149, 1592, 1272; **HRMS** calcd for $C_9H_{16}N_3OS$: 214.1014, found: 214.1010.

(*E*)-3-Amino-2-thiocyanato-but-2-enoic acid p-tolylamide (3h)



Pale yellow solid; m.p. 123 - 125 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.44 (s, 3H), 5.60 (s, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 8.25 (s, 1H), 10.15 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.9, 24.0, 75.4, 111.7, 121.1, 129.5, 134.1, 135.1, 166.8, 167.8; **IR** (KBr) (cm^{-1}): υ 3330, 2156, 1592, 1503, 1231, 803; **HRMS** calcd for $C_{12}H_{14}N_3OS$: 248.0858, found: 248.0853.

(*E*)-3-Amino-2-thiocyanato-but-2-enoic acid phenylamide (3i)

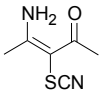


Pale yellow solid; m.p. 139 - 140 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 5.61 (s, 1H), 7.15 (t, J = 7.2 Hz, 1H), 7.35-7.39 (m, 2H), 7.52 (d, J = 7.6 Hz, 2H), 8.32 (s, 1H), 10.17 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.0, 75.4, 111.7, 120.9, 124.4, 129.0, 137.8, 166.9, 168.0; **IR** (KBr) (cm^{-1}): υ 3387, 3335, 2152, 1529, 1230,

View Article Online
DOI: 10.1039/C6GC00666C

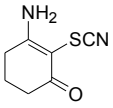
751; **HRMS** calcd for $C_{11}H_{12}N_3OS$: 234.0701, found: 234.0695.

(*E*)-4-Amino-3-thiocyanato-pent-3-en-2-one (3j)[3]



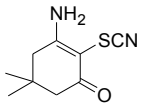
Pale yellow solid; m.p. 122 - 123 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.51 (s, 3H), 5.98 (s, 1H), 10.97 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.0, 29.0, 87.0, 113.0, 169.5, 198.1; **IR** (KBr) (cm^{-1}): υ 3419, 2978, 2150, 1612, 1255; **HRMS** calcd for $C_6H_7N_2OS$: 155.0279, found: 155.0289.

(*E*)-3-Amino-2-thiocyanato-cyclohex-2-enone (3k)[4]



Deep green solid; m.p. 96 - 100 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.78-1.84 (m, 2H), 2.31 (t, J = 6.4 Hz, 2H), 2.61 (t, J = 6.0 Hz, 2H), 7.79 (s, 1H), 8.19 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 20.6, 30.3, 37.2, 86.7, 112.9, 171.6, 190.3; **IR** (KBr) (cm^{-1}): υ 3396, 3311, 3193, 2148, 1615, 1522, 1297; **HRMS** calcd for $C_7H_7N_2OS$: 167.0279, found: 167.0285.

(*E*)-3-Amino-5,5-dimethyl-2-thiocyanato-cyclohex-2-enone (3l)[4]

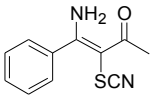


Pale yellow solid; m.p. 149 - 151 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.11 (s, 6H), 2.41 (s, 2H), 2.52 (s, 2H), 5.47 (s, 1H), 6.08 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6):

View Article Online
DOI: 10.1039/C6GC00666C

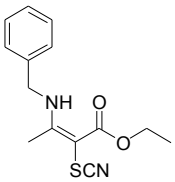
δ 27.8, 31.8, 43.4, 50.6, 85.4, 112.9, 170.0, 189.8; **IR** (KBr) (cm^{-1}): υ 3392, 3311, 3182, 2964, 2145, 1622, 1527, 1318; **HRMS** calcd for $C_9H_{11}N_2OS$: 195.0592, found: 195.0600.

(*E*)-3-Amino-1-phenyl-2-thiocyanato-but-2-en-1-one (3m)



Pale yellow solid; m.p. 141 - 144 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.54 (s, 3H), 6.29 (s, 1H), 7.45-7.47 (m, 3H), 7.52-7.54 (m, 2H), 11.22 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.4, 86.7, 113.6, 126.8, 128.1, 129.9, 141.0, 171.9, 196.3; **IR** (KBr) (cm^{-1}): υ 782, 729, 699, 658, 540; **HRMS** calcd for $C_{11}H_9N_2OS$: 217.0436, found: 217.0444.

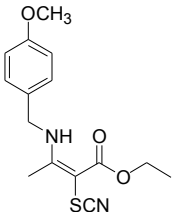
(*E*)-ethyl-3-(benzylamino)-2-thiocyanatobut-2-enoate (3o)



Pale yellow oil; liquid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.35 (t, J = 7.2 Hz, 3H), 2.44 (s, 3H), 4.22 (q, J = 7.2 Hz, 2H), 4.53 (d, J = 5.6 Hz, 2H), 7.25-7.40 (m, 5H), 10.57 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 17.9, 48.4, 60.7, 74.8, 113.8, 126.9, 128.0, 129.1, 136.6, 169.3, 169.5; **IR** (KBr) (cm^{-1}): υ 2981, 2147, 1575, 1455, 1235, 1069; **HRMS** calcd for $C_{14}H_{15}N_2O_2S$: 275.0854, found: 275.0792.

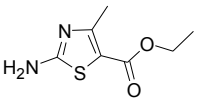
(*E*)-ethyl 3-(4-methoxybenzylamino)-2-thiocyanatobut-2-enoate (3p)

View Article Online
DOI: 10.1039/C6GC00666C



White solid; m.p. 64 - 66 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.36 (t, J = 7.2 Hz, 3H), 2.47 (s, 3H), 3.83 (s, 3H), 4.22 (q, J = 7.2 Hz, 2H), 4.47 (d, J = 5.6 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H),10.48 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 17.9, 48.0, 55.3, 60.7, 74.6, 113.9, 114.5, 128.4, 128.4, 159.4, 169.3, 169.3. **IR** (KBr) (cm^{-1}): υ 3447, 2148, 1635, 1576, 1516, 1252; **HRMS** calcd for $C_{15}H_{17}N_2O_3S$: 305.0960, found: 305.0965.

Ethyl 2-amino-4-methylthiazole-5-carboxylate (4a)[5]



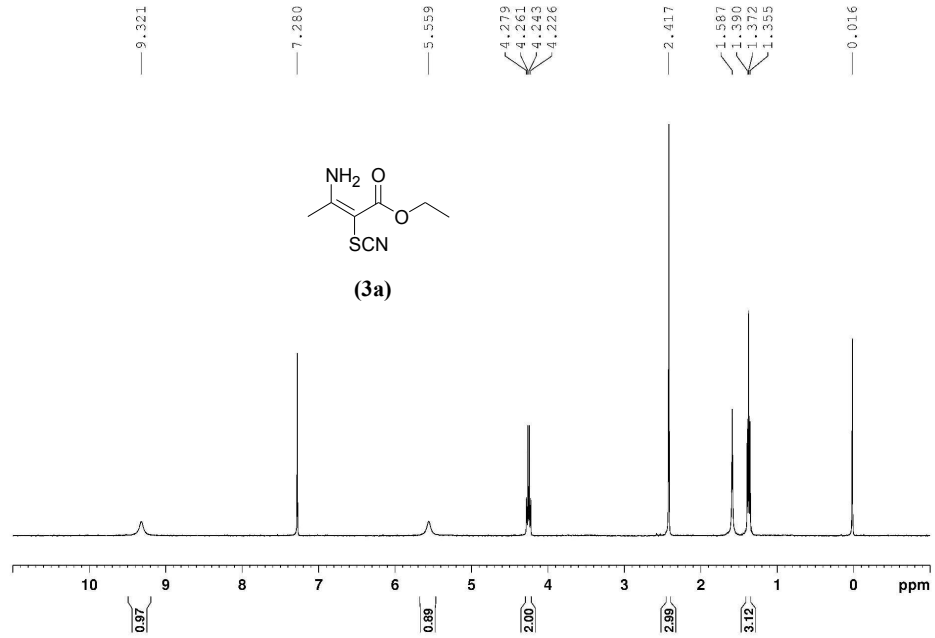
White solid; m.p. 173 - 175 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.35 (t, J = 7.2 Hz, 3H), 2.55 (s, 3H), 4.28 (q, J = 7.2 Hz, 2H), 5.39 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 17.2, 60.6, 111.5, 160.0, 162.5, 169.2.

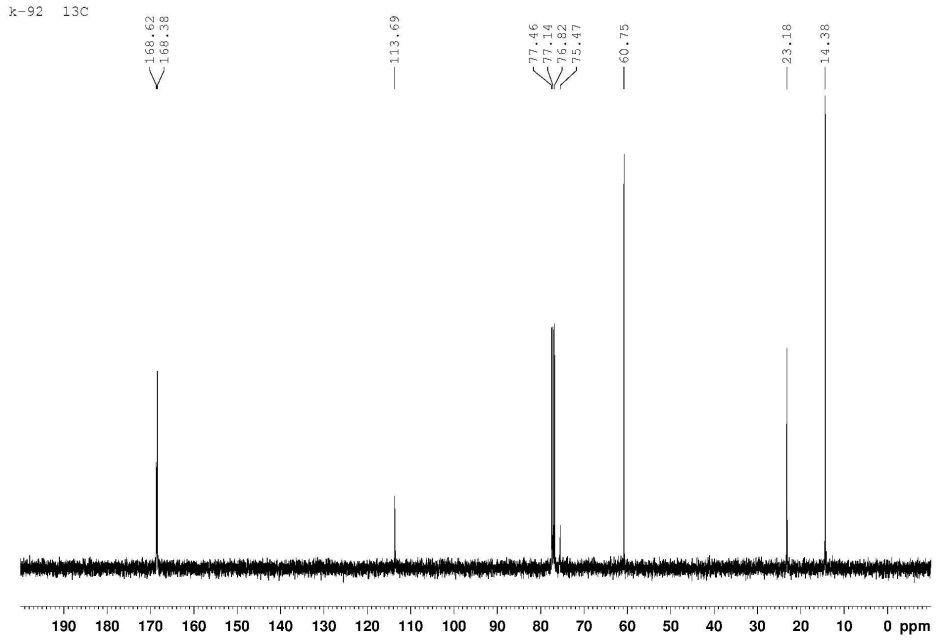
References

[1] Y. S. Park and K. Kim, *Tetrahedron Lett.,* 1999, **40**, 6439.
[2] J. M. Chen and X. Huang, *Synlett*., 2004, **3**, 552.
[3] Chandler, C. *Sci. Synth.*, 2008, **32**, 385.
[4] M. V. Stasevych, *Heteroat Chem*., 2005, **16**, 205.
[5] N. Azizi, *Comptes Rendus Chimie,* 2015*,* **18***,* 626.

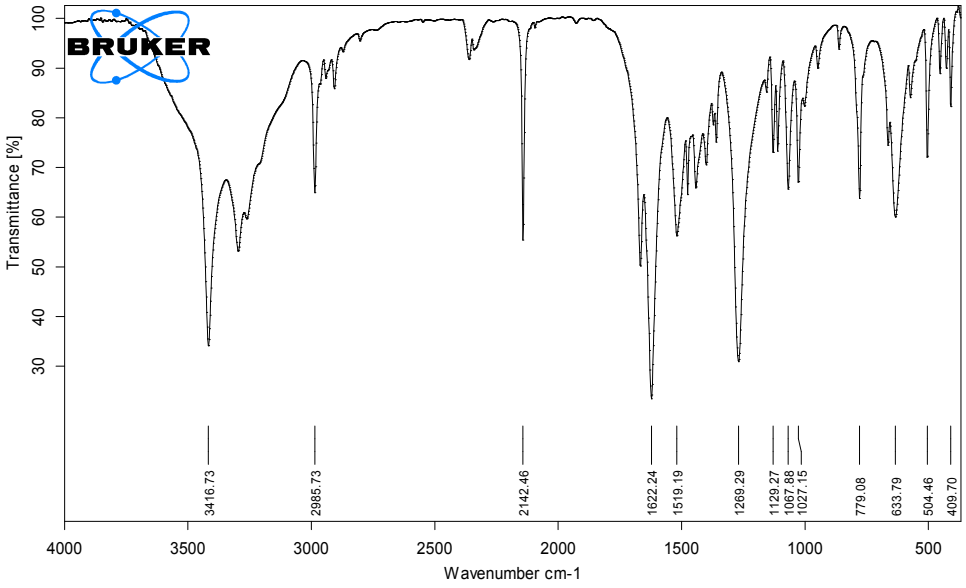
View Article Online
DOI: 10.1039/C6GC00666C

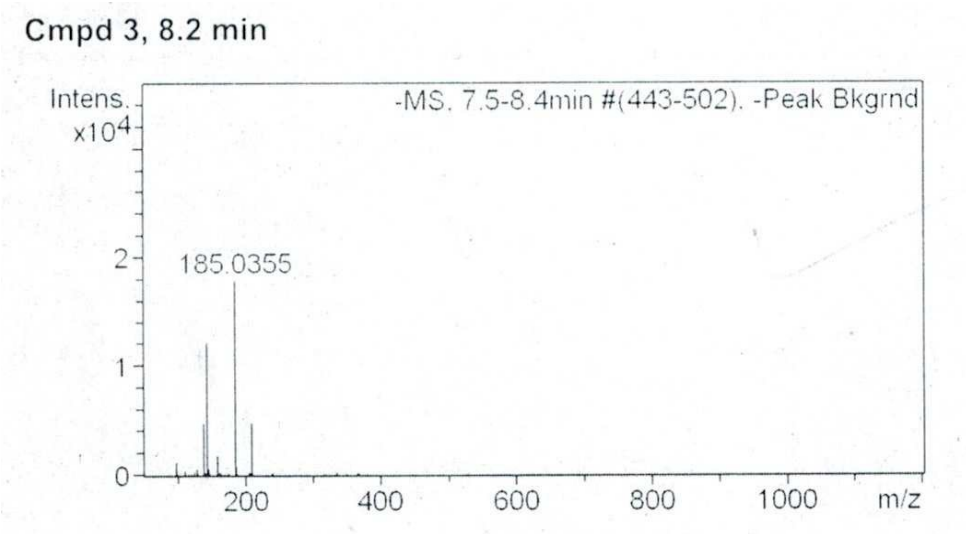
3. Spectroscopy



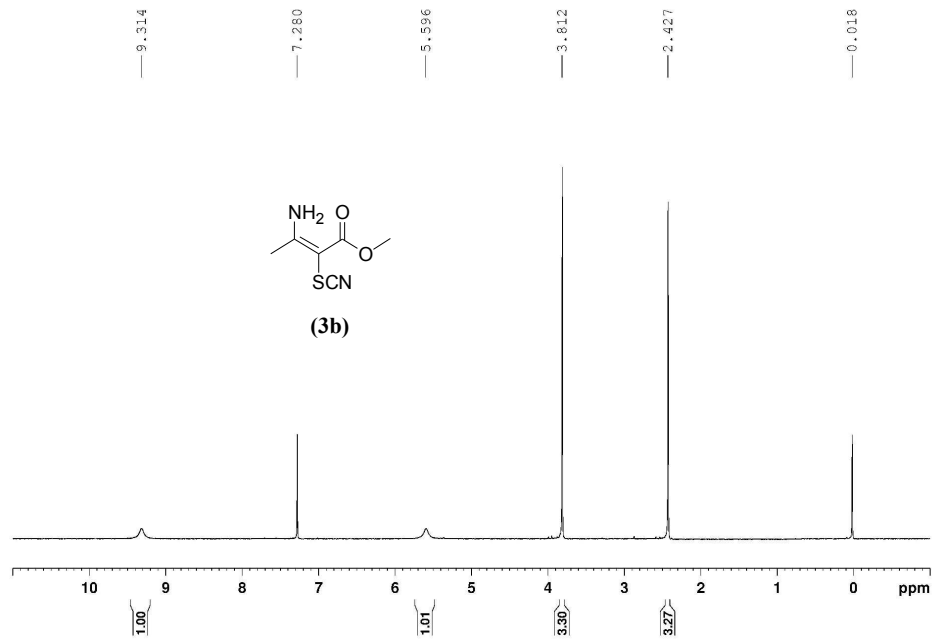


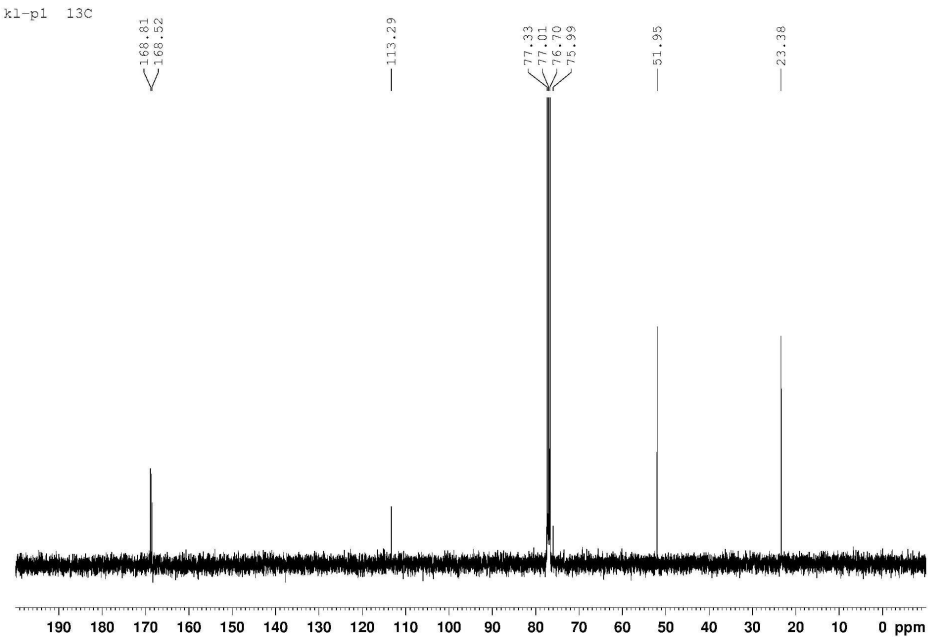
View Article Online
DOI: 10.1039/C6GC00666C



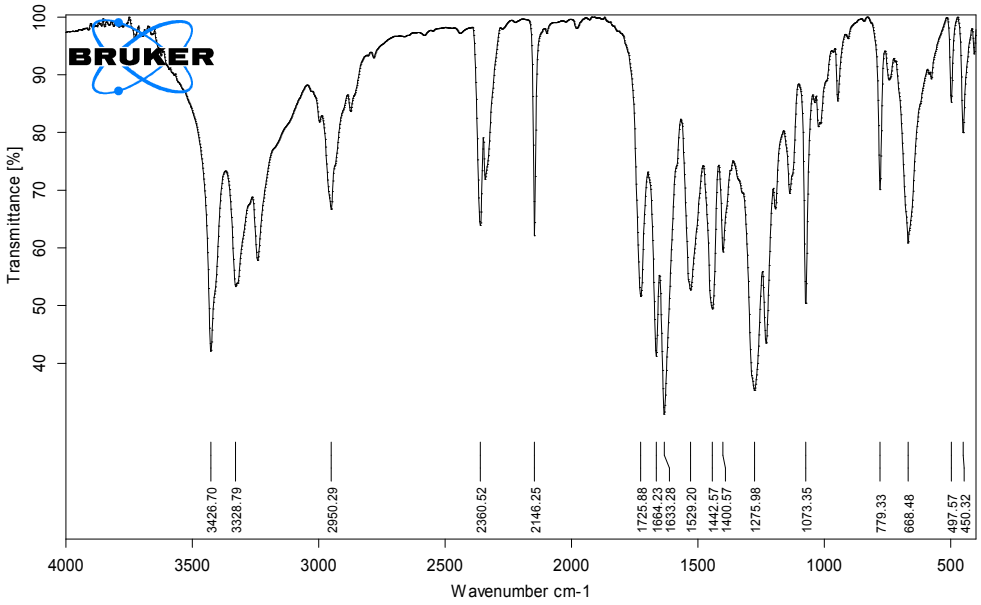


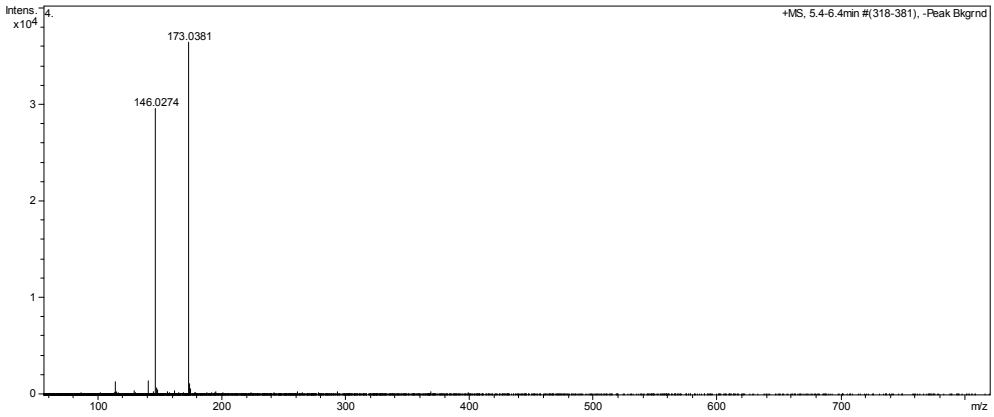
View Article Online
DOI: 10.1039/C6GC00666C



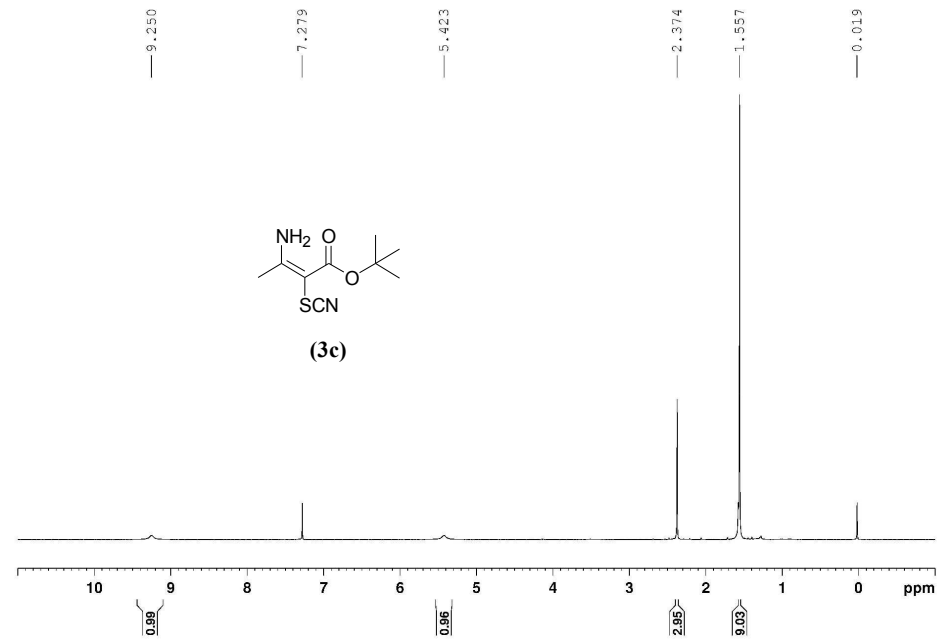


View Article Online
DOI: 10.1039/C6GC00666C

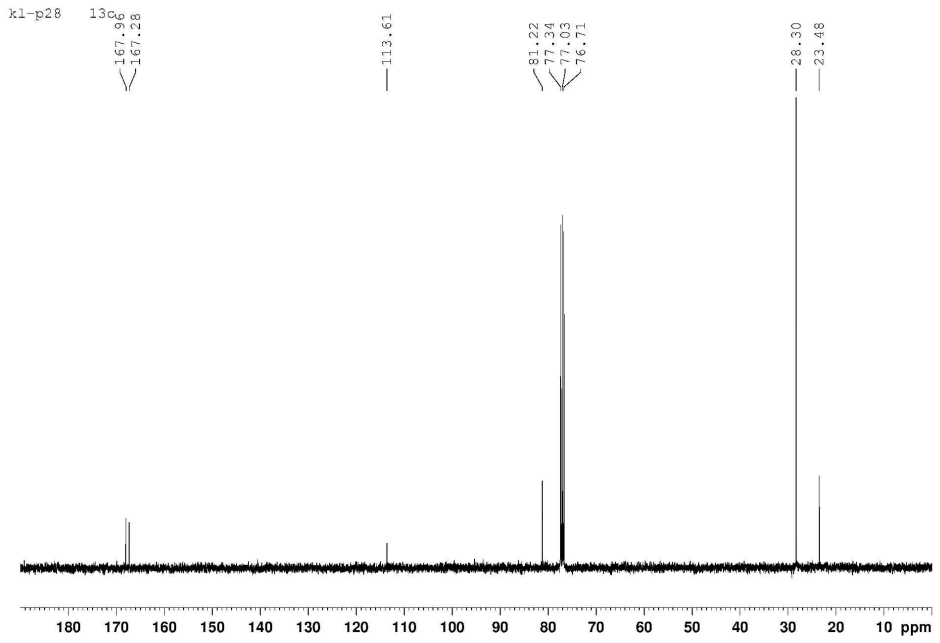




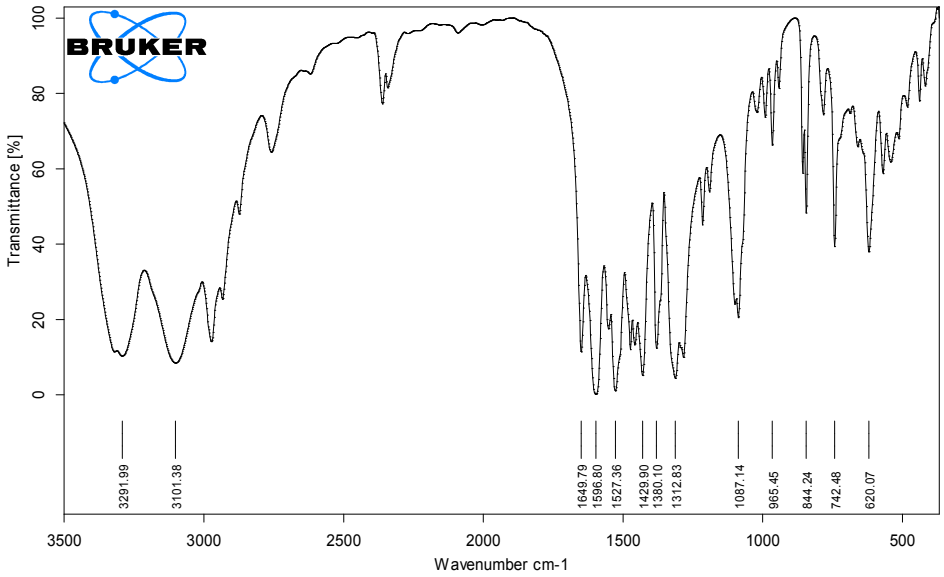
View Article Online
DOI: 10.1039/C6GC00666C

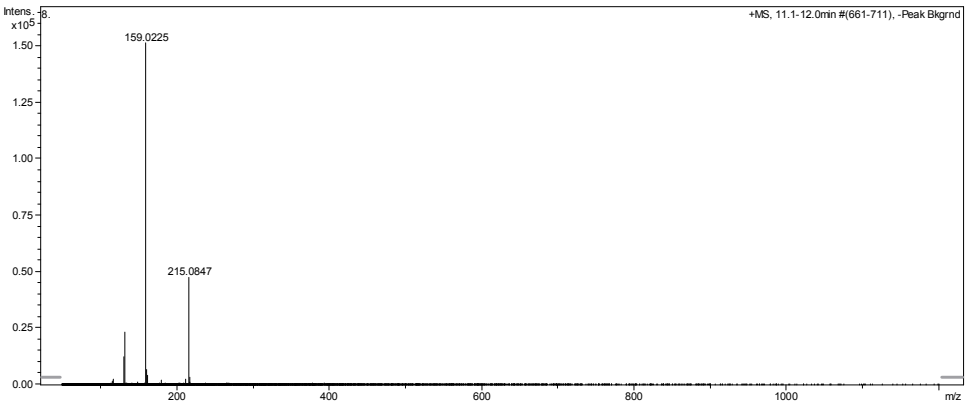


(3c)

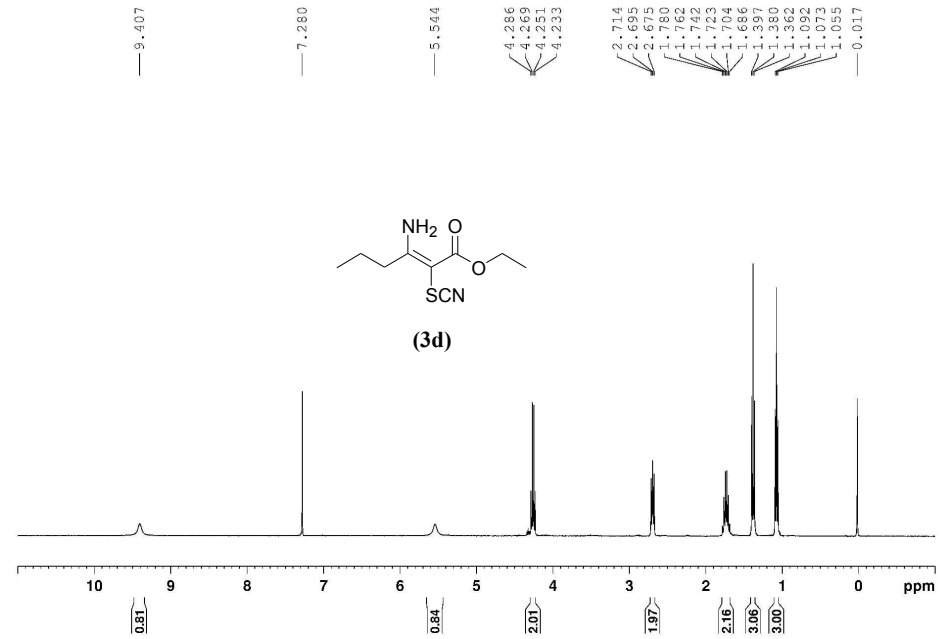


View Article Online
DOI: 10.1039/C6GC00666C

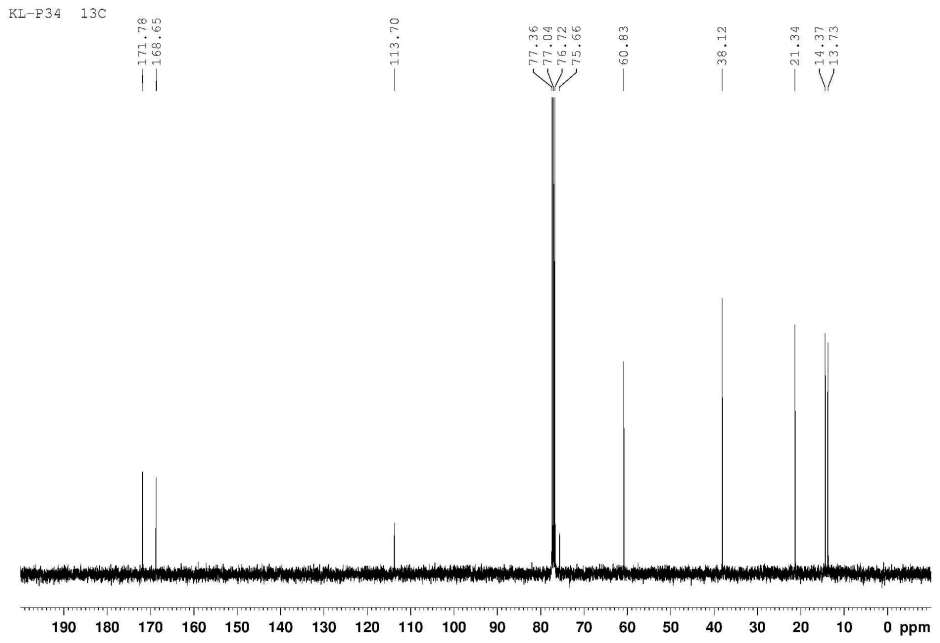




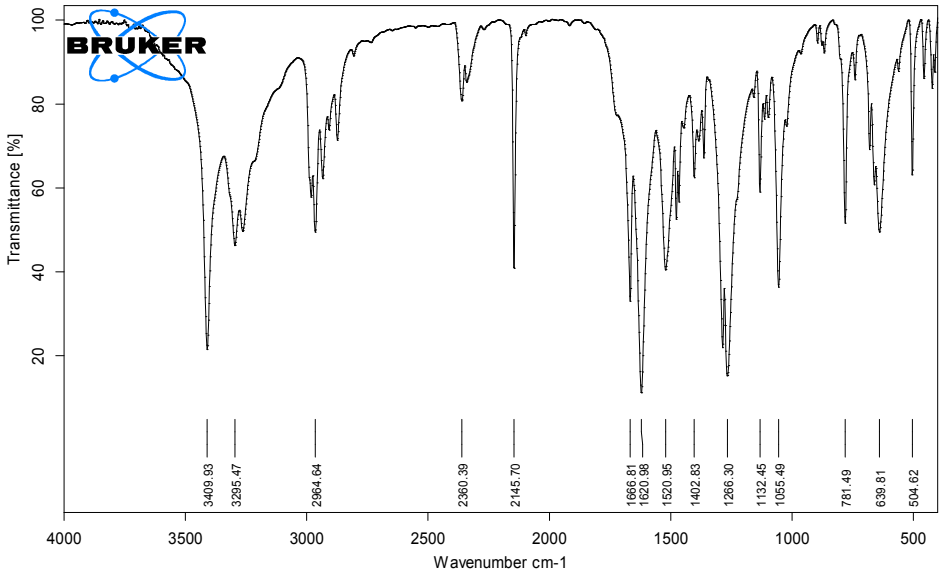
View Article Online
DOI: 10.1039/C6GC00666C

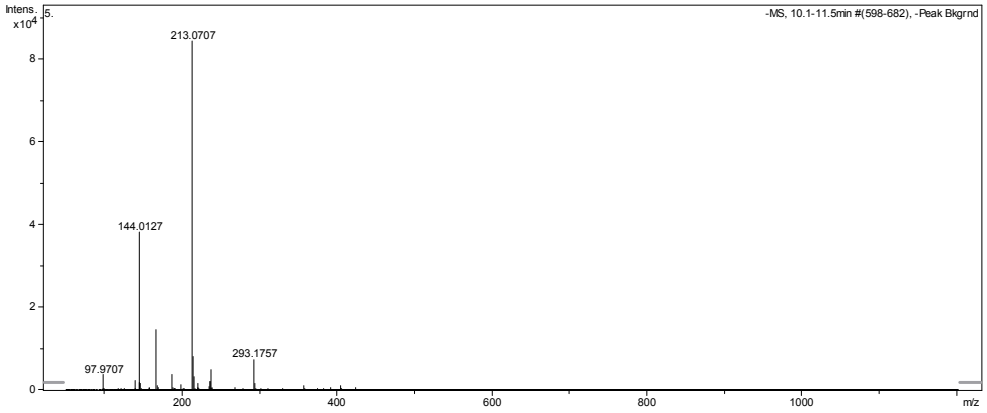


(3d)

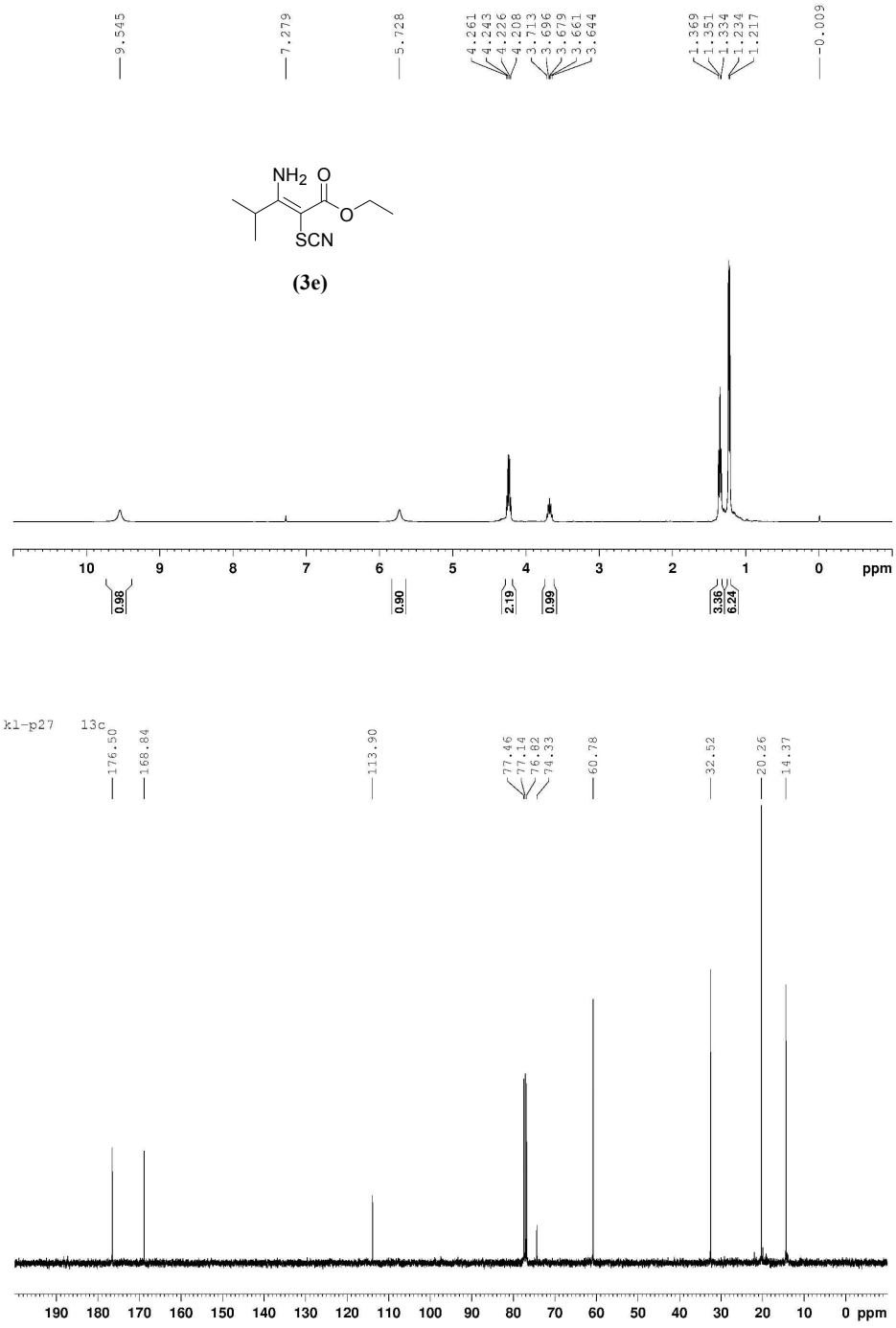


View Article Online
DOI: 10.1039/C6GC00666C

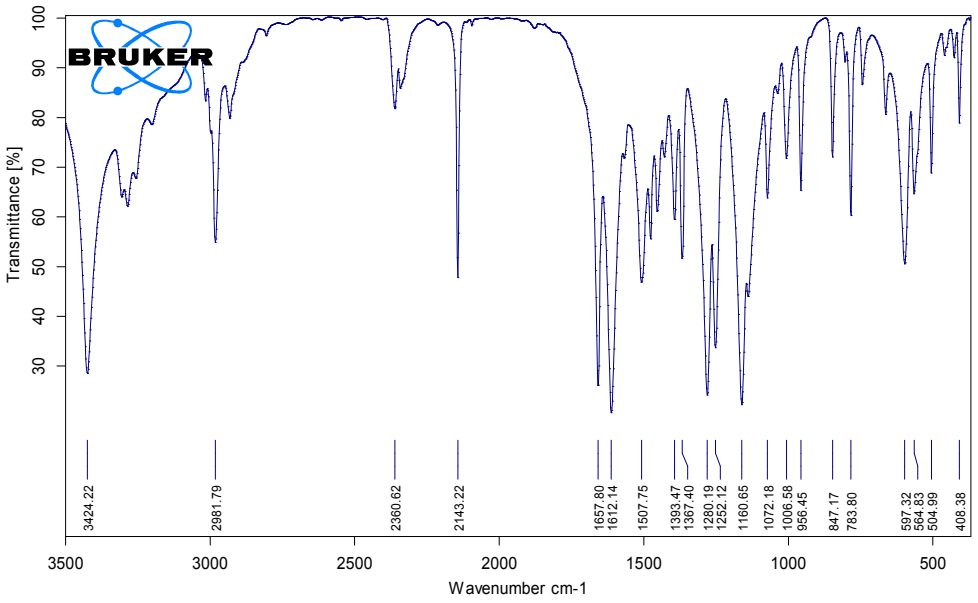


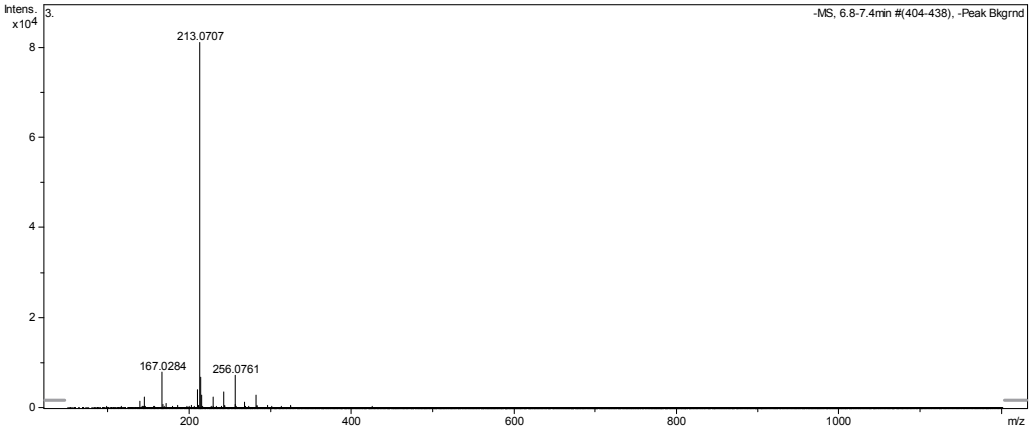


View Article Online
DOI: 10.1039/C6GC00666C

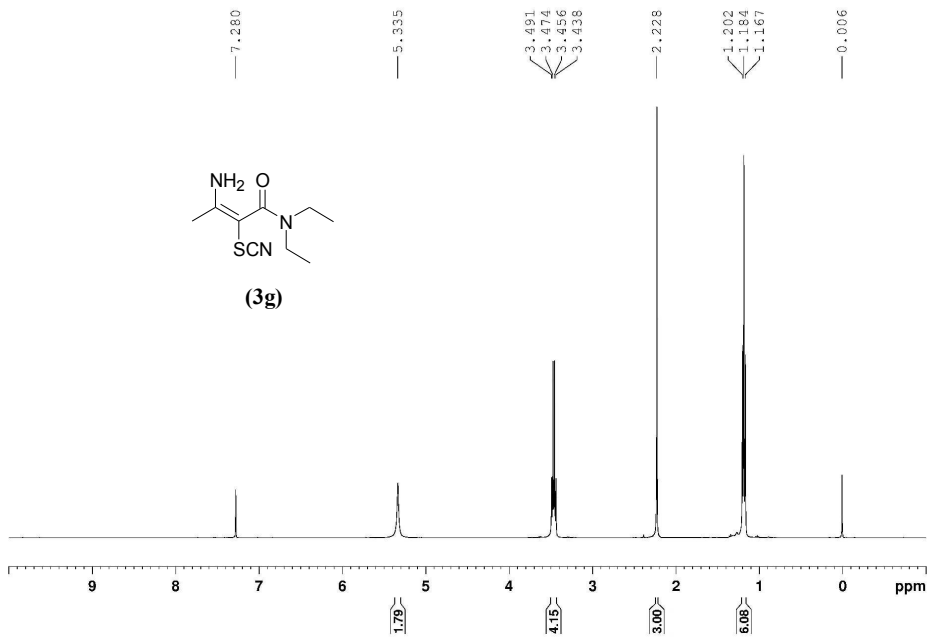


View Article Online
DOI: 10.1039/C6GC00666C

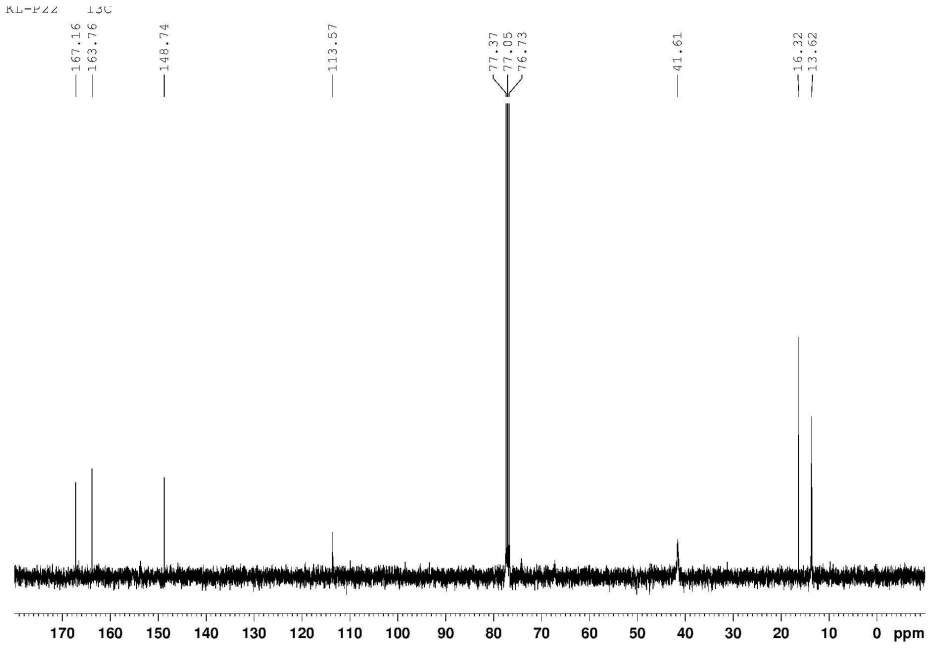




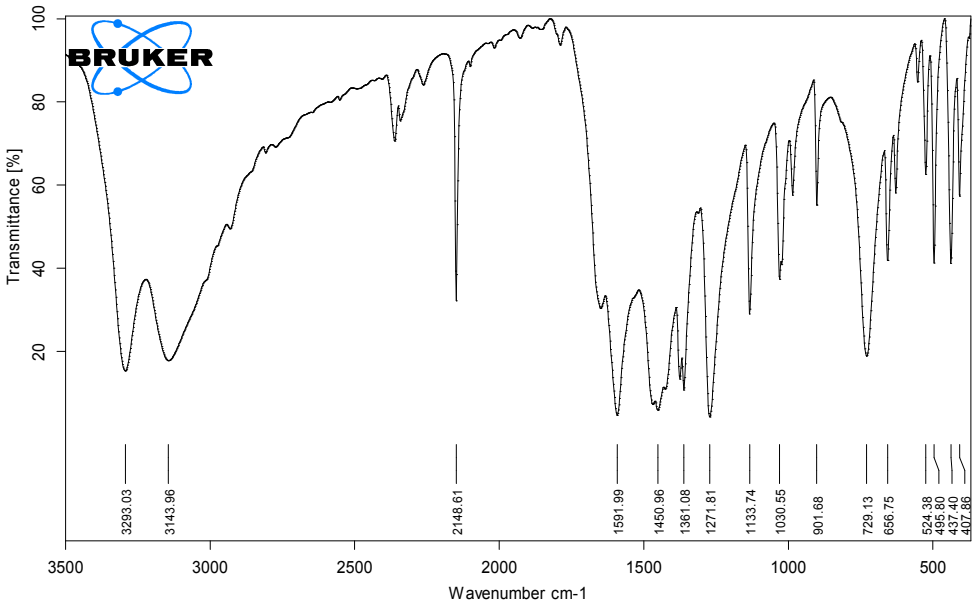
View Article Online
DOI: 10.1039/C6GC00666C

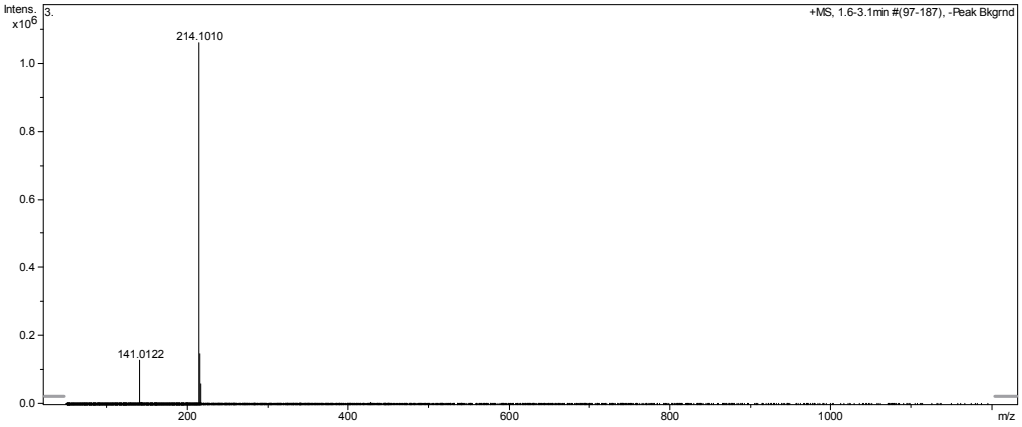


(3g)

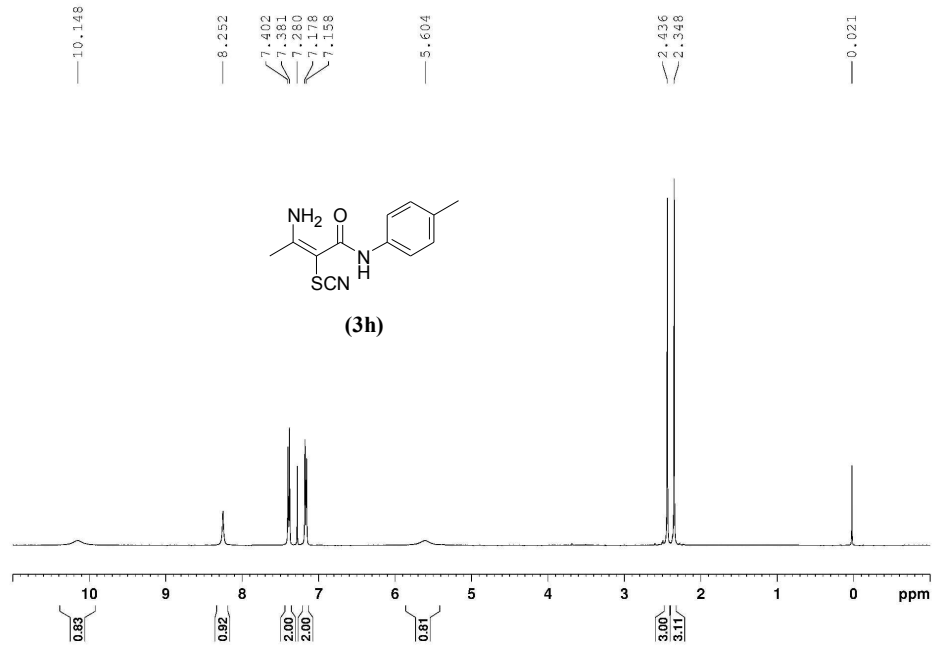


View Article Online
DOI: 10.1039/C6GC00666C

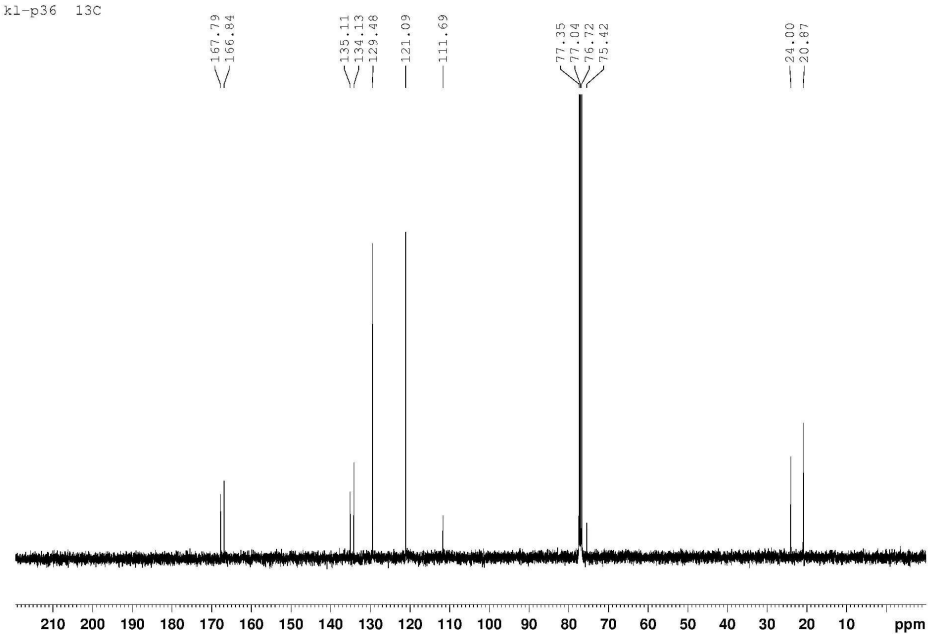




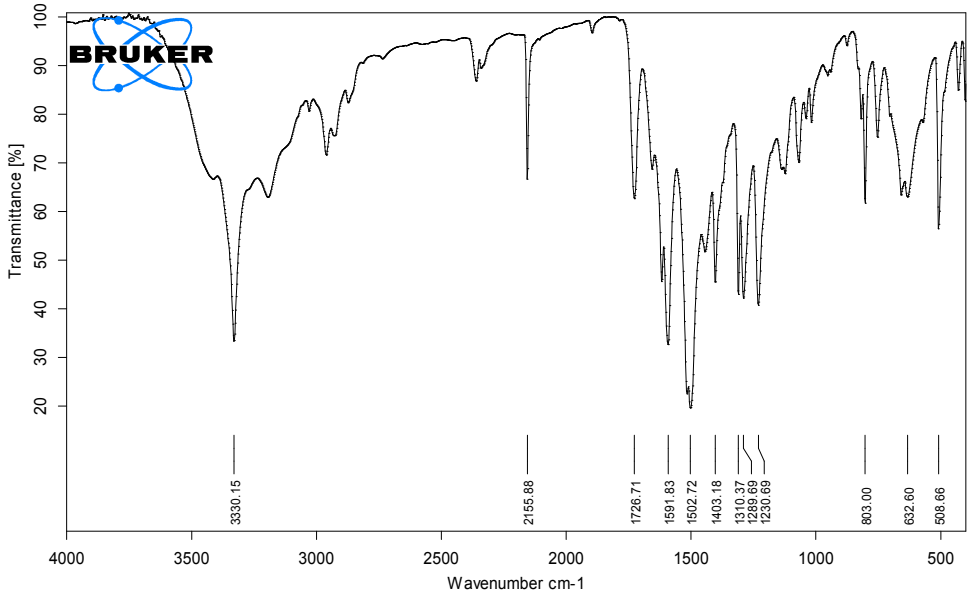
View Article Online
DOI: 10.1039/C6GC00666C

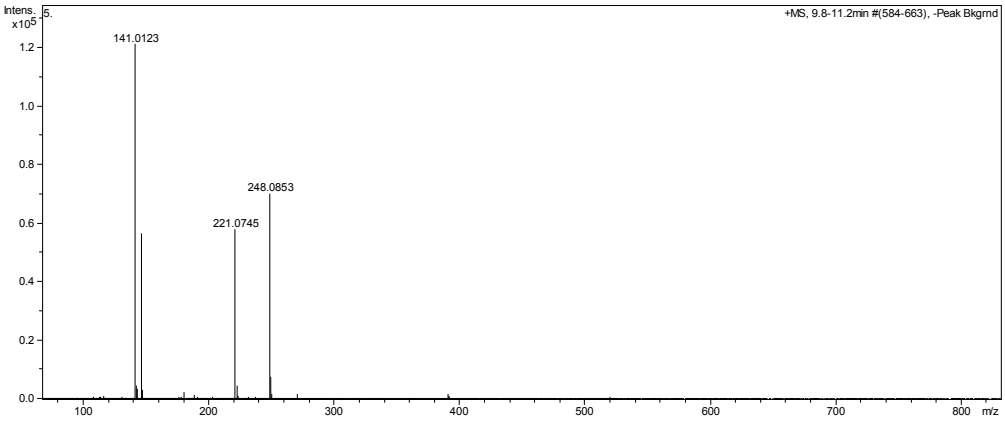


(3h)

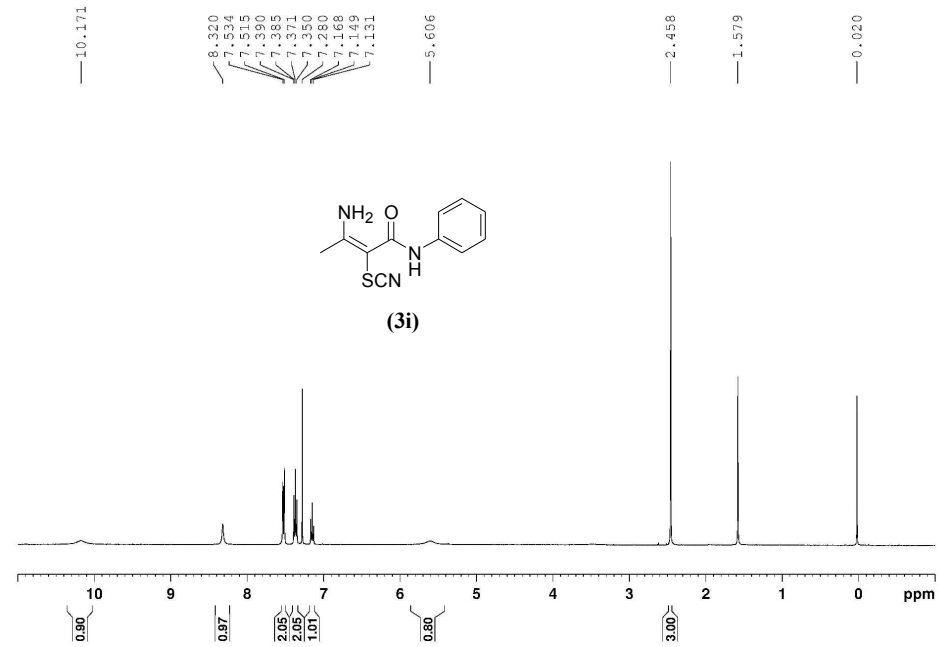


View Article Online
DOI: 10.1039/C6GC00666C

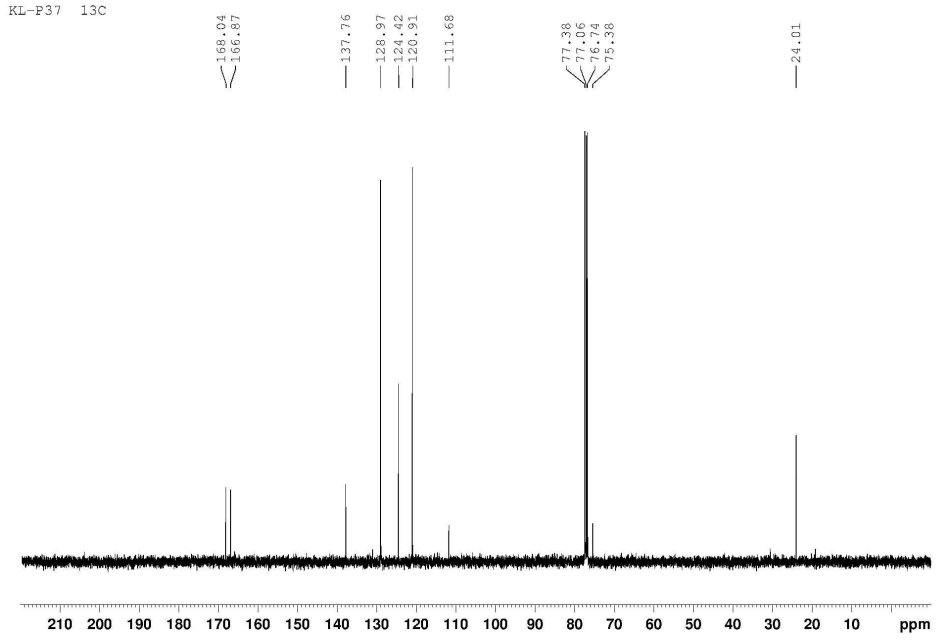




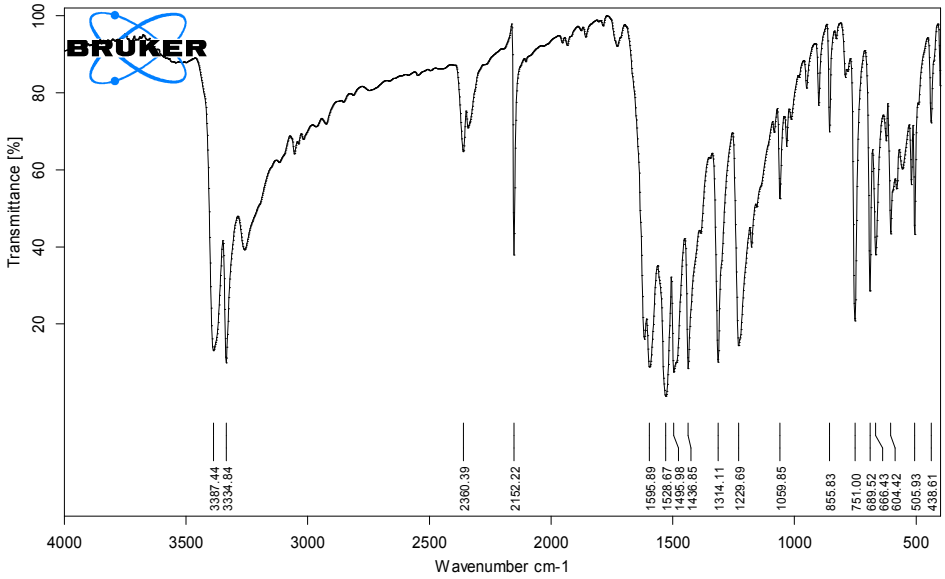
View Article Online
DOI: 10.1039/C6GC00666C

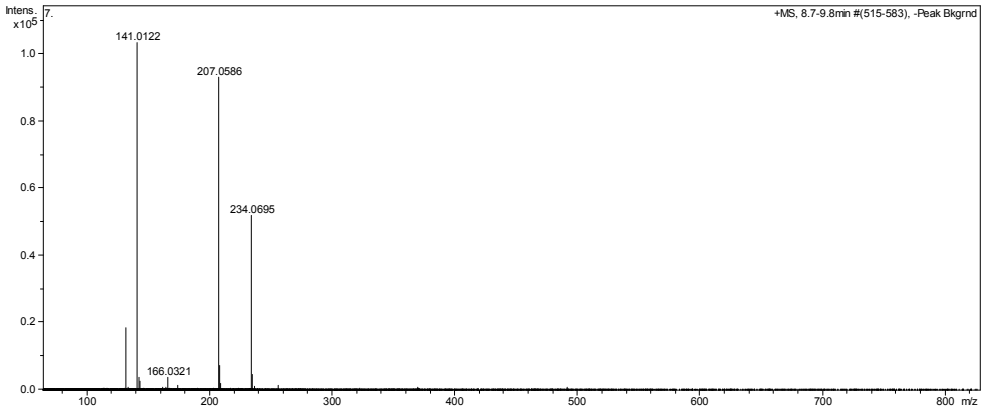


(3i)

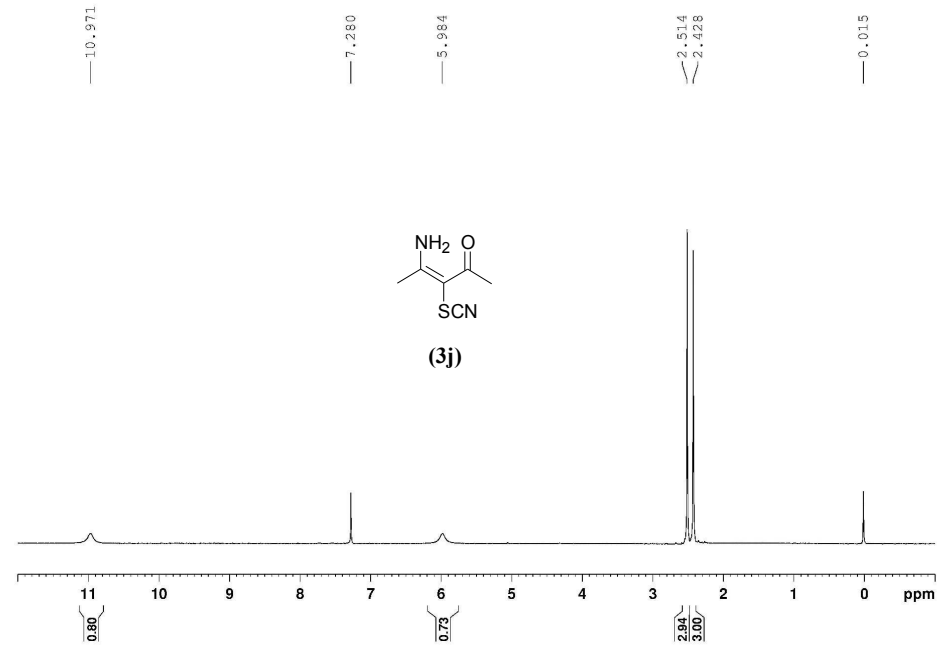


View Article Online
DOI: 10.1039/C6GC00666C

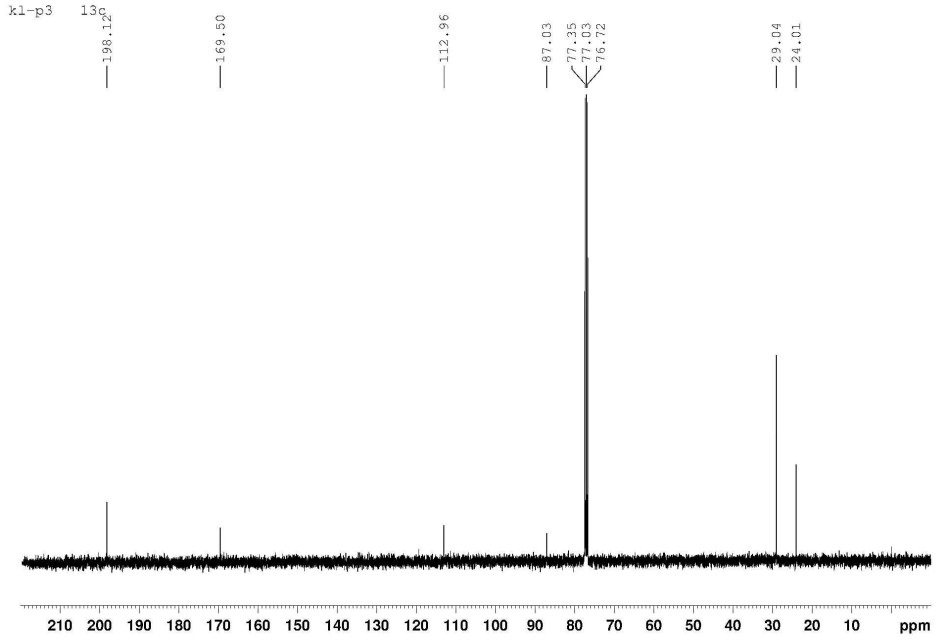




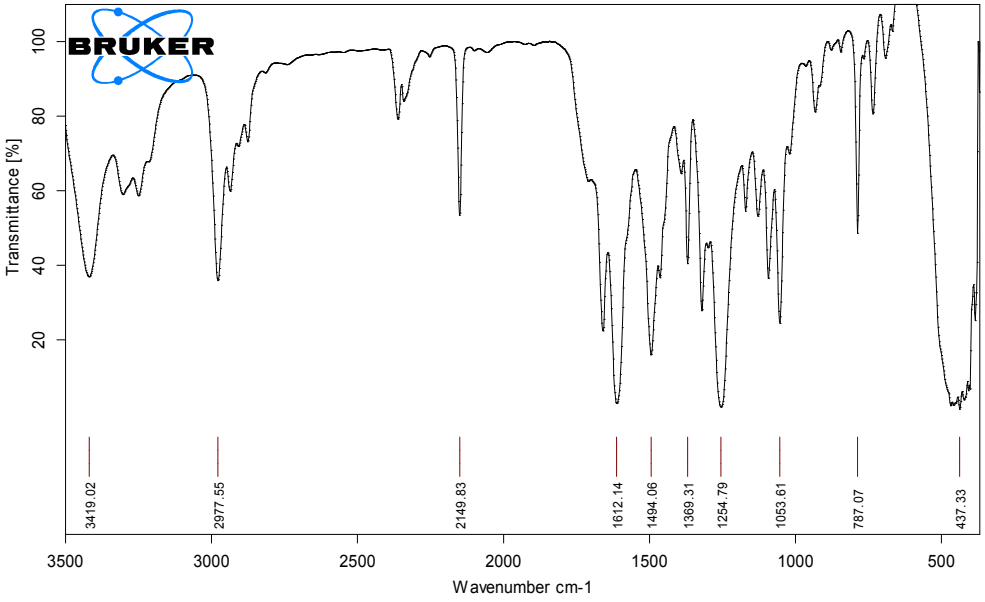
View Article Online
DOI: 10.1039/C6GC00666C

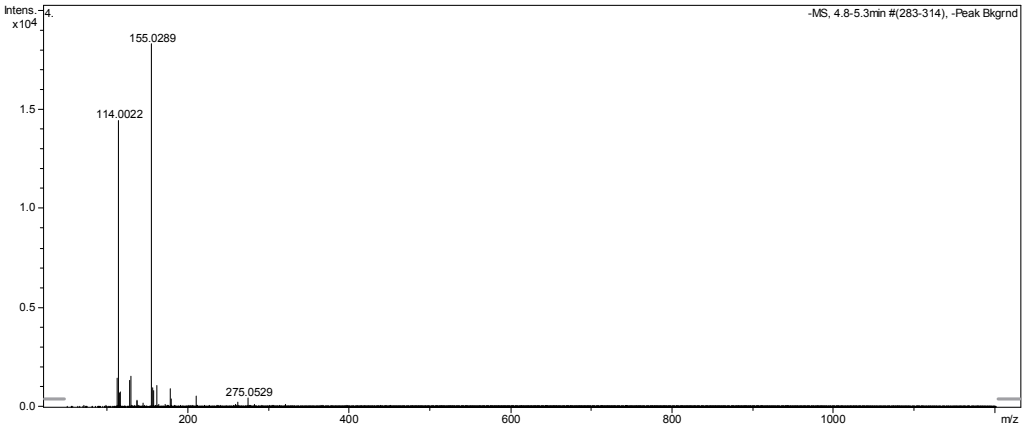


(3j)

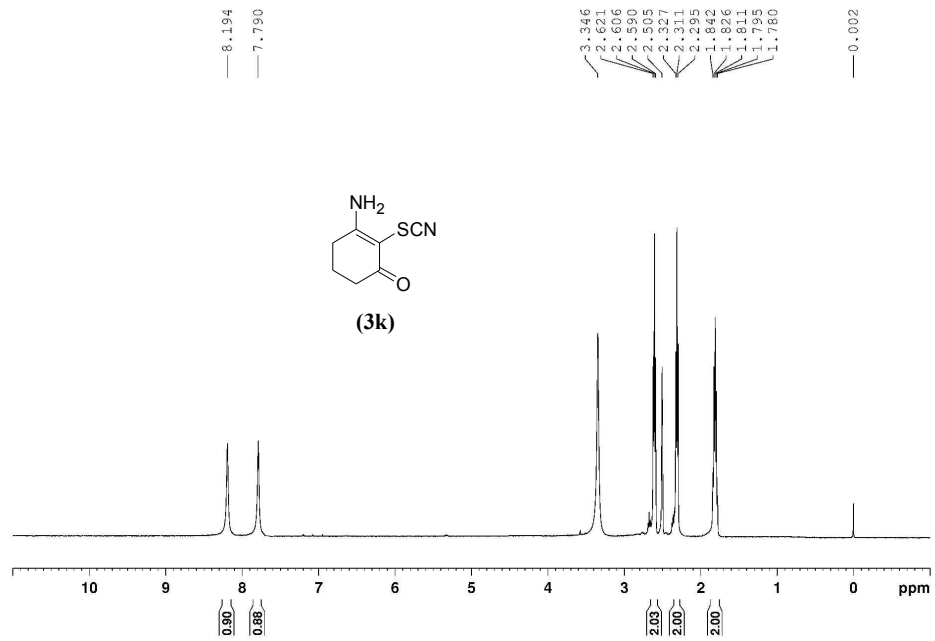


View Article Online
DOI: 10.1039/C6GC00666C

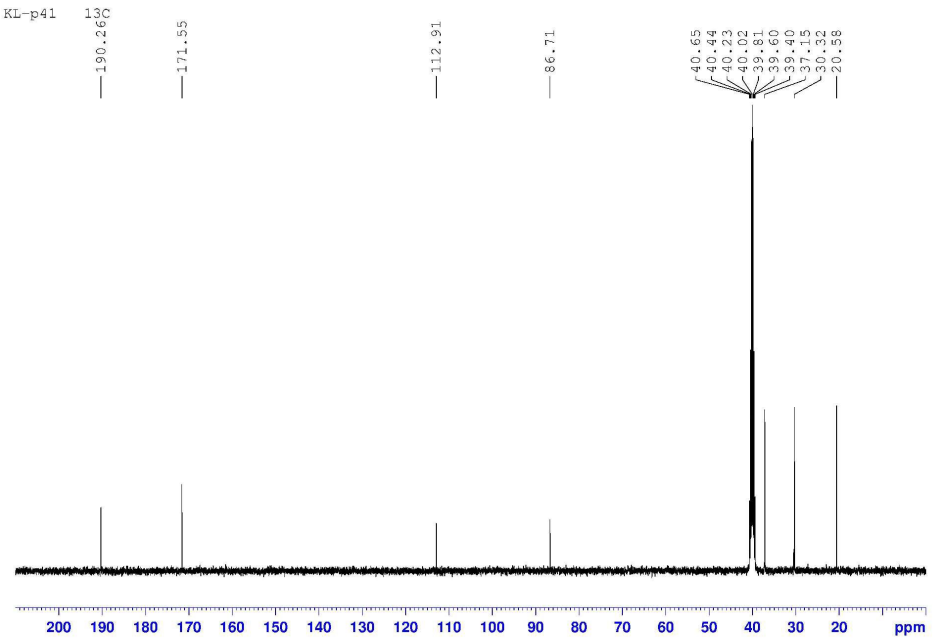




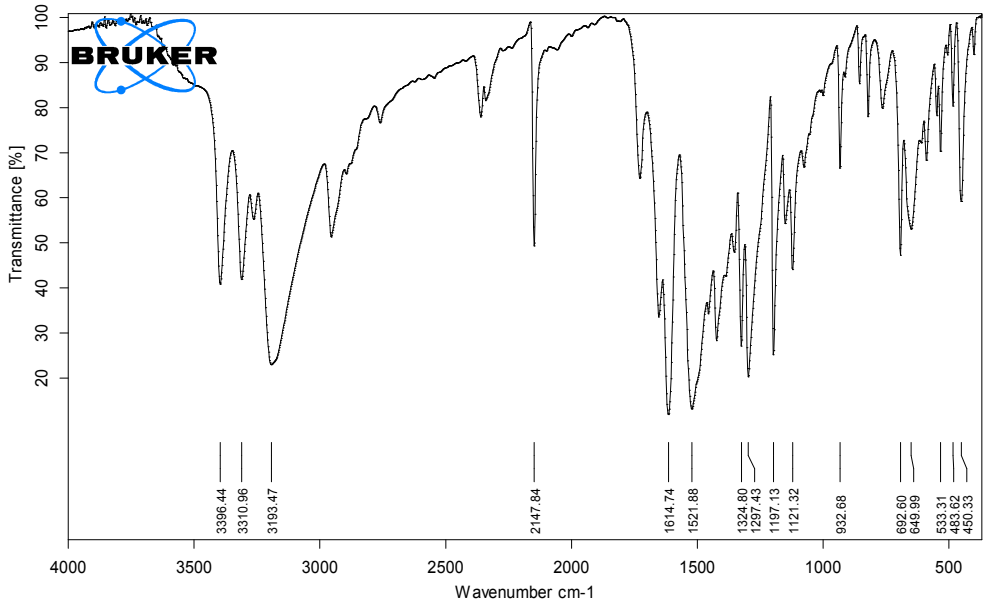
View Article Online
DOI: 10.1039/C6GC00666C

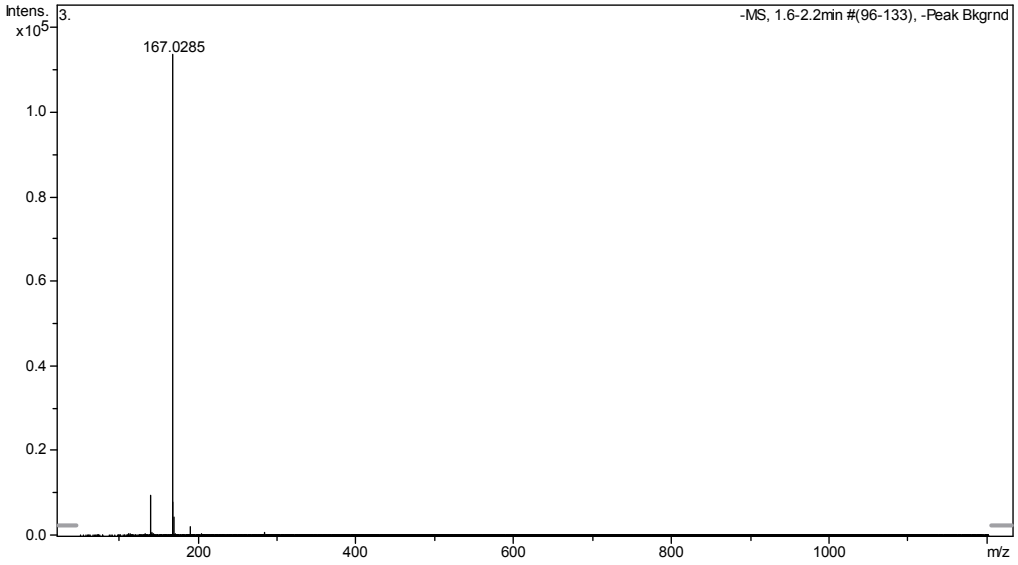


(3k)

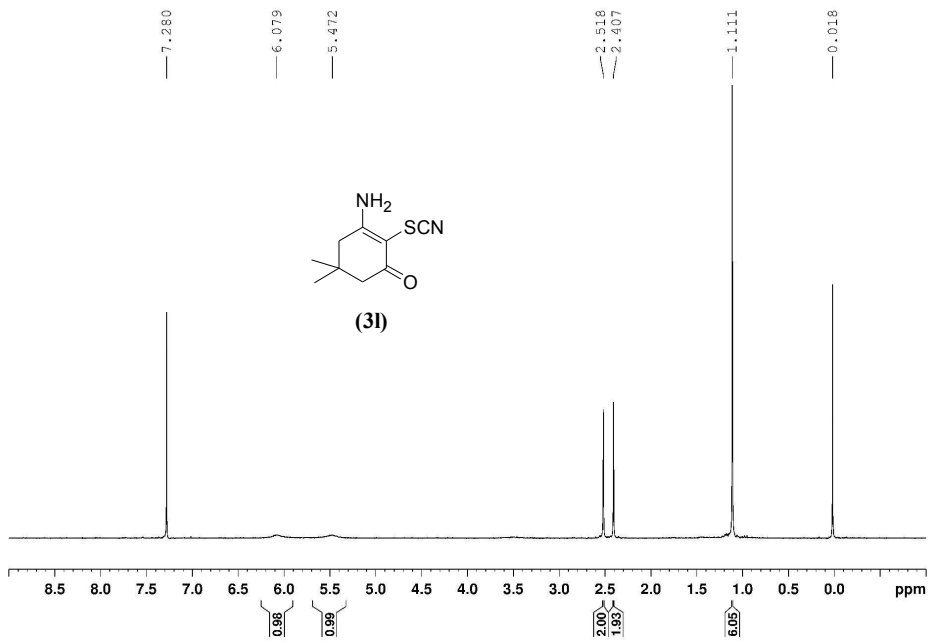


View Article Online
DOI: 10.1039/C6GC00666C

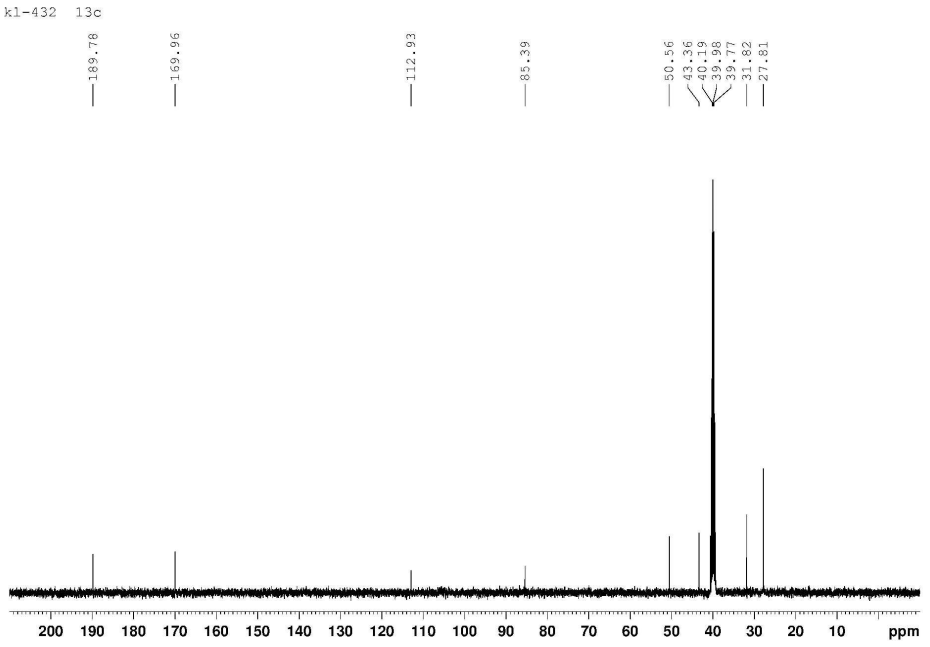




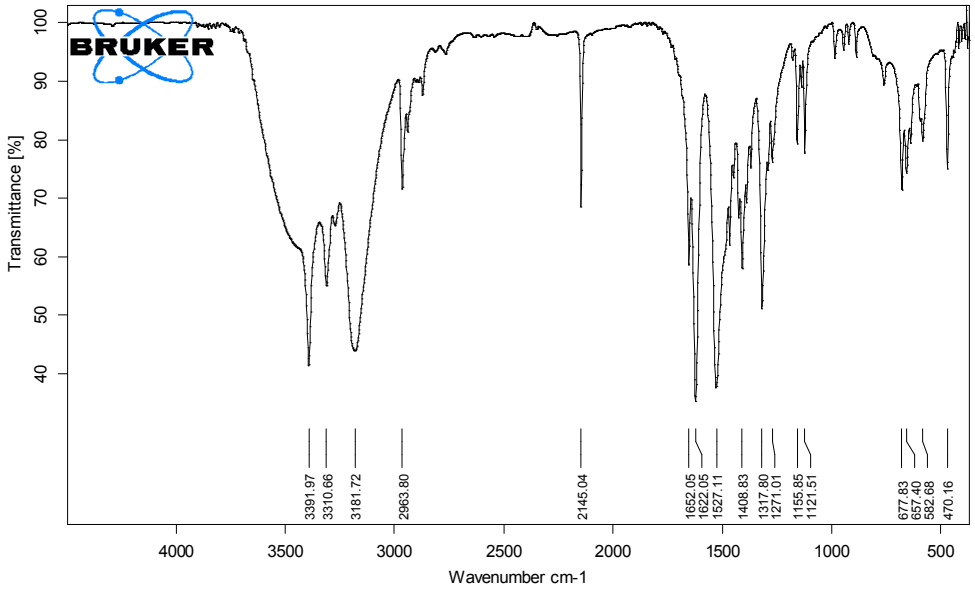
View Article Online
DOI: 10.1039/C6GC00666C

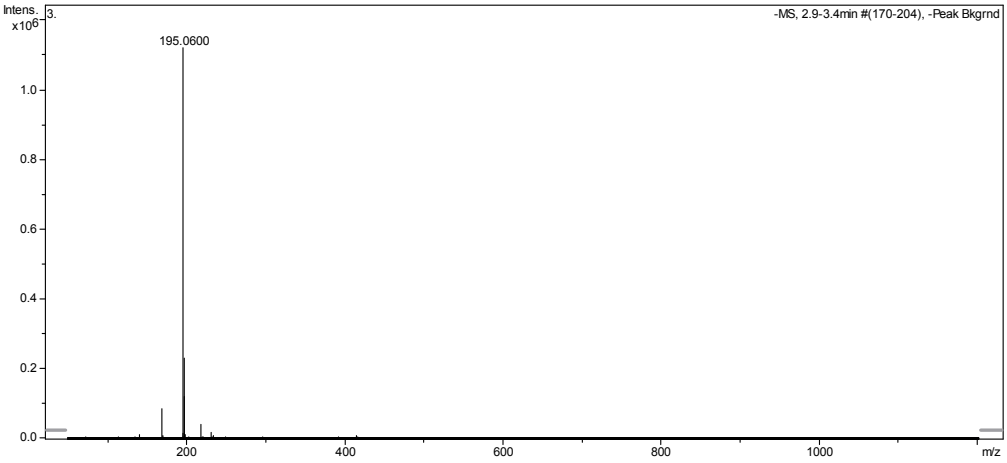


(3l)

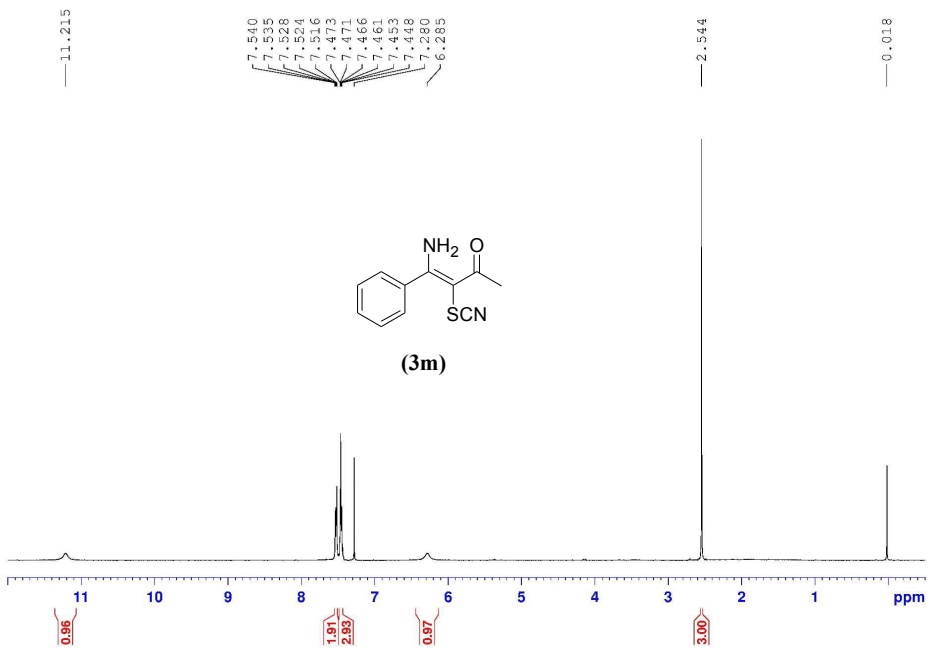


View Article Online
DOI: 10.1039/C6GC00666C

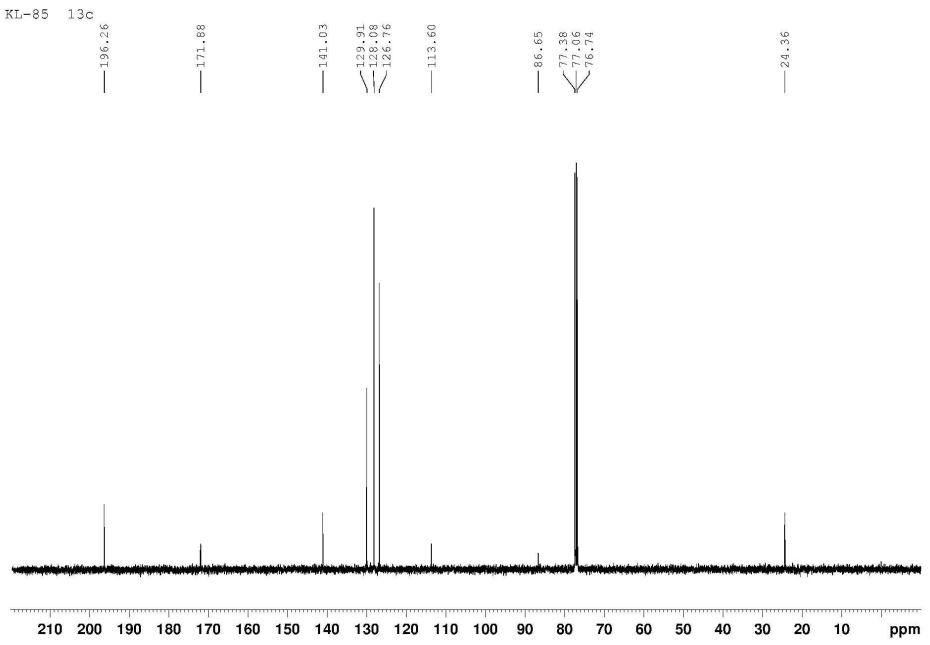




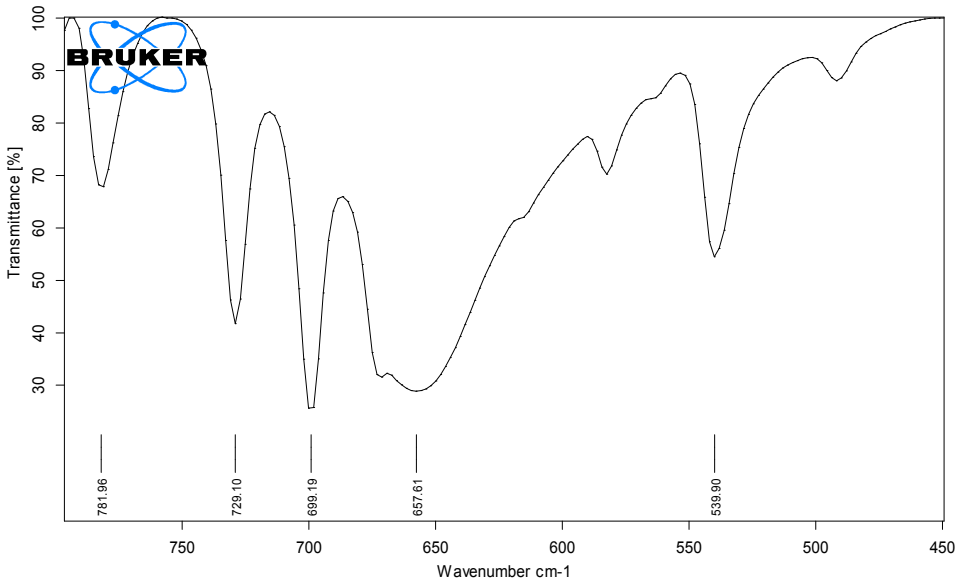
View Article Online
DOI: 10.1039/C6GC00666C

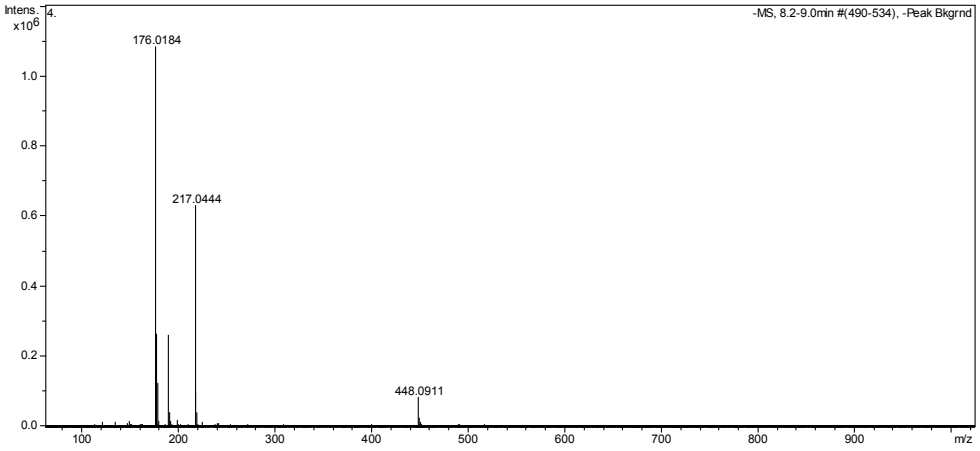


(3m)

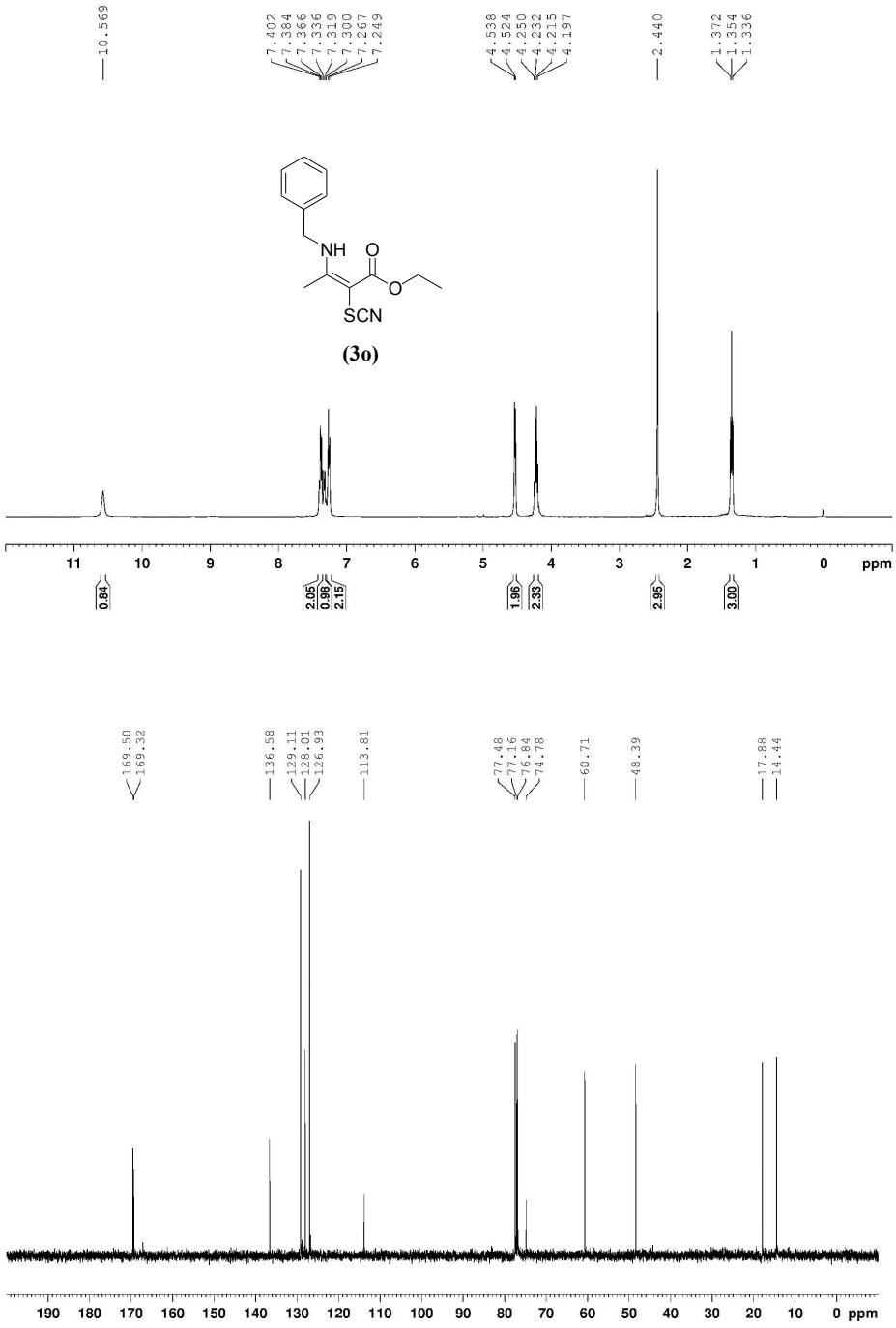


View Article Online
DOI: 10.1039/C6GC00666C

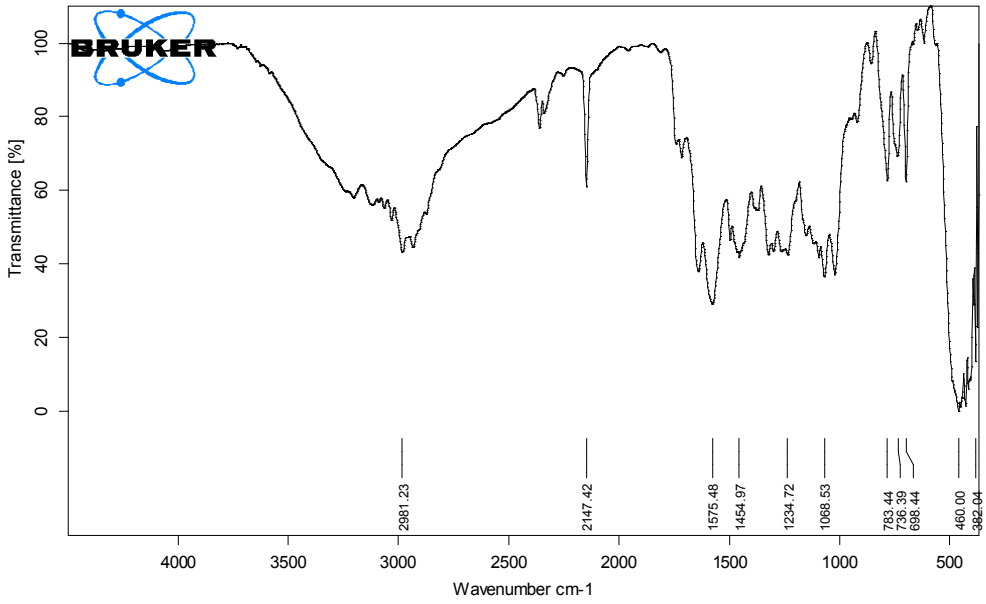


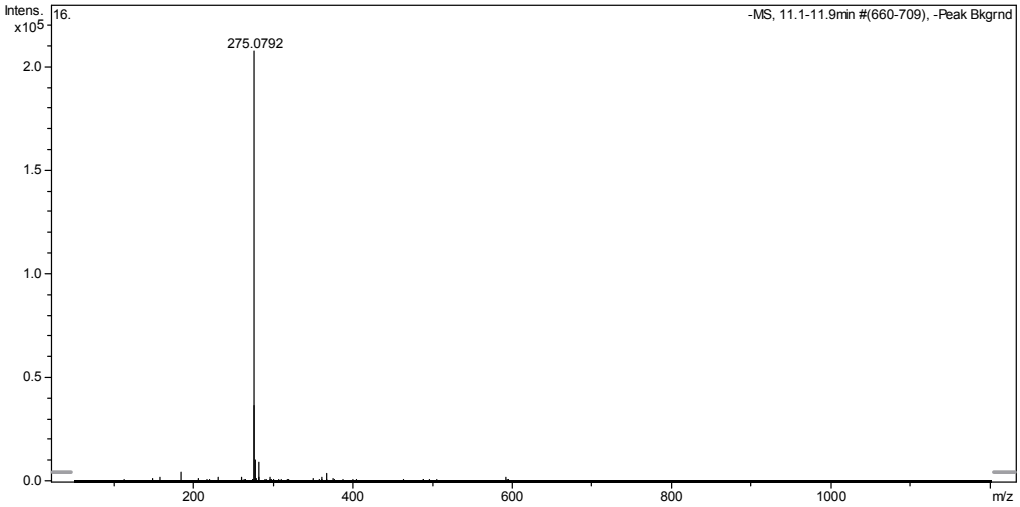


View Article Online
DOI: 10.1039/C6GC00666C

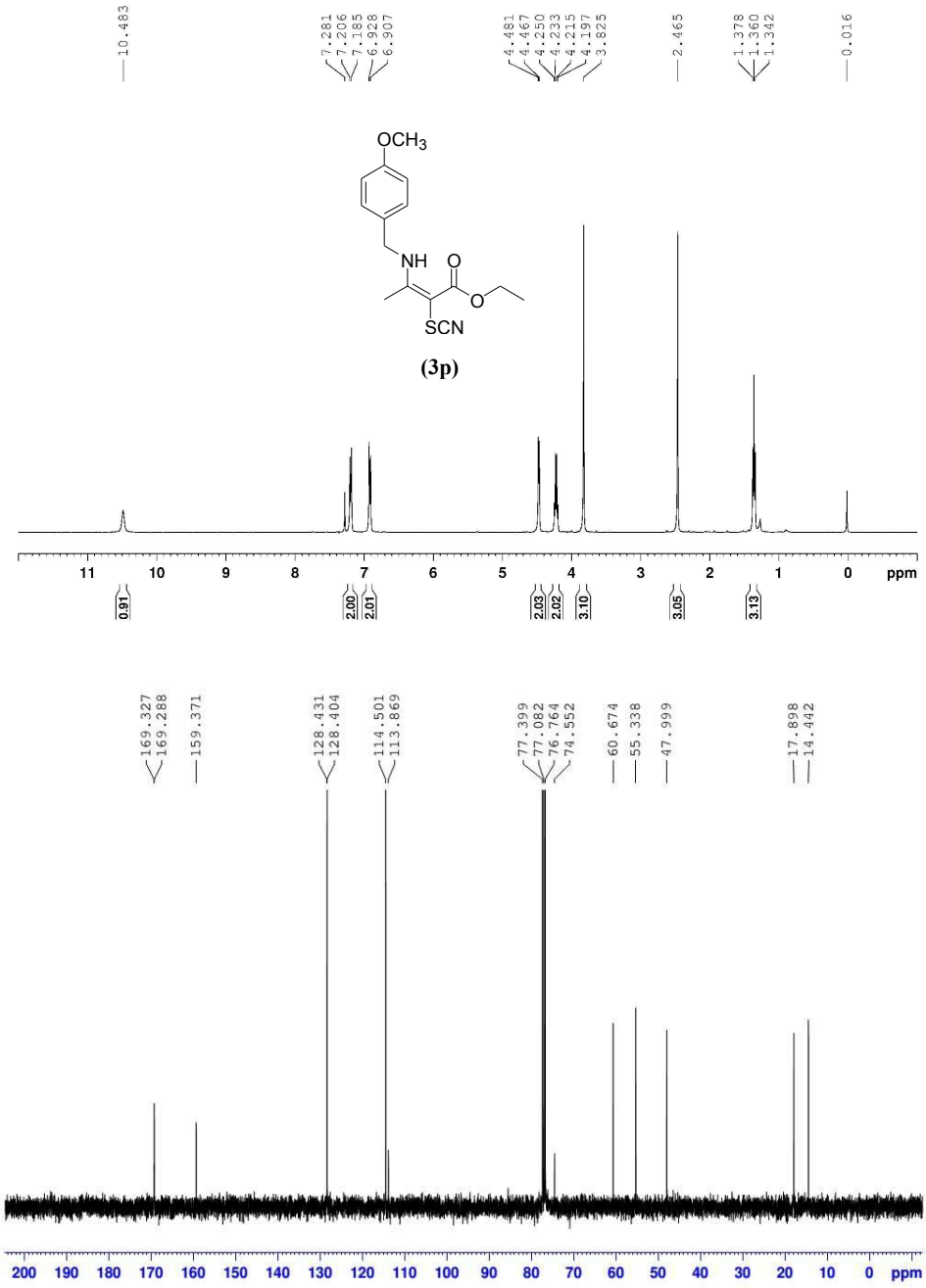


View Article Online
DOI: 10.1039/C6GC00666C

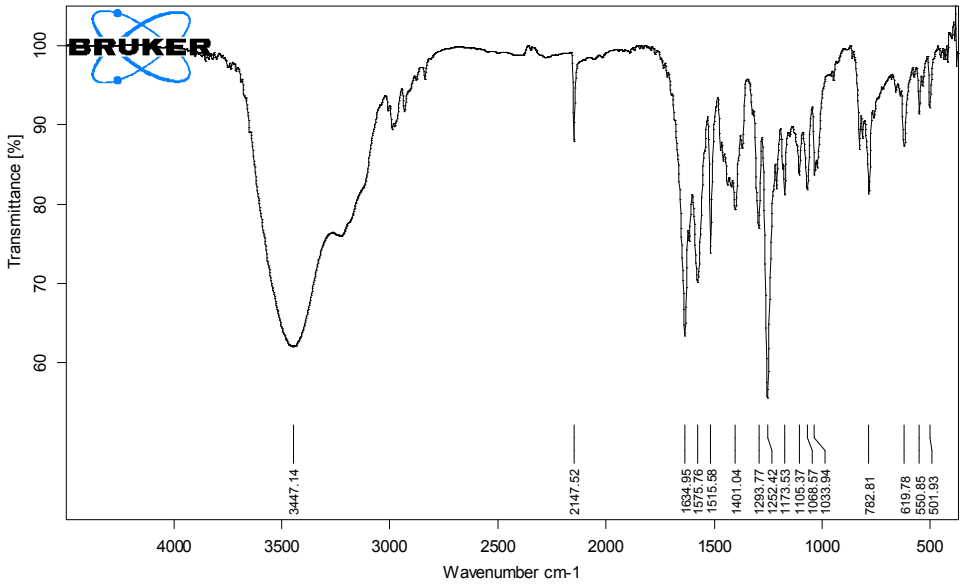


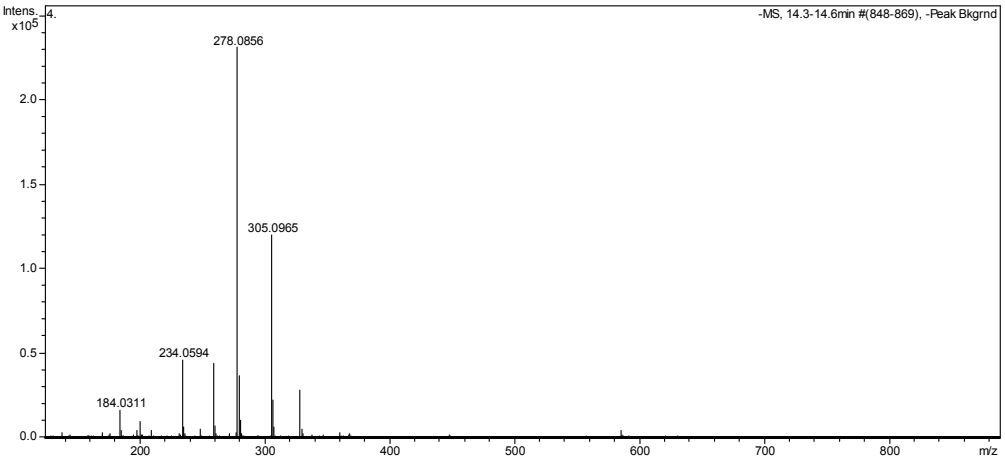


View Article Online
DOI: 10.1039/C6GC00666C

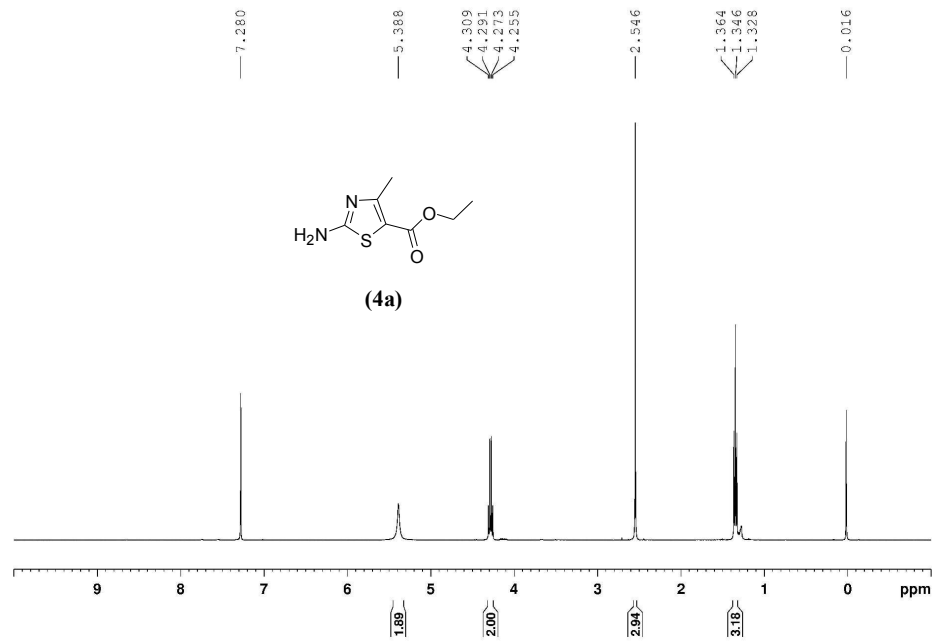


View Article Online
DOI: 10.1039/C6GC00666C





View Article Online
DOI: 10.1039/C6GC00666C



(4a)