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RESEARCH LETTER

A simple way of recycling of homogeneous catalyst in Suzuki reaction

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A simple and practical method of recycling homogeneous catalysts in the Suzuki reaction using appropriate work up conditions is reported here. The commonly used and commercially available homogeneous catalysts **1** (Pd-100) dichlorobis(tri-phenylphosphine)palladium(II), **2** (Pd-106) dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)-dichloromethane adduct, and **3** (Pd-118) 1,1'-bis(di-*tert*-butylphosphino)ferrocene] dichloropalladium(II) selected for our study and were recycled successfully for three times using simple acidic and basic work up conditions depending on the presence of amino or carboxylic acid functional group in the product.

Keywords: homogeneous catalyst; catalyst recycling; Suzuki reaction; Pd-100; Pd-106; Pd-118

Introduction

The Green Chemistry is the utilization of a set of principles that enhance the atom economy and reduce or eliminate the use or generation of hazardous substances in the design, manufacture, and application of chemical products. It can be achieved through many ways, for example, design of environmental friendly process, catalysis, and recycling (1–3). The application of transition metal mediated homogeneous catalyst for the construction of C–C, C–N, C–O bonds having wide industrial application continued to attract chemists (4,5), because of its efficiency to carry out the reaction under mild conditions with better selectivity and yield (6–17). However, the stability, cost, and availability of the catalysts (ligands and metal) can limit their applications at the commercial scale (18,19). Developing simpler and better ways of recycling of these expensive homogeneous catalysts to overcome these issues would widen their industrial application. The current methods adapted for the recycling of homogeneous catalyst involve anchoring of them on to a heterogeneous support (20–22) and on nanoparticles (23,24). However, this would further add to the initial cost of the catalyst and moreover many of such anchored catalysts could be under patent protection which would have its own legal and financial issues for their commercial utilization.

Recently successful attempts on recycling of the homogeneous catalyst have been reported in the literature. For example use of membranes (25), supercritical liquids (26), ionic liquids (27), and polyethylene/methanol mixtures (28) to separate catalyst from product and further recycling have been reported in the recent literature. Recycling of Pd(OAc)₂ in the presence fluorous solvent has been reported in the Heck couplings of iodoarenes and acrylic acids/esters (29). Dumrath et al. (30) have also reported the recycling of Pd(OAc)₂ in the presence of cationic imidazolium-based phosphane ligands for amination aryl halides. However, generality of these techniques and their application at the commercial level needs to be evaluated. Considering the solubility of the homogeneous catalysts in many organic solvents and the insensitivity of many reactions to the presence of water we thought, to explore the possibility of recycling homogeneous Pd catalyst in the Suzuki reaction by separating the catalyst from the product through manipulation of work up conditions depending on the functional group (carboxylic acid, amine) present in the substrate/product. This idea appeared to us a feasible one, simple to adapt at the commercial scale level, and would bring the cost advantage along with an environmental benefit, as the environmental impact of many of the ligands used in the preparation of the homogeneous catalyst is currently not well understood. This article describes a

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simple method of recycling homogeneous catalysts **1** (Pd-100), **2** (Pd-106), and **3** (Pd-118) (Figure 1) used in Suzuki coupling reactions wherein the product has a carboxylic acid or amine functional group. It is known that amount of catalyst required for the Suzuki reaction depends on the nature of functional group present in the reactant and property of the catalyst. After the preliminary evaluation with the selected catalyst and reactants, use of 5 mol% catalyst was found to be optimum for this study.

Results and discussion

Initially, to check the feasibility of the recycling concept of homogeneous catalyst, Suzuki reaction between phenylboronic acid (**4**) and 4-bromobenzoic acid (**7**) was considered. Reaction was carried in a mixture of 2-MeTHF and water using potassium carbonate as a base and **1** (Pd-100) catalyst (Scheme 1). The reaction and workup were performed under nitrogen atmosphere and all the solvents including water were degassed before use. The reaction mass after the addition of the catalyst was slowly warmed at 50–60°C and the progress of the reaction was monitored by high-performance liquid chromatography (HPLC). The reaction got completed in 4 h with 94.3% product (**9a**) formation by HPLC (Table 1, Entry 1). The reaction mixture was then cooled to room temperature; the aqueous layer having the product and the organic 2-MeTHF layer having the homogeneous catalyst were separated. The organic layer containing the catalyst **1** (Pd-100) was then taken for the recycling experiment. Molar quantities of reactants and a degassed solution of aqueous potassium carbonate were then added to the above separated organic layer and the reaction was carried out under the same conditions. As expected, the reaction was completed at the same time (4 h) with 96% product (Table 1, Entry 2). The layers were separated again and the organic layer containing the Pd catalyst was recycled for the next Suzuki coupling. It was good to see that the second recycle reaction was also complete with 94.5% product formation in 3 h (Table 1, Entry 3). The above experimental results indicate that the catalyst **1** (Pd-100) retained its

catalytic activity under aqueous work up condition even after two cycles. The aqueous layer containing the product was acidified with dilute hydrochloric acid and precipitated product was isolated by filtration, and its identity was confirmed by ¹H NMR and mass spectroscopy. A preliminary assessment of catalyst recovery shown to be 70–80% in the organic layer of each cycle (atomic absorption spectrometry) and about 15–20% catalyst leaching to the aqueous layer in each cycle.

The above promising results encouraged us to look for the recycling capabilities of other homogeneous Pd catalysts under similar reaction conditions. We then carried out the recycling experiments with commonly used catalysts **2** (Pd-106) and **3** (Pd-118). The results were similar to **1** (Pd-100) indicating that these catalysts were also stable and retaining the activity under the aqueous basic work up conditions (Table 1, Entry 10–12, 19–21). Furthermore, to prove the generality of this recycling concept, Suzuki reactions between substituted phenylboronic acid (**5** and **6**) and 4-bromobenzoic acid (**7**) were carried under the above experimental conditions using **2** (Pd-106) and **3** (Pd-118) catalysts to yield **9b** and **9c**. In all the cases we could easily recycle the catalyst for two times without losing the activity of the catalysts (Table 1, Entry 13–18, 22–27). Furthermore, the concept was extended to Suzuki reaction between 2-bromobenzoic (**8**) acid and phenylboronic acid (**4**) using **3** (Pd-118) catalysts to yield **9d** and it was successfully recycled consecutively for three times (Table 1, Entry 28–30). These results confirm the recyclability of **1** (Pd-100), **2** (Pd-106), and **3** (Pd-118) in Suzuki reaction under aqueous basic workup conditions.

Encouraged by the above results we then thought to explore the recyclability of these catalysts under acidic workup conditions. The Suzuki reaction between 4-bromoaniline (**10**) and 2-fluorophenylboronic acid (**5**) was then selected for our study. The Suzuki reaction was performed again in 2-MeTHF–water solvent medium using **3** (Pd-118) catalyst under similar conditions. The reaction was completed in 1 h with 98% conversion to product **12a** (Table 2, Entry 1). After the completion of the reaction the reaction

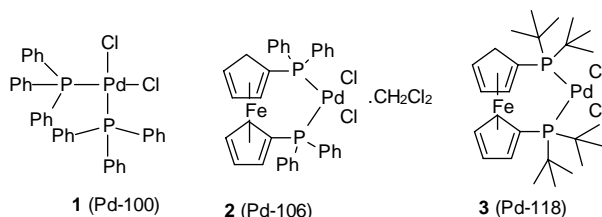
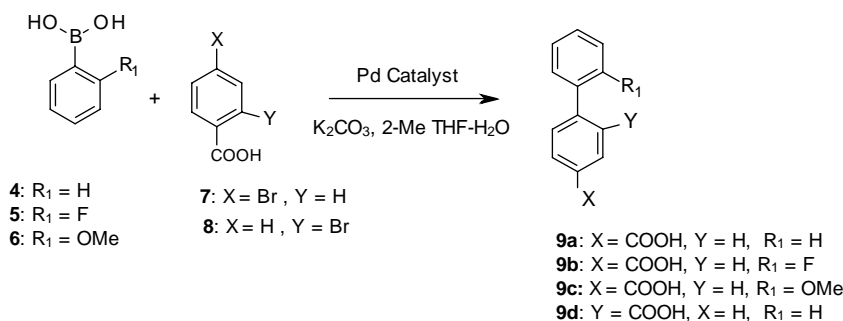


Figure 1. Structures of the homogeneous catalysts **1** (Pd-100), **2** (Pd-106) and **3** (Pd-118).



Scheme 1. Suzuki coupling of phenylboronic acid and aromatic carboxylic acid.

mass was then acidified to pH 1–2 with dilute HCl. The product in the form hydrochloride salt was thus extracted into aqueous solution leaving behind the catalyst in organic layer. The biphasic solution was then separated; 2-MeTHF layer containing the **3** (Pd-118) catalyst was taken for the next Suzuki reaction. Interestingly, the reaction occurred well in 1 h with 98% product (Table 2, Entry 2). Employing the

similar workup procedure the catalyst was taken for one more cycle. These results clearly indicated that **3** (Pd-118) preserves its catalytic activity even under acidic workup conditions. With this encouraging result, the same transformation was then carried using **1** (Pd-100). Though recycling of the catalyst was successful, only moderate conversion was observed in all the cycles (Table 2, Entry 4–6). This

Table 1. Recycling of homogeneous catalyst in Suzuki reaction with basic work up (Scheme 1).

Entry	Comp No	R ₁	X	Y	Cycle	Catalyst (5 mol%)	% Conv (time in h) ^a	% Yield/purity by HPLC
1	9a	H	COOH	H	1	Pd-100	94.3 (4)	85/97.0
2	9a	H	COOH	H	2	–	96.0 (4)	82/98.2
3	9a	H	COOH	H	3	–	94.5 (3)	70/99.0
4	9b	F	COOH	H	1	Pd-100	94.5 (3)	77/95.0
5	9b	F	COOH	H	2	–	96.0 (3)	76/96.9
6	9b	F	COOH	H	3	–	75.6 (3)	65/96.5
7	9c	OMe	COOH	H	1	Pd-100	93 (2)	81/97.9
8	9c	OMe	COOH	H	2	–	96.0 (17)	80/98.2
9	9c	OMe	COOH	H	3	–	93.3 (10)	80/94.3
10	9a	H	COOH	H	1	Pd-106	82.2 (3)	*
11	9a	H	COOH	H	2	–	93.2 (3)	*
12	9a	H	COOH	H	3	–	88.2 (3)	*
13	9b	F	COOH	H	1	Pd-106	97.0 (3)	*
14	9b	F	COOH	H	2	–	97.7 (3)	*
15	9b	F	COOH	H	3	–	96.6 (3)	*
16	9c	OMe	COOH	H	1	Pd-106	93.2 (3)	*
17	9c	OMe	COOH	H	2	–	89.2 (3)	*
18	9c	OMe	COOH	H	3	–	95.5 (3)	*
19	9a	H	COOH	H	1	Pd-118	96.2 (3)	*
20	9a	H	COOH	H	2	–	91.8 (3)	*
21	9a	H	COOH	H	3	–	94.7 (3)	*
22	9b	F	COOH	H	1	Pd-118	96.8 (3)	*
23	9b	F	COOH	H	2	–	97.1 (3)	*
24	9b	F	COOH	H	3	–	97.1 (3)	*
25	9c	OMe	COOH	H	1	Pd-118	95.4 (3)	*
26	9c	OMe	COOH	H	2	–	96.3 (3)	*
27	9c	OMe	COOH	H	3	–	96.9 (3)	*
28	9d	H	H	COOH	1	Pd-118	94.5 (3)	*
29	9d	H	H	COOH	2	–	94.6 (3)	*
30	9d	H	H	COOH	3	–	93.3 (4)	*

^a% Conversion to product, with respect to starting material; *Product was not isolated.

Table 2. Recycling of homogeneous catalyst in Suzuki reaction with acidic work up (Scheme 2)

Entry	Product	X	R ₁	Cycle	Catalyst (5 mol%)	% Conv (time in h) ^a
1	12a	H	F	1	Pd-118	98 (1)
2	12a	H	F	2	–	98 (1)
3	12a	H	F	3	–	92 (1)
4	12a	H	F	1	Pd-100	85 (2)
5	12a	H	F	2	–	72 (4)
6	12a	H	F	3	–	57 (4)
7	12b	N	F	1	Pd-118	90 (4)
8	12b	N	F	2	–	88 (5)
9	12b	N	F	3	–	72 (5)
10	12b	N	F	1	Pd-100	71 (24)
11	12b	N	F	2	–	53 (24)
12	12b	N	F	3	–	27 (24)

^a% Conversion to product, with respect to starting material.

could be due to low reactivity of the catalyst for the given conditions. As some un-reacted aniline was always retained in the organic layer, conversion to the product in the subsequent cycles appeared to be lower when comparing to the starting material.

To test the generality of the recycling of Pd catalyst in Suzuki reaction under acidic work up conditions, Suzuki reactions were carried out between 2-Bromo 5-amino pyrazine (**11**) and 2-fluorophenylboronic acid (**5**) using **1** (Pd-100) and **3** (Pd-118) catalyst to give **12b**. Moderate to good conversion was obtained in these experiments (Table 2, Entry 7–12).

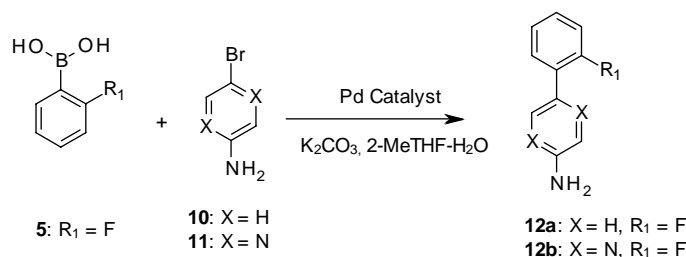
To summarize, we have demonstrated a simple and efficient method for the recycling of homogeneous catalyst in Suzuki coupling reactions. From this study it is very clear that homogeneous catalysts **1** (Pd-100), **2** (Pd-106), and **3** (Pd-118) are quite stable under both acidic and basic workup conditions and can be recycled through simple manipulation of work up conditions. A major advantage of this technique is that, in a single operation, product, and catalyst can be separated easily, and the solution having the catalyst can be recycled without further isolation of the catalyst or loss in their activity. This method could be easily applied in the industry for the

commercial scale manufacturing process, which could reduce the cost, operations, and environmental impacts and would increase the efficiency of manufacturing process. This strategy could be extended with varieties of homogeneous catalyst for other chemical transformation. To best of our knowledge, this is the first report where homogeneous catalyst has been recycled successfully in both acidic and basic conditions. Further study on Pd-based homogeneous catalyst and its optimum usage or application on large scale is under way.

Experimental

General procedure for the recycling catalyst in basic work up

A 25 mL three-neck round bottom flask was equipped with condenser, N₂-inlet was charged 2-MeTHF (5 mL) and water (5 mL), then degassed through with N₂ bubbling for about 5 min. To this, 2-methoxy phenyl boronic acid **6** (0.47 g; 0.0031 mmol), potassium carbonate (1.03 g, 0.0075 mmol), 4-bromobenzoic acid **7** (0.50 g, 0.0025 mmol), and then Pd catalyst (0.0085 g, 5 mol%) were added. The reaction mass was heated on an oil bath at 55–60°C and progress was monitored by HPLC. After the



Scheme 2. Suzuki coupling of phenylboronic acid and aromatic amine.

desired conversion, it was cooled to room temperature and biphasic solution was separated. To the organic layer, reactants and degassed solution of aqueous potassium carbonate was added, and then the reaction was carried under same conditions. The same procedure had been utilized for the recycling experiments and all the operations were performed under nitrogen atmosphere. For product isolation, aqueous layer was acidified with dilute HCl and precipitated product was filtered and dried to give the desired product. Identity of the product confirmed by ^1H NMR and mass spectroscopy.

General procedure for the recycling of catalyst in acidic work up

A 25 mL three-neck round bottom flask fitted with condenser and N_2 -inlet was charged 2-MeTHF (5 mL) and water (5 mL) then degassed with N_2 bubbling for about 5 min. To this, 4-bromoaniline **10** (0.50 g, 0.0029 mmol), 2-fluorophenyl boronic acid **5** (0.42 g, 0.0031 mmol), potassium carbonate (0.68 g, 0.0043 mmol), and then Pd catalyst (0.0085 g, 5 mol%) were added. Reaction mass was heated to reflux on oil bath and progress was monitored by HPLC. After the desired conversion, it was cooled to room temperature. Reaction mass was acidified with dilute HCl to pH 1–2, stirred for 10–15 min and biphasic solution was separated. To the organic layer, reactants and degassed solution of aqueous potassium carbonate was added, and then the reaction was carried under same conditions. The same procedure was followed for three times and all the operations were performed under nitrogen atmosphere.

Acknowledgements

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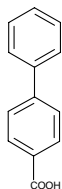
Supporting information ^1H , ^{13}C NMR spectral data, HPLC chromatogram and Mass data for compounds **9a-c** are available.

General information

All the reagents and solvents were commercial grade, and used without purification. Reactions were monitored by HPLC, % conversion to the product was quantified, respectively, to starting material. Compounds **9a-c** (Table 1) were isolated as given in general procedure and characterized by ^1H , ^{13}C NMR, and mass spectrometer. Compounds **9d**, **12a**, and **12b** were identified by mass using LC-MS. NMR was recorded on a 400 MHz Bruker instrument using $\text{d}_6\text{-DMSO}$ as solvent. Chemical shifts (δ) are expressed in parts per million (ppm) coupling constants (J) are in Hz. The ^1H and ^{13}C NMR chemical shifts are reported relative to the resonance of the residual protons of the solvent was used as internal standard for ^1H ($\delta = 2.50$ DMSO- d_6) and all deuterium solvent signals for ^{13}C ($\delta = 39.5$ DMSO- d_6). All measurements were carried out at 298 K. Abbreviations used in the description of NMR data are as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Purity of the product was recorded on Agilent 1200 series HPLC. C_{18} column was used with linear gradient acetonitrile and water system. LC-MS analyses were recorded on a Waters LC-MS equipped with a Waters X-Terra MS, C_8 -column, (3.5 μm , 100 mm \times 3.0 mm i.d.). The MS was equipped with an electrospray ion source operated in a negative ion mode. The capillary voltage was 3 kV and the MS was typically scanned between m/z 100 and 700. Palladium content was analyzed using atomic absorption method using Perkin Elmer AAnalyst 700.

^1H , ^{13}C , and mass spectral data

Biphenyl-4-carboxylic acid (**9a**)

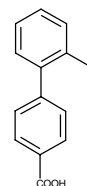


^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$): $\delta = 8.07$ (d, $J = 8.5$ Hz, 2H), 7.84 (d, $J = 8.5$ Hz, 2H), 7.78 (d, $J = 7.6$ Hz, 2H), 7.55 (t, $J = 7.0$ Hz, 2H), 7.47 (t, $J = 7.0$ Hz, 1H).

^{13}C NMR (400 MHz, $\text{d}_6\text{-DMSO}$): 167.1, 144.2, 139.0, 129.9, 129.7, 129.0, 128.2, 126.9, 126.8.

MS (EI): $m/z = 197(\text{M}-1)$.

2'-Fluorobiphenyl-4-carboxylic acid (**9b**)

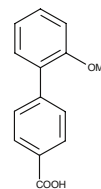


^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$): $\delta = 8.04$ (d, $J = 6.4$ Hz, 2H), 7.68 (d, $J = 8.5$ Hz, 2H), 7.59 (t, $J = 7.5$, 1H), 7.47 (t, $J = 8.5$ Hz, 1H), 7.35 (m, 2H).

^{13}C NMR (400 MHz, $\text{d}_6\text{-DMSO}$): 166.9, 157.8, 139.3, 131.6, 131.2, 130.6, 130.0, 129.5, 129.2, 125.1, 116.3, 116.0.

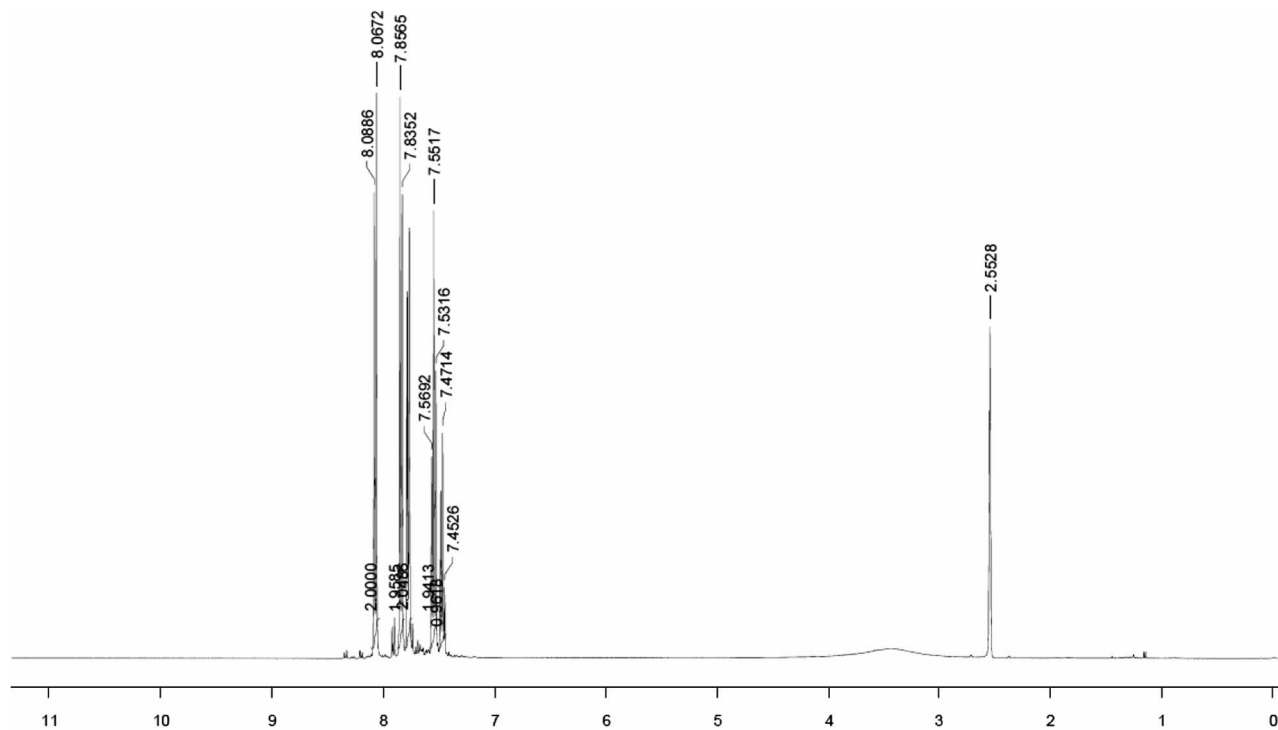
MS (EI): $m/z = 215(\text{M}-1)$

2'-Methoxybiphenyl-4-carboxylic acid (**9c**)

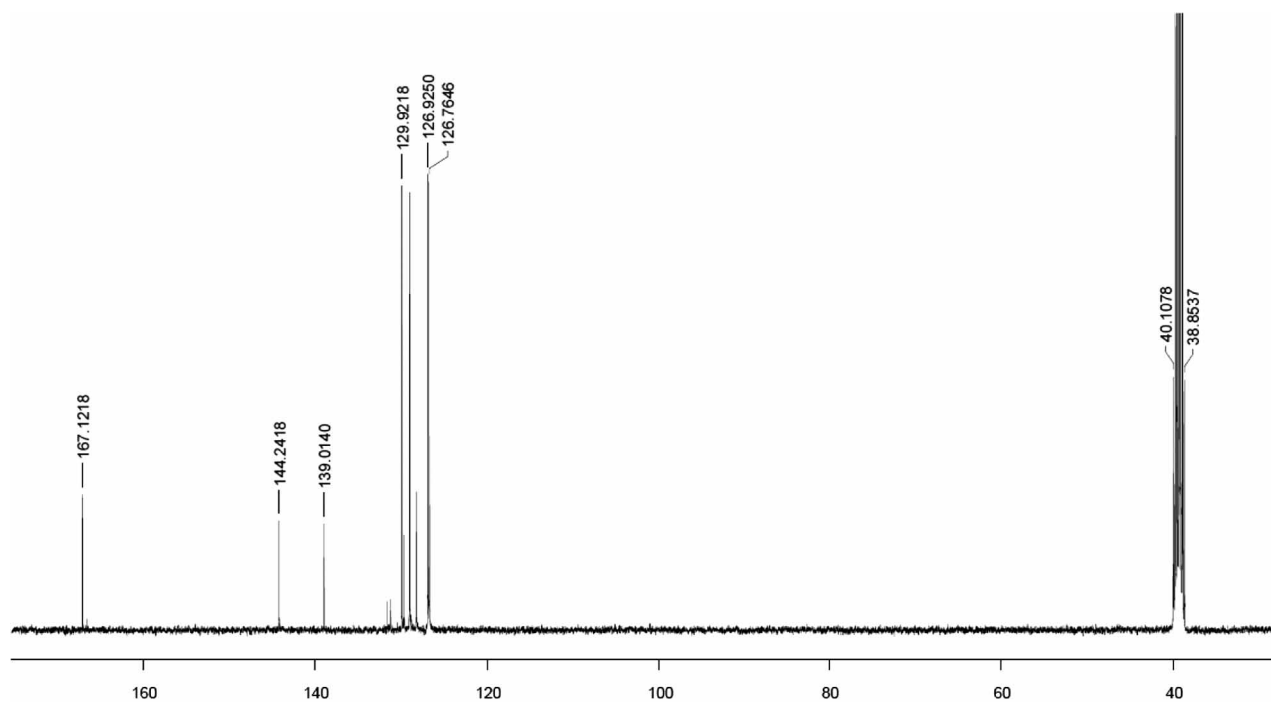


^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$): $\delta = 12.97$, (s, 1H), 7.97 (d, $J = 8.5$ Hz, 2H), 7.60 (d, $J = 8.0$ Hz, 2H), 7.39 (t, $J = 7.5$ Hz, 1H), 7.34 (d, $J = 7.5$ Hz, 1H), 7.14 (d, $J = 8.2$ Hz, 1H), 7.06 (t, $J = 7.0$ Hz, 1H) 3.77 (s, 3H).

MS (EI): $m/z = 227(\text{M}-1)$

^1H , ^{13}C NMR spectra, and HPLC chromatogram for 9a-c

JView Version 1.00 - for C&M see notebook P5676 /NMRB400/SamTrack/nmr/110721045/1/pdata/1/
Anil Alban, SH-07 P1, 1 H in DMSO
Printed by klw936 on Fri Jul 22 09:07:37 IST 2011. nucleus: 1H, freq: 400.13 MHz, solvent: DMSO, temperature:298K

Figure 1. ^1H NMR spectra of compound 9a.

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Figure 2. ^{13}C NMR spectra of compound 9a.

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 project: SW-07 P1
 Solvent: 2 250mM AmAc Column: 1 BEH-C18, 30x 4.6mm, 1.7um

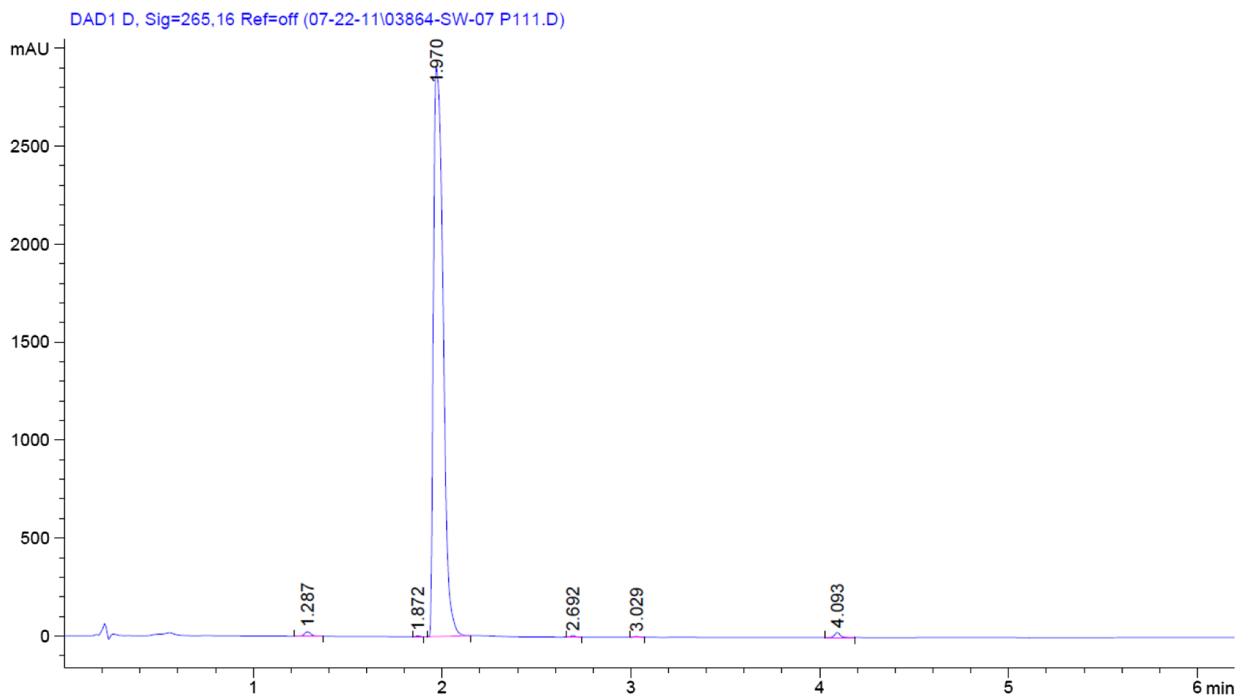


Figure 3. HPLC for compound **9a**.

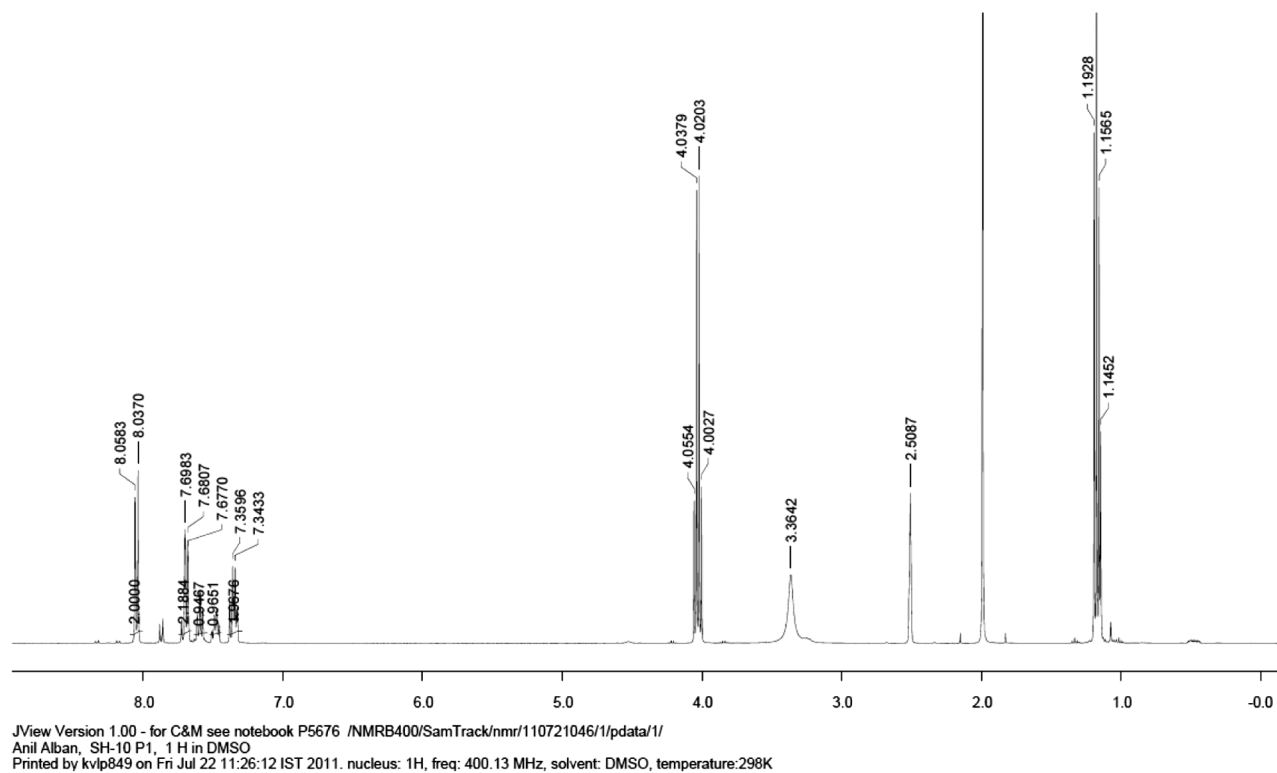
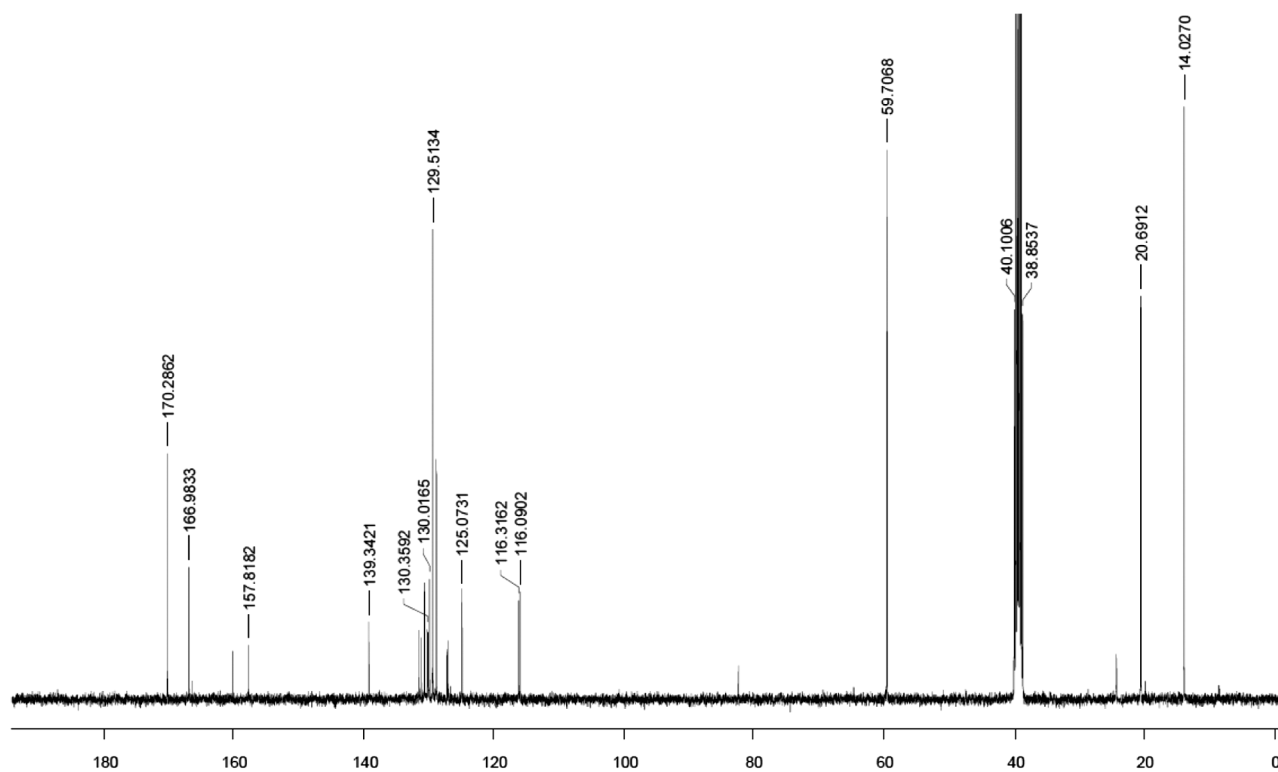


Figure 4. ¹H NMR spectra of compound **9b** (Note: peak at 1.18 (t), 1.92 (s), and 4.03 (q) ppm corresponds to residual ethylacetate).



JView Version 1.00 - for C&M see notebook P5676 /NMRB400/SamTrack/nmr/110721046/2/pdata/1/
 Anil Alban, SH-10 P1, 1 H in DMSO
 Printed by klw936 on Fri Jul 22 09:22:23 IST 2011. nucleus: 13C, freq: 100.61 MHz, solvent: DMSO, temperature:298K

Figure 5. ^{13}C NMR spectrum of compound **9b** (Note: peak at 14.0, 20.7, and 170.3 ppm are corresponds to residual ethylacetate).

Sample Info : SW-10 P1
 Easy-Access Method: 'BEH-C18_ACN_AmAc_G8'
 batch number: SW-07 P2
 project: SW-10 P1
 Solvent: 2 250mM AmAc Column: 1 BEH-C18, 30x 4.6mm, 1.7um

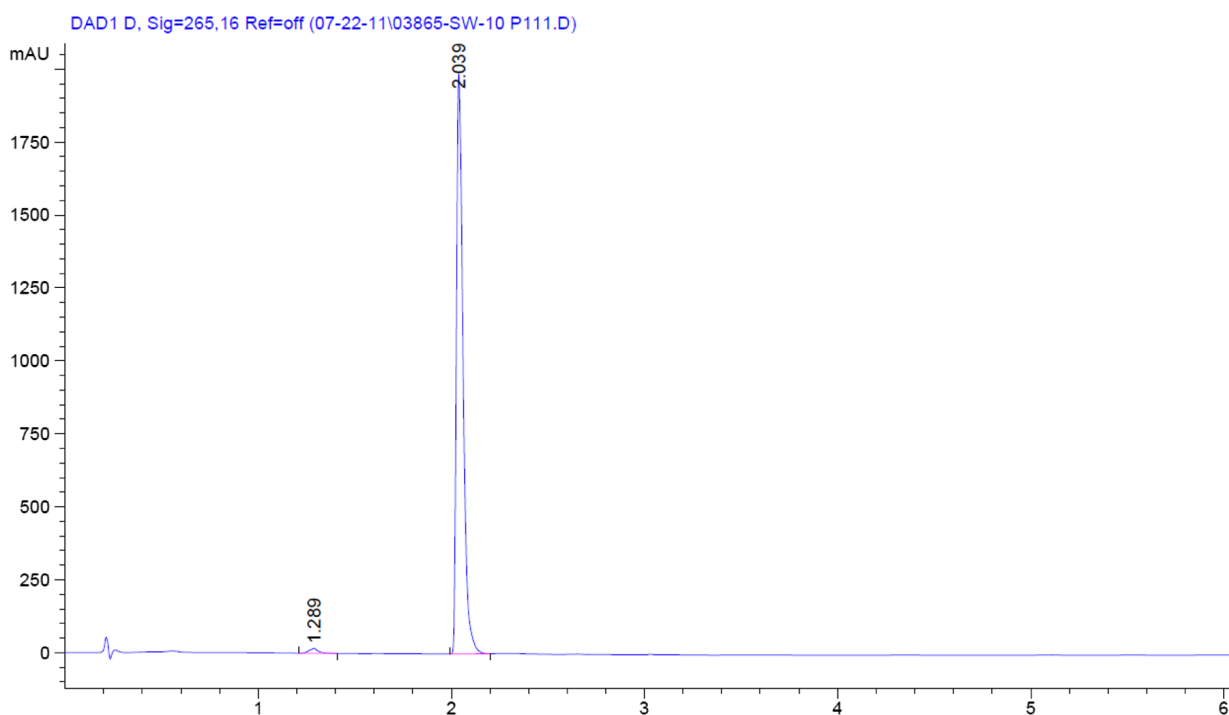
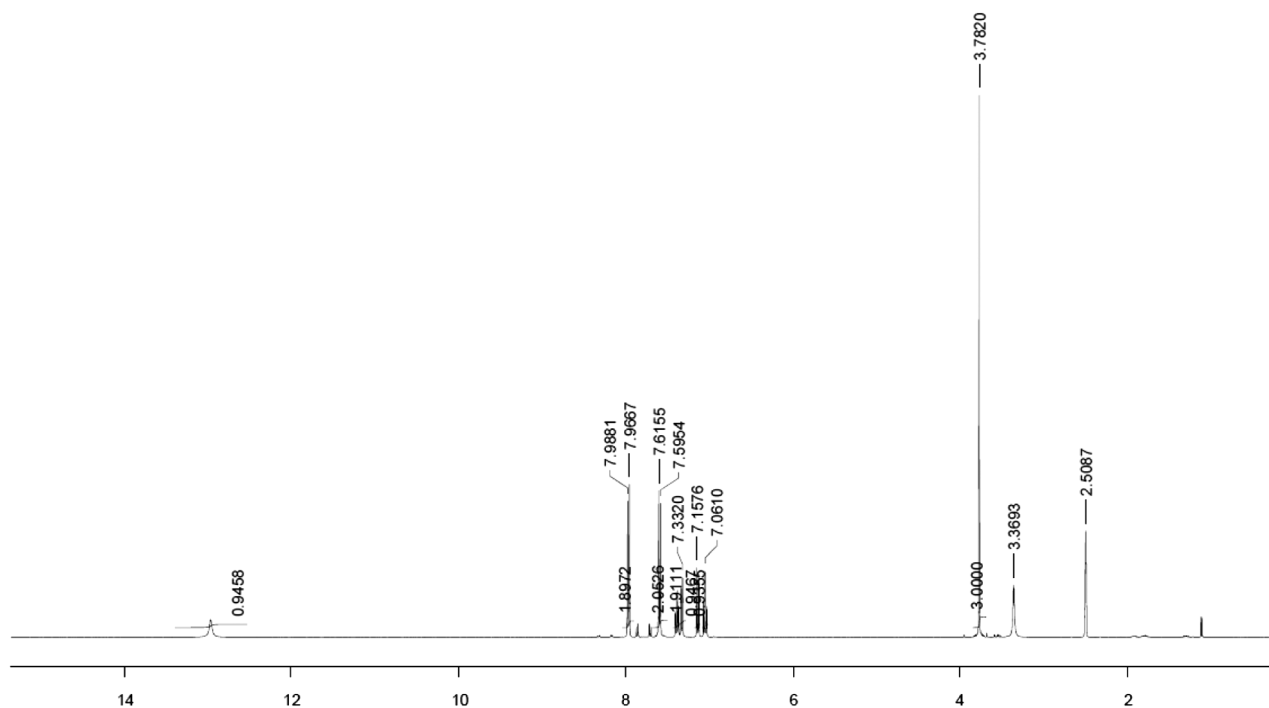
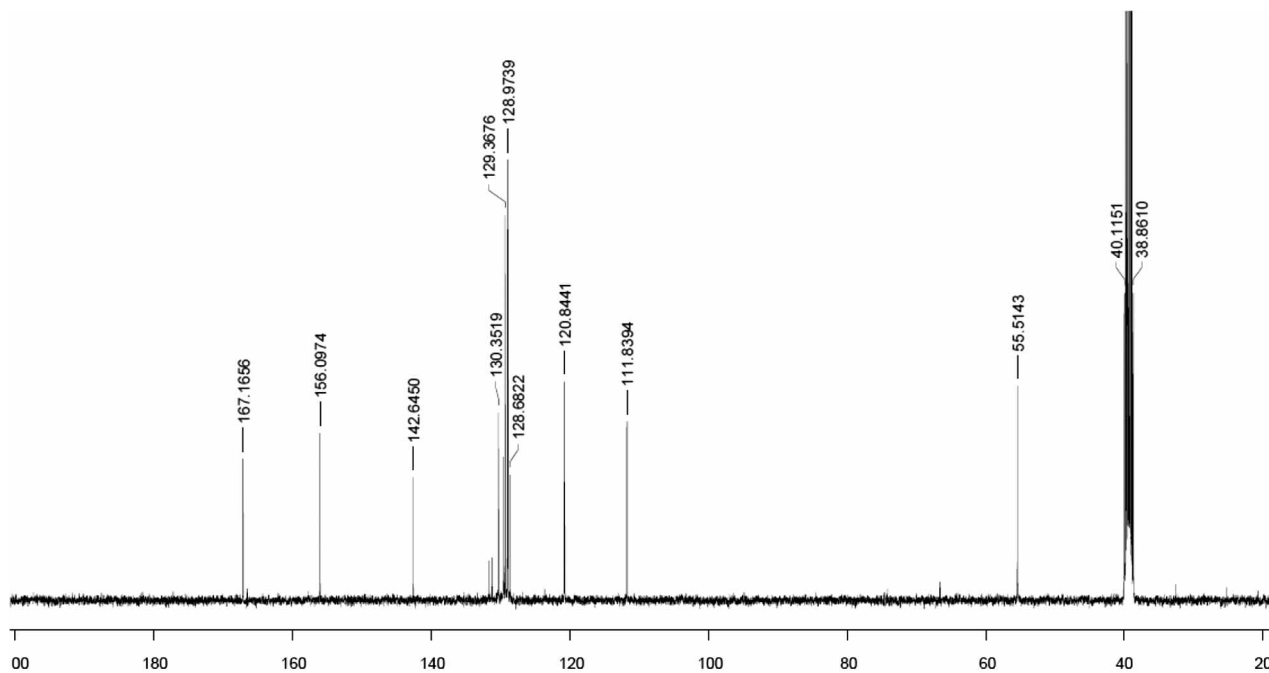


Figure 6. HPLC for compound **9b**.



JView Version 1.00 - for C&M see notebook P5676 /NMRB400/SamTrack/nmr/110714013/1/pdata/1/
 Anil Alban, 04-SW-P1, 1 H in DMSO
 Printed by klww936 on Thu Jul 14 15:07:04 IST 2011. nucleus: 1H, freq: 400.13 MHz, solvent: DMSO, temperature:298K

Figure 7. ¹H NMR spectra of compound 9c.



JView Version 1.00 - for C&M see notebook P5676 /NMRB400/SamTrack/nmr/110714013/2/pdata/1/
 Anil Alban, 04-SW-P1, 1 H in DMSO
 Printed by klww936 on Fri Jul 15 16:53:36 IST 2011. nucleus: 13C, freq: 100.61 MHz, solvent: DMSO, temperature:298K

Figure 8. ¹³C NMR spectra of compound 9c.

Acq. Method : C:\CHEM32\1\METHODS\FLAP-9.M
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 Last changed : 7/18/2011 10:51:37 AM by Smitha
 (modified after loading)
 Method Info : FLAP
 Sample Info : 04 P1

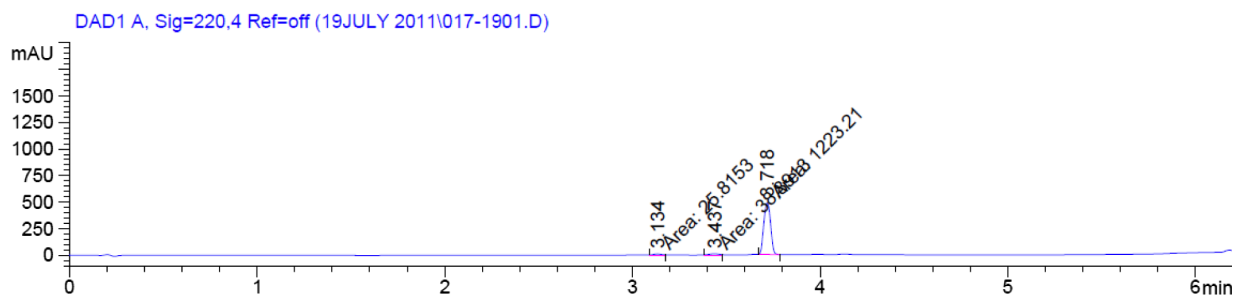


Figure 9. HPLC for compound **9c**.

Palladium recovery/leaching of the catalyst 1 (Pd-100) in the synthesis of compound 9a

	% Pd recovery in org. layer	% Pd recovery in aq. layer
Pre-reaction condition ^a	77.8	NA
First cycle	77.3	15.7
Second cycle	77.2 ^b	20.8
Third cycle	69.1 ^c	21.6

^aAnalysis was performed for the organic layer before subjected to reaction.

^bCalculation was done based on the first cycle catalyst input.

^cCalculation was done based on the second cycle catalyst input.