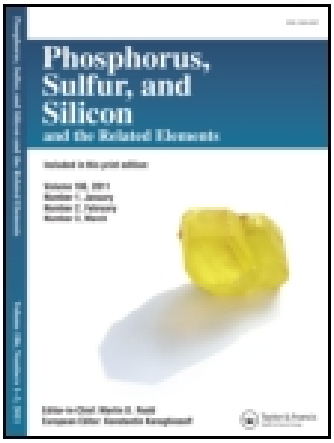

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Copper (I) Iodide-Catalyzed Solvent-Free Synthesis of α-Aminophosphonates

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COPPER (I) IODIDE-CATALYZED SOLVENT-FREE SYNTHESIS OF α-AMINOPHOSPHONATES

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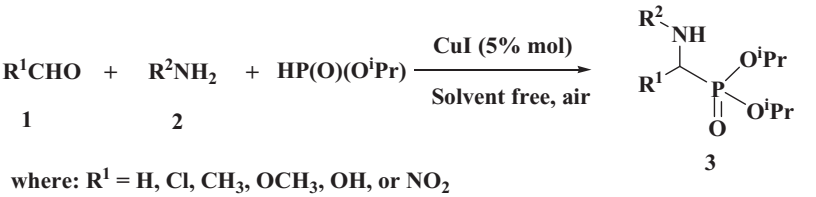
GRAPHICAL ABSTRACT



1 2 3

where: R^1 = H, Cl, CH_3, OCH_3, OH, or NO_2
R^2 = Ph, CH_2Ph, *p*-$OMeC_6H_4$, *p*-MeC_6H_4, *p*-ClC_6H_4, n

Abstract *A method for the synthesis of α-aminophosphonates through the three-component coupling reaction of aldehydes, amines, and diisopropyl phosphite using copper (I) iodide salt catalyst is demonstrated, The reaction is highly efficient, economic, and also environment friendly.*

[Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental resource*: *Table S1, Figures S1–S9.]*

Keywords α-Aminophosphonate; Kabachnik–Fields reaction; copper (I) iodide

INTRODUCTION

Aminophosphonic acids are structural analogues of natural α-aminocarboxylic acids, and have been found to act as inhibitors of specific enzymes as HIV protease, thrombin, and human collagenaze, and to suppress the growth of various tumors and viruses.[1] Furthermore,

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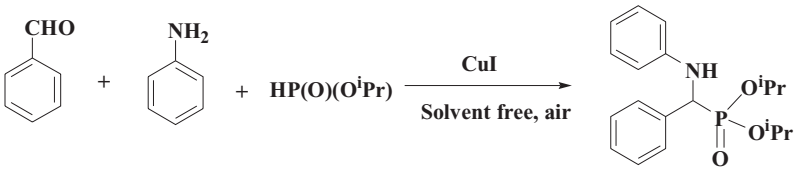
α-aminophosphonates are an important class of compounds used widely in biochemical and pharmaceutical chemistry, such as peptidomimetics,[2] herbicides,[3] antibiotics, and inhibitors of phosphatase activity.[4] Among the methods given in literature, the Kabachnik–Fields reaction is one of the most convenient approaches to obtain α-aminophosphonates. In recent years, three-component α-aminophosphonate synthesis from aldehydes, amines, and diisopropyl phosphite or triisopropyl phosphite catalyzed by Lewis acids[5] or under microwave condition has been reported.[6] Generally, α-aminophosphonates are prepared by the nucleophilic addition of phosphite to imine in the presence of Brønsted acid or Lewis acids such as $ZnCl_2$, BF_3-Et_2O, CdI_2/benzene, and CdI_2/microwave.[7] The reaction can be catalyzed by metal triflate, SmI_2, $TaCl_5$-SiO_2, $Mg(ClO_4)_2$, and polymer-supported sulfonic acid.[8] However, some of these are either expensive or somewhat difficult to prepare.

Recently, the use of copper (I) iodide as a catalyst in organic reactions has received great attention in the Ullmann reactions,[9] Heck additions,[10] Diels–Alder reactions,[11] and cycloaddition reactions.[12] Here, we describe a very practical green alternative for the synthesis of α-aminophosphonates by a three-component condensation of aldehydes, amines, and diisopropyl phosphite at 50°C in neat solvent and catalytic amount of a readily available copper (I) iodide salt (Scheme 1). In this work we report on the synthesis, spectral characterization, and single-crystal X-ray diffraction analysis of some novel α-aminophosphonates.

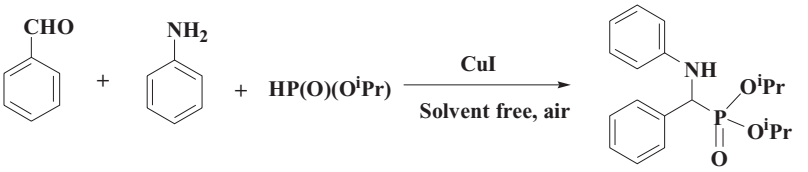


Scheme 1 Synthesis of α-aminophosphonates using CuI.

RESULTS AND DISCUSSION

As described previously, CuI has recently attracted much attention as a catalyst in various organic reactions. Inspired by these results, we conceived that CuI might also act as an efficient organo-catalyst in α-aminophosphonate synthesis. Initial studies were performed by using CuI (1 mol%) as a catalyst in the reaction of benzaldehyde and aniline with diisopropyl phosphite at 50°C in THF solvent. We observed the formation of the corresponding product **3a** in 68% isolated yield, which was obtained after 8-h reaction (Table 1, entry 1). Further study showed that this reaction was carried out smoothly under solvent-free conditions. When the reaction was performed in solvent-free conditions using 2% and 5% catalyst, respectively, the desired P–C product was formed in 75% and 88% isolated yield and ^{31}P nuclear magnetic resonance (NMR) spectroscopy showed that the starting materials disappeared after 8 h (Table 1, entry 2–3). However, entry 6 in Table 1 showed that it was not necessary to perform the reaction with 10% catalyst. Shortening or lengthening of reaction time can slightly influence the isolated yield (Table 1, entry 4–5). It is noteworthy that this reaction could be run in air without loss of efficiency. It is not enough to merely indicate that other reagents are available for this reaction. Various copper salts were tested for the proposed reaction, which showed relative lower catalytic efficiency

Table 1 Effect of reaction condition on the CuI-catalyzed reaction of aldehydes, amines, and diisopropyl phosphite at 50°C



Entry	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	CuI (1)[a]	8	68
2	CuI (2)	8	75
3	CuI (5)	8	88
4	CuI (5)	4	80
5	CuI (5)	24	86
6	CuI (10)	8	72
7	CuCl (5)	8	30
8	Cu_2O (5)	8	58
9	CuO (5)	8	Trace

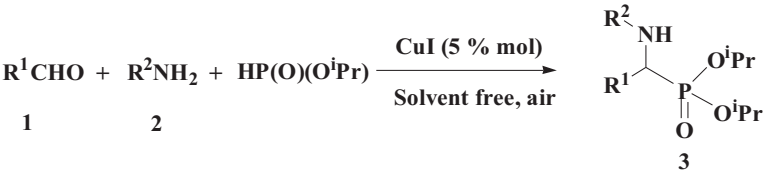
[a]The reactions were carried out with aldehyde (1 mmol), amine (1 mmol), and diisopropyl phosphite (1 mmol), solvent-free at 50°C, 4–24 h; [b]isolated yield.

compared with CuI under same conditions and thus CuI was chosen as a catalyst for further optimization (Table 1, entry 7–9).

In order to demonstrate the generality of this method, we next investigated the scope of this reaction under the optimized conditions (solvent-free, 5 mol% of CuI, air, 50°C) and the results are summarized in Table 2. As shown in Table 2, several sensitive functionalities, such as OH, OMe, Cl, and NO_2, are well tolerated under the present reaction conditions, and the desired α-aminophosphonates were obtained in moderate to good yields (Table 2). In contrast to the substitution effect of the aldehyde, the presence of electron-withdrawing groups on the aldehyde resulted in the corresponding products in low yields and the reaction was sluggish (Table 2, entry **3f**); however, aldehydes possessing electron-donating groups afforded the corresponding α-aminophosphonates in shorter reaction time and in higher yields. The reaction of benzylamine with benzaldehyde and diethyl phosphite provided moderate yields of α-aminophosphonates and the reaction might expend a longer time. The yields were comparably lower with that obtained using aniline (Table 2, entry **3g–3j**). Aliphatic amines were also examined in the one-pot reaction with benzaldehyde and phosphite, but no substantial amount of α-aminophosphonates could be obtained. We attribute this to the slow formation and unstable nature of the imine formed from the examined aliphatic aldehydes.

Crystals of diisopropyl phenyl(phenylamino)methylphosphonate (**3a**) were grown from a petroleum ether/dichloromethane solution (v/v = 5:1). X-ray data were collected on a Bruker SMART CCD X-ray area detector diffractometer at room temperature using Mo Kα radiation (λ = 0.7173 Å) with φ and ω scans (Table 3). Computations were carried out using the SHELXTL-97[13] program package. Figure 1 shows an ORTEP plot of the molecule (**3a**). Bond lengths and angles are comparable with those found in other α-aminophosphonates.[14] The crystal structure is stabilized by strong intermolecular N(1)–H(1A) · · · O'(1) hydrogen

Table 2 One-pot synthesis of α-aminophosphonates catalyzed by CuI



Product[a]	R^1	R^2	Reaction time/h	Yield (%)[c]
3a	Ph	Ph	8[b]	88
3b	*p*-ClC_6H_4	Ph	8	78
3c*	*p*-MeC_6H_4	Ph	8	84
3d	*p*-$OMeC_6H_4$	Ph	8	94
3e	*o*-OHC_6H_4	Ph	8	83
3f*	*p*-$NO_2C_6H_4$	Ph	24	74
3g*	Ph	CH_2Ph	24	75
3h	*p*-ClC_6H_4	CH_2Ph	24	70
3i*	*p*-MeC_6H_4	CH_2Ph	24	71
3j	*p*-$OMeC_6H_4$	CH_2Ph	24	82
3k	Ph	*p*-$OMeC_6H_4$	8	89
3l*	*p*-MeC_6H_4	*p*-$OMeC_6H_4$	8	79
3m*	*p*-$OMeC_6H_4$	*p*-$OMeC_6H_4$	8	79
3n	Ph	*p*-MeC_6H_4	8	90
3o*	*p*-ClC_6H_4	*p*-MeC_6H_4	8	87
3p*	*p*-MeC_6H_4	*p*-MeC_6H_4	8	92
3q	Ph	*p*-ClC_6H_4	8	95
3r*	*p*-$OMeC_6H_4$	*p*-ClC_6H_4	8	92

[a]Products were characterized by their NMR and mass spectra; [b]reaction condition: aldehyde (1 mmol), amine (1 mmol) and diisopropyl phosphite (1 mmol), solvent-free at 50°C, 8–24 h, 5% CuI; [c]isolated yield. *The gear stands for novel compounds.

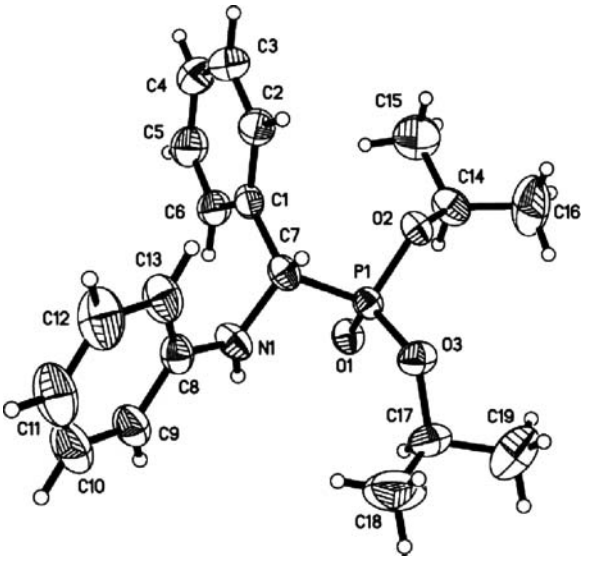


Figure 1 Molecular structure of **3a** and ORTEP diagram (30 % probability ellipsoids) showing crystallographic atom numbering.

Table 3 Crystal structure and data refinement parameters for compound **3a**

Compound	**3a**
Empirical formula	$C_{19}H_{26}NO_3P$
Formula weight	347.38
Crystal system/space group	Triclinic/P-1
a/Å	10.261 (4)
b/Å	11.707 (5)
c/Å	25.939 (8)
α/°	86.4 (4)
β/°	80.2 (2)
γ/°	76.7 (7)
V/Å^3	2987.3 (2)
Z	6
D_{calc} (g/cm^3)	1.159
μ (mm^{-1})	0.153
Crystal size (mm)	0.40 × 0.22 × 0.18
Color/shape	Chunk
Temp (K)	293
Theta range for collection	$3.02^\circ \leq \theta \leq 25.00^\circ$
Reflections collected	10459
Independent reflections	7317 [R (int) = 0.0254]
Data/restraints/parameters	7317/0/649
Goodness of fit on F^2	1.045
Final R indices [I > 2σ(I)]	$R_1 = 0.0654$, $wR_2 = 0.1780$
R indices (all data)	$R_1 = 0.0770$, $wR_2 = 0.2047$
Largest difference peak/hole (eÅ^{-3})	0.623/−0.435

bonds (Table S1 Supplemental Materials). Further details of the crystallographic data can be found in the supporting information (CCDC deposition number 764833).

CONCLUSIONS

In conclusion, copper (I) iodide has been found to be an efficient and convenient catalyst in the one-pot synthesis of α-aminophosphonates in neat solvent, giving moderate to good yields. The reaction process is highly efficient, economic, and also environment friendly.

EXPERIMENTAL

Infrared (IR) spectra were measured on a Bruker VERTEX-70 spectrometer. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on a Bruker 400 MHz spectrometer

Table S1 Hydrogen-bond geometry of compound **3a**

D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A (°)
N1—H1A···O1'^{i}	0.86	2.24	2.977(3)	144
N1'—H1'A···O1^{ii}	0.86	2.13	2.969(3)	166
N1"—H1"A···O1"^{iii}	0.86	2.31	3.070(3)	147

Symmetry codes: (i) $x-1$, y, z, (ii) $x+1$, y, z, (iii) $-x$, $-y+1$, $-z$.

in $CDCl_3$ solution. High-resolution mass spectra were determined on Micromass-LCT Premier Time of Flight (TOF) mass spectrometer (Waters, USA). A Bruker SMART CCD X-ray diffractometer was used. The aldehydes, amines, and diisopropyl phosphite are all commercial materials and were distilled before use. Spectral and analytical data of the α-aminophosphonates, not reported earlier, are presented below in Table 2 in order of their entries.

General Procedure

A mixture of aldehyde (1 mmol), amine (1 mmol), and diisopropyl phosphite (1 mmol) was stirred at 50°C (oil bath) in neat without any solvent for an appropriate time (monitored by TLC). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3 × 20 mL). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged on small silica gel column and eluted with a mixture of ethyl acetate–petroleum ether (v/v = 1:3) to afford pure α-aminophosphonates. This procedure was followed for the synthesis of all the α-aminophosphonates listed in Table 2. As an example, the characterization of 3c is presented here. Additional characterization for other novel compounds, plus selected 1H, 13C, and 31P NMR spectra for 3m, 3o, and 3i are found in the Supplemental Materials (Figures S1–S9).

Diisopropyl (phenylamino)(p-tolyl)methylphosphonate 3c. m p 72–73 °C, ν_{max} (KBr)/cm^{-1} 3284, 1603, 1498, 1234, δ_H 7.38–7.36 (m, 2H, ArH), 7.15–7.10 (m, 4H, ArH), 6.71–7.69 (m, 1H, ArH), 6.62–6.60 (m, 2H, ArH), 4.78–4.70 (m, 2H, 2OC<u>H</u>$(CH_3)_2$),

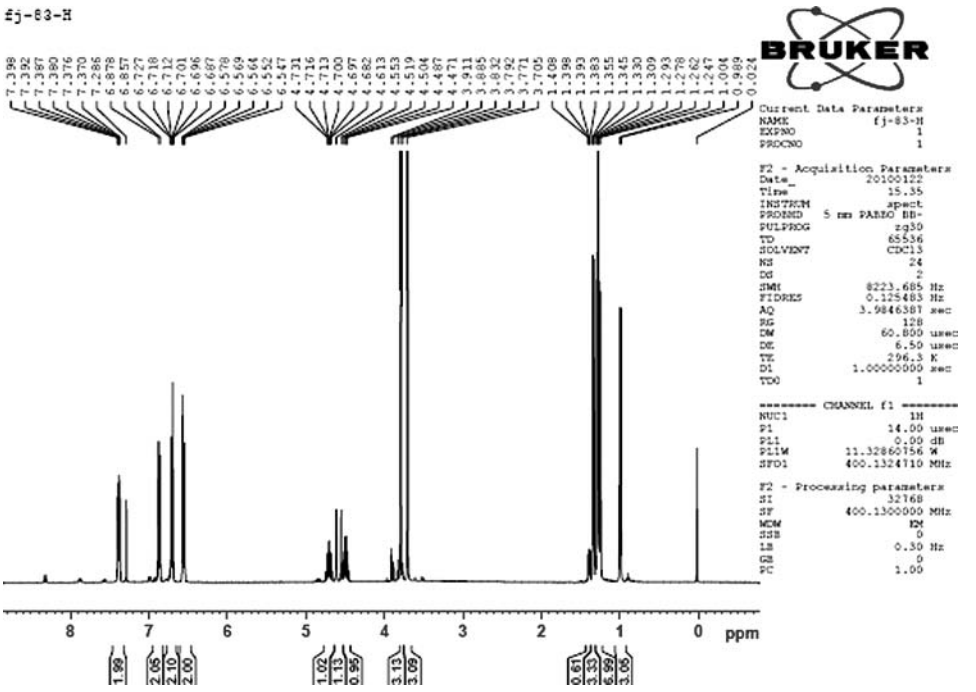


Figure S1

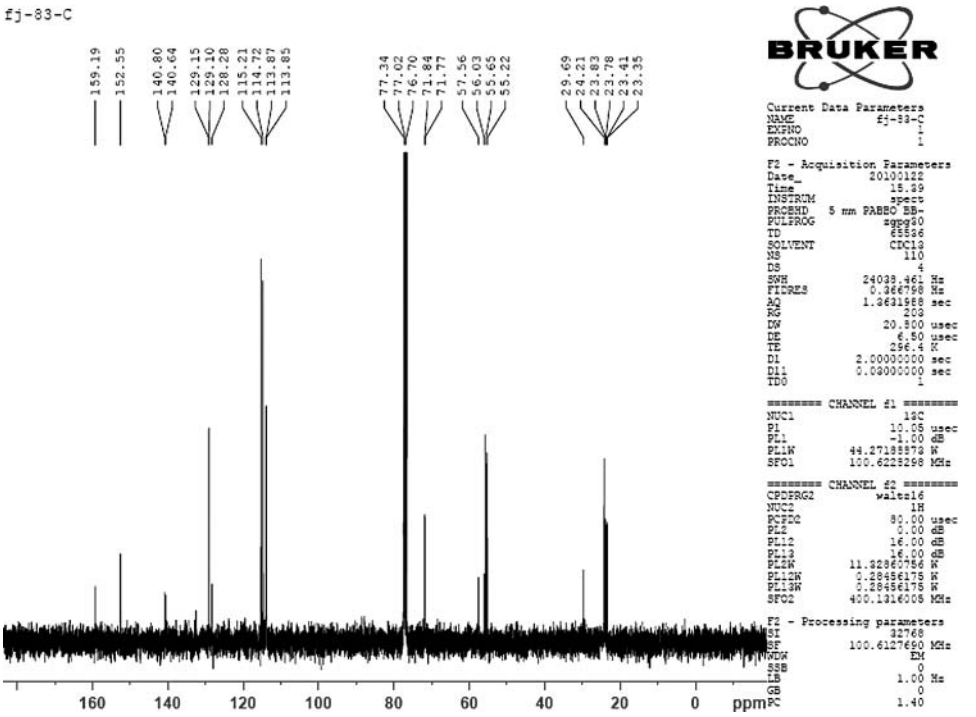


Figure S2

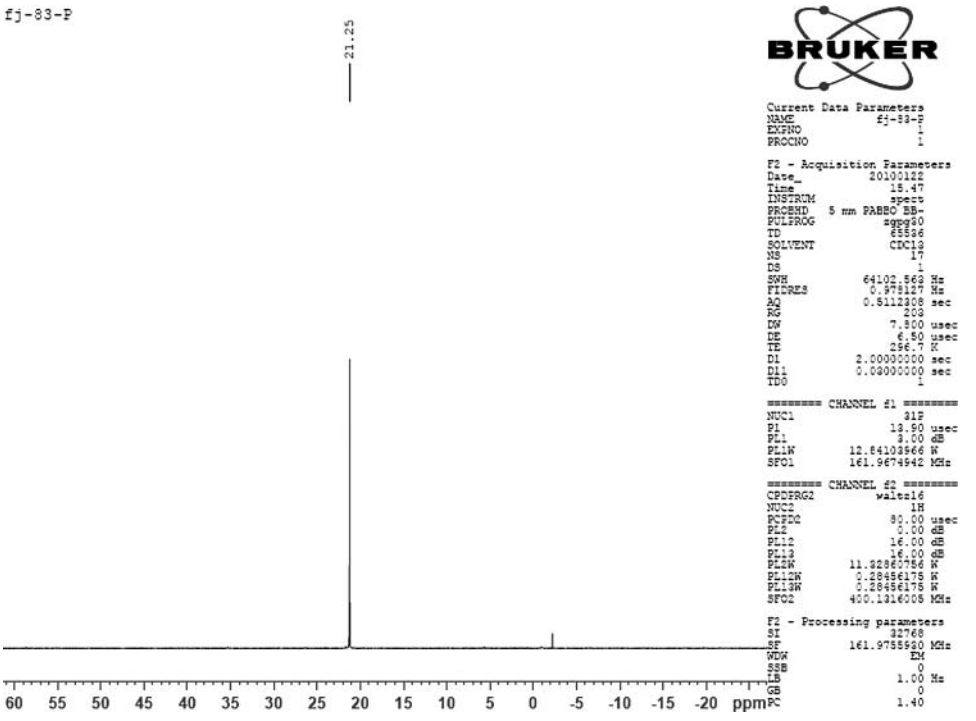


Figure S3

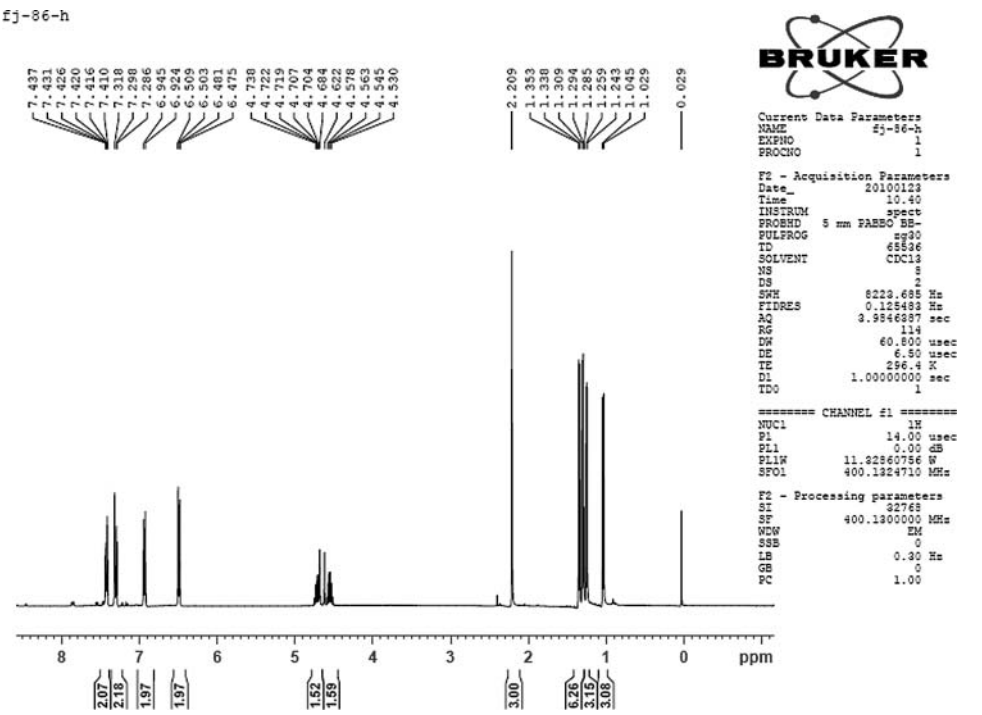


Figure S4

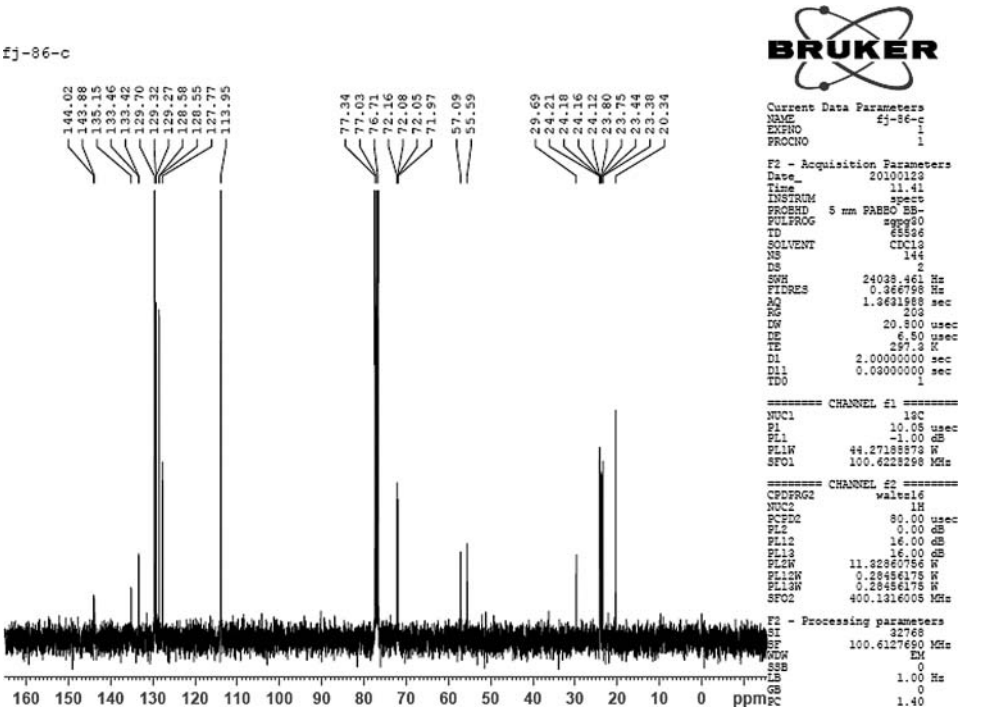


Figure S5

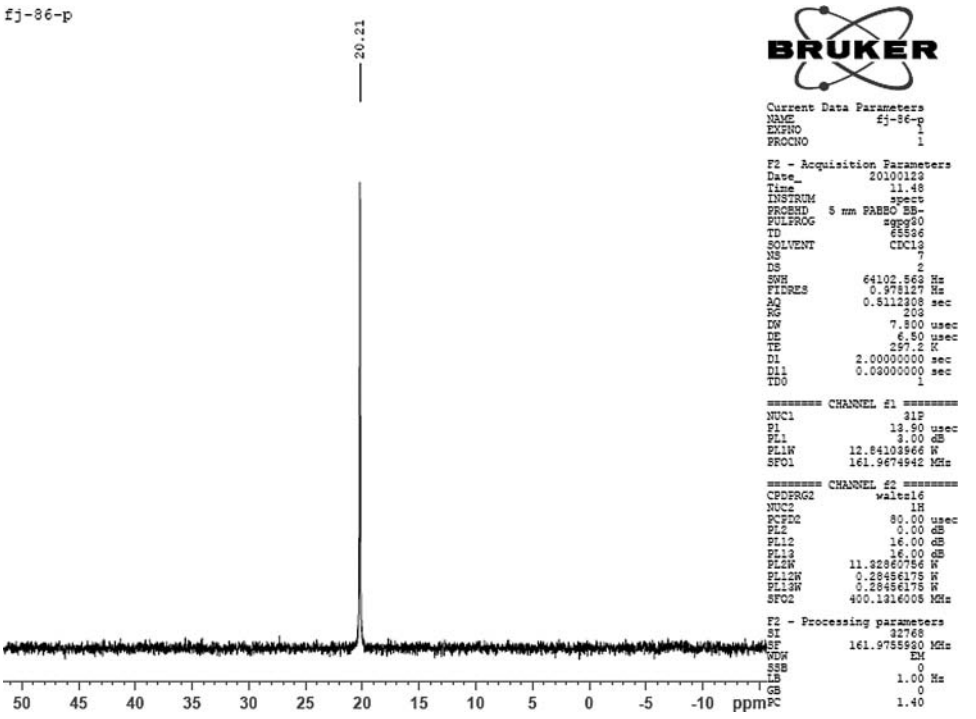


Figure S6

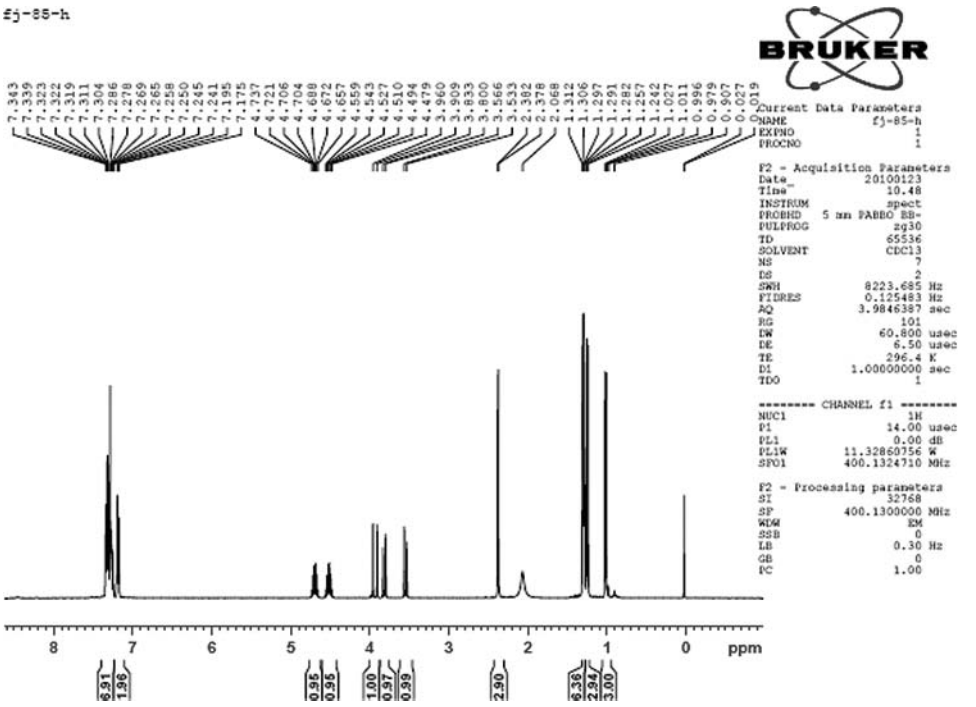


Figure S7

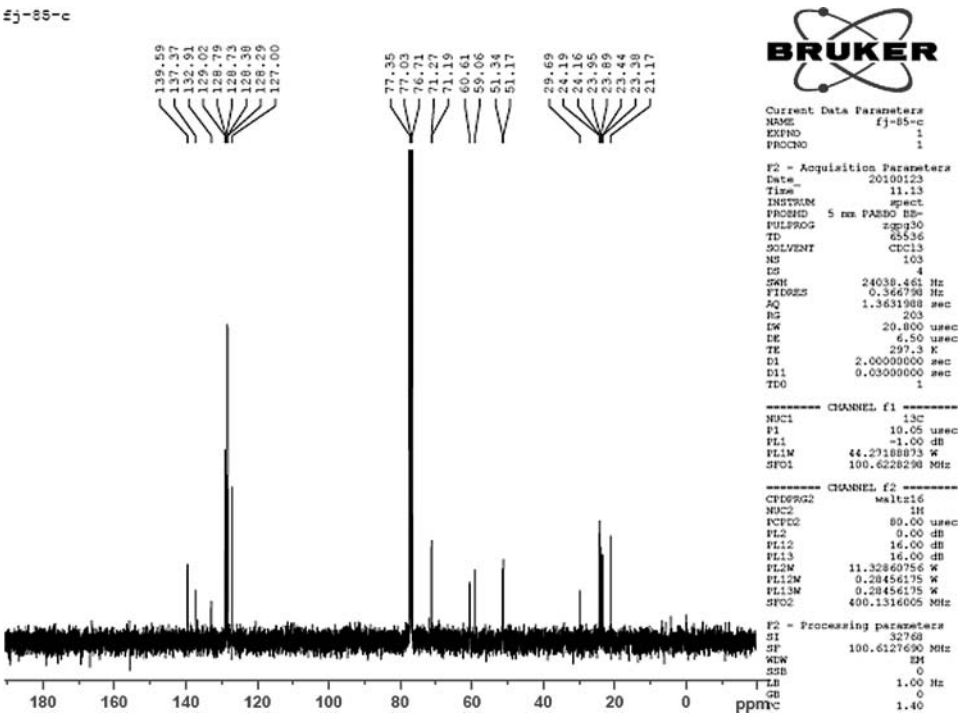


Figure S8

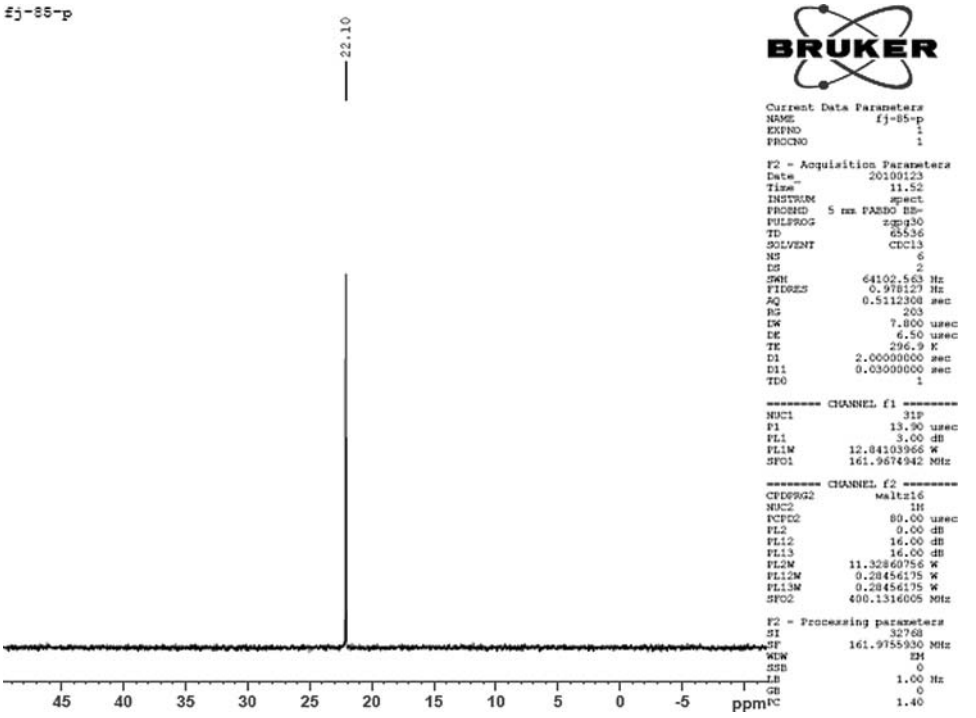


Figure S9

4.66–4.63 (m, 1H, CH), 4.55–4.45 (m, 1H, NH), 2.33 (s, 3H, CH_3), 1.40–1.35 (m, 3H), 1.33–1.25 (m, 6H), 1.19–1.17 (m, 3H), δ_C 146.7, 146.6, 137.4, 133.1, 129.1, 127.9, 127.8, 118.2, 113.8, 71.9, 71.8 (d, $J = 4.0$ Hz), 56.3 (d, $J_{PC} = 150$ Hz, CH), 29.7, 24.2, 23.8, 23.2, 21.0 (d, $J = 4.6$ Hz, CH_3), δ_P 21.0, MS *m/z* 362 $[M+H]^+$, 384 $[M+Na]^+$, 301, 197, HRMS (ESI) calcd. for $[C_{20}H_{28}NO_3P+H]^+$ 362.1885, found 362.1880.

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