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MICROWAVE ASSISTED ECO FRIENDLY SYNTHESIS OF 2H-PYRIDO [1, 2-a] PYRIMIDINE-2-ONE

Sharulatha V[1], Indumathi U[2], Priyadharshini S[3]

[1]*Assistant professor, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore*
[2]*Research Scholar, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore*
[3]*Research Scholar Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore*

Abstract

Pyrido primidines are important class of heterocylic compounds because of their use in medicinal and agro chemistry as scaffolds for active agents such as antiviral, antiulcer, antimalarial, antifungal and herbicidal agents. Herein we report the synthesis of 2H-pyrido[1,2-a]pyrimidine-2-ones by the reaction of itaconic acid with 2-amino pyridine in tow steps under classical and microwave technology.

Keywords: *microwave synthesis 2H-pyrido [1, 2-a] pyrimidine-2-one*

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1. INTRODUCTION

The organic reactions under microwave irradiation are more advantageous over the conventional methods, owing to shortening of reaction time, mild temperature conditions, and good-to-high yield[1], eco-friendliness and non-use of expensive reagents [2]. The pyrimidine framework is an important structural moiety present in various biologically active molecules including DNA and RNA[3]. Benzo- and hetero-fused pyrimidines are known to exhibit promising antiviral, antiabacterial, anti-AIDS, and antinociceptive activities. The relevance of fused pyrimidines as antiplatelet and antithrombotic drugs has been firmly established by clinical trials[4].One such fused pyrimidine core with nitrogen at ring junction is pyrido[1,2-a]pyrimidine.

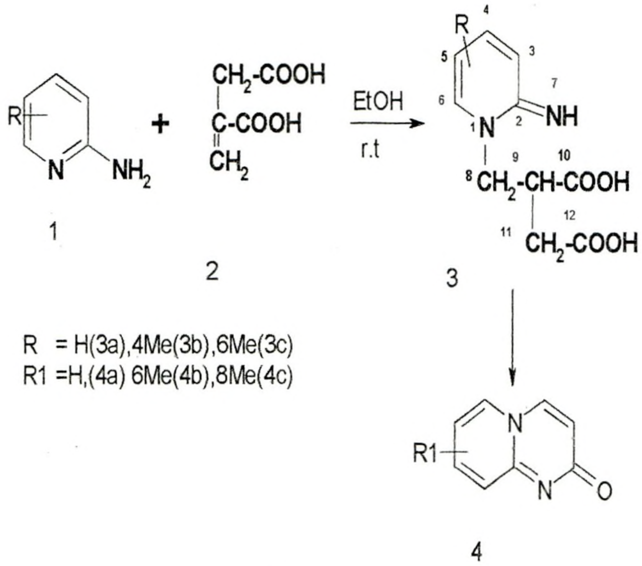
Pyrido[1,2-a]pyrimidine-4-one derivatives, were found to be aldols reductase (ALR2) inhibitor **[5],** human leukocyta elastase inhibitor [6], antibacterial agents [7], potential antiviral agents **[8].** In light of the important biological properties of Pyrido[1,2-a]pyrimidines , the development of simple and convenient methodology for the synthesis of this structural motif represents an interesting area of research in synthetic organic and medicinal chemistry.

Generally, the pyridopyrimidine ring is constructed by condensation based on the amidine fragment of 2-aminopyridine or its derivatives with various acylating and alkylating agents [9].Most of the reported methods involve the use high temperatures and pressure and use of acid catalysts with low yields and formation of significant amount of by products.

Herein we report the convenient and versatile synthesis of 2H-pyrido[1,2-a]pyrimidine-2-one with high yields and purity by the reaction of 2-amno pyridine with the inexpensive reagent itaconic acid under conventional and microwave heating. PTSA(p-toluene sulfonic acid) was used as cylcizing agent, Since it makes the reaction process convenient, cost effective and environmentally benign**[10].**

2. RESULTS AND DISCUSSION

The title compound was synthesized by a convenient two step reaction, outlined in **scheme -1**.



Scheme - 1

The 2-amino pyridine was stirred with itaconic acid with alcohol in the first step to provide compound 3 (imino 1,2(H) pyridine itaconic acid) as white solid. Recrystallisation of the 2- imino 1,2(H) pyridine itaconic acid**(3)** yielded white crystals with 95%.Then imino 1,2(H) pyridine itaconic acid was heated with catalytic amounts of p-toluene sulfonic acid in alcohol to yield compound 2H-pyrido[1,2-a]pyrimidine-2-one**(4)** as white solid. Again recrystallization with alcohol provided white crystals with 82% yield.

Lelle Vasvari-Debreczy[11] reported the cyclization of 2-(2-pyridylaminomethylene)succinates in ethanolic sodium ethoxide. But the succinates gave equilibrium mixture of pyridopyrimidines and dihydropyyrolone a dimer at room temperature and at elevated temperature a mixture of products were obtained. But in our case the cyclization of imino 1,2(H) pyridine itaconic acid proceeded smoothly with the higher yield of pyridopyrimidine and formation of by products was found to be lesser. The reactions were also carried out by microwave heating. A comparison of conventional method vs microwave heating were summarized in the following table.

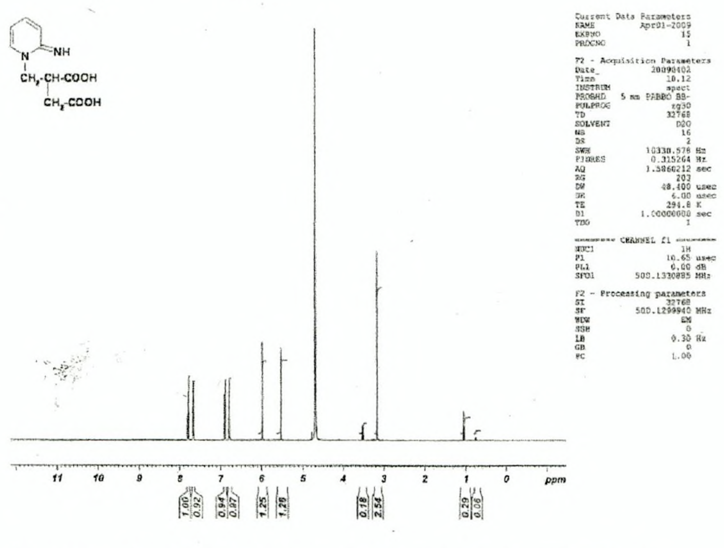
Table -1: Comparison of Conventional Heating vs Microwave heating of the synthesized compounds

Compounds	**Room temperature**		**Microwave heating**		**Compounds**	**Conventional heating**		**Microwave heating**	
	Yield (%)	**Time (min)**	**Yield (%)**	**Time (min)**		**Yield (%)**	**Time (min)**	**Yield (%)**	**Time (min)**
3a	96.8	45	97.2	1	4a	81	60	94.2	15
3b	97.6	45	98.2	1	4b	82	60	95.1	15
3c	97.8	45	98.0	1	4c	81	60	95.6	15

In the formation of the 2-imino 1,2(H) pyridine itaconic acid reaction was completed at forty five minutes in conventional method and the time was drastically reduced to one minute in the case of microwave heating. In the case of cylisation time was reduced to fifteen minutes from one hour. The yield of the product was also found to be higher than the conventional method. The products were also obtained with greater purity in microwave heating.

The synthesized compounds were characterized by IR, ^{1}H and ^{13}C NMR spectral methods. 2- imino 1,2(H) pyridine itaconic acid **3a** showed 3 sets of signals at δ 3.2, 5.5 – 5.9, 6.8 – 7.8 for ^{1}H NMR**(figure-1)** The singlet at δ 3.2 integrating to two protons was assigned to the C_{11} methylene protons. The doublet integrating at δ 5.5 – 5.9 for two protons was assigned to C_8 methylene protons. The protons integrating at 6.8 – 7.8 confirmed aromatic ring. The IR spectrum exhibited absorption at 3382 cm^{-1} due to O-H stretch of acids and absorption at 1662 cm^{-} due to imines. The ^{13}C NMR**(figure-2)**spectrum showed, totally ten signals corresponding to 10 carbon atoms. The signals at δ178 and δ175 corresponded to two carboxyl groups, The signal at 4.7 δ was assigned to the C_9 methine carbon atom. The signal at δ 45 corresponded to C_{11} methylene carbon. The signal at δ 130 corresponded to C_8 methylene carbon. The C=N (C_2) carbon appeared at δ 161 and the aromatic carbon in the region of δ141-145. The elemental analysis of the compound revealed the presence of ten carbon atoms, twelve hydrogen atoms, two nitrogen and four oxygen atoms. Hence the formula was found to be $C_{10}H_{12}N_2O_4$.

Fig 1 : NMR Spectrum of 2 imino 1, 2(H) Pyridine itaconic acid



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PROCNO                 1

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TD                 32768
SOLVENT              D2O
NS                    16
DS                     2
SWH            10330.578 Hz
FIDRES          0.315264 Hz
AQ             1.5860212 sec
RG                   203
DW                48.400 usec
DE                  6.00 usec
TE                 294.8 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
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P1                 10.65 usec
PL1                 0.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
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WDW                   EM
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LB                  0.30 Hz
GB                     0
PC                  1.00
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Fig-1 ^{1}H NMR of 2-imino1,2(H) pyridine itaconic acid

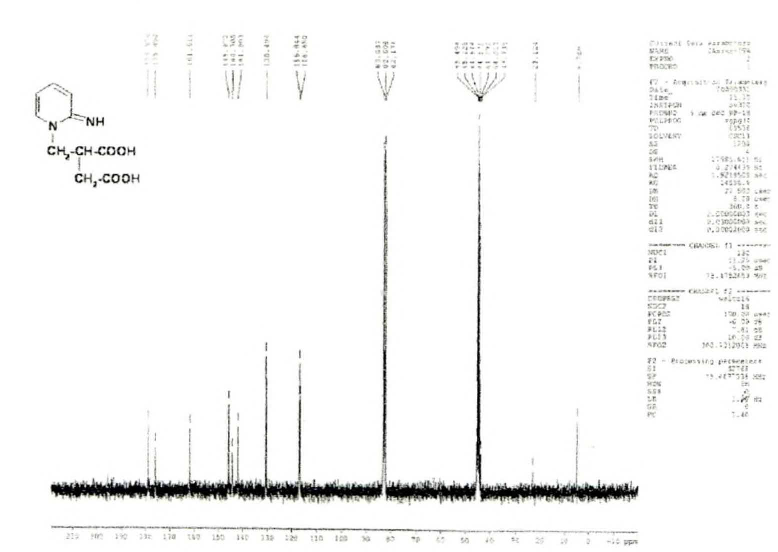
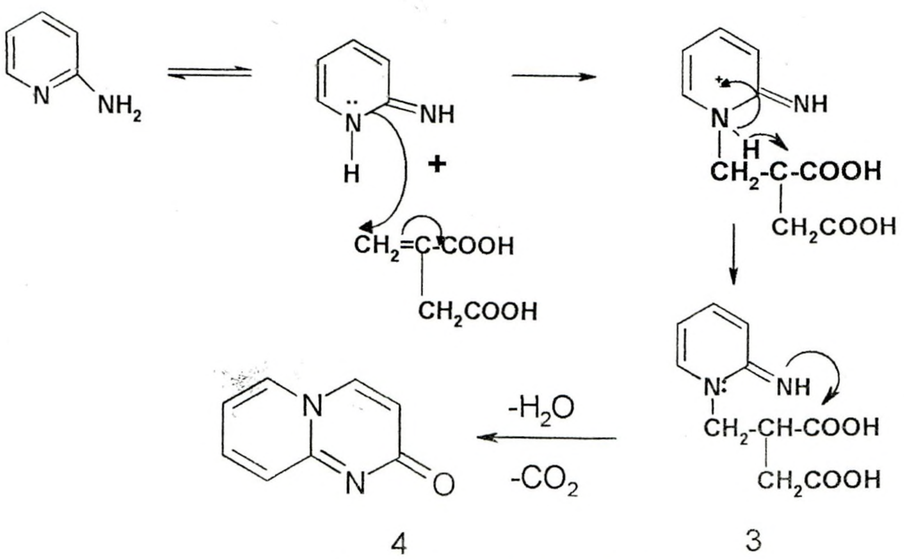


Fig-2 ^{13}C NMR of 2-imino1,2(H) pyridine itaconic acid

In the NMR spectrum of 2H-pyrido [1,2-a]pyrimidine-2-one **(4c)**totally four signals were observed for the four sets of protons. The signal observed at δ1.84 and δ2.27 indicated the presence of two methyl groups. The remaining four protons resonated at the aromatic region at δ7.72 and δ7.6. The deshielded proton at 6th position will show absorbance at δ9.0 in 4-oxo isomer due to the anisotropy of the carbonyl group [12]. But in our case the resonance of proton at 6th position was observed only at δ7.72 which confirmed the formation of 2-oxo isomer. ^{13}C spectrum accounted for nine carbons at δ 23 δ 24 δ 169 δ 120 δ122 δ 151 δ 123 δ 111 δ 156.From the elemental analysis the percentage of carbon, hydrogen and nitrogen were found to be 68.50,5.6 and16.0 respectively.

The mechanism of the reaction is illustrated in **scheme-2**. 2-amino pyridine exists in two tautomeric forms. The ring nitrogen of 2-amino pyridine adds to the double bond of the methyl succinic acid, to give a carbanion intermediate. This carbonion abstracts a proton from the amino group to give the product **3**. The product **3** gives **4** by the internal attack of the amino nitrogen on the carboxylic group with the elimination of water subsequently by the elimination of carbon dioxide.



Scheme -2 Mechanism of the Reaction

3. EXPERIMENTAL

3.1 General

Melting points were determined using Biochem melting point apparatus, and were uncorrected.The infrared (IR) spectra were recorded in KBr pellet technique on a Perkin-Elmer spectrophotometer. Absorption frequencies were quoted in reciprocal centimeter.

Nuclear Magnetic Resonance (^{1}H-NMR) spectra were determined by Bruker modern 500 MHz NMR instrument in D_2O with tetra methyl silicane as the internal reference. Chemical shift were quoted in parts per million (ppm) (s =singlet; d = doublet; t = triplet and m = multiplet).

Thin layer chromatography (TLC) was performed using glass plates coated with silica gel G to monitor and check the completion of each reaction.

etroleum ether (60-80˚C); ethyl acetate; ethyl alcohol were used as the developing solvents. Spots were detected with iodine.The solvents and reagents used for the synthesis were of reagent grade and were purified by standard methods.

Microwave experiments were performed in domestic microwave oven LG model MS-1947C output 750 power watts. The reactions were conducted in a specially adapted cylindrical vensil vessel.

3.1.1 Preparation of 2-imino 1,2(H) Pyridine Itaconic Acid(3a)

Dried itaconic acid (0.02mole) and 2-aminopyridine (0.01mole) were dissolved in ethyl alcohol separately. At room temperature one reactant was added to another drop wise and stirred well. The completion of the reaction was monitored by TLC. Recrystallisation with alcohol yielded pure compound. Melting point =117˚C; Yield 94.4%.CHN Analysis: Found: C, 53.27%; H, 5.57%; N, 12.07%.

3.1.2 Preparation of 2H-pyrido[1,2-a] pyrimidine-2-one 4b

A mixture of 8-methyl 2- imino 1, 2(H) pyridine itaconic acid (0.1) and p-toluenesulphonic acid (0.1) in alcohol was heated to reflux on a steam bath, till the reaction was complete (1 hr). After the completion of the reaction, the mixture was neutralized with 10% sodium hydroxide till the solution becomes neutral. The solution was concentrated under reduced pressure, and the solid was collected and purified recrystallisation from suitable solvent. Melting point =119˚C; Yield 82%.CHN Analysis: Found: C, 68.50; H, 5.6; N, 16.0 %

3.2 Microwave Oven

3.2.1 General Procedure

Itaconic acid (0.02 mole) and (0.01 mole) of 2-amino pyridine were dissolved in ethyl alcohol and then irradiated at 800 watts in domestic microwave oven. The completion of the reaction was monitored by TLC.

A mixture of 2- imino 1, 2(H) pyridine itaconic acid (0.1) and p-toluenesulphonic acid (0.1) in alcohol was irradiated at 800 watts in domestic microwave oven. The completion of the reaction was monitored by TLC. After the completion of the reaction, the mixture was neutralized with 10% sodium hydroxide till the solution becomes neutral. The solution was concentrated under reduced pressure, and the solid was collected and purified recrystallisation from suitable solvent.

4. CONCLUSIONS

We have reported a simple and cost effective two step process of synthesis of 2H-pyrido[1,2-a]pyrimidine-2-one from itaconic acid by microwave technology. The microwave assisted reaction was faster and yielded pure products.

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2D ^{1}H and ^{13}C NMR studies of 2-Chloro-4-methyl-1-p-bromo 1H-pyrrolo [2, 3-b]quinoline

Senthilvadivu N., Sharulatha V. and Sivakamasundari S.
Avinashilingam University for Women, Coimbatore-641043, Tamil Nadu, India
E-mail: bharathi_cit2001@yahoo.co.in

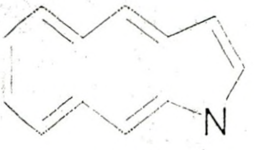
Abstract

Several derivatives of pyrrolo(2,3-b)quinoline system have been reported to possess several interesting pharmacological activities such as anti-inflammatory,anti-bacterial, ntihypertensive, antipyretic and anticonvulsant6 properties and interferon inducing activity. Since pyrrolo quinoline derivatives are much valued due to their medicinal properties the complete structural elucidation of these biologically active compounds tends to play a vital role in organic synthesis and pharmacological studies. This paper reports the complete structure assignment of pyrrolo quinolines by 1H 13C NMR and 2D NMR methods.

Keywords: pyrrolo quinoline, NMR studies

1. Introduction

Pyrroloquinolines are characterized by the possession of pyrrole ring fused to a quinoline nucleus. They can be classified broadly into two types: (i) those in which the pyrrole ring is fused to the pyridine half, (ii) those in which it is fused to the benzene half of the quinoline moiety. Of these, pyrrolo (2,3-b) quinoline (1) is of considerable interest for it is the 'aza' analogue of furo (2,3-b) quinoline system (1a) which constitutes the parent ring feature of several alkaloids of Rutaceae [1]. Further several derivatives of pyrrolo(2,3-b) quinoline system have been reported to possess several interesting pharmacological activities such as anti-inflammatory [2], antibacterial [3], antihypertensive [4], antipyretic [5] and anticonvulsant [6] properties and interferon inducing activity [7]. Since pyrrolo quinoline derivatives are much valued due to their medicinal properties the complete structural elucidation of these biologically active compounds tends to play vital role in organic synthesis and pharmacological studies. This paper reports the complete structure assignment of 2-chloro-4-methyl-1-p-bromo-1H pyrrolo (2,3-b) pyrrolo quinolines by 1H, 13C NMR and 2D NMR methods.



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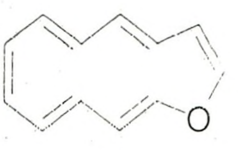
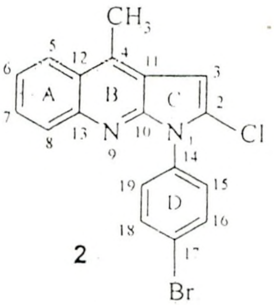


1a

2. Results and discussion

The proton NMR spectrum of the compound 2-chloro-4-methyl-1-p-bromo-1H-pyrrolo (2,3-b) quinoline (2) showed seven clear signals arising from the nine sets of protons.



2

The spectrum showed two singlet's at 3.1 and 6.8 ppm integrating respectively for three and one protons corresponding for the methyl and C_3-H protons. The values of two low field signals at 8.04 and 8.14 ppm accounted for the C_9-H and C_5-H protons of the quinoline nucleus. Since the C_8-H proton is adjacent to the ring nitrogen, it experienced a little shielding effect, hence a slightly upfield shift was observed. A multiplet was observed at 7.5 ppm integrating for three protons. The overlapping signals at 7.5 ppm was resolved through COSY spectrum (Figure-I). COSY spectrum clearly indicated the strong correlation between the doublet of doublet at the most downfield proton at 8.14 ppm with the proton at 7.48ppm with the coupling constant of 8.5 Hz indicating that these two protons are ortho to each other. Hence, 8.14 ppm was assigned to C_5-H, and 7.48 ppm was assigned to C_6-H of the quinoline core nuclei. Likewise the doublet at 8.05 ppm for C_8-H, showed cross peak at 7.6 ppm for C_7-H with the coupling constant of 7Hz again indicating the ortho coupling. A slightly less intense cross peaks were also observed for, 7.53 ppm with protons at 7.7 ppm. The coupling constant these two were found to be 7Hz. Hence the signal at 7.7 ppm was assigned to the protons, ortho to the bromo group of the 'D' ring, and the peak at 7.53 ppm integrating for two protons were assigned to the protons, meta to the bromo group of the 'D' ring. **Table 1** lists the ^{1}H NMR spectral data along with the multiplicities coupling constants and the assignments of chemical shifts

Table 1: ^{1}H NMR spectral data for 2-Chloro-4-methyl-1-p-bromo-1H-pyrrolo [2,3-b] quinoline

S. No.	Chemical shift (δ, ppm)	Nuclei / Multiplicity	J (Hz)
1.	3.00	4-CH$_3$, S, 3H	-
2.	6.80	3-H, S, 1H	-
3.	7.50	7-H, 15-H, 19H, m, 3H	9
4.	7.60	6-H, ddd, 1H	7
5	7.70	16-H, 18-H ,m, 2H	7
6.	8.05	5-Hd, 1H	7
7.	8.14	8-H, dd, 1H	9

The ^{13}C NMR spectrum showed 18 signals, corresponding to 18 Carbon atoms. In DEPT 135 totally 10 positive peaks were observed. The signal at 14.84 corresponds to the methyl group, and the remaining nine was attributed to the nine CH groups. The assignments for these proton-bearing carbons were obtained directly from the HETCOR spectrum (Fig.2). Table 2 lists the ^{13}C-NMR shifts for 2-chloro-4-methyl-1-p-bromo-1H-pyrrolo [2, 3-b] quinoline

Table 2: ^{13}C-NMR spectrum of 2-chloro-4-methyl-1-p-bromo-1H-pyrrolo [2,3-b]quinoline

0	Chemical shift (δ, ppm)	Dept 135	^{13}C
1.	14.8	+ ve	4-CH$_3$
2.	98.9	+ ve	3-CH
3.	120.9	-	4-C
4.	122.2	-	13-C
5.	123.6	+ ve	7-CH
6.	123.8	+ ve	8-CH
7.	124.7	-	14-C
8.	127.9	+ ve	6-CH
9.	128.3	+ ve	15-CH
10.	128.8	+ ve	5-CH
11.	129.9	-	17-C
12.	130.2	+ ve	19-CH
13.	132.3	+ ve	18-CH
14.	133.9	-	2-C

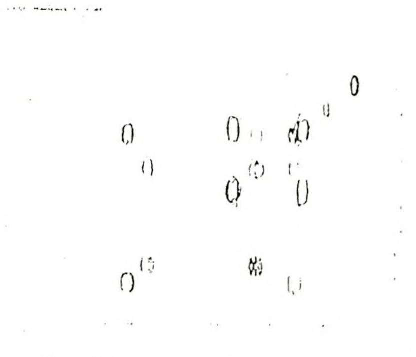


Fig. 1: ^{1}H-^{1}H COSY spectrum of 2-chloro-4-methyl-1-p-bromo-1H-pyrrolo [2,3-b] quinoline

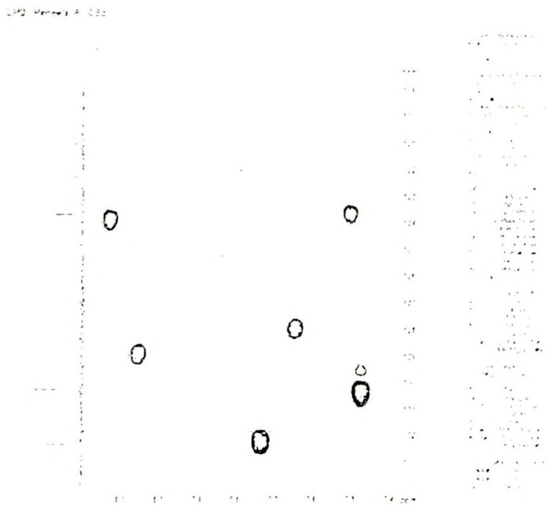


Fig. 2: HETCOR spectrum of 2-chloro-4-methyl-1-p-bromo-1H-pyrrolo [2,3-b]quinoline

3. Materials and methods

Compound 2 was prepared following the literature procedure Melting points were determined using Biochem melting point apparatus, and were uncorrected.

^{1}H and ^{13}C NMR spectra of the compound 2 in CDCl$_3$ were recorded on Bruker modern 500MHz NMR spectrometeroperating at 500.03MHz for ^{1}H and 125.75MHZ for^{13}C with tetra methyl silicane as the internal reference. Chemical shift were quoted in parts per million (ppm) (s = singlet; d = doublet; t = triplet and m = multiplet). Spectra were measured in CDCl$_3$ solution at room temperature using 5 mm diameter NMR tubes. The following spectral parameters were used: For ^{1}H NMR, dwell time (DW)=48.4 μs, acquisition time (AQ) =1.5860s, number of transient (NS)=32, recycle delay(RD)=1.0s, flipangle=30, and sweep width 10330.578 Hz. For ^{13}C-NMR, dwell time (DW)=16.80 sec μs, acquisition time (AQ) =0.55055sec, number of transient (NS)=1024, recycle delay (RD)=2.00s, decoupling multiple resonance method waltz –16 and, sweep width 29761.90 Hz. For COSY experiment 1024 points in the F$_2$ dimension and 256 increments in F$_1$ dimension.

4. Acknowledgement

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