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Tetra Acetoxymethyl Glycoluril as an Efficient and Novel Reagent for Acylation of Amines

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Abstract : New glycoluril derivative tetra acetoxymethylglycoluril was synthesized via the electrophilic substitution of an acetyl group at oxygen atoms of hydroxymethylglycoluril using acetic anhydride. Direct N-acetylation of primary amines by using tetra acetoxymethylglycoluril as new efficient, effective, and mild acetylating agent. The N-acetylation reaction was carried out using classical and mechanochemical methods in dichloromethane to obtain the correspondent acylated amines in good yields.The structures of the compounds were confirmed using 1HNMR, 13CNMR, and FTIR spectroscopy.
Keywords : Acetoxymethylation, Acetylation, Amine, Amide,Glycoluril, Mechanochemistry.

Introduction

The protection of amino groups by the formation of amides, especially acetamides, is one of the most fundamental and widely used procedures in organic syntheses. This goal is often necessary during the course of various transformations in a synthetic sequence especially in the construction of poly-functional molecules.[1]

N-Acetylation reaction finds immense applications in organic syntheses[2]; the amide bond is found to be present in a large number of pharmacologically active molecules. Owing to its nucleophilic as well as reactive nature, selective protection of an amino group is usually needed during most of the multi-step organic syntheses including the synthesis of a diverse array of biological molecules such as amino acids, peptides, amino glycosides, β-lactams, nucleosides, alkaloids, *etc*[3].

N-Acetylation reaction is usually carried out with acetic anhydride or acetyl chloride in the presence of either acidic[4] or basic[5]catalysts in different conditions. These reactions bear certain advantages as well as a lot of disadvantages; such advantages and disadvantages were extensively described recently by Katritzky*et al*.[6]. Some alternative methods have also been reported for *N*- acetylation of primary and secondary amines, where a

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variety of acetylating agents other than the conventional acetic anhydride or acetyl chloride were used.[7] Some methods utilizing microwave irradiation have also been reported.[8]

Hence, development of novel and green methodologies using simple, mild and effective reagent is still required for its usefulness in synthetic organic chemistry as well as in medicinal chemistry. Having this background, it is felt pertinent to report herein an effective as well as an environmentally benign methodology for *N*-acetylation of amines. It has been found that tetra N-acetoxymethylglycoluril, a new benign and facile to prepare, alone without any catalyst can act as *N*-acetylating agent for the acetylation of amines. Since the examples of the O-acylation of the hydroxymethylglycolurils are absent in the literature, we are the first who synthesized tetra N-acetoxymethylglycoluril (TAMGU) in good yield from the reaction of teterahydroxymethylglycoluril[9] with acetic anhydride in the presence of pyridine or triethylamine as base catalyst.

Furthermore, the use of TAMGU as acetylating agent for amines is not reported under classical organic synthesis or under mechanochemical activation.

The present work highlighted the preparation of TAMGU as new reagent, and uses it as mild and eco-friendly N-acetylating agent.

Experimental section

General

Melting points (mp) were determined in open capillaries using Buchi apparatus and are uncorrected.[1].

Nuclear magnetic resonance (1H NMR, 13C NMR) spectra were recorded on a BrukerAvance III D spectrometer (400 MHz) at room temperature. Chemical shifts (d) are reported relative to tetramethylsilane peak set at 0.00 ppm. In the case of multiplets the signals are reported as intervals. Signals were abbreviated as s, singlet; d, doublet; t, triplet; m, multiplet. Coupling constants were expressed in Hz.

Reaction progress was controlled by thin-layer chromatography and observed under UV light (254/365 =λnm) with Ehrlich's reagent and ethanol-benzene (20:80) as eluent.

Fourier-transform infrared (FTIR) spectra were obtained directly from the products using the high-attenuated total reflectance technique in a Bruker Tensor 27 FT-IR Spectrometer.

The spectra were recorded in the range of 400 to 4000 cm-1 with a resolution of 4 cm-1 over 16 scans.

Melting points were obtained with Buchi apparatus without correction.

Tetra N-acetoxyethylglycoluril*2* *:*

0.3g (0.6mmol) Acetic anhydride (5 ml) and the **1** (5 mmol) were added to dry pyridine (5 ml) and the product was stirred to complete solution at 20°C and held at this temperature for 24 hours. The solvent was distilled off and the residue was triturated with ether of give the precipitated **2**, which was filtered off and recrystallized from methanol.

Compound *2* : Rf= 0.71 (C_6H_6: CH_2Cl_2: CH_3OH / 5:5:1). Yield= 95%. Mp=145°C. IR (cm-1): 2925 (=C-H), 1727(C=O), 1250, 1219 (C-O-C).^{1}H NMR (300 MHz, CDCl3), δH, ppm: 5.64 (s, 2H, CH), 5.30 (d, 2H, CH2), 5.6 (d, 2H, CH2), 2.07 (s, 3H, CH3). 13C NMR (CDCl3, 75 MHz), δC, ppm: 171.09 (C=O acetyl), 156.04 (C=O glycoluril), 77.14 (CH), 20.82 (CH3), 67(CH2).

Synthesis of Compounds 4(a-e):

Method A :

Into a suitable reaction vessel equipped with stirrer, thermometer, and condenser were charged 2.2 g (5 mmol) of TAMGUl and 20 ml of dichloromethane. To this solution, 2mL (22 mmol) of anilne was added, and the reaction mixture was heated to 55 °C with stirring. In about 1 hour, the tetramethylolglycoluril precipitate

was formed.after reaction completion (monitored by TLC), the tetramethylolglycoluril was filtred and the filtrate was concentrated to give the correspondent acetamides.

Method B :

The mixture of aniline 2 ml (22 mmol) and TAMGU 2.2 g (5 mmol) were placed in ceramic mortar and grinded with pestle for 5 minutes at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC). Upon completion of reaction the mixture was solved in ethanol and filtered, mother liquor was evaporated to obtain 1 g of 4(a, b, c, d, e).

N-phenylacetamide 4a: Rf= 0.46 (C_6H_6: C_2H_5OH / 80:20). Yield= 92%. Mp=116°C. IR (cm-1) 3289.23 (NH), 3196.35, (C-Harom) 3000-3100 cm^{-1}, 1657.89 (C=O).^{1}H NMR (300 MHz, CDCl3), δH, ppm: 2.135 (s, 3H, CH3), 6.99 (m, 1H, aromatic H), 7.19 (m, 1H, aromatic H), 7.43 (m, 1H, aromatic H), 7.94 (s, 1H, NH).13C NMR (CDCl3, 75 MHz), δC, ppm: 120-138 (CH aroma), 169 C=O, 24.41 (**C**H3CO).

N-benzylacetamide 4b: Rf= 0.44 (C_6H_6: C_2H_5OH / 80:20). Yield= 96%. Mp=61 °C. IR (cm-1):3373 (NH), 3027-3106 (CH), 1658 (NH), 1496 and 1605 (C=C aromatic), 1026 (C–N). ^{1}H NMR (300 MHz, CDCl3), δH, ppm: 4.35 (m, 2H, CH2), 6.54 (s, 1H, NH-CO), 7.01-7.21 (m, 5H, aromatic), 1.95 (*s*, 3H, COCH3). 13C NMR (CDCl3, 75 MHz), δC, ppm: *δ*129.01 (C–1), 128.2 (C–2), 129.6 (C–3), 128.3 (C–4), 130.1 (C–5), 138.6 (C–6), 43.60(−CH2NH), 170.2 (C=O), 23.03 (–COCH3).

N-cyclohexylacetamide 4c: Rf= 0.5 (C_6H_6: C_2H_5OH / 80:20). Yield= 87%. Mp=104 °C.IR (cm-1):3276 and 3366 (NH2), 2864-2924 (CH2), 1606 (NH2), 1370 and 1450 (CH2).^{1}H NMR (300 MHz, CDCl3), δH, ppm: 1.83 and 1.62 (m, 4H, CH2), 1.22 (m, 2H, CH2), 1.085 (m, 2H, CH2), 1.88 (s, 3H, CH3), 3.66(m, 1H, CH), 5.92 (s, 1H, NHCO). 13C NMR (CDCl3, 75 MHz), δC, ppm: 169.22 (C=O), 48.05 (CH), 33.06 (2CH2); 25.49 (CH2); 25.36(CH2); 23.36 (**C**H3CO).

N-Acetyl-4-aminoantipyrine4d: Rf= 0.24 (C_6H_6: C_2H_5OH / 80:20). Yield= 90%. Mp=197 °C.IR (cm-1): 1709 (C=O), 1688 (C=O) amide, 3290 cm^{-1} (NH), 1384, 1354 and 1295 cm^{-1} (C-N), 1438 and 1407 cm^{-1} (C-CH3). ^{1}H NMR (300 MHz, DMSO), δH, ppm: 9.08 (s, 1H, NH), 7.30 (m, 3H, aromatic H), 7.50 (m, 3H, aromatic H), 3.028 (s, 3H, N-CH3), 2.09 (s, 3H, C-CH3), 1.97 (s, 3H, CH3CO).13C NMR (DMSO, 75 MHz), δC, ppm: 124-136 (C aromatic), 162 (C=O), 169.46 (C=O), 154 (C=**C**-NH2), 108.25 (C=C), 36.60 (N-CH3), 11.79 (CH3), 23.13 (**C**H3-C-O).

2-acetamido 4- phenylthiazole 4e: Rf= 0.32 (C_6H_6: C_2H_5OH / 80:20). Yield= 88%. Mp=206 °C.IR (cm-1): 3240 (NH), 1667 (C=O), 1600 (C=C), 1520 (C=N). ^{1}H NMR (300 MHz, DMSO), δC, ppm: 7.31 (m, 1H, aromatic), 7.40(m, 2H, aromatic), 7.89(m, 2H, aromatic) (m, 3H, aromatic), 7.58 (s, 1H, thiazole-H5), 9.00 (s, 1H, NHCO), 2.16 (s, 3H, CH3CO). 13C NMR (DMSO, 75 MHz), δC, ppm: 158.51 (C=N), 169.76 (C=O), 108.4 (C=C), 126.22-134.86 (C arom), 149.26(C=C-Ph),24.60 (CH3CO).

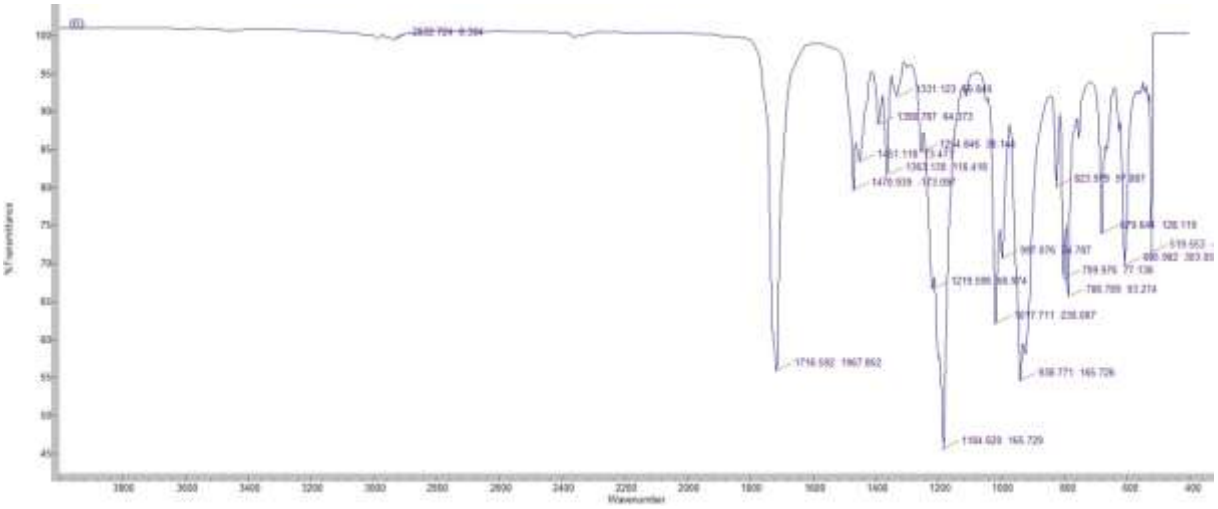


Figure 1. IR spectrum of compound 2

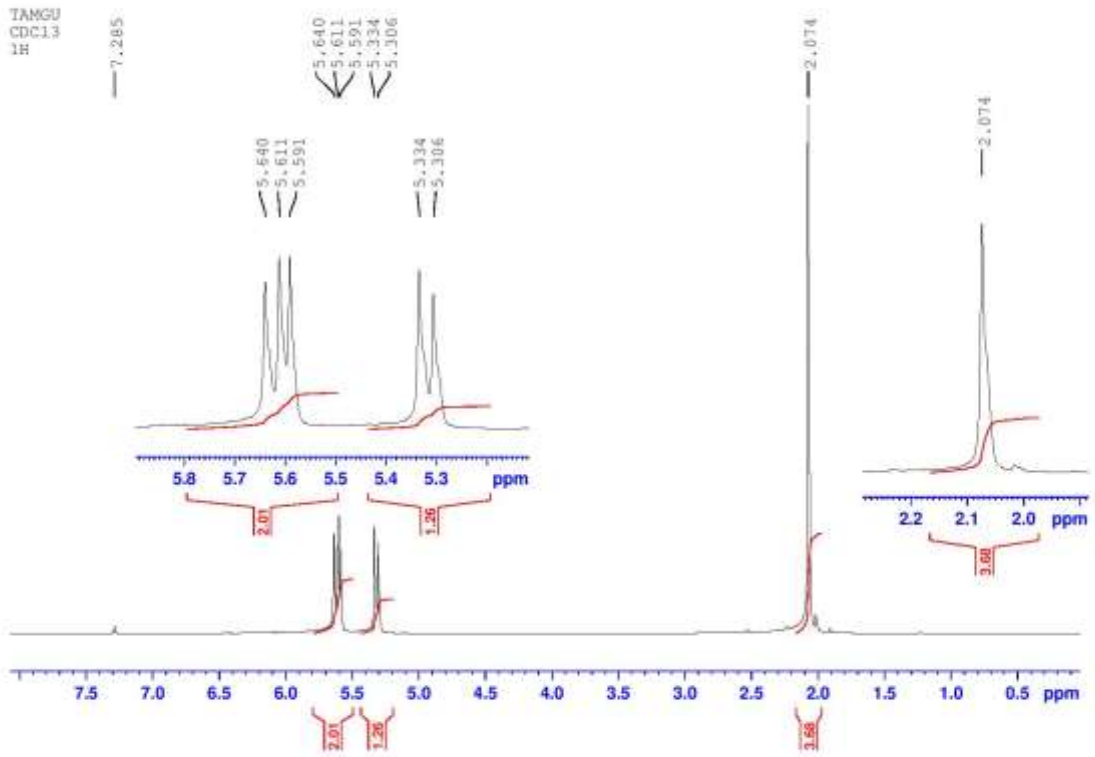


Figure 2. 1H NMR spectrum of compound 2

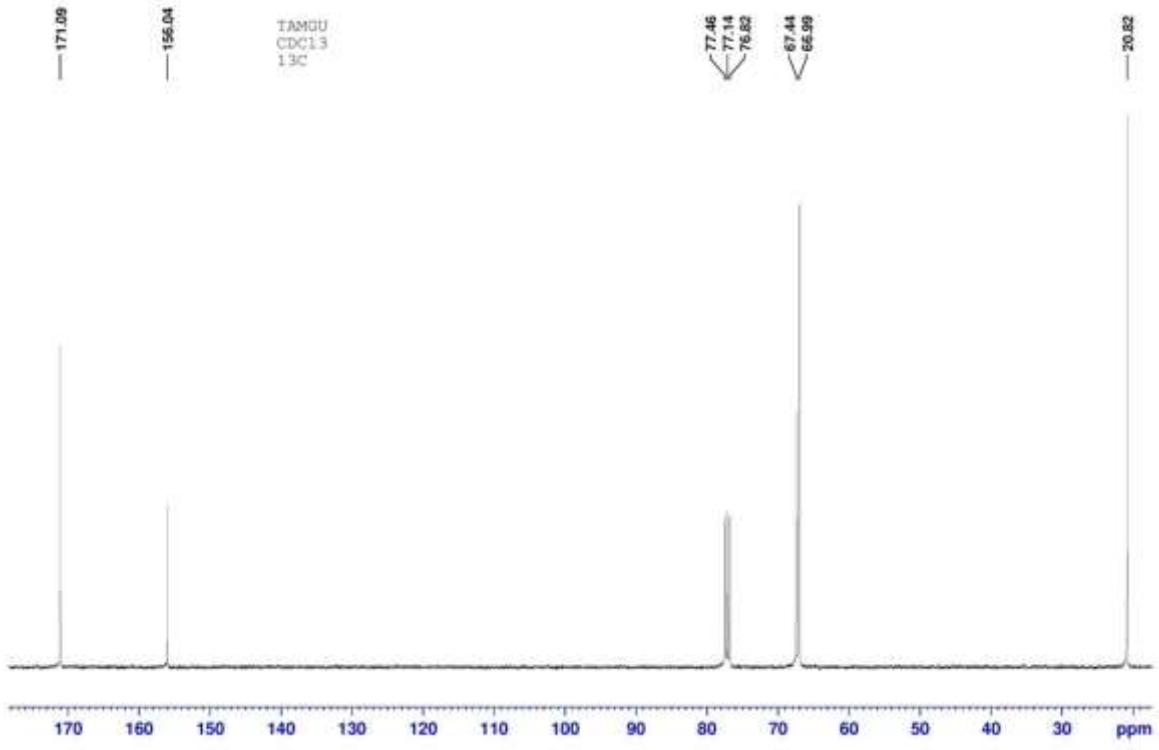


Figure 3. 13C NMR of compound 2

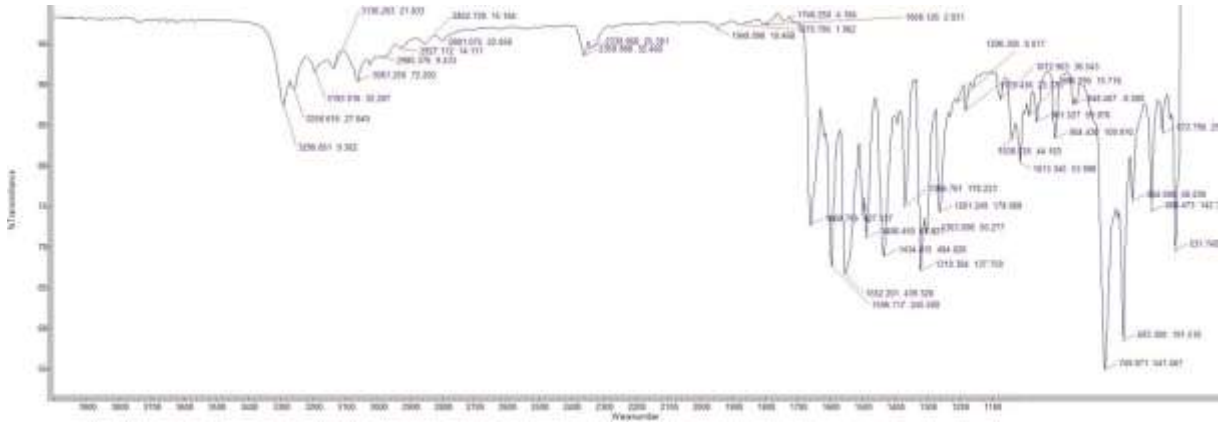


Figure 4. IR spectrum of compound 4a

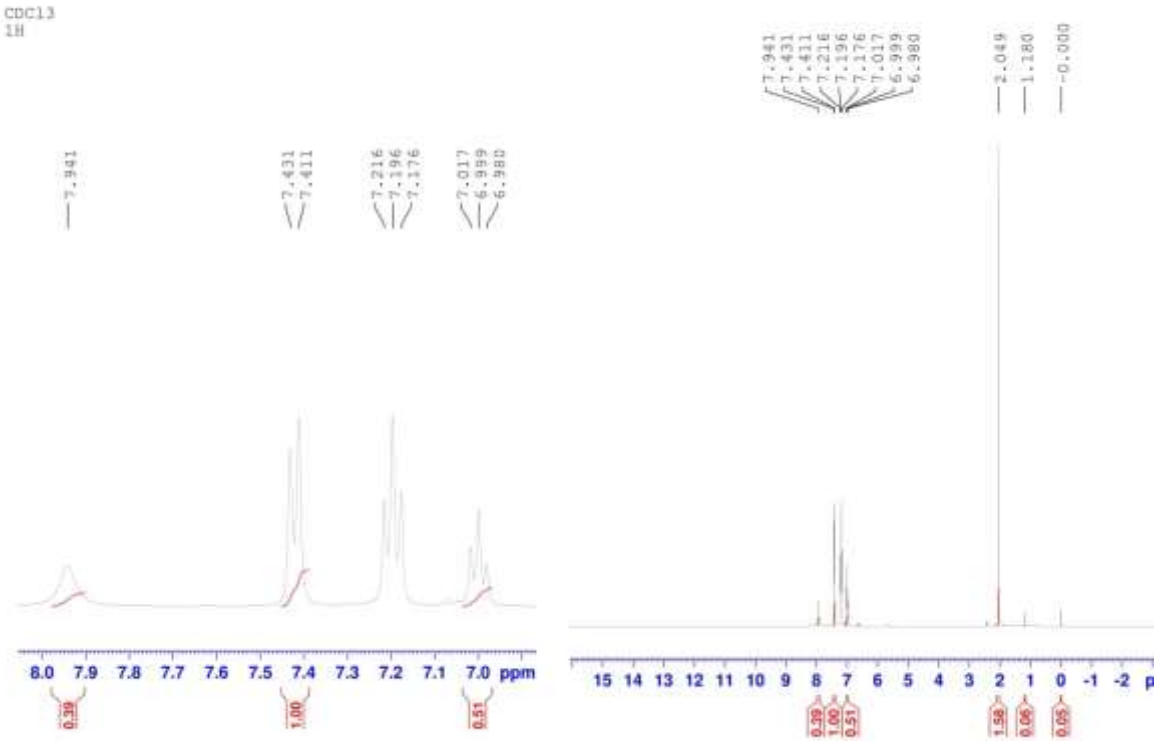


Figure 5. 1H NMR spectrum of compound 4a

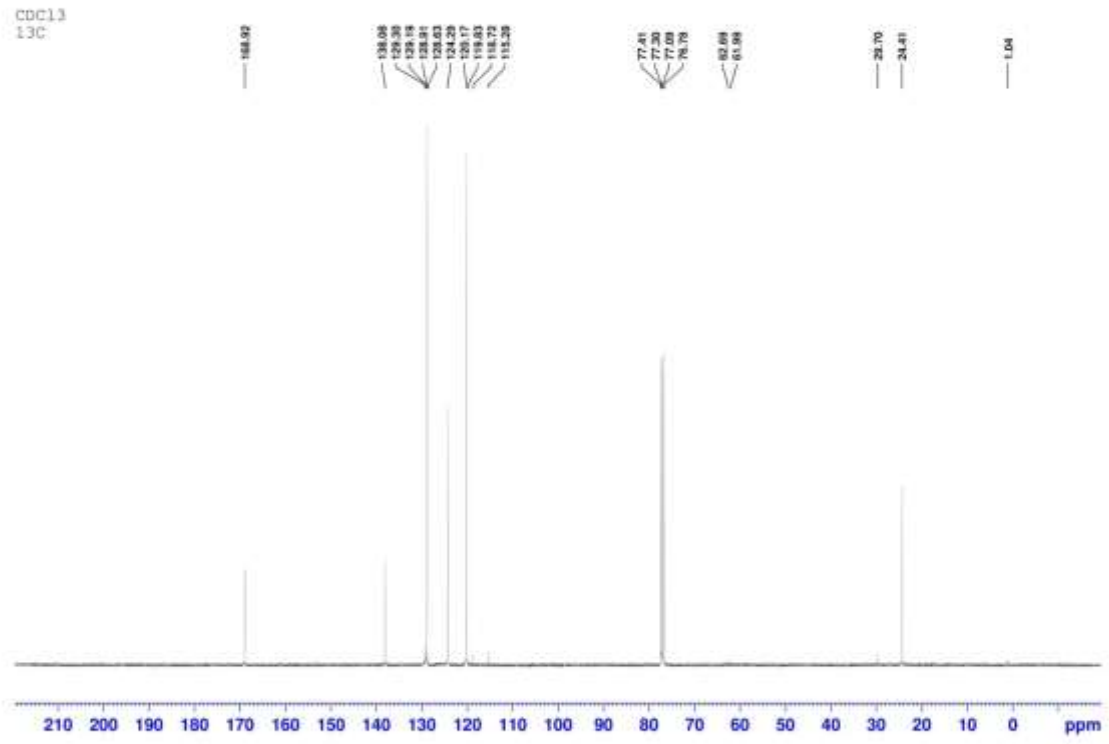


Figure 6. 13C NMR of compound 4a

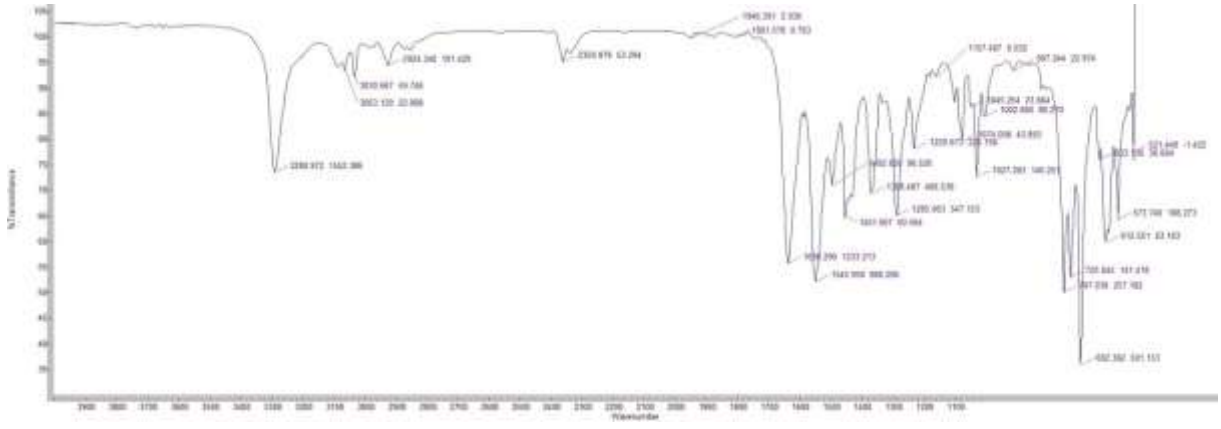


Figure 7. IR spectrum of compound 4b

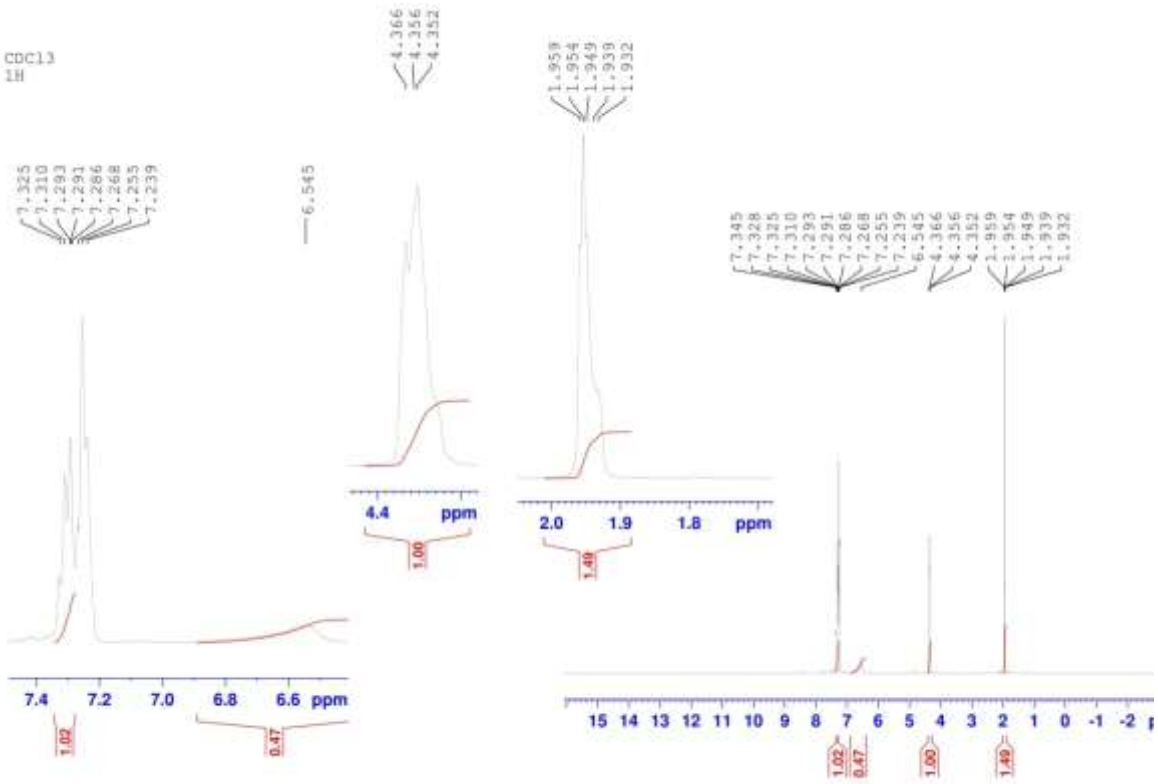


Figure 8. 1H NMR spectrum of compound 4b

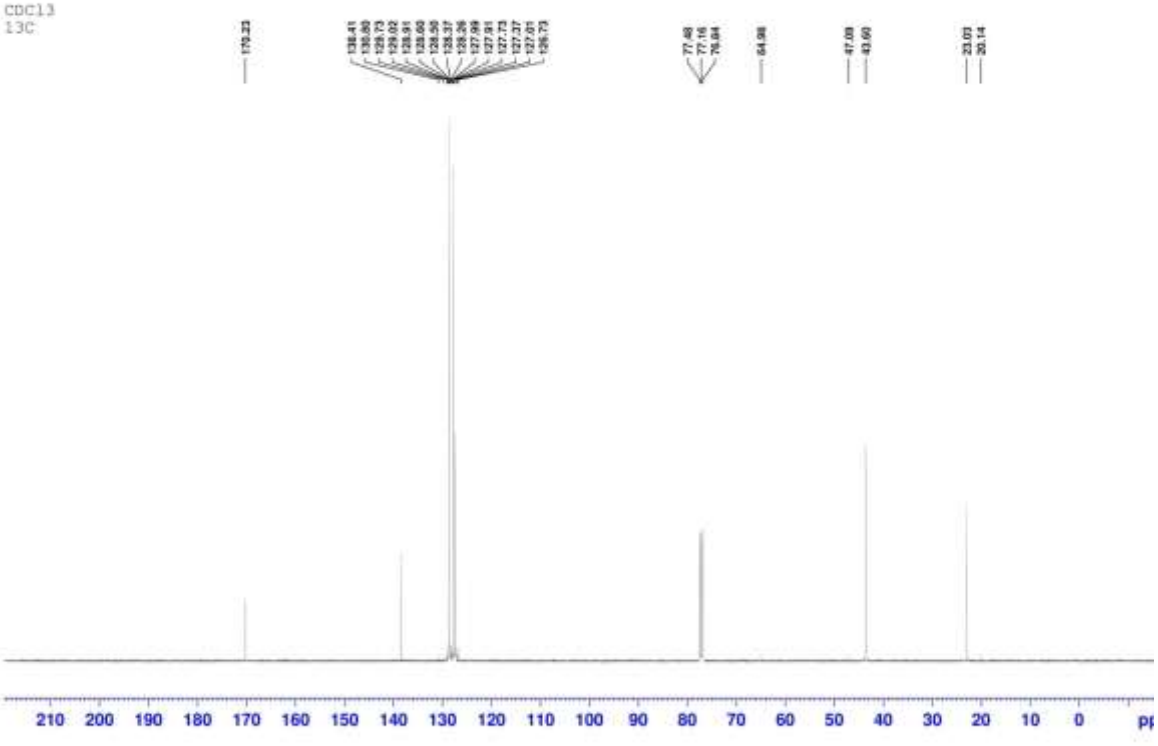


Figure 9. 13C NMR spectrum of compound 4b

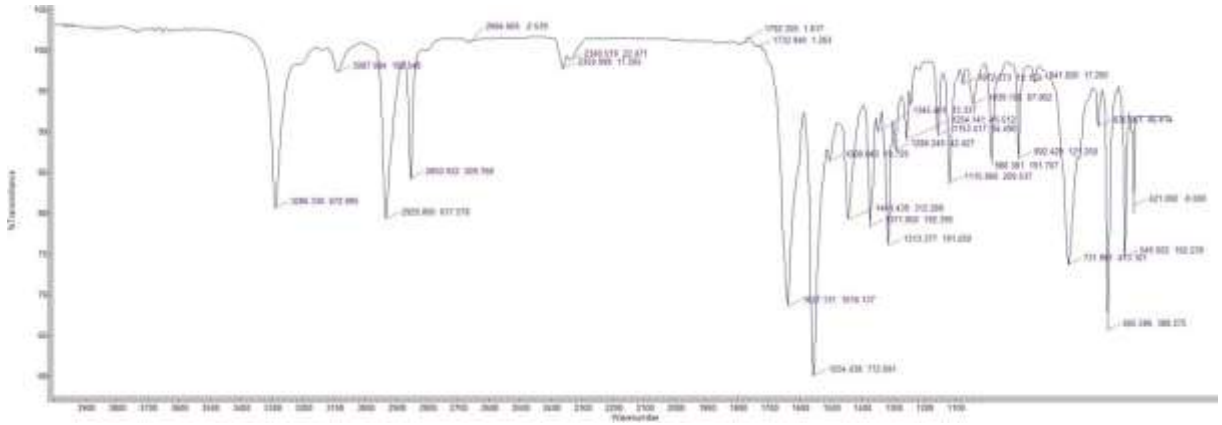


Figure 10.IR spectrum of compound 4c.

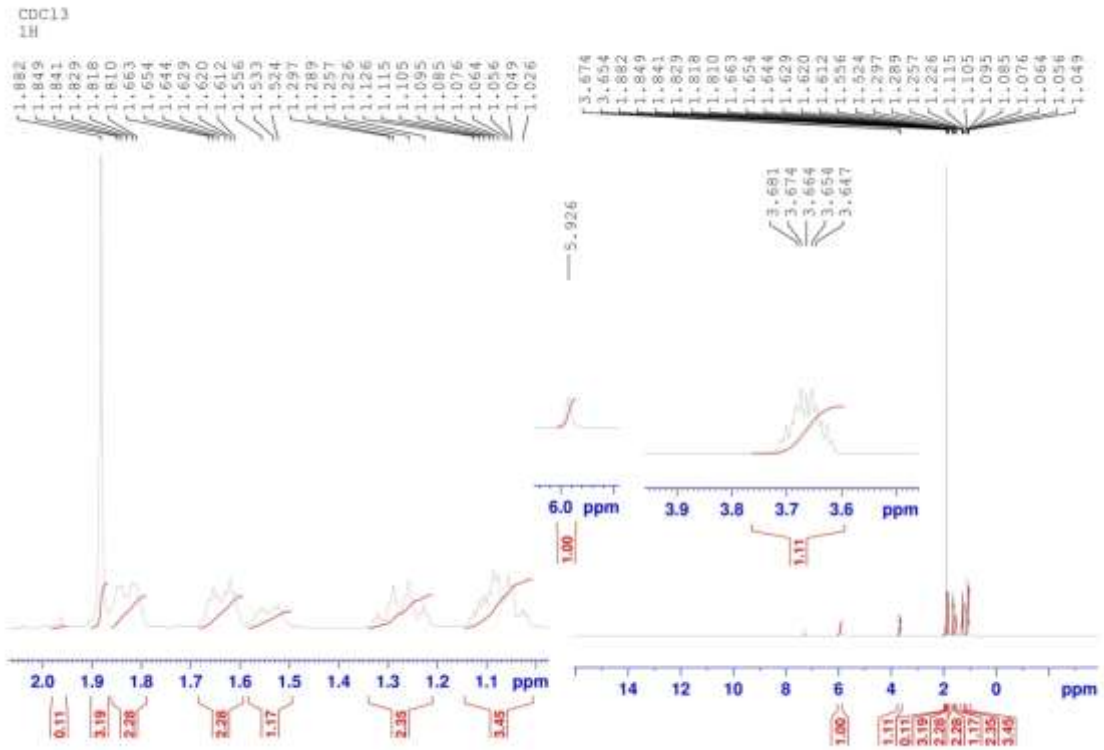


Figure 11.1H NMR spectrum of compound 4c.

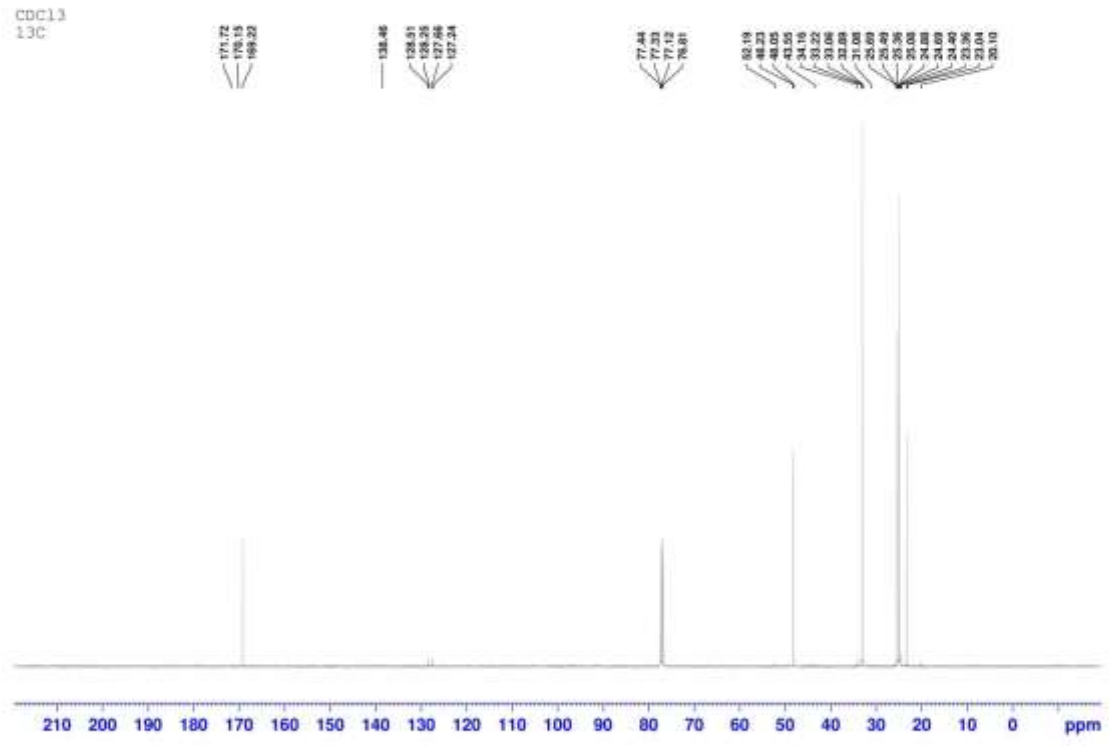


Figure 12. 13C NMR spectrum of compound 4c

Figure 13.IR spectrum of compound 4d.

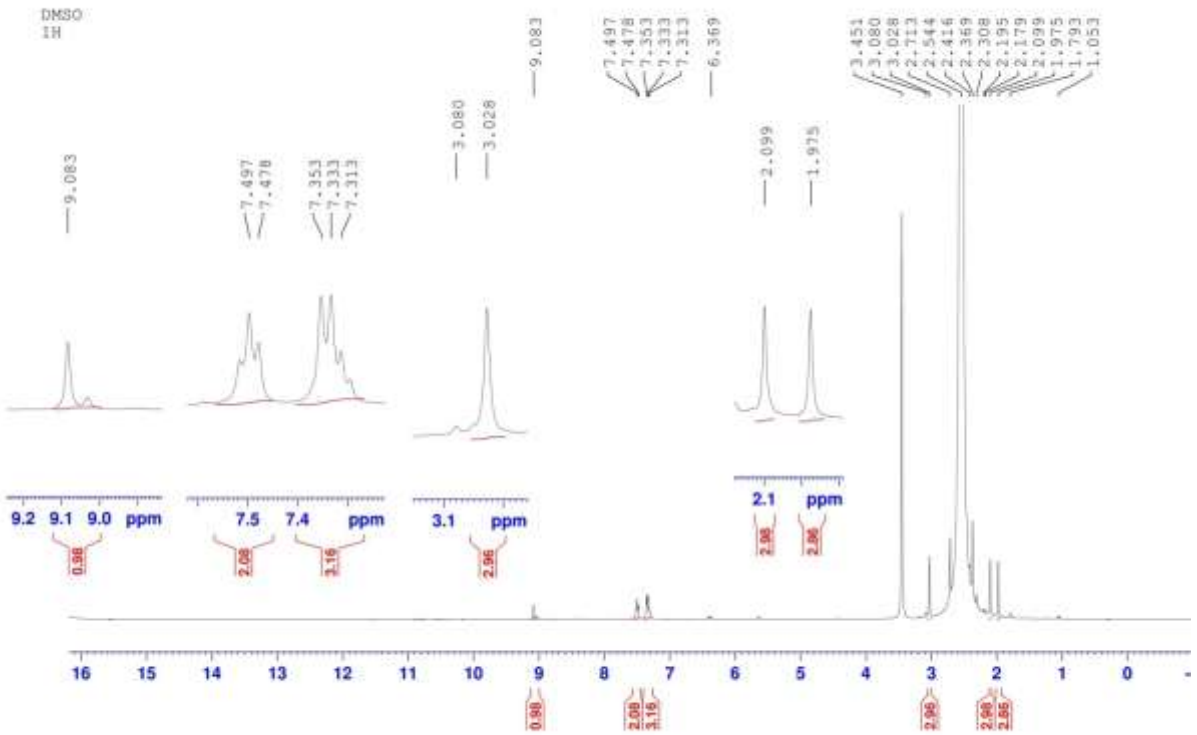


Figure 14.1H NMR spectrum of compound 4d.

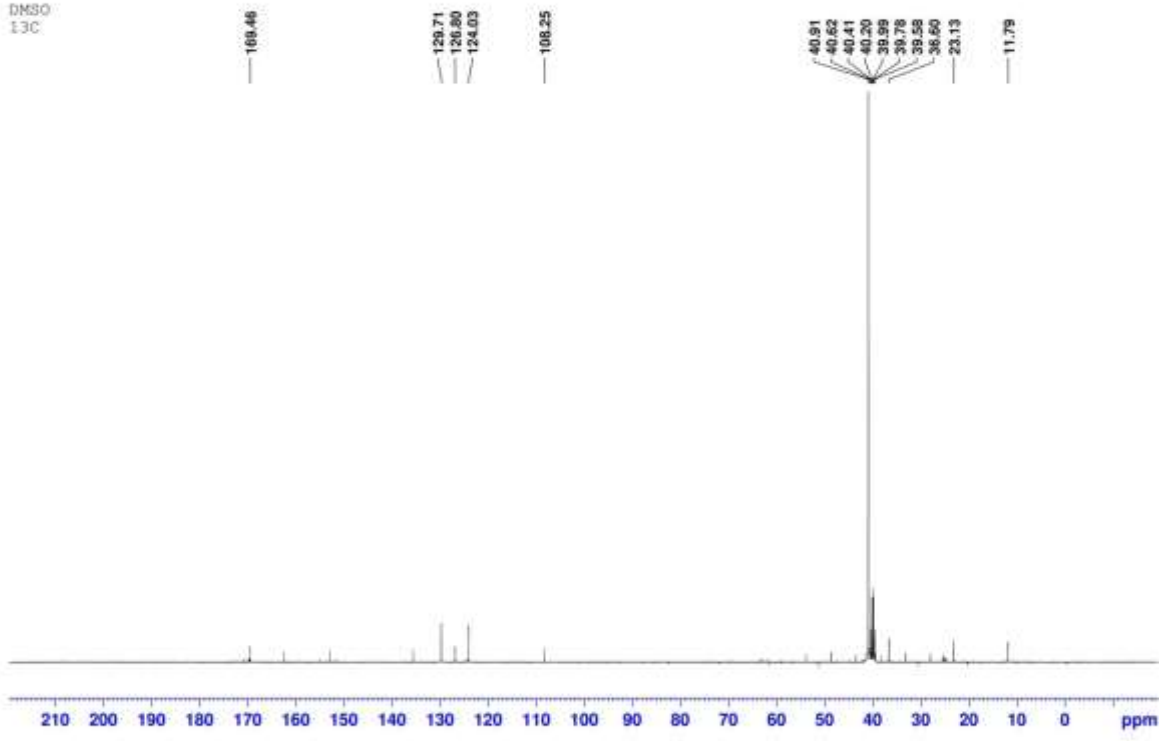


Figure 15.13C NMR spectrum of compound 4d.

Figure 16.IR spectum of compound 4e.

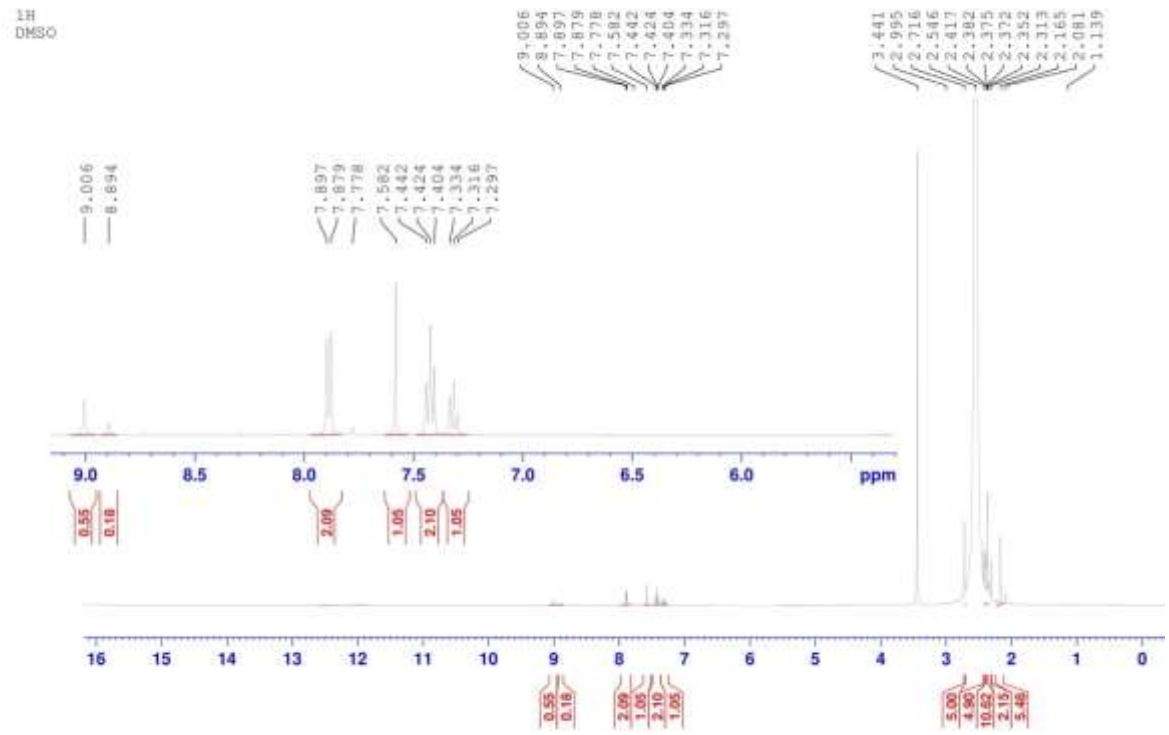


Figure 17. 1H NMR spectrum of compound 4e

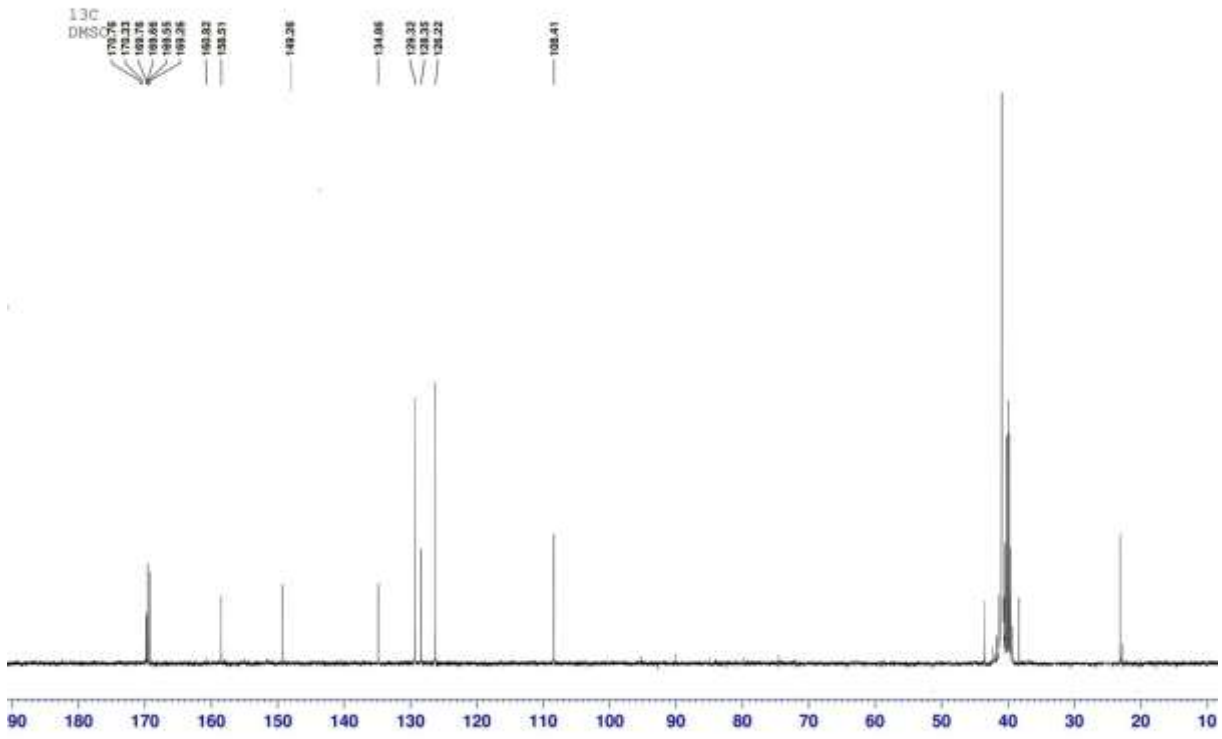
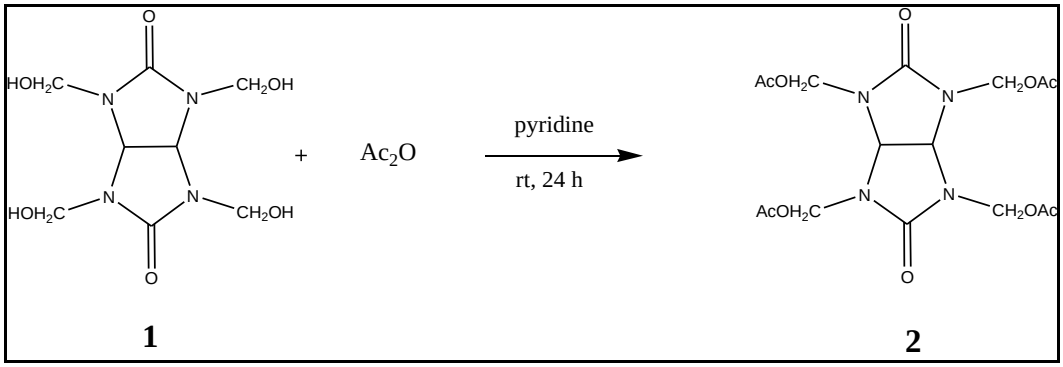
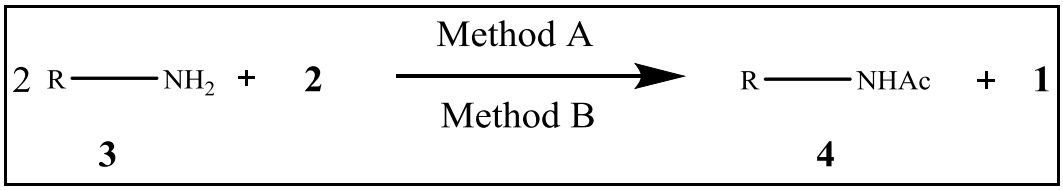


Figure 18.13C NMR spectrum of compound 4e.

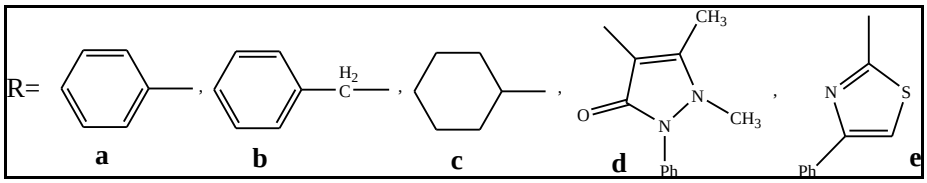
Results and Discussion



Scheme 1. Synthesis of tetra N-acetoxyethyl glycoluril.



Scheme 2. N-acetylation of amines (3a, 3b, 3c, 3d, 3e) using TAMGU.



2,4,6,8-tetra-(hydroxymethyl)glycoluril (**1**) using in this study as raw material was synthesized by condensation of the glycoluril in a suspension of paraformaldehyde in aqueous base solution at pH 10-12 and a temperature of 50-60°C.[9]

The introduction of an acetyl group at the N atom of glycoluril was successfully obtained by khauling et al [10] using acetic anhydride in the presence of HClO4 or NaOAc or with acetyl chloride in the presence of triethylamine and this may be related to steric factors. This latter was already used as acetylating agent for the amines.[11, 12]

To investigate the O-acetylation of glycoluril we have chosen the most readily available N-hydroxymethylglycoluril. O-Acetylation was carried out using acetic anhydride in pyridine at room temperature over 24 h to give the target molecule (TAMGU) with excellent yield 95 %. On the basis of the 1H and 13C NMR spectroscopic data it was found that all of the hydroxymethyl groups had undergone acetylation. (Scheme 1).

The structure of compound (**2**) was indicated by the absence of the characteristic O-H stretching vibration at 3200-3600 cm-1and the formation of C=O absorption band at 1716 cm -1, in addition the absorption bands of the C-O at 1184 and 1220 cm -1. The 13C NMR spectrum of the displayed the presence of C=O at 171.09, which affirmed the presence of acetyl group, in addition the peak of the bond (CH3-CO) at 20.82.

The 1H NMR spectrum of compound (**2**) showed a two doublet at δ 3.30 ppm and 5.6 ppm, which was attributable to the CH2 groups. As well as a singlet representing a methine protons at 5.64 ppm. A singlet at δ 2.07 ppm, assignable to the acetate methyl.

The requirement of the amount of TAMGU was also standardized using different amounts of it. It was observed that for 1eq of amine 2eq of TAMGU was enough for the complete conversion of the starting material.

A number of primary amines underwent N-acetylation smoothly with TAMGU in dichloromethane at reflux temperature in good yields. The course of the reaction of the compounds **3** (**a-e**)was monitored every 15 min using TLC on Silufol plates in the system C_6H_6- EtOH (8:2). At the end of 1 h the reaction mixture contained virtually no starting TAMGU 2. At the end of 2 h the picture had not changed, which explained the reaction completion. After complete conversion of the amine, the crude reaction mixture was evaporated and then dried in vacuum.

Mechanochemical synthesis of compound**4** (**a-e**) in this report also has been studied by reacting 1eq of compound **3** (**a-e**) with 2eq of TAMGU in dichloromethane as a solvent at room temperature for 10 min (schema 2). The reaction completion was checked by using TLC, which has shown the total conversion of amines into amides.

The workup and isolation of the products were easy. All the acetylated products were obtained in good yields and characterized by comparison of their TLC, IR spectra, 1H-NMR spectra, and melting points with authentic samples obtained via conventional processes.

The structures of compounds **4**(**a**–**e**) were deduced from their spectral data. The solid state IR spectra of these compounds reveal a Sharp carbonyl (C=O) stretching vibrations were seen around 1650–1695 cm^{-1}. The presence of primary amide N–H in the skeleton was confirmed from the stretching frequencies between 3225 and 3334 cm^{-1}.

All other peaks in the spectra are in well agreement with the contents of functionalities in the synthesized molecules. The ^{1}H NMR data of all compounds showed a characteristic singlet around 6–9 ppm, which indicates the presence of N–H of an amide in the skeleton. Furthermore the Presence of singlet around

1.90–2.2 ppm reveals the presence CH3 of an acetyl group. The ^{13}C NMR spectrum of all the isolated amides displayed the presence of –CH3 signal between 23 and 25 ppm, that confirmed the presence of acetyl group, in addition it has revealed a peak at 169 ppm, which proves the presence of carbonyl group of an amide.

Conclusion

In this report, we have described the synthesis of a new eco-friendly and mild acetylating agent TAMGU, and use it in very simple, high yielding and environment-friendly method for the acetylation of amines. This method represents a tremendous opportunity for the practice of green chemistry. The notable advantages of the method are: (i) operational simplicity, (ii) moderate to good yields, (iii) no chromatographic separation, (iv) general applicability. The method is environmentally friendly with respect to by-products and the effluent is innocuous. The by-product tetrahydroxymethyl glycoluril is a useful to regenerate TAMGU. We believe this will present a better and more practical alternative method to the existing methodologies for acylation of primary amines and thus will find useful application in the synthesis of complex natural products where amino groups are presented.

Acknowledgments

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