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Green approach toward protection of secondary amine in pyrazole nucleus by PEG-400 and Boc catalyst

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ABSTRACT

The objective of the present study is the protection of secondary amine in the substituted pyrazole derivative with the help of a green catalyst to facilitate the synthesis of anticancer compounds. Di-*tert*-butyl dicarbonate (Boc) has been used as a protecting agent with various catalysts such as Polyethylene glycols-400, Dimethyl aminopyridine, and *N, N*-Diisopropyl ethylamine. In this study, five different synthetic methods have been applied, but success has been achieved in only two. The very first method has been reported for the protection of secondary amine in pyrazole, associated with these catalysts. These synthetic methods had given a good yield and fewer side products, and it also a green approach toward synthetic chemistry.

INTRODUCTION

Cancer is a main community health problem all over the globe because of its significantly high rate of morbidity and mortality. It is the next most important reason for death in the present society after cardiovascular disease (De Martel *et al*., 2012). There are various types of cancers, the maximum of these types are treatable leaving behind a number of serious side effects. Now, the area of interest is to develop new anticancer drug candidate with fewer side effects and a more potent drug profile (Pisani, 2009). There are various categories of drugs, such as antimetabolites (Peter *et al*., 2000), alkylating agent (Singh *et al*., 2018), anthracyclines (Takimoto and Calvo, 2008), plant alkaloids, epipodophyllotoxins, and topoisomerase (Glam *et al*., 2005) inhibitor which are used in a cancer chemotherapy but they all show several adverse effects, such as infertility, cardiotoxicity (Jarkowski *et al*., 2011), hepatotoxicity (Perry, 2010), nephrotoxicity (Kintzel, 2001), encephalopathy (Schacht *et al*., 2012), bone marrow depression, alopecia, drug-induced cancer, and many more (Finley and Volpp, 1969). Other than chemotherapy, radiation therapy, laser therapy, hormone therapy, hyperthermia, and surgery had also emerged as a treatment but they also carry many side effects (Frankish, 2013).

In the past few years, many researchers had revealed the synthesis, structure–activity relationships, and pharmacological activities [such as antitumor (Ingale *et al*., 2018), anti-inflammatory, and anti-bacterial (Karrouchi, 2018)] of the pyrazole nucleus (Bernatowicz *et al*., 1992). This potential activity profile of pyrazole motivated us to synthesize some new pyrazole derivatives (Fustero *et al*., 2009). So, in this research, we have been synthesized some protected pyrazole derivatives which are characterized by various spectral techniques (Chankeswara and Chakraborti, 2006; Nadia *et al*., 2004).

EXPERIMENTAL

Materials and methodology

All chemicals were procured from Aldrich, Fluka, and HIMEDIA companies in the pure form. Melting point was measured with VMP-D melting point apparatus and uncorrected. The changes in the reaction were observed with the help of

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silica gel-G coated thin-layer chromatography (TLC) plates with a suitable visualizing agent. ^{1}H NMR, ^{13}C NMR spectra were measured with Bruker-Avance-II (400 MHz) spectrometer in $CDCl_3$ solvent and tetramethylsilane as an internal reference and chemical shifts are in δ (ppm). IR spectra were measured with Fourier-transform infrared spectroscopy (FTIR)-9050S-CE (SHIMADZU) and FTIR (CARY-660) Agilent. Elemental analyses were measured with Perkin Elmer CHNS/O Analyzer series-II Model 2400.

Synthesis of 4-acetylpyrazole derivative (2)

3, 5-dimethyl pyrazole (0.1 moles, 8.16 g) was slowly added into the solution of acetic anhydride (0.1 moles, 3.02 g) and then two drops of 96% sulfuric acid. The reaction mixture was condensed for 15 hours and checked by TLC to determine reaction proceeding. Excess acetic anhydride was distilled off by rotary evaporator. After evaporation residue was obtained, this was again refluxed for 20 minutes after the addition of 40 ml concentrated hydrochloric acid and 2 g charcoal. The reaction mixture was cooled and filtered to take away the charcoal. The filtrate was concentrated on a rotary evaporator. The dry residue thus obtained was solubilized in 10 ml of water and slowly made alkaline with 15 g of sodium acetate trihydrate. The crude product precipitate was separated off. The excess solvent was evacuated on a rotary evaporator and purified with column chromatography (Silica Gel, 10% Ethanol/Hexane) to the desired compound. Yield: 98%; Melting Point: 109°C–110°C.

Synthesis of Boc-protected pyrazole derivative (3)

In the present research work, we have adopted five methods for the synthesis of compound 3.

CONVENTIONAL METHOD-A

The mixture of substituted pyrazole (**2**) (1.0 mmol), $(Boc)_2O$ (1.4 mmol), and PEG-400 (1.0 ml) was continuously stirred at room temperature for 2.5 hours followed by the TLC until it shows total reactant consumption. After reaction completion, the solution was drained into the water and extracted with dry ether. The organic layer with anhydrous Na_2So_4 was dried, concentrated on a rotary evaporator, and purified with column chromatography (benzene/methanol, 8:2) to give a purified product. The PEG-400 was recovered with the extracted aqueous layer and reused without loss of chemical and physical properties. Yield: 95%; Melting Point: 110°C–111°C.

CONVENTIONAL METHOD-B

In 50 ml round bottom flask, substituted pyrazole (**2**) (1 mmol) was dissolved in dichloromethane on magnetic stirrer to obtain a clear yellow solution. In this clear solution, add *N, N*-diisopropylethylamine (DIPEA) (1 mmol) and 4-dimethylamino pyridine (DMAP) in a catalytic amount at 0°C temperature. After 15 minutes, $(Boc)_2O$ (1 mmol) was added and the reaction was stirred at room temperature for 2 hours till TLC shows the total disappearance of the reactant. After completion, dichloromethane was evaporated and the remaining raw product was purified with column chromatography (20% Ethanol/Hexane) to give the desired product. Yield: 85%; Melting Point: 112°C–114°C.

CONVENTIONAL METHOD-C

In an RBF, the solution of substituted pyrazole (**2**) (1 mmol), $(Boc)_2O$ (1 mmol) and a catalytic quantity of iodine (10 mol%) were mixed through stirring without any solvent at room temperature. After reaction completion, dry ether (10 ml) was added and washed by using Na_2SO_4. The reaming solvent was concentrated on a rotary evaporator and the crude product was purified with column chromatography (10% Ethanol/Hexane) to give the pure product. Yield: 20%; Melting Point: 113°C–114°C.

CONVENTIONAL METHOD-D

In 50 ml RBF, the solution of distilled water (9.5 ml), acetone (0.5 ml), and substituted pyrazole (**2**) (1 mmol) were mixed with stirring at room temperature for 30 minutes and dichloromethane (5 ml) was added. After completion of the reaction, the organic layer was dried on anhydrous Na_2SO_4 and reduced under vacuum. The precipitate was purified with column chromatography (CH_2Cl_2/ MeOH, 9:1). Yield: 50%; Melting Point: 100°C–110°C.

CONVENTIONAL METHOD-E

In 250 ml RBF, the solution of tetrahydrofuran (40 ml) and substituted pyrazole (**2**) (14.4 mmol) were mixed at 20°C temperature to give a transparent solution. In this solution, formaldehyde (1.0 eq., 3% water solution) was added and stirred for 4 hours to obtain a uniform solution. The solvent was removed with a rotary evaporator. Yield: 60%; Melting Point: 105°C–108°C.

RESULTS AND DISCUSSION

In the present research work, we try to develop an eco-friendly, novel, and efficient methods for the protection of secondary amine of 4-acetyl-3, 5-dimethylpyrazole (**2**) with the help of protecting agent. To the finest of our information, this is the first report of the use of PEG-400 and DMAP, DIPEA catalyst for the protection of secondary amine of pyrazole nucleus using Boc. PEG-400 has been found to be an adequate and eco-friendly reaction medium for the chemoselective transformation of amines to *N*-(tert-butoxycarbonyl) amines. Correlated to the previously reported methods, these both protocols (method A and B) offer several advantages such as mild reaction circumstances, easy operation, small reaction period, and high yield (Agami and Couty, 2003; Kelly and Mcneil, 1994; Pisár *et al*., 2018; Raju *et al*., 2009; Sharma *et al*., 2004; Varela *et al*., 2006).

Some various procedures apply for the protection of secondary amine in pyrazole but only two methods (A and B) was succeeded and the other three (C, D, and E) were failed (Fig. 1). For the use of method A, the product (**3**) was obtained in good to excellent yield (95%) when reproduced again and again, and in the case of method (B), the product (**4**) yield was 85% with no formation of any side product (Scheme1). Method A product was obtained with higher impurity as compared to another one, so the melting point of the same structured product but with different synthetic procedures (Chankeswara, 2006; Giampietra, 2007; Heydari *et al*., 2007; Krystof, 2006; Sook Hoo, 2007) is different from each other.

1-(3,5-dimethyl-1H-pyrazole-4-yl) ethanone (**2**): Pale yellow amorphous solid, Yield: 98%,m.p 112°C–115°C; FTIR (KBr) cm^{-1}: 3,242 cm^{-1} (N-H), 2,985 CH_3 (str.), 1,769 C=O, 1,667 C=C (str.); ^{1}H NMR ($CDCl_3$): δ 13.7 (s,1H,NH), 2.79 (s, 6H, CH_3), 2.55 (s, 3H,CH_3); ^{13}C NMR: δ 148.0, 114.5, 199.8 (C), 11.0, 11.2,

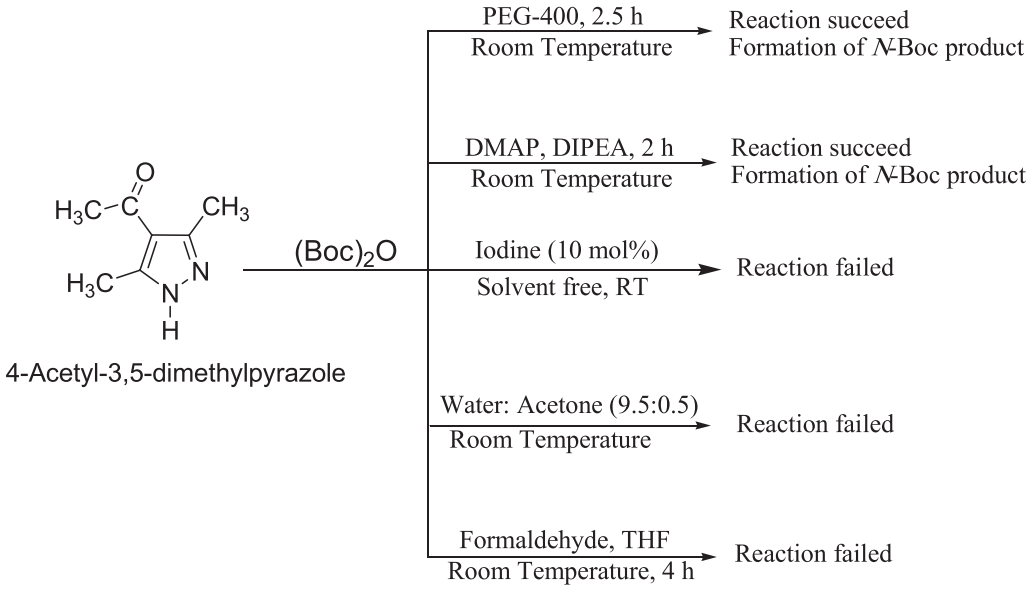
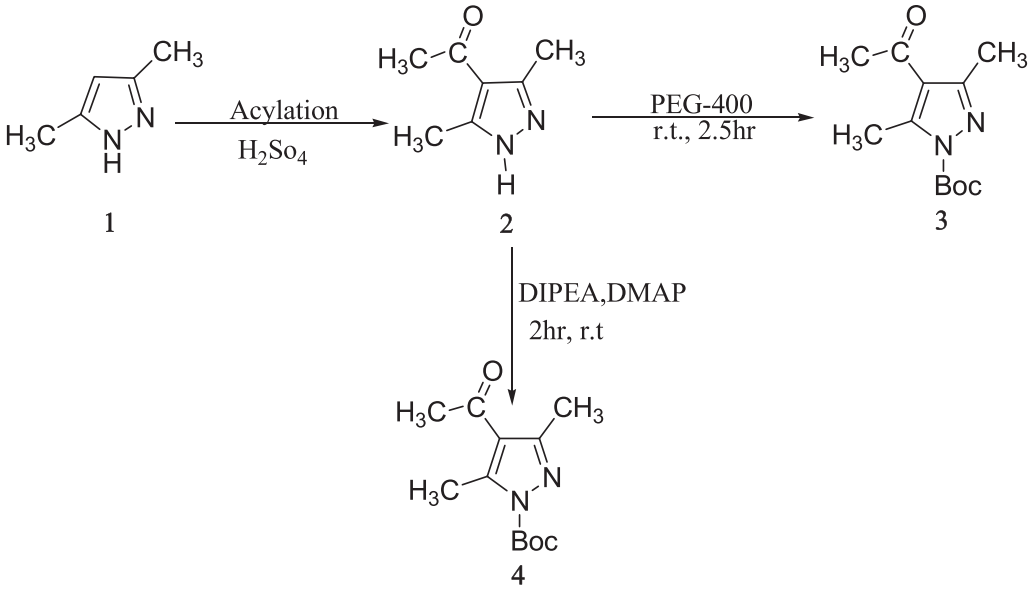


Figure 1. Procedures applied for the protection of secondary amine in substituted pyrazole.



Scheme 1. *N*-Boc protection of secondary amine by PEG-400 and DIPEA, DMAP.

29.3 (CH3); anal. calcd. for $C_7H_{10}N_2O$ (139.09): C, 60.41; H, 7.97; N, 20.13. Found: C, 60.65; H, 7.30; N, 20.28.

tert-butyl-4-acetyl-3,5-dimethyl-*1H*-pyrazole-1-carboxylate (**3**): Pale yellow amorphous solid, Yield: 95%, m.p 68°C–70°C; FTIR (KBr) cm^{-1}: 2,985 CH_3 (str.), 1,769 C=O, 1,667 C=C (str.);^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 9H, Boc), δ 2.55 (s, 3H, CH_3), δ 2.79 (s, 9H, CH_3); ^{13}C NMR: δ 28.5 (CH_3, Boc), 79.6 (Cq, Boc), 149.2 (C=O), 29.3, 11.0, 4.2 (CH_3), 199.8, 147, 106, 144.2; anal. calcd. for $C_{12}H_{18}N_2O_2$ (222.14): C, 64.84; H, 8.16; N, 12.60. Found: C, 60.49; H, 7.61; N, 12.01.

tert-butyl-4-acetyl-3,5-dimethyl-*1H*-pyrazole-1-carboxylate (**4**): Pale yellow amorphous solid, Yield: 85%, m.p 70°C–75°C; FTIR (KBr) cm^{-1}: 2,985 CH_3 (str.), 1,769 C=O, 1,667 C=C (str.);^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 9H, Boc), δ 2.55 (s, 3H, CH_3), δ 2.79 (s, 9H, CH_3); ^{13}C NMR: δ 28.5 (CH_3, Boc), 79.6 (Cq, Boc), 149.2 (C=O), 29.3, 11.0, 4.2 (CH_3), 199.8, 147, 106, 144.2; anal. calcd. for $C_{12}H_{18}N_2O_2$ (222.14): C, 64.84; H, 8.16; N, 12.60. Found: C, 60.49; H, 7.61; N, 12.01.

CONCLUSION

In summary, protected pyrazole has been synthesized and characterized. In the present research work on the use of PEG-400, it is a green and eco-friendly approach. This method was easy and adequate for the *N*-Boc protection of amines because of eco-friendly reaction medium at room temperature (Scheme1) (**3**) to obtain good to excellent yield. No side product such as isocyanate, urea, or *N, N*-di-Boc derivatives were showed in TLC, infrared spectroscopy (IR), ^{1}H NMR, and ^{13}C NMR analysis.

We also apply a conventional method of Boc protection of secondary amine in pyrazole. This reaction was performed at room temperature in the presence of catalyst DMAP and DIPEA (Scheme1) (**4**). This reaction completed very fast with pyrazole moiety as compared to other nucleus and formation of side product is less in number.

ACKNOWLEDGMENTS

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CONFLICT OF INTERSET

Authors declare that there are no conflicts of interest.

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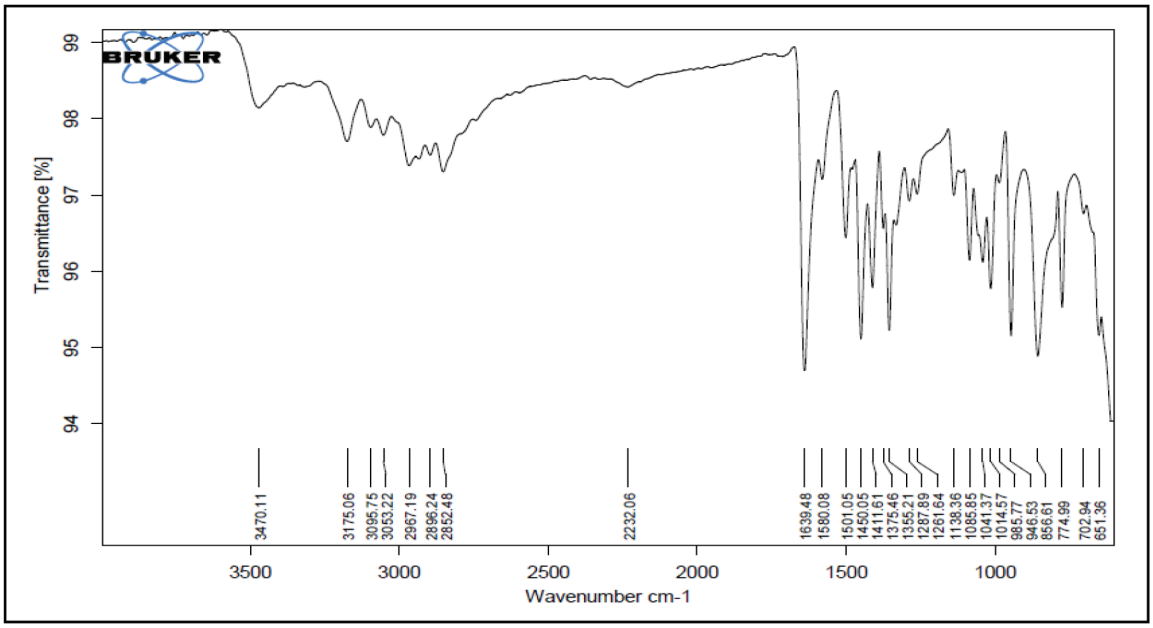
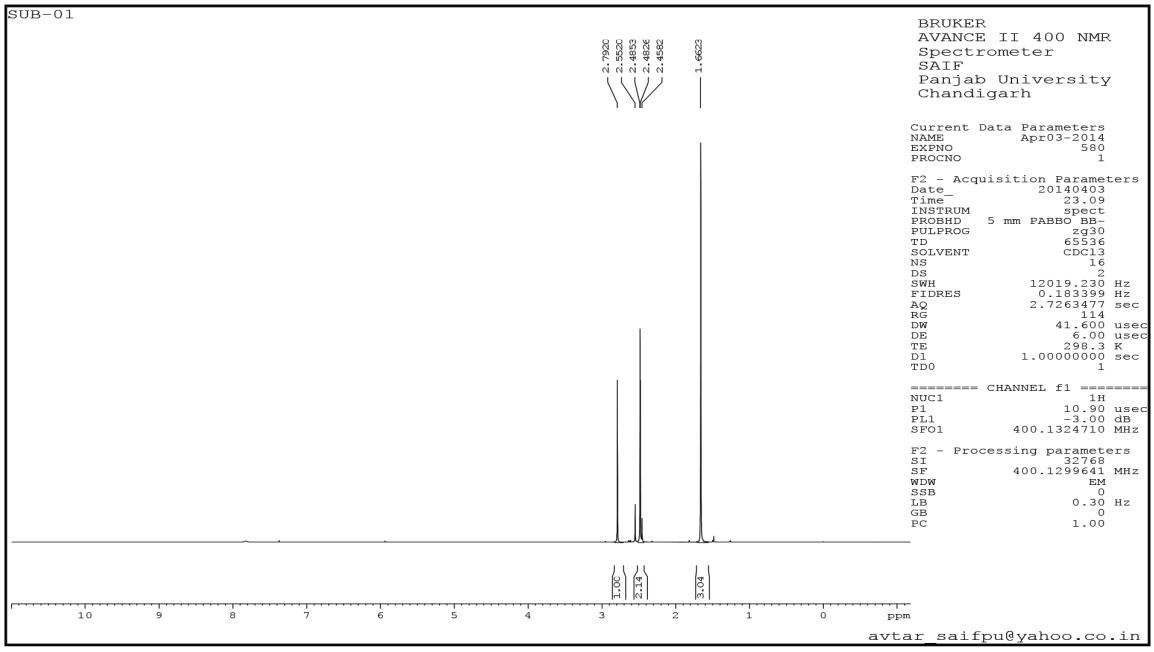
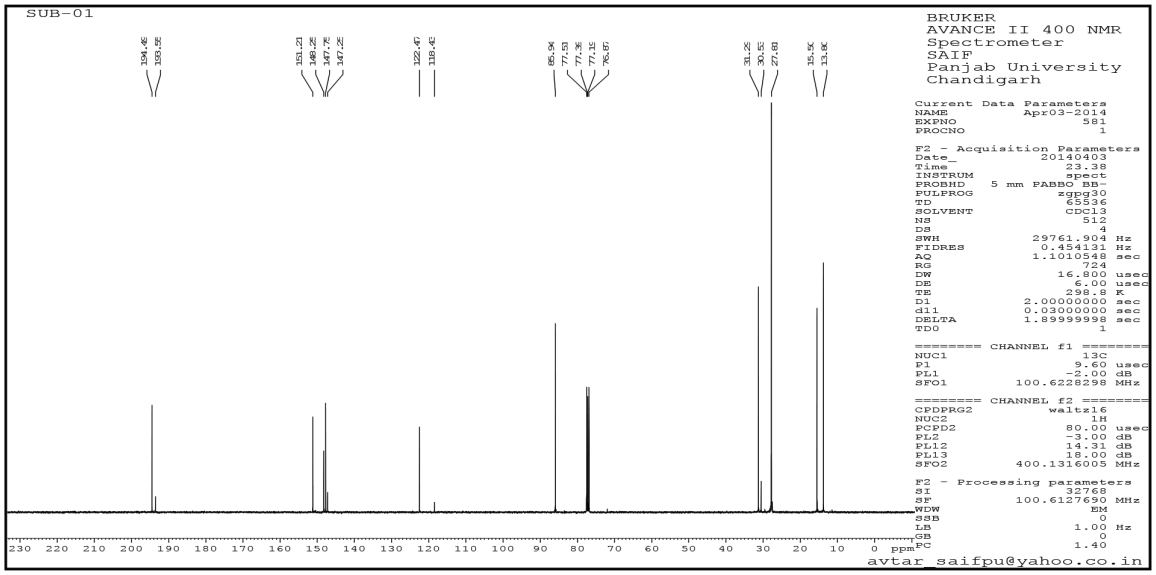
SUPPLEMENTARY MATERIAL



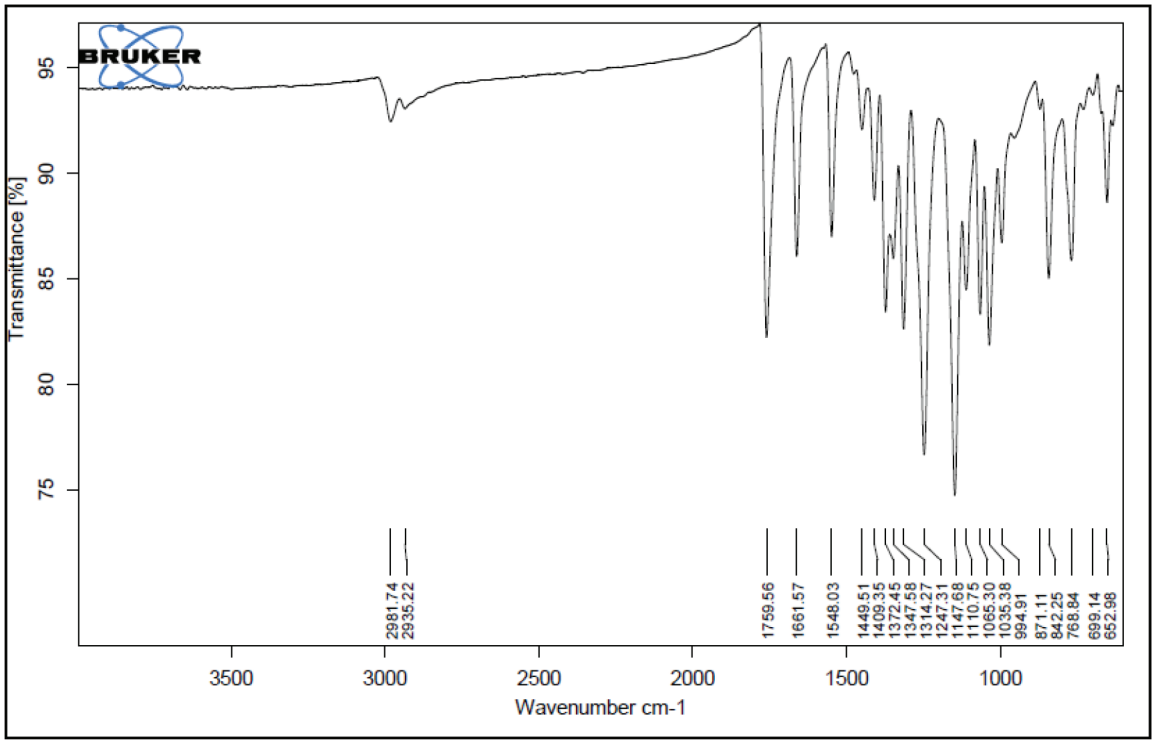
Supplementary Figure 1. [1]H NMR Spectra.



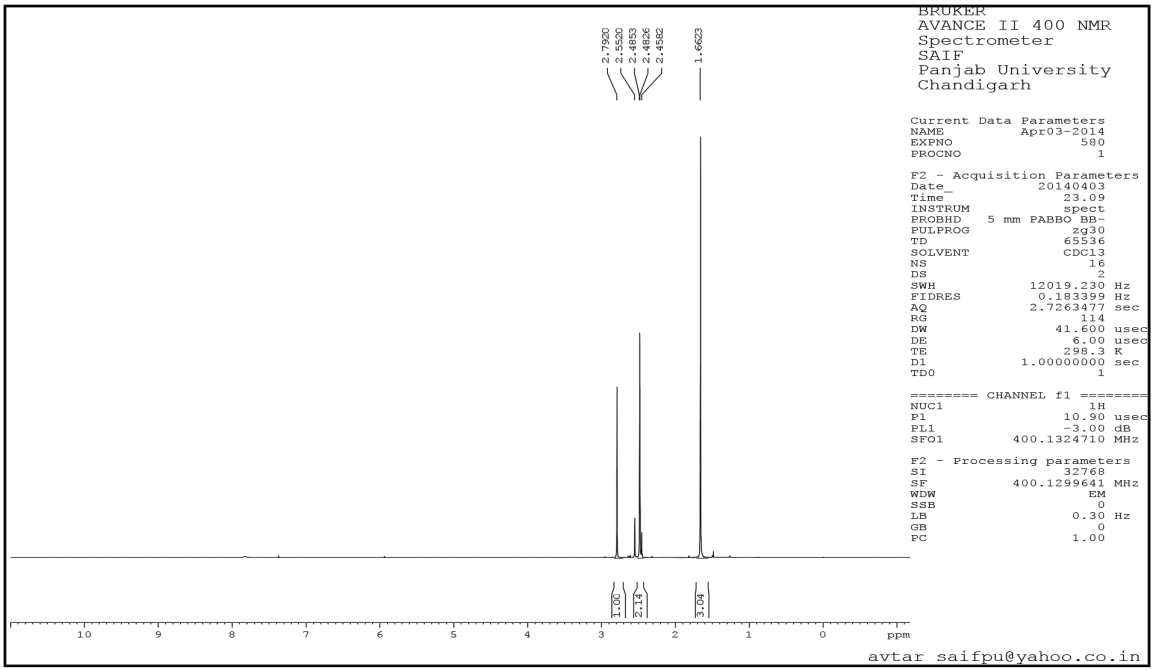
Supplementary Figure 2. [13]C NMR spectra.



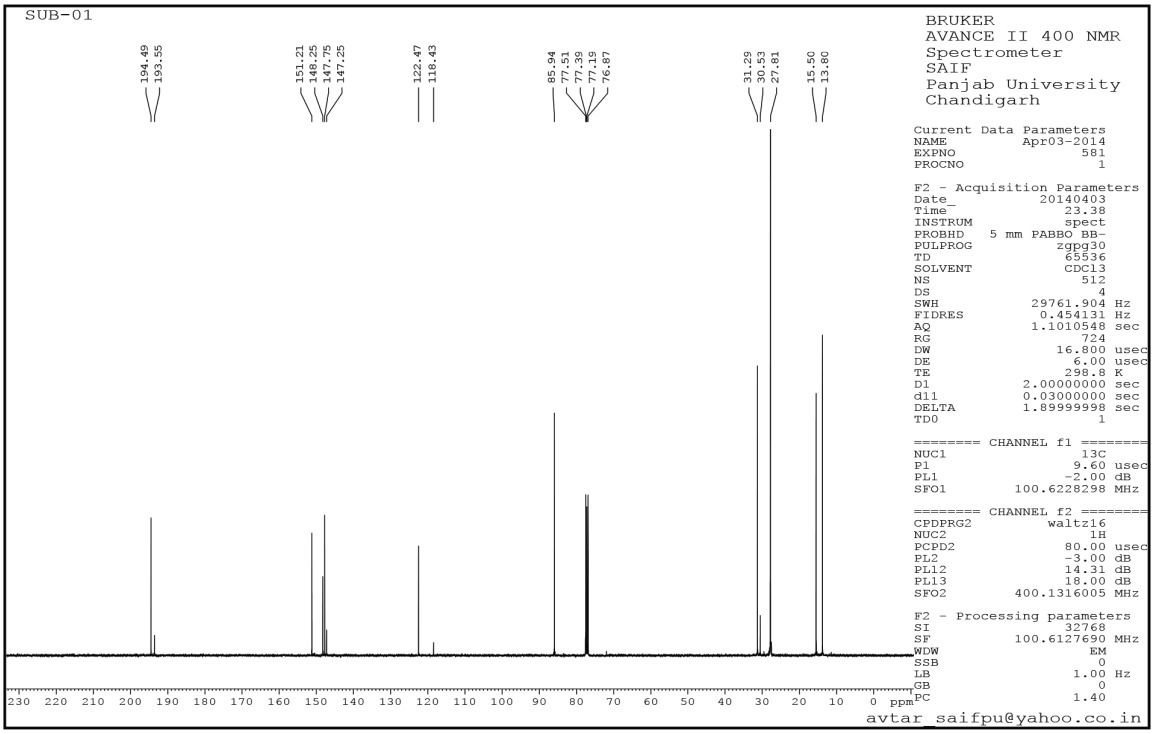
Supplementary Figure 3. *tert*-butyl-4-acetyl-3,5-dimethyl-*1H*-pyrazole-1-carboxylate (**3**).



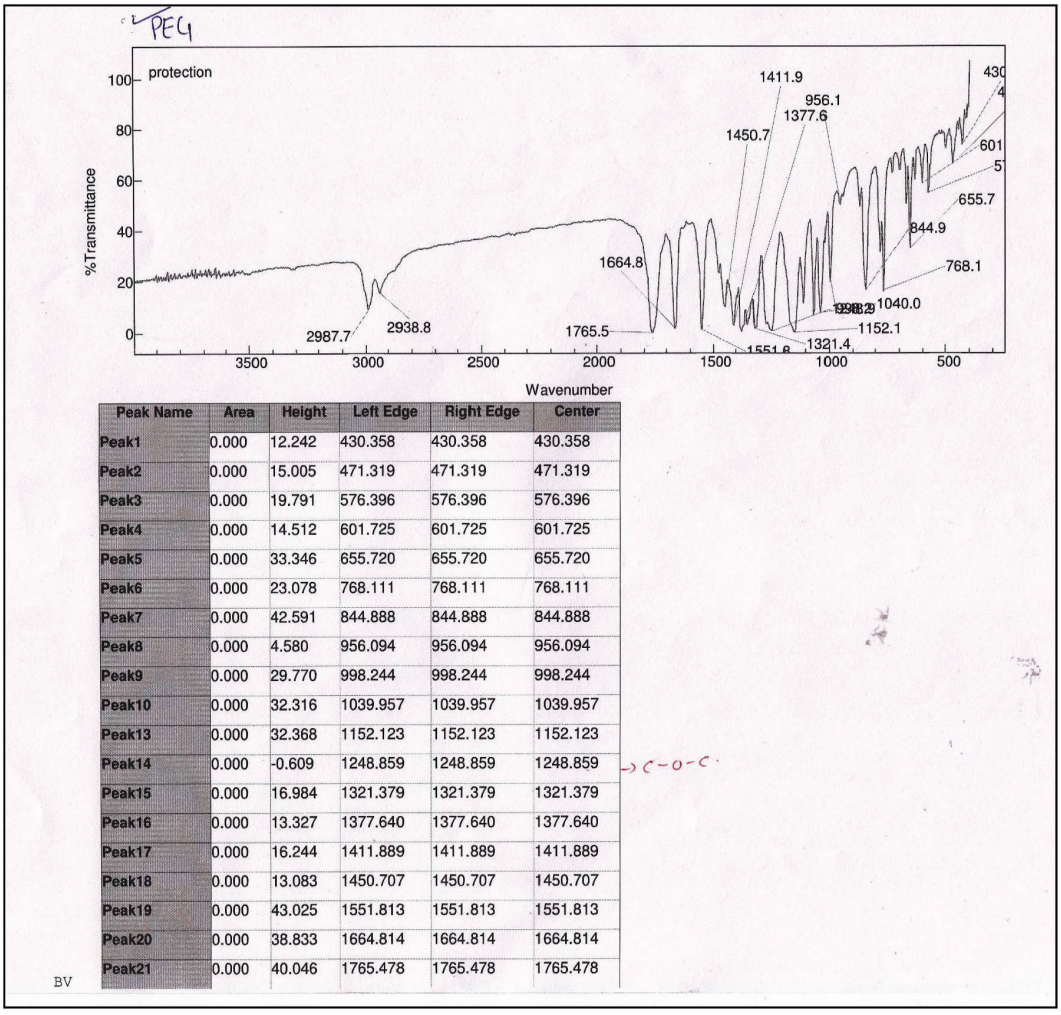
Supplementary Figure 4. ^{1}H NMR Spectra.



Supplementary Figure 5. ^{13}C NMR Spectra.

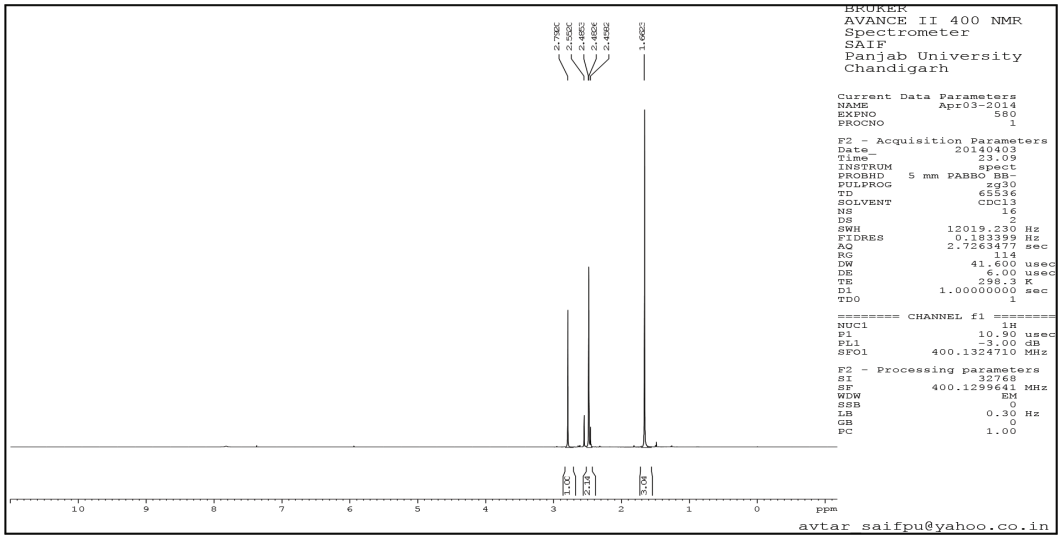


Supplementary Figure 6. *tert*-butyl-4-acetyl-3,5-dimethyl-*1H*-pyrazole-1-carboxylate (**4**).

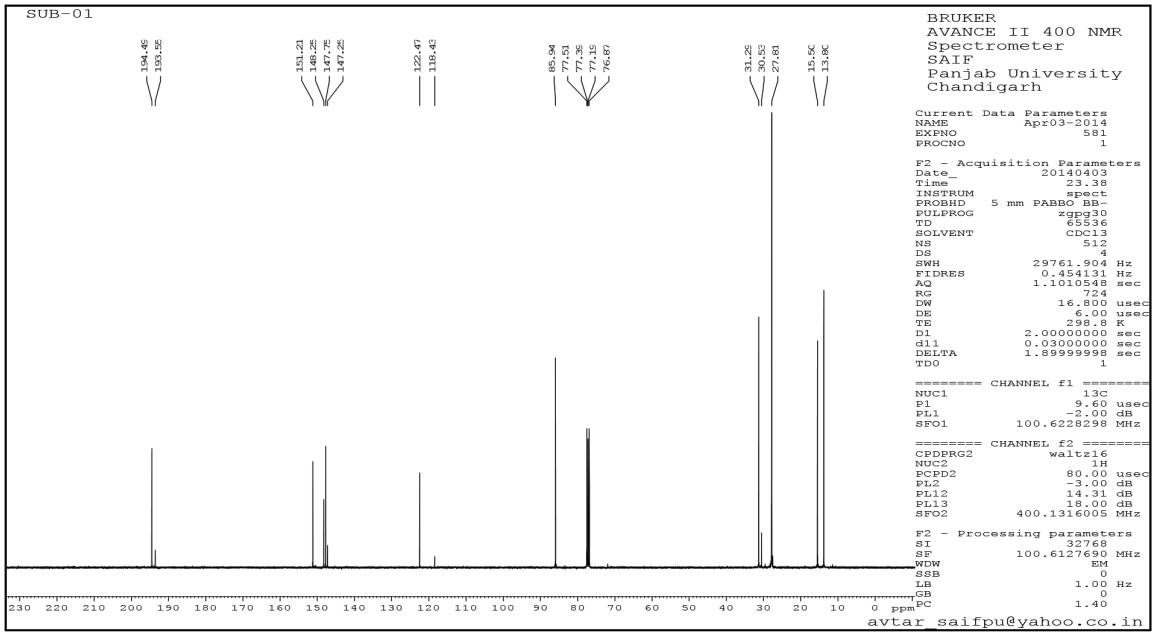


Peak Name	Area	Height	Left Edge	Right Edge	Center
Peak1	0.000	12.242	430.358	430.358	430.358
Peak2	0.000	15.005	471.319	471.319	471.319
Peak3	0.000	19.791	576.396	576.396	576.396
Peak4	0.000	14.512	601.725	601.725	601.725
Peak5	0.000	33.346	655.720	655.720	655.720
Peak6	0.000	23.078	768.111	768.111	768.111
Peak7	0.000	42.591	844.888	844.888	844.888
Peak8	0.000	4.580	956.094	956.094	956.094
Peak9	0.000	29.770	998.244	998.244	998.244
Peak10	0.000	32.316	1039.957	1039.957	1039.957
Peak13	0.000	32.368	1152.123	1152.123	1152.123
Peak14	0.000	-0.609	1248.859	1248.859	1248.859
Peak15	0.000	16.984	1321.379	1321.379	1321.379
Peak16	0.000	13.327	1377.640	1377.640	1377.640
Peak17	0.000	16.244	1411.889	1411.889	1411.889
Peak18	0.000	13.083	1450.707	1450.707	1450.707
Peak19	0.000	43.025	1551.813	1551.813	1551.813
Peak20	0.000	38.833	1664.814	1664.814	1664.814
Peak21	0.000	40.046	1765.478	1765.478	1765.478

Supplementary Figure 7. ^{1}H NMR.



Supplementary Figure 8. ^{13}C NMR.



Supplementary Figure 9. ^{1}H NMR.