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...
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 $\delta$ (ppm). IR spectra were measured with Fourier-transform infrared spectroscopy (FTIR)-9050SC (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)$_2$O (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$_2$SO$_4$ 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), (Boc)$_2$O (1 mmol) and PEG-400 (1 ml) was continuously stirred at room temperature for 2 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$_2$SO$_4$ 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-C**

In an RBF, the solution of substituted pyrazole (2) (1 mmol), (Boc)$_2$O (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$_2$SO$_4$. 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$_2$SO$_4$ and reduced under vacuum. The precipitate was purified with column chromatography (CH$_2$Cl$_2$/ 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 Meneil, 1994; Pisar 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 (Chanksawai, 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%, mp 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$_3$): $\delta$ 13.7 (s,1H,NH), 2.79 (s, 6H, CH$_3$), 2.55 (s, 3H,CH$_3$); $^{13}$C NMR: $\delta$ 148.0, 114.5, 199.8 (C), 11.0, 11.2,
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 (Scheme 1) (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), ¹H NMR, and ¹³C NMR analysis.

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.
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.

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CONFLICT OF INTEREST

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. ³H NMR Spectra.
Supplementary Figure 5. $^{13}$C NMR Spectra.

Supplementary Figure 6. tert-butyl-4-acetyl-3,5-dimethyl-1H-pyrazole-1-carboxylate (4).
Supplementary Figure 7. $^1$H NMR.

Supplementary Figure 8. $^{13}$C NMR.
Supplementary Figure 9. $^1$H NMR.