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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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**To cite this article:** Suman Punia, Vikas Verma, Devinder Kumar, Gurjaspreet Singh & Subash C. Sahoo (2020): Regioselective synthesis of 1,2,4-trisubstituted imidazole from a mechanistic and synthetic prospective, Synthetic Communications, DOI: 10.1080/00397911.2020.1712608

**To link to this article:** https://doi.org/10.1080/00397911.2020.1712608

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https://doi.org/10.1080/00397911.2020.1712608

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# Regioselective synthesis of 1,2,4-trisubstituted imidazole from a mechanistic and synthetic prospective

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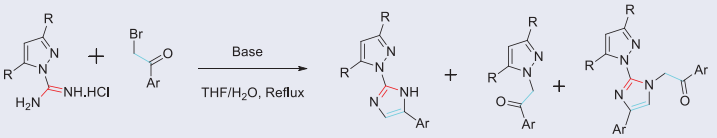
**ABSTRACT**

The highly substituted 1,2,4-trisubtituted imidazole was regioselectively synthesized *via* base mediated domino reaction of amidine scaffold with phenacyl bromide followed by *in situ* N-alkylation of imidazole. The reaction conditions were optimized in order to access three phenomenon (neutralization, condensation, and N-alkylation) in a single pot. A mechanism for the formation of N–H imidazole and its subsequent N-alkylation is depicted by isolation of reaction of intermediates. Electron donating group facilitate N-alkylation, whereas no N-alkylation was observed in the presence of electron withdrawing ($NO_2$) group. The synthesized compounds and reaction intermediate were characterized using NMR, FTIR, and HRMS. Exact orientation of various aromatic rings in regioselective N-alkylated product was confirmed using single crystal X-ray analysis.

**GRAPHICAL ABSTRACT**




**ARTICLE HISTORY**
Received 10 October 2019

**KEYWORDS**
Domino reaction; imidazole; pseudo-multicomponent; regioselectivity

## Introduction

Imidazole is a vital subunit of many natural products,[1] as well as synthetic bioactive compounds.[2] Many synthetic compounds, containing imidazole unit, showed excellent antifungal,[3] anticancer,[4] anti-inflammatory,[5] antioxidant,[6] antiepilestic,[7] and antibacterial activity.[8] In addition, inhibition of hNaV1.2 sodium channels[9] by 2, 4(5)-diarylimidazole and selective inhibition of COX-2[10] by 1,5-disubstituted imidazole has been reported. Pyrazole containing heterocyclic compounds represent one of the biological active class of compounds and possess a broad range of pharmaceutical activities.[11] Several drugs have been designed from pyrazole derivatives, e.g., rimonabant

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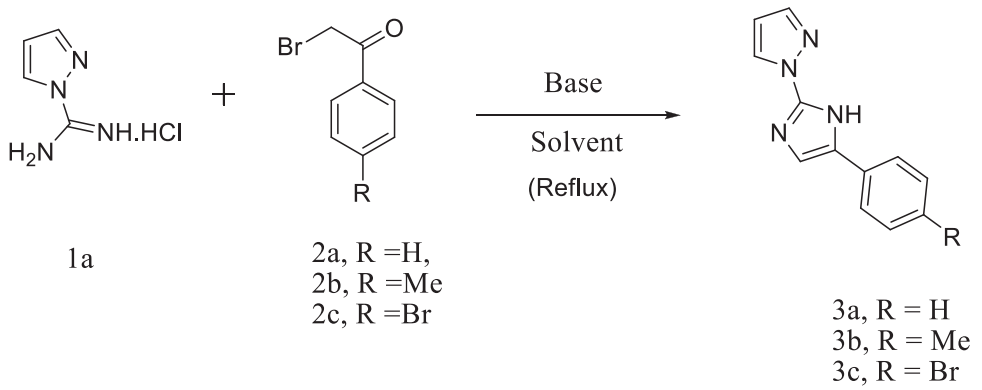
functions as a cannabinoid receptor and is utilized to treat obesity; sildenafil inhibits phosphodiesterase; celecoxib demonstrates anti-inflammatory effects and inhibits COX-2; fomepizole inhibits alcohol dehydrogenase.[12]

The development of new approaches for chemical transformation toward imidazole continues to attract attention in contemporary synthetic chemistry. A series of Cu, Fe, Ag catalyzed methods of imidazole derivatives has been developed recently by the group of Li,[13] Chen,[14] and Neuville.[15] Moreover, transition metal-catalyzed direct N–H functionalization provide a powerful tool for the synthesis of substituted imidazole. Metal-free multicomponent reactions for building the heterocyclic core are advantageous because of complicated purifying procedure to remove the metal residue in reactions. Wang and coworkers[16] reported an elegant method for imidazole synthesis by reaction of *in situ* generated diketone from bromoacetylene with amidine. The virtue of simple handling of amidine salt and its reactivity with different electrophiles[17–20] motivates to synthesize imidazole on amidine scaffold.

In light of the significance of pyrazole and imidazole in medicinal chemistry, the present study focuses on the regioselective synthesis of imidazole containing pyrazole derivatives *via* base mediated pseudo-multicomponent domino reaction of amidine scaffold with phenacyl bromide including mechanistic studies.

## Results and discussion

Amidines are more nucleophilic than their corresponding salts. Hence, 1H-pyrazole-1-carboximidamide hydrochloride (**1a**) was neutralized with different base to generate free amidine, and the resulted free amidine was reacted with equimolar amount of phenacyl bromide (**2a–2c**) under different reaction conditions (Scheme 1). Microwave irradiation of **1a**, **2a–2c** and diisoprppylethyamine (DIPEA) as base without solvent and with ethanol as solvent does not yield **3a–3c** (Entries 1 and 2, Table 1). Refluxing reactants **1**, **2a–2c** and DIPEA in ethanol also do not yield **3a–3c** (Entry 3). Further, when DIPEA was changed to $Et_3N$, the pyrazolylimidazoles **3a–3c** were formed but the yield was very low (Entry 4). Refluxing in another polar immiscible solvent system ($CHCl_3/H_2O$) with $Et_3N$ and $K_2CO_3$ also did not yield **3a–3c** (Entries 5 and 6, Table 1). Further refluxing




**Scheme 1.** Synthesis of compound 3.

**Table 1.** Optimization of reaction conditions.

| Entry | Compound | Solvent | Base | Base equivalent | Time (in h) | % Yield |
|---|---|---|---|---|---|---|
| 1 | **3a** | – | DIPEA (MW) | 20[a] | 0.50 | NR |
| | **3b** | | | | | |
| | **3c** | | | | | |
| 2 | **3a** | Ethanol | DIPEA (MW) | 20[a] | 0.83 | NR |
| | **3b** | | | | | |
| | **3c** | | | | | |
| 3 | **3a** | Ethanol | DIPEA | 20[a] | 24 | NR |
| | **3b** | | | | | |
| | **3c** | | | | | |
| 4 | **3a** | Ethanol | $Et_3N$ | 5.0[b] | 24 | 6 |
| | **3b** | | | | | 5 |
| | **3c** | | | | | 3 |
| 5 | **3a** | $CHCl_3/H_2O$ | $Et_3N$ | 2.0 | 72 | NR |
| | **3b** | | | | | |
| | **3c** | | | | | |
| 6 | **3a** | $CHCl_3/H_2O$ | $K_2CO_3$ | 2.0 | 72 | NR |
| | **3b** | | | | | |
| | **3c** | | | | | |
| 7 | **3a** | $THF/H_2O$ | $NaHCO_3$ | 2.0[b] | 36 | 16 |
| | **3b** | | | | | 8 |
| | **3c** | | | | | 7 |
| 8 | **3a** | $THF/H_2O$ | $K_2CO_3$ | 2.0[b] | 36 | 39 |
| | **3b** | | | | | 15 |
| | **3c** | | | | | 14 |

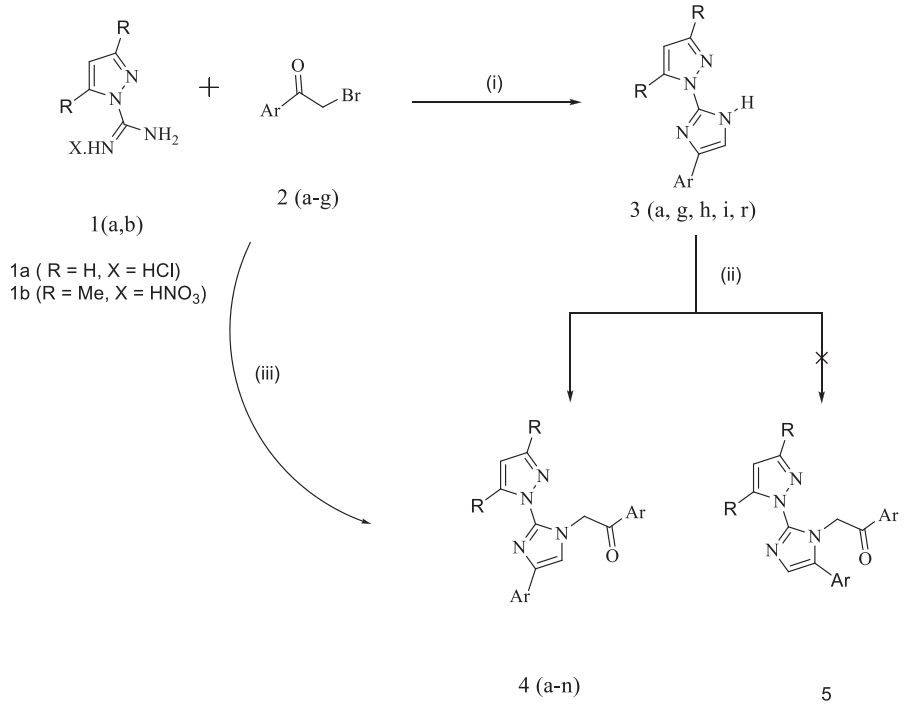
a: mmol; b: mol%; NR: no reaction.

of **1a** and **2a–2c** in miscible polar solvent system ($THF/H_2O$) with $NaHCO_3$ or $K_2CO_3$ as base yield **3** (Entries 7 and 8, Table 1). Hence, $THF/H_2O$ and $K_2CO_3$ are the optimized solvent system and base for Scheme 1.

However, the reaction of **1** with 1.2/2.5 equivalent of **2** in the presence of 2.5 equivalent of $K_2CO_3$ yields compound **3** and then regioselectively compound **4** instead of **5** (Scheme 2). When 1.2 equivalent of phenacyl bromide (**2a–2c**) is reacted with 1.0 equivalent of **1a**, N–H imidazole (**3a–3c**) is isolated, whereas 2.5 equivalent (one equivalent added after 36 h) of corresponding phenacyl bromide (**2a–2c**) furnished N-alkylated imidazole (**4a–4c**). Phenacyl bromides **2d–2f** give N-alkylated product predominantly (**4d–4f, 4k–4m**) by reacting with **1** whether it is taken 1.2 or 2.5 equivalent. N-alkylated product is not obtained with phenacyl bromide containing a strong electron withdrawing group (**2g**) even with 2.5 equivalent of it is used. Further with phenacyl bromide (**2a–2f**) N-alkylated product **4** is obtained instead of **5** (Scheme 2). Isolation of **4d** and **4k** even with 1.0 equivalent of 4-methoxyphenacyl bromide and **3g** and **3n** with 2.0 equivalent of **2g** establish that electronic factor is more important than solvation and steric hindrance of amidine.[21]

## Mechanism of reaction

A plausible mechanism for the formation of N–H imidazole and its subsequent N-alkylation is depicted in Scheme 3. The free amidine (**8**), generated from its salt, reacts as a binucleophile with phenacyl bromide (**2**) through SN2 approach to give initially monoalkylated intermediate (**9**) which on intramolecular cyclocondensation furnished 4-H imidazole (**10**) *via* path A. Subsequent dehydration to gain aromaticity affords imidazole




2a; Ar = phenyl
2b; Ar = 4-methylphenyl
2c; Ar = 4-bromophenyl
2d; Ar = 4-methoxyphenyl
2e; Ar = 4-chlorophenyl
2f; Ar = 4-flurophenyl
2g; Ar = 3-nitrophenyl

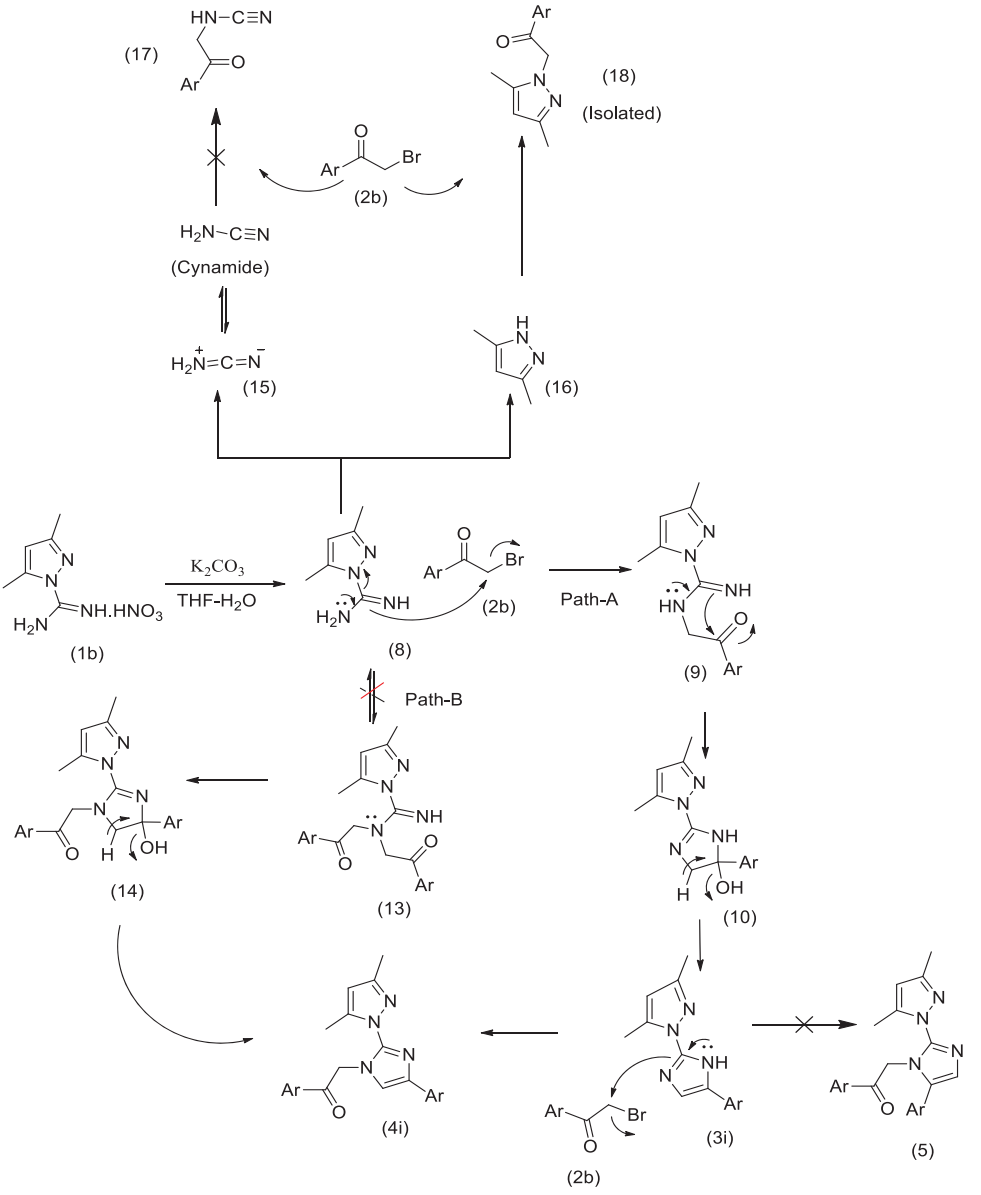
3a; Ar = phenyl; R = H
3b; Ar = 4-methylphenyl; R = H
3c; Ar = 4-bromophenyl; R = H
3d; Ar = 4-methoxyphenyl; R = H
3e; Ar = 4- chlorophenyl; R = H
3f; Ar = 4-flurophenyl; R = H
3g; Ar = 3-nitrophenyl; R = H
3h; Ar = phenyl; R = Me
3i; Ar = 4-methylphenyl; R = Me
3j; Ar = 4-bromophenyl; R = Me
3k; Ar = 4-methoxyphenyl; R = Me
3l; Ar = 4- chlorophenyl; R = Me
3m; Ar = 4-flurophenyl; R = Me
3n; Ar = 3-nitrophenyl; R = Me

4a; Ar = phenyl; R = H
4b; Ar = 4-methylphenyl; R = H
4c; Ar = 4-bromophenyl; R = H
4d; Ar = 4-methoxyphenyl; R = H
4e; Ar = 4- chlorophenyl; R = H
4f; Ar = 4-flurophenyl; R = H
4g; Ar = 3-nitrophenyl; R = H
4h; Ar = phenyl; R = Me
4i; Ar = 4-methylphenyl; R = Me
4j; Ar = 4-bromophenyl; R = Me
4k; Ar = 4-methoxyphenyl; R = Me
4l; Ar = 4- chlorophenyl; R = Me
4m; Ar = 4-flurophenyl; R = Me
4n; Ar = 3-nitrophenyl; R = Me

**Scheme 2.** Reaction Conditions: (i) amidine (1 equiv.), phenacyl bromide (1.2 equiv.), $K_2CO_3$ (2.5 equiv.), THF:$H_2O$ (5:1), refluxing. (ii) phenacyl bromide (1.2 equiv.) more added in same port after 36 h of step (i). (iii) amidine (1 equiv.), phenacyl bromide (2.5 equiv.), $K_2CO_3$ (2.5 equiv.), THF:$H_2O$ ((5:1), refluxing.

(**3i**) that is N-alkylated with phenacyl bromide *in situ* to afford 1,2,4-trisubstituted imidazole (**4**) in a regioselective manner instead of **5**. Isolation of 3,5-dimethyl-1-(5-(p-tolyl)-1H-imidazol-2-yl)-1H-pyrazole (**3i**) when 2-bromo-1-(p-tolyl)ethanone (**2b**) was used as a phenacyl bromide support that reaction proceed *via* path A rather than literature[18] assumed path B involving the intermediacy of **13** and **14**, albeit isolated N-alkylated product (**4i**) through both the pathways can be obtained. However, path B cannot be completely ruled out as reaction was not spectroscopically monitored.

Scaffold **8**, generated by neutralization of corresponding amidine salt, is labile to decompose into **15** and **16** (Scheme 3) which then may compete for phenacyl bromide.




**Scheme 3.** Mechanism of the reaction.

To study this possibility, 3,5-dimethyl-1H-pyrazole-1-carboximidamide nitrate was treated with two equivalent of 2-bromo-1-(4-tolyl)ethanone in refluxing THF/$H_2O$ solvent system. The workup of the reaction mixture afforded the crude product that showed the appearance of two weak bands at 2351.23 $cm^{-1}$ and 2326.15 $cm^{-1}$ in infrared spectrum besides other bands thereby suggesting the possibility decomposition of amidine scaffold into cynamide and 3,5-dimethyl-1H-pyrazole as shown in Scheme 3. The crude product was separated into different components using column chromatography (silica mesh 60–120) using ethylacetate/hexane (10:90 v/v) to elute the imidazole product (**3i**) followed using ethylacetate/hexane (30:70 v/v) to elute N-alkylated imidazole (**4i**) and

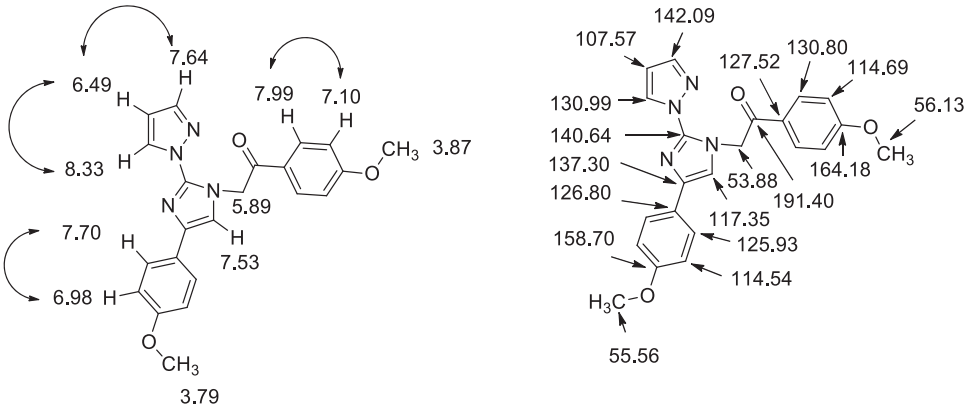



**Figure 1.** $^{1}$H NMR and $^{13}$C NMR of compound **4d** and COSY correlation.

N-alkylated pyrazole (**18**) products. The structure of isolated components was confirmed using spectroscopic analysis, including IR, $^{1}$H and $^{13}$C NMR, and mass spectral analysis. Isolation of n-alkylated pyrazole compound (**18**) confirmed the decomposition and account for low yield of n-alkylated imidazole products.

Compound **1a** was reacted with p-methoxyphenacyl bromide (**2d**) to give regioselectively N-alkylated product **4d** instead of **5** and N–H imidazole product **3d**. A detailed study of 1D and 2D NMR, HRMS, and FTIR spectra of purified product, indicated that 1-(4-methoxyphenyl)-2-(4-(4-methoxyphenyl)-2-(1H-pyrazol-1-yl)-1H-imidazol-1-yl)ethanone (**4d**) compound has been formed. Regioselectivity of N-alkylated product **4b** has been confirmed using single crystal X-ray analysis.[22]

$^{1}$H NMR spectra of the representative molecule **4d** (Fig. 1) indicate the presence of 20 protons. Protons with coupling constant 1.2–2.4 Hz shows the presence of pyrazole ring in the molecule. Singlet at $\delta$ 7.53 with integration of one proton might be due to imidazole ring proton as another singlet due to methylene protons appears with the integration of two proton ($\delta$ = 5.89). In 2D-NMR, e.g., COSY (Correlation spectroscopy): $\delta$ 7.53 does not correlate with any other proton showing that it is the proton of imidazole ring and the signal at $\delta$ 6.49 (t, $J$ = 2.0, 2.4 Hz) correlate with $\boldsymbol{\delta}$ 8.33 and 7.64 justifying that it is due $C_4$–H of pyrazole ring. Consequently, the protons at $\boldsymbol{\delta}$ 6.49, 8.33, and 7.64 are the protons of pyrazole ring. Mutual correlation of signal at $\boldsymbol{\delta}$ 7.70 with signal at 6.98 and $\boldsymbol{\delta}$ 7.99 with 7.10 along with $J$ value in phenyl ring range support our assignment of these signals to the phenyl ring. Due to anisotropy and electron withdrawing ability of carbonyl group, protons of N-alkylated benzene ring appears at higher chemical shift.

$^{13}$C NMR of **4d** (Fig. 1) indicated the presence of 18 signals. DEPT135 $^{13}$C NMR spectrum (Supplementary information) clearly show the presence of 8 tertiary, 2 primary and 1 secondary carbon thereby suggesting that the remaining 7 signals were due to quaternary carbons. In order to establish the assignment of each carbon HSQC (Heteronuclear Single-Quantum Coherence Spectroscopy) and HMBC (Heteronuclear Multiple Bond Correlation Spectroscopy), 2D NMR (Supplementary information) was scanned. HSQC revealed the assignment of primary, secondary and tertiary carbons at $\delta$ 142.09, 130.99, 130.80, 125.93, 117.35, 114.69, 114.54, 107.57, 56.13, 55.56, and 53.88.

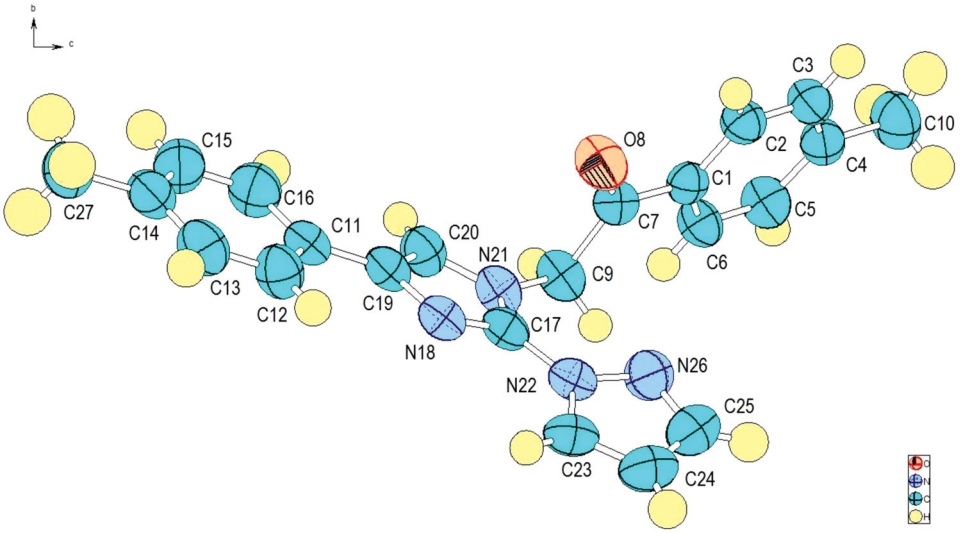



**Figure 2.** ORTEP drawing compound **4b**.

These were assigned on the basis of key correlation found in HSQC spectra as follow; $\delta$ 8.33 → 130.99, 7.99 → 130.80, 7.70 → 125.93, 7.64 → 142.09, 7.53→117.35, 7.10 → 114.69, 6.98 → 114.54, 6.49 → 107.57, 5.89 → 53.88, 3.87 → 56.13, and 3.79 → 55.56. HMBC experiment established the assignment of quaternary carbon signals through two bond correlations at 191.40, 164.18, 158.70, 140.64, 137.30, 127.52, and 126.80. The above assignment was confirmed through the correlation of signals at $\delta$ 8.33 → 142.09 and 107.57; 7.99 → 191.40, 164.18 and 130.80; 7.70 → 158.70, 125.93 and 137.30; 7.53 → 140.64 and 137.30; 7.10 → 164.18, 127.52 and 114.69; 6.98 → 158.70, 126.80 and 114.54; 5.89 → 191.40, 117.35 and 140.64; 3.86 → 164.18 and 3.78 → 158.70.

Recrystallization of the 2-(2-(1H-pyrazol-1-yl)-4-(p-tolyl)-1H-imidazol-1-yl)-1-(p-tolyl) ethanone (**4b**) from methanol afforded crystal of suitable size and quality for single-crystal X-ray diffraction analysis. The X-ray crystallography of **4b** (Fig. 2) confirmed the formation of **4** rather than **5**. Bond angles $C_{20}C_{19}C_{11}$ = 129.9(3), $N_{21}C_{17}N_{22}$ = 124.1(2) and $C_{17}N_{21}C_9$ = 129.7(2)/° are typical of **4b**. The selected crystal structure data are presented in Supplementary information.

## Conclusion

Imidazole hybrids were efficiently synthesized *via* pseudo-multicomponent reaction in one pot utilizing amidine and phenacyl bromide followed by *in situ* N-alkylation of imidazole. Out of two possible regioisomers **4** and **5**, product **4** is obtained exclusively whose structure has been confirmed by 2 D NMR spectroscopy and single crystal X-ray analysis. Reaction proceed *via* monoalkylation of *in situ* generated free amidine and then cyclization leading to formation of 1H-imidazole. Electronic influence of the substituent, present on imidazole ring accomplish that N-alkylation is followed by cyclization facilitating a two-step process in single pot.

## Experimental section

### *Procedure for synthesis of compound 2-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)-4-(4-methoxyphenyl)-1H-imidazol-1-yl)-1-(4-methoxy pheyl)ethanone (4k)*

A two neck 100 ml round bottom flask, equipped with reflux condenser and pressure equalizing funnel is charged with 3,5-dimethyl-1-(5-phenyl-1H-imidazol-2-yl)-1H-pyrazole (1 mmol) in 10 ml of THF:$H_2O$ (5:1) solvent. Then, slow and portion wise addition of potassium carbonate (2.5 mmol) with vigorous refluxing is carried out. A solution of 2-bromo-1-(p-tolyl)ethan-1-one (2.2 mmol) in THF is constantly added drop wise *via* pressure equalizing funnel over a period of 20 min while refluxing. The progress of reaction is monitored using thin layer chromatography (TLC). After completion of the reaction, THF is removed under reduced pressure using rotatory evaporator. Crude product is filtered and transferred to a 100 ml round bottom flask and stirred in 50 ml of hexane for one hour. Isolated product is purified by column chromatography (60–120 mesh silica, hexane/ethylacetate 90/10).

Buff colored solid. *mp*: 210–212 °C. $^1$H NMR (400 MHz, DMSO) $\delta = 7.93$ (d, $J = 8.8$ Hz, 2 H, imidazole $N_1$-aryl $C_2$-**H,** $C_6$–**H**), 7.68 (d, $J = 8.8$ Hz, 2H, imidazole 4-methoxyphenyl $C_2$–**H,** $C_6$–**H**), 7.56 (s, 1H, imidazole **H**), 7.07 (d, $J = 8.8$ Hz, 2H, imidazole $N_1$-aryl $C_3$–**H,** $C_5$–**H**), 6.97 (d, $J = 8.4$ Hz, 1H, imidazole 4-methoxyphenyl **$C_3$–H, $C_5$–H**), 6.00 (s, 1H, pyrazole $C_4$–**H**), 5.60 (s, 2H, C**$H_2$**), 3.86 (s, 3H, OC**$H_3$**), 3.78 (s, 3H, OC**$H_3$**), 2.34 (s, 3H, C**$H_3$**), 1.97 (s, 3H, C**$H_3$**). $^{13}$C NMR (100 MHz, DMSO) $\delta = 191.40$, 164.20, 158.83, 149.70, 142.70, 140.08, 137.65, 130.68, 127.83, 127.22, 125.99, 116.94, 114.66, 106.98, 79.55, 56.11, 55.67, 52.70, 13.44, 11.87. IR (KBr, $\nu_{max}/cm^{-1}$): 3001.24, 2939.52, 2853.36, 1685.79, 1598.99, 1550.77, 1242.16. HRMS: *m/z* Cacld. $(M + H)^+$ for $C_{24}H_{26}N_4O_3$: 417.1921 found 417.1900.

Additional Supporting information may be found online in the supporting information tab for this article.

## Acknowledgments

Authors are highly thankful to DST-PURSE (SR/PURSE Phase 2/40(G)), New Delhi and Dr. APJ Abdul Kalam CIL, GJUS&T, Hisar.

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[22] CCDC 1917074 (4b) contains the supplementary crystallographic data for the paper. Crysatallographic details for this compound are included in supplementary information.