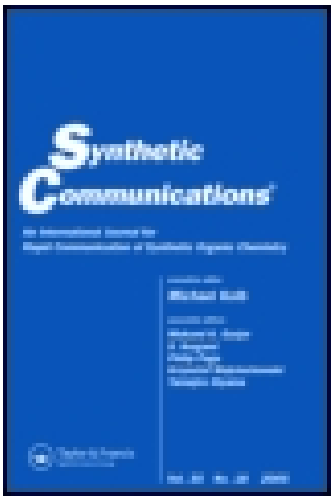



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# Condensation of ortho-Phenylenediamines and Phenylhydrazines with Ethyl 4-Chloro-3-oxobutanoate: A Facile Approach for the Synthesis of Substituted 1H-Benzimidazoles, Pyrazolones, and Pyrazoles

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# CONDENSATION OF *ORTHO*-PHENYLENEDIAMINES AND PHENYLHYDRAZINES WITH ETHYL 4-CHLORO-3-OXOBUTANOATE: A FACILE APPROACH FOR THE SYNTHESIS OF SUBSTITUTED 1*H*-BENZIMIDAZOLES, PYRAZOLONES, AND PYRAZOLES

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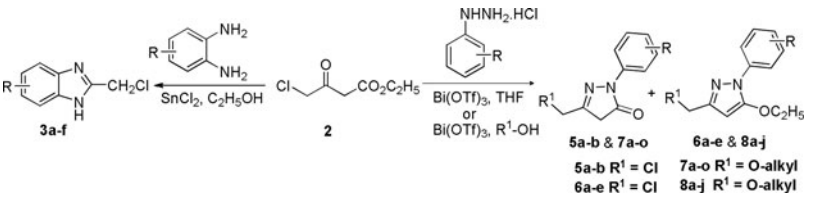
*Natural Products Chemistry Division, CSIR Indian Institute of Chemical Technology, Hyderabad, India*

## GRAPHICAL ABSTRACT




**Abstract** *Substituted 1H-benzimidazoles, pyrazolones, and pyrazoles have been synthesized by the condensation of ortho-phenylenediamines and phenylhydrazines, respectively, with ethyl 4-chloro-3-oxobutanoate in good yields. The present approach is novel, straightforward, and being reported for the first time with ethyl 4-chloro-3-oxobutanoate.*

**Keywords** Ethyl 4-chloro-3-oxobutanoate; Lewis acids; pyrazoles; pyrazolones; substituted 1H-benzimidazoles

## INTRODUCTION

Benzimidazoles, pyrazolones, and pyrazoles are important heterocyclic compounds and drug substances in the pharmaceutical industry because of their potential biological activities.[1–6] The benzimidazole ring is an important pharmacophore in modern drug discovery and synthesis of benzimidazoles has led to potent drug molecules such as omeprazole, lansoprazole, rabeprazole, and pantoprazole.[7] Phenazone, propyphenazone, ampyrone, edaravone, and metamizole sodium are useful pyrazolone drugs, whereas celecoxib and acomplia are potential pyrazole drugs.[1–6] The high-profile applications of benzimidazoles, pyrazolones, and pyrazoles, and in continuation of our previous research, prompted us to conduct further studies on these

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heterocyclic compounds.[8–11] Previously Chen et al. and Reddy Vaddula et al. reported pyrazolones by using ethyl 3-oxobutanoates and phenyl hydrazine.[12,13]

Our studies focused on feasible reactions of carbonyl compounds/salicylaldehydes with 3-oxobutanoates bearing chloro/trifluoro substituents. In this context, we studied the reactivity of salicylaldehydes with ethyl 4-chloro-3-oxobutanoate to provide 2*H*-chromenes,[14] and these derivatives were successfully converted to useful heterocyclic compounds.[15–17] We also studied the reactivity of various carbonyl compounds with ethyl 4,4,4-trifluoro-3-oxobutanoate to provide a series of (*E*)-α,β-unsaturated esters and ketones.[18,19] The present article describes a systematic study for the preparation of 1*H*-benzimidazoles, pyrazolones, and pyrazoles by the condensation of *ortho*-phenylenediamines and phenylhydrazines with ethyl 4-chloro-3-oxobutanoate.

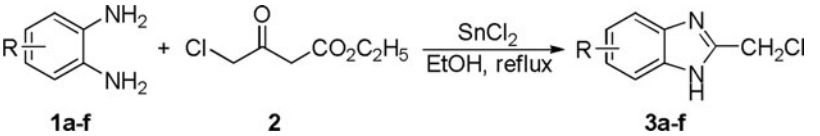
## RESULTS AND DISCUSSION

In a model reaction, ethyl 4-chloro-3-oxobutanoate **2** (1 mmol) was added to a stirred solution of *ortho*-phenylenediamine **1a** (1 mmol) in MeCN (2 mL) at room temperature (38 h). This furnished a pale yellow product (40% yield; Scheme 1) that was identified as 2-(chloromethyl)-1*H*-benzo[*d*]imidazole **3a** based on spectral data. However, ethyl 2-(quinoxalin-2-yl)acetate was obtained in a previous study with *ortho*-phenylenediamine and ethyl 4-chloro-3-oxobutanoate.[20,21] The present reaction has been investigated with various solvents and catalysts, and the results are summarized in Table 1 (entries 1–8). The compound **3a** was obtained in 68% yield with EtOH under reflux conditions (entry 6). To improve the yield of **3a**, the reaction was carried out with various catalysts such as AcOH (entry 9), *p*-TsOH (entry 10), and Lewis acids (entries 11–18). The yield of **3a** was improved to 82% in the presence of $SnCl_2$ in EtOH under reflux conditions.[22]

To evaluate the scope of this methodology, substituted *ortho*-phenylenediamines were reacted with **2** having electron-withdrawing and electron-donating substituents, such as nitro (entry 2), chloro (entry 3), benzoyl (entry 4), and methyl (entries 5 and 6), to give a series of 2-(chloromethyl)-1*H*-benzo[*d*]imidazoles **3b-f**[22] in good yields (Table 2). Electron-withdrawing groups afforded better yields than electron-donating groups.

A plausible mechanism is depicted in Scheme 2. Condensation of **1** with **2** provides **A** (Schiff base) and subsequent intramolecular nucleophilic addition to the imine C-atom provides ethyl 2-(2-(chloromethyl)-2,3-dihydro-1*H*-benzoimidazolyl) acetate **B**. Finally, **B** provides **3** via the elimination of AcOEt.

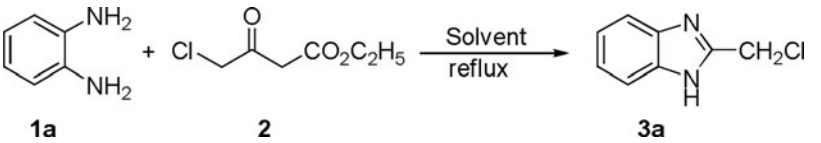
Having succeeded in the preparation of 2-chloromethyl-1*H*-benzimidazoles, next we have studied the reaction of phenylhydrazines **4a–e** with ethyl 4-chloro-3-oxobutanoate **2** (Scheme 3). In a model reaction, **2** (1 mmol) was added to a stirred solution of phenylhydrazine hydrochloride **4a** (1 mmol) in THF (2 mL) at room temperature. This reaction furnished two compounds, i.e., as 3-(chloromethyl)-1-phenyl-1*H*-pyrazol-5




**1a-f** **2** **3a-f**

**Scheme 1.** Preparation of substituted 2-chloromethyl 1*H*-benzimidazoles.

**Table 1.** Synthesis of 2-(chloromethyl)-1*H*-benzo[*d*]imidazole **3a**[a]



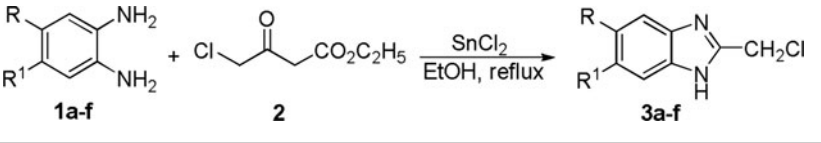

**1a** **2** **3a**

| Entry | Catalyst | Solvent | Reaction time (h) | Yield[d] (%) **3** |
|---|---|---|---|---|
| 1 | – | MeCN[b] | 38 | 40 |
| 2 | – | MeCN[c] | 20 | 40 |
| 3 | – | MeOH[b] | 18 | 48 |
| 4 | – | MeOH[c] | 12 | 62 |
| 5 | – | EtOH[b] | 32 | 56 |
| 6 | – | EtOH[c] | 12 | 68 |
| 7 | – | THF[c] | 24 | 52 |
| 8 | – | $CH_2Cl_2$[c] | 18 | 63 |
| 9 | AcOH | EtOH[c] | 10 | 70 |
| 10 | *p*-TsOH | EtOH[c] | 12 | 72 |
| 11 | $AlCl_3$ | EtOH[c] | 8 | 65 |
| 12 | CuI | EtOH[c] | 8 | 70 |
| 13 | $CuCl_2$ | EtOH[c] | 10 | 65 |
| 14 | $Cu(OAc)_2$ | EtOH[c] | 9 | 60 |
| 15 | $SnCl_2$ | EtOH[c] | 6 | 82 |
| 16 | $La(OTf)_3$ | EtOH[c] | 10 | 66 |
| 17 | $Sc(OTf)_3$ | EtOH[c] | 8 | 69 |
| 18 | $Bi(OTf)_3$ | EtOH [c] | 8 | 72 |

[a]Conditions: *Ortho*-phenylenediamine (1 mmol), ethyl 4-chloro-3-oxobutanoate (1 mmol), catalyst (0.1 mmol).
[b]Rt.
[c]Reflux.
[d]Yields of isolated products.

(4*H*)-one (**5a,** 40%, Table 3, entry 5) and 3-(chloromethyl)-5-ethoxy-1-phenyl-1*H*-pyrazole (**6a**, 18%). These compounds were separated by column chromatography and characterized by spectral data.

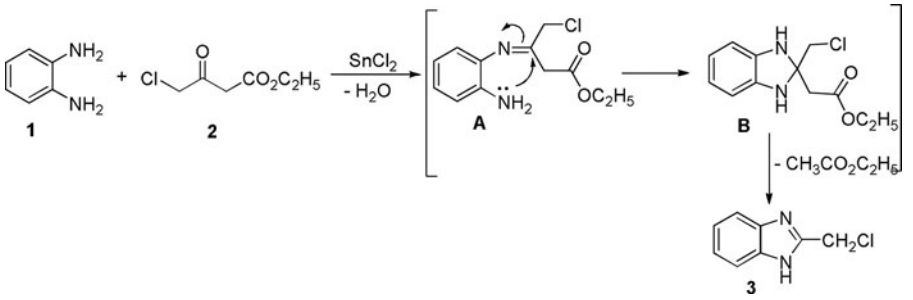
**Table 2.** Synthesis of 2-(chloromethyl)-1*H*-benzo[*d*]imidazoles **3a–f**



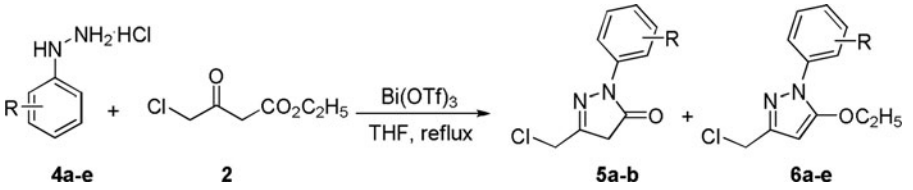

**1a-f** **2** **3a-f**

| Entry | Reactant **1** | R | $R^1$ | Reaction time (h) | Product **3** | Yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | H | H | 6 | **3a** | 82 |
| 2 | **1b** | $NO_2$ | H | 5 | **3b** | 75 |
| 3 | **1c** | Cl | H | 6 | **3c** | 72 |
| 4 | **1d** | COPh | H | 8 | **3d** | 60 |
| 5 | **1e** | $CH_3$ | H | 6 | **3e** | 65 |
| 6 | **1f** | $CH_3$ | $CH_3$ | 8 | **3f** | 62 |

[a]Yields of isolated products.

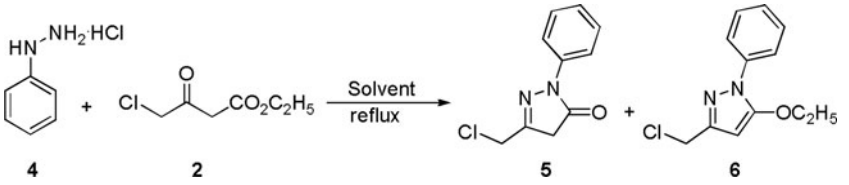


**Scheme 2.** Plausible mechanism.



**Scheme 3.** Preparation of pyrazolones **5a,b** and pyrazoles **6a–e**.

**Table 3.** Synthesis of 1*H*-pyrazolone **5** and pyrazole **6**[a]



| Entry | Catalyst | Solvent | Reaction time (h) | Yield[c] (%) **5** | Yield[c] (%) **6** |
|---|---|---|---|---|---|
| 1 | — | $CH_2Cl_2$[b] | 24 | — | — |
| 2 | — | $CH_2Cl_2$ | 24 | — | — |
| 3 | — | Toluene | 48 | — | — |
| 4 | — | MeCN | 14 | 30 | 15 |
| 5 | — | THF | 18 | 40 | 18 |
| 6 | AcOH | THF | 16 | 42 | 15 |
| 7 | *p*-TsOH | THF | 18 | 35 | 14 |
| 8 | $FeCl_3$ | THF | 20 | 28 | 10 |
| 9 | $AlCl_3$ | THF | 24 | 32 | 13 |
| 10 | $Cu(OAc)_2$ | THF | 20 | 30 | 14 |
| 11 | $CuCl_2$ | THF | 18 | 20 | 08 |
| 12 | $SnCl_2$ | THF | 20 | 25 | 11 |
| 13 | $La(OTf)_3$ | THF | 18 | 46 | 14 |
| 14 | $Sc(OTf)_3$ | THF | 18 | 50 | 11 |
| 15 | $Bi(OTf)_3$ | THF | 12 | 62 | 05 |
| 16 | $Bi(OTf)_3$ | MeCN | 12 | 56 | 08 |

[a] Conditions: Phenylhydrazine hydrochloride (1 mmol), ethyl 4-chloro-3-oxobutanoate (1 mmol), catalyst (0.1 mmol), under reflux.

[b] Rt.

[c] Yields of isolated products.

To study the product selectivity, various catalysts and solvents were investigated and summarized in Table 3. Tetrahydrofuran (THF) solvent provided pyrazolone **5a** in 62% yield when **4a** (1 mmol) was reacted with **2** (1 mmol) in the presence of $Bi(OTf)_3$(0.1 mmol) under reflux conditions (entry 15), and hence THF was chosen as the solvent for further reactions. The catalysts such as protic acid (entry 6), *p*-TsOH (entry 7), and Lewis acids (entries 8–16) were examined. In all the reactions, pyrazolone **5a** and pyrazole **6a** have been obtained but in poor yields.

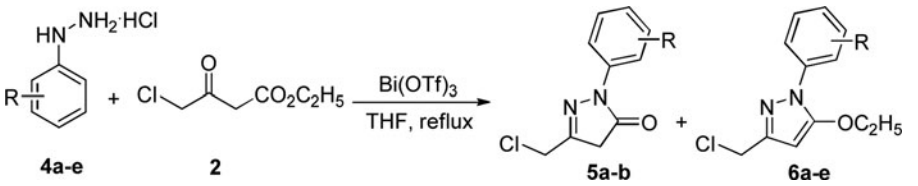
To evaluate the efficiency of this methodology, substituted phenylhydrazine hydrochlorides having electron-withdrawing and electron-donating substituents **4a–e** were reacted with **2** to provide corresponding pyrazolones **5a,b** and pyrazoles **6a–e** (Table 4, entries 2–5).

A plausible mechanism is depicted in Scheme 4. Condensation of **4** with **2** provides **A** (Schiff base). Then, the nucleophilic addition of amine to the ester C=O group provides 3-(chloromethyl)-5-ethoxy-1-phenyl-4,5-dihydro-1*H*-pyrazolol **B**. Finally, elimination of EtOH leads to pyrazolone **5** and the elimination of water provides pyrazole **6**.

Further, the condensation reaction has been carried out with **4a** (1 mmol) and **2** (1 mmol) in the presence of $Bi(OTf)_3$(0.1 mmol) in MeOH under reflux conditions (Scheme 5). This reaction furnished two pale yellow products identified as 3-(methoxymethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one **7a** (52% yield, Table 5, entry 1) and 5-ethoxy-3-(methoxymethyl)-1-phenyl-1*H*-pyrazole **8a** (15%).

This reaction provided an interesting result that the nucleophilic substitution has been occurred in situ. The reaction prompted us to study in detail with various alcoholic solvents and the results are summarized in Table 5. Under similar conditions, the reaction of **4a** with **2** in EtOH provided ethoxy 1*H*-pyrazolone **7b** and pyrazole **8b** (entry 2). However, isopropyl alcohol, isobutanol, and *n*-butanol provided selectively corresponding 1*H*-pyrazolones **7c-e** (Table 5, entries 3–5). To evaluate the efficiency of this methodology, phenylhydrazine hydrochlorides having electron-withdrawing and electron-donating substituents **4b–g** were reacted with **2** in

**Table 4.** Synthesis of 1*H*-pyrazolones **5a,b** and pyrazoles **6a–e**[a]

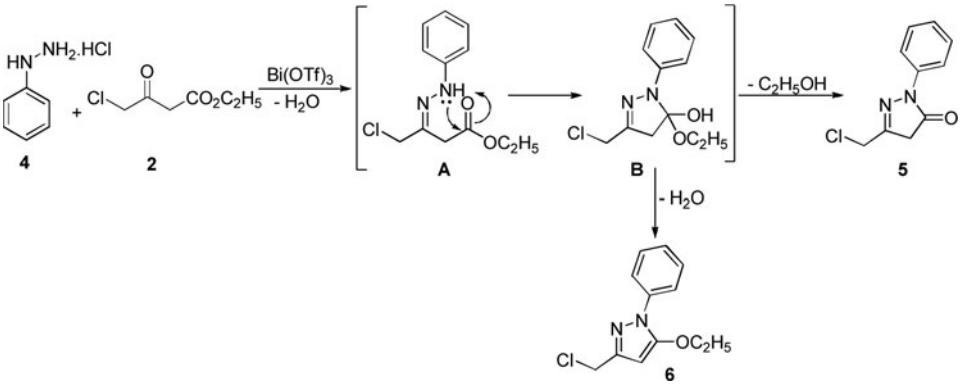



**4a-e** **2** **5a-b** **6a-e**

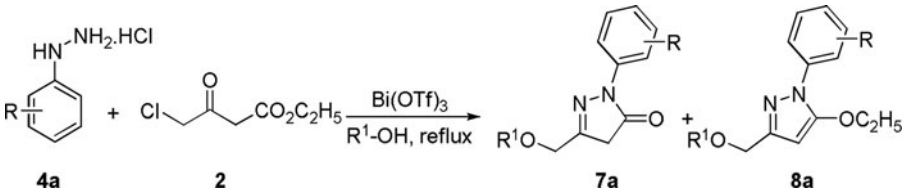
| Entry | Reactant **4** | R | Reaction time (h) | Product **5** | Yield[b] (%) | Product **6** | Yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | H | 12 | **5a** | 62 | **6a** | 05 |
| 2 | **4b** | *m*-$NO_2$ | 18 | **5b** | 52 | **6b** | 10 |
| 3 | **4c** | *p*-F | 20 | — | — | **6c** | 18 |
| 4 | **4d** | *p*-$CH_3$ | 24 | — | — | **6d** | 20 |
| 5 | **4e** | *p*-$NO_2$ | 32 | — | — | **6e** | 22 |

[a]Conditions: Phenylhydrazine hydrochloride (1 mmol), ethyl 4-chloro-3-oxobutanoate (1 mmol), $Bi(OTf)_3$ (0.1 mmol), under reflux.

[b]Yields of isolated products.

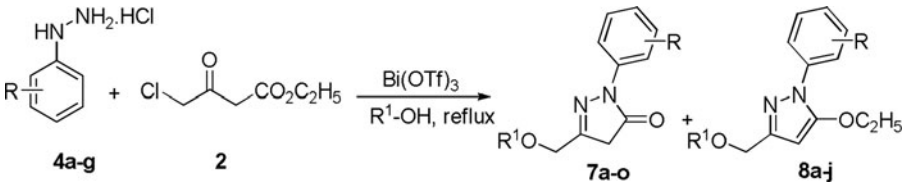



**Scheme 4.** Plausible mechanism for pyrazolones and pyrazoles.




**Scheme 5.** Preparation of alkoxymethyl 1*H*-pyrazolone **7a** and pyrazole **8a**.

**Table 5.** Synthesis of alkoxymethyl 1*H*-pyrazolones **7a–o** and pyrazoles **8a–j**[a]

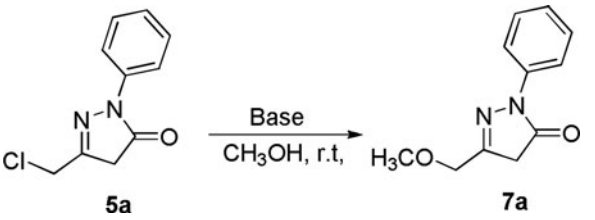



| Entry | Reactant **4** | R | $R^1$ | Time (h) | Product **7** | Yield[b] (%) | Product **8** | Yield[b] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **4a** | H | $CH_3$ | 16 | **7a** | 52 | **8a** | 15 |
| 2 | **4a** | H | $C_2H_5$ | 20 | **7b** | 45 | **8b** | 18 |
| 3 | **4a** | H | $(CH_3)_2CH$ | 18 | **7c** | 39 | — | — |
| 4 | **4a** | H | $(CH_3)_2CHCH_2$ | 20 | **7d** | 36 | — | — |
| 5 | **4a** | H | *n*-$C_4H_9$ | 20 | **7e** | 35 | — | — |
| 6 | **4c** | *p*-F | $CH_3$ | 16 | **7f** | 56 | **8c** | 14 |
| 7 | **4e** | *p*-Br | $CH_3$ | 20 | **7g** | 54 | **8d** | 18 |
| 8 | **4f** | *p*-$OCH_3$ | $CH_3$ | 16 | **7h** | 50 | — | — |
| 9 | **4d** | *p*-$CH_3$ | $CH_3$ | 18 | **7i** | 51 | **8e** | 12 |
| 10 | **4g** | *m*-Cl | $CH_3$ | 18 | **7j** | 55 | **8f** | 15 |
| 11 | **4b** | *m*-$NO_2$ | $CH_3$ | 14 | **7k** | 58 | **8g** | 10 |
| 12 | **4d** | *p*-$CH_3$ | $C_2H_5$ | 20 | **7l** | 45 | **8h** | 15 |
| 13 | **4g** | *m*-Cl | $C_2H_5$ | 18 | **7m** | 39 | **8i** | 16 |
| 14 | **4b** | *m*-$NO_2$ | $C_2H_5$ | 20 | **7n** | 51 | **8j** | 11 |
| 15 | **4g** | *m*-Cl | $(CH_3)_2CH$ | 22 | **7o** | 45 | — | — |

[a]Conditions: Phenylhydrazine hydrochloride (1 mmol), ethyl 4-chloro-3-oxobutanoate (1 mmol), Bi $(OTf)_3$ (0.1 mmol), under reflux.

[b]Yields of isolated products.

**Table 6.** Preparation of methoxymethyl-1*H*-pyrazolone[a]




| Entry | Base | Reaction time (h) | Yield[b] (%) **7a** |
|---|---|---|---|
| 1 | NaOH | 3 | 91 |
| 2 | KOH | 3 | 90 |
| 3 | Piperidine | 5 | 82 |
| 4 | Triethylamine | 6 | 75 |

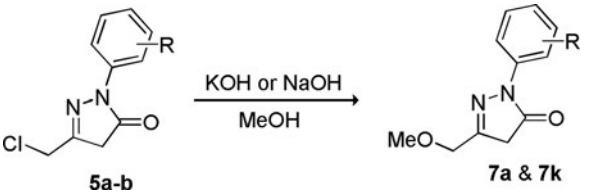
[a]Conditions: 3-(Chloromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (1 mmol), base (1 mmol), rt.
[b]Yields of isolated products.



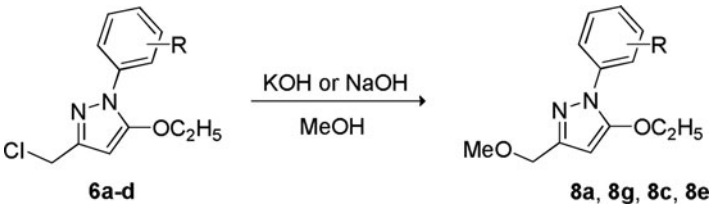
the presence of $Bi(OTf)_3$ in MeOH and EtOH (Table 5, entries 6–14) to give a series of corresponding 1*H*-pyrazolones **7f–o** and pyrazoles **8c, 8d**, and **8e–j**.

Further, to examine the nucleophilic substitution reaction on pyrazolones **5** and pyrazoles **6**, the individual reaction of **5a** and **6a** have been carried out with MeOH at room temperature (48 h) without catalyst. This provided corresponding 1*H*-pyrazolone **7a** and pyrazole **8a** in poor yields. Next, the nucleophilic substitution reaction of **5a** has been studied with various bases such as NaOH, KOH, piperidine, and $Et_3N$ in MeOH at room temperature (Table 6). This provided 1*H*-pyrazolone **7a** in 91% yield with NaOH and 90% yield with KOH than did other bases.

Further, the nucleophilic substitution reaction of chloromethylpyrazolones **5a, b** and pyrazoles **6a–d** have been carried out with NaOH and KOH in MeOH at room temperature (Schemes 6 and 7) and provided corresponding alkoxy pyrazolones **7a**




**Scheme 6.** Preparation of alkoxypyrazolones.




**Scheme 7.** Preparation of alkoxypyrazoles.

and **7k** and pyrazoles **8a, 8 g, 8c**, and **8e** in good yields. The compounds **7a, 7k, 8a, 8 g, 8c**, and **8e** were well characterized by spectral data.

In conclusion, we developed a method for the preparation of 1*H*-benzimidazoles, pyrazolones, and pyrazoles by the condensation of *ortho*-phenylenediamines and phenylhydrazines with ethyl 4-chloro-3-oxobutanoate for the first time. In situ nucleophilic substitution of pyrazolones and pyrazoles with protic solvents provided corresponding alkoxy derivatives. All the products **3a–f, 5a,b, 6a–e, 7a–o**, and **8a–j** were characterized by spectral data ($^1$H NMR, $^{13}$C NMR, IR, and mass spectra).

## EXPERIMENTAL

### General Procedure for the Synthesis of 2-(Chloromethyl)-1*H*-benzo[*d*]imidazoles (3a–f)

The synthesis of 2-(chloromethyl)-1*H*-benzo[*d*]imidazoles (**3a–f**) is the same as described for compound **3a**.

$SnCl_2$ (0.1 mmol) was added to a stirred solution of *ortho*-phenylenediamine (**1,** 1 mmol) and ethyl 4-chloro-3-oxobutanoate (**2,** 1 mmol) in EtOH (2 mL) at rt. The mixture was stirred under reflux for 6 h. After completion of the reaction, monitored by thin-layer chromatography (TLC), the solvent was removed under reduced pressure. The crude product was subjected to column chromatography (hexane/AcOEt 84:16) to give the pure benzimidazoles.

### 2-(Chloromethyl)-1*H*-benzo[*d*]imidazole (3a)

Pale yellow solid; yield: 82%; mp 152–154 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 4.85$ (s, 2H, $CH_2Cl$), 7.19–7.28 (m, 2H, Ar-H), 7.55–7.62 (m, 2H, Ar-H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta = 37.4$, 114.6, 121.7, 137.9, 148.7; MS ($ESI^+$) $m/z = 167$ $(M+H)^+$.

### General Procedure for Synthesis of 3-(Chloromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-ones (5a,b, 6a–e)

The syntheses of 3-(chloromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-ones (**5a,b** and **6a–e**) are the same as described for those of compound **6a.**

$Bi(OTf)_3$ (0.1 mmol) was added to a stirred solution of phenylhydrazine hydrochloride (**1,** 1 mmol) and ethyl 4-chloro-3-oxobutanoate (**2,** 1 mmol) in THF (3 mL). The mixture was stirred under reflux for 12 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure. The crude product was subjected to column chromatography (hexane/AcOEt 8:2) to give pure pyrazolones and pyrazoles.

### 3-(Chloromethyl)-5-ethoxy-1-phenyl-1*H*-pyrazole (6a)

Yellow liquid; yield: 5%; IR (KBr) 2928, 1561, 1262, 1140, 1044, 758, 690 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 1.45$ (t, $J = 7.0$ Hz, 3H, $CH_3$), 4.18 (q, $J = 7.0$ Hz, 2H, $OCH_2$), 4.57 (s, 2H, $CH_2$), 5.75 (s, 1H, CH), 7.27 (tt, $J = 1.1$, 7.5 Hz, 1H, Ar-H), 7.41 (t, $J = 7.5$ Hz, 2H, Ar-H), 7.69 (dd, $J = 1.0$, 8.5 Hz, 2H, Ar-H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 4.5$, 39.8, 68.0, 85.6, 122.1, 126.3, 128.7,

138.3, 148.5, 155.0.; MS ($ESI^+$) $m/z = 236$ $(M+H)^+$; HRMS ($ESI^+$) calcd. for $C_{12}H_{13}ClN_2ONa$ $(M+Na)^+$ 259.0608; found 259.0614.

### General Procedure for the Synthesis of 3-(Chloromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-ones (7a–o, 8a–j)

The syntheses of 3-(chloromethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-ones (**7a–o** and **8a–j**) are the same as described for those of compound **7a.**

$Bi(OTf)_3$ (0.1 mmol) was added to a stirred solution of phenylhydrazine hydrochloride (**1,** 1 mmol) and ethyl 4-chloro-3-oxobutanoate (**2,** 1 mmol) in alcohols such as MeOH and EtOH (3 mL). The mixture was stirred under reflux for 16 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure. The crude product was subjected to column chromatography (hexane/AcOEt 8:2) to give pure pyrazolones and pyrazoles.

### 3-(Methoxymethyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (7a)

Pale yellow solid; yield: 52%; mp 122–124 °C; IR (KBr) 2925, 2821, 1737, 1553, 1396, 1111, 1029, 755, 686 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 3.42$ (s, 3H, $OCH_3$), 3.54 (s, 2H, $CH_2$), 4.28 (s, 2H, $OCH_2$), 7.19 (t, $J = 7.4$ Hz, 1H, Ar-H), 7.40 (t, $J = 7.7$ Hz, 2H, Ar-H), 7.85 (d, $J = 7.7$ Hz, 2H, Ar-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 40.3$, 58.8, 69.6, 118.9, 125.2, 128.8, 137.8; MS ($ESI^+$) $m/z = 205$ $(M+H)^+$; HRMS ($ESI^+$) calcd. for $C_{11}H_{13}N_2O_2$ $(M+H)^+$ 205.0970; found 205.0971.



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## SUPPLEMENTARY MATERIAL

Spectral data for the synthesized compounds can be accessed on the publisher's website.

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