ONE-POT TANDEM SYNTHESIS OF TETRASUBSTITUTED PYRAZOLES VIA 1,3-DIPOLAR CYCLOADDITION BETWEEN ARYL HYDRAZONES AND ETHYL BUT-2-YNOATE

Srikantamurthy Ningaiah,1 Shridevi D. Doddaramappa,2 Chandra,3 Mahendra Madegowda,3 Shubakara Keshavamurthy,1 and Umesha K. Bhadraiah1

1Department of Chemistry, Yuvaraja’s College, University of Mysore, Mysore, India
2Department of Studies in Chemistry, Manasagangotri, University of Mysore, Mysore, India
3Department of Studies in Physics, Manasagangotri, University of Mysore, Mysore, India

GRAPHICAL ABSTRACT

Abstract 1,3,4,5-Tetrasubstituted pyrazoles are rapidly and regioselectively synthesized in a one-pot, three-step sequence consisting of condensation, nitrilimine generation, and cycloaddition using mercuric acetate. Newly synthesized compounds were characterized by spectral studies. Regiochemistry of compounds 6a and 8a was determined as 1,4- and 1,5-regioisomers respectively by X-ray crystallography.

Keywords 1,3-Dipolar cycloaddition; ethyl but-2-ynoate; regioselective; tetrasubstituted pyrazoles; X-ray crystallography

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Address correspondence to Umesha K. Bhadraiah, Department of Chemistry, Yuvaraja’s College, University of Mysore, Mysore 570005, India. E-mail: kbu68umesha@rediffmail.com

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INTRODUCTION

Pyrazoles are important heterocycles with two adjacent nitrogen atoms in the ring, and they have extensive uses in the pharmaceutical industry.[1] Pyrazole and its derivatives show a broad spectrum of biological activities such as anti-inflammatory, analgesic, antihypertensive, antipyretic, antibacterial, and sedative[2,3] activities. To date, a number of pyrazole-containing compounds have been successfully commercialized, such as Celebrex, Viagra, Fipronil, Lonazolac, and Rimonabant.[4]

1,3-Dipolar cycloaddition reaction has been employed as one of the most powerful synthetic tools to provide substituted pyrazoles.[5] These reactions are staggeringly useful also because they are stereospecific, diastereoselective, and regioselective.[6,7]

Although they provide a multitude of choices to contrive substituted pyrazoles, the existing synthetic methods[8–11] suffer from lack of regiospecificity, longer reaction time, exhaustive workup, poor yield, and multistep procedures, which have limited the exploitation of these methods in high-throughput synthesis. Thus an improved, efficient, rapid, and regioselective approach to tetrasubstituted pyrazoles is of current interest to organic chemists.

To the best of our knowledge, there are only very few reports on the regioselective synthesis of tetrasubstituted pyrazoles from substituted alkynes.[12] Thus we were interested in a mild one-pot conversion of various aldehyde, phenyl hydrazine, and ethyl but-2-ynoate to the corresponding 1,3,4,5-tetrasubstituted pyrazoles with good to excellent yields. Such transformation would be particularly useful for medicinal chemists because it would give them direct access to useful pyrazoles in a single chemical transformation.

RESULTS AND DISCUSSION

Our initial studies were focused on the stepwise strategy for the synthesis of target pyrazole (6), which involves the formation of benzaldehyde phenyl hydrazine (3) from respective benzaldehydes (1) and phenyl hydrazine (2), in situ generation of nitrilimine (4) using chloramine-T (CAT),[13,14] and an addition of ethyl but-2-ynoate (5) to nitrilimine (Scheme 1). The sequential transformation was monitored with thin-layer chromatography (TLC), and each step requires a minimum of 1–2 h, except for the last step, which requires heating to 120–150°C for about 48 h. Unfortunately with these conditions we end up with the poor yield of 27%. This might be because of the poor reactivity of alkynes toward cycloaddition and formation of undesired cycloadduct (7) from nitrilimines generated in situ as they were very reactive species.[15] (See Table 1 for reaction conditions and various reagents employed for nitrilimine generation). In all the reactions we have used absolute EtOH as a solvent, because the solvent polarity has less impact on the yield and rate of the reaction.[16]

The methods of generating nitrilimine from hydrazonoyl chlorides, tetrazole, or its precursors would require strong background reaction and suffer from lower yields and/or require high temperature.[17–21] Hence we have employed mild oxidizing agents like CAT,[22] Phl(OAc)2,[23] Pb(OAc)2,[24] and Hg(OAc)2[25] for the generation of nitrilimine. Gratifyingly, it was found that the reaction gave promising results in the presence of Hg(OAc)2 at room temperature (Table 1, entry 12). Although, Hg(OAc)2
was employed for the synthesis of trisubstituted pyrazolines, here we have studied the use of Hg(OAc)$_2$ for the cycloaddition between an alkyne and nitrilimines, which give direct access to the tetrasubstituted pyrazoles with a good tolerable substituent scope and which can be utilized as building blocks for further study.

Prompted by these observations we next probed the concatenation of the three individual steps to a consecutive one-pot reaction. The subsequent condensation–imine generation–cycloaddition reaction of various benzaldehydes 1(a–l), phenyl

### Table 1. Reaction condition for stepwise synthesis of 6a

| Entry | Oxidant   | Equiv | Temp. (°C) | Time (h) | Yield$^a$ of 6a (%) |
|-------|-----------|-------|------------|----------|---------------------|
| 1     | CAT       | 1.0   | rt         | 24       | NR                  |
| 2     | CAT       | 1.0   | 80         | 24       | Trace               |
| 3     | CAT       | 1.0   | 120        | 24       | 27                  |
| 4     | CAT       | 2.0   | 150        | 48       | 29                  |
| 5     | PhI(OAc)$_2$ | 1.0 | rt         | 24       | NR                  |
| 6     | PhI(OAc)$_2$ | 1.0 | 80         | 24       | Trace               |
| 7     | PhI(OAc)$_2$ | 1.0 | 120        | 24       | Trace               |
| 8     | Pb(OAc)$_2$ | 1.0 | rt         | 24       | NR                  |
| 11    | Pb(OAc)$_2$ | 2.0 | 120        | 24       | 32                  |
| 12    | Hg(OAc)$_2$ | 1.0 | rt         | 1        | 67                  |

$^a$Isolated yields; NR, no reaction.

*Note.* All reactions were carried out in 1-mmol scale of reactants in 5 mL of EtOH.
hydrazine 2(a–l), and an alkyne (ethyl but-2-ynoate) 5 with Hg(OAc)₂ furnished the
tetrasubstituted pyrazole 6(a–l) within a time period of 0.5–2 h in good to excellent
yields (Table 2).

With the optimized one-pot procedure in hand, we investigated the scope
for the synthesis of pyrazole 6 with commercially available arylaldehyde 1 and aryl-
hydrazines 2. The R₁ and R₂ in the aromatic rings of the aldehyde and hydrazines
respectively were substituted with groups of atoms with various electronic properties
as shown in Table 3. As is evident from Table 3, the electronic effect of the
substituted groups on the aromatic rings was not apparent. Both the electron-rich
and electron-deficient aldehydes and hydrazines provided the desired product in
good to excellent yields.

Good yield and shorter reaction time was attributed to the catalytic effect of
metal ion that would alter the orbital coefficient of reacting atoms as well as frontier
molecular orbitals (FMOs) of either the 1,3-dipole or the dipolarophile, when
coordinated to metal. This principle of activation can be applied to the 1,3-dipolar
cycloaddition reaction of nitrilimine and (1,3-dipole) and ethyl but-2-ynoate
dipolarophile). Compared to sequential reaction, the yield was greater in the
one-pot condition because the (-complex formed during the course of the reaction
was readily available for cyclization with nitrilimine generated in situ, thereby
decreasing the formation of undesired cycloadduct.

| Entry | Equiv | Temp. (°C) | Time (h) | Yield² of 6a (%) |
|-------|-------|------------|----------|-----------------|
| 1     | 0.5   | rt         | 0.5      | 52              |
| 2     | 0.5   | rt         | 1.0      | 55              |
| 3     | 0.5   | rt         | 2.0      | 56              |
| 4     | 1.0   | rt         | 0.5      | 72              |
| 5     | 1.0   | rt         | 1.0      | 80              |
| 6     | 1.5   | rt         | 0.5      | 88              |
| 7     | 1.5   | rt         | 1.0      | 98              |
| 8     | 1.5   | rt         | 2.0      | 90              |
| 9     | 1.5   | 80         | 1.0      | 86              |
| 10    | 2.0   | rt         | 0.5      | 88              |
| 11    | 2.5   | rt         | 0.5      | 84              |
| 12    | 2.5   | rt         | 1.0      | 80              |
| 13    | 2.5   | rt         | 2.0      | 78              |
| 14    | 2.5   | 80         | 0.5      | 82              |

²Reaction conditions: benzaldehyde 1 1.0 mmol, phenylhydrazine 2 1.1 mmol, ethyl but-2-ynoate 5 1.5 mmol, and EtOH 5 mL.

²Isolated yield.

Table 2. Optimization of reaction conditions for the one-pot synthesis of 6a
According to the previous work on the mechanism of 1,3-dipolar
cycloaddition,\[26\] the Huisgen cycloaddition occurs by a concerted process. In the
case of nitrilimine and ethyl but-2-ynoate, the regiochemistry can be interpreted
by the dominant interaction between the highest occupied molecular orbital
(HOMOdipole) and lowest unoccupied molecular orbital (LUMOdipolarophile), and
thus coordinating with metal ion would decrease the energy gap between the
interacting FMO, which leads to faster reaction rates.\[27\] Compounds
6a and 8a were
determined to be 1,4- and 1,5-regioisomers, respectively, by X-ray crystallography\[28\]
(see Fig. 1 for ORTEP diagrams of both the isomers).

On the basis of this information and earlier reports,\[25\] a possible mechanism is
proposed as shown in Scheme 2.

**EXPERIMENTAL**

**General One-Pot Procedure for the Preparation of Ethyl
5-Methyl-1,3-diaryl-1H-pyrazole-4-carboxylates 6**

Phenyl hydrazine (0.119 g, 1.00 mmol, 1.1 equiv) was added to a stirred
solution of benzaldehyde (0.106 g, 1.00 mmol) in EtOH (5 mL). After stirring at
room temperature for 15 min, the benzaldehyde phenyl hydrazone was formed

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**Table 3. One-pot synthesis of tetrasubstituted pyrazoles 6(a-l) and 8a**

| No. | R1     | R2     | Product | Time (h) | Ratio of (6:8)² | Yield¹ (%) |
|-----|--------|--------|---------|----------|----------------|------------|
| 1   | C6H5   | C6H5   | 6a      | 0.5      | 1:0.2          | 98         |
| 2   | 4-Cl-C6H4 | C6H5 | 6b      | 1.5      | 1:trace        | 92         |
| 3   | 4-CH3O-C6H4 | C6H5 | 6c      | 0.5      | No²           | 98         |
| 4   | 4-NO2-C6H4 | C6H5 | 6d      | 2        | No             | 79         |
| 5   | 4-Br-C6H4   | C6H5 | 6e      | 1        | No             | 90         |
| 6   | 3-NO2-C6H4  | C6H5 | 6f      | 2        | No             | 74         |
| 7   | 3-Cl-C6H4   | C6H5 | 6g      | 1.5      | 1:trace        | 88         |
| 8   | 2-OH-C6H4   | 4-CH3-C6H4 | 6i   | 1.5      | No             | 98         |
| 9   | C6H5   | 4-CH3-C6H4 | 6j   | 2        | No             | 87         |
| 10  | C6H5   | 2,4-CH3-C6H3 | 6k   | 1.5      | 1:trace        | 91         |
| 11  | C6H5   | 4-Cl-C6H4   | 6l   | 2        | No             | 90         |
| 12  | 4-Cl-C6H4 | C6H5 | 6m      | 0.5      | No             | 98         |

²Reaction conditions: benzaldehyde 1 1.0 mmol, phenylhydrazine 2 1.1 mmol, ethyl but-2-ynoate 5 1.5 mmol, and EtOH 5 mL.

³The ratio of 6:8 was determined by the isolated yields of 6 and 8.

⁴Isolated yields.

⁵No isomer observed.
Figure 1. ORTEP diagram of the molecules at 50% probability.
(based on thin-layer chromatographic, TLC, analysis). Hg(OAc)$_2$ (0.478 g, 1.5 mmol, 1.5 equiv) in 5 ml EtOH and ethyl but-2-ynoate (0.224 g, 2.00 mmol, 2.0 equiv) were added simultaneously to the reaction mixture from two separate droppers. The contents were then allowed to stir at room temperature for 30 min (1.0 h total). On completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layer was washed with 1 M KBr solution (to remove mercury salts) and with brine, dried over anhydrous Na$_2$SO$_4$, and then concentrated under reduced pressure. The crude product was purified by column chromatography ($n$-hexane/EtOAc 95/05) to give two fractions. On evaporation, 6a was obtained as a white solid (0.277 g, 96%) and 8a as an off-white solid (0.057 g, 2%).

**Compound 6a**

White solid; mp 102–104 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.15 (t, $J = 7.2$ Hz, 3H), 2.41 (s, 3H), 4.13 (q, $J = 7.2$ Hz, 2H), 7.29–7.36 (m, 4H), 7.41–7.45 (m, 4H), 7.49–7.57 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 12.75, 14.10, 60.10, 110.63, 125.85, 127.65, 128.15, 128.23, 128.68, 129.25, 129.48, 133.18, 138.84, 144.79, 153.62, 164.21; LC-MS $m/z$ 307.6 (M+$\text{+H}$)$^+$. Anal. calcd. for C$_{19}$H$_{18}$N$_2$O$_2$: C, 74.50; H, 5.90; N, 9.14. Found: C, 74.56; H, 5.91; N, 9.10.

**Compound 8a**

White solid; mp 100–102 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.14 (t, $J = 7.2$ Hz, 3H), 2.51 (s, 3H), 4.13–4.19 (q, $J = 7.0$ Hz, 2H), 7.38–7.42 (m, 3H), 7.49–7.53 (m, 1H), 7.55–7.61 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 11.40, 14.30, 61.10, 110.01, 124.35, 126.70, 127.53, 127.80, 128.20, 129.00, 132.48, 141.10, 141.20, 149.50, 163.10; LC-MS $m/z$ 307.1 (M+$\text{+H}$)$^+$. Anal. calcd. for C$_{19}$H$_{18}$N$_2$O$_2$: C, 74.42; H, 5.88; N, 9.20. Found: C, 74.45; H, 5.90; N, 9.15.
CONCLUSIONS

In conclusion, we have developed a rapid, one-pot, regioselective synthesis of tetrasubstituted pyrazoles with a highly flexible substitution pattern in good yields by utilizing easily available and economical chemicals as starting materials. This reaction is quite broad in scope, generating a diverse set of pyrazole products in moderate to excellent yields. The effectiveness of this protocol can be attributed to the easy access of the starting materials, shortened reaction time, and simple and clean reaction profiles. Finally, this method gives a facile approach to N-substituted pyrazole carboxylates, which can be utilized as building blocks for further reactions.

The arguments on the type of mechanism involved remain unresolved to date. A via media conclusion is that the reactions are concerted but not synchronous. Therefore, density functional theory (DFT) and kinetic studies of the reaction and the utilization of other disubstituted alkynes are in progress and will be reported in due course.

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SUPPLEMENTARY DATA

Full experimental details and $^1$H and $^{13}$C NMR spectra can be accessed on the publisher’s website.

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