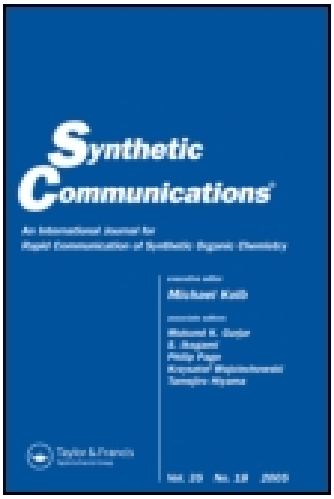


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

One-Pot Tandem Synthesis of Tetrasubstituted Pyrazoles via 1,3-Dipolar Cycloaddition Between Aryl Hydrazones and Ethyl But-2-ynoate

Srikantamurthy Ningaiah [a], Shridevi D. Doddaramappa [b], Chandra [c], Mahendra Madegowda [c], Shubakara Keshavamurthy [a] & Umesha K. Bhadraiah [a]

[a] Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore, India

[b] Department of Studies in Chemistry, Manasagangotri, University of Mysore, Mysore, India

[c] Department of Studies in Physics, Manasagangotri, University of Mysore, Mysore, India

Accepted author version posted online: 15 Apr 2014.Published online: 06 Jun 2014.

To cite this article: Srikantamurthy Ningaiah, Shridevi D. Doddaramappa, Chandra, Mahendra Madegowda, Shubakara Keshavamurthy & Umesha K. Bhadraiah (2014) One-Pot Tandem Synthesis of Tetrasubstituted Pyrazoles via 1,3-Dipolar Cycloaddition Between Aryl Hydrazones and Ethyl But-2-ynoate, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:15, 2222-2231, DOI: 10.1080/00397911.2014.891744

To link to this article: http://dx.doi.org/10.1080/00397911.2014.891744

Synthetic Communications®, 44: 2222–2231, 2014

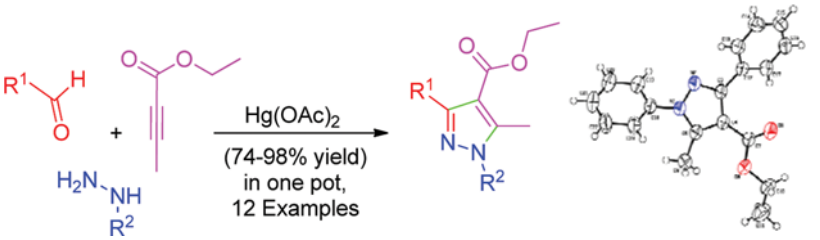
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2014.891744

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. Bhadraiah[1]

[1]*Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore, India*
[2]*Department of Studies in Chemistry, Manasagangotri, University of Mysore, Mysore, India*
[3]*Department 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

Received November 4, 2013.

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]

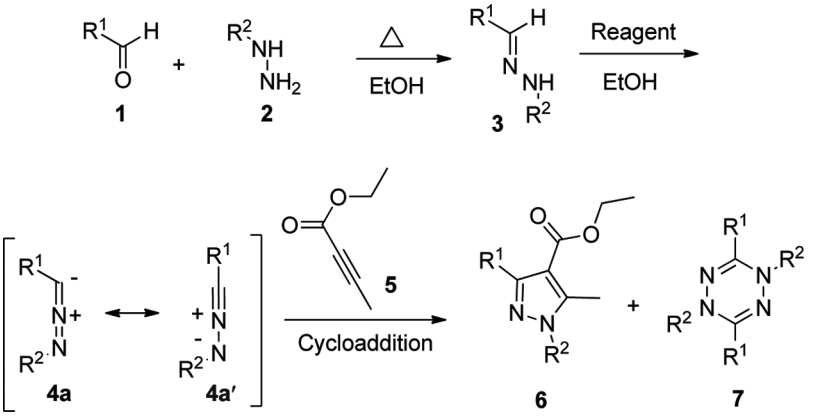
Although they provide a multitude of choices to contrive substituted pyrazoles, the existing synthetic methods[8–11] suffer from lack of regiospecificity, longer reaction time, exhaustive workup, poor yield, and multistep procedures, which have limited the exploitation of these methods in high-throughput 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] $PhI(OAc)_2$,[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, $Hg(OAc)_2$

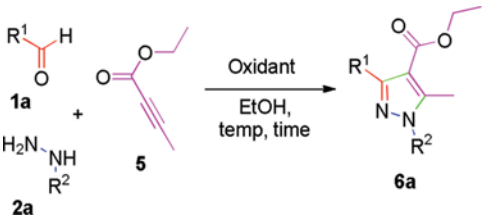


Scheme 1. 1,3-Dipolar cycloaddition strategy: Sequential steps to pyrazole synthesis.

was employed for the synthesis of trisubstituted pyrazolines,[25] 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 R^1 and R^2 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.

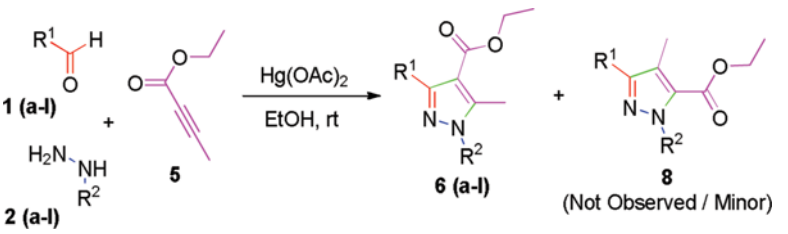
Good yield and shorter reaction time was attributed to the catalytic effect of metal ion that would alter the orbital coefficient of reacting atoms as well as frontier molecular orbitals (FMOs) of either the 1,3-dipole or the dipolarophile, when coordinated to metal. This principle of activation can 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.

Table 2. Optimization of reaction conditions for the one-pot synthesis of **6a**[a]

Entry	Equiv	Temp. (°C)	Time (h)	Yield[b] 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

[a]Reaction conditions: benzaldehyde **1** 1.0 mmol, phenylhydrazine **2** 1.1 mmol, ethyl but-2-ynoate **5** 1.5 mmol, and EtOH 5 mL.
[b]Isolated yield.

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



No.	R^1	R^2	Product	Time (h)	Ratio of (6:8)[b]	Yield[c] (%)
1	C_6H_5	C_6H_5	**6a**	0.5	1:0.2	98
2	4-Cl-C_6H_4	C_6H_5	**6b**	1.5	1:trace	92
3	4-CH_3O-C_6H_4	C_6H_5	**6c**	0.5	No[d]	98
4	4-NO_2-C_6H_4	C_6H_5	**6d**	2	No	79
5	4-Br-C_6H_4	C_6H_5	**6e**	1	No	90
6	3-NO_2-C_6H_4	C_6H_5	**6f**	2	No	74
7	3-Cl-C_6H_4	C_6H_5	**6g**	1.5	1:trace	88
8	2-OH-C_6H_4	C_6H_5	**6h**	0.5	No	98
9	C_6H_5	4-CH_3-C_6H_4	**6i**	1.5	No	83
10	C_6H_5	2,4-CH_3-C_6H_3	**6j**	2	No	87
11	C_6H_5	4-Cl-C_6H_4	**6k**	1.5	1:trace	91
12	4-Cl-C_6H_4	2,4-Cl-C_6H_3	**6l**	2	No	90

[a]Reaction conditions: benzaldehyde **1** 1.0 mmol, phenylhydrazine **2** 1.1 mmol, ethyl but-2-ynoate **5** 1.5 mmol, and EtOH 5 mL.
[b]The ratio of 6:8 was determined by the isolated yields of **6** and **8**.
[c]Isolated yields.
[d]No isomer observed.

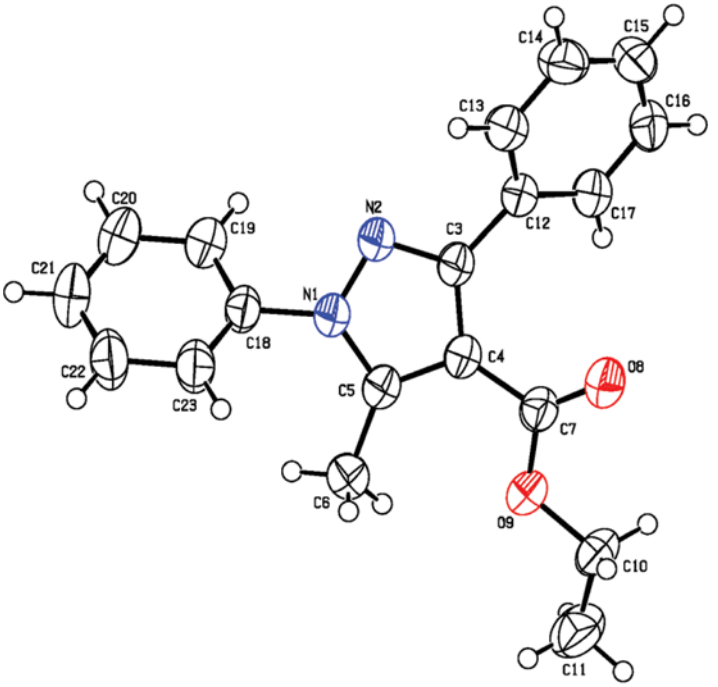
According to the previous work on the mechanism of 1,3-dipolar cycloaddition,[26] the Huisgen cycloaddition occurs by a concerted process. In the case of nitrilimine and ethyl but-2-ynoate, the regiochemistry can be interpreted by the dominant interaction between the highest occupied molecular orbital ($HOMO_{dipole}$) and lowest unoccupied molecular orbital ($LUMO_{dipolarophile}$), 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.

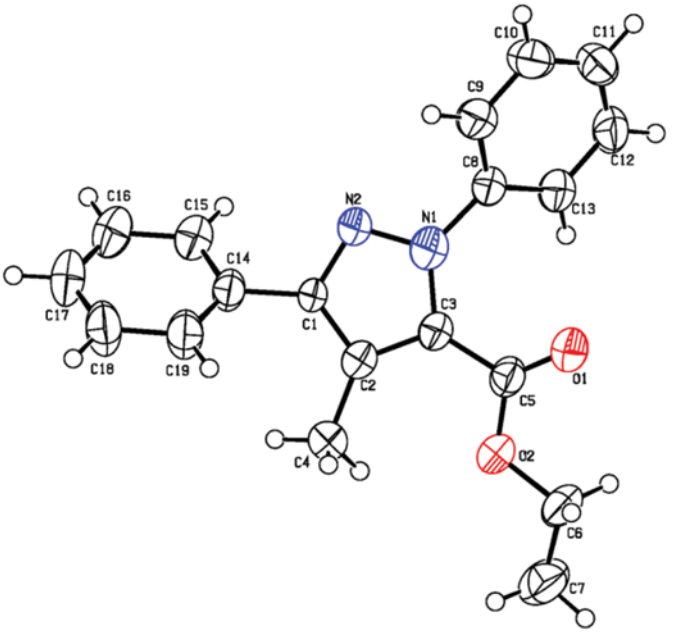
EXPERIMENTAL

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

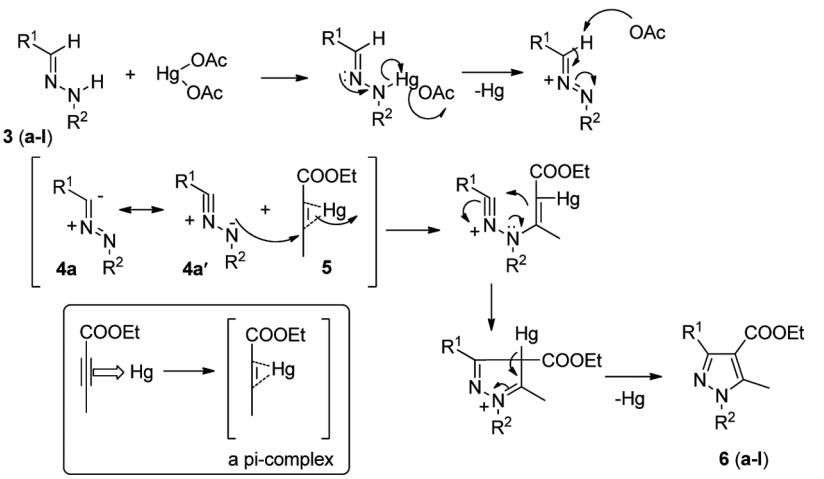


(6a)



(8a)

Figure 1. ORTEP diagram of the molecules at 50% probability.



Scheme 2. Possible mechanism.

(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 (3×5 mL). The combined organic layer was washed with 1 M KBr solution (to remove mercury salts) and with brine, dried over anhydrous Na_2SO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 12.75, 14.10, 60.10, 110.63, 125.85, 127.65, 128.23, 128.68, 129.25, 129.48, 133.18, 138.84, 144.79, 153.62, 164.21; LC-MS *m/z* 307.6 $(M+H)^+$. Anal. calcd. for $C_{19}H_{18}N_2O_2$: 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $(M+H)^+$. Anal. calcd. for $C_{19}H_{18}N_2O_2$: 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.[26] Thus 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.

ACKNOWLEDGMENTS

The authors are thankful to K. Yeshoda Nanjappa, assistant professor of English, Yuvaraja's College, University of Mysore (UOM), Mysore, for proofreading the article and to the principal, Yuvaraja's College, UOM, Mysore, for providing necessary facilities and constant encouragement.

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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