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An Efficient Synthesis of Disubstituted Pyrazoles From 2-Propyn-1-ol Through Propargyl Hydrazides

N. Srinivasan[1]*, B.Venkateswara Rao[1], J. D. Lilakar[1], Y.L.N. Murthy[1], P. Mahesh[1]
1.Department of Organic Chemistry, Andhra University, Visakhapatnam– 531001, India

ABSTRACT

An efficient synthesis process access to disubstituted pyrazoles have been demonstrated from 2-propyn-1-alcohols using an effective catalyst Polymer bound pTSA. This conversion proceeds via an acid catalyzed propargylation of N,N-diprotected hydrazines followed by base-mediated cyclization to furnish 3,5-Disubstituted-1H-pyrazoles in optimum yields.

Keywords: 2-Propyn-1-ol, Cyclization, Substituted Pyrazole, Heterocyclic moieties, and coupling reactions.

*Corresponding Author Email: sriniau2@gmail.com
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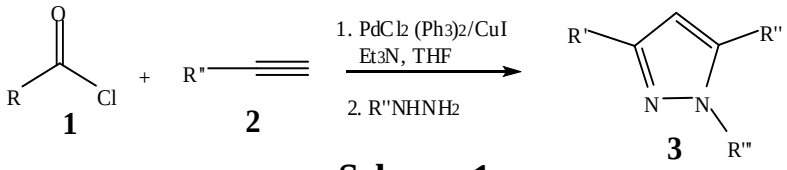
INTRODUCTION

Pyrazole is a class of organic compounds[1] of the heterocyclic series comprised by a ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions. The simplest member of the pyrazole family is pyrazole itself, a compound with molecular formula $C_3H_4N_2$. Many synthetic pyrazole compounds are of importance as various kinds of medicines, amidst of them are Rimonabant used as anorectic antiobesity drug[2]; celecoxib used as an analgesic[3-4]; Sildenafil used in treatment of erectile dysfunction[5] and pulmonary arterial hypertension[6]. Pyrazole is a prevalent scaffold in drug discovery programs. Analogues of pyrazole are often used for their anticonvulsant, antidiabetic, antibacterial, anti-inflammatory and antipyretic activities.

The pyrazole ring is present as the main constituent in a variety of leading nonsteroidal anti-inflammatory drugs and antihypertensive drugs. Pyrazines were also found utility in metal catalysis, and in various building blocks for pharmaceutical and agricultural research.

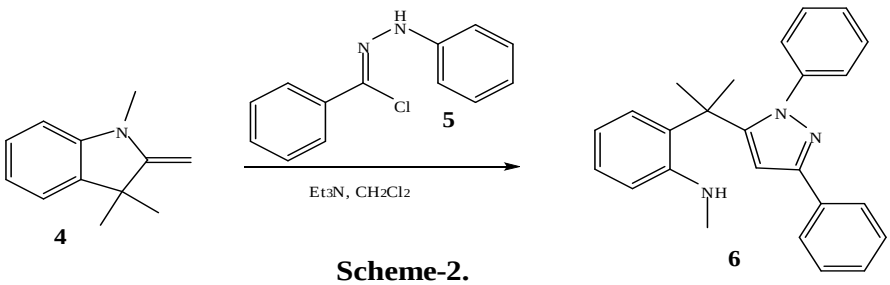
The pyrazole compounds are not known to occur in nature, they are more often prepared by the reaction of hydrazines with 1, 3-diketones; reaction of 1,3-dipolar cycloaddition of diazo compounds with alkynes; and the reaction of α,β-unsaturated aldehydes and ketones with hydrazines. In this context, focus was given for the synthetic strategies developed for the synthesis of pyrazole analogues in recent years as follows:

Tandem coupling cyclocondensation sequence catalyzed by Pd(PPh3)2Cl2/CuI was reported for the construction of pyrazoles[7] (Scheme-1).



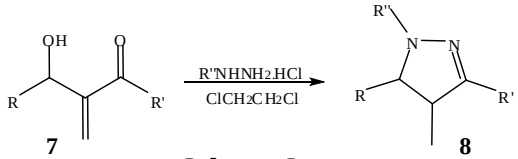
Scheme-1.

Huisgen cycloaddition of 2-methylene-1, 3, 3-trimethylindoline and an *in situ* generated nitrile imine. The newly formed spiro-pyrazoline intermediate presumably then undergoes a ring opening/elimination process to afford a novel 1,3,5-trisubstituted pyrazole derivative[8] (Scheme-2).



Scheme-2.

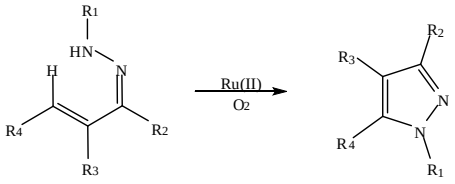
Reaction of Baylis–Hillman adduct and phenyl hydrazine in dichloroethane furnishes the tetrasubstituted pyrazole derivatives[9] (Scheme-3).



7 **8**

Scheme-3.

A novel Ru(II)-catalyzed oxidative C-N coupling method has been reported for the synthesis of highly diversified tri- and tetrasubstituted pyrazoles[10] from easily accessible starting materials (Scheme-4).



9 **10**

Scheme-4.

MATERIALS AND METHOD

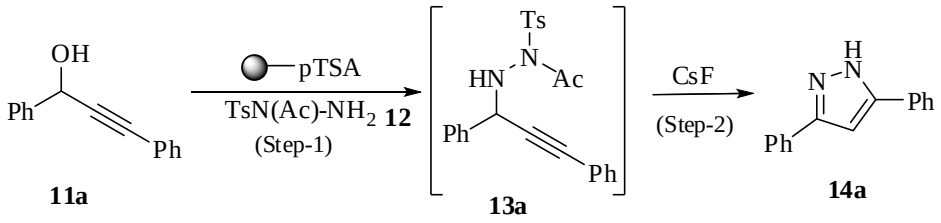
^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on 300 MHz, 500 MHz or 75 MHz spectrometer at ambient temperature. Chemical shifts δ is given in ppm, coupling constant *J* are in Hz. The chemical shifts are reported in ppm on scale downfield from TMS as internal standard and signal patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; td, triplet of doublet; t, triplet; m, multiplet; bs, broad singlet. FTIR spectra were recorded as KBr thin films or neat. For low (MS) and High (HRMS) resolution, *m/z* ratios are reported as values in atomic mass units. All the reagents and solvents were reagent grade and used without further purification unless specified otherwise. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60-120 mesh) packed in glass columns. All the reactions were performed under an atmosphere of nitrogen.

RESULTS AND DISCUSSION

Most often the synthesis procedures (scheme 1-4) of pyrazole involves the utilization of heavy metal reagents, tedious workup procedures as a result of which end up with low yields on account of poor reaction conversions.

Therefore, provided an access to 3,5-disbustituted pyrazoles (Scheme-5) with a metal free, reusable and economic reagent Polymer bound pTSA. 1*H*-pyrazole derivatives (Table-1) were

synthesized acid catalyzed polymer bound pTSA, thereby base meadited cyclization using CsF by a one pot synthesis of two component reaction between 2-Propyn-1-ol **11a** and Tosyl hydrazide **12**.



Scheme-5.

General experimental procedure for the synthesis of 3,5-disubstituted 1*H*-pyrazoles:

To a stirred solution of propargyl alcohol **11** (1 mmol) in acetonitrile (5 mL) was added *N*,*N*-acyltosylhydrazine (**12**, 0.95 mmol), 6 mol% polymer bound pTSA and the reaction mixture was stirred at room temperature for given time. Then, CsF (2 mmol) was added and the reaction was stirred at 70 ^{o}C (Table 1). After completion of the reaction, the mixture was evaporated *in vacuo* and the crude mixture was diluted with ethyl acetate (10 mL), washed with water (5 mL) and brine (5 mL). The ethyl acetate layer was evaporated and the residue was purified by column chromatography on silica gel using ethyl acetate and hexanes as eluent to give the corresponding pyrazole (**14**).

Spectral data for compounds:

***3,5-Diphenyl-1H-pyrazole* (14a):** Viscous liquid. IR (KBr): ν_{max} 3097, 2923, 1461, 1181, 972, 753 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75-7.70 (m, 4H, Ar), 7.44-7.31 (m, 6H, Ar), 6.85 (s, 1H, =CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.7, 131.2, 128.3, 127.4, 125.1, 99.0. HRMS (ESI): (*m/z*) calcd. for $C_{15}H_{13}N_2$ $[M+H]^+$ 221.1073; found 221.1072.

***3-(4-Methoxyphenyl)-5-phenyl-1H-pyrazole* (14b):** White solid; Mp: 150-154 ^{o}C. IR (KBr): ν_{max} 2925, 2854, 1461, 1252, 1176, 764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 7.1 Hz, 2H, Ar), 7.63 (d, J = 8.6 Hz, 2H, Ar), 7.43-7.30 (m, 3H, Ar), 6.91 (d, J = 8.5 Hz, 2H, Ar), 6.75 (s, 1H, =CH), 3.83 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 147.8, 131.4, 128.1, 127.1, 126.2, 124.9, 113.5, 98.2, 54.7. HRMS (ESI): (*m/z*) calcd. for $C_{16}H_{15}NO_2$ $[M+H]^+$ 251.1178; found 251.1178.

***5-(Benzyloxymethyl)-3-(4-methoxyphenyl)-1H-pyrazole* (14c):** White solid; Mp: 97-100 ^{o}C.
IR (KBr): ν_{max} 2925, 2855, 1511, 1251, 1029, 835 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 8.7 Hz, 2H, Ar), 7.39-7.29 (m, 5H, Ar), 6.95 (d, J = 7.8 Hz, 2H, Ar), 6.49 (s, 1H, =CH), 4.64 (s, 2H, CH_2O), 4.60 (s, 2H, CH_2Ph), 3.85 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 148.1,

145.8, 137.6, 128.4, 127.9, 127.7, 126.8, 124.1, 114.1, 101.4, 72.2, 64.3, 55.2. HRMS (ESI): (*m/z*) calcd. for $C_{18}H_{19}N_2O_2$ $[M+H]^+$ 295.1441; found 295.1440.

3-(4-Methoxyphenyl)-5-propyl-1H-pyrazole **(14d):** Viscous liquid. IR (KBr): ν_{max} 2960, 2871, 1457, 1249, 1177, 834 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 8.3 Hz, 2H, Ar), 6.93 (d, J = 8.3 Hz, 2H, Ar), 6.30 (s, 1H, =CH), 3.84 (s, 3H, OCH_3), 2.64 (t, J = 7.5 Hz, 2H, $N=CH_2$), 1.77-1.64 (m, 2H, CH_2-CH_3), 0.99 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 149.2, 147.8, 126.9, 125.1, 114.0, 100.4, 55.2, 28.3, 22.4, 13.7. HRMS (ESI): (*m/z*) calcd. for $C_{13}H_{17}NO_2$ $[M+H]^+$ 217.1335; found 217.1335.

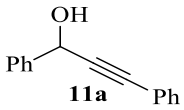
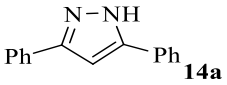
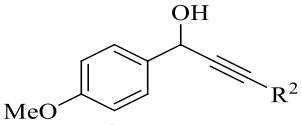
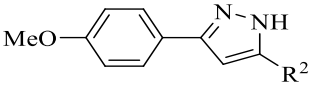
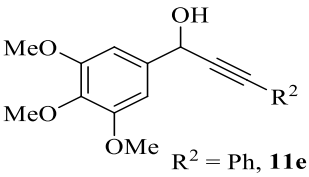
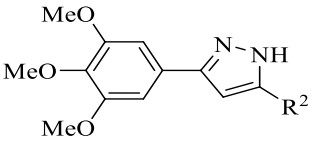
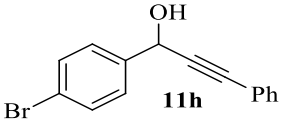
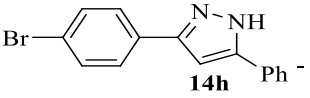
5-Phenyl-3-(3,4,5-trimethoxyphenyl)-1H-pyrazole **(14e):** Viscous liquid. IR (KBr): ν_{max} 2929, 1590, 1468, 1239, 1127, 765 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 7.3 Hz, 2H, Ar), 7.37-7.29 (m, 3H, Ar), 6.94 (s, 2H, Ar), 6.74 (s, 1H, =CH), 3.86 (s, 3H, OCH_3), 3.81 (s, 6H, $(OCH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.3, 149.4, 147.6, 137.8, 130.4, 128.6, 128.0, 127.0, 125.3, 102.5, 99.4, 60.7, 55.7. HRMS (ESI): (*m/z*) calcd. for $C_{18}H_{19}N_2O_3$ $[M+H]^+$ 311.1390; found 311.1388.

5-(Benzyloxymethyl)-3-(3,4,5-trimethoxyphenyl)-1H-pyrazole **(14f):** Viscous liquid. IR (KBr): ν_{max} 2932, 1589, 1468, 1126, 772 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38-7.29 (m, 5H, Ar), 6.95 (s, 2H, Ar), 6.50 (s, 1H,=CH), 4.63 (s, 2H, $PhCH_2$), 4.59 (s, 2H, CH_2O), 3.90 (s, 6H, $(OCH_3)_2$), 3.87 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 149.3, 144.5, 137.9, 137.3, 128.4, 127.8, 127.5, 104.1, 102.8, 101.8, 72.3, 63.8, 60.8, 56.0. HRMS (ESI): (*m/z*) calcd. for $C_{20}H_{23}N_2O_4$ $[M+H]^+$ 355.1652; found 355.1652.

5-Propyl-3-(3,4,5-trimethoxyphenyl)-1H-pyrazole **(14g):** Viscous liquid. IR (KBr): ν_{max} 2959, 2933, 1590, 1467, 1236, 1126, 1004 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.97 (s, 2H, Ar), 6.33 (s, 1H, =CH), 3.90 (s, 6H, $(OCH_3)_2$), 3.87 (s, 3H, OCH_3), 2.64 (t, J = 7.5 Hz, 2H, CH_2), 1.78-1.64 (m, 2H, CH_2-CH_3), 0.99 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.3, 150.0, 147.4, 137.8, 128.4, 102.9, 100.7, 60.7, 55.9, 28.1, 22.4, 13.6. HRMS (ESI): (*m/z*) calcd. for $C_{15}H_{21}N_2O_3$ $[M+H]^+$ 277.1546; found 277.1546.

3-(4-Bromophenyl)-5-phenyl-1H-pyrazole **(14h):** White solid, Mp: 210-213 ^oC. IR (KBr): ν_{max} 3448, 2922, 1488, 1453, 1067, 759 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 7.82-7.71 (m, 4H, Ar), 7.54 (d, J = 8.3 Hz, 2H, Ar), 7.42 (t, J = 7.5 Hz, 2H, Ar), 7.32 (t, J = 7.5 Hz, 1H, Ar), 6.88 (s, 1H, CH).^{13}C NMR (125 MHz, $CDCl_3$): δ 130.2, 127.3, 126.4, 125.6, 123.9, 119.6, 98.0. MS (ESI): (*m/z*) = 299 $[M + H]^+$. HRMS (ESI): (*m/z*) calcd. for $C_{15}H_{12}BrN_2$ $[M+H]^+$ 299.0178; found 299.0188.

Table 1: Polymer bound pTSA Catalyzed & CsF mediated cyclization of pyrazoles

entry	2-propyn-1-ol	time (min) step-1/step-2	Pyrazole[b]	yield (%)[c]
1	 **11a**	15/20	 **14a**	85
2	 R^2 = Ph, **11b**	12/25	 R^2 = Ph, **14b**	84
3	$R^2 = CH_2OBn$, **11c**	10/25	$R^2 = CH_2OBn$, **14c**	87
4	$R^2 = C_3H_7$, **11d**	15/30	$R^2 = C_3H_7$, **14d**	81
5	 R^2 = Ph, **11e**	10/25	 R^2 = Ph, **14e**	83
6	$R^2 = CH_2OBn$, **11f**	15/25	$R^2 = CH_2OBn$, **14f**	85
7	$R^2 = C_3H_7$, **11g**	10/15	$R^2 = C_3H_7$, **14g**	82
8	 **11h**	15/30	 **14h**	84

[a]*Reaction conditions*: 2-propyn-1-ol (1 mmol), **2** (0.96 mmol), Polymer bound pTSA (6 mol%)/rt, CsF(2 equiv.)/70 °C; [b]Characterized by ^1H, ^{13}C NMR, and mass spectra; [c]Isolated yields.

CONCLUSION

In conclusion, we have provided a simple and efficient method for the preparation of 3,5-disubstituted pyrazoles through propargyl hydrazides using the mild reagent Polymer supported pTSA, which is economic reagent and commercially available and found as selective in the synthesis of the targeted molecules in providing the optimum yields.

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REFERENCES

1. Schmidt, A. Dreger. Recent Advances in the Chemistry of Pyrazoles. Properties, Biological Activities, and Syntheses. Curr. Org. Chem. 2011; 15 (9): 1423–1463
2. Adan R. A. H., Vanderschuren L. J. M. J., la Fleur S. E. Anti-obesity drugs and neural circuits of feeding. Trends Pharmacol. Sci. 2008; 29, 208–217.
3. Driessen B, Reimann W; Reimann. Interaction of the central analgesic, tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain in vitro. British Journal of Pharmacology. 1992; 105 (1), 147–51.
4. Coldrey JC, Upton RN, Macintyre PE. Advances in analgesia in the older patient. Clin Anaesthesiol 2011; 25(3), 367-78.
5. Berookhim BM, Bar-Chama N. Medical implications of erectile dysfunction. Med Clin North Am. 2011; 95(1), 213-221.
6. Montani D, Günther S, Dorfmüller P, Perros F, Girerd B, Garcia G, Jaïs X, Savale L, Artaud-Macari E, Price LC, Humbert M, Simonneau G, Sitbon O. Pulmonary arterial hypertension. Orphanet J Rare Dis. 2013; 8, 97.
7. Hai-Ling Liu, Huan-Feng Jiang, Min Zhang, Wen-Juan Yao, Qiu-Hua Zhu, Zhou Tang. One-pot three component synthesis of pyrazoles through a tandem coupling-cyclocondensation sequence. Tetrahedron Lett. 2008; 49, 3805-3809.
8. Sureshbabu D, Valente EJ, Hamme II AT. A novel synthesis of 1, 3, 5-trisubstituted pyrazoles through a spiro-pyrazoline intermediate via a tandem 1,3-dipolar cycloaddition /elimination. Tetrahedron Lett. 2009; 50, 291-294.
9. Lee KY, Kim JM, Kim JN. Regioselective synthesis of 1,3,4,5-tetrasubstituted pyrazoles from Baylis–Hillman adducts. Tetrahedron Lett. 2000; 44, 6737-6740.
10. Hu J, Chen S, Sun Y, Yang J, Yu R. Synthesis of tri- and tetrasubstituted pyrazoles via Ru(II) catalysis: Intramolecular aerobic oxidative C-N coupling. Org Lett. 2012; 14(19), 5030-5033.