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A Novel Methodology for Synthesis of Dihydropyrazole Derivatives as Potential Anticancer Agents

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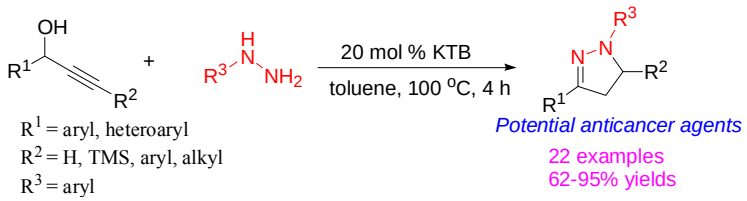
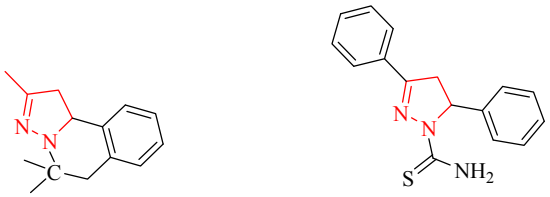


A novel, simple, and efficient method for the synthesis of 4,5-dihydropyrazole derivatives has been developed. The reaction proceeded through the base-induced isomerization of easily accessible propargyl alcohols and followed by cyclization of α,β-unsaturated hydrazones. Furthermore, selected compounds **3ab** and **3ac** exhibited good activities against Bel-7404 (human hepatoma cancer), HepG2 (human liver cancer), NCI-H460 (human lung cancer) and SKOV3 (human ovarian cancer) cell lines with IC_{50} in the range of 22−46 μmol/L.

Pyrazolines play an important role in organic synthesis and medicinal chemistry. Pyrazoline derivatives are reported to possess antitumor,[1] immunosuppressive,[2] antibacterial,[3] antitubercular agents,[4] anti-inflammatory,[5] antidiabetic,[6] antidepressant,[7] antimalarial,[8] antiamoebic[9] and anti-WN virus activities.[10] In particular, some trisubstituted dihydropyrazole derivatives serve as valuable precursors in various

biologically and pharmaceutically active organic molecules,[11] such as 2,5,5-trimethyl-1,5,6,10*b*-tetrahydro-pyrazolo[5,1-*a*]isoquinoline and 3,5-diphenyl-4,5-dihydro-pyrazole-1-carbothioic acid amide (Fig. 1).[12]



2,5,5-Trimethyl-1,5,6,10b-tetrahydro-pyrazolo[5,1-*a*]isoquinoline

3,5-Diphenyl-4,5-dihydro-pyrazole-1-carbothioic acid amide

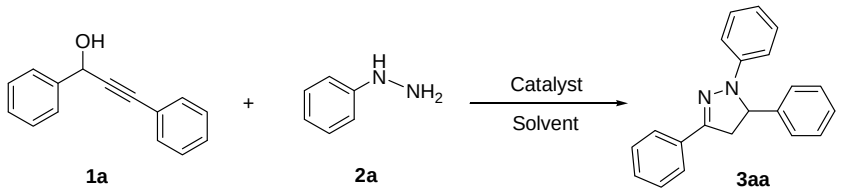
Fig. 1. Disclosed Trisubstituted Dihydropyrazoles as Active Organic Molecules.

Due to the attractive medicinal properties of the dihydropyrazole skeleton, various efficient approaches have been developed for the preparation of these compounds.[13] Nevertheless, the synthesis of substituted dihydropyrazoles directly from simple and readily available substrates is still in great demand. Recently, we reported a novel and efficient $Cu(OTf)_2$-catalyzed sp^3-sp^2 C-C bond formation reaction through the direct coupling of propargylic alcohols with terminal alkenes.[14] Based on this work, we now report novel methodology for the synthesis of dihydropyrazoles from hydrazines and propargyl alcohols using *t*-BuOK (KTB) as a catalyst that accommodates functionality including fluoro, chloro, bromo, methyl, methoxy and hydroxy groups.

To identify suitable conditions for the reaction, a series of catalysts and solvents were screened as shown in Table 1. Initially, propargyl alcohol **1a** (0.5 mmol) was treated with hydrazine **2a** (0.6 mmol) in the presence of 20 mol % of *t*-BuOK in toluene at 100 ^oC for 4 h, and the desired 1,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole **3aa** was isolated in 92% yield (Table 1, entry 1).[15] With other catalysts including CH_3ONa, KOH, NaOH, Cs_2CO_3, and CH_3COONa, the desired product **3aa** was obtained in 60%, 55%, 40%,

30%, and 20% yields in 24 h at 100 ^{o}C, respectively (Table 1, entries 2-6). However, when Na_2CO_3 or K_2CO_3 was used as the catalyst, the reaction did not afford desired product **3aa** under the same reaction conditions (Table 1, entries 7 and 8). Further optimization suggested that solvents had a strong effect on this process. Thus, a variety of solvents, such as DMSO, DMF, dioxane, DCE and CH_3CN, were screened (Table 1, entries 9-13). DMSO and DMF as solvents were also able to facilitate this reaction, while the use of toluene instead of DMSO and DMF reduced the reaction time from 24 to 4 h (Table 1, entry 1 *vs.* entries 9 and 10). Other solvents, including dioxane, DCE and CH_3CN, did not promote the reaction (Table 1, entries 11-13). Notably, the yield of product **3aa** decreased upon lowering the reaction temperature to 90 ^{o}C (Table 1, entry 14). A very slow reaction rate and low yield were also observed when the catalytic amount of *t*-BuOK decreased from 20 % to 10 mol % (Table 1, entry 15), but no improvement in the yield could be obtained as the amount of *t*-BuOK was increased to 30 mol % (Table 1, entry 16). Hence, **1a** (0.5 mmol), **2a** (0.6 mmol), *t*-BuOK (20 mole %) and toluene (2 mL) as solvent at 100 ^{o}C for 4 h were chosen as the optimized conditions.

Table 1 Optimization of the Formation of Substituted 4,5-Dihydropyrazole[a]



1a + **2a** → **3aa**

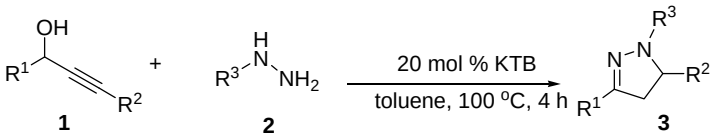
Entry	Solvent	Catalyst	Time (h)	Temp (^{o}C)	Yield (%)[b]
1	Toluene	*t*-BuOK	4	100	92
2	Toluene	CH_3ONa	24	100	60
3	Toluene	KOH	24	100	55
4	Toluene	NaOH	24	100	40
5	Toluene	Cs_2CO_3	24	100	30
6	Toluene	CH_3COONa	24	100	20
7	Toluene	Na_2CO_3	24	100	0
8	Toluene	K_2CO_3	24	100	0
9	DMSO	*t*-BuOK	48	100	77
10	DMF	*t*-BuOK	48	100	75
11	Dioxane	*t*-BuOK	48	100	0
12	DCE	*t*-BuOK	48	80	0
13	CH_3CN	*t*-BuOK	48	80	0
14	Toluene	*t*-BuOK	48	90	64
15[c]	Toluene	*t*-BuOK	24	100	42
16[d]	Toluene	*t*-BuOK	4	100	93

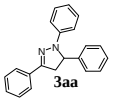
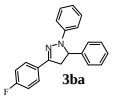
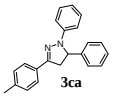
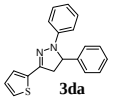
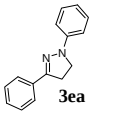
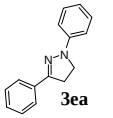
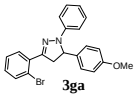
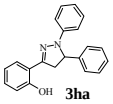
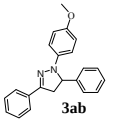
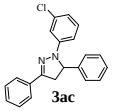
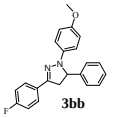
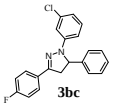
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), and catalyst (20 mol% to **1a**) in solvent (2 mL). [b] Isolated yield of pure product based on **1a**. [c] The reaction was carried in 10 mol% catalyst. [d] The reaction was carried in 30 mol% catalyst.

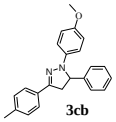
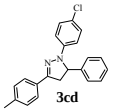
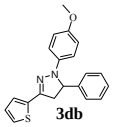
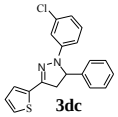
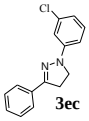
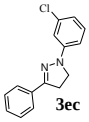
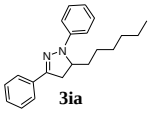
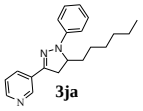
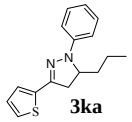
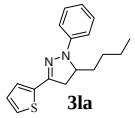
With the optimized reaction conditions established, the reaction was applied to a range of substrates. Typical results are shown in Table 2. Using hydrazine as a model substrate, secondary propargylic alcohols **1** bearing not only terminal alkyne groups but also internal alkyne groups participated well in the reaction. The propargyl alcohols **1c** and **1h** possessing an electron-donating group at the aryl ring (R^1 = 4-MeC_6H_4, 4-OHC_6H_4) afforded the desired products **3ca** and **3ha** in 93% and 89% yields, respectively (Table 2, entries 3 and 8). The crystallization of compound **3ca** from anhydrous ethanol gave single crystals suitable for X-ray analysis (Fig. 2). Substrates

1b possessing an electron-withdrawing group (R^1 = 4-FC_6H_4) at the benzene ring also reacted smoothly and afforded the desired product **3ba** in 87% yield (Table 2, entry 2). We also have observed some variation in yields as a function of electronic effects: that is, aromatic propargyl alcohols with an electron-donating group at the benzene ring gave the corresponding products in higher yields than propargyl alcohol which possessed an electron-withdrawing group on the benzene ring (Table 2, entries 2, 3 and 8). The electron-donating group presumably facilitated the rearrangement that converted propargyl alcohols into α,β-unsaturated carbonyl compounds. Additionally, the aromatic propargyl alcohol **1g** bearing both electron-donating group and electron-withdrawing group was able to afford the corresponding product **3ga** in excellent yield (Table 2, entry 7), and propargyl alcohol bearing a heterocyclic substituent such as **1d** (R^1 = 2-thienyl) gave the desired product **6da** in 88% yield (Table 2, entry 4). Moreover, compared to propargylic alcohols bearing internal alkyne groups, propargylic alcohol **1e** bearing terminal alkyne group gave slightly low yields (Table 2, entries 5 and 17). Interestingly, propargyl alcohol **1f** (R^1 = Ph; R^2 = TMS) was treated with hydrazines **2a** and **2c** under the optimal condition to afford **3ea** and **3ec** lacking the TMS group. Internal propargylic alcohols **1i** (R^2 = Hexyl), **1j** (R^2 = Hexyl), **1k** (R^2 = Propyl) and **1l** (R^2 = Butyl) also gave good results (Table 2, entries 19-22).

Table 2 Synthesis of Substituted 4,5-Dihydropyrazoles from Hydrazines and Propargyl Alcohols[a]



Entry	Propargyl alcohol	Hydrazine	Product	Yield (%)[b]
1	**1a**: $R^1 = R^2 =$ Ph	**2a**: $R^3 =$ Ph	 **3aa**	92
2	**1b**: $R^1 = 4\text{-}FC_6H_4$; $R^2 =$ Ph	**2a**: $R^3 =$ Ph	 **3ba**	87
3	**1c**: $R^1 = 4\text{-}MeC_6H_4$; $R^2 =$ Ph	**2a**: $R^3 =$ Ph	 **3ca**	93
4	**1d**: $R^1 =$ 2-Thienyl; $R^2 =$ Ph	**2a**: $R^3 =$ Ph	 **3da**	88
5	**1e**: $R^1 =$ Ph; $R^2 =$ H	**2a**: $R^3 =$ Ph	 **3ea**	85
6	**1f**: $R^1 =$ Ph; $R^2 =$ TMS	**2a**: $R^3 =$ Ph	 **3ea**	72
7	**1g**: $R^1 = 2\text{-}BrC_6H_4$; $R^2 = 4\text{-}MeOC_6H_4$	**2a**: $R^3 =$ Ph	 **3ga**	94
8	**1h**: $R^1 = 4\text{-}OHC_6H_4$; $R^2 =$ Ph	**2a**: $R^3 =$ Ph	 **3ha**	89
9	**1a**: $R^1 = R^2 =$ Ph	**2b**: $R^3 = 4\text{-}MeOC_6H_4$	 **3ab**	95
10	**1a**: $R^1 = R^2 =$ Ph	**2c**: $R^3 = 3\text{-}ClC_6H_4$	 **3ac**	87
11	**1b**: $R^1 = 4\text{-}FC_6H_4$; $R^2 =$ Ph	**2b**: $R^3 = 4\text{-}MeOC_6H_4$	 **3bb**	89
12	**1b**: $R^1 = 4\text{-}FC_6H_4$; $R^2 =$ Ph	**2c**: $R^3 = 3\text{-}ClC_6H_4$	 **3bc**	85

13	**1c**: R^1 = 4-MeC_6H_4; R^2 = Ph	**2b**: R^3 = 4-$MeOC_6H_4$	 **3cb**	94
14	**1c**: R^1 = 4-MeC_6H_4; R^2 = Ph	**2d**: R^3 = 4-ClC_6H_4	 **3cd**	82
15	**1d**: R^1 = 2-Thienyl; R^2 = Ph	**2b**: R^3 = 4-$MeOC_6H_4$	 **3db**	92
16	**1d**: R^1 = 2-Thienyl; R^2 = Ph	**2c**: R^3 = 3-ClC_6H_4	 **3dc**	84
17	**1e**: R^1 = Ph; R^2 = H	**2c**: R^3 = 3-ClC_6H_4	 **3ec**	79
18	**1f**: R^1 = Ph; R^2 = TMS	**2c**: R^3 = 3-ClC_6H_4	 **3ec**	62
19	**1i**: R^1 = Ph; R^2 = Hexyl	**2a**: R^3 = Ph	 **3ia**	87
20	**1j**:R^1=3-Pyridine; R^2 = Hexyl	**2a**: R^3 = Ph	 **3ja**	85
21	**1k**: R^1 = 2-Thienyl; R^2 = Propyl	**2a**: R^3 = Ph	 **3ka**	82
22	**1l**: R^1 = 2-Thienyl; R^2 = Butyl	**2a**: R^3 = Ph	 **3la**	80

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), *t*-BuOK (20 mol % to **1**), toluene (2 mL), at 100 °C for 4 h. [b] Isolated yield of pure product based on **1**.

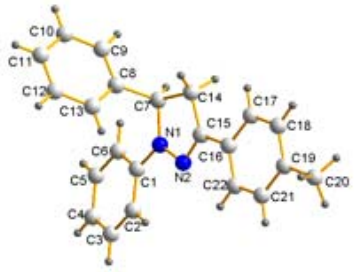
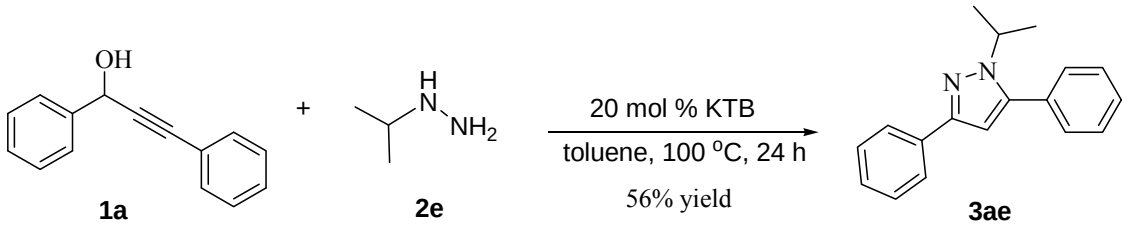


Fig. 2. X-ray Crystal Structure of Dihydropyrazole **3ca**.

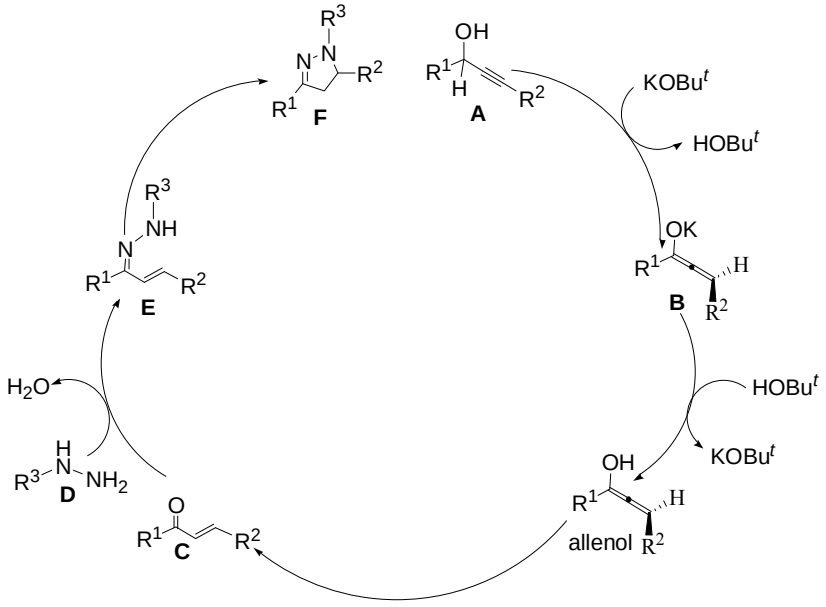
To expand the scope of hydrazine substrates, various hydrazines including **2b** (R^3 = 4-$MeOC_6H_4$), **2c**(R^3 = 3-ClC_6H_4) and **2d** (R^3 = 4-ClC_6H_4) were examined. Obviously, electron-rich hydrazines provided the desired products in higher yields than electron-poor hydrazines (Table 2, entries 9-18).

To our delight, the reaction of 1,3-diphenyl-prop-2-yn-1-ol with isopropyl-hydrazine produced the product 1-isopropyl-3,5-diphenyl-1*H*-pyrazole **3ae** in 56% yield after 24 h (Scheme 1).

Scheme 1. Synthesis of 1-isopropyl-3,5-diphenyl-1*H*-pyrazole **3ae** from 1,3-diphenyl-prop-2-yn-1-ol **1a** and isopropyl-hydrazine **2e**.



Scheme 2. Possible Reaction Mechanism.

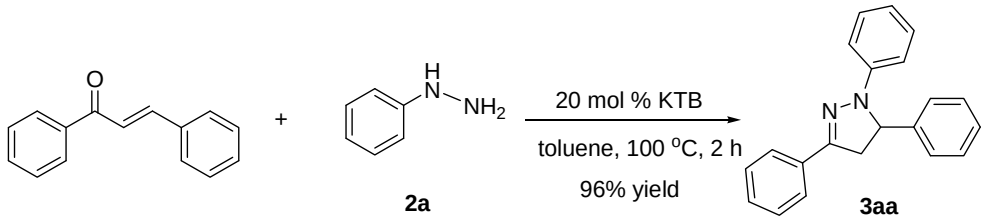


On the basis of others' previous work,[16] a possible reaction mechanism is proposed

as shown in Scheme 2. The first step is the formation of the compound **B** *via* the abstraction of the acidic propargyl C–H proton in the presence of *t*-BuOK. Stabilization of compound **B** through delocalization followed by protonation with the conjugate acid of *t*-BuOK delivers the corresponding allenol. Allenol–enone tautomerism gives the reactive α,β-unsaturated carbonyl compound **C**. And then the reaction of hydrazine **D** and compound **C** affords α,β-unsaturated hydrazones **E**. Finally, compound **E** through the *5-endo-trig* to afford 4,5-dihydropyrazole **F**.

To further prove this mechanism, (*E*)-chalcone and phenyl-hydrazine **2a** were examined under the current reaction conditions. The 1,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole **3aa** was obtained 96% yield after 2 h in this case (Scheme 3). The result indicated that the step from intermediate **C** to **3aa** is feasible *via* the cyclization process.

Scheme 3. Synthesis of 1,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole **3aa** from (*E*)-chalcone and phenyl-hydrazine.



Subsequently, the *in vitro* antitumor activities with selected compounds **3ab** and **3ac** were evaluated by MTT assay against NCI-H460, HepG2, Bel-7404, SKOV3 tumor cell lines and HUVEC non-transformed human cells, using 5-fluorouracil (5-FU) as the positive control. The tested results were shown in Table 3. The compound **3ab** and **3ac**

exhibited moderate to good cytotoxicities. Especially, the compound **3ab** exhibited the best cytotoxicities against NCI-H460, HepG2 and SKOV3 cells with IC_{50} 22, 26 and 20 μmol/L.

Table 3 *In vitro* Anticancer Activities of **3ab** and **3ac**

	IC_{50} (μmol/L)[a]				
Compound	SKOV3	NCI-H460	HepG2	Bel-7404	HUVEC
3ab	20 ± 2	22 ± 3	26 ± 2	42 ± 3	120 ± 2
3ac	42 ± 3	34 ± 2	44 ± 3	30 ± 3	150 ± 3
5-FU	24 ± 1	36 ± 3	27 ± 2	26 ± 1	

[a]IC_{50}(μmol/L) is 50% inhibitory concentration and values are the means of three experiments each done in duplicate.

In conclusion, we have successfully developed a flexible and rapid route to synthesize series of dihydropyrazole derivatives from propargyl alcohols and hydrazines using *t*-BuOK as a catalyst. The reaction completed under air atmosphere, and displayed wide functional group compatibility. In addition, the dihydropyrazole derivatives showed promising anticancer potency through preliminary biological studies. The current study provides a clue for the further development of new types anticancer agents.

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Electronic supplementary information (ESI) available: Experimental section and NMR data of the prepared compounds.

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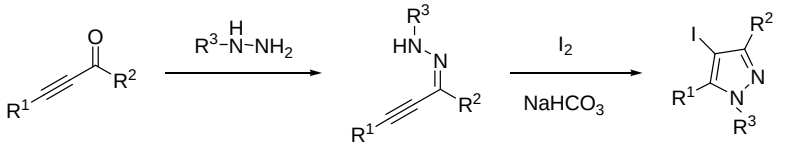

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