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A one-pot approach to 4,5-dihydropyrazoles from ketones, arylacetylenes, and hydrazines

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ABSTRACT

An efficient and straightforward one-pot strategy for the synthesis of 4,5-dihydropyrazole derivatives from ketones, arylacetylenes, and hydrazines in the presence of KO^{t}Bu/DMSO is described. This strategy provides a flexible and rapid route to polysubstituted 4,5-dihydropyrazoles.

1. Introduction

Dihydropyrazole is a useful scaffold known for a wide variety of pharmaceutical (antifungal, antibacterial, anti-inflammatory, antitumor, and antiviral) and agrochemical activities.[1] Recently, more and more chemical compounds bearing dihydropyrazole moiety as potential anticancer agents have been confirmed.[2] For example, Liu et al. have disclosed a series of 4,5-dihydropyrazole derivatives as potential V600E mutant BRAF kinase (BRAF^{V600E}) inhibitors, which are aimed to treat human cancer with good potency, pharmacokinetics, and water solubility.[2d] More recently, Luo et al. reported some aryl-2*H*-pyrazole derivatives as potential telomerase inhibitors, which exhibit high activities against human gastric cancer cell SGC-7901 and human melanoma cell B16-F10.[2e] Moreover, dihydropyrazoles are also of great importance in the preparation of natural products and applications in asymmetric synthesis.[3] It is no wonder that the building up of a dihydropyrazole moiety invokes ever growing synthetic efforts.

Commonly, dihydropyrazole derivatives are constructed by the reaction of chalcones with hydrazine hydrate,[4] semicarbazide hydrochloride or thiosemicarbazide.[5] They are also formed via catalytic enantioselective 1,3-dipolar cycloadditions of diazoalkanes,[6] diazoacetates,[7] and catalytic asymmetric [3+2] cycloadditions of azomethine imines,[8] nitrile imine dipole precursors,[9] and hydrazones.[10] Recently, Brière et al. reported a powerful domino aza-Michael addition/cyclocondensation reaction for the enantioselective synthesis of 3,5-diaryldihydropyrazoles by phase-transfer catalysis.[11] Furthermore, Bolm et al. described an unprecedented strategy to access highly enantioenriched dihydropyrazoles by formal [4+1] cycloadditions of in situ-derived azoalkenes and sulfur ylides catalyzed by a chiral copper/Tol–BINAP complex.[12]

Despite numerous diverse approaches toward the synthesis of dihydropyrazole have been developed so far, the development of more convenient methodologies, especially one-pot multicomponent reactions, from readily available starting materials is still highly desirable. Herein, we report a new one-pot strategy for the synthesis of 5-benzyl-4,5-dihydropyrazoles **4** from ketones **1**, arylacetylenes **2**, and hydrazines **3** in the presence of KO^{t}Bu/DMSO (Scheme 1).

2. Results and discussion

To identify the suitable conditions for the three-component tandem process, a series of bases and solvents were screened using acetophenone **1a**, phenylacetylene **2a**, and phenylhydrazine **3a** as a model reaction (Table 1). As shown in Table 1, the base/DMSO

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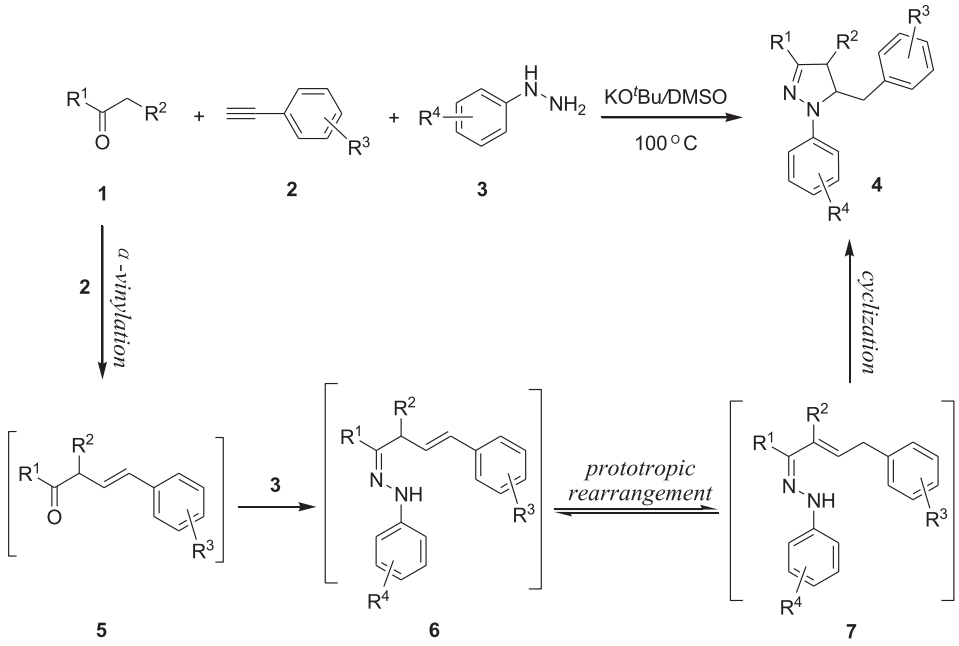
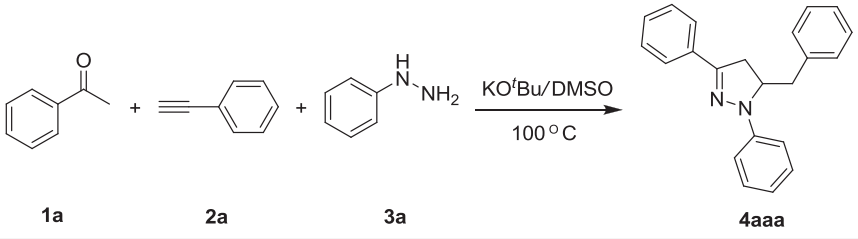


Scheme 1. One-pot synthesis of 5-benzyl-4,5-dihydropyrazoles **4** from ketones **1**, arylacetylenes **2**, and Hydrazines **3**.

Table 1
Optimization of the formation of 5-benzyl-4, 5-dihydropyrazole[a]



Entry	Base	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	$NaOC_2H_5$	DMSO	70–100	8	0
2	Cs_2CO_3	DMSO	70–100	8	0
3	LiOH	DMSO	70–100	8	0
4	NaOH	DMSO	100	8	Trace
5	KOH	DMSO	100	8	15
6	KOH/Bu^{t}OH	DMSO	100	8	25
7	KO^{t}Bu	DMSO	70	8	56
8	KO^{t}Bu	DMSO	100	4	78
9	KO^{t}Bu	DMF	100	8	0
10	KO^{t}Bu	THF	100	8	0
11	KO^{t}Bu	Dioxane	100	8	0
12	KO^{t}Bu	Toluene	100	8	0
13	KO^{t}Bu	DMSO	100	8	0[c]
14	KO^{t}Bu	DMSO	100	8	48[d]

[a] Reaction conditions: 1.2 equiv of acetophenone **1a** (1.2 mmol), and 1.0 equiv of phenylacetylene **2a** (1.0 mmol), 1.5 equiv of base (1.5 mmol), solvent (4 mL), at 70–100 °C for 30 min, 1.2 equiv of phenylhydrazine **3a** (1.2 mmol) then added for the period of time indicated at the same temperature.
[b] Isolated yield of pure product based on phenylacetylene **2a**.
[c] KO^{t}Bu (10 mol %).
[d] KO^{t}Bu (1.0 equiv).

system (except for $NaOC_2H_5$, Cs_2CO_3, LiOH) promoted the formation of the expected product **4aaa** (trace to 25% yield) (Table 1, entries 1–6), and the system of KO^{t}Bu/DMSO proved to be the most effective (yield of **4aaa** being 78%) (Table 1, entries 7 and 8). Other potentially promoting base systems, such as KO^{t}Bu/DMF, KO^{t}Bu/THF, KO^{t}Bu/dioxane, and KO^{t}Bu/toluene pairs appeared to be inefficient in the reaction studied (Table 1, entries 9–12). These results suggest that the solvent plays a crucial role for the success formation of 5-benzyl-4,5-dihydropyrazole. Notably, the reactant molar ratio of KO^{t}Bu also has a key effect on the reaction results: with 10 mol % of KO^{t}Bu no product **4aaa** was detected (Table 1, entry 13), whereas with 1 equiv of KO^{t}Bu, only a 48% yield of **4aaa** was obtained (Table 1, entry 14).

With the optimal conditions in hand, we examined the KO^{t}Bu/DMSO system for one-pot synthesis of 5-benzyl-4,5-dihydropyrazoles from various ketones **1**, arylacetylenes **2**, and hydrazines **3**. Table 2 illustrates the wide generality and substrate scope of this tandem reaction. As follows from Table 2, this strategy