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Zinc-Catalyzed Synthesis of Pyrazolines and Pyrazoles via Hydrohydrazination

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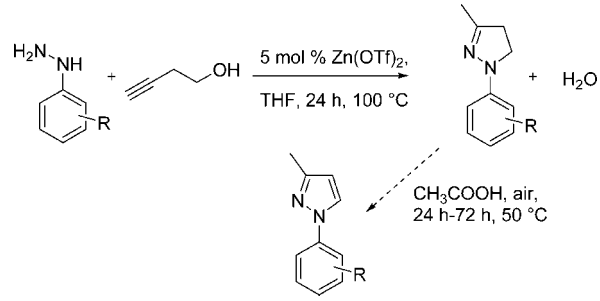
ABSTRACT



A novel regioselective synthesis of aryl-substituted pyrazolines and pyrazoles has been developed. Substituted phenylhydrazines react with 3-butynol in the presence of a catalytic amount of zinc triflate to give pyrazoline derivatives. The resulting products are easily oxidized in a one-pot procedure to the corresponding pyrazoles.

Pyrazoline and pyrazole derivatives play an important role in the pharmaceutical and agrochemical industries. For example, pyrazolines have been reported to show a wide range of biological activity, including antidepressant, anticancer, and antibacterial activity.[1] On the other hand, the pyrazole motif is found in blockbuster drugs such as celecobix (Celebrex),[2] sildenafil (Viagra),[3] and rimonabant (Acomplia).[4]

In general, pyrazoles are obtained by condensation of 1,3-diketones with hydrazine derivatives.[5] Unfortunately, this reaction often results in a mixture of regioisomers. Notably, the use of α,β-unsaturated ketones with hydrazines presents a modification of the common method, wherein pyrazole and pyrazoline derivatives can be synthesized with high regioselectivity.[6] In addition, several other methods have also been reported for the preparation of pyrazoles.[7]

In recent years, catalytic processes have also become of interest. In this regard, Buchwald et al. demonstrated an elegant copper-catalyzed domino coupling/hydroamidation reaction,[8] and Mori et al. developed an efficient palladium-catalyzed four-component coupling[9] for the synthesis of pyrazoles.

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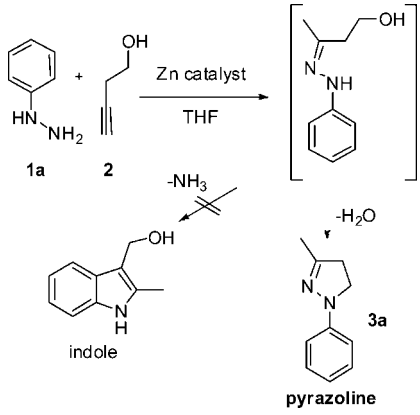
Over the past years, we investigated catalytic reactions of arylhydrazines with alkynes in more detail.[10] Most recently, we succeeded in an intermolecular zinc-mediated and -catalyzed hydrohydrazination reaction of alkynes, which allows a general synthesis of substituted indoles.[11] Following these investigations, we discovered that the reaction of phenylhydrazine **1a** with 3-butynol **2** in the presence of a stochiometric amount of zinc chloride did not result in the expected indole motif. Instead, the formation of the pyrazoline **3a** occurred via hydrohydrazination of the alkyne and condensation reaction (Scheme 1).

Scheme 1. Synthesis of Pyrazoline **3a**



Apparently, in the first step the hydrohydrazination of 3-butynol gave the corresponding arylhydrazone. In general, the arylhydrazone undergoes Fischer indole cyclization in the presence of a stochiometric amount of Lewis acid, such as $ZnCl_2$.[11] However, in the case of 3-butynol, the pyrazoline was formed by an unusual nucleophilic substitution of the hydroxy group.

To study this novel pyrazoline formation in more detail, we investigated the influence of different catalysts, solvents, and temperatures on the reaction of phenylhydrazine **1a** with 3-butynol **2**. Selected results are presented in Table 1. The model reaction proceeded in excellent yield (93%) in the presence of a stochiometric amount of $ZnCl_2$ (Table 1, entry 1). Unfortunately, when 5 mol % of $ZnCl_2$ was used, only 36% yield was observed. Similarly, in the presence of a catalytic amount of $Zn(OAc)_2$ we obtained only low conversion and yield (Table 1, entry 2). To our delight applying 5 mol % $Zn(OTf)_2$ an excellent product yield (98%) was observed (Table 1, entry 3). Dioxane gave a somewhat lower yield compared to tetrahydrofuran and toluene as solvent (Table 1, entries 4 and 5). Also in the presence of a stoichiometric amount of phenylhydrazine a high product yield was obtained (Table 1, entry 10).

Table 1. Reaction of Phenylhydrazine **1a** with 3-Butynol **2** under Different Conditions[a]

entry	catalyst	solvent	T (°C)	time (h)	conv[b] (%)	yield[b] (%)
1	$ZnCl_2$	THF	100	24	67 (100[c])	36 (93[c])
2	$Zn(OAc)_2$	THF	100	24	26	12
3	$Zn(OTf)_2$	THF	100	24	100	98
4	$Zn(OTf)_2$	dioxane	100	24	63	57
5	$Zn(OTf)_2$	toluene	100	24	100	96
6	$Zn(OTf)_2$	THF	80	24	64	62
7	$Zn(OTf)_2$	THF	120	24	100	93
8	$Zn(OTf)_2$	THF	100	9	85	76
9	$Zn(OTf)_2$	THF	100	16	94	94
10[d]	$Zn(OTf)_2$	THF	100	24	91	85

[a] Reaction conditions: 3-butynol (1.0 mmol), phenylhydrazine (1.3 mmol), 5 mol % of catalyst, solvent (2 mL). [b] Yield is determined by GC analysis with dodecane as internal standard. [c] 100 mol % of catalyst. [d] Phenylhydrazine (1.0 mmol).

Next, we studied reactions of 3-butynol **2** with various substituted arylhydrazines **1a**−**k** under optimized conditions in the presence of 5 mol % $Zn(OTf)_2$. In general, hydrohydrazination and condensation reactions proceeded smoothly, and it was possible to isolate the pyrazoline derivatives **3a**−**k** in good to excellent yields (Table 2).

For example, reaction of *p*-tolylhydrazine (**1b**) proceeded in 96% yield, while the more sterical hindered *o*-tolylhydrazine (**1c**) gave a lower yield of 88% (Table 2, entry 3). A similar effect was observed for the reaction of the *p*-chlorophenylhydrazine, which led to pyrazoline **3d** in 98% yield compared to the *o*-chlorophenyl-substituted pyrazoline **3e** (52% yield) (Table 2, entries 4 and 5).

In addition, bromo-, cyano-, methylsulfonyl-, and isopropylphenyl-substituted pyrazolines were synthesized in up to 99% yield (Table 2, entries 6−9). Dichloro-substituted phenylhydrazines in *para* and *meta* positions gave the corresponding pyrazolines **3j** and **3k** in 98% and 97% yields, respectively.

In agreement with previous studies the aryl-substituted pyrazolines were easily oxidized to the corresponding pyrazoles. Due to the ease of reaction conditions and environmental advantages we applied air as oxidant.[12,13] As shown in Scheme 2 after successful formation of the pyrazolines, we added acetic acid to the reaction mixture and heated the reaction mixture for additional 24−72 h in air. The reaction time depended largely on the substituent on the aryl group. While *p*-methyl- and *p*-isopropylphenyl-substituted pyrazolines were easily oxidized (Table 3, entries

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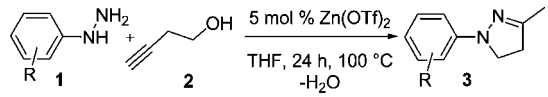
Table 2. Reaction of Arylhydrazines **1** with 3-Butynol **2** to Various Substituted Pyrazolines[a]



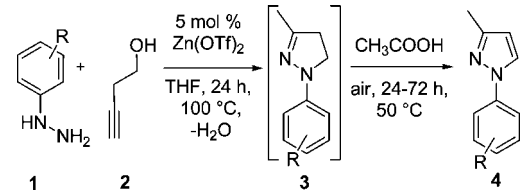
entry	hydrazine **1**	pyrazoline **3**	yield (%)[b]
1	**1a**	**3a**	96
2	**1b**	**3b**	96
3	**1c**	**3c**	88
4	**1d**	**3d**	98
5	**1e**	**3e**	52
6	**1f**	**3f**	99
7	**1g**	**3g**	96
8	**1h**	**3h**	87
9	**1i**	**3i**	99
10	**1j**	**3j**	98
11	**1k**	**3k**	97

[a] Reaction conditions: 3-butynol (1.5 mmol), phenylhydrazine derivative (1.95 mmol), 5 mol % of $Zn(OTf)_2$, THF (3 mL), 24 h, 100 °C. [b] Isolated yield.

1, 3), the more deactivated *o*-methyl- and *p*-bromophenyl-substituted pyrazolines needed a longer reaction time for full conversion (Table 3, entries 2, 4).

Interestingly, there was no significant difference in yield between the synthesis of the pyrazoles by one-pot or sequential reactions. For example, **4a** was obtained in 56% yield by adding acetic acid directly to the reaction mixture compared to 61% yield observed with the pure pyrazoline **3b** (Table 3, entry 1). Advantageously, a purification of the reaction mixture is not necessary for the direct synthesis of pyrazoles **4**. Notably, when 4-pentynol instead of 3-butynol

Scheme 2. One-Pot Formation of the Pyrazoles



is used, indole derivatives are obtained via a domino amination−cyclization sequence. Apparently, in the case of 3-butynol, the formation of the five-membered ring is preferred compared to the Fischer indole cyclization.

Table 3. Synthesis of Different Pyrazole Derivatives Starting from Phenylhydrazines **1** and 3-Butynol **2**[a]

entry	pyrazole **4**	time (h)	yield (%)[b]
1	**4a**	24	56 (61[c])
2	**4b**	48	48 (60[c])
3	**4c**	24	63
4	**4d**	72	67

[a] Reaction conditions: (step 1) 3-butynol (1.5 mmol), phenylhydrazine derivative (1.95 mmol), 5 mol % of $Zn(OTf)_2$, THF (3 mL), 24 h, 100 °C; (step 2) CH_3COOH, air, 24−72 h, 50 °C. [b] Isolated yield. [c] Yield only for the last step using the purified pyrazoline as educt.

In summary, we have developed a novel method for the synthesis of aryl-substituted pyrazolines and pyrazoles. Various substituted arylhydrazines react with 3-butynol in the presence of a catalytic amount of $Zn(OTf)_2$ to give pyrazoline derivatives in excellent yields. Subsequent one-pot oxidation with air led to the corresponding pyrazoles. This methodology is complementary to the classical pyrazoline synthesis from hydroxy ketones.

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Supporting Information Available: Experimental procedures and spectroscopic characterization data of all compounds mentioned in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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