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# A Novel One-Pot Method for the Preparation of Pyrazoles by 1,3-Dipolar Cycloadditions of Diazo Compounds Generated in Situ

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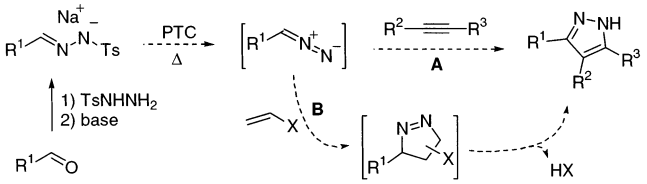
**Abstract:** A convenient one-pot procedure for the preparation of pyrazoles by 1,3-dipolar cycloaddition of diazo compounds generated in situ has been developed. Diazo compounds derived from aldehydes were reacted with terminal alkynes to furnish regioselectively 3,5-disubstituted pyrazoles. Furthermore, the reaction of *N*-vinylimidazole and diazo compounds derived from aldehydes gave exclusively 3-substituted pyrazoles in a one-pot process.

The synthesis of pyrazoles remains of great interest due to the wide applications of such heterocycles in the pharmaceutical and agrochemical industry.[1,2] The most important methods for preparing this class of heterocycles are the reaction between hydrazines with $\beta$-difunctional compounds[3] and 1,3-dipolar cycloadditions of diazo compounds onto triple bonds.[4] The former process, considered to be the best method for the preparation of pyrazoles, involves the double condensation of 1,3-diketones with hydrazine or its derivatives.[5] This method has a wide scope not only because of the readily availability of 1,3-diketones but also because one carbonyl of the diketone starting material can be replaced by an acetal, a hemiacetal, a chlorovinyl group, dihalides, etc.[3] The cycloaddition approach to pyrazoles has been essential in the mechanistic understanding of the 1,3-dipolar cycloaddition reactions but to date is second in importance for preparative purposes due the need to prepare and handle diazo compounds which are known to be toxic and potentially explosive. We recently reported a new method for generating aryldiazomethanes from stable tosylhydrazone derivatives. This procedure has proven to be a highly effective and safe alternative to handling aryldiazomethanes[6] and has been employed in the sulfur ylide-mediated synthesis of epoxides from carbonyl compounds,[7] cyclopropanation of alkenes,[8] and homologation of aldehydes.[9] We were therefore keen to examine whether this new process could solve some of the traditional problems inherent in the 1,3-dipolar cycloaddition approach to pyrazoles. In this paper, we report our success in achieving this goal and the development of a new user-friendly one-pot procedure for the preparation of pyrazoles from aldehydes in which not only the diazo compound but also the tosylhydrazone is generated in situ.

**SCHEME 1. Proposed Synthesis of Pyrazoles Using Diazo Compounds Generated in Situ**




We proposed two different routes to pyrazoles using diazo compounds generated in situ: first, direct 1,3-dipolar cycloaddition of diazo compounds onto alkynes (route A, Scheme 1), or second, employing an olefin bearing a leaving group **X**, which would afford the pyrazole after an elimination/aromatization of the cycloadduct intermediate (route B, Scheme 1).[10] The diazo compounds involved in these [3 + 2] approaches to pyrazoles would be generated in situ from tosylhydrazone salts.

Preliminary experiments showed that diazo compounds could also be generated in situ from aldehydes in a one-pot process. Condensation of tosylhydrazine with benzaldehyde followed by treatment with an aqueous solution of sodium hydroxide led to a solution of benzaldehyde tosylhydrazone sodium salt, which upon warming to 50 °C gave a reddish solution of phenyldiazomethane. Prior to warming the reaction mixture, phenylacetylene was added and the desired 3,5-diphenylpyrazole was obtained in good yield as a single regioisomer (entry 1, Table 1). This new procedure for the preparation of a pyrazole from

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(1) Elguero, J. In *Comprenhensive Heterocyclic Chemistry*; Katritzky, A., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, pp 277−282.
(2) Elguero, J. In *Comprenhensive Heterocyclic Chemistry II*; Shinkai, I., Ed.; Elseiver: Oxford, 1996; Vol. 3, pp 3−75.
(3) Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1966**, *6*, 347−429.
(4) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Vol. I.
(5) Wiley, R. H.; E., H. P. *Org. Synth.* **1951**, *31*, 43−44.
(6) Aryldiazomethanes have been prepared by vacuum pyrolysis of the hydrazone salt. See: Creary, X. *Org. Synth.* **1986**, *64*, 207. We have carried out the Creary preparation a large number of times over a 5-year period but on three occasions experienced minor explosions. We therefore sought methods for generating the diazo compound in situ to avoid the need to carry out the vacuum pyrolysis.
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(10) The formation of pyrazoles from pyrazolines by elimination reactions has been previously described. For eliminations of $H_2O$, see: Singh, S. P.; Kumar, D.; Jones, B. G.; Threadgill, M. D. *J. Fluorine Chem.* **1999**, *94*, 199−203. Flores, A. F. C.; Martins, H. A. P.; Rosa, A.; Flores, D. C.; Zannatta, N.; Bonacorso, H. G. *Synth. Commun.* **2002**, *32*, 1585−1594. For eliminations of HBr, see: Chandrasekhar, S.; Rajaiah, G.; Srihari, P. *Tetrahedron Lett.* **2001**, *42*, 6599−6601. Jiang, B.; Xu, J. Y. *J. Fluorine Chem.* **1994**, *67*, 83−86. For eliminations of *p*-TolSOH, see: Midura, W. H.; Krysiah, J. A.; Mikolajczyk, M. *Tetrahedron* **1999**, *55*, 14791−14802. For eliminations of $HNO_2$, see: Mancera, M.; Rodriguez, E.; Roffe, I.; Galbis, J. A. *Carbohydr. Res.* **1994**, *253*, 307−316.

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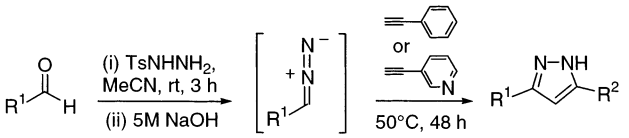
**TABLE 1. Yields and Regioselectivities of 3,5-Disubstituted Pyrazoles Formed from Alkynes and Aldehydes**



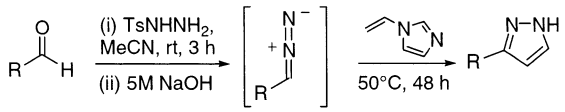

| entry | $R^1$ | $R^2$ | yield[a] (%) | ratio of regioisomers (3,5/3,4)[b] |
|---|---|---|---|---|
| 1 | Ph | Ph | 61 | 99.8:0.2 |
| 2 | *p*-$CNC_6H_4$ | Ph | 67 | 99.8:0.2 |
| 3 | *p*-$MeOC_6H_4$ | Ph | 51 | 99.8:0.2 |
| 4 | 3-pyridyl | Ph | 33 | 97:3 |
| 5 | Ph | 3-pyridyl | 36 | 97:3 |
| 6 | *p*-$CNC_6H_4$ | 3-pyridyl | 19 | 99.8:0.2 |
| 7 | *p*-$MeOC_6H_4$ | 3-pyridyl | 54 | 99.8:0.2 |
| 8 | 3-pyridyl | 3-pyridyl | 24 | 95:5 |

[a] Isolated yields. [b] Determined by GC−MS.

an aldehyde and an alkyne was tested with a selection of four aromatic aldehydes as precursors of diazo compounds and two alkynes as dipolarophiles, phenylacetylene (entries 1−4, Table 1) and 3-ethynylpyridine (entries 2−8, Table 1). The desired pyrazoles were obtained in moderate to high yield with excellent regioselectivity in favor of the 3,5-disubstituted pyrazoles. The yields of these reactions can be improved by preforming the corresponding tosylhydrazone sodium salt, e.g., the yield obtained in entry 1 was increased up to 71% starting from benzaldehyde tosylhydrazone salt. Clearly, the process can be applied to the generation of a library of pyrazoles as a large variety of the starting aldehydes and acetylenes are readily available. The high regioselectivity observed in these 1,3-dipolar cycloadditions is in keeping with previous literature reports involving cycloadditions onto arylacetylenes.[11] This can be explained by both the steric interaction of the substituents of the reactants and the atomic orbital coefficients of the HOMO (diazo compound)−LUMO (alkyne) favored interaction expected for this type of cycloaddition.[4]

The 1,3-dipolar cycloaddition of diazo compounds onto acetylene would lead to 3-substituted pyrazoles.[12] However, acetylene is a very inconvenient dipolarophile to use due to the difficulties in handling this volatile alkyne, whose boiling point at atmospheric pressure is −83 °C. We therefore decided to explore the use of monosubstituted alkenes bearing a potential leaving group as an acetylene equivalent in the newly developed one-pot 1,3-dipolar cycloaddition of diazo compounds generated in situ from aldehydes. The choice of leaving group (X) was considered to be critical. It had to be a good enough leaving group for elimination to occur rapidly, thus avoiding extrusion of nitrogen with formation of the corresponding cyclopropane, but at the same time if H−X was too acidic it would protonate the hydrazone salt and inhibit formation of the diazo compound. Considering these issues, two acetylenes equivalents were tested: *N*-vinylimidazole and vinyl acetate. However, the reaction of tosylhydrazone salt **1** with vinyl acetate gave a complex mixture of products (**2**, **3**, **4**, and **5**). In addition to the hydrazone itself, the benzylated hydrazone **5**[13] was formed together with some of the desired pyrazole **2** and the acyl pyrazole **3**. Clearly, the elimination of acetic acid caused significant side reaction and protonation of the hydrazone salt itself. In contrast, the desired pyrazole **2** was obtained in good yield using *N*-vinylimidazole as the substrate. The imidazole byproduct, being less acidic than acetic acid, did not interfere in any side reaction, and it was easily removed from the crude reaction by an aqueous workup. Indeed, the process generated exclusively water-soluble byproducts, sodium *p*-toluenesulfinate, and imidazole, and after aqueous wash, the pyrazole was isolated in essentially pure form. The possible cycloadduct intermediates of the initial dipolar cycloaddition were never detected by TLC or GC−MS, suggesting that the elimination was occurring under the reaction conditions.

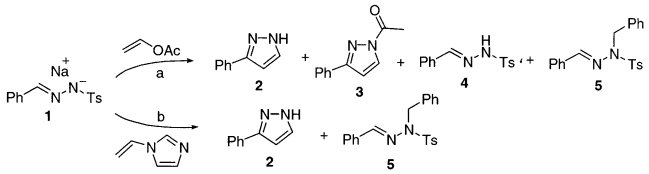
**TABLE 2. Yields of 3-Substituted Pyrazoles Formed from Reaction of *N*-Vinylimidazole and Aldehydes**




| entry | R | yield[a] (%) |
|---|---|---|
| 1 | Ph | 56 |
| 2 | *o*-$MeC_6H_4$ | 47 |
| 3 | *p*-$MeOC_6H_4$ | 62 |
| 4 | *p*-$CNC_6H_4$ | 79 |
| 5 | *p*-$ClC_6H_4$ | 71 |
| 6 | 2-furyl | 33 |
| 7 | 2-thienyl | 32 |
| 8 | 3-pyridyl | 32 |

[a] Isolated yields.

**SCHEME 2. Preparation of 3-Phenylpyrazole[a]**




[a] Reagents and conditions: (a) $BnEt_3NCl$ (0.1 equiv), vinyl acetate (20 equiv), 1,4-dioxane, 30 °C, 48 h; (b) $BnEt_3NCl$ (0.1 equiv), *N*-vinylimidazole (5 equiv), 1,4-dioxane, 30 °C, 48 h, 81%.

The effectiveness of this procedure for the preparation of 3-substituted pyrazoles is illustrated by the use of a series of diazo precursors derived from aromatic and heteroaromatic aldehydes (entries 2−8, Table 2). Although yields can again be improved by starting from the preformed hydrazone salt (route b, Scheme 2), the operational simplicity and speed of the current protocol may outweigh the issue concerning the moderate yields obtained.

In conclusion, we have developed a simple one-pot procedure for the preparation of 1*H*-pyrazoles by the

(11) Bastide, J.; Henri-Rousseau, O. *Bull. Soc. Chim. Fr.* **1973**, 2294−2296. 1,3-Dipolar cycloadditions onto electron-rich acetylenes form the 3,4-regioisomer and cycloaddition onto electronically neutral acetylenes (alkyl substituted) give regioisomeric mixtures of pyrazoles. See ref 4.

(12) 3-Substituted pyrazoles can also be prepared by cycloaddition of diazomethane with monosubstituted acetylenes. See: Kirmse, H. *Justus Liebigs Ann. Chem.* **1958**, *614*, 1.

(13) The formation of side product **5** could be formed by reaction of the tosylhydrazone salt **1** with phenyldiazomethane in the presence of a protic source.

novel 1,3-dipolar cycloaddition reactions of diazo compounds generated in situ from aldehydes. 1*H*-3-Substituted pyrazoles were easily prepared by 1,3-dipolar cycloadditions of diazo compounds, generated from various aldehydes, with *N*-vinylimidazole as an acetylene equivalent. Diazo compounds, generated in situ from aldehydes, reacted regioselectively with monosubstituted alkynes, providing a convergent method for the preparation of 3,5-disubstituted pyrazoles.

## Experimental Section

**General Procedure for the Preparation of 3-Substituted Pyrazoles (Tables 1 and 2).** The aldehyde (1.5 mmol) was added to a solution of *p*-toluenesulfonyl hydrazide (279 mg, 1.5 mmol). After the mixture was stirred for 3 h at rt, a solution 5 N NaOH (300 $\mu$L, 1.5 mmol) was added and the mixture was stirred for a further 20 min. The dipolarophile (7.5 mmol) was added, and the mixture was stirred at 50 °C for 48 h. The volatiles were evaporated under reduced pressure, and the residue was dissolved in a 1:1 mixture of water−ethyl acetate (70 mL). The organic layer was separated and dried over $MgSO_4$. After filtration and removal of the solvent under reduced pressure, the crude material was purified by flash chromatography.

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**Supporting Information Available:** General methods and representative procedures for the synthesis of pyrazoles, as well as characterization data of the pyrazoles synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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