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Reaction of *N*-Monosubstituted Hydrazones with Nitroolefins: A Novel Regioselective Pyrazole Synthesis

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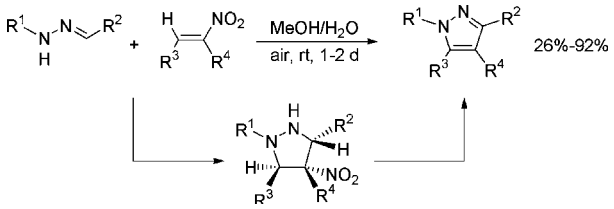
ABSTRACT



A novel regioselective synthesis of substituted pyrazoles from *N*-monosubstituted hydrazones and nitroolefins is described. The reaction is performed in a one-pot manner and the yields range from moderate to excellent. A key nitropyrazolidine intermediate is characterized and a plausible mechanism is proposed.

Substituted pyrazoles are important synthetic targets in the pharmaceutical industry because the pyrazole motif makes up the core structure of numerous biologically active compounds,[1] including blockbuster drugs such as Celebrex[2] and Viagra.[3] Although numerous methods have been developed, regioselective synthesis of the pyrazole ring remains a significant challenge for organic chemists.[4] For example, the prevalent method of reacting hydrazines with 1,3-dicarbonyl compounds often results in a mixture of regioisomers when the reactivity of the two carbonyl groups is not drastically different. A modification of this method, replacing 1,3-dicarbonyl compounds with α,β-ethynyl ketones or esters, affords various regioselectivity, depending on specific substrates.[5] Another important method, 1,3-dipolar cycloaddition of diazoalkanes or nitrilimines with olefins or alkynes, has found only limited applications in pyrazole synthesis because 1,3-dipoles are often difficult to prepare and are potentially explosive.[6] Nevertheless, one feature of 1,3-dipolar cycloaddition was particularly intriguing to us, i.e., it is often highly regioselective.

Hydrazones have been reported to react with activated alkenes[7] or alkynes[8] to afford pyrazolidines or pyrazoles, respectively, probably proceeding via 1,3-dipole species

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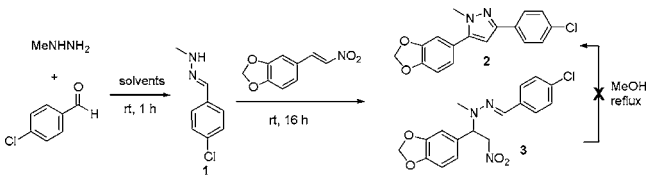
generated in situ.[9] However, harsh conditions are normally required because of hydrazones' weak nucleophilicity. In addition, removal of activating groups is often problematic. Nitroolefins, strong electrophiles that are widely used in organic synthesis,[10] are also known to react with diazo compounds to prepare pyrazoles.[11] We reasoned that hydrazones and nitroolefins might be good partners for a general, regioselective method to synthesize pyrazoles. Furthermore, because numerous hydrazones and nitroolefins are readily available, the reaction would be ideal to prepare large libraries of substituted pyrazoles for drug discovery efforts.

In connection with one of our drug discovery projects, we needed to prepare *N*-substituted pyrazoles. Reaction of *N*-monosubstituted hydrazones with nitroolefins to synthesize pyrazole products was rarely documented. In 1979, Snider and co-workers observed that phenylhydrazones reacted with *trans*-β-nitrostyrene neat to afford 4-nitropyrazoles.[12] Surprisingly, nitro-eliminated pyrazole products were obtained when D-galactose phenyl or methylhydrazones were used in DMF/H_2O.[13] These results prompted us to study this reaction in detail.

Our orienting experiments were performed with methylhydrazone **1**, which was prepared in situ, followed by the addition of 3,4-methylenedioxy-β-nitrostyrene (Table 1).

Table 1. Solvent Effect on the Pyrazole Formation Reaction



solvents	Et_2O	DMF	DMF/H_2O	MeOH[b]	EtOH	IPA	AcOH
2:3 Ratio[a]	1:99	4:96	41:59	94:6	93:7	71:29	99:1
solvents	DCM	THF	EtOAc	CH_3CN[c]	Toluene	Pyridine	Et_3N
2:3 Ratio[a]	94:6	6:94	20:80	8:92	0:0	10:90	9:91

[a] Determined by HPLC analysis at 254 nm (UV), not corrected. [b] The isolated yield of compound **2** was 83%. [c] The isolated yield of compound **3** was 90%.

Because some hydrazones are not stable upon isolation,[14] the reaction was always performed in a one-pot manner.[15] Two solvents employed in the literature, Et_2O and DMF, were tested first. To our surprise, Michael addition product **3** was the dominant product, in contrast to nitropyrazole and nitro-eliminated pyrazole obtained in the literature. Although hydrazone is an ambident nucleophile that can react with electrophiles on both C and N positions, this reaction is highly regioselective, exclusively on the N position. The desired 1-methyl-3,5-diarylpyrazole regioisomer **2** was isolated only in low yields. Interestingly, addition of water (1:10 v/v) as cosolvent to DMF substantially increased the ratio of pyrazole product **2** (Table 1). Intrigued by the above results, we conducted a solvent screen and the results are summarized in Table 1. *N*-Methylhydrazone was formed cleanly in all the solvents tested, as indicated by HPLC analysis; however, subsequent reaction with nitroolefin was very solvent dependent. Nonpolar solvents such as toluene are not a good choice for the reaction, neither **2** nor **3** was isolated. Aprotic polar solvent generally favored the formation of Michael addition product **3**, with the exception of CH_2Cl_2. In the case of CH_3CN, the reaction was almost quantitative with the isolated yield of compound **3** at 90%. Protic polar solvent favored the formation of pyrazole **2**. Although AcOH and CH_2Cl_2 also afforded high 2:3 ratios, the reaction in alcoholic solvents such as MeOH and EtOH is much cleaner to provide the best isolated yields of **2**. These results suggest that protic polar solvent may help in stabilizing the 1,3-dipole species generate in situ, thus, facilitate the cylcoaddition reaction to form pyrazoles.[7c,16,17] The structure of regioisomer **2** was assigned by the characteristic C-4 proton NMR resonance at 6.50 ppm[18] and was further confirmed by NOE studies. One interesting observation was that when isolated compound **3** was subjected in MeOH to reflux temperature for days, no reaction was observed whatsoever, thus excluding it as an intermediate to compound **2**.[19]

Once MeOH was identified as the favored solvent,[20] we investigated the scope of this unique one-pot pyrazole formation reaction, and the results are summarized in Table 2. The reaction was monitored with HPLC analysis. Hydrazone formation was usually complete within 1−2 h whereas pyrazole formation required 1−2 days at room temperature unless otherwise specified. Different nitroolefins were first investigated. Either aryl (entries 1 and 2) or alkyl (entry 3) groups at the R^3 position afford corresponding pyrazoles in excellent yields. Substitution at the R^4 position of nitroolefins is also well tolerated (entries 2 and 3). Variation of the aldehyde component (R^2) was then explored. It appears that steric effects play a small role at the R^2 position; for example, sterically highly congested 2,2-dimethylpropionaldehyde affords pyrazole **7** in 56% yield (entry 5). In contrast,

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(11) (a) Mancera, M.; Rodriguez, E.; Roffe, I.; Galbis, J. A. *J. Org. Chem.* **1988**, *53*, 5648−5651. (b) Parham, W. E.; Braxton, H. G., Jr.; O'Connor, P. R. *J. Org. Chem.* **1961**, *26*, 1805−1807. (c) Parham, W. E.; Bleasdale, J. L. *J. Am. Chem. Soc.* **1950**, *72*, 3943−3846.

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(13) (a) Gomez-Guillen, M.; Conde-Jimenez, J. L. *Carbohydr. Res.* **1988**, *180*, 1−17. (b) Gomez-Guillen, M.; Hans-Hans, F.; Lassaletta-Simon, J. M.; Martin-Zamora, M. E. *Carbohydr. Res.* **1989**, *189*, 349−358.

(14) Buckingham, J. *Q. Rev. Chem. Soc.* **1969**, *23*, 37−56.

(15) An identical result was obtained when isolated methylhydrazone **1** was used.

(16) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 212−224.

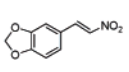
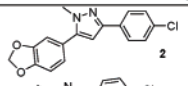
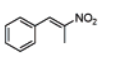
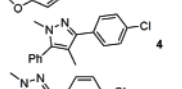
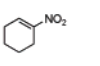
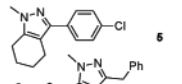
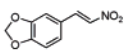
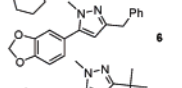
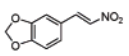
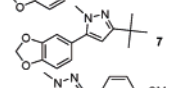
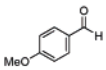
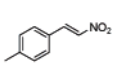
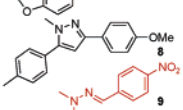
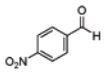
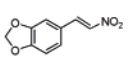
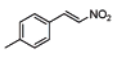
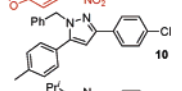
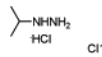
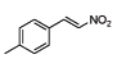
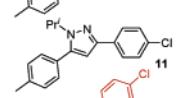
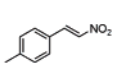
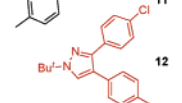
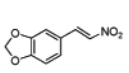
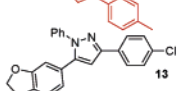
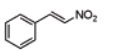
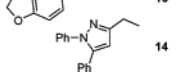
(17) Le Fevre, G.; Sinbandhit, S.; Hamelin, J. *Tetrahedron* **1978**, *35*, 1821−1824.

(18) Murray, W. V.; Wachter, M. P. *J. Heterocycl. Chem.* **1989**, *26*, 1389−1392.

(19) The analogous addition product was proposed as the key intermediate in ref 13.

(20) When hydrazines come as HCl salt, 10% water was added as the cosolvent to facilitate the formation of hydrazones.

Table 2. Three-Component Reaction for Pyrazole Synthesis

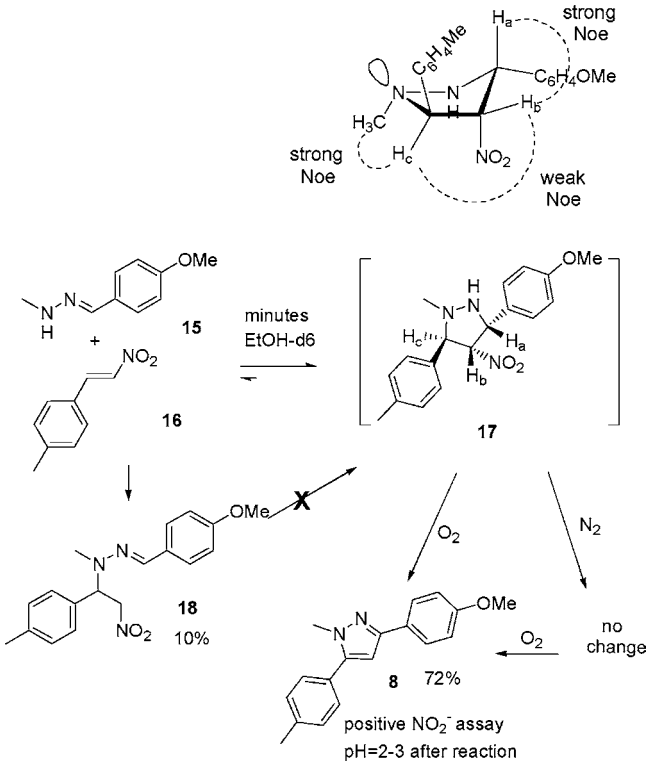
entry	hydrazine	aldehyde	nitro-olefin	product	yield
1	MeNHNH$_2$			 2	83%
2	MeNHNH$_2$			 4	92%
3	MeNHNH$_2$			 5	81%
4	MeNHNH$_2$			 6	82%
5	MeNHNH$_2$			 7	56%
6	MeNHNH$_2$			 8	72%
7	MeNHNH$_2$			9	90%
8[a]				 10	90%
9[a,b]				 11	26%
10[a,c]				 12	15%
11[c]	PhNHNH$_2$			 13	42%
12	PhNHNH$_2$			 14	76%

[a] 10:1 MeOH/H_2O was used as solvent. [b] Room temperature, 7 days. [c] Reflux, 4 days.

electronic effects play a much greater role in these reactions. Whereas electron-donating or slightly electron-withdrawing aldehydes provide pyrazole products smoothly, electron-demanding 4-nitrobenzaldehyde gives the Michael addition product **9** in 90% yield (entry 7), which does not cyclize even at reflux temperature. With respect to the substituents on the hydrazine component, it appears both electronic and steric effects are important. The pyrazole formation reaction proceeds smoothly with primary alkyl hydrazones such as methyl hydrazones (entries 1−7) and benzyl hydrazone (entry 8). However, as the bulk of the R^1 group increases, the reaction slows or requires higher temperature. For example, with isopropylhydrazine, the pyrazole formation reaction was not complete after 7 days at room temperature with only 26% isolated yield (entry 9). In the case of *tert*-butylhydrazine, after refluxing for 4 days, a different 1-*tert*-butyl-3,4-diarylpyrazole regioisomer **12** was isolated in 15% yield (entry 10). Presumably in this case, *tert*-butylhydrazone reacted with the nitroolefin at the C position instead of the N position to avoid the sterically unfavorable R^1−R^3 interaction. An electronic effect related to the hydrazone substituents is apparent with electron-deficient phenylhydrazine. In entry 11, reflux temperature was required for 4 days to give a 42% yield of pyrazole **13**. Interestingly, this effect can be moderated through the use of an electron-donating aldehyde such as propionaldehyde, which gives a 76% yield of pyrazole **14** at room temperature (entry 12). The above results suggest that the electron density of hydrazones is essential to the success of the pyrazole formation reaction.

During the course of our study, we made the following observations on the pyrazole formation reaction: (1) the reaction needs air to proceed; (2) after the reaction is complete, the reaction solution is acidic (pH ∼2−3) and the benzidine assay for nitrite ion[21] is positive; and (3) a stable intermediate is first generated from hydrazone and nitroolefin and then the pyrazole product is formed. To detect this intermediate, hydrazone **15** was generated in EtOH-d_6 and then nitroolefin **16** was added. Observation by means of ^{1}H NMR spectroscopy demonstrated that the intermediate formed in several minutes. At this point, no Michael addition product **18** was observed by ^{1}H NMR. The intermediate is one single diastereomer with only one set of ^{1}H NMR peaks. Careful analysis of the NMR spectrum, especially the characteristic doublet−quartet−doublet coupling pattern of the three protons ($H_aH_bH_c$) between 4.0 and 5.5 ppm, suggests the cyclized pyrazolidine structure **17**.[9] Mass spectrometry (*m*/*z* found, 328.1649 [M + H]$^+$) and IR analysis (characteristic NO_2 asymmetrical stretching band at 1547 cm^{-1}) further confirmed the assigned structure. The relative stereochemistry was assigned by NOE studies, as shown in Scheme 1. Under N_2, intermediate **17** remained

Scheme 1. Pathway for Pyrazole Formation



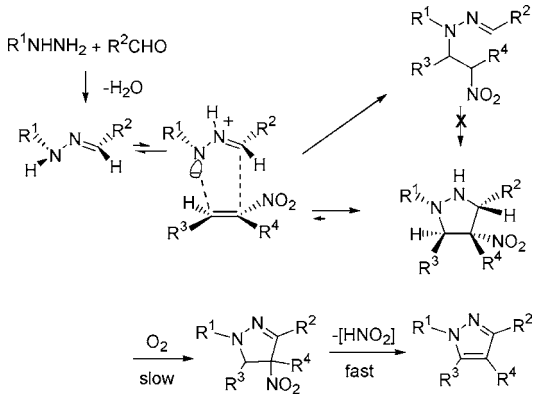
unchanged in EtOH-d_6 solution for hours. Upon exposure to air, intermediate **17** slowly disappeared along with

(21) Tsao, Y.-Y.; Ko, F.-M. *J. Chin. Chem. Soc.* **1937**, *5*, 55−59.

concurrent appearance of the pyrazole product **8**. No other intermediate was observed by ^{1}H NMR during the reaction process. After the reaction was complete, approximately 10% of Michael addition product **18** was also isolated, which again did not cyclize to compound **8** under the reaction conditions, suggesting that the cycloaddition step might be reversible.

On the basis of the above information, a plausible mechanism is proposed as shown in Scheme 2. The first step

Scheme 2. A Plausible Mechanism



is a reversible, concerted cycloaddition to give a 4-nitropyrazolidine intermediate, probably proceeding through a 1,3-dipole intermediate generated in situ, as proposed in the literature on the reaction of hydrazones with other electron-deficient olefins.[9,22] This process is in competition with an irreversible Michael addition process.[23] The key pyrazolidine intermediate then undergoes a slow oxidation by air, followed by a fast elimination of HNO_2[24] to afford the pyrazole product.

In conclusion, we have developed a simple, regioselective pyrazole synthesis, which proceeds from *N*-monosubstituted hydrazone and nitroolefin starting materials. This reaction is quite broad in scope, generating a diverse set of pyrazole products in moderate to excellent yields. Furthermore, the readily available starting materials combined with the rapid one-pot assembly of a complex core should make the reaction suitable for library synthesis in drug discovery efforts. Finally, a key nitropyrazolidine intermediate was fully characterized and a plausible mechanism was proposed.

The research on the reaction of electron-deficient hydrazones and nitroolefins is ongoing in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental details and characterization of compounds **2**−**14**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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