JOC*Note*

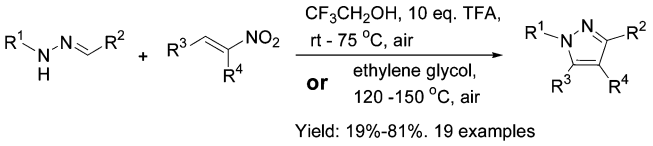
Regioselective Synthesis of 1,3,5-Tri- and 1,3,4,5-Tetrasubstituted Pyrazoles from *N*-Arylhydrazones and Nitroolefins

Xiaohu Deng* and Neelakandha S. Mani

Johnson & Johnson Pharmaceutical Research & Development, L.L.C., 3210 Merryfield Row, San Diego, California 92121

xdeng@prdus.jnj.com

Received December 7, 2007



Two general protocols are developed for the regioselective synthesis of 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles by the reaction of electron-deficient *N*-arylhydrazones with nitroolefins. Studies on the stereochemistry of the key pyrazolidine intermediate suggest a stepwise cycloaddition mechanism.

Substituted pyrazoles are an important class of compounds in the pharmaceutical industry.[1] Particularly interesting to medicinal chemists are the 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles, which constitute the core structures of commercial drugs such as Celebrex, Viagra, and Acomplia, as well as numerous developmental compounds across a wide spectrum of therapeutic areas such as anti-inflammatory,[2] analgesic,[3] antibacterial,[4] and anti-cancer.[5] 1,3,5-Triarylpyrazoles have also been employed as novel ligands in transition-metal-catalyzed cross-coupling reactions.[6] Accordingly, pyrazole synthesis has long been the subject of interest, which goes back to the 19th century when Knorr prepared 1,3,5-trisubstituted pyrazoles via condensation of hydrazines with 1,3-diketones.[7] Since then, the Knorr pyrazole synthesis has been adapted as the standard method because of its convenience and versatility. However, the Knorr reaction suffers one major drawback, i.e., the lack of regiospecificity (Scheme 1, path a).[8] Modifications of this method by replacing the 1,3-diketones with acetylenic or olefinic ketones usually allow better control of the regioselectivity.[9] Nevertheless, in the cases that Ar^2 and Ar^3 are similarly substituted with only minor differences both electronically and sterically, the complete control of regioselectivity becomes a daunting task. Meanwhile, 1,3-dipolar cycloaddition reactions have long been utilized in the syntheses of heterocyclic compounds including pyrazoles, usually regioselectively.[10] Sporadic examples are found in the literature that describe the reaction of N-monosubstituted hydrazones and nitroolefins affording pyrazole or pyrazolidine products (path b), presumably proceeding through the 1,3-dipolar azomethine imine intermediates generated in situ from hydrazones.[11] Compared to Knorr pyrazole synthesis where regioselectivity relies on differentiating the reactivity of the two carbonyl groups, path b is intrinsically more regiospecific because of the significant electronegativity difference of the N and the C atoms of the hydrazone.

Recently, we have shown that indeed excellent regioselectivity can be achieved on the reaction of N-monosubstituted hydrazones with various nitroolefins in MeOH at room temperature under air atmosphere.[12] Good yields of pyrazole products were usually obtained with electron-rich hydrazones such as *N*-alkylhydrazones. However, even at reflux temperature, electron-deficient *N*-arylhydrazones gave low yields of *N*-arylpyrazole products that are of most interest to the pharmaceutical industry.[1−5] Hence, there was a clear need of improved reaction conditions suitable for electron-deficient hydrazones. Herein, we report two complementary general protocols, one neutral and the other acidic, for the syntheses of a wide range of 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles. The ready availability of *N*-arylhydrazones and nitroolefins makes this method particularly appealing for the library synthesis of the pharmaceutically relevant pyrazole compounds for drug discovery efforts. A revised, stepwise mechanism is also proposed based on the new stereochemistry evidence of the key pyrazolidine intermediates.

(1) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Targets Heterocycl. Syst.* **2002**, *6*, 52−98.

(2) (a) Sui, Z.; Guan, J.; Ferro, M. P.; McCoy, K.; Wachter, M. P.; Murray, W. V.; Singer, M.; Steber, M.; Ritchie, D. M.; Argentieri, D. C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 601−604. (b) Bekhit, A. A.; Abdel-Aziem, T. *Bioorg. Med. Chem.* **2004**, *12*, 1935−1945. (c) Selvam, C.; Jachak, S. M.; Thilagavathi, R.; Chakraborti, A. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1793−1797.

(3) Katoch-Rouse, R.; Pavlova, L. A.; Caulder, T.; Hoffman, A. F.; Mukhin, A. G.; Horti, A. G. *J. Med. Chem.* **2003**, *46*, 642−645.

(4) Tanitame, A.; Oyamada, Y.; Ofuji, K.; Fujimoto, M.; Suzuki, K.; Ueda, T.; Terauchi, H.; Kawasaki, M.; Nagai, K.; Wachi, M.; Yamagishi, J.-I. *Bioorg. Med. Chem.* **2004**, *12*, 5515−5524.

(5) (a) Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2000**, *43*, 4934−4947. (b) Stauffer, S. R.; Huang, Y.; Coletta, C. J.; Tedesco, R.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2001**, *9*, 141−150.

(6) (a) Singer, R. A.; Caron, S.; McDermott, R. E.; Arpin, P.; Do, N. M. *Synthesis* **2003**, 1727−1732. (b) Singer, R. A.; Dore, M.; Sieser, J. E.; Berliner, M. A. *Tetrahedron Lett.* **2006**, *47*, 3727−3731.

(7) Knorr, L. *Ber.* **1883**, *16*, 2587.

(8) (a) Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Elguero, J. *Eur. J. Org. Chem.* **2004**, 4348−4356. (b) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675−2678.

(9) (a) Huang, Y. R.; Katzenellenbogen, J. A. *Org. Lett.* **2000**, *2*, 2833−2836. (b) Wang, X.-J.; Tan, J.; Grozinger, K. *Tetrahedron Lett.* **2000**, *41*, 4713−4716. (c) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V.; Steel, P. J. *J. Org. Chem.* **2001**, *66*, 6787−6791. (d) Bishop, B. C.; Brands, K. M. J.; Gibb, A. D.; Kennedy, D. J. *Synthesis* **2004**, 43−52. (e) Singh, S. K.; Reddy, M. S.; Shivaramakrishna, S.; Kavitha, D.; Vasudev, R.; Babu, J. M.; Sivalakshmidevi, A.; Rao, Y. K. *Tetrahedron Lett.* **2004**, *45*, 7679−7682. (f) Peruncheralathan, S.; Yadav, A. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 9644−9647. (g) Gosselin, F.; O'Shea, P. D.; Webster, R. A.; Reamer, R. A.; Tillyer, R. D.; Grabowski, E. J. J. *Synlett* **2006**, *19*, 3267−3270.

(10) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565−632. (b) Padwa, A., Pearson, W. H., Eds. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; John Wiley & Sons: New York, 2002.

(11) (a) Snider, B. B.; Conn, R. S. E.; Sealfon, S. *J. Org. Chem.* **1979**, *44*, 218−221. (b) Gomez-Guillen, M.; Conde-Jimenez, J. L. *Carbohydr. Res.* **1988**, *180*, 1−17. (c) Gomez-Guillen, M.; Hans-Hans, F.; Lassaletta-Simon, J. M.; Martin-Zamora, M. E. *Carbohydr. Res.* **1989**, *189*, 349−358. (d) Arrieta, A.; Carrillo, J. R.; Cossio, F. P.; Diaz-Ortiz, A.; Gomez-Escalonilla, M. J.; De la Hoz, A.; Langa, F.; Moreno, A. *Tetrahedron* **1998**, *54*, 13167−13180.

(12) Deng, X.; Mani, N. S. *Org. Lett.* **2006**, *8*, 3505−3508.

10.1021/jo7026195 CCC: $40.75
Published on Web 02/16/2008

SCHEME 1. Pyrazole Synthesis

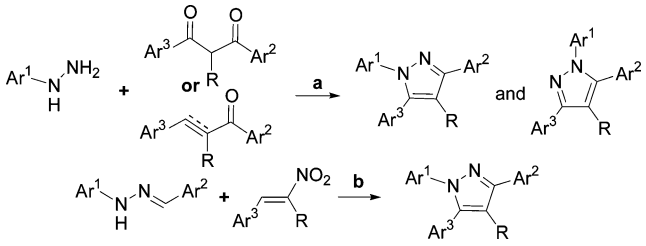
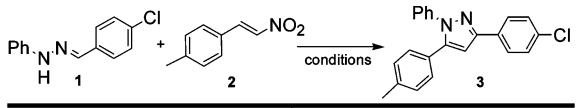
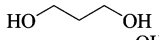
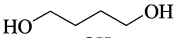
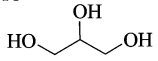


TABLE 1. Solvent Screening on the Pyrazole Formation Reaction

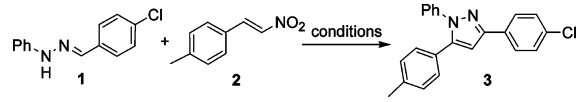


entry	solvent	bp, °C	condition	result
1	MeOH	65	reflux, 4 d	35%
2	CF_3CH_2OH	78	reflux, 1 d	trace
3	IPA	82	reflux, 2 d	trace
4	*t*-amylOH	102	reflux, 2 d	trace
5	1-pentanol	136	120 °C, 16 h	trace
6	1-heptanol	174	150 °C, 16 h	trace
7	1-octanol	196	180 °C, 16 h	trace
8	ethylene glycol	196	120 °C, 16 h	69%
9		187	120 °C, 16 h	38%
10		214	120 °C, 16 h	incomplete
11		230	120 °C, 16 h	incomplete
12		180/ 20mmHg	120 °C, 16 h	25%
13	DMF	153	120 °C, 16 h	no reaction
14	DMSO	189	120 °C, 16 h	no reaction

During our previous study on the pyrazole-forming reaction between hydrazones and nitroolefins, alcoholic solvents (MeOH, EtOH) proved to be optimal.[12] However, when then optimized conditions were applied to electron-deficient hydrazones such as *N*-phenylhydrazone **1**, a low yield of pyrazole **3** was isolated even after refluxing for 4 days (Table 1, entry 1). Changing to higher boiling point alcohols and increasing reaction temperatures did not show any improvement (entries 2−7). Interestingly, diols effectively facilitated the reaction at 120 °C affording the desired pyrazole **3** (entries 8−11), which suggests that perhaps temperature is not the lone determining factor. Among the diols, ethylene glycol gave the cleanest reaction in 69% isolated yield after heating at 120 °C for 16 h (entry 8). Glycerol also provided the desired pyrazole **3**, however in low yield (25%), probably due to the poor solubility of the substrates even at 120 °C (entry 12). In contrast, polar, aprotic solvents such as DMF and DMSO were not effective for this reaction (entries 13 and 14).

The above solvent screening results suggested that protonation-deprotonation might play an important role in the reaction pathway. Literature reports also indicated that acids assisted the cycloaddition reactions of hydrazones with various dipolarophiles.[13] Indeed, with AcOH (pK_a = 4.7[14]) as the solvent, pyrazole **3** was obtained at reflux temperature (118 °C) in 58% yield (Table 2, entry 1). Using a stronger acid, TFA (pK_a = −0.25) as the solvent, however, caused mostly decomposition even at a lower temperature (72 °C, entry 2). Encouraged by these results, we set out to screen various acids as additives with the aim to perform the reaction at ambient temperature. MeOH (pK_a = 15.5) was first chosen as the solvent. With 10 equiv of TFA (pK_a = −0.25) as the additive, no formation of pyrazole **3** was observed at room temperature (entry 3). Whereas $MeSO_3H$ (pK_a = −2.6) and H_2SO_4 (pK_a = −3.0) gave complicated reaction mixtures (entries 4−5), HCl solution (pK_a = −8.0) in MeOH[15] did facilitate a room-temperature pyrazole formation reaction in 52% yield (entry 6). At least 2 equiv of HCl was required for the reaction to go to completion. However, varying the equivalents of HCl did not improve the yield. Various acid additives were also screened in ethylene glycol (pK_a = 14.1) that was the optimal solvent under thermal conditions as shown previously. Slightly elevated temperature (50−70 °C) had to be employed due to the poor solubility of the substrates. In this case, weaker acids such as AcOH (pK_a = 4.7) and TFA (pK_a = −0.25) were sufficient to provide pyrazole **3** in 45% and 62% yield, respectively (entries 7, 8). TsOH (pK_a = −2.1), $MeSO_3OH$ (pK_a = −2.6), and HCl(aq) (pK_a = −8.0) all caused decomposition (entries 9−11). The above results appear to suggest that more acidic alcoholic solvent (pK_a = 14.1 for ethylene glycol vs 15.5 for MeOH) would require less acidic additive (pK_a = −0.24 for TFA vs −8.0 for HCl). This observation prompted us to choose CF_3CH_2OH (pK_a = 12.5) as the solvent. Now the pyrazole-forming reaction could be performed at room temperature with TFA (pK_a = −0.25) as the additive (entries 12 and 13). Whereas 5 equiv of TFA was sufficient, 10 equiv of TFA afforded a slightly better isolated yield at 70%. It is important to note that Lewis acids such as $BF_3{\cdot}Et_2O$, $SnCl_4$, $TiCl_4$, $AlCl_3$, $FeCl_3$, $ZnCl_2$, ZnI_2, $Zn(OTf)_2$, $Sc(OTf)_3$, and $Yb(OTf)_3{\cdot}H_2O$ are not effective promoters for the pyrazole-forming reaction. These results suggest that Bronsted acidity, not Lewis acidity, is a critical factor for this reaction.

TABLE 2. Acid Additive Screening and Optimization



entry	solvent	acid	conditions	result
1		AcOH	118 °C, 16 h	58%
2		TFA	72 °C, 16 h	complex mixtures
3	MeOH	TFA, 10 equiv	rt, 3 d	0%
4	MeOH	$MeSO_3H$, 10 equiv	rt, 3 d	complex mixtures
5	MeOH	H_2SO_4, 10 equiv	rt, 3 d	complex mixtures
6	MeOH	HCl,[a] 10 equiv	rt, 3 d	52%
7	$HO(CH_2)_2OH$	AcOH, 2 equiv	70 °C, 16 h	45%
8	$HO(CH_2)_2OH$	TFA, 2 equiv	50 °C, 16 h	62%
9	$HO(CH_2)_2OH$	TsOH, 2 equiv	70 °C, 16 h	complex mixtures
10	$HO(CH_2)_2OH$	$MeSO_3H$, 2 equiv	70 °C, 16 h	complex mixtures
11	$HO(CH_2)_2OH$	HCl/aq, 4 equiv	50 °C, 16 h	complex mixtures
12	CF_3CH_2OH	TFA, 5 equiv	rt, 16 h	63%
13	CF_3CH_2OH	TFA, 10 equiv	rt, 16 h	70%

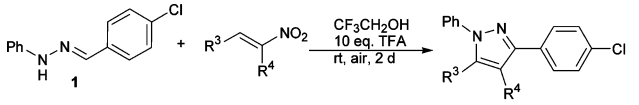
[a] HCl solution in MeOH (ca. 1.25 mol/L from Aldrich).

(13) (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 212−224. (b) Le Fevre, G.; Sinbandhit, S.; Hamelin, J. *Tetrahedron* **1978**, *35*, 1821−1824. (c) Shimizu, T.; Hayashi, Y.; Miki, M.; Terashima, K. *J. Org. Chem.* **1987**, *52*, 2277−2285. (d) Kobayashi, S.; Hirabayashi, R.; Shimizu, H.; Ishitani, H.; Yamashita, Y. *Tetrahedron Lett.* **2003**, *44*, 3351−3354.

(14) pK_a values in water were used.

(15) Used as the solvent (1.25 mol/L, Aldrich). Bubbling HCl (g) into MeOH gave a very messy reaction.

TABLE 3. Reaction Scope with Respect to Nitroolefin



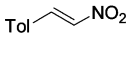
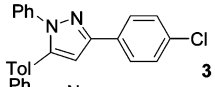
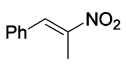
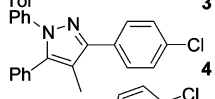
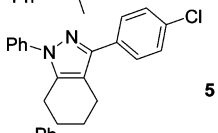
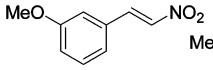
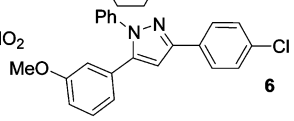
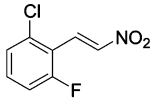
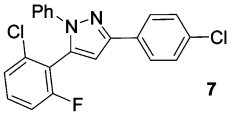
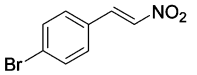
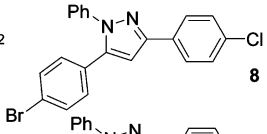
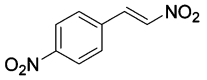
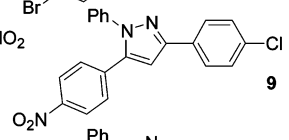
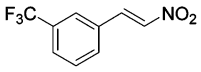
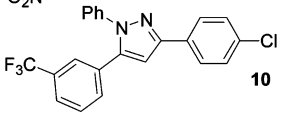
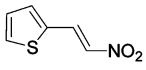
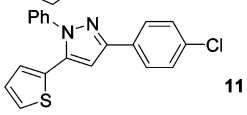
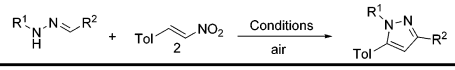
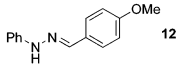
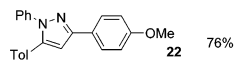
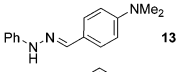
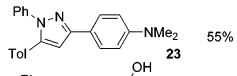
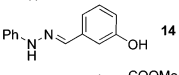
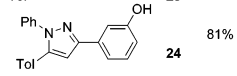
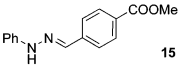
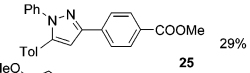
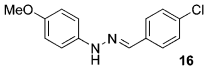
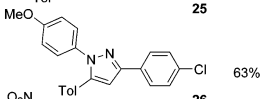
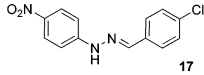
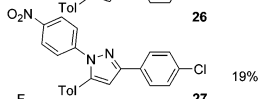
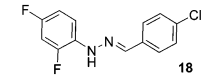
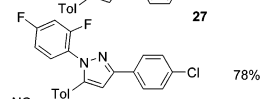
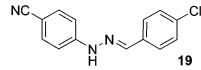
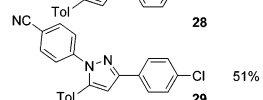
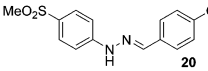
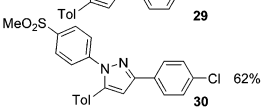
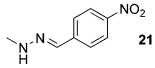
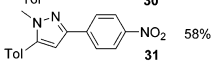
entry	nitroolefin	product	yield
1		 **3**	70%
2		 **4**	38%
3		 **5**	52%
4		 **6**	56%
5		 **7**	56%
6		 **8**	68%
7		 **9**	31%
8		 **10**	36%
9		 **11**	55%

TABLE 4. Reaction Scope with Respect to Hydrazone



entry	hydrazone	condition[a]	product	yield
1	 **12**	**A**, 120 °C, 16 h	 **22**	76%
2	 **13**	**A**, 120 °C, 16 h	 **23**	55%
3	 **14**	**B**, rt, 2 d	 **24**	81%
4	 **15**	**A**, 120 °C, 16 h	 **25**	29%
5	 **16**	**A**, 120 °C, 16 h	 **26**	63%
6	 **17**	**A**, 150 °C, 16 h	 **27**	19%
7	 **18**	**B**, 50 °C, 3 d	 **28**	78%
8	 **19**	**B**, 75 °C, 16 h	 **29**	51%
9	 **20**	**B**, 50 °C, 3 d	 **30**	62%
10	 **21**	**A**, 120 °C, 16 h	 **31**	58%

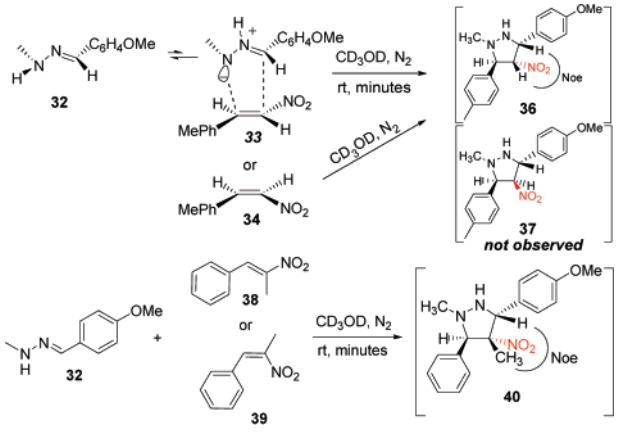
[a] Key: (**A**) ethylene glycol, heating; **(B)** CF_3CH_2OH, 10 equiv of TFA.

With the optimized CF_3CH_2OH/TFA system, the reaction scope on nitroolefins was probed with hydrazone **1** (Table 3). All reactions were performed under the standard conditions without individual optimization. Substitutions at the R^4 position are well tolerated (entries 2 and 3). At the R^3 position, various electron-donating and electron-withdrawing groups on the aryl ring are compatible with the reaction conditions (entries 4−8). An aliphatic nitroolefin also affords good yield of pyrazole product (entry 3). It is noteworthy that even a sterically demanding nitroolefin affords reasonably good yield of the pyrazole product (entry 5). Heterocycles such as a thiophene are also compatible with the reaction conditions (entry 9).

We next turned our attention to defining the scope of the reaction with respect to the hydrazones (Table 4). Either the thermal condition in ethylene glycol (**A**) or the acidic condition in CF_3CH_2OH/TFA (**B**) was applied, depending on functional group compatibility. The electronic properties of the hydrazone substituents appear to be the dominant factor controlling reactivity. For example, hydrazones with electron-donating substitution at R^2 position afford the pyrazole products in decent yields under standard conditions (entries 1−3). In contrast, the yield is much lower with electron-deficient hydrazones (entry 4). The same trend was observed at the R^1 position. Whereas heating at 120 °C in ethylene glycol was sufficient for the reaction to proceed with electron-rich hydrazone **16** (entry 5), electron-poor hydrazone **17** demanded even higher temperature (150 °C) and the yield was very low (19%, entry 6). Similarly, other electron-withdrawing substituents such as F, CN, and SO_2-Me at the R^1 position also called for higher reaction temperatures (entries 7−9). We find that the two sets of reaction conditions, one neutral and the other acidic, are complementary to each other in terms of functional group compatibility. When the functional groups are insensitive to acid, the CF_3CH_2OH/TFA system is preferred. For example, in the reaction shown in entry 3, which involves an acid-stable yet temperature-sensitive phenolic substrate, the CF_3CH_2OH/TFA system works well at room temperature to furnish the desired pyrazole product in excellent yield. Alternatively, for the acid-sensitive substrates, heating in ethylene glycol is a viable option (entries 2, 4, and 10). Entry 10 is a particularly interesting example. In our previous study involving the same substrates with MeOH as the solvent, a Michael addition product was the exclusive product in 90% yield, even at room temperature.[12] Simply switching the solvent to ethylene glycol, the pyrazole product **31** was obtained in 58% yield (entry 10). Notably, the isolated Michael addition product does not cyclize to pyrazole **31** upon heating in ethylene glycol even at 150 °C. This observation indicates that the formation of Michael addition product is irreversible.

Previously, we had demonstrated that the pyrazole-forming reaction goes through a pyrazolidine intermediate. Analogous to the mechanism proposed for the reaction of hydrazones with

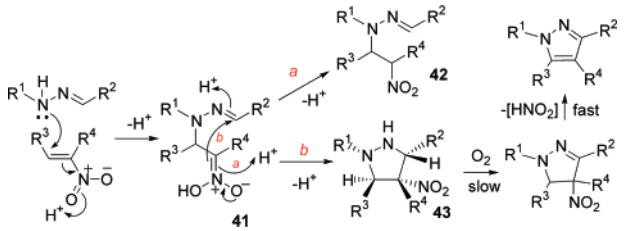
SCHEME 2. NMR Study on the Stereochemistry of the Pyrazolidine Intermediates



other electron-negative olefins,[16] we proposed a concerted cycloaddition pathway in which the hydrazone tautomerized to azomethine imine and then underwent a 1,3-dipolar cycloaddition reaction with nitroolefins (Scheme 2) to generate the pyrazolidine intermediate.[11d,12] However, definitive evidence for a concerted mechanism was not obtained at that time. To differentiate a concerted or stepwise mechanism in a cycloaddition reaction, stereochemistry is arguably the best tool.[17] If the pyrazolidine formation step is concerted, the configuration of the nitroolefin should be retained in the pyrazolidine intermediate. Our previous study did show that the trans configuration of nitroolefin **33** was retained in pyrazolidine **36**.[12] However, we recently found that under the same reaction conditions, *cis*-nitroolefin **34** also afforded the same pyrazolidine **36** exclusively. No pyrazolidine **37** with the retention of the cis configuration was observed whatsoever. This was further complicated that *cis*-nitroolefin **34** isomerized to trans isomer **33** in the reaction mixture, although it remained stable in pure CD_3OD.[18] To avoid the confusion, *cis*-nitroolefin **39** was prepared, which does not isomerize in the reaction solution during the time frame of the experiments. Both *trans*-**38** and *cis*-**39** were then reacted with hydrazone **32** in CD_3OD in NMR tubes under N_2. In both experiments, the same pyrazolidine **40** in the trans configuration was again generated exclusively. The lack of stereospecificity in the pyrazolidine formation step clearly indicate a stepwise mechanism.

In light of the above results, a revised mechanism of pyrazole formation may be proposed as outlined in Scheme 3. Nucleophilic attack of hydrazone on nitroolefin affords a neutral intermediate **41**. Since the C−C single bond between R^3 and R^4 can rotate freely, either *trans*- or *cis*-nitroolefin affords the same intermediate **41**, which results in the nonstereospecificity

SCHEME 3. A Revised, Stepwise Pathway



of the pyrazolidine formation step. From intermediate **41**, two competing reaction pathways can take place. One is an irreversible protonation to afford the Michael addition product **42**. The other is an intramolecular cyclization to furnish the pyrazolidine intermediate **43**. The key intermediate **43** then undergoes a slow oxidation by air, followed by a fast elimination of HNO_2 to furnish the pyrazole product.[12]

In conclusion, a practical, regioselective synthesis of 1,3,5-tri- or 1,3,4,5-tetrasubstituted pyrazoles from electron-deficient *N*-arylhydrazones and nitroolefins has been demonstrated. Two general protocols were developed, which are complementary to each other in terms of functional group compatibility. This pyrazole formation reaction is quite general with respect to hydrazones and nitroolefins with a variety of substituents, and the yields range from moderate to good. A revised stepwise cycloaddition mechanism was also proposed.

Experimental Section

General Procedures for Pyrazole Synthesis. Method A. A mixture of 4-methyl-β-nitrostyrene (163 mg, 1 mmol, 1.0 equiv) and 4-chlorobenzaldehyde phenylhydrazone (276 mg, 1.2 mmol, 1.2 equiv) in ethylene glycol (10 mL) was heated at 120 °C open to air for 16 h and then cooled to room temperature. The reaction solution was partitioned between EtOAc and brine. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with EtOAc/hexanes as eluent to afford the pure compound as a light yellow solid (235 mg, 0.69 mmol, 69%). **Method B.** A mixture of 4-methyl-β-nitrostyrene (163 mg, 1 mmol, 1.0 equiv) and 4-chlorobenzaldehyde phenylhydrazone (276 mg, 1.2 mmol, 1.2 equiv) was dissolved in CF_3CH_2OH (10 mL), and TFA (0.77 mL, 10 mmol, 10 equiv) was added. The reaction mixture was stirred at room temperature open to air for 2 days. The solvent was evaporated, and the residue was directly purified by flash column chromatography with EtOAc/hexanes as eluent to afford the pure compound as a light yellow solid (239 mg, 0.70 mmol, 70%).

Acknowledgment. We thank Prof. Scott E. Denmark, University of Illinios at Urbana−Champaign, for helpful discussions and Dr. Jiejun Wu and Ms. Heather McAllister for analytical support.

Supporting Information Available: Experimental details and characterization of compounds **1**, **3**−**31**, and **40**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7026195

(16) (a) Grigg, R.; Dowling, M.; Jordan, M. W.; Sridharan, V. *Tetrahedron* **1987**, *43*, 5873−5886. (b) Padmavathi, V.; Reddy, K. V.; Padmaja, A.; Reddy, D. B. *Synth. Commun.* **2002**, *32*, 1227−1235.

(17) Huisgen, R. *Adv. Cycloaddition* **1988**, *1*, 1−31.

(18) Same isomerization of *cis*-nitroolfin was observed in the following literature: Burdisso, M.; Gamba, A.; Gandolfi, R.; Pevarello, P. *Tetrahedron* **1987**, *43*, 1835−1846.