ORGANIC LETTERS

2008
Vol. 10, No. 6
1307−1310

Base-Mediated Reaction of Hydrazones and Nitroolefins with a Reversed Regioselectivity: A Novel Synthesis of 1,3,4-Trisubstituted Pyrazoles

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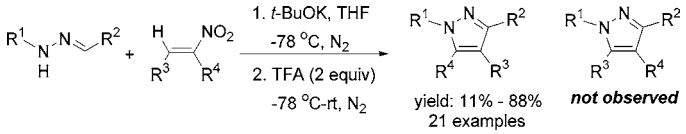
Received January 28, 2008

ABSTRACT

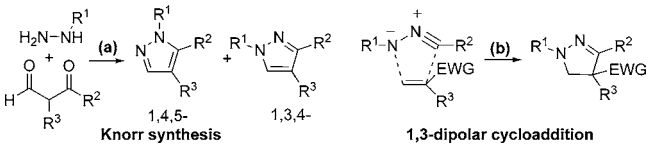


A regioselective synthesis of 1,3,4-tri- or 1,3,4,5-tetrasubstituted pyrazoles by the reaction of hydrazones with nitroolefins is described. Mediated with strong bases such as *t*-BuOK, the reaction exhibits a reversed, exclusive 1,3,4-regioselectivity. Subsequent quenching with strong acids such as TFA is essential to achieve good yields. A plausible stepwise cycloaddition reaction mechanism is proposed.

Pyrazoles are an important class of compounds in the pharmaceutical industry. Compounds containing the pyrazole motif are being developed in a wide range of therapeutic areas including CNS, metabolic diseases and endocrine functions, and oncology.[1] A number of pyrazole-containing compounds have been successfully commercialized, such as the blockbuster drugs Viagra, Celebrex, and Acomplia. Substituted pyrazoles have also been applied as ligands for the transition-metal-catalyzed cross-coupling reactions.[2]

The synthesis of multi-substituted pyrazoles have been extensively studied, and two methods have certainly stood out in terms of generality and convenience.[3] One is the venerable Knorr reaction involving the condensation of substituted hydrazines with 1,3-dicarbonyl compounds or their derivatives (Scheme 1, eq **a**).[4] The other method is the 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines with olefins or alkynes (eq **b**).[5] As successful as these two methods are in preparing pyrazoles with various substitution patterns, both are not particularly suitable for the regioselective synthesis of 1,3,4-trisubstituted pyrazoles. 1,3,4-Trisubstituted pyrazoles are pharmaceutically important, yet less represented in the literature, probably due to synthetic difficulties.[6] In the Knorr reaction, the condensation of substituted hydrazines with β-ketoaldehydes usually favors 1,4,5-trisubstitituted pyrazoles.[7] One solution to this issue is to prepare 3,4-disubstituted pyrazole with unsubstituted hydrazine (NH_2NH_2) and introduce the R^1 substituent subsequently. However, the *N*-substitution step is usually not regiospecific, either.[8] 1,3-Dipolar cycloaddition reactions have been successfully employed in the synthesis of 1,3,4-trisubstituted pyrazoles or pyrazolidines, usually regioselectively.[9] However, the difficulty in generating and handling

Scheme 1. Two General Methods for the Pyrazole Synthesis



(1) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Targets in Heterocyclic Systems* **2002**, *6*, 52−98 and references therein.

(2) (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.

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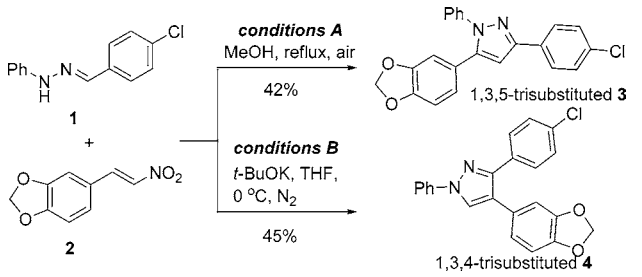
10.1021/ol800200j CCC: $40.75
Published on Web 02/27/2008

reactive 1,3-dipoles often limits their synthetic utility. Therefore, a general, convenient method for the synthesis of 1,3,4-substituted pyrazoles is highly desirable. Herein, we report a regioselective synthesis of 1,3,4-tri- or 1,3,4,5-tetrasubstituted pyrazoles from readily available hydrazones and nitroolefins mediated with strong bases. To the best of our knowledge, this is the first time that this transformation has ever been documented. The reaction scope is quite broad on a range of substrates, and the functional group compatibility is excellent. Paired with our previously reported methodology to prepare 1,3,5-trisubstituted pyrazoles from the same starting material but under neutral or acidic conditions,[10] the reaction of hydrazones and nitroolefins should offer a powerful tool for the pyrazole synthesis in general.

Recently, we have reported a regioselective synthesis of 1,3,5-trisubstituted pyrazoles through the reactions of hydrazones with nitroolefins under either neutral (heating in MeOH or ethylene glycol) or acidic conditions (10 equiv of TFA in CF_3CH_2OH) (Scheme 2, conditons ***A***).[10] Excellent

Scheme 2. Complementary Regioselectivity



1,3,5-regioselectivity is achieved, presumably resulting from the different nucleophilicity of the aniline N atom and the benzylic C atom of phenyl hydrazone **1**. We speculated that by modulating the relative nucleophilicities of the nitrogen and the carbon atoms of the hydrazone, 1,3,4-regioselectivity might instead be accomplished. In the literature, it has been shown that the reaction of nitroolefins with diazoalkanes, in which the C atom is more nucleophilic than the N atom, affords 3,4-disubstituted pyrazoles.[11] 1,3,4-Trisubstituted pyrazoles have also been obtained as the minor products from the reaction of hydrazones with nitroolefins under microwave heating conditions.[12] We envisioned that the N and C atoms of a deprotonated hydrazone might possess reversed nucleophilicities toward Michael receptors such as nitroolefins. Indeed, when *t*-BuOK was added to hydrazone **1** in THF at 0 °C under N_2, followed by the addition of nitroolefin **2**, 1,3,4-trisubstituted pyrazole **4** was isolated in 45% yield after 30 min reaction time (Scheme 2, conditons ***B***). No formation of 1,3,5-trisubstituted pyrazole **3** was observed whatsoever. Notably, air is not required under base-mediated conditons ***B***, which is essential for the reaction to proceed under conditions ***A***. In fact, under conditons ***B*** in the presence of air, oxidative dimerization of the hydrazone itself was the dominant reaction.[13]

Encouraged by the initial results, we tried to increase the yield of reaction ***B***. However, optimization efforts by varying reaction parameters such as solvent, base and temperatrue were largely unsuccessful. With CH_3CN or CH_2Cl_2 as the solvent, little reaction was observed, whereas the reactions in DMF or DMA afforded similar yields as in THF. The reaction proceeds at as low as −78 °C, but the yield did not improve. Changing the counter cation of the base by employing $NaOBu^t$ or $LiOBu^t$ gave essentially the same yield as well. Using NaHMDS, LiHMDS and ^{i}PrMgCl as the base all provided desired pyrazole **4**, but the reactions gave lower yields. Other bases, such as PhMgCl and LDA, afforded only trace amounts of desired product **4**. Changing the addition order of the reagents, by adding *t*-BuOK to the solution of hydrazone **1** and nitroolefin **2** in THF, did not increase the yield, either.

A solution to the problem emerged when we made the breakthrough observation that the outcome of the reaction depended on the quenching reagents used (Scheme 3). The reaction was performed by adding *t*-BuOK to a THF solution of hydrazone **5** under N_2 at −78 °C, followed by the addition of nitroolefin **6** after 10 min. After stirring at −78 °C for 15 min, both hydrazone **5** and nitroolefin **6** were completely

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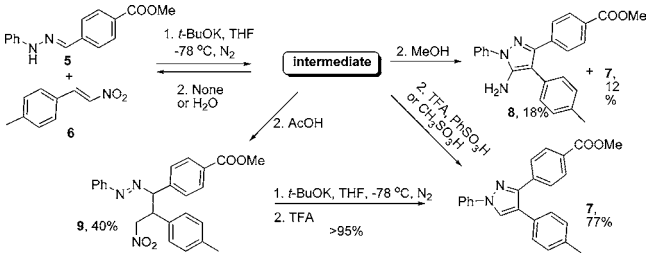
(13) For the structure of the dimer **4b**, see the Supporting Information. For self-oxidation of hydrazone, see: Harej, M.; Dolenc, D. *J. Org. Chem.* **2007**, *72*, 7214−7221.

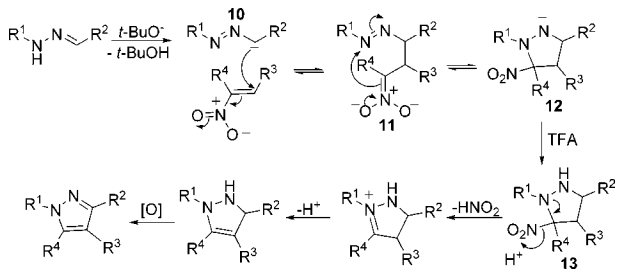
Scheme 3. Study of Different Quenching Methods



consumed based on HPLC analysis. Two equivalents of quenching reagents such as H_2O, MeOH, AcOH, $PhSO_3H$, CH_3SO_3H and TFA were then added. After stirred at −78 °C for further 2 h, the reaction solution was warmed to room-temperature slowly overnight. The results are depicted in Scheme 3. When no quenching reagent or water was employed, starting materials were mostly recovered. Quenching with MeOH (pK_a = 15.5) caused a messy reaction. In addition to the desired pyrazole **7** isolated in 12% yield, the major side product was 5-aminopyrazole **8** in 18% yield, which perhaps came from an internal Redox process. With AcOH (pK_a = 4.7) as the quenching reagent, the major product was Michael addition product **9** in 40% isolated yield. Finally, when TFA (pK_a = −0.25) was employed as the quenching reagent, the reaction was quite clean to afford desired pyrazole **7** in 77% isolated yield. Similar yields were also obtained with $PhSO_3H$ (pK_a = 2.1) and CH_3SO_3H (pK_a = −2.6) as the quenching reagents. It is important to note that when Michael addition product **9** was subjected to the *t*-BuOK/TFA quenching sequence, pyrazole **7** was obtained almost quantitatively, suggesting the intermediacy of compound **9** in the pyrazole formation process.

Based on the above information, we proposed a possible mechanism for the pyrazole formation reaction (Scheme 4).

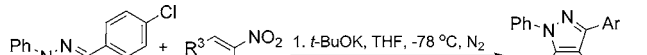
Scheme 4. A Plausible Reaction Pathway

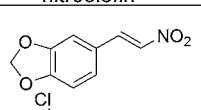
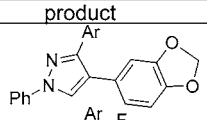
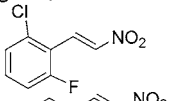
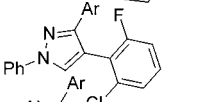
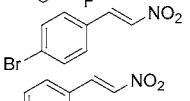
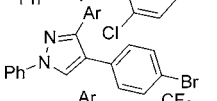
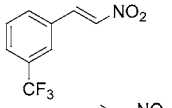
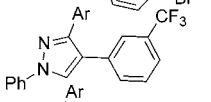
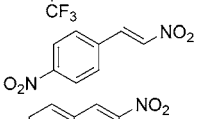
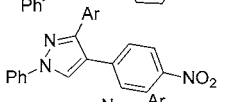
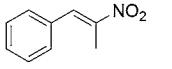
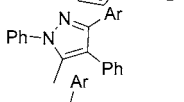
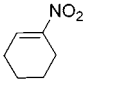
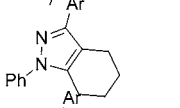
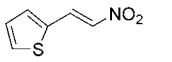
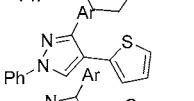
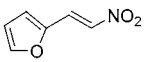
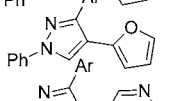
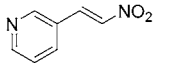
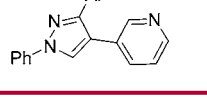


Michael addition of deprotonated hydrazone **10** to a nitroolefin affords intermediate **11**.[14] An intramolecular cyclization then furnishes intermediate **12**. It is not clear whether intermediate **11** or **12** be the resting stage. Low-temperature NMR experiments at −25 °C showed the disappearance of the starting materials several minutes after the sequential addition of *t*-BuOK and nitroolefin **6**, but failed to provide a clean spectrum of the intermediate. Nevertheless, these first two steps are most likely reversible due to the fact that the starting materials are recovered when no quenching or water quenching are employed. The role of the acid quenching is not entirely clear. One possible explanation is that the strong acid such as TFA efficiently protonates intermediate **12** to afford intermediate **13** irreversibly, thus driving the equilibrium toward the desired pyrazole formation pathway. Intermediate **13** then undergoes an elimination of HNO_2, followed by an oxidative aromatization to furnish the desired pyrazole product. Since the reaction is performed under N_2 with no external oxidants present, the byproduct HNO_2 presumably serves as an internal oxidant.

With the optimized *t*-BuOK/TFA quenching conditions in hand, we set out to explore the reaction scope on nitroolefins (Table 1). A diverse set of representative nitroolefins were reacted with hydrazone **1** under the standard *t*-BuOK/TFA quenching conditions without individual optimization. At the R^3 position, both electron-donating and electron-withdrawing substituents on the aromatic rings are compatible with the reaction conditions (entries 1−5). Notably, even a sterically

Table 1. Reaction Scope with Respect to the Nitroolefin



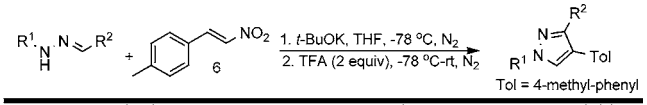
entry	nitroolefin	product	yield
1		 **4**	79%
2		 **14**	88%
3		 **15**	81%
4		 **16**	76%
5		 **17**	52%
6		 **18**	82%
7		 **19**	63%
8		 **20**	73%
9		 **21**	51%
10		 **22**	42%

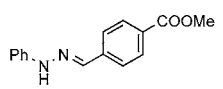
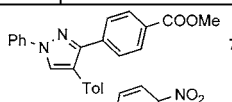
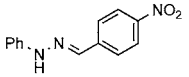
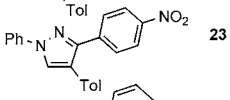
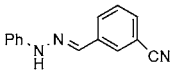
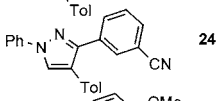
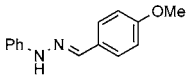
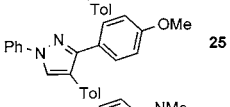
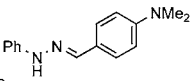
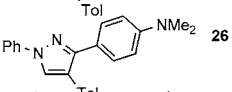
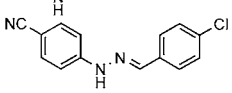
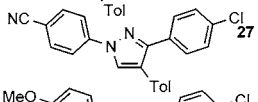
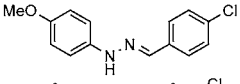
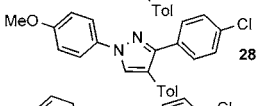
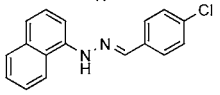
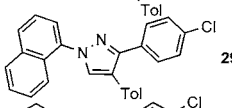
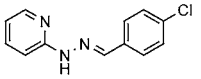
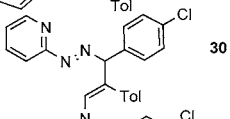
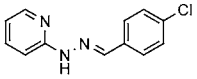
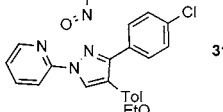
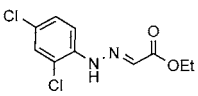
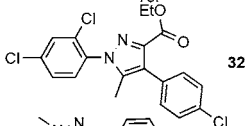
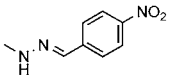
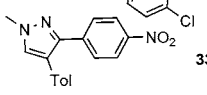
(14) (a) Fernandez, R.; Gasch, C.; Lassaletta, J-M.; Llera, J-M. *Tetrahedron Lett.* **1994**, *35*, 471−472. (b) Enders, D.; Syrig, R.; Raabe, G.; Fernandez, R.; Gasch, C.; Lassaletta, J.-M.; Llera, J.-M. *Synthesis* **1996**, 48−52.

hindered di-ortho-substituted nitroolefin afforded an excellent yield of pyrazole product **14** (entry 2). Substitutions at the R^4 position were well tolerated (entries 6 and 7). Nitroolefins with aliphatic group (entry 7) or heterocyclic groups such as thiophene, furan, and pyridine (entries 8−10) at the R^3 position afforded good yields of pyrazoles as well.

The reaction scope with respect to the hydrazone was next examined (Table 2). Aromatic substitution at the R^2 position was first investigated. Excellent yields were achieved with hydazones bearing electron-withdrawing substituents on the aryl ring (entries 1−3). Electron-donating substitutuents on the aryl ring, on the other hand, led to significant yield loss (entries 4 and 5). A possible explanation for the preference of an electron-withdrawing substituent at R^2 position is that it helps stabilize deprotonated hydrazone **10** (Scheme 4), thus facilitating the Michael addition step. Aromatic substitutions at the R^1 position were then investigated. Interestingly, the electronic requirement at R^1 position is reversed vis-a-vis the R^2 position: At R^1 position, an electron-withdrawing substituent on the aryl ring afforded a very poor yield of pyrazole product (entry 6), whereas an electron-donating substituent apparently facilitated the reaction (entry 7). We reasoned that although an electron-withdrawing group at R^1 position might have facilitated the first Michael addition step, it also significantly increased the electron-density of the nitrogen atom adjacent to R^1 in intermediate **11**, thus impeding the formation of intermediate **12** on the subsequent addition step (Scheme 4). Compared with electronic properties, the steric influence of substituents at the R^1 position is less prominent. A bulky naphthyl hydrazone furnished pyrazole **29** in 67% yield (entry 8). Entry 9 is an interesting case, which again demonstrated the importance of the quenching method. When no quenching reagent was employed, desired pyrazole **31** was isolated in a low 16% yield (entry 9b). In contrast, with the standard TFA quenching method, open-chain nitroso compound **30** was obtained in 81% yield (entry 9a), presumably through the dehydration of protonated intermediate **11**. Substituents at the R^1 and R^2 positions are not limited to aryl rings. Hydrazone with an electron-withdrawing ester group at the R^2 position furnished an excellent yield of pyrazole **32** (entry 10), which is the regioisomer of the key precursor for the synthesis of Acomplia. An electron-donating methyl group at the R^1 position is also compatible with the reaction conditions (entry 11).

Table 2. Reaction Scope with Respect to the Hydrazone



entry	hydrazone	product	yield
1		 **7**	77%
2		 **23**	80%
3		 **24**	83%
4		 **25**	25%
5		 **26**	31%
6		 **27**	11%
7		 **28**	83%
8		 **29**	67%
9a		 **30**	81%
9b[a]		 **31**	16%
10[b]		 **32**	78%
11		 **33**	41%

[a] No quenching. [b] 1-Chloro-4-(2-nitropropenyl)benzene was used in this reaction.

In conclusion, we have developed a novel regioselective synthesis of 1,3,4-tri- or 1,3,4,5-tetrasubstituted pyrazoles with hydrazones and nitroolefins as the starting materials. Mediated with strong base, a reversed 1,3,4-regioselectivity pattern was obtained exclusively. The Michael addition product was shown to be the key intermediate and a plausible stepwise cycloaddition reaction mechanism was proposed.

Acknowledgment. We thank Prof. Scott E. Denmark, University of Illinios at Urbana−Champaign, for helpful discussions, Dr. Daniel J. Pippel and Dr. Christie Morrill for proofreading the manuscript, and Dr. Jiejun Wu and Ms. Heather McAllister for analytical support.

Supporting Information Available: Experimental details and characterization of compounds **4**, **4b**, **7**−**9**, and **14**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800200J