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Convenient Synthesis of Highly Functionalized Pyrazolines via Mild, Photoactivated 1,3-Dipolar Cycloaddition

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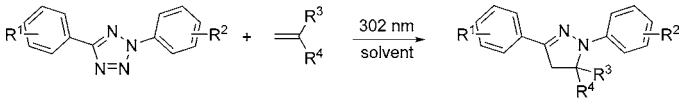
ABSTRACT

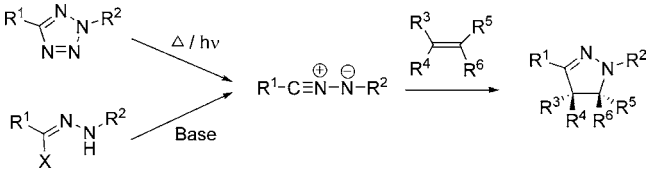


R^1, R^2 = OMe, Cl, Br, CO_2H, NMe_2
R^3, R^4 = CO_2Me, CN, CHO, CONHR, alkyl, Ph

A mild, photoactivated 1,3-dipolar cycloaddition procedure was successfully developed for the synthesis of polysubstituted pyrazolines. This procedure involved the in situ generation of the reactive nitrile imine dipoles using a hand-held UV lamp at 302 nm, followed by spontaneous cycloaddition with a broad range of 1,3-dipolarophiles with excellent solvent compatibility, functional group tolerance, regioselectivity, and yield.

Pyrazolines are an important class of heterocycles with myriad biological activities, including anticancer activity by inhibiting kinesin spindle proteins, antibacterial activity against *Helicobacter pylori*, antiviral activity against the West Nile virus, anti-obesity agents by antagonizing CB1 receptors, and therapeutic candidates for Parkinson's disease.[1] Among various synthetic methods to prepare pyrazolines, 1,3-dipolar cycloaddition between nitrile imine dipoles and alkene dipolarophiles is particularly attractive because of the high regioselectivity and broad functional group tolerance.[2] The nitrile imine dipole can be generated either by treating α-halohydrazones with base[3] or by subjecting tetrazole precursors to heating[4] or photolysis[5] (Scheme 1). We are particularly interested in the photoactivation approach because of the potential of the use of tetrazoles as photoactivatable building blocks in the protein target-guided in situ synthesis of small-molecule inhibitors.[6]

Scheme 1. Synthesis of Functionalized Pyrazolines via 1,3-Dipolar Cycloaddition



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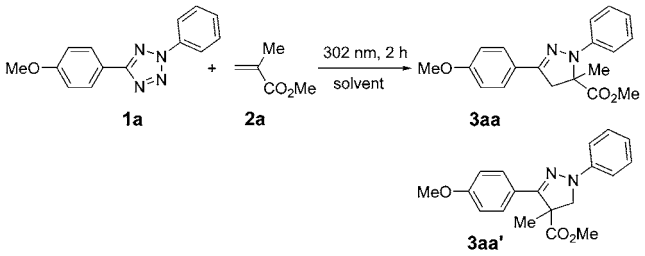
The photoactivated 1,3-dipolar cycloaddition reaction was first reported by Huisgen and co-workers between 2,5-diphenyltetrazole and methyl crotonate in benzene.[5a] The presence of the short-lived nitrile imine intermediate was established by the ^{15}N-labeled fragmentation study.[7] A remarkable rate acceleration was observed when the reaction was performed in aqueous medium,[8] consistent with a concerted reaction mechanism. However, in all the photoactivation approaches, an intense 450-W Hanovia immersion lamp with broad emission spectrum was used, severely limiting the range of applications suitable for the reaction. As a result, there were only a few reports in the literature in the past 40 years that utilized this photoactivation approach for the synthesis of pyrazoline compounds.[5b,c] Herein, we report an extremely mild photoactivation procedure that allows for rapid synthesis of highly functionalized pyrazolines from easily accessible diaryl-tetrazole building blocks.[9]

Because of high quantum yield of the photolysis (0.5−0.9) in generating the reactive nitrile imine intermediate,[10] we found that a hand-held benchtop UV lamp (UVP, 302 nm, 0.16 AMPS, typically used in the lab for TLC monitoring) was sufficiently robust to initiate the reactions. In our initial study, a reaction mixture containing 1 equiv of tetrazole (**1a**) and 20 equiv of methyl methacrylate (**2a**) in common organic solvents, as well as an EtOH/H_2O solvent mixture, was irradiated for 2 h at room temperature. In almost all cases, pure product (**3aa**) was obtained in quantative yields after evaporation of solvents and excess reagents (Table 1), based on the ^1H NMR and mass spectrometry data. The cycloaddition was found to be insensitive to solvent polarity (entries 1−10) and tolerant of protic solvents including H_2O (entries 2−4, 11). The reaction was highly regioselective as the opposite regioisomer **3aa′** was not observed in all conditions we tested. Further experiments indicated that the amount of dipolarophile **2a** can be reduced to 1 equiv without detectable decrease in yield and regioselectivity.

Next, we examined the reactivity of a range of 1,3-dipolarophiles toward tetrazole **1a** using this mild photoactivation procedure, and the results are summarized in Table 2. The regiochemistry was determined by NMR signals of the pyrazoline ring protons. All electron-deficient alkenes gave excellent yields and exclusive regioselectivity with the electron-withdrawing group residing at the C^5-position, for example, monosubstituted ethylenes (entries 2, 3) and *gem*-disubstituted ethylenes (entries 7−9). It is noteworthy that the in situ generated reactive nitrile imine reacted selectively with alkenes over the nitrile and aldehyde groups (entries 2, 9). Simple alkenes such as 1-decene afforded the pyrazoline product with a moderate yield after 2 h irradiation (entry 10). Conjugate alkenes such as styrene derivatives were also efficient dipolarophiles (entries 11−19). Yields were generally higher when styrene rings carry electron-withdrawing groups such as halogens and the cyano group (entries 14−18). Interestingly, a cyclic styrene analog, indene, also participated in this photoactivated cycloaddition, giving the fused ring product with 87% isolated yield (entry 19). A small amount of oxidized pyrazole products was isolated for methyl acrylate and styrene dipolarophiles (entries 1, 11); however, it appears the occurrence is structure-dependent because it was not observed for other dipolarophiles we tested. For electron-rich alkenes such as *n*-butyl vinyl ether, tetrazine (dimer of nitrile imine) was isolated instead of the pyrazoline adduct, presumably due to MO mismatch between the nitrile imine dipole and the electron-rich dipolarophiles.[11]

Table 1. Photoactivated 1,3-Dipolar Cycloaddition of **1a** and **2a** in Various Solvents[a]



entry	solvent	yield (%)[b] 3aa	3aa′
1	PhH	99.2	
2	^{i}PrOH	96.3	
3	EtOH	97.7	
4	MeOH	85.0	
5	EtOAc	100	
6	CH_2Cl_2	100	
7	THF	100	
8	hexane	100	
9	MeCN	92.1	
10	DMF	100	
11	7:3 EtOH/H_2O	100	

[a] Reactions were conducted by irradiating 5.5 mg of **1a** and 20 equiv of **2a** in 2 mL of solvent in quartz test tubes. [b] Crude yields after evaporation of solvent and excess **2a**.

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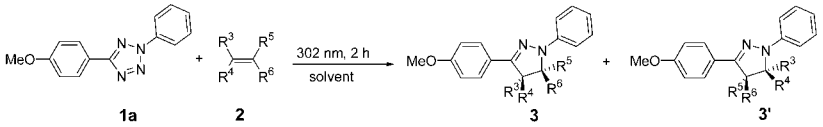
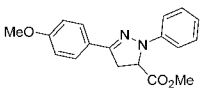
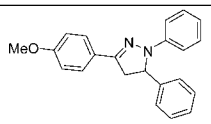
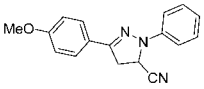
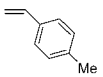
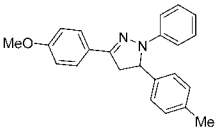
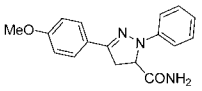
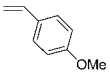
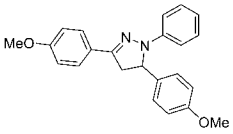
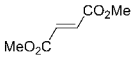
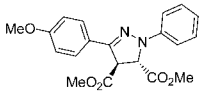
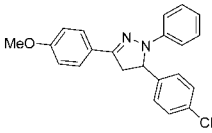
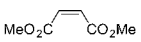
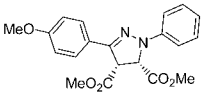
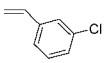
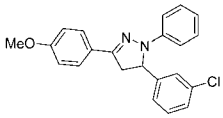
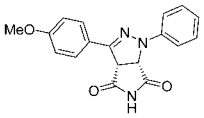
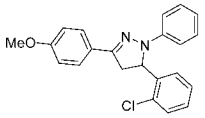
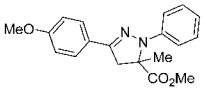
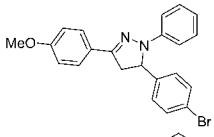
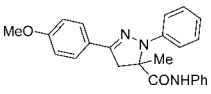
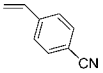
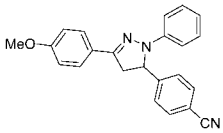
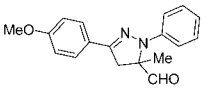
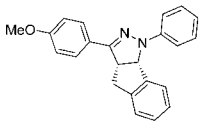
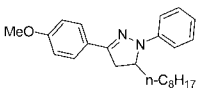
Table 2. Photoactivated 1,3-Dipolar Cycloaddition of **1a** with Diverse Dipolarophiles[a]

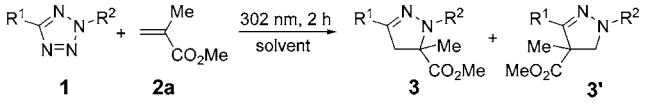


entry	2	product	yield (%)[b]	entry	2	product	yield (%)[b]
1			67 (27)[c]	11			68 (27)[c]
2			97[c]	12			80[c]
3			88[d]	13			70 (9)[c]
4			100[e]	14			100
5			100[e]	15			94
6			100[e]	16			100[e]
7			100[e]	17			92
8			100[e]	18			93
9			100	19			87
10			62				

[a] Reactions were conducted by irradiating 5.5 mg of **1a** and 2.0 equiv of **2** in 2 mL of benzene in quartz test tubes for 2 h using a hand-held 302 nm UV lamp unless otherwise specified. Yields were isolated yields. [b] The yield of the oxidized side product was given in the parenthesis. [c] Reactions were conducted by irradiating 13.0 mg of **1a** and 2.0 equiv of **2** in 2 mL of benzene for 2 h. [d] EtOH was used as the solvent. [e] EtOAc was used as the solvent.

We further examined the reactivity of various 2,5-disubstituted tetrazoles, and the results are summarized in Table 3. Both electron-rich and electron-neutral diaryltetrazoles reacted with **2a** regioselectively and afforded the pyrazoline products in excellent yields (entries 1−6, 8, 9). However, when a nitro group was introduced into either the N^2- or C^5-phenyl ring, the photolysis of tetrazoles slowed down significantly such that an estimated 80−90% of starting materials remained after 2 h photoirradiation (entries 7, 13). It is noteworthy that carboxylic acid can be tolerated during the reaction (entry 10). In addition, a tetrazole directly substituted with a carboxylate group at the C^5-position gave

Table 3. Photoactivated 1,3-Dipolar Cycloaddition of **2a** with Various Tetrazoles[a]



	tetrazole			yield (%)[b]
entry	no.	R^1	R^2	(recovered **1** (%))
1	**1a**	*p*-MeOPh	Ph	100
2	**1b**	*p*-MeOPh	*p*-MePh	100
3	**1c**	*p*-MeOPh	*p*-ClPh	100
4	**1d**	*p*-MeOPh	*p*-BrPh	100
5	**1e**	*p*-MePh	Ph	89
6	**1f**	*p*-MePh	*p*-MePh	99
7	**1g**	*p*-MePh	*p*-O_2NPh	20 (80)[c]
8	**1h**	2,4-$(MeO)_2$Ph	*p*-BrPh	95
9	**1i**	2,4-$(MeO)_2$Ph	*p*-ClPh	100
10	**1j**	*p*-(HOOC)Ph	Ph	93[d]
11	**1k**	*p*-EtOOCPh	*p*-NMe_2Ph	82
12	**1l**	2-Pyridyl	Ph	88
13	**1m**	*p*-O_2NPh	*p*-MePh	10 (90)[c]
14	**1n**	EtOOC	*p*-ClPh	98

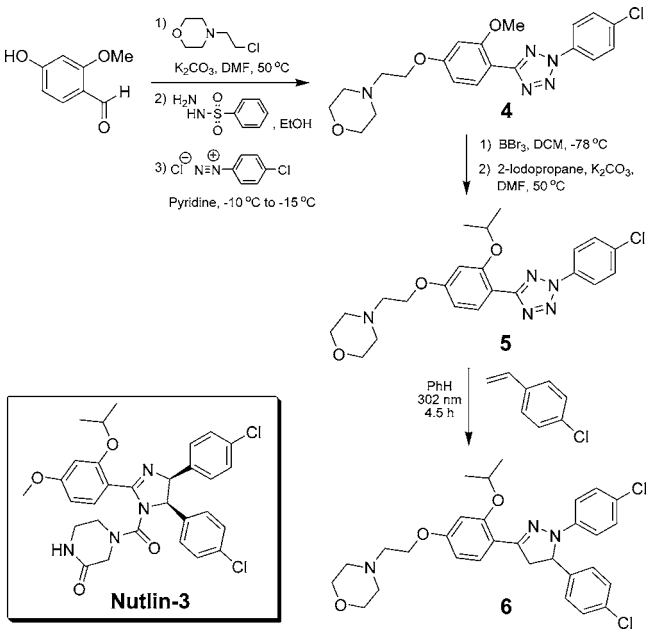
[a] Reactions were conducted by irradiating 6 μL of **2a** and 1 equiv of **1** in 2 mL of benzene, unless otherwise indicated, in quartz test tubes for 2 h. [b] Crude yields after solvent romoval. [c] Yields were determined by ^{1}H NMR. [d] Reaction was performed in EtOH.

an excellent yield during the cycloaddition (entry 14), suggesting that the tetrazole structure can be significantly expanded beyond the diaryl system.

To illustrate the utility of this mild photoactivation procedure in synthesizing highly functionalized pyrazolines, we prepared a water-soluble pyrazoline analog **6**, which contains an isomeric core while retaining three key hydrophobic appendages of Nutlin-3,[12] a potent MDM2 inihibitor (Scheme 2). An appropriately functionalized 2,5-disubstituted tetrazole **4** was prepared from 4-hydroxy-2-methoxybenzaldehyde in three steps with an overall yield of 42%. The isopropyl-containing tetrazole **5** was subsequently obtained by treating **4** with 0.6 equiv of BBr_3 to selectively remove

(12) Vassilev, L. T.; Vu, B. T.; Graves, B.; Carvajal, D.; Podlaski, F.; Filipovic, Z.; Kong, N.; Kammlott, U.; Lukacs, C.; Klein, C.; Fotouhi, N.; Liu, E. A. *Science* **2004**, *303*, 844−848.

Scheme 2. Synthesis of Nutlin-3 Analog via Photoactivated 1,3-Dipolar Cycloaddition



the methyl group followed by alkylation with 2 equiv of 2-iodopropane at 50 °C under the basic condition. Irradiating **5** with a 302 nm hand-held UV lamp in the presence of 1.25 equiv of 4-chlorostyrene for 4.5 h afforded the pyrazoline analog **6** with an isolated yield of 54%.

In summary, we have shown a mild, photoactivated 1,3-dipolar cycloaddition procedure for the synthesis of polysubstituted pyrazolines. The employment of this procedure for protein target-guided in situ synthesis of pyrazoline analogs is currently underway.

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Supporting Information Available: Experimental details and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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