

Aldehydes as Photoremovable Directing Groups: Synthesis of Pyrazoles by a Photocatalyzed [3+2] Cycloaddition/Norrish Type Fragmentation Sequence

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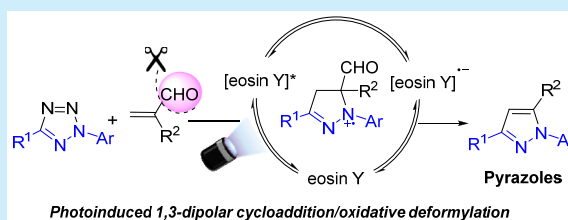


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ABSTRACT: A straightforward methodology for the regioselective synthesis of pyrazoles has been developed by a domino sequence based on a photoclick cycloaddition followed by a photocatalyzed oxidative deformylation reaction. Distinguishing features of this protocol include an unprecedented photoredox-catalyzed Norrish type fragmentation under green-light irradiation and the use of α,β -unsaturated aldehydes as synthetic equivalents of alkynes, where the aldehyde is acting as a novel photoremovable directing group.

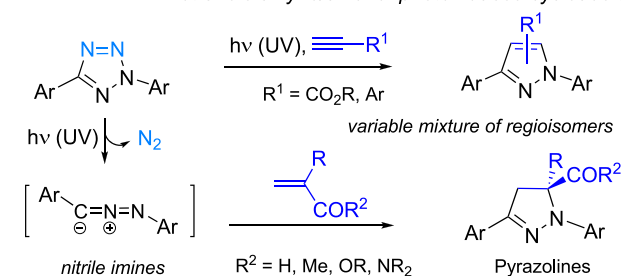


Pyrazoles are privileged structures in organic and medicinal chemistry, because they are present in numerous natural products and therapeutic agents based on small molecules, such as Celecoxib, Rimonabant, or Lersivirine, among others.¹ Furthermore, pyrazoles have been extensively used as ligands in transition metal-catalyzed processes.² Accordingly, the development of new methods to facilitate the concise preparation of structurally diverse pyrazoles is a very appealing synthetic goal. Among the plethora of reported methodologies for pyrazole synthesis, the traditional condensation of hydrazine derivatives with diverse substituted carbonyl compounds has been the most commonly employed.³ Alternatively, 1,3-dipolar cycloaddition has also played a prevalent role due to its great versatility.⁴ The use of diazoalkanes⁵ or nitrile imines⁶ as dipoles and activated alkynes as dipolarophiles is a straightforward procedure for the preparation of pyrazoles. With activated alkenes as dipolarophiles, the resulting pyrazolines required an extra elimination⁷ or oxidation step⁸ for aromatization to synthesize pyrazoles. However, non-activated alkyl-substituted alkynes or alkenes have been scarcely studied because they usually lead to regioisomeric mixtures in low conversions.

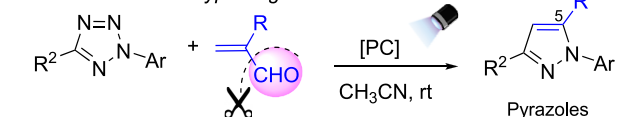
Traditionally, the nitrile imine dipoles can be generated *in situ* either from α -halohydrates in the presence of a base⁹ or from tetrazole precursors. Of special relevance is the light-induced 1,3-dipolar cycloadditions of 1,3-diaryltetrazoles that have been widely applied in biological and material chemistry (Scheme 1).¹⁰ Huisgen and co-workers¹¹ reported the first example of this photoactivated cycloaddition for the synthesis of pyrazolines. More recently, Lin and co-workers¹² have proven the usefulness of this clean and atom-economical transformation with a wide range of alkenes as dipolarophiles (Scheme 1, pyrazolines).

Scheme 1. Synthesis of Pyrazoles and Pyrazolines from Tetrazoles

Previous work: Tetrazole alkyne/alkene photoinduced cycloaddition



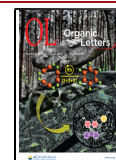
This work: Photoinduced cycloaddition/Eosin based photocatalytic Norrish type fragmentation



α,β -Unsaturated aldehydes have been extensively used as dipolarophiles in 1,3-dipolar cycloadditions¹³ with a great variety of dipoles.^{14,15} The synthetic versatility of the formyl group is beyond any doubt because it can be straightforwardly converted into many other functional groups. However, examples of reactions involving C–C bond cleavage by formyl

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group elimination are scarce. Conversely, the photochemical UV-induced cleavage of aldehydes or ketones into two radical intermediates, known as the Norrish reaction, has been widely studied, including several applications in natural product synthesis.¹⁶ Because there are not reported procedures for the efficient utilization of non-activated alkynes as dipolarophiles in this kind of cycloaddition, we envisaged that an α,β -unsaturated aldehyde could act as an alkyne surrogate, increasing the reactivity and temporally controlling the regioselectivity of the cycloaddition. Herein, we report a sequential dipolar photoclick reaction followed by a Norrish type deformylation step under green-light irradiation using eosin Y as a photoredox catalyst. To the best of our knowledge, there are no photocatalytic examples for this fragmentation besides the important advantages of this approximation.^{17,18}

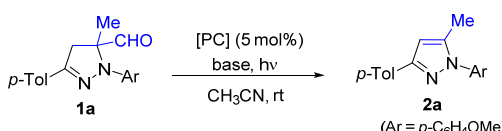
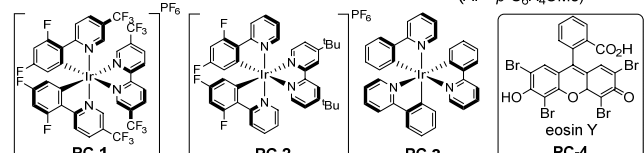
In connection with our previous work on tetrazole photoclick 1,3-dipolar cycloadditions,¹⁹ we set out to explore the application of this methodology to the synthesis of pyrazoles using unsaturated aldehydes as synthetic equivalents of alkynes.

For this purpose, we initially studied the Norrish type deformylation reaction of formyl pyrazoline **1a**, previously prepared by a UV-light-induced dipolar cycloaddition reaction between the corresponding diaryltetrazole and methacrolein.²⁰ UV-light irradiation of **1a** gave the desired pyrazole **2a** in 44% yield after 24 h (Table 1, entry 1). This result evidenced the potential use of methacrolein as a synthetic equivalent of propyne gas leading to a regioselective synthesis of pyrazole **2a**. Our next purpose was to evaluate the C–C fragmentation process using a photocatalyst under irradiation with a less

energetic light. We were pleased to find that iridium PC-1 (5 mol %) was able to catalyze the oxidative deformylation reaction under blue light (420 nm), affording **2a** in 66% yield after 6 h (Table 1, entry 2). The addition of Et₃N significantly increased the reaction rate, allowing the isolation of **2a** in 72% yield after 30 min (entry 3). Control experiments showed that light irradiation and a photocatalyst were indispensable for the reaction to proceed (entries 4–6). The use of other bases such as 2,6-lutidine or K₂CO₃ gave similar results, although cleaner reaction mixtures were obtained in the latter case (entries 7 and 8). Other iridium sources such as PC-2 or PC-3 successfully worked (entries 9 and 10). Finally, the reaction using inexpensive eosin Y (5 mol %), as an organic photocatalyst, under green LED irradiation provided **2a** in 78% yield (entry 11). The reaction without the base displayed a similar efficiency (entry 12). A control experiment proved that green-light irradiation was necessary for the reaction to take place (entry 13). The organic catalyst loading could be decreased to 1 mol % without impairing the reaction yield (entry 14). The transformation was also successfully performed on a gram scale (entry 15).

With the optimized reaction conditions in hand, we wondered if this pyrazole scaffold could be accessed from 1,3-diaryltetrazoles in a domino process that would embrace a photoclick dipolar cycloaddition followed by an oxidative deformylation. For this purpose, an Ultra-Vitalux (OSRAM) lamp²⁰ was used as the irradiation source. This lamp has emission signals at λ values of 315 nm (UV), 440 nm (blue), and 540 nm (green), which would allow both UV-light-promoted cycloaddition and the blue- or green-light-photocatalyzed deformylation process, providing an easier reaction setup.²¹ Gratifyingly, the reaction between tetrazole **3a** and methacrolein gave **2a** as a single regioisomer in 72% yield, after 5 h at rt (Scheme 2).

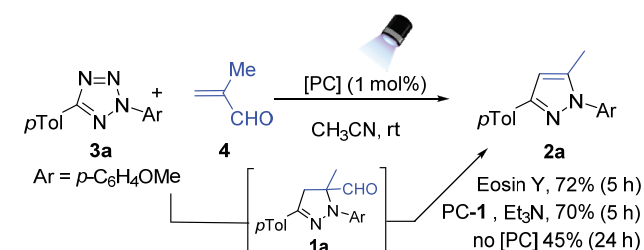
Table 1. Optimization of the Reaction Conditions

entry	[PC]	$h\nu$	base	time (h)	yield (%) ^a
1	none	UV ^b	none	24	44
2	PC-1	blue	none	6	66
3	PC-1	blue	Et ₃ N ^c	0.5	72
4	—	blue	—	6	0
5	—	blue	Et ₃ N ^c	6	0
6	PC-1	—	Et ₃ N ^c	6	0
7	PC-1	blue	2,6-lutidine ^c	0.5	71
8	PC-1	blue	K ₂ CO ₃ ^c	0.5	75
9	PC-2	blue	K ₂ CO ₃ ^c	0.5	76
10	PC-3	blue	K ₂ CO ₃ ^c	0.5	78
11	PC-4	green	K ₂ CO ₃ ^c	0.5	78
12	PC-4	green	—	0.5	73
13	PC-4	—	—	18	0
14	PC-4 ^d	green	—	0.5	76
15	PC-4 ^d	green	—	8	72 ^e

^aIsolated yield after purification. ^bUV λ 315 nm. ^cWith 1.5 equiv. ^dWith 1 mol % eosin Y. ^eOn a 3.5 mmol scale (gram-scale). Blue LEDs at a λ of 420 nm and green LEDs at a λ of 535 nm.

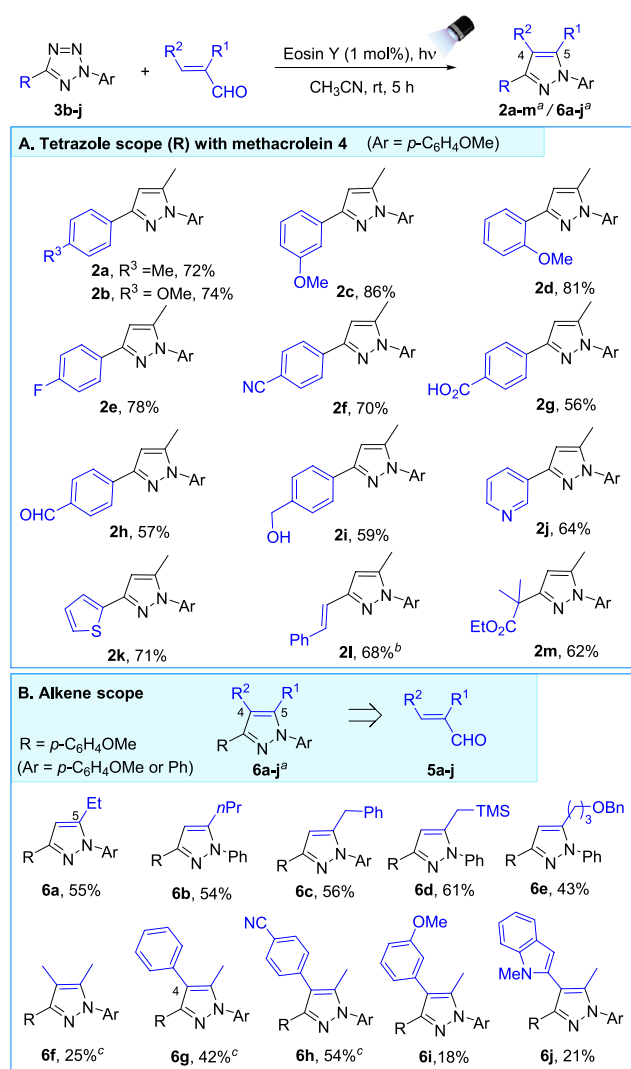
Scheme 2. Domino Photoinduced Cycloaddition/Oxidative Deformylation Sequence



The process using Ir-PC-1 and Et₃N also gave **2a** in a 70% yield. The use of blue or green LEDs as the single irradiation source resulted in the full recovery of tetrazole **3a**, underlining that the photoredox catalyst was exclusively catalyzing the second step. The reaction without any photocatalyst under the Ultra-Vitalux lamp gave pyrazole **2a** in significantly lower yield and longer reaction times (irradiation for 24 h) (Scheme 2). The global process using the photoredox catalyst opens the possibility of using the formyl group as novel photoremovable directing groups under mild reaction conditions.²²

The simple one-step preparation of pyrazoles led us to study the scope of the process with regard to the substitution at the nitrile imine precursor. As shown in Scheme 3, different electron-donating and electron-withdrawing groups underwent the dipolar/oxidative deformylation process successfully. *o*-,

Scheme 3. Scope of the Domino Sequence



^aIsolated yield. ^bEosin Y (5 mol %). ^cEosin Y (2 mol %).

m-, and *p*-methoxy-substituted phenyl tetrazoles furnished the corresponding pyrazoles in good yields (2b–d, respectively). Different functional groups such as fluoro, cyano, or carboxylic acids were perfectly compatible (2e–g, respectively). Interestingly, because no external oxidant was required in this protocol, groups sensitive to oxidant conditions such as formyl or benzylic alcohol were well tolerated (2h and 2i). Similarly, 3-heteroaromatic substituted pyrazoles, such as pyridyl or thienyl derivative 2j or 2k, respectively, were also obtained in good yields. The cycloaddition of tetrazole 3l bearing an alkenyl substituent proceeded similarly, giving rise to 2l as the only detectable isomer (no isomerization of the remaining double bond was observed).²³ Alkyl-substituted pyrazole 2m was also obtained in good yield.

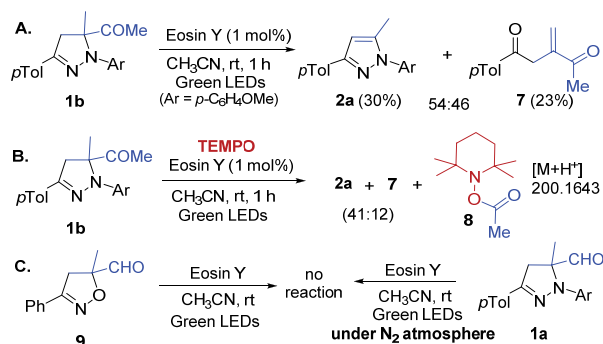
Next, we studied the compatibility of this photocatalyzed cycloaddition/fragmentation sequence with other α,β -unsaturated aldehydes as dipolarophiles (Scheme 3B). The reaction of 2-ethyl and 2-propyl acrolein under the optimized reaction conditions afforded pyrazoles 6a and 6b in 55% and 54% yields, respectively. A benzyl substituent in the aldehyde was also well tolerated, leading to pyrazole 6c in 56% yield. The reaction sequence proceeded in similar yields with function-

alized alkyl groups at the α -position of the aldehyde (pyrazoles 6d and 6e).

To evaluate the scope of this reaction with more sterically challenging substrates, α,β -disubstituted aldehydes were next evaluated (Scheme 3B). Despite a decrease in the reactivity observed in the first dipolar cycloaddition step, pyrazoles 6f–j could be obtained as single regioisomers. All of these results pointed out that this protocol opens a regioselective access to 5-alkyl tri- and tetrasubstituted pyrazoles, which was elusive with other cycloaddition methodologies.^{5–8}

It is known that ketones are also suitable substrates for Norrish fragmentation reactions. Therefore, we next studied the possibility of expanding the scope of this methodology to the use of α,β -unsaturated methyl ketones as dipolarophiles. For this purpose, we prepared pyrazoline 1b, with a pendant methyl ketone, through the corresponding 1,3-dipolar cycloaddition between 3a and 3-methyl-3-buten-2-one. The reaction of 1b under optimized reaction conditions was completed after 1 h, affording pyrazole 2a together with compound 7, in a 54:46 ratio (Scheme 4A). Although in this case pyrazole 2a

Scheme 4. Photocatalyzed Fragmentation of 1b, 9, and 1a

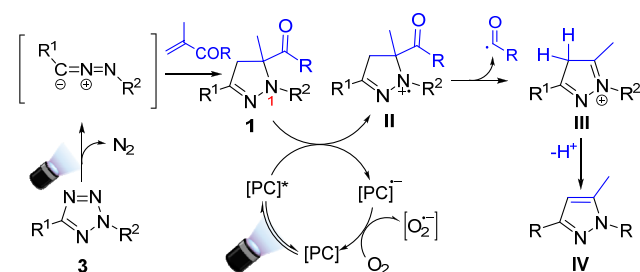


was obtained in moderate yield, this result highlights the significant potential of this green-light-catalyzed C–C fragmentation. The reaction with other 2-methyl α,β -unsaturated carbonyl derivatives, such as the carboxylic acid, the ethyl ester, or the *N*-methyl amide, gave the corresponding pyrazolines from the dipolar reaction; however, no carbonyl fragmentation was observed in any case.²⁴

To improve our understanding of the reaction pathway, we conducted a series of experiments. The addition of radical scavenger TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] to the photoreaction of 1b slowed the fragmentation process. As a result, a mixture of starting pyrazoline 1b, pyrazole 2a, and compound 7 was observed in a 47:41:12 ratio after irradiation for 1 h (detected by ¹H NMR). This reaction was also monitored by ESI-MS detecting the [M + H]⁺ ion (*m/z* 200.1643) that corresponds to TEMPO adduct 8, which indicates the involvement of the acyl radical (Scheme 4B).^{20,25} Moreover, the reaction did not proceed with formyl dihydroisoxazole 9, recovering the starting material unaltered. This is suggestive of the involvement of N-1 of the pyrazoline under the photoredox process. We also observed that the reaction was completely inhibited in the absence of O₂ (reaction under N₂ through a “freeze–pump–thaw” cycle) (Scheme 4C).

On the basis of all of these results, a plausible mechanism is proposed in Scheme 5. First, photolysis of tetrazole 3 generates nitrile imine dipole that, upon 1,3-dipolar cycloaddition with

Scheme 5. Mechanistic Proposal for the Domino Photoinduced Cycloaddition/Oxidative Deformylation



the α,β -unsaturated compound, leads to pyrazoline **1**. Visible-light irradiation of eosin **Y** generates an excited-state oxidant ($E_{1/2} = 0.86$ V vs SCE) that can accept a single electron transfer from N-1 of pyrazoline (for **1a**, $E_{1/2} = 0.68$ V vs SCE),²⁰ thus forming aminyl radical cation **II** and the reduced state of the photocatalyst.²⁶ Radical cation **II** evolves via a C–C bond fragmentation of the carbonyl group, generating a formyl ($R = H$) or an acyl radical ($R = Me$) favored by the formation of pyrazolinium cation **III** that aromatizes to the corresponding pyrazole **IV** after losing a proton. Oxidation of the photocatalyst by oxygen completes the catalytic cycle. The lack of reactivity under a nitrogen atmosphere supports the proposed reductive quenching cycle. Moreover, the formation of byproduct **7** (Scheme 4A) in the reaction with 3-methyl-3-buten-2-one supported the formation of radical cation **II** ($R = Me$), which can evolve via β -hydrogen abstraction of the methyl group, followed by a ring opening of the heterocycle. The formation of **2a** without a photocatalyst (Table 1, entry 1) and under UV light could be rationalized on the basis of a similar photoclick reaction followed in this case by a UV-light Norrish type I formyl fragmentation¹⁶ and oxidation sequence.

In conclusion, an innovative procedure for the preparation of pyrazoles has been developed using a domino photoinduced 1,3-dipolar cycloaddition/photoredox-catalyzed formyl fragmentation sequence. To the best of our knowledge, this is the first report describing an oxidative deformylation reaction using a photoredox catalyst under visible-light irradiation. An important advantage is that the domino sequence took place in the presence of an inexpensive organic photocatalyst such as eosin **Y**. The regiocontrol exerted by the formyl group allowed better access to tri- and tetrasubstituted 5-alkyl pyrazoles. Moreover, this protocol is compatible with the presence of groups sensitive to oxidizing conditions. These results demonstrate the possibility of using aldehydes as a clean photoremovable directing group and open the door for further investigations of other different systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c01665>.

General experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor Carmen Carreño on the occasion of her retirement from Universidad Autónoma de Madrid.

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(24) For other α,β -unsaturated aldehydes and ketones that were not suitable for this study as dipolarophiles, see the [Supporting Information](#).

(25) All of the attempts to detect the formyl radical formed in the reaction among **3a**, methacrolein, and TEMPO were unsuccessful.

(26) Stern–Volmer quenching studies between a photocatalyst (**PC-1** or eosin Y) and pyrazoline **1a** were inconclusive due to the fluorescent properties of **1a** ($\lambda_{\text{em}} = 476$ nm, and $\lambda_{\text{ex}} = 420$ nm).