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Photoinduced 1,3-Dipolar Cycloadditions of Cyclic Enones and 2,5-Disubstituted Tetrazoles: An Unprecedented Pathway to Polysubstituted Pyrazolines and Pyrazoles

Chiraz Labassi,^[a, b] Nicolas Fournier-Le Ray,^[a] Fabienne Gauffre,^[a] Jean-Luc Fillaut,^{✉[a]} and Rafik Gatri^[b]

We report herein the syntheses of original pyrazolines and pyrazoles through 1,3-dipolar cycloaddition of cyclic enones with 2,5-disubstituted nitrile imines achieved *via* photochemical activation of 2,5-diaryl substituted tetrazoles. Monitoring of the reactions, similar to nitrile imine-mediated tetrazole-ene cycloadditions (NITEC), could be performed by means of UV-vis absorption and emission

measurements. The presence or absence of substituents in the alpha position of the ketone function makes it possible to direct these reactions towards the selective formation of pyrazoles or pyrazolines. The choice of the cyclic enones and 2,5-disubstituted tetrazoles proved crucial for the fluorescence properties of the polycyclic derivatives obtained.

Introduction

The design and synthesis of nitrogen-containing heterocyclic compounds are of increasing interest because of their wide applications in the pharmaceutical and agrochemical industries.^[1] Among them, derivatives of pyrazoline and pyrazole (Figure 1) which are widely studied for their therapeutic potentials, including anticancer,^[2] anti-inflammatory,^[3] and antimicrobial activities^[4] among others,^[5–12] occupy a prominent place.

The development of new synthetic strategies for substituted pyrazolines and pyrazoles is therefore of real importance. These partially hydrogenated five-membered heterocycles with neighboring nitrogen atoms can be obtained through different approaches, such as the condensation of hydrazine derivatives with 1,3-dicarbonyl^[13] compounds or dipolar cycloadditions.^[14] In particular, the 1,3-dipolar cycloadditions of unsaturated systems and *in situ*

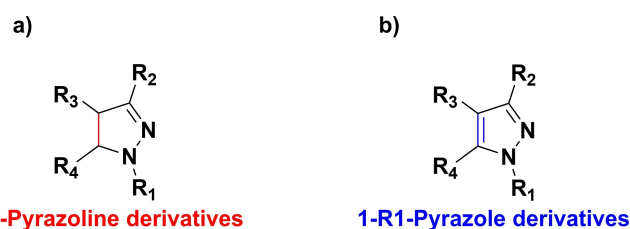


Figure 1. Generic structures of pyrazoline and pyrazole derivatives.

generated nitrile-imines constitute a versatile method for the synthesis of five-membered heterocycles.^[15] Nitrile imines are typically generated *in situ* from the corresponding hydrazonyl halides and have been widely used in various cycloaddition reactions to construct pyrazoles, pyrazolines, and other heterocycles.^[15]

The 1–3 dipolar cycloaddition can also proceed through photochemical activation, involving the generation of nitrile imines by photolysis of tetrazoles^[15f–16] and their reaction with a dipolarophile (Scheme 1). The first example of this photoinduced process, commonly known as nitrile imine-mediated tetrazole-ene cycloaddition (NITEC), concerned intramolecular 1,3-dipolar cycloadditions of alkenyl-substituted nitrile imines.^[17]

The NITEC reaction has been used for the synthesis of small molecules,^[18] macromolecules,^[19] polymers,^[20] functionalized surface materials^[21] and nanoparticles.^[22] Thanks to the emissive nature of the formed pyrazolines,^[23] this process was also widely applied for the development of fluorescent markers for the biologists.^[24] Interestingly, light-induced chemical reactions proceed relatively fast at ambient temperature and can provide unique spatiotemporal control over the chemical process.^[24b]

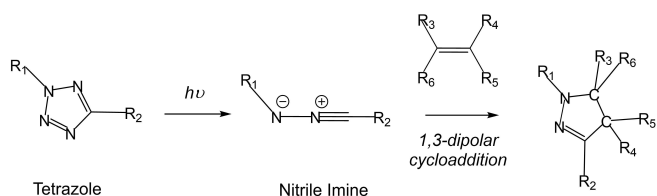
To our knowledge, the generalization to cyclic enones has not been described: the only reported reactions for the formation of pyrazoles or pyrazolines using enones involved the

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Scheme 1. Principle of the NITEC reaction.

chemical generation of nitrile imines from hydrazone chlorides.^[15f,25,26] For instance, M. Comes-Franchini *et al.* developed a regiocontrolled one-pot synthesis of cyclic enones with pyrazoles through the reaction of 2,4-enones with 5, 6, and 7-membered C-carboxymethyl-N-aryl nitrile imines generated *in situ* from hydrazone chlorides.^[26] These authors also reported a partial aromatization of the obtained pyrazolines into pyrazoles. The extent of such a partial aromatization is depending on the conditions and starting materials. It is noteworthy that the aromatization can be completed by treating the crude product with an oxidizing agent.

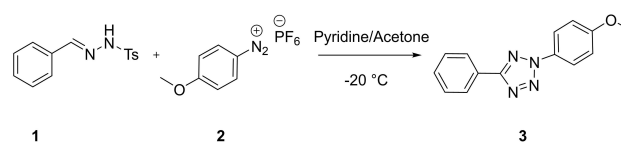
On the other side, a few groups explored the visible light triggered photolysis of tetrazoles to access pyrazoles via 1,3-dipolar cycloaddition between nitrile imines generated *in situ* photo-chemically in the presence of alkyne.^[16b,c] This direct aromatization to pyrazoles obviates further oxidative treatments of pyrazolines and can be performed either inter- or intramolecularly.

α,β -unsaturated carbonyl compounds being important functional compounds applied in synthetic chemistry, medical chemistry and material chemistry,^[27] we decided to study the photo-induced nitrile imine cycloaddition in the presence of cyclic enones with 5 and 6-membered rings, to access original pyrazole and pyrazoline derivatives.

Results and Discussion

In this study, we were interested in investigating the 1,3-dipolar cycloadditions of cyclic enones with nitrile imines obtained by the photochemical extrusion of nitrogen from the 2,5-diphenyl-tetrazole **3** (Scheme 2) and 2,5-dinaphthyltetrazole **6** (Scheme 3). The choice of **6** is based on the interest of 2,5-dinaphthyltetrazoles as biphotonic absorbers enable for generating a two-photon-induced dipolar cycloaddition,^[28] and on the fluorescence properties of the formed compounds. Indeed, one of the interests of NITEC reactions, in addition to the synthetic aspects, is the fluorescent nature of the formed pyrazolines, a characteristic that can be enhanced by the presence of naphthyl groups. It is interesting to note at this stage that the pyrazoles and pyrazolines derived from **6** are not accessible through conventional chemical routes due to the difficulties associated with the synthesis of the corresponding hydrazone chlorides precursor.

The tetrazoles **3** and **6** were obtained using adapted procedures of the Kakehi method.^[29] According to this scheme, the syntheses of tetrazoles **3** and **6** require the preparation of



Scheme 2. Preparation of 2-(4-methoxyphenyl)-5-phenyl-2H-tetrazole **3**.

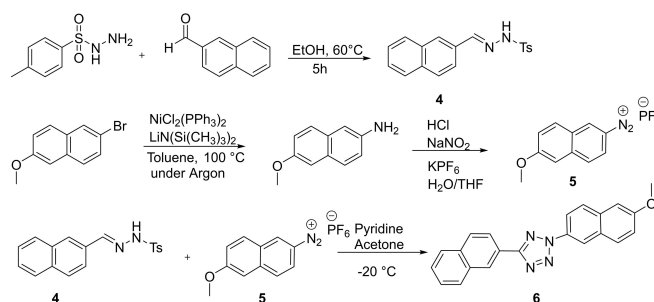
two precursors: hydrazones **1** and **4** and diazonium salts **2** and **5** (Schemes 2 and 3). Hydrazone **1** is obtained by condensation between p-toluenesulfonyl hydrazide and benzaldehyde in ethanol solution. The product **1** spontaneously precipitates as a white solid upon returning to room temperature after 5 hours of reaction at 60 °C.

The diazonium salt **2** was prepared from 4-methoxyaniline and sodium nitrite at $-10\text{ }^{\circ}\text{C}$ in the presence of HCl in a mixture of H₂O/THF. The diazonium salt in its hexafluorophosphate form, which is more stable,^[30] was obtained upon addition of potassium hexafluorophosphate.

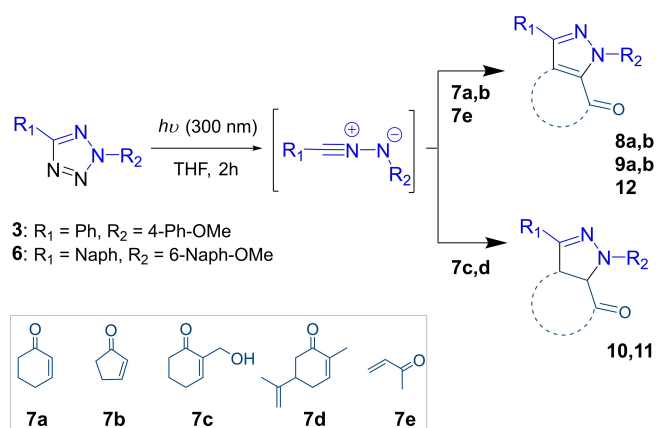
Tetrazole **3** was obtained by the slow addition of diazonium **2**, in acetone, at low temperature, to a solution of **1** in the presence of pyridine (Scheme 2).

Tetrazole **6** was obtained by applying a similar reaction process, starting from the naphthyl hydrazine **4** and the diazonium salt **5** (Scheme 3). The 6-methoxynaphthalen-2-amine resulted from the reaction of 6-methoxynaphthalen-2-bromine and lithium bis(trimethylsilyl)amide in the presence of catalytic amounts of anhydrous dichlorobis(triphenylphosphine)nickel(II).^[31]

The cycloaddition of the light-generated nitrile-imine issued from tetrazole **3** and 1,2-cyclohexenone resulted in the synthesis of pyrazole **8a** (Scheme 4 and Figure 2). It served as a model reaction and was then adapted to the various enones studied (Scheme 4). In a typical reaction, 50 mg (0.198 mmol) of tetrazole **3** and 40 equivalents (*vide infra*) of 1,2-cyclohexenone **7a** were dissolved in 30 mL of THF under an inert atmosphere. The use of THF for photochemical reactions was determined by the solubility of studied tetrazoles.^[29c] The reaction mixture was placed in a quartz container and exposed in a Rayonet® photoreactor equipped with 16 UV lamps, of 21 W, emitting at 300 nm, in accordance with the absorption spectra of tetrazoles **3** and **6**, which exhibit absorption bands with maxima at 295 nm (**3**) or 315 nm (**6**) in THF. After 2 hours of irradiation,



Scheme 3. Preparation of 2-(6-methoxynaphthalen-2-yl)-5-(naphthalen-2-yl)-2H-tetrazole **6**.



Scheme 4. Generic scheme of the NITEC from **3** and **6** leading to the formation of pyrazoles **8a,b**, **9a,b** and **12** (Figure 2) or pyrazolines **10–11** (Figure 2). The enones **7a–e** used in this study are shown in the frame. **7c** was prepared as described in ref.^[32]

monitoring by thin-layer chromatography (TLC) indicated complete consumption of the starting tetrazole. Removal of solvents and residual 1,2-cyclohexenone, followed by column chromatography, afforded pyrazole **8a** in crystalline form with a yield of 32%. Compounds **8b**, **9–12** (Figure 2) were obtained in a similar manner. **8b** was obtained with a slightly lower yield (24%), similar to that obtained for **9b**. Generally, the yields were higher with cyclohexenones, from 32% for (**8a**) to 52% for (**10**). The lowest yield was observed for **12**, starting from methylvinylketone, a non-cyclic enone (21%).

All compounds were characterized by NMR, which established that the compounds **8a,b**, **9a,b** and **12** displayed pyrazole-type structures (Figure 3), while **10–11** showed pyrazoline structures. To support these observations, for example, the study of the aliphatic signals for **9a** revealed the absence of signals expected for a pyrazoline. Instead, three multiplets were observed at 3.22 ppm, 2.72 ppm and 2.30 ppm, each multiplet integrating for two protons (Figures SI–7).

In contrast, the proton spectra for the compounds obtained from the cycloaddition with 2-hydroxymeth-

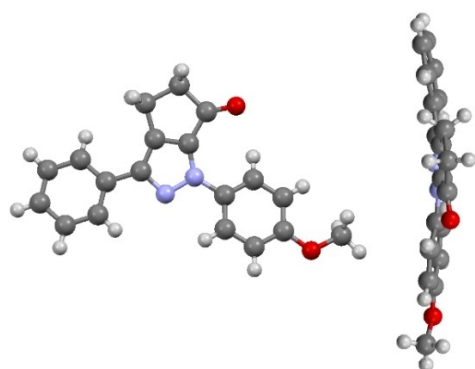


Figure 3. Perspective views of the molecular structure of **8b** (C₁₉H₁₆N₂O₂). The thermal ellipsoids are scaled to 50% probability.

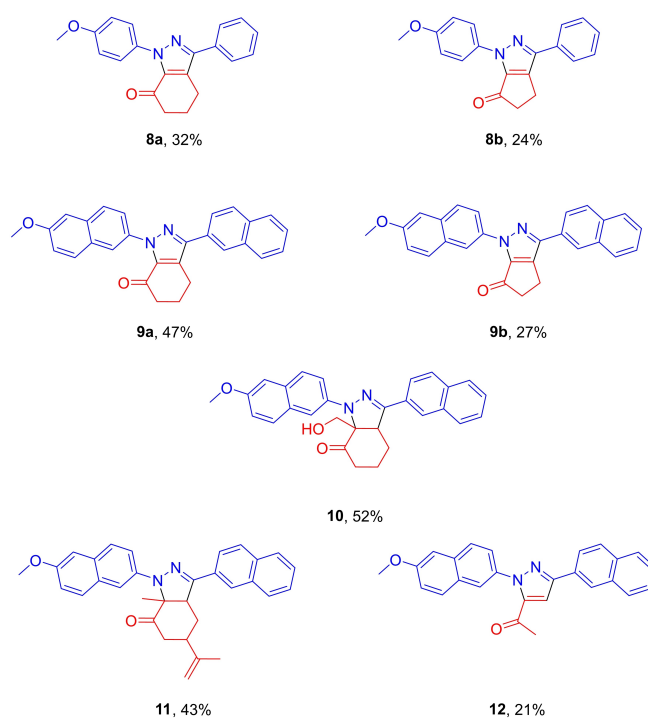


Figure 2. Products and reaction yields of photoactivated 1,3-dipolar cycloaddition of nitrile imines derived from tetrazoles **3** and **6** with enones **7a–e**.

ylcyclohexenone **7c** (compound **10**, Figure SI–15) or R-carvone **7d** (compound **11**, Figure SI–19) showed signals at 2.72 and 2.94 ppm, integrating for one proton, consistent with the CH groups of the corresponding pyrazolines **10** and **11**.

The cycloaddition is regioselective: only one adduct could be identified based on ¹H, ¹³C NMR data (see Supporting Information). Notably, the application of a NOESY sequence (Figure SI–8) confirmed the structure of **9a**. The off-diagonal cross-peaks in the NOESY spectra indicate the spatial proximity between the protons carried by carbon atoms C3 (δ = 3.23 ppm) and C26 (δ = 8.25 ppm).

This orientation was further confirmed by X-ray crystallography for **8b** and **9a** (Figures 3 and 4), which showed how the cyclocondensation of the enones with the imine nitriles directed the relative orientation of the carbonyl function and the nitrogen atoms of the heterocyclic core. It also confirms their pyrazole-type structures, independently of the aromatic rings carried by the imine nitrile or the nature of starting enone (cyclopentenone or cyclohexenone).

A plausible explanation for the regioselectivity would be that a two-center interaction takes place between the carbenoid C3 carbon of the nitrile-imine and the electrophilic β conjugated position of the carbonyl group of the cyclic enone.^[33]

One distinguishing feature of these compounds is their planarity. The arrangement of all the rings in **8b** is nearly planar (Figure 3). In contrast, for **9a**, the two naphthyl groups form an angle close to 145° (Figure 4). The presence of the carbonyl group from the enone and its relative proximity to the aromatic

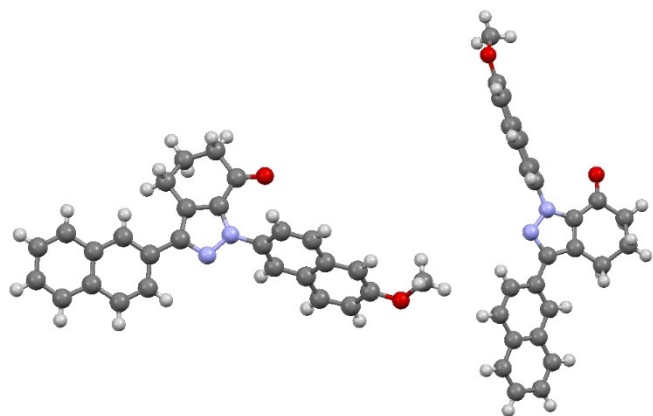


Figure 4. Perspective views of the molecular structure of **9a** (C₂₈H₂₂N₂O₂). The thermal ellipsoids are scaled to 50% probability.

rings (distances O22–C6 = 3.630 Å in **8b**, O16–C8 = 3.060 Å in **9a**) result in steric hindrance on the alignment of the three rings in the same plane for **9a**.

Compounds **10** and **11** are the only pyrazolines formed in the whole series. This is obviously due to the presence of methyl or methyl-hydroxy groups on the α -carbon of the ketone function in the starting enones **7c** and **7d**. For all the other cyclic enones, the formation of a pyrazole necessarily involved the intermediate formation of a pyrazoline, which would oxidize spontaneously under the experimental conditions.^[34] Note that this step did not require specific conditions (temperature, catalyst, presence of an oxidant) (*vide infra*).

In order to clarify these aspects, we carried out some kinetic studies using absorption and emission spectroscopy, with tetrazoles **3** and **6** in the presence of the different ketones studied.

The evolution of the absorption spectra is similar in each case: upon irradiation, a gradual decrease in absorbance where the tetrazoles **3** and **6** absorb (around 300 nm) is observed, while a new band grows at lower energy (Figure 5: example of **8a**, resulting from the irradiation of **3** in the presence of 40 equivalents of 2-cyclohexen-1-one).

These new bands are attributed to the formation of a cycloaddition adduct of the enone on the photoinduced nitrile imine. If the initial curves suggest the formation of an isobestic point, the latter deviate from it, whatever the enone or tetrazole used.

In parallel, an emission around 500 nm is observed, which could be attributed to the formation of pyrazolines during irradiation (Figure 5, top frame). Figure 6 shows this evolution in the case of the reaction of **3** in the presence of a varying number of equivalents (3, 10, and 40) of 2-cyclohexen-1-one. Figure 6a indicates the low impact of these variations on the transformation of the tetrazole, and thus on the formation of an imine nitrile intermediate. Figure 6b shows that, in all three cases, the intensity of emission increases rapidly until reaching a maximum and then decreases. Surprisingly, the kinetics of formation of the emissive species seem to be more favorable in

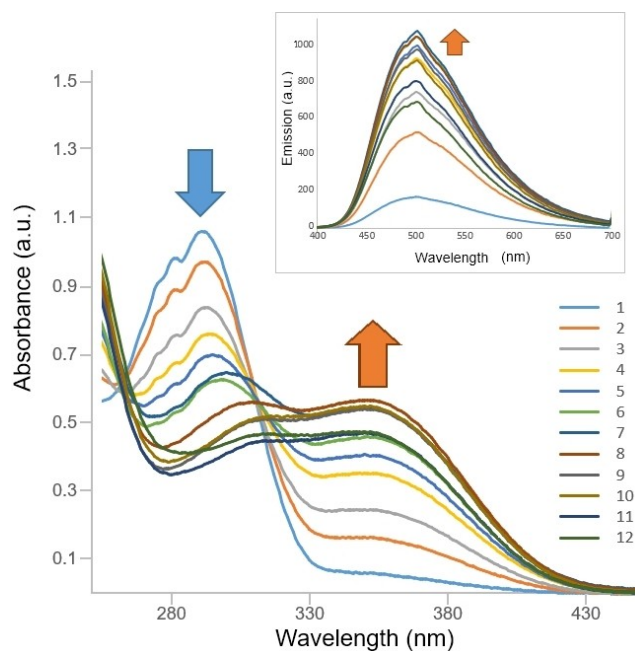


Figure 5. Time evolution of the absorbance during the irradiation of tetrazole **3** (6.6×10^{-3} mol/L in THF) in the presence of 40 equivalents of 2-cyclohexen-1-one. Top frame left side: evolution of the emission spectra ($\lambda_{\text{exc}} = 355$ nm).

the presence of 3 or even 10 equivalents of cyclohexenone than with 40 equivalents. This counter-intuitive observation actually suggests that the excess of cyclohexenone participates to the transformation of initially formed emissive species onto non-emissive species. We assume that this sequence corresponds to the initial formation of an emissive pyrazoline, which is transformed into pyrazole upon light irradiation, with the enone participating in this photoinduced oxidative process.^[34–35] Remaining traces of pyrazoline can explain the persistence of the fluorescent emission of the solutions before extraction (*vide infra*).

An attempt to monitor the formation of pyrazoline during the reaction of **3** in the presence of 3, 10, and 40 equivalents of 2-cyclohexen-1-one, by ¹H NMR spectroscopy in deuterated

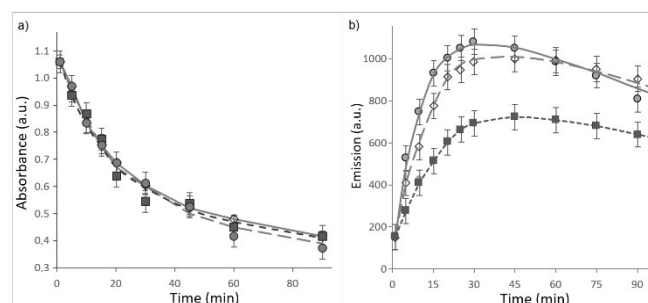


Figure 6. a) Evolution of the absorbance measured at 290 nm during irradiation of **3** in the presence of 3 (○), 10 (◇), and 40 (■) equivalents of 1-cyclohexen-2-one. b) Evolution of emission intensities at 500 nm observed during irradiation of **3** ($\lambda_{\text{exc}} = 355$ nm) in the presence of 3 (○), 10 (◇), and 40 (■) equivalents of 1-cyclohexen-2-one. (Initial tetrazole concentration 6.6×10^{-3} mol/L in THF).

THF, did not allow us to observe any signals that might belong to a pyrazoline, even if the samples were emissive. This suggests that the quantities of pyrazoline present are not detectable at the NMR scale (concentrations below 10 micromoles per liter).

§ Abbreviations: λ_{abs} = absorption maxima, λ_{em} = emission maxima, Φ_{F} = quantum yields [estimated by using quinine bisulfate (QBS) as a reference,^[36] Φ_{F} = 54% (THF, RT)]. Emission spectra of **8–12** were measured by exciting at their absorption maxima (3×10^{-5} mol/L in THF, RT).

Figure 7 shows time evolution of fluorescence intensity during the photo-cycloaddition of **6** in the presence of 40 equivalents cyclohexenone (Figure 7a) or R-carvone (Figure 7b). These figures are representative of the observations made in this work (see also Supporting information for other compounds). They allow us to distinguish two families, depending on whether the final species is emissive or not.

In the case of the reaction of **6** in the presence of 1-cyclohexen-2-one, the emission intensity increases until reaching a maximum and then tends to decrease (Figure 7a). The same observation is made for the reaction in the presence of methyl-vinyl-ketone. Conversely, for the other examples studied, the emission intensity of the reaction media measured at 500 nm, the average wavelength at which the studied systems emit, increases rapidly before reaching a plateau (Figure 7b: reaction of **6** in the presence of R-carvone).

Unexpectedly, although the same fluorophore groups exist in the structures of compounds **8a**, **9a** and **8b**, **9b**, the fluorescence emission profiles of these series of compounds are significantly different from each other. Thus, the two pyrazole-type compounds **8b** and **9b**, which derived from the cycloaddition with cyclopentenone, are emissive, unlike their quasi non-emissive homologues **8a** and **9a** derived from the cycloaddition with cyclohexanone (Table 1). This observation can be correlated with the steric impossibility, mentioned above, of orienting the three rings in the same plane for **9a** due to the presence of the carbonyl group derived from the enone (Figure 4). Finally, the comparison of the yields of compounds **8b** (26%) and **9b** (70%) highlights the benefits of introducing naphthyl groups to increase the emission of compounds due to wider electron delocalization.

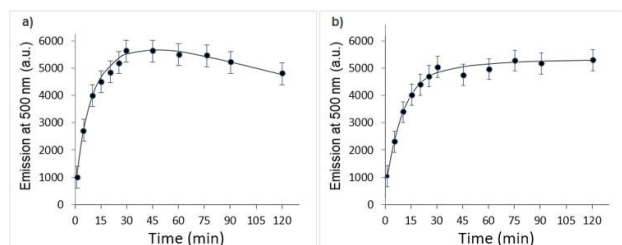


Figure 7. Evolution of the emission intensities of the reaction media at 500 nm observed during irradiation of **6** in the presence of 40 equivalents of a) 1-cyclohexen-2-one **7a** ($\lambda_{\text{exc}} = 375$ nm) and b) R-carvone **7d** ($\lambda_{\text{exc}} = 380$ nm).

	λ_{abs} (nm)	λ_{em} (nm)	Φ_{F} (%) [§]
8a	352	500	0.5
8b	360	485	26
9a	369	503	4.3
9b	368	500	70.2
10	378	502	15.5
11	373	496	70.0
12	376	501	1.3

Conclusions

The photoinduced 1,3-dipolar cycloaddition of 2,5-disubstituted diaryl tetrazoles in the presence of cyclic enones constitutes an efficient and facile strategy for the selective synthesis of novel pyrazolines and pyrazoles. The cycloaddition reaction is perfectly regioselective, the cyclocondensation of the enones with the imine nitriles being directed by the relative orientation of the carbonyl function and the nitrogen atoms of the heterocyclic core. These results have been confirmed by ¹H, ¹³C, and 2D NMR spectroscopy, as well as X-ray structures. Pyrazolines **10** and **11**, whose transformation into pyrazoles is prevented by methyl or hydroxymethyl functions originating from cyclohexenones, were found to be emissive. The other pyrazolines, which exhibit emission during photochemical irradiation, spontaneously transformed into pyrazoles. The significance of the size of cyclic enones is evident from the fluorescence properties of these pyrazoles: while the pyrazoles derived from cyclohexenones are non-emissive, their counterparts derived from cyclopentenone exhibit interesting emission properties. Several parameters, including the nature of by-products, substituents on the tetrazoles for improved reactivity of the photo-generated nitrile-imines, solvent effects, remain to be investigated to further improve the understanding and applicability of the described methodology.

Experimental Section

General experimental procedures, characterization data (¹H, ¹³C NMR, MS), and spectroscopic data for the kinetic study of the reaction on the new compounds are available in the Supporting Information.

Deposition Numbers 2269852 (for **8b**) and 2269851 (for **9a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: cyclic enones · cycloaddition (NITEC) · mediated tetrazole-ene · nitrile imine · photoinduced reactions · pyrazole · pyrazoline

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