

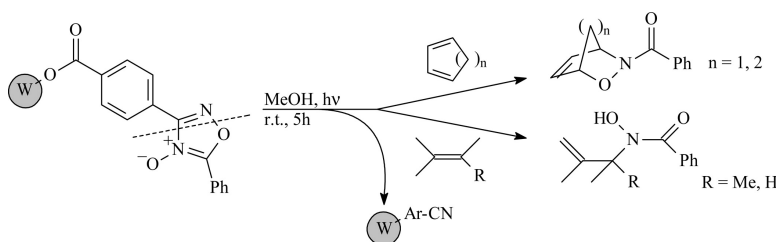
Article

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# Photochemical Generation of Nitrosocarbonyl Intermediates on Solid Phase: Synthons toward Hetero Diels–Alder and Ene Adducts through Photocleavage

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The synthesis of 1,2,4-oxadiazole-4-oxides on polystyrenic solid phase docked at the position 3 of the heterocyclic ring has been performed through the cycloaddition of stable supported nitrile oxides to amidoximes. The photochemical cycloreversion of these heterocycles afforded the free nitrosocarbonyl intermediates that were trapped by suitable dienes or enes. The method is proposed as a clean and environmental friendly approach to the fleeting nitrosocarbonyl intermediates, which afford valuable adducts for various synthetic applications. The isomeric heterocycles docked at the position 5 of the ring have also been obtained by cycloaddition of nitrile oxides to supported amidoximes. Their photolysis afforded resin-bound nitrosocarbonyls that were trapped with dienes affording valuable supported adducts suitable for further elaboration on solid-phase chemistry.

## Introduction

Nitrosocarbonyls (RCONO) **1** are well-known versatile fleeting intermediates<sup>1</sup> for organic synthesis<sup>2</sup> due to their high reactivity as  $\pi^2$  components in hetero Diels–Alder (HDA) cycloadditions<sup>3,4</sup> and ene reactions.<sup>5</sup> From the pioneering work by Kirby,<sup>6</sup> who generated these intermediates by periodate oxidation of hydroxamic acids **2** (Scheme 1), other methods have been proposed for the in situ preparation of nitrosocarbonyls. The oxidation of hydroxamic acids with various periodate derivatives is widely applied<sup>4,5</sup> together with the use of transition metal catalyzed reactions<sup>4c,d,i,7</sup> and  $\text{PhI}(\text{OAc})_2$ .<sup>8</sup> The in situ generated nitrosocarbonyls **1** are then trapped with a variety of dienes to afford the corresponding HDA adducts **5**. Thermal cycloreversion of the adducts offers an alternative source of these intermediates that can be trapped with different dienes or even with olefins in an ene addition affording the adducts **6**. The oxidative generation is not compatible with the ene reaction since it does appear to degrade initially formed adducts **6** by further oxidation.<sup>5a</sup>

Recently, we developed the oxidation of nitrile oxides **3** with *N*-methylmorpholine *N*-oxide (NMO)<sup>9</sup> as well as the clean photolysis of 1,2,4-oxadiazole-4-oxides **4**,<sup>10</sup> which provides the mildest route for the generation of these intermediates. Both these procedures are compatible either with the HDA and ene routes. The photochemical cleavage of **4** is the softest route to nitrosocarbonyls and was applied to the first and unique detection of nitrosocarbonyls by Toscano and co-workers<sup>1</sup> through the laser photolysis of 1,2,4-oxadiazole-4-oxides **4** during his studies in the biological chemistry of nitrogen oxides. All these protocols contribute largely to the extensive application of nitrosocarbonyl intermediates for many different synthetic purposes in various

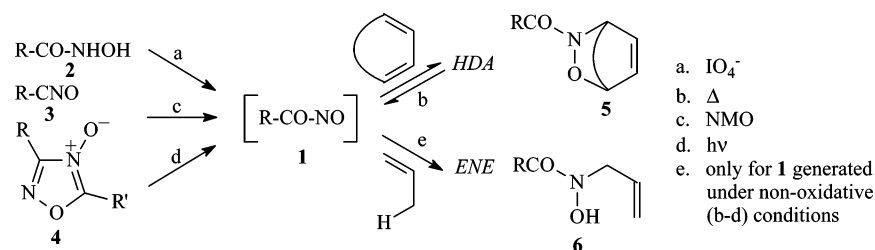
experimental conditions. Nevertheless all these methods have remained substantially at the margin of solid phase (SP) chemistry.

In recent years, the solid phase organic synthesis (SPOS) has become the way to find more rapid and clean synthetic approaches in the search of new biologically active compounds.<sup>11</sup> In this field, the area occupied by the 1,3-dipolar cycloadditions<sup>12</sup> and specifically by the SP chemistry of nitrile oxides<sup>13</sup> was quite restricted to only a few cases. Usually supported nitrile oxides are obtained in situ from appropriate precursors and immediately trapped by suitable dipolarophiles.<sup>14</sup> We have recently proposed a method to prepare stable aromatic nitrile oxides on SP.<sup>15</sup> From the stable hydroximoyl chlorides on Wang resin,<sup>14f,g</sup> the corresponding nitrile oxides were generated by adding to the suspended resin in dichloromethane (DCM) an excess  $\text{Et}_3\text{N}$  at room temperature for 2 h. Under the SP conditions, the nitrile oxide moieties are long-lived because of the site–site isolation of the nitrile oxide moieties on the solid support, which eradicates the well-known tendency of nitrile oxides in solution to dimerize to furoxanes.<sup>16</sup> The longer half-life of these dipoles under SP conditions allowed for a more convenient use in 1,3-dipolar cycloaddition reactions and also for further transformations on the nitrile oxide moieties such as their oxidation to nitrosocarbonyl intermediates with NMO. Hence, the fleeting nitrosocarbonyls could be generated on SP and instantly trapped with suitable dienes to afford the resin-supported HDA cycloadducts in moderate yields.

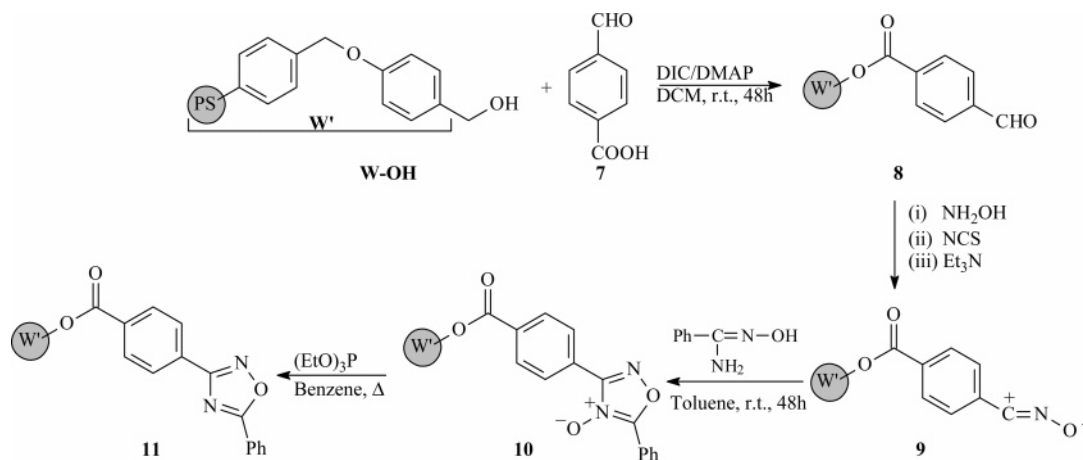
In the search for obtaining simpler handling of nitrosocarbonyls, we tried to adapt the photochemical generation method to the conditions required by the SP chemistry, and we started to explore the synthesis on a polystyrenic support of 1,2,4-oxadiazole-4-oxides, a class of valuable heterocycles never mentioned in SPOS.<sup>17,18</sup> In this paper, we report a

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## Scheme 1



## Scheme 2



convenient procedure that allows the simple generation of nitrosocarbonyls through the photolysis of 1,2,4-oxadiazole-4-oxides which have been docked at position 3 or position 5 of the heterocyclic ring on a Wang resin toward useful synthons for applications in the SP chemistry.

## Results and Discussion

Wang resin [*p*-benzyloxybenzyl alcohol polystyrene (PS) resin, loading 1.00 mmol/g; **W-OH**; Scheme 2] was coupled with 4-carboxybenzaldehyde **7** according to the standard DIC/DMAP coupling procedure<sup>19</sup> to afford the resin-bound aldehyde **8**. This was converted into the stable supported nitrile oxide **9** following the previously established protocols<sup>15</sup> depicted in Scheme 2.

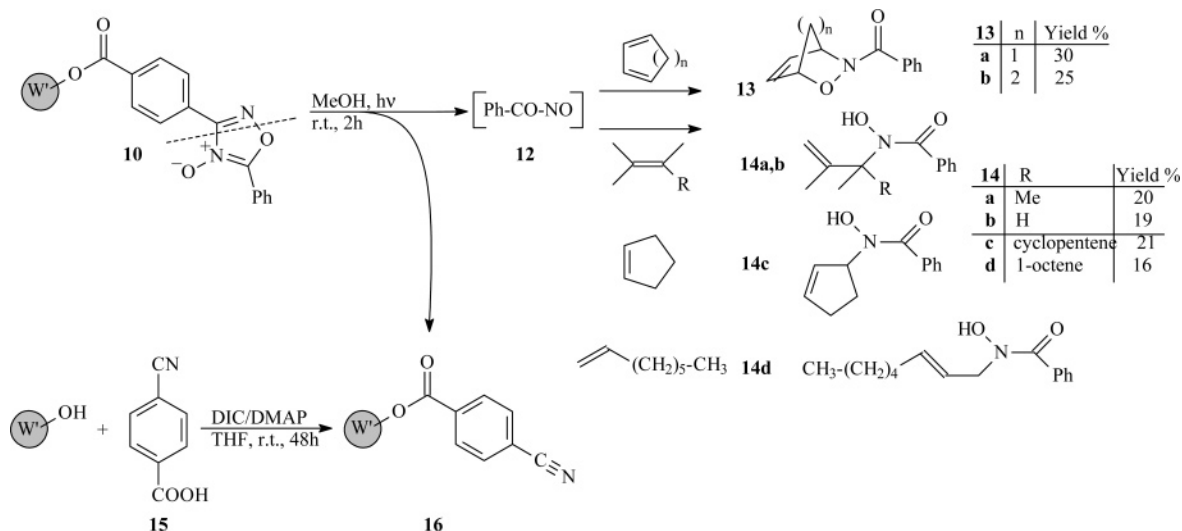
Having the supported stable nitrile oxide in hand, the synthesis of the 5-phenyl-1,2,4-oxadiazole-4-oxide docked to the resin at position 3 of the heterocyclic ring was accomplished by adapting the cycloadditions of nitrile oxides to amidoximes that we previously developed for the preparation of these heterocycles.<sup>20</sup> The Wang resin supported nitrile oxide **9** and excess benzamidoxime (2 equiv) in an anhydrous toluene suspension was left to react at room temperature for 48 h, and after the usual washings with toluene and DCM, the dry resin **10** was submitted to spectroscopic analyses. In the FT-IR (diffuse reflectance, DR) spectrum, the nitrile oxide band at  $2296\text{ cm}^{-1}$  has disappeared giving evidence of the consumption of the nitrile oxide. On the other hand the FT-IR and the gel-phase  $^{13}\text{C}$  NMR<sup>21</sup> spectra were not diagnostic because of the typical aromatic bands and signals of the resin that mask those belonging to the heterocycle.<sup>22</sup> Since the rather sensitive 1,2,4-oxadiazole-4-oxide does not survive under the detachment usually performed by acid cleavage with TFA or the transesterification procedure, we

have reduced the supported *N*-oxide **10** to the corresponding 1,2,4-oxadiazole **11** by heating with an excess of  $(\text{EtO})_3\text{P}$  in benzene overnight.<sup>23</sup> The detachment have been now easily carried out by transesterification<sup>15</sup> affording the 3-(4-carbomethoxyphenyl)-5-phenyl-1,2,4-oxadiazole in 17% yield, whose physical and spectroscopic data were identical to those reported in the literature.<sup>24</sup>

To test the synthetic potentialities of the photochemical generation of nitrosocarbonyl intermediates, the Wang supported 1,2,4-oxadiazole-4-oxide **10** has been irradiated either in the sunlight or at 310 nm (15 W lamps) in a methanol suspension in the presence of an excess (5 equiv) of freshly distilled cyclopentadiene or 1,3-cyclohexadiene (Scheme 3,  $n = 1, 2$ ). After 1–2 h under stirring, the resin was filtered off, the methanolic phase was concentrated, and the HDA cycloadducts **13a,b**<sup>9</sup> were isolated in a 30% and 25% yield, respectively, after purification by column chromatography. Almost identical results were obtained by performing the reactions in DCM as solvent, allowing better conditions of swelling for the resins. Similarly, the reaction can be performed in the presence of the olefins with the aim to obtain the corresponding ene adducts. The 2,3-dimethyl-2-butene (tetramethyl-ethylene, **a**:  $\text{R} = \text{Me}$ ), 2-methyl-2-butene (trimethyl-ethylene, **b**:  $\text{R} = \text{H}$ ), cyclopentene **c**, and 1-octene **d** are typical olefins that can be used to perform the ene reactions from photochemically generated nitrosocarbonyls.<sup>5</sup> After irradiation of the resin **10** suspension in methanol in the presence of 10 equiv of the olefins, the ene adducts **14a–d**<sup>5,10</sup> were isolated upon filtration and purification on column chromatography in fair yields (Scheme 3).

The photolysis of the resin supported 1,2,4-oxadiazole-4-oxide **10** releases in solution the nitrosocarbonyl benzene **12**, which is trapped by dienes or enes and leaves on the

## Scheme 3

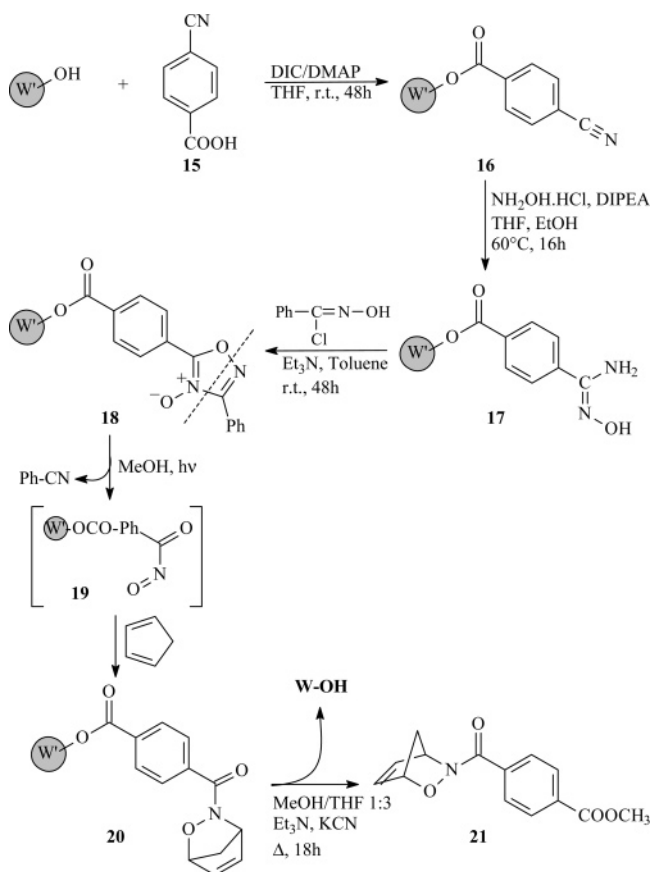


resin the nitrile moiety. In fact the nitrile group was detected in the FT-IR spectrum of the Wang resin **16** as a sharp band at  $2227\text{ cm}^{-1}$  and the gel-phase  $^{13}\text{C}$  NMR spectrum shows the CN signal at  $115.0\ \delta$ . These spectroscopic data are identical with those of an authentic sample prepared through the classical DIC/DMAP coupling between the Wang resin **W-OH** and 4-cyano-benzoic acid **15**.

The Wang resin supported benzonitrile **16** from DIC/DMAP coupling served as starting material for the parallel synthesis on the SP of the reversed 1,2,4-oxadiazole-4-oxide docked on the solid support at position 5 of the heterocyclic ring. The first step is the conversion of the supported nitrile **16** into the amidoxime **17** by adapting a reported protocol<sup>25</sup> through the addition of free  $\text{NH}_2\text{OH}$  in THF/EtOH solution and heating the suspension at  $60\text{ }^\circ\text{C}$  for 16 h (Scheme 4). The characterization of resin **17** has been carried out through the FT-IR spectrum, which indicates only the presence of a broad band between  $2500$  and  $3500\text{ cm}^{-1}$  attributable to the OH and  $\text{NH}_2$  groups of amidoxime. In the gel-phase  $^{13}\text{C}$  NMR spectrum, the nitrile signal at  $117.9\ \delta$  has disappeared and a signal at  $151.8\ \delta$  attributable to the  $\text{N}-\text{C}=\text{N}$  of amidoxime moiety is present.<sup>26</sup> The supported amidoxime **17** was used to prepare the supported reversed 1,2,4-oxadiazole-4-oxide by applying again the cycloaddition of nitrile oxides to amidoximes.<sup>20</sup> To the swollen resin **17** in toluene an excess (2 equiv) of benzhydroximoyl chloride was added along with 2.2 equiv of  $\text{Et}_3\text{N}$ , and the reaction was conducted under stirring for 48 h at room temperature. After filtration, resin **18** was washed carefully with toluene, methanol, and DCM and finally dried on vacuum. The FT-IR and the  $^{13}\text{C}$  NMR spectra show the absence of signals attributable to the amidoxime but do not allow for the detection of supported 1,2,4-oxadiazole-4-oxide since all the aromatic signals of these heterocycles stand below the resin bulk signals.

The presence of the reversed 1,2,4-oxadiazole-4-oxide was then detected through its photolysis and trapping of the resin-bound nitrosocarbonyl moiety with cyclopentadiene. Resin **18** was suspended in MeOH and, after addition of an excess (5 equiv) of cyclopentadiene, was irradiated in the usual way. From the usual workup procedures a residue was obtained

## Scheme 4



upon evaporation of the solvent in which the presence of benzonitrile was unequivocally determined through FT-IR analysis. The collected resin **20** contains the HDA cycloadduct of the resin-bound nitrosocarbonyl **19** to cyclopentadiene and the gel-phase  $^{13}\text{C}$  NMR spectrum showed the signals at  $48.2$ ,  $84.8$ , and  $165.2\ \delta$ , identical with the diagnostic signals for the HDA cycloadduct on resin already obtained by generation of nitrosocarbonyl from NMO oxidation of supported nitrile oxide.<sup>15</sup> The cleavage through the previously reported transesterification protocol<sup>15</sup> afforded the cycloadduct **21** in 18% yield along with the Wang resin **W-OH** suitable for recycling.

A few attempts have been made to check the lifetime of the supported nitrosocarbonyl **19** by adding cyclopentadiene 0.5–5 min after the beginning of the irradiation of samples of the resin **20**. No HDA adduct could be detected, pointing out that the supported 1,2,4-oxadiazole-4-oxide undergoes a fast photochemical fragmentation despite the short time of light exposure. Apparently, the site–site isolation of the nitrosocarbonyl moieties generated from resin **20** is not enough to impart stabilization to the intermediate under these conditions. Presumably nitrosocarbonyls undergo a photochemical cleavage to benzoyl radicals and NO,<sup>9b</sup> analogous to the photochemical cleavage of  $\alpha$ -hydroxy ketones<sup>27a,b</sup> or in Norrish Type I processes.<sup>27c</sup> Previous results in fact showed that irradiation of the 1,2,4-oxadiazole-4-oxide in the absence of trapping agents affords various benzoylated compounds that may derive from the radical decomposition of nitrosocarbonyls.<sup>10</sup>

### Conclusions

For the first time the 1,2,4-oxadiazole-4-oxide ring has been docked on SP either at position 3 or position 5 of the heterocycle. These kind of heterocycles are thermally stable<sup>28</sup> up to 130 °C and can be stored indefinitely if kept in the dark, but they easily undergo a photochemical cycloreversion to nitriles and nitrosocarbonyls.

Docking at position 3 can be performed by adding the supported nitrile oxides to amidoximes. The procedure rests on the prolonged stability of nitrile oxides on a solid polystyrenic support, allowing for an easy approach to the target heterocyclic ring. The photolysis generates the nitrosocarbonyl intermediates that are released in solution and trapped by suitable dienes in the case of HDA cycloadditions or by olefins in the case of ene reactions. Both the type of adducts are obtained in good yields, easily isolated from the solutions once the resin has been filtered off. Docking at position 5 takes place by supporting a nitrile moiety on the resin and converting it into the corresponding amidoxime. In situ generation of nitrile oxide in the presence of the supported amidoxime affords the heterocyclic ring. Photolysis releases benzonitrile in solution and affords supported nitrosocarbonyl intermediates, which can be trapped yielding resin-bound HDA adducts suitable for further synthetic elaboration on SP.

The docked heterocycles at position 3 or position 5 represent valuable and clean synthetic tools to prepare useful synthons either as free products in solution or resin-bound. The resins collected after the last steps are not simply a “waste” for their reuse ensures a saving of the starting material. Finally, these results will be also applied to the synthesis of relevant synthons for the preparation of carbocyclic nucleosides<sup>29</sup> through the chemistry of nitrosocarbonyls as we have recently showed, applying the classical solution protocols.

### Experimental Section

All melting points (mp) are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AVANCE 300 spectrometer (CDCl<sub>3</sub>). Chemical shifts are expressed in ppm from internal tetramethylsilane ( $\delta$ ): s, singlet; bs, broad singlet; m, multiplet. IR spectra (Nujol mulls for standard compounds

and DR in KBr for resins) were recorded on an FT-IR Perkin-Elmer RX-1 spectrophotometer, and absorptions ( $\nu$ ) are in cm<sup>-1</sup>. Column chromatography and TLC: silica gel H60 and GF<sub>254</sub> (Merck), respectively; eluant: cyclohexane/ethyl acetate 90:10 to pure ethyl acetate. The identification of samples from different experiments was secured by mixed mps and superimposable IR spectra as well as <sup>1</sup>H NMR spectra.

**Starting and Reference Materials.** Wang resin **W-OH** was purchased from Novabiochem: *p*-benzyloxy benzyl alcohol polystyrene resin, 100–200 mesh, loading 1.00 mmol/g.

Benzhydroximoyl chloride was obtained by treatment of benzaldoxime with sodium hypochlorite.<sup>30</sup> Addition of a slight excess of Et<sub>3</sub>N to a DCM solution of benzhydroximoyl chloride furnished in situ benzonitrile oxide (BNO),<sup>16</sup> which was used to perform the cycloaddition to supported benzamidoxime **17** to afford the reversed 1,2,4-oxadiazole-4-oxide **18**. Benzamidoxime was prepared following the well-known procedures.<sup>16,31</sup>

The synthesis of stable supported nitrile oxide **9** was performed starting from the Wang resin **W-OH** and 4-carboxybenzaldehyde (Aldrich) following the synthetic steps indicated in Scheme 2 and already reported.<sup>15</sup> The supported intermediates belonging to the synthetic route have been spectroscopically checked (FT-IR and gel-phase <sup>13</sup>C NMR) at the end of every single step and were found to be identical to previously described samples. In all the synthetic routes, the resin loadings have been considered constant (1 mmol/g) and the yields for the SP steps quantitative for the following steps.

**Synthesis of Supported 1,2,4-Oxadiazole-4-oxide 10.** Wang-supported nitrile oxide **9** (12 g, 12 mmol) was swollen in 40 mL of dry toluene, and 2 equiv of benzamidoxime (3.28 g) was added. The mixture was shaken at room temperature for 48 h and then filtered. Resin **10** was washed with toluene, methanol, and DCM and finally dried. The collected resin has been submitted to spectroscopic analysis. In the FT-IR (DR) the nitrile oxide band at 2296 cm<sup>-1</sup> was absent and the gel-phase <sup>13</sup>C NMR spectrum showed the usual pattern of a Wang resin. No diagnostic signals are detectable.

**General Procedure for the Photochemical Generation of Nitrosocarbonylbenzene from Resin 10 and Trapping with Dienes and Olefins.** To 3 g (3 mmol) of resin **10** suspended in methanol (30 mL) in a flat Pyrex reactor, an excess (5 equiv) of dienes in the first case (**a**: cyclopentadiene; **b**: 1,3-cyclohexadiene) or an excess (10 equiv) of olefins in the second case (**a**: 2,3-dimethyl-2-butene; **b**: 2-methyl-2-butene; **c**: cyclopentene; **d**: 1-octene) is added. The degassed suspensions were irradiated either in the sunlight or with 2 × 15 W 310 nm lamps for 5 h under shaking. After this period of time the resins were filtered off, washed with methanol and DCM, and dried while the organic solution concentrated to dryness. In duplicate experiments, the reactions were performed in DCM as solvent affording essentially identical results.

In the first case, the HDA cycloadducts **13a,b** were collected and purified through column chromatography in

30% and 25% yields, respectively. Cycloadducts **13a,b** were found identical to samples previously prepared according to the solution chemistry protocols.<sup>9</sup>

In the second case, the ene adducts **14a–d** were isolated from the concentrated solutions and purified through column chromatography in fair yields, as reported in Scheme 3. The adducts **14a–d** were compared to the samples derived from solution chemistry preparation and found to be identical.<sup>5,10</sup>

The dried resins correspond to the nitrile-supported derivatives **16** from the indications of FT-IR (DR) spectra, where the nitrile band was found at 2227 cm<sup>-1</sup> and of the gel-phase <sup>13</sup>C NMR spectra where the CN signal was found at 115.0 δ.

#### Independent Synthesis of Supported Nitrile Resin **16**.

To a suspension of Wang resin **W-OH** (5 g, 5 mmol) in dry THF (60 mL), 1.26 g (10 mmol) of DIC and 1.47 g (10 mmol) of 4-cyanobenzoic acid **15** (Aldrich) were added under shaking. After few minutes a catalytic amount of DMAP (10% molar) was added and the reaction continued at room temperature for 48 h. After filtration, the resin was washed with THF, methanol, and DCM and finally dried on vacuum.

In the FT-IR (DR) spectrum the CN band was found at 2230 cm<sup>-1</sup>, and the gel-phase <sup>13</sup>C NMR spectrum showed the typical chemical shift of the CN signal at 117.9 δ. For comparison the ν<sub>CN</sub> in benzonitrile is found at 2229 cm<sup>-1</sup>, and the same band in the 4-cyanobenzoic acid is found at 2231 cm<sup>-1</sup> while in the methyl 4-cyanobenzoate the CN band is found at 2250 cm<sup>-1</sup>.<sup>32</sup> Similarly, the CN signal of benzonitrile is at 118.8 δ and at 117.9 δ for the 4-cyanobenzoic acid and the corresponding methyl ester.<sup>33</sup>

**Synthesis of Supported Amidoxime **17**.** Nitrile resin of type **16** (loading 1 mmol/g) was suspended in THF (10 mL/g) and allowed to swell for few minutes. A 1 M solution of hydroxylamine in ethanol (25 mL/g) was prepared by adding DIPEA (9.17 mL, 52.5 mmol) to hydroxylamine hydrochloride (3.51 g, 50 mmol) in 100 mL of absolute ethanol until the solution is clear. The reaction mixture was heated at 60 °C for 16h under shaking. The resulting resin-bound amidoxime of type **17** was filtered off and washed carefully with methanol, THF, and DCM and finally dried on vacuum.

The characterization of resin **17** has been carried out through the FT-IR (DR) spectrum, which indicates only the presence of a broad band between 2500 and 3500 cm<sup>-1</sup> corresponding to the OH and NH<sub>2</sub> groups. In the gel-phase <sup>13</sup>C NMR spectrum the typical CN signal at 117.9 δ has disappeared, and the signal at 151.8 δ can be attributed to the C=N of amidoxime moiety.<sup>24,28</sup>

**Synthesis of Supported Reversed 1,2,4-Oxadiazole-4-oxide **18**.** Resin-bound amidoxime **17** (3 g, 3 mmol) are suspended in toluene (40 mL), and 2 equiv of benzhydroxymoyl chloride (0.93 g) was added along with 2.2 equiv of Et<sub>3</sub>N (0.71 g, 0.97 mL), and the reaction mixture was shaken at room temperature for 48 h. Resin **18** is then filtered off and carefully washed with toluene, methanol, and DCM. The dried resin has checked spectroscopically both with the FT-IR (DR) and the gel-phase <sup>13</sup>C NMR; in this latter the signal at 115.8 δ corresponding to the amidoxime has disappeared.

**Photochemical Generation of Nitrosocarbonyl on Resin **18** and Trapping with Cyclopentadiene.** Resin **18** (3 g, 3

mmol) was suspended in methanol (30 mL) in a flat Pyrex reactor, and an excess (5 equiv) of freshly distilled cyclopentadiene was added. The degassed suspension was then irradiated either in the sunlight or at 310 nm (2 × 15 W lamps) for 5 h under occasional shaking. The resin **20** was filtered off and washed with methanol and DCM and finally dried on vacuum. The gel-phase <sup>13</sup>C NMR spectrum gave the signals at 48.2, 84.8, and 165.2 δ in keeping with the diagnostic signals for the HDA cycloadduct on resin (see ref 15, p 1182: the missing C=O signal at 171.0 δ is in this case presumably too low in intensity to be detected). The organic solution was concentrated to dryness, and the presence of the benzonitrile coming from the photochemical cleavage was checked on TLC upon comparison with a reference sample (R<sub>f</sub> = 0.26; eluants: cyclohexane/ethyl acetate 90/10) as well as through the FT-IR of the dry residue (ν<sub>CN</sub>: 2229 cm<sup>-1</sup>).

**Cleavage by Transesterification from Resin **20**.** Resin **20** (3 g, 3 mmol) was allowed to swell in 50 mL of a 1:3 mixture of MeOH/THF, and a large excess (10 equiv) of Et<sub>3</sub>N was added. KCN (2 equiv) was added afterward, and the mixture was gently boiled overnight. The cooled suspension was filtered, and the resin was carefully washed with THF, methanol, and DCM. The collected organic phase was evaporated, and the residue was purified on column chromatography. The separation afforded the HDA cycloadduct **19** in 18% yield, identical to an authentic specimen previously prepared.<sup>15</sup>

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**Supporting Information Available.** Copy of FT-IR (DR) of **9**; copies of FT-IR (DR) and gel-phase <sup>13</sup>C NMR spectra of **10**, **16**, **17**, and **18**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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