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# Synthesis of 4-Phosphonylpyrrolidin-3-ones via [3+2] Cycloaddition of Nitrones with Phosphinylallenes

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**Abstract.** A variety of 4-phosphinylpyrrolidin-3-ones was prepared in good yields and excellent diastereoselectivity via a [3+2] cycloaddition between aryl aldonitrones and phosphinylallenes. Under the reaction conditions, the cycloadducts directly undergo a rearrangement to afford selectively the corresponding pyrrolidin-3-ones. DFT calculations provide some insights into the mechanism.

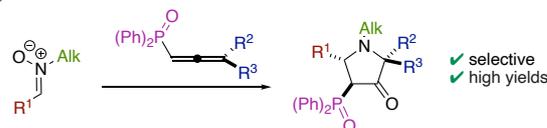
**Keywords:** Nitrones; allenes; heterocycles; cycloaddition; rearrangement

1,3-Dipolar cycloadditions constitute efficient methods for the preparation of five-membered heterocycles, often with excellent stereocontrol. Nitrones are among the most useful classes of 1,3-dipoles used in cycloaddition reactions in combination with structurally diverse alkenes or alkyne-derived dipolarophiles affording isoxazolidines,<sup>1</sup> isoxazolines,<sup>2</sup>  $\beta$ -lactams,<sup>3</sup> or acylaziridines.<sup>4</sup> Within the numerous studies on 1,3-dipolar cycloadditions of nitrones, only a few examples of pyrrolidinones synthesis are described from functionalized allenes, the latter generally bearing strong electron-withdrawing groups (CN, SO<sub>2</sub>R, CO<sub>2</sub>R...).<sup>5</sup> The cycloaddition between a less electron-deficient phosphorus-substituted allene and a *N*-aryl nitrone is limited to the formation of an indole derivative in low yield, involving the *N*-aryl substituent in a rearrangement (Scheme 1, a).<sup>6</sup> Our previous and undergoing research interest into nitrones and allenes prompted us to reexamine this transformation,<sup>4b,7</sup> focusing on *N*-alkyl nitrones with the aim to synthesize phosphorous substituted pyrrolidinones. Herein we report the first 1,3-dipolar cycloaddition of *N*-alkyl nitrones with phosphinoyl-substituted allenes, affording 4-phosphinylpyrrolidin-3-ones in high yield and excellent diastereoselectivity (Scheme 1, b).

a) Previous work (Anderson, 2014)<sup>6</sup>



b) This work

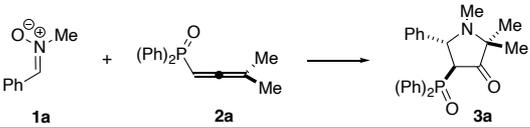


**Scheme 1.** Reaction of nitrones with phosphorus-substituted allenes.

Among the different strategies described to access functionalized allenes, isomerization of alkynes is a very attractive method.<sup>8</sup> Phosphorous substituted allenes can be prepared by the rearrangement of tertiary propargylic alcohols in the presence of an electrophilic phosphorus reagent, spontaneously delivering the corresponding phosphorous substituted allenes, with oxidation of the phosphorous atom.<sup>9</sup> The easy access to numerous *C*-aryl *N*-alkyl nitrones and phosphorous substituted allenes was therefore key for the rapid evaluation of the synthetic potential of a [3+2] cycloaddition/rearrangement sequence. We began our investigation using the (*Z*)-*N*-methylphenylnitronone **1a**. While a first reaction with a phosphonate substituted dimethyl allene did not lead to any isolated pyrrolidinone, switching for a slightly more electrophilic phosphinoyl group proved to be much more rewarding. With the symmetrical (3-methylbuta-1,2-dien-1-yl) diphenylphosphine oxide **2a**, heating in toluene at 100 °C for 48 hours resulted in the formation of pyrrolidinone **3a** as a single diastereomer in 50% yield (Table 1, entry 1). Using

THF, DCE or acetonitrile at 100 °C in sealed tubes led to reduced amounts of pyrrolidinone **3a**, accompanied by many side products (Table 1, entries 2-4). The use of cyclohexane under the same conditions proved much more rewarding, with 84% of the desired product (Table 1, entry 5). Under classical thermal activation, the concentration and the temperature could be further increased to 0.25 mol.l<sup>-1</sup> and 150 °C to lower the reaction time to a more practical 2 hours, though with a slightly lower yield (Table 1, entries 6-7). Concentrating further the reaction mixture led to the formation of the pyrrolidinone with an inseparable side-product (Table 1, entries 8). We also explored the reaction under microwave activation. While in toluene or ethyl acetate the yield remained lower (Table 1, entries 9 and 10), in cyclohexane, the outcome remained similar at 0.25 mol.l<sup>-1</sup> and 150 °C, but the concentration could be increased four times, from 0.25 mol.l<sup>-1</sup> to 1.0 mol.l<sup>-1</sup> (Table 1, entries 11 and 12). Thus, at 150 °C in cyclohexane for 2 hours, the full conversion of the starting material was observed, affording the pyrrolidinone **3a** with a very good yield of 79%, and notably without any side product (Table 1, entry 12). The relative *trans* configuration of the pyrrolidinone **3a** was first determined by nOe experiments and ascertained by single-crystal X-ray crystallography (Scheme 2). Throughout this optimization of the reaction conditions, a potential intermediate cycloadduct was never observed.

**Table 1.** Screening of reaction conditions.<sup>[a]</sup>

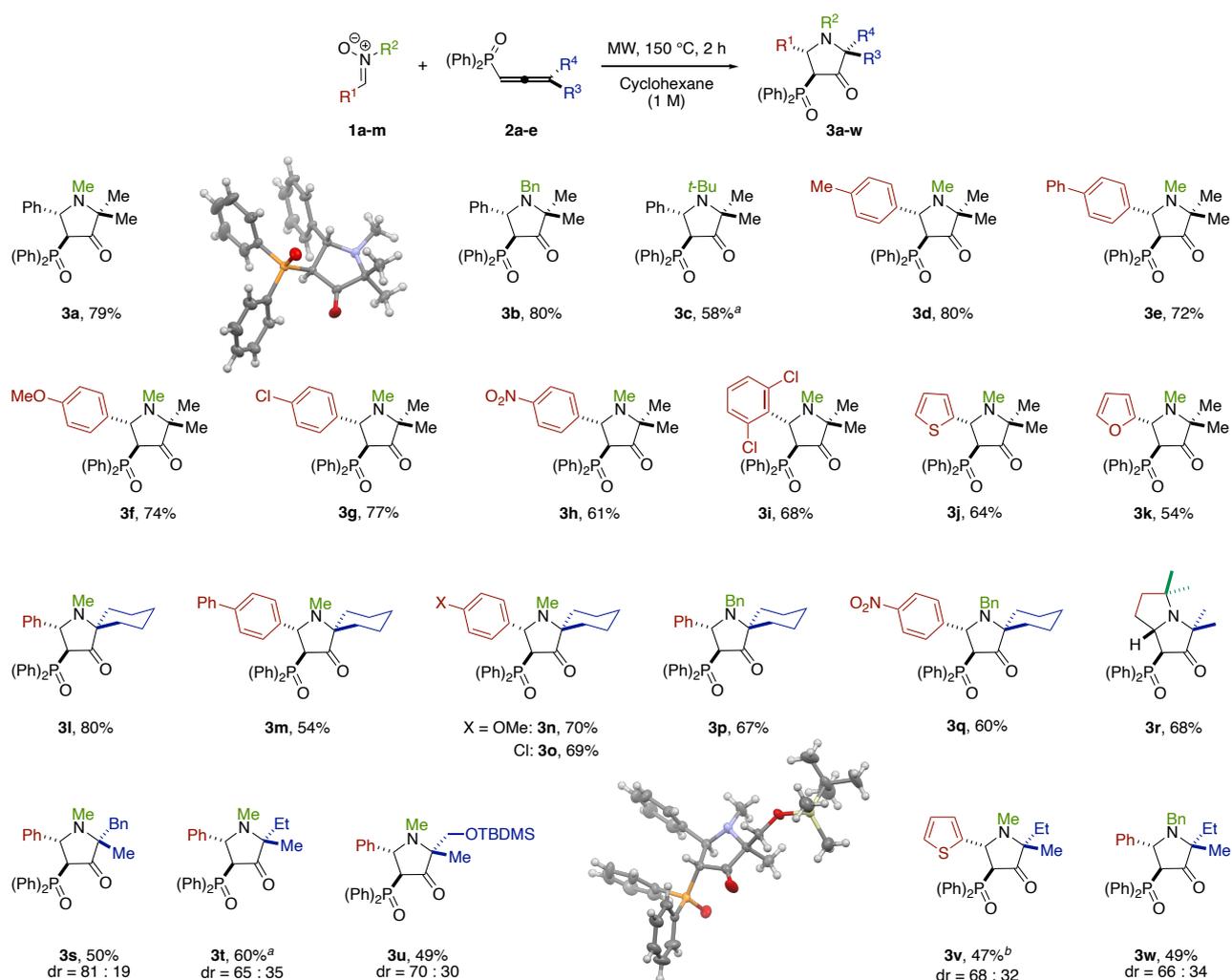


Entry	Solvent	[C] mol.l <sup>-1</sup>	Temp. (°C)	Time (h)	Yield (%) <sup>[d]</sup>
1	toluene	0.08	100 <sup>[b]</sup>	48	50
2	THF	0.08	100 <sup>[b]</sup>	48	37
3	1,2-DCE	0.08	100 <sup>[b]</sup>	48	<27 <sup>[c]</sup>
4	MeCN	0.08	100 <sup>[b]</sup>	48	<25 <sup>[c]</sup>
5	cyclohexane	0.08	100 <sup>[b]</sup>	48	84
6	cyclohexane	0.25	100 <sup>[b]</sup>	48	76
7	cyclohexane	0.25	150 <sup>[b]</sup>	2	72
8	cyclohexane	1.0	150 <sup>[b]</sup>	2	75 <sup>[f]</sup>
9	AcOEt	0.25	150 <sup>[c]</sup>	2	55
10	toluene	0.25	150 <sup>[c]</sup>	2	61
11	cyclohexane	0.25	150 <sup>[c]</sup>	2	70
<b>12</b>	<b>cyclohexane</b>	<b>1.0</b>	<b>150<sup>[c]</sup></b>	<b>2</b>	<b>79</b>

<sup>[a]</sup> Reaction conditions: **1a** (1 equiv.) and **2a** (1 equiv.) in sealed tubes, with different solvents warmed at X °C for Y hours. <sup>[b]</sup> Conventional heating. <sup>[c]</sup> Microwave irradiation. <sup>[d]</sup> Isolated yield after silica gel column chromatography. <sup>[e]</sup> Conversion determined by <sup>1</sup>H NMR. <sup>[f]</sup> Contaminated by an unidentified side-product. 1,2-DCE = 1,2-dichloroethane.

With the optimal conditions in hand, a variety of 4-phosphonylpyrrolidin-3-ones **3** was prepared using variously decorated allenes **2a-e** and nitrones **1a-m**

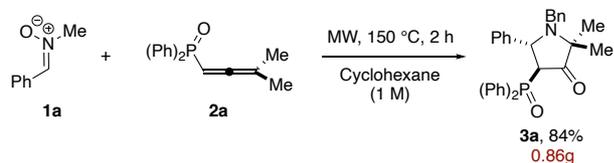
(Scheme 2). First, we tested the influence of the nitrogen substituent of the nitronium: a benzyl group instead of a methyl afforded the pyrrolidinone in a similar yield (**3b**-80% vs **3a**-79%), whereas a *tert*-butyl group was less efficient, affording **3c** in 58% yield, and requiring a longer reaction time of 3 hours for complete conversion. We next tested the modification of the *C*-aryl substituent of the nitronium, which proved to be quite flexible. The pyrrolidinones with 4-methyl, or 4-phenyl substituent on the aromatic ring were formed with equal efficiency (Scheme 2, **3d,e**). The reaction turned out to be quite insensitive to electronic density on the aromatic ring: a 4-methoxy and a 4-chloro substituent affording the products in good yield (Scheme 2, **3f,g**, 74 % and 77% respectively), while the strongly withdrawing nitro group being only slightly less favorable (Scheme 2, **3h**, 61%). The more sterically demanding 2,6-dichlorophenyl was also well tolerated (Scheme 2, **3i**, 68%). Heteroaromatics also afforded the expected pyrrolidinones, albeit in slightly lower yields, most probably due to the inherent lesser stability of the starting nitronium (Scheme 2, **3j,k**, 64 and 54%). Next, we tested the variation on the allenic reagents: replacing the *gem*-dimethyl substitution by a cyclohexyl ring delivered the expected cycloaddition product with nitronium **1a** in similar yield (Scheme 2, **3l**, 80%) whereas pyrrolidinones bearing 4-phenyl, 4-methoxy or 4-chloro substituents were obtained in slightly lower yields (Scheme 2, **3m-o**). With the *N*-benzyl nitronium **1b**, the reaction also proved compatible with the cyclohexylidene, affording the pyrrolidinones in similar to slightly lower yields, still as a single *trans* diastereomer (Scheme 2, **3p-q**). We also tested the cyclic aldonitronium 5,5-Dimethyl-1-pyrroline *N*-oxide (DMPO) which pleasingly afforded the bicyclic pyrrolizidine **3r** bearing two tetrasubstituted carbon atoms next to the nitrogen, in a good 68% yield, paving the way for further synthetic applications. We then turned our attention to the reaction with chiral allenes. In these cases, a mixture of diastereomers were obtained, with ratio ranging from 65:35 to 81:19. The methyl-ethyl substituted allene gave the lowest diastereoselectivity and the methyl-benzyl the highest one, while the silyloxymethyl-methyl allene gave a 70:30 diastereomeric ratio (Scheme 2, **3s-3u**). The relative configuration of the major diastereomer was assigned again by 1D and 2D NMR analysis, and confirmed by X-ray diffraction for pyrrolidinone **3u** (Scheme 2). X-ray analysis of a single crystal of the minor diastereomer of **3s** also confirmed that the two diastereomeric products both have a 4,5-*trans* configuration. The difference between the two diastereomers comes from the relative configuration at C-2: on the major one the bulkiest group at C-2 lays in relative *trans* position to the phosphine oxide moiety (2,4-*trans*), and on the same side as the aryl substituent of the starting nitronium (2,5-*cis*). Similar diastereoselectivities and yields were obtained from the methyl-ethyl allenyl derivatives with nitronium **1j** and **1b** (Scheme 2, **3v,w**).



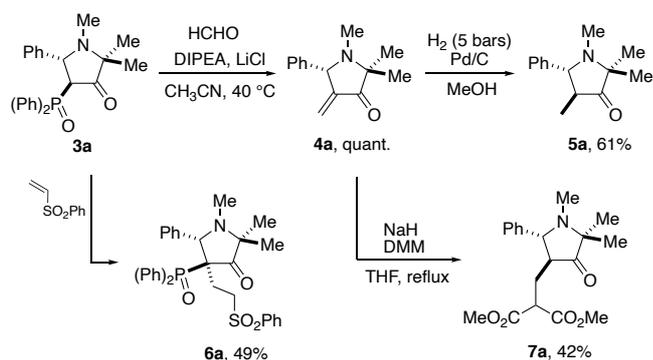
**Scheme 2.** Reaction Scope. Reaction conditions: A solution of **1** (0.5 mmol), **2** (0.5 mmol) in cyclohexane (0.5 mL) was stirred for 2 h at 150 °C under microwave (MW) irradiation. Isolated yields after silica gel column chromatography. Diastereomeric ratios (dr) were determined by <sup>1</sup>H NMR on the crude reaction mixture. <sup>[a]</sup> 3 h at 150 °C. <sup>[b]</sup> 6 h at 150 °C.

The one-pot cycloaddition-rearrangement sequence was then tested on five times the standard scale (2.5 mmol), affording 0.86 g of the pyrrolidinone **3a** in an excellent 84% yield (Scheme 3).

Five time scale reaction



**Scheme 3.** Larger scale reaction.

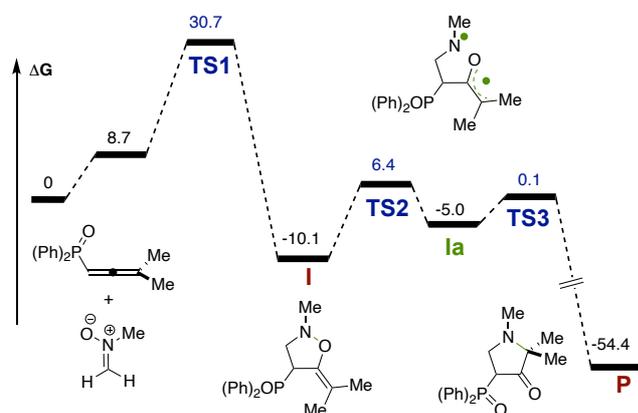


**Scheme 4.** Functionalization of the 4-phosphonylpyrrolidin-3-ones **3a**.

To illustrate the synthetic potential of the 4-phosphonylpyrrolidin-3-ones, a Horner-Wadsworth-Emmons (HWE) reaction was performed on **3a** with paraformaldehyde in the presence of *N,N*-

diisopropylethylamine and LiCl (Scheme 4). The expected enone **4a** was obtained quantitatively. The subsequent catalytic hydrogenation afforded pyrrolidinone **5a** and the Michael addition with dimethyl malonate delivered the addition product **7a**, both obtained as single diastereomers (Scheme 4). On the other hand, the Michael addition of **3a** onto phenylvinylsulfone generated a tetrasubstituted stereogenic center, with a moderate 49% yield, but as a single diastereomer (Scheme 4, **6a**).

We next questioned about the mechanism involved in this sequence where the initial [3+2] cycloaddition product, never identified, rearranges to the obtained pyrrolidinone through the N–O bond cleavage and subsequent C–N recombination. Such a transformation has previously been observed, but no clear insight into the mechanism was given, and contradictory mechanisms have been proposed.<sup>10</sup> We thus engaged in DFT exploration of this transformation on a simple model substrate (see SI for details) and the resulting free energy profile for the whole reaction is given in Figure 1.



**Figure 1.** Free energy ( $\text{kcal}\cdot\text{mol}^{-1}$ ) of the overall transformation. The zero point is the nitron and the allene taken isolated. **I** cycloadduct; **Ia** di-radical species; **P** final pyrrolidinone.

The initial activation barrier for the [3+2] cycloaddition (TS1) is computed at  $30.7 \text{ kcal}\cdot\text{mol}^{-1}$  thus compatible with the temperature of the reaction. The N–O bond opening was found to occur through homolytic cleavage, leading to a diradical species. The related activation energy (TS2) of  $16.5 \text{ kcal}\cdot\text{mol}^{-1}$  is almost twice lower than for the initial step, explaining the impossibility to isolate or identify the intermediate cycloadduct **I**. The bi-radical formation is energetically favored over the polar intermediate by  $18 \text{ kcal}\cdot\text{mol}^{-1}$  (see SI for the heterolytic mechanism). The subsequent diradical recombination (TS3) occurs with a very low barrier ( $5.1 \text{ kcal}\cdot\text{mol}^{-1}$ ) involving the nitrogen and the carbon which bears most of the radical characters in intermediate **Ia** (see SI). The reaction is highly exergonic as can be seen from the free energy of the pyrrolidinone **P**. Additional studies are undergoing to gain further insight into the relative configuration,

including the diastereoselectivity origin with chiral allene, and the lower reactivity of phosphonates.

In conclusion, we have reported a one-pot nitron phosphinylallenes [3+2] - rearrangement sequence, involving the homolytic N–O bond cleavage of the intermediate cycloadduct, affording a wide variety of pyrrolidinones as single 4,5-*trans* diastereomers in good to excellent yields, and applicable to large scale. Chiral tetrasubstituted center can be generated in modest selectivity using chiral allenes. Further exploration of this reaction is ongoing and will be reported in due course.

## Experimental Section

In a sealed tube, nitron **1a** (0.5 mmol), phosphinyl allene **2a** (0.5 mmol) and cyclohexane (0.5 ml) were heated at  $150^\circ\text{C}$  under microwave irradiation for 2 hours. After the completion of the reaction, the mixture was concentrated under reduced pressure and the crude material was purified by column chromatography over silica gel (pentane / EtOAc 50:50) to afford pure 4-phosphonylpyrrolidin-3-one **3a** (158 mg, 79%) as a white solid: m.p.  $192\text{--}195^\circ\text{C}$ ; IR (neat)  $\nu = 1747, 1250, 1189, 1118 \text{ cm}^{-1}$ ;  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  27.17;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.80 (ddd,  $J = 12.0, 8.2, 1.6 \text{ Hz}$ , 2H), 7.52 – 7.42 (m, 5H), 7.33 (dt,  $J = 7.6, 4.5 \text{ Hz}$ , 1H), 7.17 (td,  $J = 7.7, 3.0 \text{ Hz}$ , 2H), 7.10 (d,  $J = 7.2 \text{ Hz}$ , 1H), 7.05 (t,  $J = 7.4 \text{ Hz}$ , 2H), 6.97 (d,  $J = 7.1 \text{ Hz}$ , 2H), 4.20 (dd,  $J = 12.0, 8.8 \text{ Hz}$ , 1H), 3.57 (dd,  $J = 10.8, 8.8 \text{ Hz}$ , 1H), 2.05 (s, 3H), 1.26 (s, 3H), 1.10 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  210.5 (d,  $J = 4.4 \text{ Hz}$ ), 141.3, 131.9 (d,  $J = 2.9 \text{ Hz}$ ), 131.8 (d,  $J = 103.6 \text{ Hz}$ ), 131.6 (d,  $J = 2.9 \text{ Hz}$ ), 131.2 (d,  $J = 101.0 \text{ Hz}$ ), 131.4 (d,  $J = 9.6 \text{ Hz}$ ), 131.1 (d,  $J = 9.5 \text{ Hz}$ ), 128.4 (d,  $J = 12.5 \text{ Hz}$ ), 128.34, 128.32 (d,  $J = 12.4 \text{ Hz}$ ), 128.0, 127.5, 66.1, 64.2 (d,  $J = 2.0 \text{ Hz}$ ), 55.9 (d,  $J = 66.1 \text{ Hz}$ ), 31.8, 23.5, 13.3; HRMS (ESI) m/z:  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{25}\text{H}_{27}\text{NO}_2\text{P}$  = 404.1773; Found = 404.1781,  $[\text{M}+\text{Na}]^+$  Calcd for  $\text{C}_{25}\text{H}_{26}\text{NNaO}_2\text{P}$  = 426.1593; Found = 426.1603.

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