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Mechanistic investigations of the phosphine-mediated nitrone deoxygenation reaction and its application in cyclic imine synthesis

Pascale Cividino [a], Marie-Louise Dheu-Andries [a], Jun Ou [b], Anne Milet [a,*], Sandrine Py [a,*], Patrick H. Toy [b,*]

[a] Département de Chimie Moléculaire, UMR-5250, ICMG FR-2607, CNRS-Université Joseph Fourier, BP 53, 38041 Grenoble Cedex 09, France
[b] Department of Chemistry, The University of Hong Kong, Pokfulan Road, Hong Kong, PR China

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ABSTRACT

Carbohydrate-derived cyclic nitrones were deoxygenated to form the corresponding imines using tributylphosphine. Experimental and theoretical investigations by the way of MP2 calculations suggest a revision of the mechanism initially proposed by Kurtzweil and Beak for the triarylphosphine-mediated deoxygenation of nitrones.

Polyhydroxylated nitrones have been recently prepared from the corresponding *O*-acetal- and *O*-benzyl-protected precursors, by means of a BCl_3-promoted dealkylation reaction.[1] While the biological activities of such nitrones have not been reported, the related polyhydroxylated endocyclic imines (i.e., polyhydroxylated pyrrolines) have been previously described to be potent glycosidase inhibitors.[2,3] For example, nectrisine (FR-900483), a natural product isolated from the fungus *nectria lucida*, is a selective inhibitor of α-glucosidases (IC_{50} 4.8×10^{-8} M, yeast α-glucosidase) and a potent immunomodulator.[4] The biological activities of such compounds and their potential applications as antiviral therapeutics have motivated numerous synthetic efforts directed toward accessing libraries of pyrrolines.[5] Thus, as part of our ongoing research regarding the synthesis of novel iminosugars using carbohydrate-derived nitrones[6] as intermediates,[7] we became interested in the transformation of functionalized endocyclic nitrones into the corresponding imines (Fig. 1).

Although several methods have been reported for the conversion of nitrones to imines,[8] only few of them afford high yields of product. With our ultimate plan being to prepare highly water-soluble polyhydroxylated imines **II** (Fig. 1), methods that did not necessitate aqueous work-up were preferred. We thus decided to investigate the nitrone deoxygenation reaction promoted by trivalent phosphorus reagents, such as phosphites[9] and phosphines.[10,11]

In our initial attempts, the treatment of nitrone **1**[7a,12] with trimethylphosphite in the presence of triethylamine[9] or with triphenyl phosphine in refluxing THF or toluene[10] did not allow for the isolation of imine **2**[13] in useful yields (Scheme 1).

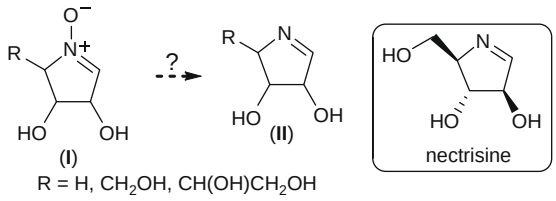
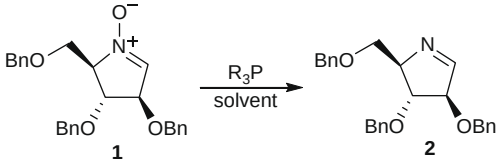


Figure 1. Synthesis of endocyclic imines from nitrones.



Scheme 1. Deoxygenation of endocyclic nitrone **1** to imine **2**. Reagents and conditions: (i) $(MeO)_3P/Et_3N$ (9:1), 50 °C, 1.5 h, 35%; (ii) Ph_3P (20 equiv), THF or toluene, reflux, 23 h, 17–35%; (iii) Bu_3P (2 equiv), THF, 65 °C, 48 h, 69%.

* Corresponding authors. Tel.: +33 0 476 51 48 04; fax: +33 0 476 51 49 27 (A.M.); tel.: +33 0 476 51 48 03; fax: +33 0 476 63 59 83 (S.P.); tel.: +852 2859 2167; fax: +852 2857 1586 (P.H.T.).
E-mail addresses: anne.milet@ujf-grenoble.fr (A. Milet), sandrine.py@ujf-grenoble.fr (S. Py), phtoy@hku.hk (P.H. Toy).

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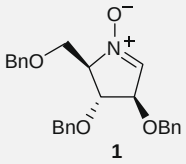
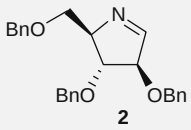
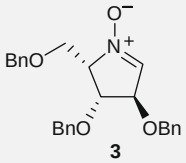
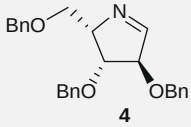
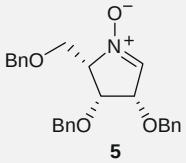
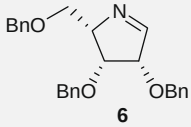
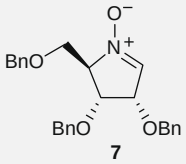
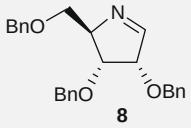
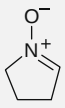
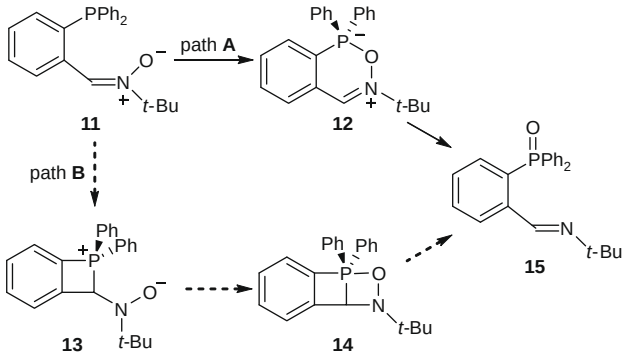
Table 1
Deoxygenation of endocyclic nitrones[a]

Entry	Substrate	Product	Conv.[b] (%)	Yield[c] (%)
1	 **1**	 **2**	>95	69
2	 **3**	 **4**	>95	60
3	 **5**	 **6**	>95	50
4	 **7**	 **8**	>95	53
5	 **9**	 **10**	60	n.d.[d]

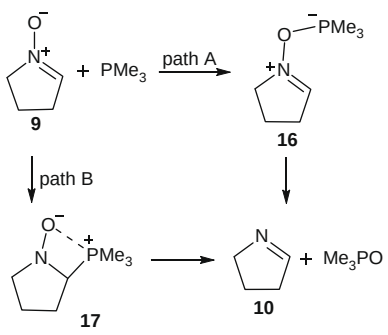
[a] Reagents and conditions: Bu_3P (2 equiv) in THF at 65 °C for 48 h.
[b] Conversion based on ^1H NMR analysis of the reaction mixture determined by integration of the nitrone and imine vinyl protons.
[c] Isolated yield.
[d] Not determined due to product instability.

However, when triphenylphosphine was replaced by tributylphosphine, the desired imine **2** could be isolated in 69% yield, after 48 h at 65 °C (Table 1, entry 1).



Scheme 2. Beak's proposed mechanisms for the transfer of oxygen from a nitrone group to phosphorous(III).

The applicability of this method to a selection of endocyclic nitrones was evaluated next. Thus, nitrones **3**,[14] **5**,[7c] **7**,[15] and **9**[16] were treated with tributylphosphine under the same reaction conditions to afford imines **4**,[17] **6**, **8**, and **10**, respectively, in moderate to good yields (Table 1, entries 2–5).[18]



Scheme 3. Mechanistic models used for MP2 calculations.

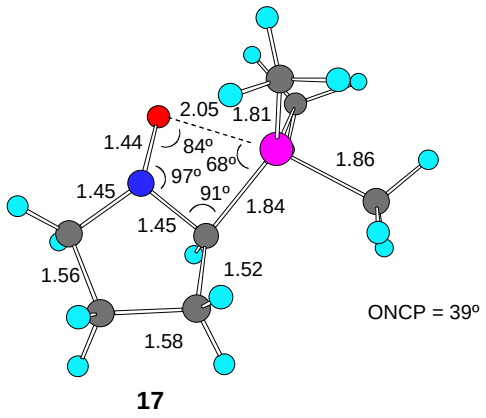


Figure 2. Intermediate **17**, distances in Å.

In general, it was found that isolated yield of the imine was always lower than what was expected from the measurement of the conversion of starting material into product by NMR analysis of crude reaction mixtures. This may be linked to the intrinsic instability of the imine products. For example, imine **10** could not be isolated in pure form (Table 1, entry 5). The role of the temperature on the reaction rate was also evaluated; performing the reactions at higher temperature in toluene, did not result in significant yield improvement, as substantial decomposition occurred when the temperature was raised above 70 °C.

In these reactions, we were surprised by the enhanced reactivity of tributylphosphine, which is more nucleophilic than trimethylphosphite and triphenylphosphine (according to Swain-Scott nucleophilicity parameters: *n*MeI = 1.3, 5.2, and 8.7, respectively, for Ph_3P, $(MeO)_3P$, and Bu_3P).[19] This prompted us to re-examine the mechanism of phosphine-mediated nitrone deoxygenation that was previously proposed by Kurtzweil and Beak.[20] The same group had previously studied the intramolecular oxygen transfer from the nitrogen of a hydroxylamine to the phosphorus of a triarylphosphine and suggested a nucleophilic addition of oxygen to the phosphorus atom rather than a substitution at the oxygen.[21] In their analysis, the endocyclic restriction test[22] was used to investigate the mechanism of intramolecular oxygen transfer (Scheme 2).

The conclusion of their studies was that an addition–elimination pathway[23] involving a valence expansion at phosphorus via intermediate **12** was likely to occur (path A), rather than initial addition of the phosphorus atom to the iminyl carbon[9] (path B).

This hypothesis was proposed based on substituents effects, as it was found that an electron-deficient phosphine was more reactive for such oxygen transfer than an electron-rich one. Because our experimental results contrast with those of Beak et al. we decided to investigate the mechanism of these reactions using MP2 calculations.[24] The MP2 perturbation theory was used at the second order in conjunction with the 6-311+G** basis set[25,26] for

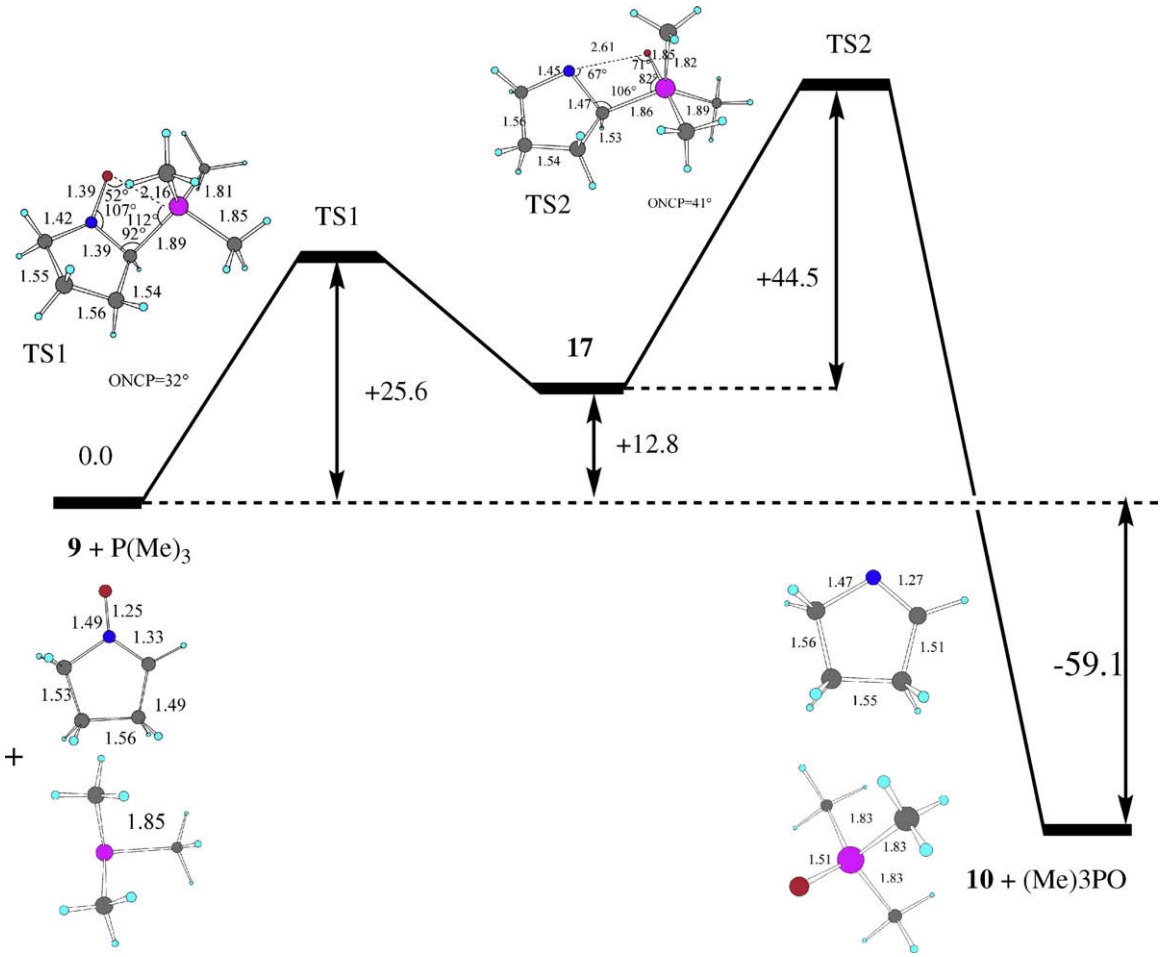


Figure 3. Reaction energy profile and optimized structures (activation energies in kcal mol^{-1} at MP2/6-311+G**//MP2/6-311+G** level and distances in Å).

investigating the possible mechanisms of intermolecular oxygen transfer from nitrones to phosphines. The reaction was modeled using nitrone **9** and trimethylphosphine. The first mechanism (Scheme 3, path A) corresponds to the mechanism proposed by Beak; a nucleophilic attack from the oxygen of the nitrone toward the phosphine to form intermediate **16**.

On the other hand, the second mechanism (Scheme 3, path B) involves the electrophilic character of the nitrone, and a nucleophilic attack by the phosphorus atom to the iminyl carbon, leading to the cyclic intermediate **17**, which may evolve toward **10**.

Despite several attempts, we failed to characterize the intermediate **16** through geometry optimization, and the latter led either to products or to intermediate **17**, depending on the starting geometry.[27] On the contrary, we were able to optimize intermediate **17**, whose geometrical parameters are gathered in Figure 2.

The distance between the phosphorus and oxygen atoms in **17** suggests a strong interaction between them, and to gain insight into the nature of this bond, an ELF analysis was performed.[28] Even if a 10% covalent contribution is present between these atoms, the ELF analysis indicates a dominant electrostatic interaction. From an energetic point of view, intermediate **17** is 12.8 kcal mol^{-1} higher in energy than the reactants. The transition state (TS) that connects the reactants and the intermediate **17** has been characterized, and the corresponding activation energy has been computed to be of 25.6 kcal mol^{-1} (Fig. 3). The TS connecting intermediate **17** and the products is also displayed in Figure 3. The structure is quite unsymmetrical toward the dissociation of the N–O and C–P bond lengths: The N–O bond length reached 2.61 Å whereas the C–P bond length is still short, with a value of 1.86 Å. The P–O bond length was determined to be 1.85 Å, compared with the 1.50 Å and 2.05 Å P–O bond lengths in trimethylphosphine oxide (product) and in **17** (intermediate), respectively. The activation energy for the second step was estimated at 44.5 kcal mol^{-1} in spite of a rather exoenergetic process, since the energy difference between the intermediate and the products is 71.9 kcal mol^{-1}. The magnitude of this energy barrier is compatible with the experimental results obtained for the deoxygenation of nitrones by tributylphosphine, as heating to 65 °C is required. Nevertheless, the whole process is strongly energetically favored due to an energy difference of 59.1 kcal mol^{-1} between the reactants and the products.

In conclusion, the mechanism of the intermolecular tributylphosphine-promoted deoxygenation of nitrones has been investigated and it appears that this process involves the formation of an azaoxaphosphetane intermediate that results from nucleophilic addition of phosphorus to the iminyl carbon of the nitrones. This observation is divergent from the proposal by Kurtzweil and Beak, who found that related intramolecular arylphosphine-mediated reactions proceed via attack of oxygen at phosphorous. Regardless of the detailed mechanism of the reaction, it was synthetically useful for preparing functionalized, carbohydrate-derived pyrrolines, which are potential precursors of glycosidase inhibitors.

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17. (2*R*,3*R*,4*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2*H*-pyrrole (**4**): MS (ESI) *m*/*z* (%): 402 $[M+H]^+$. IR: ν (cm^{-1}) 3059, 3024, 2916, 2898, 2872, 1497. ^1H NMR (300 MHz, $CDCl_3$): δ 3.77 (dd, 2H, J = 4.5, 1.5 Hz, $^5CH_2$); 4.18 (dd, 1H, J = 6.5, 4.5 Hz, ^3CH); 4.33–4.38 (m, 1H, ^4CH); 4.50–4.68 (m, 7H, ^2CH and $^{Bn}CH_2$); 7.25–7.36 (m, 15H, ^{Ar}CH); 7.67 (d, 1H, J = 2 Hz, ^1CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.9 ($^5CH_2$); 72.5 ($^{Bn}CH_2$); 72.6 (^4CH); 72.7 ($^{Bn}CH_2$); 73.4 ($^{Bn}CH_2$); 83.0 (^3CH); 88.5 (^2CH); 126.9–128.6 (^{Ar}CH); 137.6 ($^{Ar}C_q$); 137.9 ($^{Ar}C_q$); 138.4 ($^{Ar}C_q$); 167.1 (^1CH).
18. *Typical procedure for tributylphosphine-mediated nitrone deoxygenation*: To a stirred solution of nitrone (0.12 mmol) in THF (2 mL) under argon, 60 μL tributylphosphine (0.24 mmol, 2 equiv) was added in one portion. The reaction mixture was heated to 65 °C and stirred at this temperature for 24–72 h, after which the solvent was evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel to afford the expected imine.
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