



Singlet Oxygenation of 1-Aminomethyl-1-*tert*-butyl-2-methoxy-2-(3-methoxyphenyl)ethylenes: Marked Effect of Allylic Nitrogen on the Reaction Pathways and Chemoselectivity

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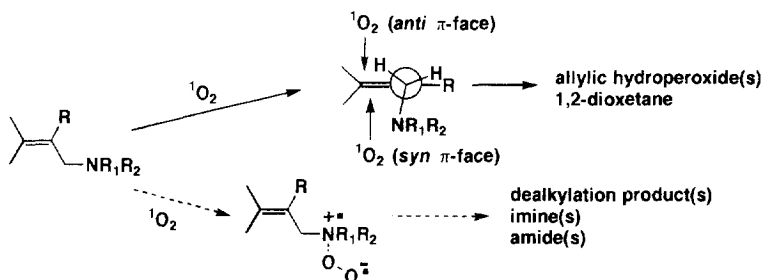
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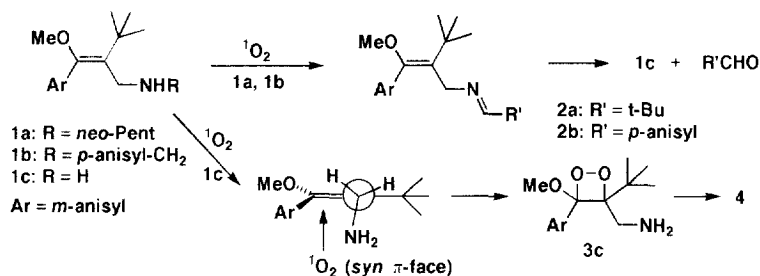
Abstract: The character of an allylic nitrogen affects significantly the reaction pathways as well as the chemoselectivity in the singlet oxygenation of allylic amines (1, 5, 7 and 11). Secondary amines (1a, b) undergo α -oxidation to give imines (2). A primary amine (1c) and amides (7a-c) undergo preferentially the 1,2-addition of singlet oxygen, whereas the singlet oxygenation of an imide (5) afforded selectively an 'ene' reaction product. For a lactum (11), the 1,2-addition and the 'ene' reaction of singlet oxygen occur concurrently. Copyright © 1996 Elsevier Science Ltd

Certain alkylamines are known to undergo α -oxidation with singlet oxygen to give amides and/or dealkylation products^{1,2,3} though alkylamines quench in general singlet oxygen effectively.⁴ However, it has very recently been reported that singlet oxygen attacks preferentially an olefinic moiety to give the 'ene' reaction product with high regio- and diastereoselectivity for allylic amines such as 4-methyl-3-penten-2-amine and its *N*-acylated derivatives.^{5,6,7} The selectivity for the parent allylic amine is attributed to the steering effect of the amino group which guides the incoming singlet oxygen to the *syn* π -face, whereas *N*-acylated analogues exhibit the *anti* π -facial selectivity owing to steric and electrostatic repulsions between the amido group and singlet oxygen. These π -facial selectivities should be reflected as well in the reaction pathways of singlet oxygen with allylic amines. In the course of our investigation of highly efficient chemiluminescent substrates, we found that the character of an allylic nitrogen affects significantly the reaction pathways as well as the chemoselectivity for the singlet oxygenation of 1-aminomethyl-1-*tert*-butyl-2-methoxy-2-(3-methoxyphenyl)ethylenes (1c) and its derivatives.

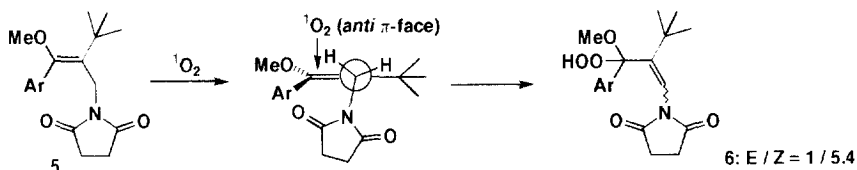
When a *N*-neopentylamino derivative (1a) (100 mg) and tetraphenylporphyrin (TPP) (1 mg) as a sensitizer in CDCl₃ (2 ml) was externally irradiated with a 180W sodium vapor lamp under an oxygen atmosphere at 0 °C for 3 min, an imine (2a) formed selectively (90 %) without any products derived from the oxygenation of the



olefinic function. The structure of **2a** was confirmed by comparing its NMR and Mass spectra⁸ with those of an authentic sample synthesized from an amine (**1c**) and dimethylacetaldehyde. The oxidation of **1a** was not observed under similar reaction conditions, when the treatment of **1a** was made in the dark or without TPP. A *p*-methoxybenzyl analogue (**1b**) was also subjected to the α -oxidation, though the final products were *p*-anisaldehyde (65 %) and **1c**. On the other hand, the singlet oxygenation of a primary amine (**1c**) (0 °C, 30 min) gave predominantly methyl *m*-methoxybenzoate (**4**) (85 %), which was produced most likely by the decomposition of an initially formed dioxetane (**3c**). The results showed that i) the chemoselectivity of singlet oxygen toward the primary amine (**1c**) is different from the case of the secondary amines (**1a** and **1b**), and ii) 1,2-addition of singlet oxygen to the olefinic moiety is a preferential mode for **1c**, though **1c** has allylic hydrogens susceptible to the 'ene' reaction. The latter (ii) suggests that the amino group guides the incoming singlet oxygen to the *syn* π -face where no allylic hydrogens are oriented to suffer the prototropic 'ene' reaction.⁹ The difference in the chemoselectivity of singlet oxygen between **1a** and **1c** is likely due to the difference in nucleophilicity of the respective amino groups. For **1a**, the coordination of the amino group with electrophilic singlet oxygen is presumably so strong that a charge transfer occurs³ between them to deprive the dioxygen of electrophilicity needed to react with the olefinic moiety.

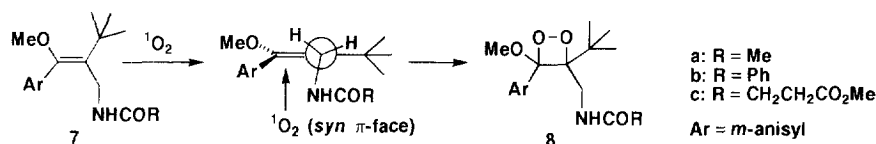


For *N*-acylated analogues of **1c**, singlet oxygen was expected to attack from the *anti* π -face, where allylic hydrogen(s) is oriented, to afford much or less an 'ene' reaction product. First, we attempted the singlet oxygenation of an imide (**5**), which should exhibit the *anti* π -facial selectivity more strongly than amides (**7**). The irradiation of **5** (0 °C, 30 min) gave selectively an allylic hydroperoxide (**6**) (*E* : *Z* = 1 : 5.4, yield: 95%).¹⁰ The result showed that singlet oxygen is preferentially guided to the *anti* π -face as expected, and furthermore, with the side selectivity due to the *anti cis* effect of a bulky *tert*-butyl group;¹¹ the now classical *cis* effect¹² by a vinylic methoxyl group must lead to a 1,2-dioxetane formation since allylic hydrogens suffering the 'ene' reaction exist at the opposite site to the methoxyl group.

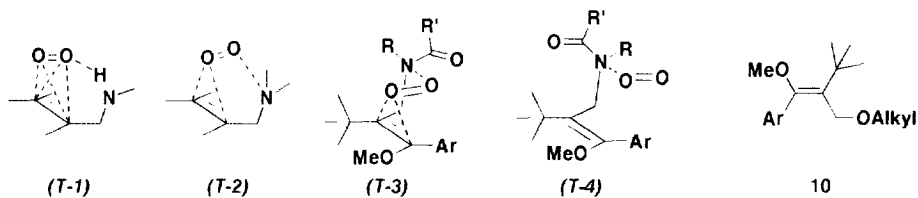


Contrary to the case of the imide (**5**), the singlet oxygenation of amides (**7a** - **c**) gave results totally different from what had been anticipated. The reaction of an acetamide (**7a**) (¹O₂/ CDCl₃/ 0 °C/ 30 min) afforded selectively a 1,2-dioxetane (**8a**) (yield: 92 %),¹³ which decomposed quantitatively into the ester (**4**) and *N*-

acetamidomethyl *tert*-butyl ketone (**9a**) by heating in toluene-*d*₈ (half-life: $t_{1/2} = 62$ days at 25 °C). Similarly, the 1,2-addition of singlet oxygen occurred preferentially for amides (**7b**) and (**7c**) to give the corresponding 1,2-dioxetanes (**8b**) (yield: 90 %, half-life: $t_{1/2} = 42$ days at 25 °C) and (**8c**) (yield: 95%, half-life: $t_{1/2} = 80$ days at 25 °C). In the present reactions, a small amount of **4** and the corresponding amidomethyl ketones (**9**) derived from **8** were always observed. The results revealed that amides (**7a - c**) undergo the 1,2-addition of singlet oxygen with high selectivity, and *an amide function still possesses the potential to steer the incoming singlet oxygen to the syn π -face*.

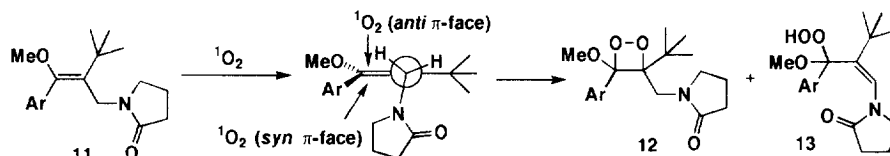


Two mechanisms has been proposed to interpret the steering effect to the *syn* π -face by allylic amines: (**mechanism a**) the steering effect is mainly due to the stabilization of an exciplex between singlet oxygen and an olefin through hydrogen bonding with N-H (or OH) at a transition state (*T-1*),^{6,7} and (**mechanism b**) the coordination of electrophilic singlet oxygen with a nucleophilic amino group (or hydroxyl) steers the incoming singlet oxygen to the *syn* π -face (*T-2*).⁵ The former is a mechanism proposed after revision of the latter and is very persuasive because even an allylic ammonium salt exhibits high *syn* (*threo*) π -facial selectivity. On the other hand, the following facts are likely accounted for by **mechanism b**; the *syn* π -facial selectivity is highly controlled by an allylic oxygen bearing no hydrogen to form hydrogen bonding for the singlet oxygenation of allylic ethers (**10**).¹⁴ In either case, a carbonyl moiety of amides, especially imides, causes electrostatic repulsion with the incoming singlet oxygen to prevent the *syn* π -facial selectivity. However, the results for the amides (**7**), which showed the *syn* π -facial selectivity, suggests that the amide functionality can attract the incoming singlet oxygen with avoiding a repulsive interaction between the carbonyl. Such attraction is probably attained when the dioxygen approaches the opposite site from the carbonyl as (*T-3*) illustrated in the scheme. A steric interaction between a *tert*-butyl and an amide function favors presumably an amide lying in a conformation as (*T-3*) but not as (*T-4*), where the coordinated dioxygen is too remote to react with an olefinic π -system.



Finally, the singlet oxygenation of a lactum (**11**) was carried out and it was found to afford a 1 : 1 mixture of a dioxetane (**12**) (half-life: $t_{1/2} = 140$ days at 25 °C) and a hydroperoxide (**13**, only *Z*-form) at 0 °C.¹⁵ The reaction temperature affected moderately the reaction pathways of singlet oxygen with **11** (**12** : **13** = 2.3 : 1 at -78 °C). The results showed that the lactum function of **11** possesses little ability to guide the incoming singlet oxygen to one side of π -faces, especially at 0 °C, and is apparently accounted for by **mechanism a**; the lactum (**11**) bears no N-H for hydrogen bonding, while the steric and electrostatic repulsion is stronger for **11**

than for 7. The following facts can not, however, be fully accounted for only by mechanism a. Control experiments showed that the lactum (**11**) is the least reactive to singlet oxygen among four types of allylic amines (**1a**, **5**, **7c**, and **11**); relative rate of the singlet oxygenation at 0 °C; **1a** : **5** : **7c** : **11** = >15 : 3 : 3 : 1. Considering that the nitrogen of **11** is perhaps equally or more nucleophilic than 7, these results suggested that the nitrogen of **11** steers the incoming singlet oxygen to the *syn* π -face similarly to the case of 7, but quenches it in part physically. For **11**, an amide functionality exists probably both in conformations (*T-3*) and (*T-4*), because a repulsive interaction of a *tert*-butyl with an α -methylene (-CH₂-N-) of a pyrrolidone ring is undoubtedly far stronger than that of H-N of 7.¹⁶ The coordination of singlet oxygen as in (*T-4*) results probably in quenching of singlet oxygen.



References and Notes

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8. Prolonged irradiation of **1a** gave a complex mixture. **2a**: ¹H-NMR (300 MHz in CDCl₃) δ 1.03 (s, 9H), 1.25 (s, 9H), 3.24 (s, 3H), 3.80 (s, 3H), 3.87 (brs, 2H), 6.80-6.88 (m, 2H), 7.22 (dd, J = 9.2 and 7.1 Hz, 1H), and 7.36 (m, 1H) ppm; Mass (m/z, %) 317 (M⁺, 4), 233 (100), 201 (20), 177 (70).
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10. Stereoisomers (*E-6*) and (*Z-6*) were isolated by chromatography (SiO₂) and their stereochemistry was determined by NOE experiment. *E-6*: ¹H-NMR (300 MHz in CDCl₃) δ 1.01 (s, 9H), 2.80 (brs, 4H), 3.25 (s, 3H), 3.85 (s, 3H), 6.48 (s, 1H), 6.89 (m, 1H), 7.19-7.24 (m, 2H), 7.29 (t, J = 8.0 Hz, 1H), and 7.87 (s, 1H) ppm; *Z-6*: ¹H-NMR (300 MHz in CDCl₃) δ 1.47 (s, 9H), 2.13-2.41 (m, 2H), 2.59-2.87 (m, 2H), 3.02 (s, 3H), 3.80 (s, 3H), 5.86 (s, 1H), 6.78-6.97 (m, 3H), 7.21 (t, J = 8.0 Hz, 1H), and 9.87 (s, 1H) ppm.
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13. **8a**: ¹H-NMR (300 MHz in CDCl₃) δ 1.26 (s, 9H), 1.74 (s, 3H), 3.00 (s, 3H), 3.49 (brs, 1H), 3.84 (s, 3H), 5.64 (brs, 1H), 6.64-7.22 (m, 3H), and 7.37 (t, J = 8.0 Hz, 1H) ppm; IR (liquid film) 1660, 1290, and 1110 cm⁻¹; Mass (m/z, %) 323 (M⁺, 1), 291 (6), 234 (4), 166 (91), and 135 (100).
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15. **12**: ¹H-NMR (300 MHz in CDCl₃) δ 1.29 (s, 9H), 1.78-2.13 (m, 4H), 2.96 (s, 3H), 3.37-3.62 (m, 4H), 3.85 (s, 3H), 6.62-7.20 (m, 3H), 7.34 (t, J = 8.0 Hz, 1H) ppm; Mass (m/z, %) 349 (M⁺, 0.5), 317 (1), 183 (20), 166 (56), 135 (70), and 98 (100). **13**: ¹H-NMR (300 MHz in CDCl₃) δ 1.44 (s, 9H), 1.50-1.84 (m, 3H), 2.22-2.50 (m, 2H), 2.81 (m, 1H), 3.03 (s, 3H), 3.80 (s, 3H), 5.66 (s, 1H), 6.79-7.15 (m, 3H), 7.22 (t, J = 8.0 Hz, 1H), 11.48 (s, 1H) ppm; Mass (m/z, %) 349 (M⁺, 0.5), 332 (3), 317 (10), 279 (12), 231 (23), 201 (52), 166 (85), and 135 (100).
16. Considering an interaction as in (*T-3*), the temperature effect observed for **11** is likely accounted for by a rotational isomerism of a trigonal flange of an amide function around an axis of N-C (allylic carbon). For a *N*-alkyl analogue of **7** bearing *N*-neopentyl, NMR analysis showed that it exists as a mixture of two rotamers even at room temperature, though they could not be unfortunately separated at present.

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