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ORIGINAL ARTICLE

The role of thiophenol in the proposed mechanism for one pot transformation of 2-phenylthio-3-aminocyclohexanols to dehydropiperidine derivatives

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KEYWORDS

Photo-induced electron transfer reaction;
2-Phenylthioalcohol;
Deoxyazasugars;
Thiophenol;
Scavenger;
Ab initio calculation

Abstract This paper describes the effect of thiophenol concentration on photochemical rearrangement of 2-phenylthio-3-aminocyclohexanols to the corresponding protected aminoaldehydes. The obtained aminoaldehyde is in equilibrium with its corresponding deoxyazasugar. The latter could be converted to the corresponding dehydropiperidine with a good yield in the same reaction media by controlling the thiophenol concentration. Also a proposed mechanism for this one pot transformation is reported.

1. Introduction

Studies on photo-induced electron transfer (PET) processes have been extensively pursued in many laboratories in the world with various basic motivations and applied as well. On the other hand, aminoaldehydes and carbinolamines are very important building blocks in organic synthesis. These classes of compounds have multiple functionalities for further manipulation toward the synthesis of natural products like piperidine derivatives and for designing pharmaceutically valuable compounds (Chen et al., 2007; Jang and Krische, 2006; Dhavale and Matin 2005; Martinek et al., 2007; Tylichová et al., 2010).

In 1973, Davidson (Davidson and Brimage 1973; Davidson and Orton, 1974) and Whitten (Ci and Whitten 1987; Kellet and Whitten 1989) reported the photochemical cleavage of 2-aminoalcohols that is a photo induced electron transfer (PET) reaction. The reaction started by an electron transfer from 2-aminoalcohol to a sensitizer and followed by removal of the acid proton of the hydroxyl group and finally the C-C bond cleavage (Scheme 1).

Later, Davidson reported decarboxylation of 2-phenylthiocarboxylic acids by the same electron transfer reaction (Davidson and Steiner 1972). Based on these results, Farmer (Gravel et al., 1990) reported a similar cleavage for 2-phenylthioalcohols. His subsequent works showed that this type of cleavage

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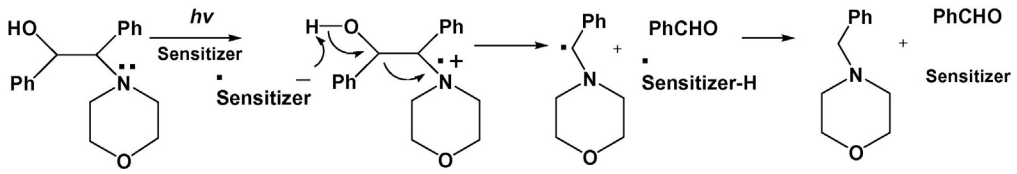
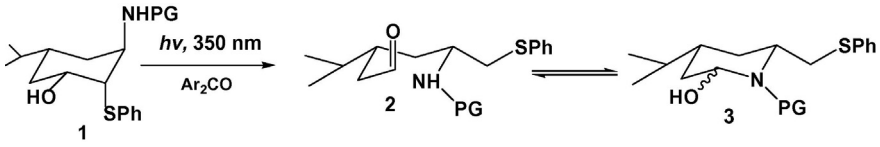
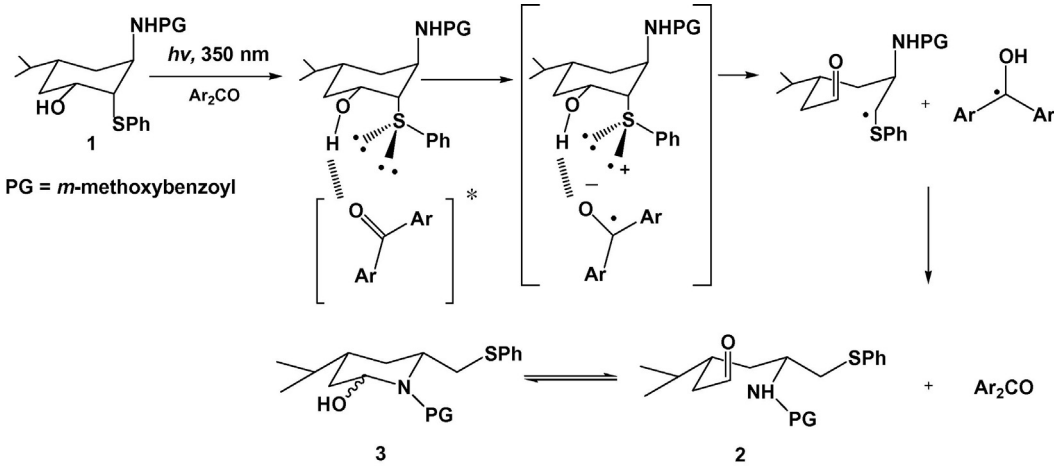


Scheme 1 Photochemical cleavage of 2-aminoalcohols in the presence of a sensitizer.



Scheme 2 Photo cleavage reaction of 2-phenylthio-3-aminocyclohexanols and their access to deoxyazasugars.



Scheme 3 Proposed mechanism for photochemical rearrangement of 2-phenylthio-3-aminocyclohexanol **1** to amidoaldehyde **2** and its corresponding deoxyazasugar **3.**

depends on the stereochemistry of the phenylthio and hydroxyl groups (Gravel et al., 1994).

He also showed that, it is non favorable and inefficient for a *trans*-diaxial relationship between the phenylthio and hydroxyl groups (Gravel et al., 1994).

Based on these results Gravel *et al*. hypothesized that replacing the axial hydroxyl group by an appropriately protected amine function would yield deoxyazasugars (Gravel et al., 1998) (Scheme 2).

However, the total yield of this transformation was not good (55%) and this was one of the most problems of this type of photolysis (Gravel et al., 1998).

Such 2-phenylthio-3-aminocyclohexanols 1 (where PG = Boc or *m*-methoxybenzoyl) have already been used by us in sulfoxidation reactions (Amoozadeh and Nemati 2009a; Amoozadeh and Nemati 2009b).

2. Results and discussion

As suggested by Davidson (Davidson and Steiner 1972) and verified by Farmer (Gravel et al., 1990; Gravel et al., 1994) carrying out the photolysis in the presence of 1 eq. of thiophenol (as a source of H) increases the yield of such photo cleavage reactions. For example in our case, as far as the photolysis was progressed the side reactions were increased dramatically monitoring by TLC. Indeed, the photolysis yielded complex mixtures of products despite variations in the thiophenol concentrations used. Based on similar reactions (Gravel et al., 1990; Gravel et al., 1994; Gravel et al. 1998; Gravel and Bordeleau 1998), we would like to have a closer look to our proposed mechanism, in analogy to observation of deoxysugars starting from phenylthiodiols (Scheme 3).

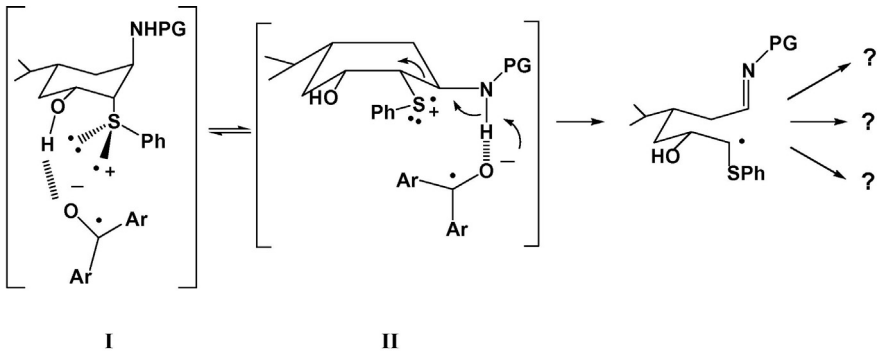
The planned study involved a photo induced electron transfer between a sensitizer (xanthon), playing the role of an excited acceptor and the protected phenylthioaminoalcohol 1, playing the role of a donor. Indeed, the resulting phenylthio radical is in the cage of solvent and if it escapes from this cage, it can be the source of undesirable radical chain reactions which decrease the total yield. One equivalent of free thiophenol could scavenge this free radical to stop undesired side reactions and enhance the total yield. Contrary to our expectations, adding 1 eq. of thiophenol decreases our yield. As shown in Table 1, the best concentration of thiophenol is 0.75 eq. Under these conditions the yield was 55% (Table 1, entry 4).

Table 1 The yields of photo cleavage reaction of 2-phenylthio-3-aminocyclohexanol **1** to amidoaldehyde **2** and corresponding deoxyazasugar **3** in different concentrations of thiophenol.

Entry	Concentration of PhSH (eq.)	Photo cleavage reaction yield %
1	0	20
2	0.25	30
3	0.50	40
4	0.75	55
5	1.00	50
6	1.25	45
7	1.50	40

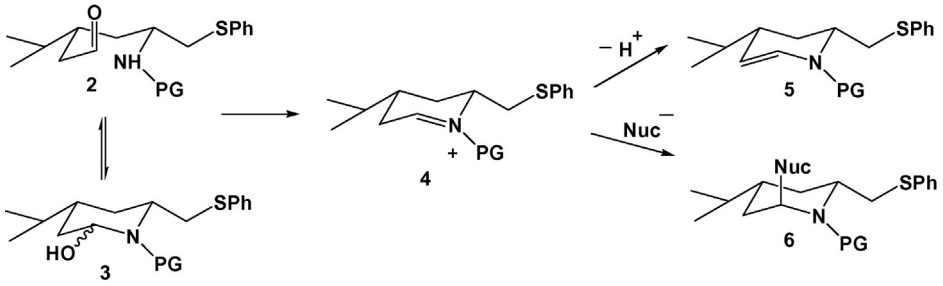
However, as the yields were not satisfactory, we investigated some mechanistic studies. Two hypotheses were considered to explain the lack of selectivity or poor yields of the desired product in the photolysis. The first one considered is the protected amino group and the cleavage of the ring might take place between these two sites because of a more acidic proton on the nitrogen (Scheme 7). This would require of course a chair-boat equilibrium in the radical ion pair along with a shift of the hydrogen bonded radical anion from OH to NH (Scheme 4).

There are no experimental data at the moment to support or disprove this hypothesis other than the fact that this phenomenon occurred at a maximum of 4% in the case of phenylthiodiols (Gravel et al., 1994). Fortunately, theoretical calculations disprove this hypothesis. We used Gaussian 98

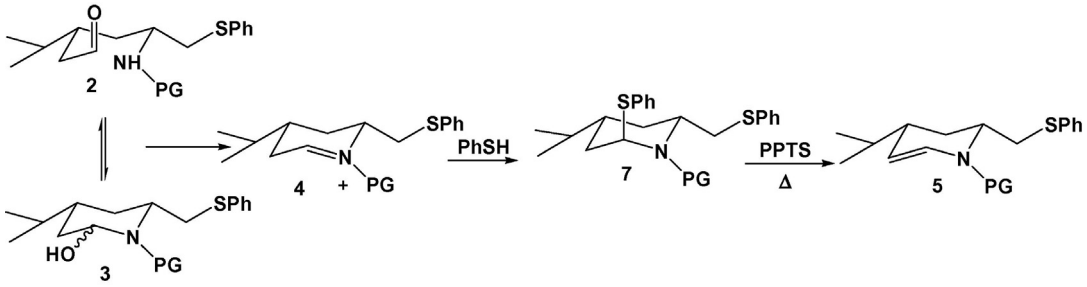


I II

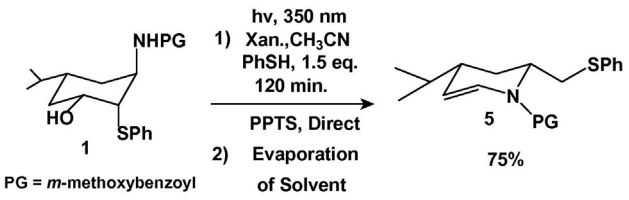
Scheme 4 Expected way for cleavage of the starting carbocycle ring between C-2 and C-3 that requires a chair-boat equilibration in the radical ion pair along with a shift in the hydrogen bonded radical anion from OH to NH.



Scheme 5 Equilibrium between protected aminoaldehyde **2** and carbinolamine **3** and its conversion to dehydropiperidine **5** and piperidine derivative **6**.



Scheme 6 The conversion of amidoaldehyde **2**, carbinolamine **3** equilibrium to dehydropiperidine **5** *via* corresponding iminium ion **4**.



Scheme 7 One pot conversion of 2-phenylthio-3-aminocyclohexanol **1** to dehydropiperidine **5**.

Table 2 The calculated stability energy of chair radical ion pair.

Future	I	II
HF/3-21G//HF/3-21G	-2083.80706351	-2083.79878106
E_{rel}	(0.0)	(+5.24)

Relative energies are with respect to the most stable isomer and total energies are in Hartree and relative energies are in kcal/mol.

program (Frisch et al., 1998) to calculate the stability energy of chair radical ion pair with a hydrogen bonded radical anion on OH and the stability energy of boat radical ion pair with a hydrogen bonded radical anion on NH (Table 2). This means that chair radical ion pair with a hydrogen bonded radical anion on OH is more stable than boat radical ion pair with a hydrogen bonded radical anion on NH (Fig. 1).

The second hypothesis was that side reactions occurred after a successful photochemical transformation i.e. either the desired deoxyazasugar **3** and/or its ring-chain tautomer, the amidoaldehyde **2**, were at the origin of the side reactions. Deoxyazasugar **3** could be converted to the corresponding iminium ion **4** which is the origin of the corresponding dehydropiperidine derivative **5**. It could be easily attacked by each nucleophile to produce the piperidine derivative **6** (Scheme 5).

Based on the results of Table 1, it seems that this proposed mechanism is right. As we indicated earlier, adding thiophenol at the first glance, increases the yield of photo cleavage amidoaldehyde **2** and carbinolamine **3** equilibrium reactions because of its scavenger property. The maximum yield is obtained at 0.75 eq. of thiophenol (Table 1, entries 2-4). So the addition of thiophenol up to 0.75 eq. increases the yield. However, further increase in the thiophenol concentration results in decrease in the yield of the reaction (Table 1, entries 5-7). This means that the excess amount of thiophenol as a good nucleophile could attack the iminium ion **4** to produce the disulfide derivative **7**. We stopped and worked up the photo cleavage reaction after 45 minutes and separated and the characterized compound **7.** It is important to note that the disulfide derivative **7**, is very sensitive to the temperature and we used this fact later to improve the total yield of one pot transformation of 2-phenylthio-3-aminocyclohexanol **1** to dehydropiperidine **5**. The disulfide derivative **7** has been easily converted to dehydropiperidine **5** by heating in toluene (Scheme 6).

With these results in hand, we proposed that if we do these transformations (photo cleavage of the starting carbocycle **1** in the presence of excess amounts of thiophenol, and transformation of results to dehydropiperidine **5**) in one pot reaction we could increase the yield significantly (Scheme 7).

Table 3 shows obtained total yield of this one pot reaction. According to our expectation it is clear that there is a direct relation between the yield of the obtained dehydropiperidine **5** and the concentration of thiophenol.

In summary the results reported in this paper clearly indicate that based on our experimental data and theoretical calculations, our proposed mechanism for this conversion is correct. With considering this mechanism we prepared dehydropiperidine **5** from 2-phenylthio-3-aminocyclohexanol **1** in one-pot reaction with a total yield of 75%. Furthermore for the first time spectroscopic data of disulfide **7** are reported.

3. Experimental

The IR spectrum was taken on a Perkin-Elmer, model 783 spectrophotometer.

The NMR spectrum has been recorded by a Bruker AMX-300 (300 MHz) spectrometer. The solvent was $CDCl_3$. The chemical shifts are expressed in ppm, and TMS was used as internal reference. The mass spectrum (MS) was taken by an AEI MS-902 model.

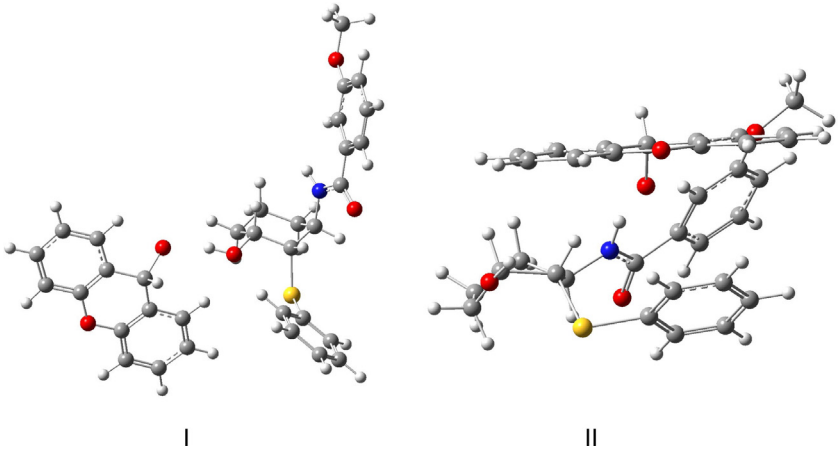


Figure 1 The most stable calculated conformations of radical ion pairs; chair form (I) which provides desired product and boat form (II) which provides side products.

Table 3 The yields of photo cleavage reaction of 2-phenylthio-3-aminocyclohexanol **1** followed by heating in presence of PPTS to produce dehydropiperidine **5** in different concentrations of thiophenol.

Entry	Concentration of PhSH (eq.)	The yield % of dehydropiperidine **5**
1	0	20
2	0.25	30
3	0.50	50
4	0.75	60
5	1.00	70
6	1.25	75
7	1.50	75

3.1. General Procedure for photochemical reactions

Photochemical reactions were carried out in spectrograde acetonitrile in the presence of one equivalent of xanthone as a sensitizer and 0-1.5 equivalent of thiophenol, using a Rayonet Photochemical Reactor. The concentrations of substrates were 10^{-3} M and the reaction mixture was degassed under nitrogen flow and ultrasonic bath for 30 minutes.

3.2. Procedure for one pot preparation of N-protected 4-isopropyl-6- phenylthiomethyl-2, 3-dehydropiperidine 5

An acetonitrile solution of the *m*-methoxybenzoylamidocyclohexanol **1** (87.0 mg, 0.22 mmol), xanthone (35.0 mg, 0.22 mmol) and thiophenol (29 μL, 0.27 mmol) in a pyrex tube was degassed under nitrogen flow and sonication for 30 minutes. It was then irradiated at 350 nm for 90 minutes in a Rayonet Photochemical Reactor. The photolysis mixture was then treated with pyridinium-*p*-toluenesulfonate (PPTS) (55.0 mg, 0.22 mmol), and the solution was stirred for 2 hours at room temperature. The solvent was removed by direct heating (very important) and flash chromatography of the residue gave N-protected-4-isopropyl-6-phenylthiomethyl-2, 3-dehydropiperidine **5**, as a pure (^{1}H NMR 300 MHz), colorless oil with a total yield of 75%.

3.3. Preparation of N-protected 4-isopropyl-2-phenylthio-6-phenyl thiomethyl-piperidine 7

a) Above procedure was followed and the photolysis was stopped after 60 minutes. The solvent was removed under vacuum (very important) and flash chromatography of the residue gave N-protected 4-isopropyl-2-phenylthio-6-phenyl thiomethyl-piperidine **7**, as a pure (^{1}H NMR 300 MHz), colorless oil with a total yield of 35%.
b) An acetonitrile solution of 5-isopropyl-2-phenylthio-3-*m*-methoxybenzoylamido cyclohexanol **1** (87.0 mg, 0.22 mmol), xanthone (35.0 mg, 0.22 mmol) and thiophenol (35 μL, 0.33 mmol) in a pyrex tube was degassed under nitrogen flow and sonication for 30 minutes. It was then irradiated at 350 nm for 60 minutes in a Rayonet Photochemical Reactor. The photolysis mixture was then treated with pyridinium-*p*-toluenesulfonate (PPTS) (54.0 mg, 0.22 mmol) and the solution was stirred for 2 h at room temperature. The solvent was removed under vacuum and flash chromatography of the residue gave N-protected-4-isopropyl-2-phenylthio-6-phenylthiomethylpiperidine, as a pure (^{1}H NMR 300 MHz), colorless oil with a total yield of 75%.

R_f:0.33 Et_2O/Hex. 30/70

IR (neat): 2957, 2870, 1629, 1578, 1459, 1430, 1368, 1341, 1287, 1265, 1045, 879, 782, 794 and 692 cm $^{-1}$.

^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.45 (dd, $J_1 = 9$ Hz, $J_2 = 2$ Hz, 2H), 7.20 (m, 10H), 6.90 (m, 1H), 6.72 (d, $J = 2$ Hz, 1H), 6.50 (d, $J = 8$ Hz, 1H), 5.41 (d, $J = 3$ Hz, 1H), 4.35 (m, 1H), 3.81 (m, 1H), 3.74 (s, 3H), 3.60 (dd, $J_1 = 13$ Hz, $J_2 = 3$ Hz, 1H), 2.15 (d, $J = 9$ Hz, 1H), 1.95 (d, $J = 9$ Hz, 1H), 1.80 (m, 1H), 1.60 (m, 3H), and 0.80 (dd, $J_1 = 15$ Hz, $J_2 = 6$ Hz, 6H)

^{13}C NMR (300 MHz, $CDCl_3$): d 173.6, 169.0, 137.4, 135.3, 129.7, 129.2, 129.0, 128.9, 128.6, 126.0, 119.4, 116.3, 112.5, 69.5, 55.2, 53.2, 38.2, 37.5, 35.3, 32.5, 32.4, 19.7, 19.6

MS(m/e): 492 (MH^+)

HRMS: Calcd: 492.20309. Found: 492.20580

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