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An efficient synthesis of quinazolines: a theoretical and experimental study on the photochemistry of oxime derivatives

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ABSTRACT

A new photochemical method for the preparation of quinazolines (**2**) through irradiation of [2-(methyleneamino)phenyl]methanone oximes (**1**) is reported. The photoreaction has been studied in depth by experimental, theoretical and photochemical methods. A six-electron electrocyclic ring closure mechanism, followed by water loss, is proposed and rationalized to explain the formation of quinazolines (**2**).

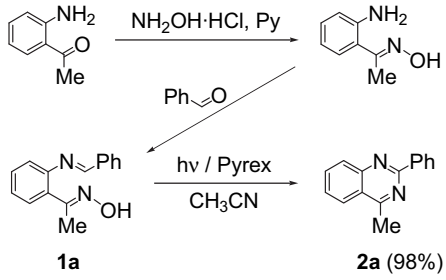
1. Introduction

The quinazoline ring system along with many alkaloids is a widely recognized moiety in organic syntheses and medicinal application,[1] e.g., it was found in HIV reverse transcriptase inhibitors.[2] The synthesis of six-membered nitrogen heterocycles by electrocyclic reaction of azatriene systems has been widely studied.[3] The presence of an oxime or an oxime methyl ether group in the triene structure is a special case because the product resulting from electrocyclization can eliminate water or methanol, respectively, for further aromatization.[4] A few examples of this kind of reaction were also carried out by photochemical methods.[5] in the context of our studies on the photochemistry of oxime derivatives[6] we focused our interest on the photochemical behavior of substituted [2-(methyleneamino)phenyl]methanone oximes as potential precursors of quinazolines. Herein, we reported an experimental and theoretical investigation into the photocyclization of such oximes.

2. Results and discussion

2.1. Irradiation of substituted [2-(methyleneamino)phenyl]-methanone oximes

We initially prepared oxime **1a** from commercial 2′-aminoacetophenone in two steps (Scheme 1). It was observed that irradiation of a solution of **1a** with a 400 W mercury lamp through Pyrex for 3 h under an Ar atmosphere[6] led to the formation of quinazoline **2a** in 98% yield after the usual work-up procedure (Scheme 1).



Scheme 1. Synthesis of quinazoline **2a**.

This excellent result prompted us to explore the photoreactivity of [2-(methyleneamino)phenyl]methanone oximes. Thus, several oximes **1** substituted by alkyl, phenyl, pyridyl or thienyl groups were synthesized and then irradiated. It was verified that our method is useful for the preparation of the corresponding quinazolines **2** from oximes **1** in moderate to almost quantitative yields (Table 1). In an attempt to confirm the photochemical nature of this transformation, a solution of oxime **1a** in dry acetonitrile was heated under reflux for 24 h under an Ar atmosphere in the dark, but reaction did not take place and starting material was quantitatively recovered.

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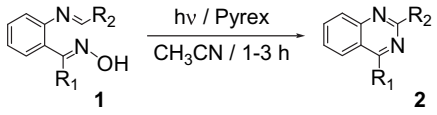
Table 1
Synthesis of quinazolines by Irradiation of Substituted [2-(methyleneamino)phenyl] methanone Oximes



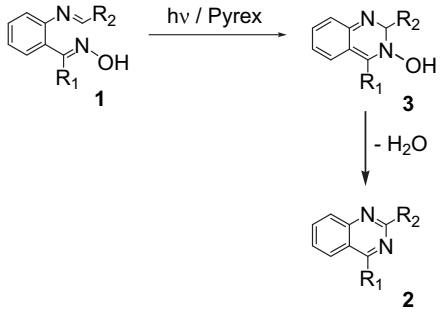
Oxime	Quinazoline	R_1	R_2	Yield[a] (%)
1a	**2a**	Me	Ph	98
1b	**2b**	Me	C_5H_{11}	78
1c	**2c**	Me	H	30
1d	**2d**	Ph	Ph	53
1e	**2e**	Me	3-Pyridyl	96
1f	**2f**	Me	2-Thienyl	73

[a] Yield of isolated product.

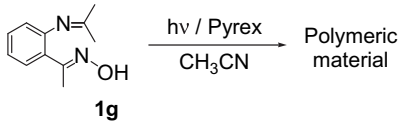
2.2. Search for intermediates

In order to gain further insights into the reaction mechanism, we decided to carry out several essays. First, the irradiation of **1a**, through Pyrex glass, in the presence of 5 equiv of tolane, which is able to react with iminyl radicals,[6a] did not affect the reaction course, since no other product apart from **2a** and tolane was observed in the reaction crude, and suggest that a mechanism involving radicals should be unlikely. Next, the incomplete irradiation of **1a** in acetonitrile (dielectric constant ϵ=37.5) or THF (dielectric constant ϵ=7.6) for 2 h gave a **2a**/**1a** rate of 1.0:0.20 or 1.0:0.23, respectively, which suggest little solvent effect.

On the other hand, the reaction could proceed with initial formation of cyclic compound **3** followed by loss of water to give **2** (Scheme 2). Thus, we tried to detect intermediates **3a**–**f**, but it was not successful, probably due to fast aromatization. We also prepared oxime **1g**, which bears two groups on the iminic carbon and therefore cannot evolve to the corresponding quinazoline (Scheme 3). Unfortunately, reaction led to polymeric material and **3g** could not be detected but its generation could not be discarded since hydroxylamines evolve with formation of radicals by photochemical cleavage of the N–O bond, which should induce polymerisation.[7]



Scheme 2. Mechanistic proposal to obtain quinazolines **2**.



Scheme 3. Irradiation of **1g**.

2.3. Photochemical aspects

The rationalization of the photoreaction mechanism requires the knowledge of the nature of the excited state involved in the reaction. Thus, a solution of **1c** (the simplest oxime) in oxygen-saturated acetonitrile was irradiated, but quenching of the reaction was not detected. This lack of quenching was also observed when solutions of **1c** in degassed acetonitrile were irradiated in the presence of different amounts of 2,5-dimethylhexa-2,4-diene (0.5, 1.0, 2.0, 3.0 and 20.0 equiv), which is a known triplet quencher. These two experiments indicate that only excited singlet states undergo the photochemical reaction. We have also determined the quantum yield for the **1c**→**2c** transformation. A value of Φ_R=0.19±0.01 was obtained for a 2.73×10^{-4} M solution of **1c** in deoxygenated acetonitrile at 313 nm, using *trans*-azobenzene as an actinometer.[8]

2.4. Computational methods

Considering the structure of **1c**, 2′-(Methyleneamino)benzaldehyde oxime (**4**) was used as a model for the calculations. All critical points were computed using fully unconstrained ab initio quantum chemical computations in the framework of a CASPT2//CASSCF[9] strategy. CASPT2 is usually employed in the computational photochemistry of organic molecules with data in good agreement with experiment.[10] This process requires the reaction coordinate to be computed at the complete active space self consistent field (CASSCF) level of theory and the corresponding energy profile to be re-evaluated at the multiconfigurational second order Møller–Plesset perturbation theory level (using the CASPT2 method implemented in MOLCAS 6.4[11]) to take into account the effect of electron dynamic correlation. All computations were made at the CASSCF level with the 6-31G* basis set. The active space included 10 electrons in 10 orbitals (π and π^* orbitals of the phenyl ring, imine, and oxime). The zeroth order wave function used in the single-point CASPT2 calculations needed for the re-evaluation of the energy profile is a three root (S_0, S_1, S_2) state average CASSCF wave function. The same type of wave function was used, where necessary, to avoid convergence problems. The structure of the conical intersection funnels associated with each path was optimized by applying the methodology included in GAUSSIAN 03.[12,13]

2.5. Computational photochemistry

Up to four different conformations were found for model compound **4** using the (10,10) active space within a few kcal/mol (see ESI for details). The global minimum (conformer 1) corresponds to a structure in which the imine and oxime moieties are separated from each other and placed out of the ring plane (53.9° and 28.9°, respectively).

Our calculations on **4** (conformer 1) indicate that after light absorption, S_2 will be mainly populated due to the relative oscillator strengths (n–π^* $S_0\rightarrow S_1$, f=0.002; π–π^* $S_0\rightarrow S_2$, f=0.08). In the Franck–Condon (**FC**) region S_2 and S_1 are quite similar (122.9 and 101.3 kcal/mol) so crossing between the two states seems probable. In fact, after relaxation in S_2 the molecule soon reaches a conical intersection[14] (CI) point after minor geometrical changes (Fig. 1). Apart from aromatic ring expansion, the main change corresponds to C–N bond elongation in the oxime moiety. This bond lengthens from 1.276 Å in FC to 1.412 Å in **CI S_2/S_1** due to π^* orbital population. Both the imine (37.4°) and the oxime (12.4°) moieties are kept outside the ring plane, although both torsion angles are lower than in **FC**.

After decay to S_1 through the CI S_2/S_1 point, further relaxation takes places and a minimum in S_1 (**Min S_1**) is reached. The phenyl ring is further expanded and the whole molecule is almost planar with the imine (0.8°) and the oxime (1.8°) in the ring plane. It is clear that in this structure, the interaction between the imine carbon atom and the oxime nitrogen atom required to form the bond present in the photoproduct will be extremely difficult. Thus, this minimum in the excited state will hardly allow the formation of the

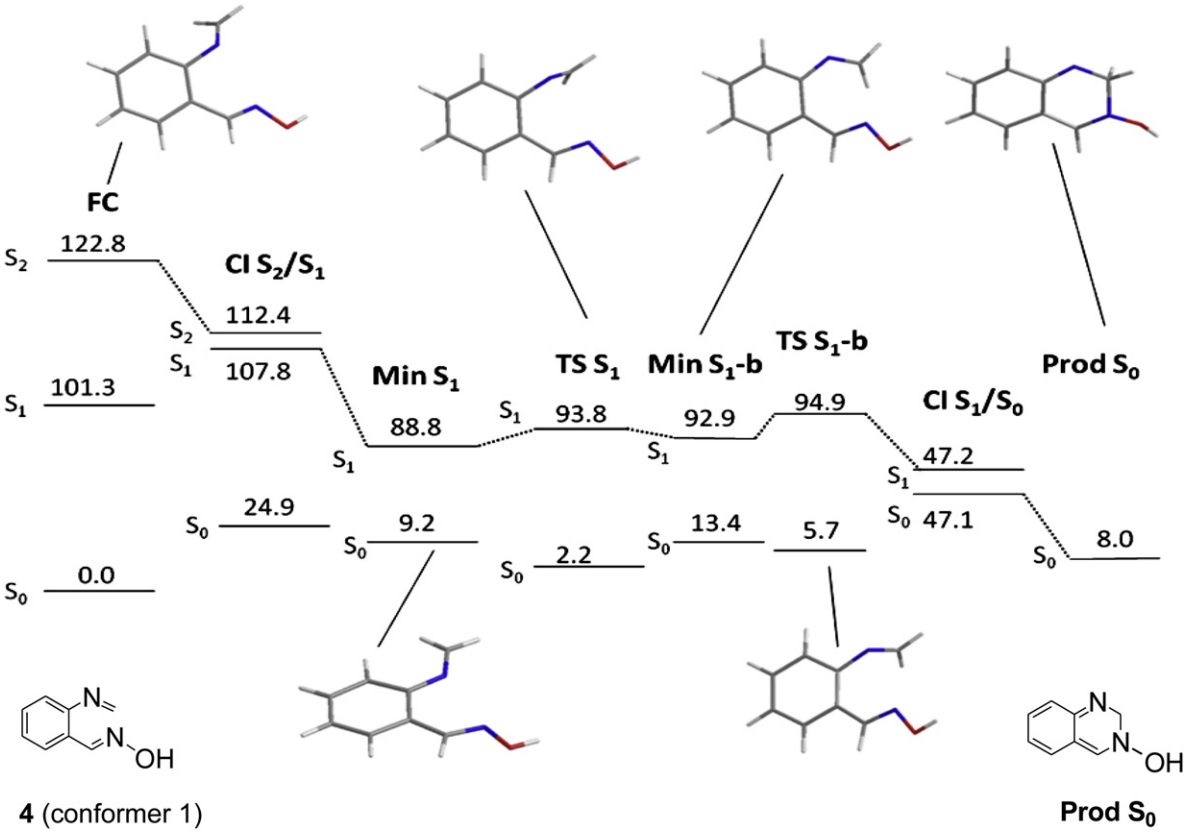


Figure 1. Critical points along the potential energy surface of **4**. Energies in kcal/mol relative to the ground state minimum.

isolated products. However, twisting along the imine-phenyl N–C single bond would yield a different conformation where this interaction could take place much more easily. In fact, we were able to find another minimum in S_1 (**Min S_1-b**) where these two atoms are closer and a transition structure (**TS S_1**) connects these two minima in the S_1 potential energy surface. **TS S_1** and **Min S_1-b** both have quite similar geometrical parameters to **Min S_1**, a situation consistent with conformational change. The main change is in the imine torsion angle, which varies from 0.8° in **Min S_1** to 85.8° in **TS S_1** and 157.9° in **Min S_1-b**. The energetic of the process also corresponds with a conformational change, with both conformers separated by 4.1 kcal/mol and an energy barrier of 5.0 kcal/mol (Fig. 1). Thus, **Min S_1-b** can be easily populated and the formation of the photoproduct could proceed from this point with ease. The distance between the imine C atom and the oxime N atom in **Min S_1-b** is only 2.954 Å. As a result, a slight deformation of the molecule could allow these two atoms to interact. In fact, a CI point connecting the excited and the ground states was found quite close (Fig. 1). **Min S_1-b** and the CI point are connected through a conformational TS (**TS-S_1-b**) located only 2.0 kcal/mol higher in energy than the minimum. This TS corresponds with the approximation between the imine C atom and the oxime N atom, which subsequently leads to conical intersection. **CI S_1/S_0** shows an incipient interaction between these two atoms (1.937 Å), together with a clear lengthening of the imine C=N bond (1.350 Å) and pyramidalization of the imine C atom. The gradient difference and derivative coupling vector of **CI S_1/S_0** are shown in Figure 2.

Clearly, one of the movements shown by these vectors leads to cyclization. In order to confirm this, we slightly deformed the **CI S_1/S_0** geometry in the four directions indicated by the vectors. As expected, three of these deformations led to reactant recovery, while the fourth movement directly led to formation of the bond between the imine C atom and the oxime N atom. Subsequent optimization in the ground state allowed us to obtain the structure of **Prod S_0**. The structure of this compound has alternate single and double bond distances, which is indicative of the absence of aromaticity. However, the aromaticity could be easily recovered, together with a considerable stabilization in energy, through dehydration in the ground state. This last step will finally lead to the product isolated from the reaction. Given that the basic structure of the compounds used to yield quinazolines is the same, little difference in the potential energy surface would be expected. Thus, the basic features shown in Figure 1 will probably be present in all of the compounds studied experimentally.

Therefore, these calculations suggest an initial photochemically induced six-electron electrocyclic ring closure, which is in agreement with the above described experiments in the presence of tolane or in different solvents and our knowledge of the photochemical cyclization of azadienes.[5e–g,i]

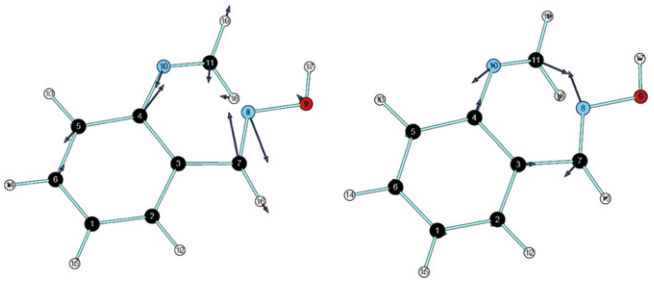


Figure 2. Derivative coupling and gradient difference vectors for the CI point responsible for quinazoline formation.

3. Conclusions

The cyclization process for [2-(methyleneamino)phenyl]methanone oximes has been studied and this is an excellent method for the preparation of quinazolines in almost quantitative yields. After checking the photochemical nature of the reaction, quenching experiments were used to demonstrate that singlet excited states undergo the reaction. We computed (CASPT2/6-31G*//CASSCF/6-31G* level, using an active space of 10 electrons in 10 orbitals) the critical points along the potential energy surface for the singlet states and the vectors for the CI point responsible for quinazoline formation. Our experimental and theoretical results are consistent with a six-electron electrocyclic ring closure mechanism.

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as internal standard. Melting points are uncorrected. All solvents were purified by standard procedures. Reagents were of commercial grades.

4.2. General procedure for the preparation of [2-(Methyleneamino)phenyl]methanone Oximes (1)

Compound **1a**, **1b**, **1c**, **1e**, **1f**, and **1g** were prepared from 2′-aminoacetophenone and **1d** was prepared from 2-aminobenzophenone. A solution of the corresponding ketone (10 mmol), hydroxylamine hydrochloride (26 mmol), and pyridine (26 mmol) in ethanol (20 mL) was heated under reflux for 14 h. The solvent was then removed under vacuum, and the residue extracted with dichloromethane (50 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The oxime was then ready to use.

4.3. Typical procedure for the irradiation of [2-(methyleneamino)phenyl]methanone oximes (1)

The oxime (0.6 mmol) was dissolved in dry acetonitrile (60 mL) and irradiated at room temperature under an Ar atmosphere through Pyrex glass with a 400 W medium pressure-mercury lamp until the oxime was consumed (1–3 h, TLC, hexane/AcOEt, 4:1). The solvent was removed with a rotary evaporator and the products were separated by column chromatography (silica gel, hexane/AcOEt).

4.3.1. 4-Methyl-2-phenylquinazoline[15] (***2a***). Yellow solid. Yield: 130 mg, 98%. Mp: 89–90 °C. ^{1}H NMR: δ 8.60 (d, 2H, J=7.5 Hz), 8.01 (d, 1H, J=9 Hz), 7.91 (d, 1H, J=9 Hz), 7.74 (t, 1H, J=7.5 Hz), 7.40–7.52 (m, 4H), 2.89 (s, 3H) ppm. ^{13}C NMR: δ 168.2, 160.0, 150.2, 138.2, 133.4, 130.4, 129.1, 128.6, 128.5, 126.8, 124.9, 122.9, 21.9 ppm. Exact mass ($C_{15}H_{12}N_2$+H) calculated 221.1073, measured 221.1082.

4.3.2. 4-Methyl-2-pentylquinazoline (***2b***). Yellow oil. Yield: 100 mg, 78%. ^{1}H NMR: δ 8.06 (d, 1H, J=8.1 Hz), 7.96 (d, 1H, J=8.7 Hz), 7.84 (t, 1H, J=8.1 Hz), 7.57 (t, 1H, J=8.1 Hz) 3.05 (t, 2H, J=7.2 Hz), 2.94 (s, 3H), 1.88–1.93 (m, 2H), 1.37–1.45 (m, 4H), 0.91 (t, 3H, J=6.9 Hz) ppm. ^{13}C NMR: δ 168.0, 167.0, 149.9, 133.4, 129.0, 126.4, 124.9, 122.4, 40.1, 30.8, 28.8, 22.5, 21.7, 14.0 ppm. Exact mass ($C_{14}H_{18}N_2$+H) calculated 215.1542, measured 215.1549.

4.3.3. 4-Methylquinazoline[16] (***2c***). Yellow oil. Yield: 26 mg, 30%. ^{1}H NMR: δ 9.19 (s, 1H), 8.13 (d, 1H, J=9 Hz), 8.04 (d, 1H, J=9 Hz), 7.91 (t, 1H, J=9 Hz), 7.66 (t, 1H, J=9 Hz), 2.98 (s, 3H) ppm. ^{13}C NMR: δ 154.6, 149.6, 133.9, 129.9, 129.1, 127.8, 125.2, 124.6, 21.9 ppm. Exact mass ($C_9H_8N_2$+H) calculated 145.0759, measured 145.0765.

4.3.4. 2,4-Diphenylquinazoline[17] (***2d***). Yellow solid. Yield: 90 mg, 53%. Mp: 119–120 °C. ^{1}H NMR: δ 8.71 (d, 2H, J=9.3 Hz), 8.16 (t, 2H, J=8.4 Hz), 7.88–7.93 (m, 3H), 7.56–7.62 (m, 3H), 7.51–7.55 (m, 4H) ppm. ^{13}C NMR: δ 168.1, 160.2, 151.9, 138.2, 138.0, 133.5, 130.5, 130.2, 129.9, 129.2, 128.9, 128.8, 128.7, 128.5, 127.0, 121.7 ppm. Exact mass ($C_{20}H_{14}N_2$+H) calculated 283.1230, measured 283.1241.

4.3.5. 4-Methyl-2-(3-pyridyl)quinazoline (***2e***). Yellow solid. Yield: 127 mg, 96%. Mp: 105–106 °C. ^{1}H NMR: δ 9.80 (s, 1H), 8.84 (dt, 1H, J_1=8.1 Hz, J_2=2.1 Hz), 8.71 (d, 1H, J=3.6 Hz), 8.03–8.07 (m, 2H), 7.86 (t, 1H, J=5.4 Hz), 7.59 (t, 1H, J=6.9 Hz), 7.42 (dd, 1H, J_1=3 Hz, J_2=5.4 Hz), 2.98 (s, 3H) ppm. ^{13}C NMR: δ 168.5, 158.1, 150.9, 150.2, 150.1, 135.7, 133.8, 133.7, 129.1, 127.3, 124.9, 123.2, 123.0, 21.9 ppm. Exact mass ($C_{14}H_{11}N_3$+H) calculated 222.1026, measured 222.1031.

4.3.6. 4-Methyl-2-(2-thienyl)quinazoline (***2f***). Yellow solid. Yield: 99 mg, 73%. Mp: 77–79 °C. ^{1}H NMR: δ 8.13 (d, 1H, J=3 Hz), 7.94–7.99 (m, 2H), 7.79 (t, 1H, J=6 Hz), 7.46–7.51 (m, 2H), 7.17 (t, 1H, J=3 Hz), 2.92 (s, 3H) ppm. ^{13}C NMR: δ 168.5, 157.1, 150.2, 144.3, 133.8, 129.7, 129.1, 128.8, 128.3, 126.6, 125.1, 122.9, 21.9 ppm. Exact mass ($C_{13}H_{10}N_2S$+H) calculated 227.0637, measured 227.0641.

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Supplementary data

Suplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.04.082. These data include MOL files and InChiKeys of the most important compounds described in this article.

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