Crystal Structure and DFT Studies of 4-Methyl-N-(1-phenylethyl)-N´-(1-phenylethylidene)benzenesulfonohydrazide. Evidence of a carbene insertion in the formation of acetophenone azine from acetophenone *p*-toluensulfonylhydrazone.

Rocío A. Valencia, Víctor M. Apolonio, Guillermo Caballero-García, Diego Martínez-Otero, Joaquín Barroso-Flores and Erick Cuevas-Yañez*

Centro Conjunto de Investigación en Química Sustentable UAEM-UNAM. Carretera Toluca-Atlacomulco Km 14.5, Toluca, Estado de México, 50200, Mexico.

*Corresponding author. Universidad Autónoma del Estado de México. Tel. +52 722 276 66 10; fax: +52 722 180 62 17, e-mail: ecuevasy@uaemex.mx.

Abstract. The crystal structure of 4-Methyl-N-(1-phenylethyl)-N′-(1-phenylethylidene) benzene sulfonohydrazide is disclosed, which is obtained from direct reaction between acetophenone tosylhydrazone and potassium tert-butoxide. Reaction mechanisms and the corresponding energy barriers were assessed through DFT calculations at the B3LYP/6-31G(d,p) level of theory and showed that this compound plays an important role as intermediate in the formation of acetophenone azine from acetophenone *p*-toluensulfonylhydrazone through a carbene insertion on this last compound.

Keywords. tosylhydrazone, azine, sulfonohydrazide, carbene insertion.

Introduction

Tosylhydrazones have attracted the interest of organic synthetic chemists because these compounds represent a practical source of both carbene and carbenoid species, in addition to their easy availability.[1] However, the reactions with tosylhydrazones sometimes present the by-product formation problem, affording a mixture of products where the azines are the most commonly found compounds in this kind of reactions. According to Kirmse,[2] two possible mechanistic pathways can explain the azine formation from diazoalkanes which in turn are generated from the fragmentation of tosylhydrazones under basic conditions. In the first instance, a dimerization between two molecules of diazoalkane **2** occurs giving the cyclic derivative **6** which eliminates nitrogen to yield the corresponding azine **5** (scheme 1).[3,4] On the other hand, diazoalkane **2** reacts with carbene **3** which is produced by nitrogen extrusion of diazoalkane **2** with the subsequent azine formation.[5] A third mechanism was proposed by Sha and Wei, based on a direct carbene insertion on the *p*-toluensulfonyl hydrazone moiety, followed by an elimination-reduction process of the sulfonyl group.[6]

Insert Scheme 1

In the course of our studies about carbenes and carbenoids derived from *p*-toluensulfonyl hydrazones, we occasionally observed the formation of azines, particularly in reactions with basic and weak nucleophiles at low concentrations.[7] A special process that drew our attention is the reaction of acetophenone tosylhydrazone **8** with some nucleophiles that gave complex mixtures under diverse conditions using potassium tert-butoxide as base. The isolation of some intermediates inspired us to examine this process in detail in order to find

a rational reaction mechanism which could describe the azine formation from tosylhydrazones to improve the carbene generation from these precursors. Herein is presented a summary of our recent successful endeavors in this area.

Results and discussion

Through a careful analysis, we noted that direct reaction between acetophenone tosylhydrazone **8** and potassium tert-butoxide afforded a mixture of acetophenone azine **10** and a compound which was identified by the conventional spectroscopic techniques as 4-Methyl-N-(1-phenylethyl)-N´-(1-phenylethylidene) benzene sulfonohydrazide **9** (scheme 2). Optimizing conditions, compound **9** was obtained as only reaction product in 80% yield, similar to that observed by Sha and Wei using NaOH.[6] Since compound **9** was a crystalline solid, it was studied by X-ray crystallography, and some interesting features were revealed therein.

Insert Scheme 2

Single-crystal X-ray diffraction analysis was performed for compound **9** confirming the spectroscopic results. An ORTEP and atom labeling diagram of compound **9** is presented in Figure 1. Crystallographic data and structural refinement parameters of **9** are summarized in table 1 and relevant bond lengths and angles data are collected in table 2. Crystals of compound **9** were grown by slow evaporation of a dichloromethane-hexane mixture, crystallizing in the orthorhombic system under a centrosymmetric space group Pbca (Figure 1), with 8 molecules in the unit cell. Compound **9** crystallized as a racemic mixture, in Figure 1 the R-enantiomer is shown. The conformation around the imine group

is E, and it is confirmed by the dihedral angle N(1)-N(2)-C(9)-C(11) with a value of 178.8(2) degrees.

Insert Figure 1

Insert Table 1

Insert Table 2

Compound **9** bears a part of the *p*-toluenesulfonylhydrazone fragment which is similar to other *N*-non hydrogen substituted, *p*-toluenesulfonyl hydrazones described in literature.[8-12] For example, the bond distance N(1)-N(2) is 1.447 Å is in the range 1.374 to 1.462 Å in this kind of compounds and depends on the nature of the substituents on the nitrogen atoms. However, a noteworthy characteristic is that compound **9** presents weak C-H---O type interactions in the crystalline structure, forming a dimer (Figure 2), the distance O(1)-H8 is 2.552 Å, slightly lower than the sum of their van der Waals radii (1.62 Å).

Insert Figure 2

The isolation and unequivocal identification of compound **9** confirms the previous observations made by Sha and Wei[6] and suggests that this compound is an intermediate in the azine formation from diazoalkanes derived from *p*-toluenesulfonylhydrazones, because subsequent experiments on compound **9** with excess potassium tert-butoxide demonstrated that acetophenone azine **10** was formed as only reaction product. Moreover, sulfinate

elimination in compound **9** is also possible using SiO_2 instead of potassium tert-butoxide (Scheme 2).

In order to get insights on the reaction mechanism, four reaction paths depicted in scheme 3 were assessed through computational chemistry methods. Reaction profiles for mechanisms 1, 2 and 3 are presented in figure 4.

Insert Scheme 3

Insert Figure 4

For mechanism 1, **TS1-1** was found in which a molecule of **2** attacks a second one with simultaneous elimination of nitrogen, the activation barrier found for this step was 35.28 kcal mol^{-1} with a reaction free energy of -68.79 kcal mol^{-1} indicating a spontaneous reaction. At first we though that **TS1-1** could yield intermediate **11** (scheme 3) which consecutively could release a nitrogen molecule to afford **5**, but that intermediate was not found and this direct mechanism was confirmed analyzing the IRC results (SI).

On the other hand, mechanism 2 was also explored, in which diazo compound **2** attacks carbene **3** to directly yield **5** through a simple addition step via transition state **TS2-2**. Activation barrier for this addition was calculated to be 25.89 kcal mol^{-1} (respect to the starting materials). Despite the fact that the barrier height for **TS2-2** is lower than that for **TS1-1**, mechanism 2 is firstly promoted by the formation of carbene **3** from nitrogen release in **2**. The activation energy needed for such elimination was found to be 31.59 kcal

mol^{-1} trough transition state **TS1-2**. Therefore, when the reaction proceeds, **TS1-1** and **TS1-2** compete to yield the corresponding products. Considering that the rate determining steps for mechanisms 1 and 2 are given by **TS1-1** (35.28 kcal mol^{-1}) and **TS1-2** (31.59 kcal mol^{-1}), respectively, with similar energies, it may be possible that both mechanisms operate in the formation of compound **5**.

The third mechanism was also studied. In order to find the [3+2]-like transition state **TS1-3**, the unrestricted functional UB3LYP was used in combination with the guess=(mix,always) keywords, yielding an activation free energy of 46.87 kcal mol^{-1}. Intermediate **12** was found in the potential energy surface, which after nitrogen release afforded azine **5** through **TS2-3** (25.06 kcal mol^{-1}). The first barrier height for this mechanism is larger in comparison with the two previous mechanisms, pointing that although this mechanism is possible it may not occur when lower-barrier transition states are available to.

These results are in agreement and complement previous kinetics studies made by Bethell and coworkers.[5,13,14]

For mechanism 4, addition of **1** in its anion form to carbene **3** yielded **TS1-4** (5.87 kcal mol^{-1}, figure 5). After several attempts we could not locate intermediate **7** as a stationary point. The IRC path indicates that addition of carbene **3** should occur simultaneously with 4-toluensulfinate elimination. Further analysis of the RMS gradient norm along the IRC path (figure 6), shows the presence of **7** as a hidden intermediate, which appears as a dip in this curve. Hidden intermediates are not stationary points on the potential energy surface,

but modifications in the reaction conditions or in the substitution pattern can make them actual intermediates and may also be isolated, which is the case for isolated compound **9**.

Insert Figure 5

Insert Figure 6

Considering the first activation energy from the four mechanisms we studied, it can be concluded that the most plausible mechanism that drives the transformation under study is mechanism 4 (5.87 kcal mol^{-1}) once the carbene **3** is formed. As for this reaction to occur it is necessary the formation of **3** (31.59 kcal mol^{-1}), mechanism 4 takes place together with the second part of mechanism 2.

On the other hand, the reaction between diazoalkanes with nucleophilic stable carbenes to give azines directly,[15] as well as the rhodium carbenoid insertions on phenylhydrazones,[16] could be extended to diazoalkanes derived from tosylhydrazones, and together with these last elements, indicate that a carbene insertion occurs on the tosylhydrazone tetrahedral nitrogen which explain the formation of compound **9** as a possible intermediate in the generation of the corresponding acetophenone azine.

Conclusion

In conclusion, this report shows the crystal structure of 4-Methyl-N-(1-phenylethyl)-N´-(1-phenylethylidene) benzene sulfonohydrazide **9** which not only complements and extends the results of Sha and Wei,[6] but also contributes to understanding of the mechanism of

azine formation from *p*-toluenesulfonylhydrazones through theoretical calculations derived thereof that will help to control this kind of processes.

Experimental

General remarks

The starting materials were purchased from Sigma-Aldrich and were used without further purification. Solvents were distilled before use. Silica plates of 0.20 mm thickness were used for thin-layer chromatography. Melting points were determined with a Krüss Optronic melting point apparatus and they are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AVANCE 300 spectrometer; the chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS) as the internal standard (0.00). For analytical purposes the mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus instrument in the electron ionization (EI) mode, 70 eV, 200 °C via direct inlet probe. Only the molecular and parent ions (m/z) are reported. IR spectra were recorded on a Bruker TENSOR 27 FT instrument.

For the RX difraction studies, crystals of compound **9** were obtained by slow evaporation of a dilute dichloromethane-hexane solution, and the reflections were acquired with a Bruker APEX DUO diffractometer equipped with an Apex II CCD detector, Mo-Kα radiation (λ = 0.71073 Å) at 293 K. Three standard reflections every 97 reflections were used to monitor the crystal stability. The structure was solved by direct methods; missing atoms were found by difference-Fourier synthesis, and refined on F2 by a full-matrix least-squares procedure using anisotropic displacement parameters using SHELX-97.

Computational Details

All gas phase DFT calculations were performed using the Gaussian 09 (Rev. D1) suite of programs[17] with the B3LYP functional[18] and the 6-31G(d,p) basis set.[19] Frequency analysis were carried out at the same level of theory at the end of each geometry optimization to verify that the corresponding structure was a local minima or a transition state, finding only one imaginary frequency for the latter and none for the former. Transition states were confirmed with intrinsic reaction coordinate (IRC) calculations to verify that the first order saddle point connected the two local minima in each side of the potential energy surface.

Coordinates for all optimized structures as well as IRC paths are provided in the supporting information.

Synthesis of 4-Methyl-N-(1-phenylethyl)-N´-(1-phenylethylidene) benzene sulfonohydrazide (9). A solution of acetophenone p-toluenesulfonylhydrazone (0.302 g, 1mmol), potassium tert-butoxide (0.224 g, 2 mmol) and tetrabutylammonium iodide (0.01 g, 0.05 mmol) in anhydrous dioxane (5 mL) was stirred at 70 °C for 24 h. The mixture was cooled at room temperature, H_2O (15 mL) was added and the product was extracted with CH_2Cl_2 (3 X 15 mL), the organic phases were joined and dried over Na_2SO_4, the solvent was removed under reduced pressure and the product was purified by column chromatography (SiO_2, hexane/AcOEt 95:5) to afford a white solid (0.31 g, 80 %), m.p. 167-168°C (lit.166-168 ºC).[6] FT-IR (ATR, cm^{-1}): 3030, 2992, 1590, 1365, 1183. ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J*=8.4 Hz, 2H), 7.68 (d, *J*=8.4 Hz, 2H), 7.48 (t, J=8 Hz, 3H), 7.41 (t, *J*=7.5 Hz, 3H), 7.29-7.21 (m, 4H), 7.20-7.17 (m, 3H), 5.26 (q, *J*=7 Hz, 1H), 2.41 (s, 3H), 2.14 (s, 3H), 1.18 (d, *J*=7 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 178.7 (C), 142.4

(C), 139.8 (C), 136.3 (C), 134.0 (C), 129.8 (CH), 128.1 (2 X CH), 127.4 (2 X CH), 127.3 (2 X CH), 127.0 (2 X CH), 126.9 (2 X CH), 126.3 (CH), 126.2 (2 X CH), 59.4 (CH), 20.5 (CH_3), 16.3(CH_3), 14.2 (CH_3). MS [EI+] m/z (%): 392 $[M]^+$ (10), 91 $[C_7H_7]$ (100).

Crystal data for **9**: formula: $C_{23}H_{24}N_2O_2S$; FW 392.50; crystal system: Orthorhombic; space group: P b c a; temp, K=296(2); λ, Å= 1.54178 Å; Unit cell dimensions a, Å= 14.6622(5); b, Å=15.5860(5); c, Å=18.5481(6); α, deg=90; β, deg=90; γ, deg=90; V, $Å^3$= 4238.7(2); V=8; $\rho_{calcld.}$, $g \cdot cm^{-3}$=1.230; μ, mm^{-1}= 1.511; F(000)= 1664; crystal size, mm^3=0.372 x 0.192 x 0.184; θ range for data collection, deg= 4.768 to 68.245; index ranges: $-17 \leq h \leq 17$, $-15 \leq k \leq 18$, $-15 \leq l \leq 22$; Reflections collected: 23616; Independent reflections (R_{int})= 3859 (0.0247); no. of data / restraints / parameters=3859 / 276 / 301; GoF on F^2=1.035; Final R indices [$I>2\sigma(I)$] R1 = 0.0407, *w*R2 = 0.1192; R1, *wR2* (all data): 0.0468, 0.1257; largest diff. peak / hole, $e \cdot Å^{-3}$=0.246 / -0.236.

Conversion of 4-Methyl-N-(1-phenylethyl)-N´-(1-phenylethylidene) benzene sulfonohydrazide 9 into acetophenone azine 10. Method A. A solution of compound **9** (0.392g, 1 mmol), potassium tert-butoxide (0.336 g, 3 mmol) in anhydrous dioxane (10 mL) was stirred at 70 °C for 48 h. The mixture was cooled at room temperature, H_2O (15 mL) was added and the product was extracted with CH_2Cl_2 (3 X 15 mL), the organic phases were joined and dried over Na_2SO_4, the solvent was removed under reduced pressure and the product was purified by column chromatography (SiO_2, hexane/AcOEt 95:5) to afford a yellow solid (0.100 g, 85 %), m.p. 120-121°C (lit.120-121 ºC).[20] FT-IR (ATR, cm^{-1}): 2919, 2888, 1605. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J*=8.4 Hz, 4H), 7.40 (m, 6H), 2.29 (s,

6H). ^{13}C NMR (75MHz, $CDCl_3$) δ 158.7 (C), 139.8 (C), 129.8 (CH), 128.1 (2 X CH), (2 X CH), 15.2 (CH_3). MS [EI+] m/z (%): 236 $[M]^+$ (80), 221 $[M - CH_3]^+$ (100).

Conversion of 4-Methyl-N-(1-phenylethyl)-N´-(1-phenylethylidene) benzene sulfonohydrazide 9 into acetophenone azine 10. Method B. A suspension of compound **9** (0.392g, 1 mmol) SiO_2 (2 g) in toluene (50 mL) was stirred at reflux temperature for 72 h. The mixture was cooled at room temperature and the solvent was removed under reduced. Purification by column chromatography (SiO_2, hexane/AcOEt 95:5) afforded compound **5** as yellow solid (0. 0508 g, 43 %). Spectral characterization and other physical data matched to those previously obtained in method A.

Acknowledgments

Financial support from CONACYT (Project No. 135053) is gratefully acknowledged. The authors would like to thank Signa S.A. de C.V. for some graciously donated solvents and reagents and to N. Zavala, A. Nuñez, L. Triana and M. C. Martínez for the technical support.

References

1.- Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem*. **2005**, 1479.

2.- Kirmse, W. in Carbene Chemistry, 2nd ed. Academic Press, New York, 1971, p. 415.

3.- Sharma, T. C.; Lal, A.; Saksena, V. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2881.

4.- Overberger, C. G.; Anseleme, J. P. I. *J. Org. Chem.* **1964**, *29*, 1188.

5.- Bethell, D.; Newall, A. R.; Stevens,G.; Whittaker, D. *J. Chem. Soc. B*, **1969**, 749.

6.- Sha, Q.; Wei, Y. *Tetrahedron*, **2013**, *69*, 3829.

7.- García, M. A.; García-Muñoz, A.; Peña, J. A.; Trujillo-Reyes, J.; Morales-Luckie, R. A.; Avalos-Borja, M.; Vilchis-Nestor, A. R.; Sánchez-Mendieta, V.; Corona, D.; Cuevas-Yañez, E. *Lett. Org. Chem.* **2012**, *9*, 2.

8.- Alyar, S.; Adem, S. *Spectrochim. Acta A,* **2014**, *131*, 294.

9.- Hashemi, S. A. *Tetrahedron Lett*. **2012**, *53*, 5141.

10.- Yuan, Z. L.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2010**,4088.

11.- Chen, Z. S.; Duan, X. H.; Wu, L. Y.; Ali, S.; Ji, K. G.; Zhou, P. X.; Liu, X. Y.; Liang, Y. M. *Chem. Eur. J.* **2011**, *17*, 6918

12.- Yao, L.; Wang, C. J. *Adv. Synth. Catal*. **2015**, *357*, 384.

13.- Bethell, D.; Whittaker, D.; Callister; J, D. *J. Chem. Soc*. **1965**, 2466.

14.- Bethell, D.; Whittaker, D. *J. Chem. Soc*. *B* **1966**, 778.

15.- Hopkins, J. M.; Bowdridge, M.; Robertson, K. N.; Cameron, T. S.; Jenkins, H. A.; Clyburne, J. A. C. *J. Org. Chem.* **2001**, *66*, 5713.

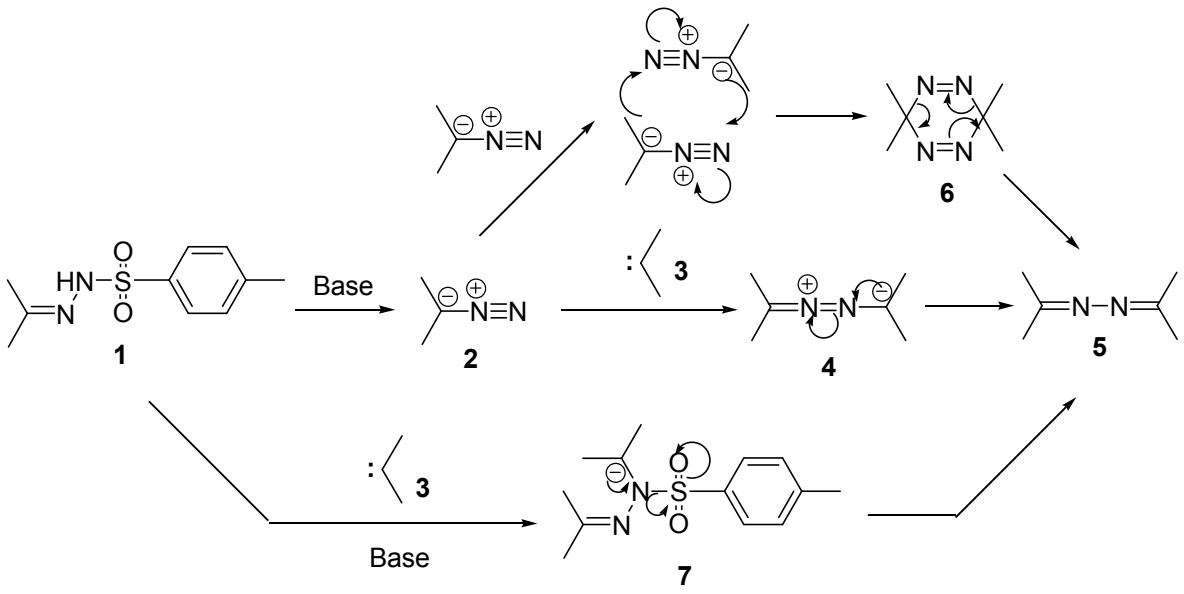
16.- Xu, X.; Zavalij, P. Y.; Doyle, M. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 9829.

17.- Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenb, D. J. Gaussian 09, Revision D.01, 2009.

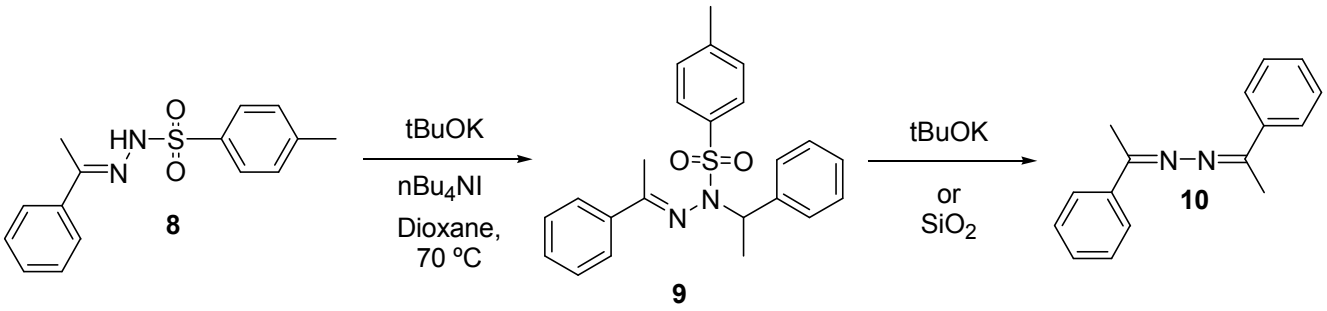
18.- Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

19.- Gill, P. M. W.; Johnson, B. G.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett*. **1992**, *197*, 499.

20.- Lloyd, F. N.; Goodwin, T. C. *J. Am. Chem. Soc*. **1949**, *71*, 633.



Scheme 1. Mechanistic pathways on the formation of azine **5** from p-toluensulfonylhydrazone **1**.



Scheme 2. Synthesis of compound **9** and transformation to azine **10**.

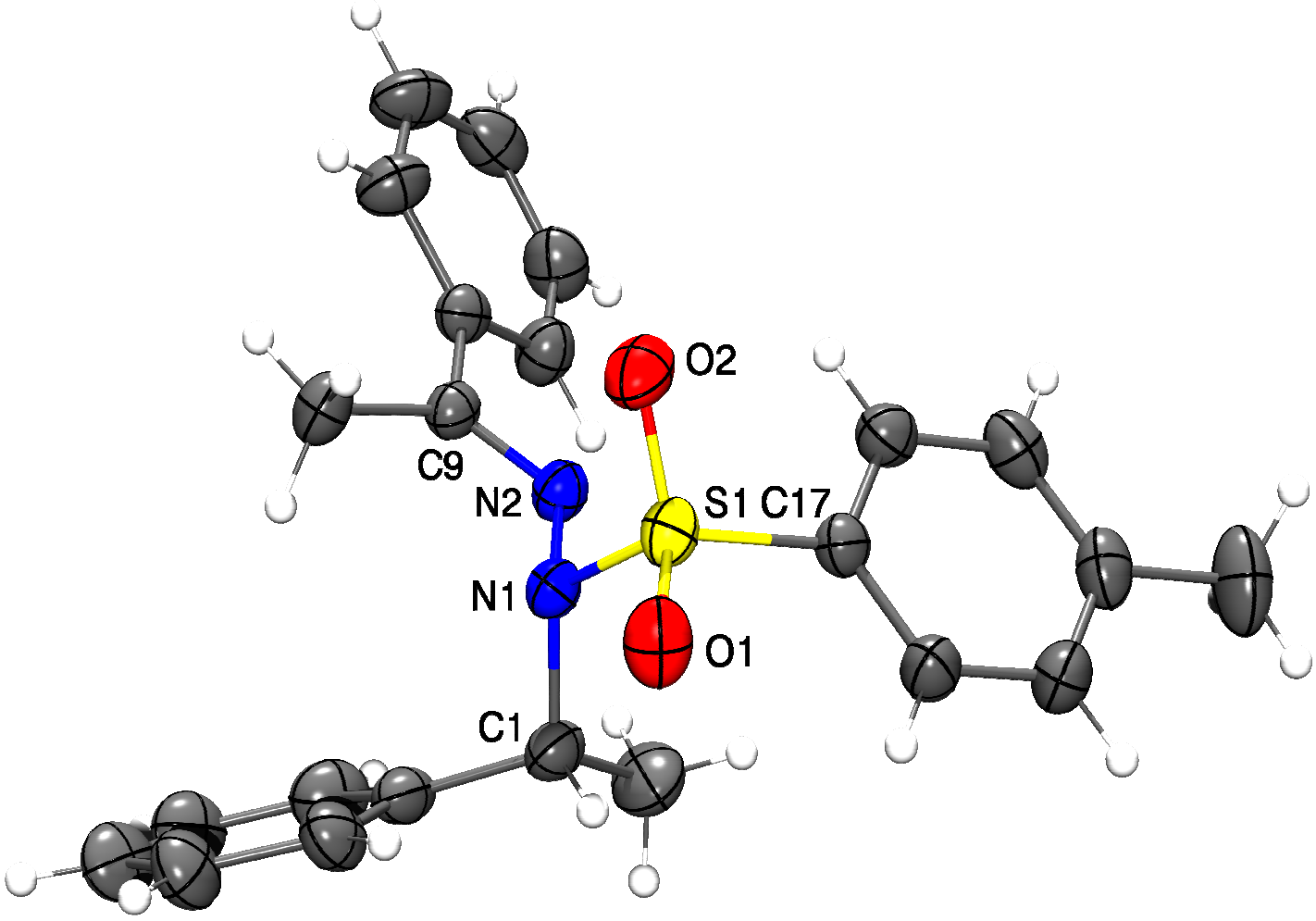


Figure 1. ORTEP diagram and atom labelling system for compound **9**.

Table 1. Crystal data and structure refinement for the compound **9**, $C_{23}H_{24}N_2O_2S$.

Crystal data	**9**	
Empirical formula	$C_{23}H_{24}N_2O_2S$	
Formula weight	392.50	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 14.6622(5) Å	α = 90°.
	b = 15.5860(5) Å	β = 90°.
	c = 18.5481(6) Å	γ = 90°.
Volume	4238.7(2) Å^3	
Z	8	
Density (calculated)	1.230 mg/m^3	
Absorption coefficient	1.511 mm^{-1}	
F(000)	1664	
Crystal size	0.372 x 0.192 x 0.184 mm^3	
Theta range for data collection	4.768 to 68.245°	
Index ranges	-17<=h<=16, -18<=k<=18, -22<=l<=22	
Reflections collected	23616	
Independent reflections	3859 [R(int) = 0.0247]	
Data / restraints / parameters	3859 / 276 / 301	
Goodness-of-fit on F^2	1.035	
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0407, $wR2$ = 0.1192	
R indices (all data)	$R1$ = 0.0468, $wR2$ = 0.1257	
Absolute structure parameter	0.06(3)	
Largest diff. peak and hole	0.246 / -0.236 (eÅ^{-3})	

Table 2. Selected bond distances (Å) and bond angles (deg) the compound **9**, $C_{23}H_{24}N_2O_2S$.

Bond	Distance (Å)
S(1)-O(2)	1.422(1)
S(1)-O(1)	1.423(1)
S(1)-N(1)	1.657(1)
S(1)-C(17)	1.756(2)
N(1)-N(2)	1.447(2)
N(1)-C(1)	1.502(2)
N(2)-C(9)	1.279(2)
Bond	**Angle (°)**
O(2)-S(1)-O(1)	120.4(1)
N(1)-S(1)-C(17)	108.6(1)
N(2)-N(1)-C(1)	112.1(1)
N(2)-N(1)-S(1)	110.3(1)
C(1)-N(1)-S(1)	117.9(1)
C(9)-N(2)-N(1)	114.1(1)

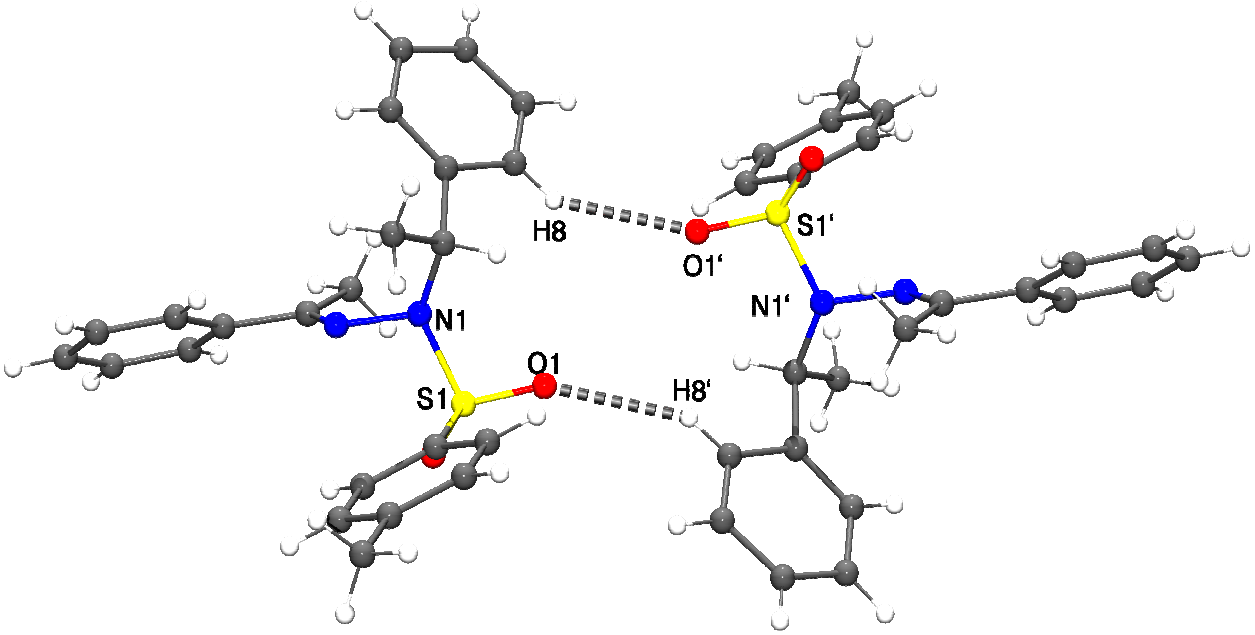
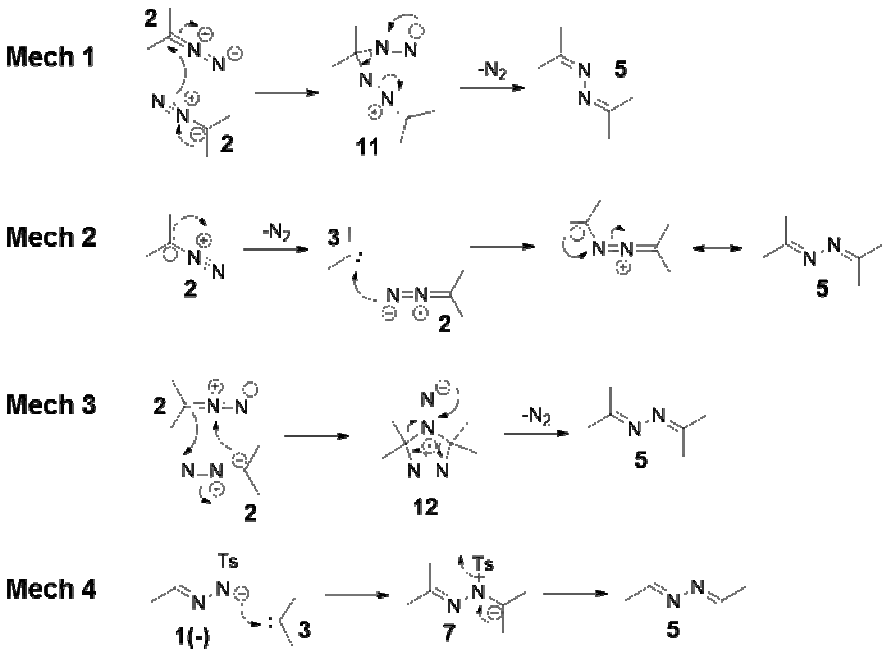


Figure 2. Crystal packing diagram of compound **1**.



Scheme 3. Studied reaction mechanisms for the formation of compound **5**.

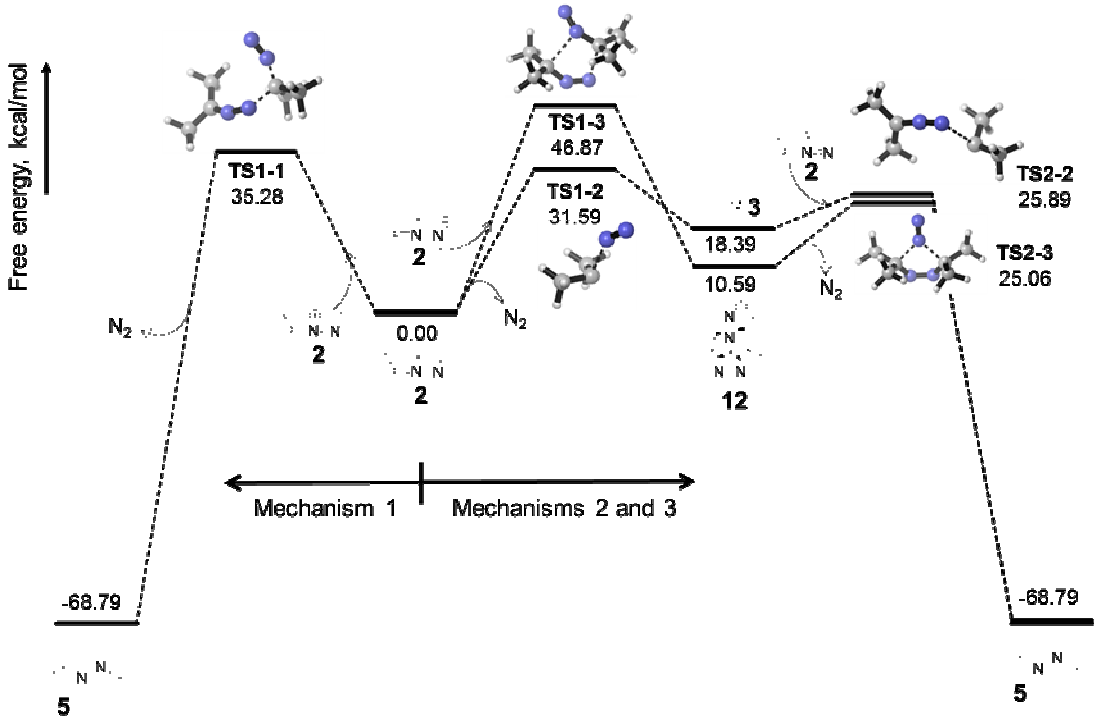


Figure 4. Energy profiles for mechanisms 1, 2, and 3. Numbers are free energies relative to the starting materials and are presented in kcal mol^{-1}.

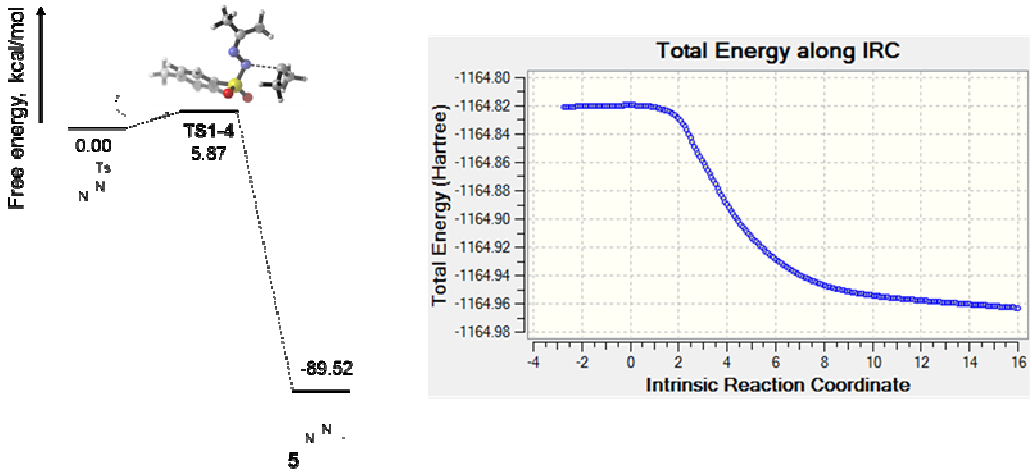


Figure 5. Reaction profile and IRC path for mechanism 4. Relative energies to that of starting materials are given in kcal mol^{-1}.

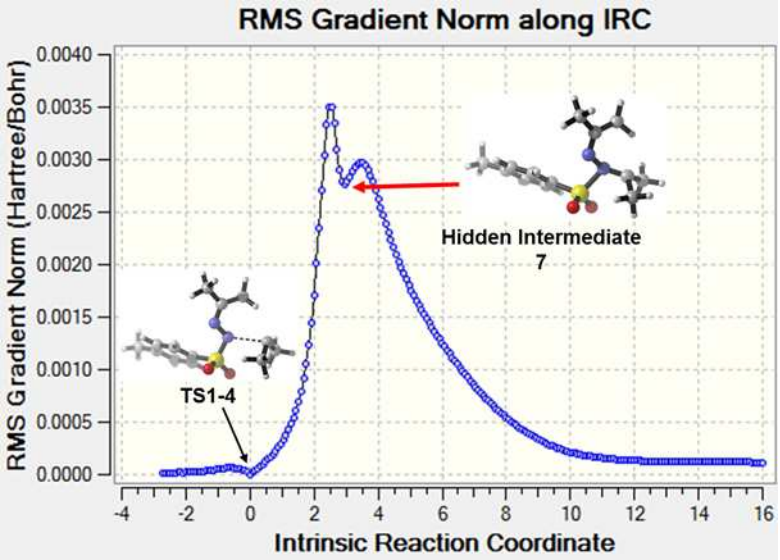


Figure 6. RMS gradient norm along the IRC path for mechanism 4. The dip in the curve shows the presence of hidden intermediate **7**.