



# Why base-catalyzed isomerization of *N*-propargyl amides yields mostly allenamides rather than ynamides

Armando Navarro-Vázquez

## Full Research Paper

Open Access

### Address:

Departamento de Química Fundamental, Centro de Ciências Exatas e da Natureza, Universidade Federal de Pernambuco, Cidade Universitária - Recife, PE - CEP 50.740-560, Brazil

### Email:

Armando Navarro-Vázquez - armando.deus@gmail.com

### Keywords:

allenamide; DFT; isomerization; ynamide

*Beilstein J. Org. Chem.* **2015**, *11*, 1441–1446.

doi:10.3762/bjoc.11.156

Received: 25 May 2015

Accepted: 30 July 2015

Published: 18 August 2015

Associate Editor: P. R. Schreiner

© 2015 Navarro-Vázquez; licensee Beilstein-Institut.

License and terms: see end of document.

## Abstract

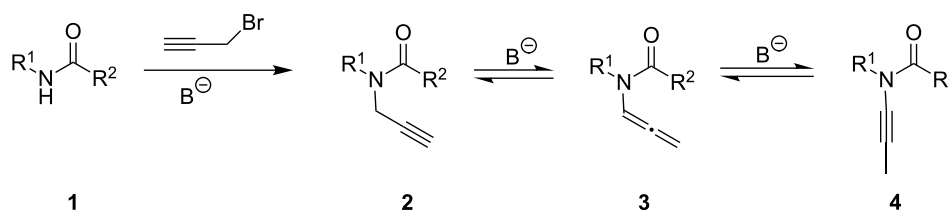
The base-catalyzed isomerization of *N*-propargylamides or carbamates may furnish *N*-allenyl compounds (allenamides/allencarbamates) or further evolve to *N*-alkynyl compounds (ynamides or yncarbamates). The particular fate of this reaction varies from experiment to experiment and there is no clear rule for predicting the reaction outcome for a particular structure. With the support of ab initio and DFT computations, this work shows that observed results can be explained by assuming an exchange equilibrium between energetically close *N*-propargyl, allenyl and *N*-alkynyl forms and that the reaction outcome correlates to a particular equilibrium mixture. Due to the very small energy gap between the *N*-allenyl and *N*-alkynyl forms, small structural changes may easily alter the equilibrium position, explaining the variety of observed experimental results. Based on CBS-QB3 computations, the ωB97 functional provided reasonably accurate isomerization energies and could successfully predict the experimentally observed behavior for several examples from the literature.

## Introduction

Allenamides [1,2] and ynamides [3-5] have become useful functional groups for organic chemistry synthesis in the last years. Reduced electron pair donation as compared to their enamine or ynamine parents strongly improves the handling of these compounds by making them resistant to hydrolysis while still retaining a rich variety of chemistry. The simplest method for the preparation of these compounds is the alkylation of a secondary amide **1** with a propargyl bromide (Scheme 1) [6,7]. Subsequent base-catalyzed isomerization of *N*-propargyl compound **2** leads to allenamide **3**. Whereas in some particular

cases the reaction leads to the final *N*-alkynyl product, in most cases, the reaction stops at the allene stage and does not further progress even when employing harsh reaction conditions. The outcome of the isomerization process seems to subtly depend on the structural features of the *N*-propargyl compound. Similar issues have been observed for carbamates or phosphoramides [8].

In summary, the isomerization process is not yet well understood and, quoting Hsung and coworkers, "...This poses an



**Scheme 1:** Preparation of propargylamides through alkylation of secondary amides and base-catalyzed isomerization to allenamides and ynamides.

interesting fundamental question as to why the thermodynamically more stable ynamide ... was not found if these isomerizations involved an equilibration mechanism...” [2].

The available experimental data strongly suggest that allenamides do not always convert to ynamides due to thermodynamic rather than kinetic reasons, and it is not necessarily the case that ynamides are more stable than the parent allenamides. Here it is hypothesized that *N*-propargylamide ↔ allenamide ↔ ynamide interconversion takes place reversibly and the outcome of the reaction is related to the equilibrium position. Structural changes can alter the equilibrium position, leading to the observation of either species or a mixture thereof [8].

This hypothesis states that the course of the reaction in Scheme 1 simply reflects the relative energy of isomers 2, 3 and 4. To test this, the relative energies for the corresponding isomers for a selected combination of starting amides or carbamates and a final urea example (Figure 1) were computed using ab initio and DFT methods.

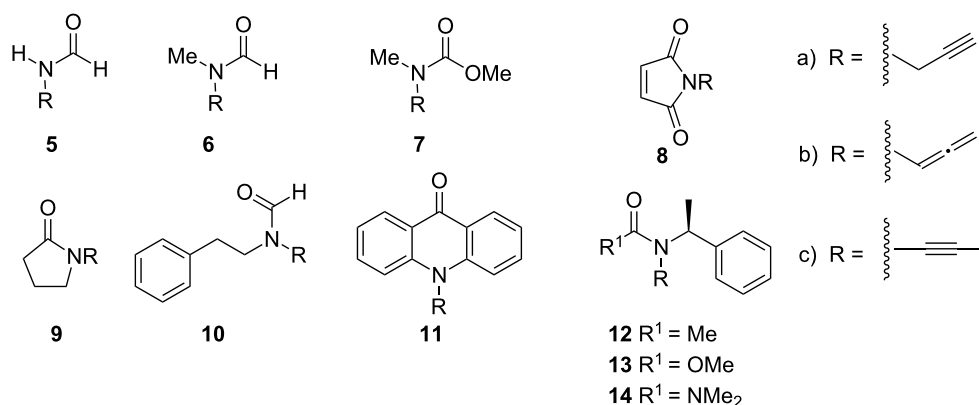
## Results and Discussion

### Computational procedures

It is known that ab initio prediction of cumulene–polyynes isomerization energies requires a very high level of theory [9], and expensive CCSD(T)/cc-pVQZ//MP2/cc-pVTZ coupled

cluster computations were needed to match the experimental propadiene to propyne isomerization energy of  $-1.4$  kcal/mol [10]. In order to choose a standard test methodology for the computation of allenamide–ynamide relative energies, the performance of the composite CBS-QB3 [11,12] methodology on the propadiene to propyne isomerization process as well in the simplest allenamide to ynamide isomerization reactions in compound 5 was evaluated. For the sake of simplicity, the conformation of the amide bond in 5a,b,c was fixed as *s-E*. This CBS-QB3 method furnished a  $\Delta H_0$  energy of  $-0.8$  kcal/mol for propadiene to propyne isomerization, which is somewhat lower than the reported experimental energy. Note, however, that the result is close to that furnished by the much more computationally expensive W1 [13] computation on the same system with a  $\Delta H_0$  value of  $-1.1$  kcal/mol (Table 1).

The best performing DFT functional for the prediction of cumulene–polyynes isomerization energies was found by Zhao and Truhlar to be the hybrid meta-GGA M05 functional [9]. Since then, new functionals of the same family have been reported such as the M06 set [14] or the  $\omega$ B97 family of long-range corrected GGAs [15]. In this work, these new functionals were tested to determine if they could provide superior performance for the given problem. In the M06 family, the non-hybrid M06L was tested, as well as the hybrid M06HF and M062X forms. From the  $\omega$ B97 family we tested the  $\omega$ B97 form, the  $\omega$ B97X,



**Figure 1:** Set of studied compounds.

**Table 1:** Isomerization energies for the propadiene to propyne and the **5a,b,c** system.

Level	$\Delta H_0^{\text{CH}_2=\text{C}=\text{CH}_2 \rightarrow \text{CH}_3\text{C}=\text{CH}}$	$\Delta H_0^{5\text{a} \rightarrow 5\text{b}}$	$\Delta H_0^{5\text{b} \rightarrow 5\text{c}}$
CBS-QB3	-0.8	-4.3	1.0
W1	-1.1	–	–
M05	0.5	-6.6	0.3
M052X	1.6	-6.8	2.8
M06L	2.3	-9.3	2.3
M06HF	0.6	-5.0	2.4
M06	0.6	-6.5	0.5
M062X	0.6	-6.0	1.3
$\omega$ B97	0.4	-5.3	1.1
$\omega$ B97X	1.0	-6.2	1.8
$\omega$ B97XD	1.9	-7.2	2.9
B3LYP	3.0	-9.2	3.8

which includes exact short-range HF exchange, and in addition the  $\omega$ B97XD functional, which also includes Grimme's dispersion correction [16]. The DFT tests employed a medium-size 6-31+G\*\* basis in search of a methodology applicable to relatively large systems. The relative energies for the propadiene–propyne isomerization process as well as for the **a,b,c** isomers of compound **5** were computed.

Although all functionals predicted the wrong sign for the propadiene to propyne reaction M05, M062X and  $\omega$ B97 provided the closest isomerization energies (Table 1). B3LYP, as previously reported by Truhlar [9], and the non-hybrid GGA M06L functional presented particularly bad performance.

In the case of the **5a,b,c** system, the CBS-QB3 computations predicted the *N*-propargyl to allenamide  $\Delta H_0^{5\text{a} \rightarrow 5\text{b}}$  isomerization to be a moderately exothermic reaction with a value of -4.3 kcal/mol (Table 1). As compared to CBS-QB3, all the DFT computations overestimated the exothermicity of this reaction by more than 1.5 kcal/mol save for the M06HF and  $\omega$ B97 functionals with  $\Delta H_0^{5\text{a} \rightarrow 5\text{b}}$  values of -5.0 and -5.3 kcal/mol, respectively. Particularly inadequate was the performance of M06L and B3LYP with  $\Delta H_0$  values far off by around 5 kcal/mol. For the reaction of interest, the allenamide–ynamide conversion, CBS-QB3 predicted a small energy gap between the two forms with a positive  $\Delta H_0^{5\text{b} \rightarrow 5\text{c}}$  value of 1.0 kcal/mol. Here M062X and  $\omega$ B97 performed best with values very close to the CBS-QB3 ones. Overall, the  $\omega$ B97 functional offered the best performance and was the chosen functional for the investigation of the larger systems.

The next investigated system was the *N*-methylformamide **6** (again the conformation of the peptidic bond was fixed as *s-E*). Both CBS-QB3 and  $\omega$ B97 predicted the allenamide **6b** to be

notably more stable than the *N*-propargyl compound **6a** (Table 2). On the other hand, the ynamide **6c** is more than 2 kcal/mol larger than the allenamide compound. The effect of solvation, which can be important in the polar solvents where the isomerization reaction is commonly carried out, was considered at the PCM level [17] by using DMSO parameters. The DFT PCM computations showed reduced exothermicity of the *N*-propargylamide  $\rightarrow$  allenamide step and increased endothermicity of the allenamide  $\rightarrow$  ynamide gap (Table 2). Hence, the results were in agreement with the experimental observation that base-catalyzed isomerization of most *N*-propargylamides commonly furnish allenamide compounds, and clearly show that simple ynamides are not inherently more stable than allenamides.

**Table 2:** Isomerization energies for the amides/carbamates outlined in Figure 1.

	$\Delta H_0^{a \rightarrow b}$		$\Delta H_0^{b \rightarrow c}$			
	CBS-QB3	$\omega$ B97	CBS-QB3	$\omega$ B97		
<b>5</b>	-4.3	-5.3 <sup>a</sup>	-3.6 <sup>b</sup>	1.0	1.1 <sup>a</sup>	1.8 <sup>b</sup>
<b>6</b>	-4.9	-5.7	-4.1	2.4	2.3	3.0
<b>7</b>	-4.6	-5.5	-3.9	3.1	3.4	2.6
<b>8</b>	-1.3	-2.4	-1.2	3.2	3.7	2.5
<b>9</b>	–	-5.5	-4.2	–	4.8	3.1
<b>10</b>	–	-5.3	-4.0	–	2.6	2.8
<b>11</b>	–	-3.3	-2.7	–	-2.3	-1.1
<b>12</b>	–	–	-2.2	–	–	-1.7
<b>13</b>	–	–	-2.3	–	–	0.0
<b>14</b>	–	–	-4.6	–	–	-1.2

<sup>a</sup>In vacuum; <sup>b</sup>PCM(DMSO).

CBS-QB3 and  $\omega$ B97 computations on the *N*-methylcarbamate system **7**, also with a fixed *s-E* conformation, showed a similar pattern to that computed for amide **6**. Note, however, that whereas inclusion of solvation increases the allenamide  $\rightarrow$  ynamide gap, the allencarbamate  $\rightarrow$  yncarbamate gap is decreased from 3.4 to 2.6 kcal/mol (Table 2).

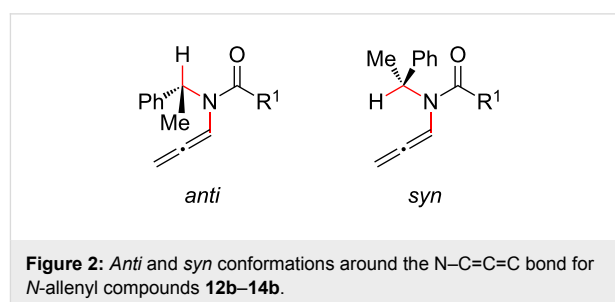
According to Hsung and coworkers, *N*-propargylphthalimide does not lead to either allenamides or ynamides under typical isomerization conditions [18]. At the CBS-QB3 level, the *N*-propargylimide **8a** is only 1.3 kcal/mol more stable than the corresponding allenamide **8b**. The now lower exothermicity of the reaction may account for the observed lack of reactivity since entropic and solvation effects could make the propargyl amide ynamide transformation endergonic. In fact, the  $\omega$ B97 reaction energy is more than 1 kcal/mol less exothermic when computed in DMSO than in vacuum. Note that in any case the  $\Delta H_0^{8b \rightarrow 8c}$   $\omega$ B97 reaction energy indicates that the reaction would very likely stop at the allenamide stage (Table 2). Nonetheless, the above results suggest that varying the reaction conditions (perhaps solvent polarity) could eventually lead to the observation of the allenimides. NMR deuteration studies could be of help to experimentally eliminate possible kinetic effects in the observed lack of reactivity [19].

Having established a reasonable performance of  $\omega$ B97 in describing the above systems, the reproducibility of experimental observations in larger systems was tested. The isomerization of lactam **9** was first studied. The isomerization of *N*-propargyllactams is known to stop at the allenamide stage [20,21]. The computations showed that the allenamide is much more stable than the *N*-propargyl compound ( $\Delta H_0^{9a \rightarrow 9b} = -5.5$  and  $-4.2$  kcal/mol) or the ynamide ( $\Delta H_0^{9b \rightarrow 9c} = 4.8$  and  $3.1$  kcal/mol), both in vacuum and DMSO, which is in agreement with the experimental observations (Table 2). Similar results, as can be seen in Table 2, were obtained for the *N*-(2-phenethyl)formamide system **10**, which was prepared during previous studies on acid-catalyzed cyclization of allenamides [22].

The isomerization of acridinone is a frequently studied process and one of the few examples where isomerization continues to the final ynamide stage [23,24]. Interestingly, the kinetics of the reaction seem to be slow enough to allow the allenamide intermediate to be obtained by simply employing a short reaction time [20]. The computations for acridinone **11** gave isomerization energies  $\Delta H_0^{10a \rightarrow 10b}$  and  $\Delta H_0^{10b \rightarrow 10c}$  of  $-3.3$  and  $-2.3$  kcal/mol, in the gas phase, and  $-2.7$  and  $-1.1$  in DMSO, respectively. This agrees with the experimental observation of the allenamide further evolving to the ynamide product. The now lower energy of the alkyne system can be attributed to

the distortion of the allenamide moiety from planarity due to strong steric interactions with the hydrogen atoms in the ortho position.

A final and more demanding test is the Hsung observation that whereas only ynamide **12** was observed upon isomerization of the corresponding *N*-propargylamide, the related carbamate **13** only evolves to the allenamide stage [18]. Furthermore, urea **14** (see page 5069 of [3], we thank one of the referees for highlighting this example) again furnished only the ynamide compound. The  $\omega$ B97 computations predict the ynamide **12c** to be more stable than allenamide **12b** by 1.7 kcal/mol (Table 2). On the other hand, the yncarbamate **13c** is nearly degenerate with the allencarbamate **13b**. For the urea **14** this trend is again reverted and the *N*-alkynyl compound **14c** is more stable than the allenamide **14b** by 1.2 kcal/mol. Note the more exothermic *N*-propargyl  $\rightarrow$  *N*-allenyl gap for **14** caused by the higher electronic donation capability of the nitrogen atom. Hence, the DFT computations are in agreement with the observed reaction trends. This could be potentially explained in terms of the destabilization of the allenamide form due to steric crowding as suggested by a less exothermic *N*-propargyl  $\rightarrow$  *N*-allenyl gap. This effect is large enough to result in the experimental observation of the ynamides **12c** and yurea **14c**, but not the yncarbamate **13c**. The difference in the *N*-allenyl  $\rightarrow$  *N*-alkynyl gap for **12** and **13** could be partially attributed to the different basal conformations adopted by allenenes **12b** and **13b** whereas the methynic proton in the benzylic chain respectively prefers an *anti* or *syn* conformation with respect to the N=C=C= bond (Figure 2). The *anti* conformation is also the one preferred by the allenyl urea **14b**.



## Conclusion

In summary, the very different outcome of the isomerization reaction of *N*-propargylamides and carbamates towards allenamides or ynamides can be simply explained in terms of the relative energy of the involved species. Simple allenamides or allencarbamates are in general more stable than the corresponding *N*-alkynyl isomers but the sign of the small energy gap can be reversed through structural changes. The  $\omega$ B97 functional gave reasonable performance for the computation of

isomerization energies, providing a suitable computational methodology for the prediction of the result of the isomerization reaction in similar systems.

## Computational Procedures

All reaction energies are reported as enthalpies at zero K ( $\Delta H_0 = \Delta E + ZPVE$ ). The structures were fully optimized at the reported levels of theory. The DFT computations used a pruned (99,590) grid (Gaussian09 ultrafine grid). The analytical frequencies were computed to verify the nature as minima of all computed structures and to obtain the zero-point vibrational energies. The zero-point vibrational energies are unscaled in the DFT computations and scaled according to method-defined factors in CBS-QB3 [11,12] and W1 [13] computations. The DFT PCM [17] computations were performed using DMSO Gaussian09 parameters. All computations were performed using the Gaussian09 package [25].

For species **9**, **10**, **12**, **13** and **14** a conformational search was accomplished using the GMMX method and the MMX force field as implemented in PCModel 9.21 [26]. The five lowest-energy conformations were then selected and the DFT was optimized at the  $\omega$ B97/PCM(DMSO) level. The structure with the lowest DFT energy was then selected for computation of isomerization energies.

## Supporting Information

### Supporting Information File 1

Computational procedures as well as energies and XYZ coordinates for all computed structures.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-156-S1.pdf>]

## Acknowledgements

The author thanks the Universidade Federal de Pernambuco for a visiting professorship and the Centro Nacional de Processamento de Alto Desempenho de Pernambuco (CENAPAD-PE) for computational time.

## References

- Lu, T.; Lu, Z.; Ma, Z.-X.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2013**, *113*, 4862–4904. doi:10.1021/cr400015d
- Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773–782. doi:10.1021/ar030029i
- DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064–5106. doi:10.1021/cr100003s
- Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840–2859. doi:10.1002/anie.200905817
- Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2013**, *47*, 560–578. doi:10.1021/ar400193g
- Dickinson, W. B.; Lang, P. C. *Tetrahedron Lett.* **1967**, *8*, 3035–3040. doi:10.1016/S0040-4039(00)90910-9
- Bousfield, T. W.; Kimber, M. C. *Tetrahedron Lett.* **2015**, *56*, 350–352. doi:10.1016/j.tetlet.2014.11.093
- Corbel, B.; Paugam, J.-P.; Dreux, M.; Savignac, P. *Tetrahedron Lett.* **1976**, *17*, 835–838. doi:10.1016/S0040-4039(00)92897-1
- Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2006**, *110*, 10478–10486. doi:10.1021/jp0630626
- Lee Woodcock, H. F.; Schaefer, A., III; Schreiner, P. R. *J. Phys. Chem. A* **2002**, *106*, 11923–11931. doi:10.1021/jp0212895
- Montgomery, J. A., Jr.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **1999**, *110*, 2822–2827. doi:10.1063/1.477924
- Montgomery, J. A., Jr.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **2000**, *112*, 6532–6542. doi:10.1063/1.481224
- Parthiban, S.; Martin, J. M. L. *J. Chem. Phys.* **2001**, *114*, 6014–6029. doi:10.1063/1.1356014
- Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215–241. doi:10.1007/s00214-007-0310-x
- Chai, J.-D.; Head-Gordon, M. *J. Chem. Phys.* **2008**, *128*, 084106. doi:10.1063/1.2834918
- Grimme, S. *J. Comput. Chem.* **2006**, *27*, 1787–1799. doi:10.1002/jcc.20495
- Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999–3093. doi:10.1021/cr9904009
- Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417–2420. doi:10.1021/ol020097p
- Bew, S. P.; Hiatt-Gipson, G. D.; Lovell, J. A.; Poullain, C. *Org. Lett.* **2012**, *14*, 456–459. doi:10.1021/ol2029178
- Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zifcsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459–466. doi:10.1016/S0040-4020(00)01014-0
- Fenández, I.; Monterde, M. I.; Plumet, J. *Tetrahedron Lett.* **2005**, *46*, 6029–6031. doi:10.1016/j.tetlet.2005.07.013
- Navarro-Vázquez, A.; Rodríguez, D.; Martínez-Esperón, M. F.; García, A.; Saá, C.; Domínguez, D. *Tetrahedron Lett.* **2007**, *48*, 2741–2743. doi:10.1016/j.tetlet.2007.02.056
- Katritzky, A. R.; Ramer, W. H. *J. Org. Chem.* **1985**, *50*, 852–856. doi:10.1021/jo00206a026
- Mahamoud, A.; Galy, J. P.; Vincent, E. J.; Barbe, J. *Synthesis* **1981**, *1981*, 917–918. doi:10.1055/s-1981-29651
- Gaussian 09*, Revision A.02; Gaussian, Inc.: Wallingford, CT, U.S.A., 2009.
- Serena Software Box 3076 Bloomington, IN 47402-3076.

## License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (<http://www.beilstein-journals.org/bjoc>)

The definitive version of this article is the electronic one which can be found at:  
[doi:10.3762/bjoc.11.156](https://doi.org/10.3762/bjoc.11.156)