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Synthesis of β-Lactams from a *N*-Rhenaimine: Effect of the Transition Metal on the Energetic Profile of the Staudinger Reaction

Eva Hevia,[†] Julio Pérez,*[,†] Víctor Riera,[†] Daniel Miguel,[§] Pablo Campomanes,[‡] M. Isabel Menéndez,[‡] Tomás L. Sordo,[‡] and Santiago García-Granda[‡]

Departamentos de Química Orgánica e Inorgánica-IUQOEM y de Química Física y Analítica, Universidad de Oviedo, 33071 Oviedo, Spain, and Departamento de Química Inorgánica, Facultad de Ciencias, Universidad de Valladolid, 47071 Valladolid, Spain

Received January 8, 2003; E-mail: japm@sauron.quimica.uniovi.es

The synthesis of β-lactams attracts considerable interest due to the presence of the 2-azetidinone ring in several types of natural and unnatural antibiotics.[1] The formal [2 + 2] cycloaddition of imines and ketenes, termed Staudinger reaction, is one of the most employed synthetic methods because of its simplicity and wide availability of substrates. Its mechanism has been extensively studied from experimental[2] and theoretical[3] perspectives, and the most generally accepted model consists of an initial imine attack to the ketene carbonyl carbon to afford a zwitterionic intermediate, followed by a conrotatory [2 + 2] cycloaddition to form the final product (see Scheme 1).[4]

We have recently found that the alkylideneamido complex [Re(N=CPh$_2$)(CO)$_3$(bpy)] (**1**) (bpy= 2, 2′-bipyridine), whose structure allows it to be considered as a N-rhenaimine,[5] reacts with alkyl and aryl isocyanates to afford products related to those obtained using *N*-silylimines. However, the reaction takes place at considerably lower temperatures, indicating that the presence of the transition metal fragment reduces the reaction kinetic barrier. We have extended now these studies to the reaction of **1** with ketenes, and here we report our results.

Complex **1** reacts with diphenylketene to afford, as single product, complex **2** (see Scheme 2), which could be isolated in good yield by crystallization and was characterized by elemental (C, H, N) analysis, IR and NMR (^{1}H and ^{13}C) and single-crystal X-ray diffraction. The IR spectrum shows three intense ν_{CO} stretches diagnostic of a *fac*-Re(CO)$_3$ fragment, which occur at wavenumber values some 15 cm^{-1} higher than those of the precursor **1**, as expected for the reaction of **1** with an electrophile. In addition, the carbonyl group within the β-lactam ring gives rise to a medium intensity band at 1668 cm^{-1}. The ^{13}C NMR spectrum of **2** contains two sets of signals for the bpy, carbonyl and β-lactam groups (in an approximate 1:1 ratio), a fact attributed to the presence of two rotamers resulting from hindered rotation around the Re−N(β-lactam) bond. Each rotamer features three ^{13}C NMR signals due to the three carbons which, along with nitrogen, constitute the four-membered cycle. The solid-state structure of **2**, shown in Figure 1, consists of a [Re(CO)$_3$(bpy)] fragment acting as a substituent on the nitrogen atom of a β-lactam ring. No previous examples of transition metal N-substituted β-lactams are known. This nitrogen, N(3), along with C(6), has its origin on the alkylideneamido ligand of complex **1**, whereas C(4) and C(5), which complete the β-lactam ring, result from diphenylketene. The sum of angles around N(3), 358.4°, reveals a nearly planar geometry, attributable to delocalization of the nitrogen lone pair involving the carbonyl group.[6] Accordingly, the C(4)−N(3) distance (1.338(7) Å) is appreciably shorter than C(6)−N(3) (1.523(6) Å). The distances and angles within the β-lactam ring are comparable with those found in the β-lactams whose structures have been determined by X-ray diffraction.[7]

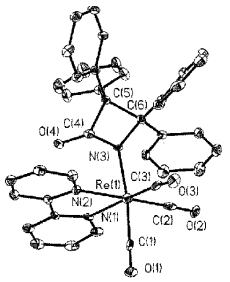
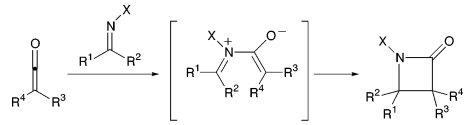
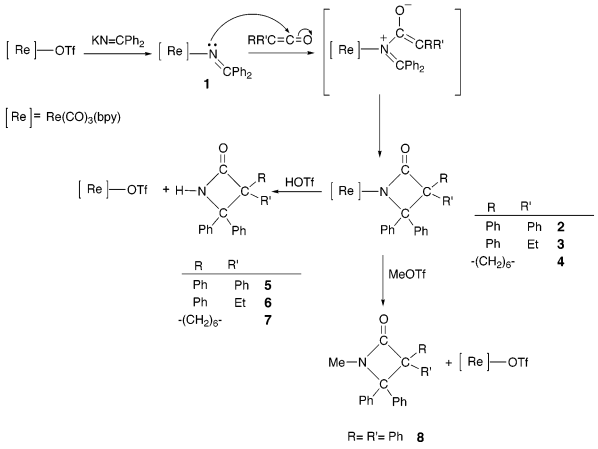


Figure 1. Molecular structure and numbering scheme of **2**.

Scheme 1



Scheme 2



Although transition metal complexes have been previously employed for the stoichiometric[8] or catalytic synthesis[9] of β-lactams, the reaction leading to **2** is, to the best of our knowledge, the only example of a β-lactam synthesis in which the N−C moiety originates from a transition metal complex. Using complexes with chiral chelates instead of the bpy ligand could lead to asymmetric induction in the synthesis of chiral β-lactams.

2 reacts with methyl triflate, affording the free *N*-methyl-β-lactam and the complex [Re(OTf)(CO)$_3$(bpy)] (which has been the precursor of complex **1**).[5] The fact that a single β-lactam is obtained

[†] Departamento de Química Orgánica e Inorgánica-IUQOEM, Universidad de Oviedo.
[‡] Departamento de Química Física y Analítica, Universidad de Oviedo.
[§] Universidad de Valladolid.

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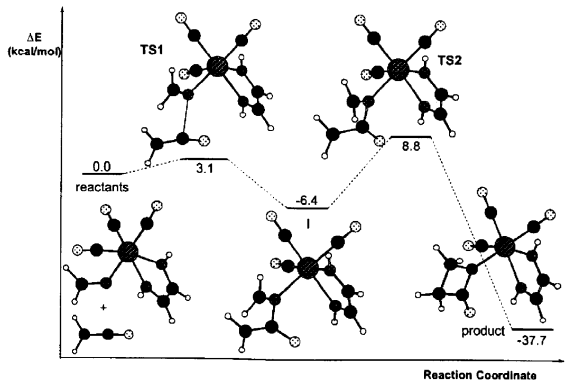

Figure 2. B3LYP/6-31+G*(LANL2DZ effective core potential for Re) relative electronic energy profile including ZPVE for the reaction between ketene and $[Re(N{=}CH_2)(CO)_3(N_2C_2H_4)$.

strongly supports that the presence of two sets of signals in the ^{13}C NMR spectrum of **2** is due to two rotamers (vide supra). **1** also reacts with ethylphenylketene and cycloheptylketene to afford **3** and **4**, respectively (see Scheme 2), which could be demetalated by treatment with MeOTf to give the corresponding *N*-methyl-β-lactams and the rhenium triflate complex. Triflic acid can also be used as demetallating agent; thus, its reaction with **2** produces the N−H β-lactam as shown in Scheme 2.

The closer precedent of the reaction of diphenylketene with **1** is the reaction with the imine $Ph_2C{=}N(SiMe_3)$.[10] Despite the enhanced reactivity against electrophiles shown by *N*-silylimines, the reaction of $Ph_2C{=}C{=}O$ with $Ph_2C{=}N(SiMe_3)$ requires 2 equiv of the ketene to obtain the β-lactam via reaction of 1 equiv to give an intermediate azabutadiene which subsequently reacts with a second equivalent to afford a N-acylated β-lactam.[11] The formation of β-lactams from *N*-silylimines and a single equivalent of ketene requires forcing conditions (T = 100 °C) to achieve ring closure;[12] in contrast, the reaction of **1** with diphenylketene takes place instantaneously at −78 °C.

A theoretical analysis has been carried out to gain information on the causes of the difference. DFT calculations (see details in Supporting Information) on the model reaction between ketene and $[Re(N{=}CH_2)(CO)_3(N_2C_2H_4)]$ render an electronic energy profile (including the zero-point vibrational energy correction (ZPVE)) that corresponds to a two-step mechanism (see Figure 2). Ketene and the *N*-metallaimine interact through a first transition state (TS), **TS1**, with an energy barrier of 3.1 kcal/mol, to yield the intermediate **I**, 6.4 kcal/mol more stable than the separate reactants. Finally, **I** transforms into the β-lactam product after surmounting a second TS, **TS2**, 8.8 kcal/mol less stable than reactants. This energy profile allows us to rationalize the behavior of the system experimentally observed. Thus, **TS1** is earlier and more stable than the corresponding TS found for the reaction between ketene and formaldimine.[13] On the other hand, the rate limiting **TS2**, presents a much greater relative stability than the corresponding TS when formaldimine is used (21.3 kcal/mol),[13] in accordance with the fast reaction between **1** and diphenylketene. The enhancement of the nucleophilicity of the imine N atom due to the presence of the metallic substituent causes the first TS to occur at a larger distance between the reactants (2.427 Å in **TS1** versus 1.745 Å in the corresponding TS for the ketene−formaldimine reaction[13]) and, consequently, with a smaller charge transfer from the imine (0.15e compared to 0.21e). The formation of the C−N bond at **I** produces a larger charge transfer (0.40e) than in the absence of the metallic substituent (0.29e). As a result, the difference in charge between the two remaining C atoms of the β-lactam ring increases and the conrotatory electrocyclic closure leading to the final β-lactam has a much lower energetic cost than for the ketene−formaldimine reaction.

To conclude, we have reported the first Staudinger reaction of a transition metal *N*-metallaimine, which is considerably faster than related reactions of nonmetal-substituted or *N*-silylimines. This diference was rationalized in terms of the different location of the intermediates and transition states in the reaction profile using the results of DFT calculations.

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Note Added after ASAP Publication: The title contained a misspelling in the version published on the Web 3/5/2003. The final Web version published 3/10/2003 and the print version are correct.

Supporting Information Available: Complete details for the synthesis of all compounds and spectroscopic data for **2** (PDF); X-ray crystallographic data for **2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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