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Preparation of $^{13}C_4$-6-Methyl Anthranilic Ester via a Diels–Alder-Type Process. An Experimental and Theoretical Study to Characterize an Unexpected Isotope Exchange

J. Lorenzo Alonso-Gómez,[||] Yolanda Pazos,[†,§] Armando Navarro-Vázquez,[‡] Johan Lugtenburg,[†] and M. Magdalena Cid*[,||]

Departamento de Química Orgánica, Universidade de Vigo, 36310 Vigo, Spain, Laboratorio de Endocrinología Molecular, Área de Investigación del Complejo Hospitalario Universitario de Santiago de Compostela, 15706 Santiago de Compostela, Spain, Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15706 Santiago de Compostela, Spain, and Leiden Institute of Chemistry, Gorlaeus Laboratory, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands

mcid@uvigo.es

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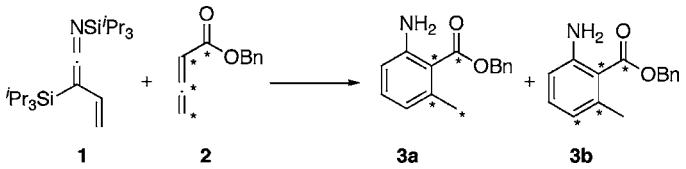
ABSTRACT



1 **2** **3a** **3b**

Buta-2,3-dienoate reacts with vinyl ketenimine to give the corresponding substituted aniline through a Diels–Alder cycloaddition. Besides the expected Diels–Alder adduct 3a, the aniline 3b was also obtained in a ratio of 91:9. The observed ^{13}C exchange is explained on the basis of a reversible [2 + 2] cycloaddition competing with the [4 + 2] process. This is supported by B3LYP DFT computations, as a stepwise pathway lies very close in energy to the [4 + 2] concerted one.

It has been reported that a vinyl ketenimine and a dienophile undergo a [4 + 2] cycloaddition reaction in such a way that the terminal vinylic carbon becomes attached to the electron-deficient carbon of the dienophile partner, the dienophile being an alkene[1] or an alkyne.[2] In fact this is a very convenient method to synthesize either cyclohexanones or substituted anilines.[3] We successfully have used 2,*N*-bistri-isopropylsilyl-1,3-butadiene ketenimine (**1**) and methyl 2-butynoate in the synthesis of anthranilic acid.[4] For our biochemical studies it was necessary to introduce ^{13}C-labeling in the aromatic core, but when we approached the synthesis of benzyl (1,2,3,4-$^{13}C_4$)-2-butynoate using a reported procedure,[5] the compound we obtained instead was the corresponding allene isomer **2**. However, we envisioned that these allenes could also be used as the dienophile partners in a Diels−Alder reaction with vinyl ketenimine in order to obtained substituted anilines.

[||] Universidade de Vigo.
[†] Leiden University.
[‡] Universidade de Santiago de Compostela.
[§] Complejo Hospitalario Universitario de Santiago de Compostela.

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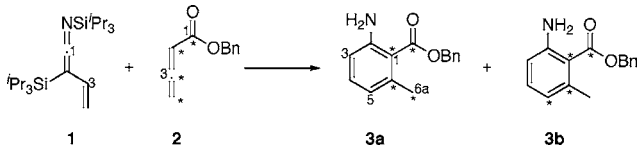
Here we report our findings regarding the cycloaddition reaction between the 2,*N*-bistriisopropylsilyl-1,3-butadiene ketenimine (**1**)[6] and benzyl (1,2,3,4-$^{13}C_4$)-2,3-butadienoate (**2**)[7]. Thus, when a mixture of ketenimine **1** and allene **2** was heated in toluene at 150 °C for 19 h, benzyl 6-methyl-2-(*N*-triisopropylsilyl)amino-3-triisopropylsilyl benzoate was initially afforded, which was desilylated using HCl and potassium fluoride in methanol under reflux for 2 h, giving the aniline **3a** and **3b** in 46% overall yield (Scheme 1).

Scheme 1. Preparation of Methyl Anthranilic Ester



The ^{1}H NMR spectra of benzyl 6-methylanthranilic ester (Figure 1) showed not only the expected ^{13}C-labeled product

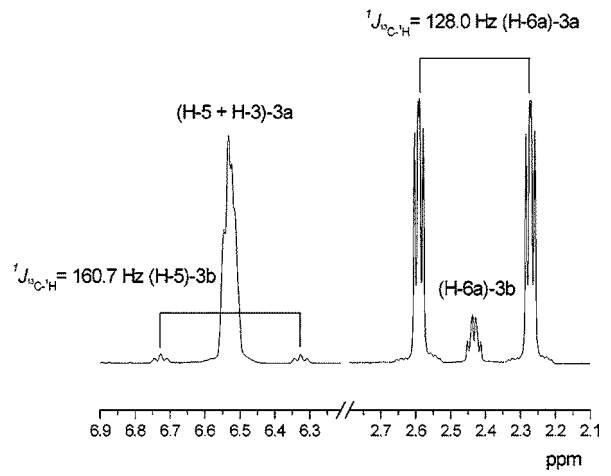


Figure 1. 400 MHz ^{1}H NMR spectrum of isotopomers **3a** and **3b** in CD_3Cl.

3a, 2.43 (ddd, J = 128.0, 5.9, 4.0 Hz, H-6a) and 6.53 (m, H-5) ppm, but also the isotopomer **3b**, 2.43 (dd, J = 5.5 and 4.1 Hz, H-6a) and 6.53 (dt, J = 160.7 and 7.1 Hz, H-5). The ^{13}C NMR showed an intense characteristic signal for C-5: 120.4 (dd, J = 58.6 and 4.6 Hz) ppm. These signals indicated that there was a minor amount of a compound not labeled in the expected methyl at C-6 position but in the C-5 aromatic carbon, as denoted by the presence of the double triplet centered at 6.53 ppm and double doublet at 2.43 ppm and supported by the increased ^{13}C signal at 120.4 ppm in the ^{1}H-decoupled carbon spectrum indicating that C-5 has been ^{13}C-enriched. The ratio between them was determined to be 91:9 by measuring the integral of the whole area of resonance between 2.25 and 2.60 ppm and that of the area corresponding to the signal at 2.43 ppm, this new signal being due to the ^{13}C labeling-loss of the methyl group. (Figure 1).

On the basis of these facts, this intriguing result could be explained by a curious and unexpected exchange of carbons between the diene and dienophile moieties during the cycloaddition as illustrated in Scheme 2.

Thus, we propose the bisallylic biradical **4** as the key intermediate that would lead to the expected compound **6a**, bissilylated tautomer of **3a**, (path i) or instead could rotate 180° around C-5−C-6 bond (path ii) to yield the crucial cyclobutyl derivative **5** through a [2 + 2] cycloaddition. Next, compound **5** could provide, via a retro [2 + 2] reaction, biradical **4a** or the isotopomer **4b**, depending on which bond is broken, that would ultimately afford compound **6b**, bissilylated tautomer of compound **3b**.

To validate this mechanistic proposal we carried out a computational study on the different possible pathways this process may follow. To reduce computer costs and complexity of the potential surface we used vinyl ketenimine **1c** (R = H) and allene aldehyde **2c** (R′ = H) as a model system, whose reaction energetics should not be essentially different from that of the experimental system.

The mechanism proposed in this work involves several open-shell singlet biradicals as intermediates. It is known that DFT, specially hybrid functionals, can efficiently handle biradical species[8] in medium-large-sized systems when broken-spin symmetry Kohn−Sham determinants (UBS)[9] are used.

All structures in this work have been optimized at the B3LYP[10]/6-31+G*[11] level of theory, using an unrestricted approach for open-shell singlet and triplet species. Wave function stability checks[12] have been performed on species with potential external instabilities. Harmonic frequencies have been computed analytically to characterize stationary

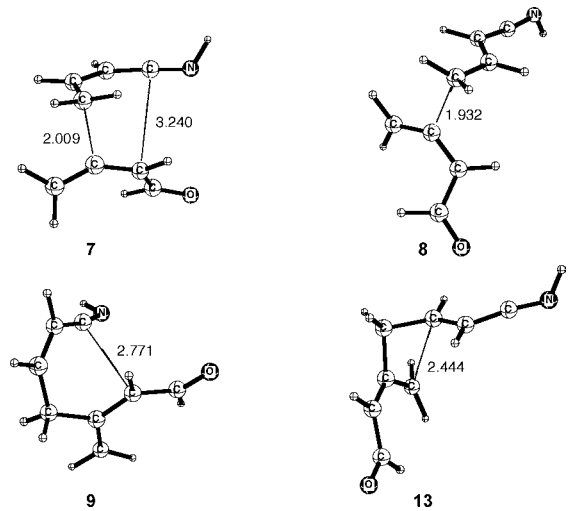
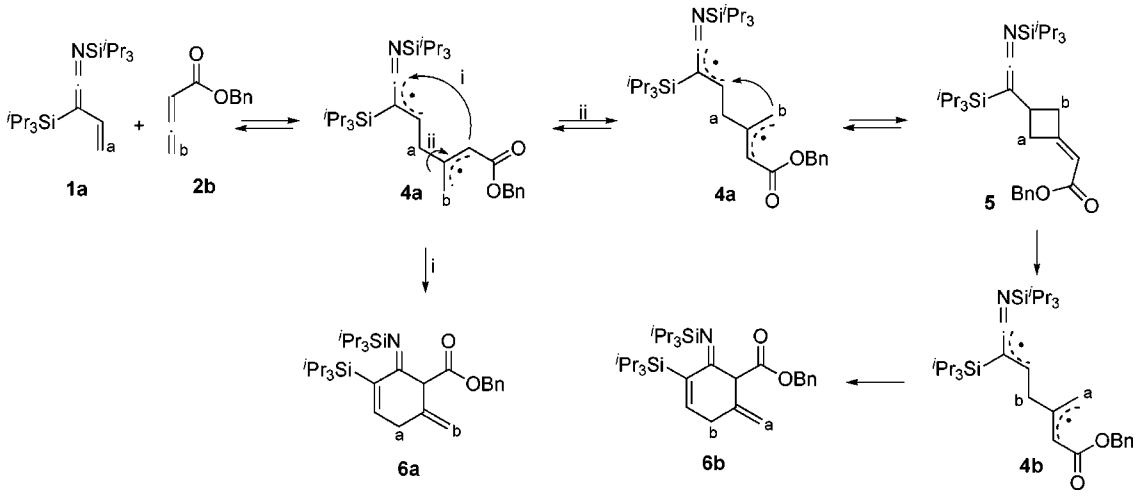


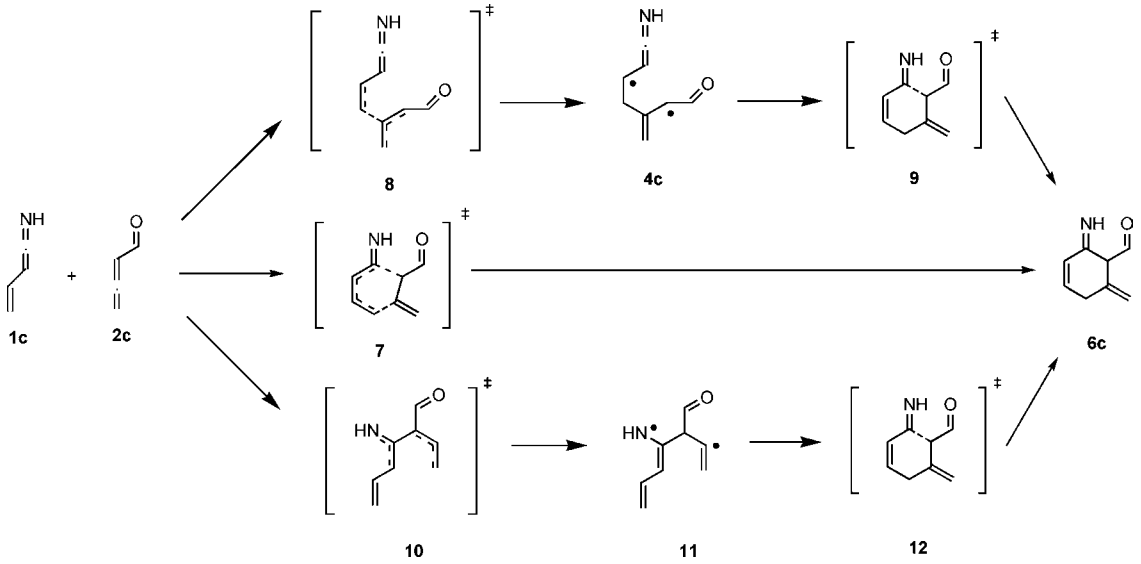
Figure 2. B3LYP/6-31+G* transition structures in the concerted and stepwise pathways for **1c** + **2c** [4 + 2] and [2 + 2] cycloadditions. Bonds distances are given in Å.

(6) It was prepared as reported in ref 2.

Scheme 2. Plausible Mechanism for the Exchange of Position a and b



Scheme 3. Proposed Mechanism for the Cycloaddition Reaction



points and to get ZPVE corrections and free energies. All computations were performed with the Gaussian03 package.[13]

The concerted transition structure **7** for cycloaddition of ketenimine **1c** and allene **2c** to give the adduct **6c** has a very asynchronous nature, with the C-5−C-6 bond being much shorter than the C-1−C-2 (2.009 vs 3.240 Å) (Figure 2).

However this structure is well described by a restricted determinant and does not present any RHF → UHF instability. Reaction and activation free energies ($\Delta G_{423.15K}$) for this process are −22.8 and 40.6 kcal/mol, respectively, and formation of singlet biradical **4c** can take place with a close barrier of 41.6 kcal/mol through transition structure **8** (shown in Figure 2). Hence, the stepwise biradical pathway can compete efficiently with the concerted reaction. The low cycloaddition yield (46%) could also be interpreted as evidence for a stepwise vs a concerted mechanism.[14]

An alternative pathway beginning with C-1−C-2 formation is much more disfavored as a result of the vinylic nature of the formed singlet biradical **11**, with a high barrier of 56.4 kcal/mol, corresponding to transition structure **10**. Biradical **11** is predicted to be 43.6 kcal/mol higher in energy than the reactants. (Scheme 3)

(7) Its synthesis is given in Supporting Information from benzyl 3-oxobutanoate, which was prepared from ethyl oxobutanoate: Mottet, C.; Hamelin, O.; Garavel, G.; Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1380.

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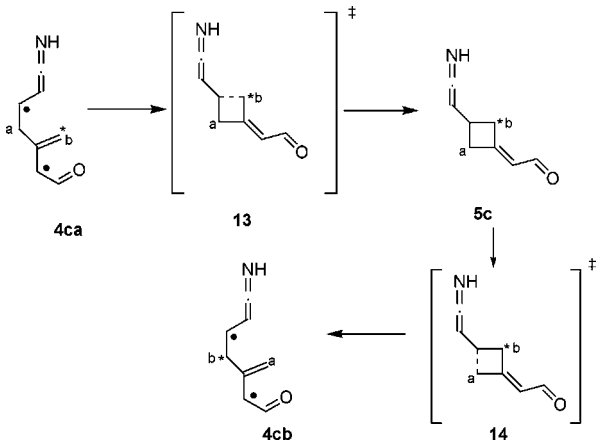
Table 1. Enthalpies and Free Energies (kcal/mol) for All Computed Species

species	**7**^{endo}	**7**^{exo}	**6c**	**8**	**4c**	**9**	**10**	**11**	**12**	**13**	**5c**	**14**
$\Delta H_0{}^a$	23.4	25.7	−42.8	25.2	9.6	13.3	39.6	28	32.3	16.4	−19.0	15.6
$\Delta G_{423.15K}{}^a$	40.6	43.0	−22.8	41.6	25.5	32.0	56.4	43.6	50.5	34.6	−0.9	33.9

[a] Relative to **1c** + **2c**.

The biradical pathway opens the possibility of a [2 + 2] cyclization to give the cyclobutyl derivative **5c**. Collapse from singlet biradical **4ca** to closed-shell species **5c** takes place with a low barrier ($\Delta G_{423.15K}$) of 9.1 kcal/mol. This species can revert to singlet biradical **4cb** through transition state **14** with an associated barrier of 34.8 kcal/mol, this last step being responsible for the exchange of the ^{13}C labels (Scheme 4). This study shows that using stable isotopes in conjunction with theoretical methods gives structural and functional information about otherwise completely hidden processes.

Scheme 4. Stepwise [2 + 2] Cycloaddition



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Supporting Information Available: Cartesian coordinates for all computed structures; tables with absolute, ZPVE energies, imaginary frequencies and representation of associated vectors; experimental procedures; characterization for compounds **2** and **3** (^{1}H NMR, ^{13}C NMR, HRMS); and full Gaussian03 citation. This material is available free of charge via the Internet at http://pubs.acs.org.

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