ORGANIC LETTERS

2011
Vol. 13, No. 22
6054–6057

A Computational Reinvestigation of the Formation of *N*-Alkylpyrroles via Intermolecular Redox Amination

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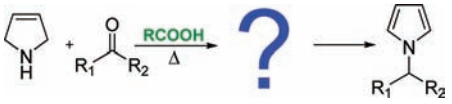
Received September 17, 2011

ABSTRACT



A detailed mechanism of *N*-alkylpyrrole formation from 3-pyrroline and 2-phenylpropanal in the presence of a Brønsted acid catalyst was investigated in depth using the MP2 and DFT theories. The two mechanisms proposed earlier in recent literatures for this internal redox process were evaluated and were found not to account perfectly for the transition state and the energetic barrier of its formation. Based on the present calculations, a new mechanism was put forth.

Redox isomerization that shows perfect redox economy has gained heightened attention in present-day organic synthesis.[1] Recently, as one of the redox neutral methods, thermal and acid catalyzed redox aminations have been intensively explored to construct polycyclic compounds and have now become a versatile method for the synthesis of important building blocks in the total synthesis of bioactive natural products.[2]

Because of the renowned importance of pyrrole-based heterocycles in many natural products,[3] medicinal agents,[4] and functional materials,[5] substantial attention has been paid to develop efficient methods for pyrroles synthesis.[6,7] In a recent publication, Tunge et al. reported an intriguing and efficient redox neutral approach to synthesize *N*-alkylpyrroles. Starting from 3-pyrroline and aldehydes, ketones, or lactols, a variety of *N*-alkylpyrroles could be prepared in excellent yields in the presence of a mild

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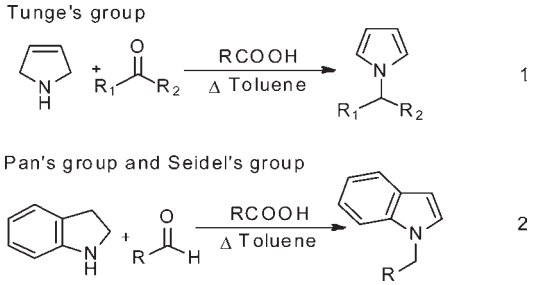
10.1021/ol2025247 © 2011 American Chemical Society
Published on Web 10/20/2011

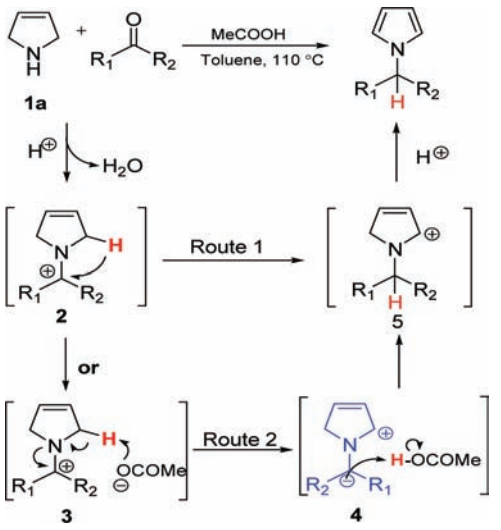
Brønsted acid catalyst (eq 1, Scheme 1).[8] More recently, Pan's group and Seidel's group reported independently a facile redox amination for the synthesis of *N*-alkylindoles from indolines and aldehydes (eq 2, Scheme 1).[9]

Scheme 1. Redox Amination Reactions Reported[8,9]



Despite the sound development of these reactions, their mechanisms remain controversial. Different mechanistic rationales were proposed for these redox isomerization processes. The iminium ion **2** and **5** were proposed to be two likely intermediates involved in these processes, and the transformation between them was proposed via a direct 1,3-hydrogen shift process (Route 1, Scheme 2).[8,9a,10] In addition, Seidel et al. put out a stepwise 1,3-hydrogen shift pathway in which the azomethine ylide (**4**) was proposed as a significant intermediate (Route 2, Scheme 2).[9b]

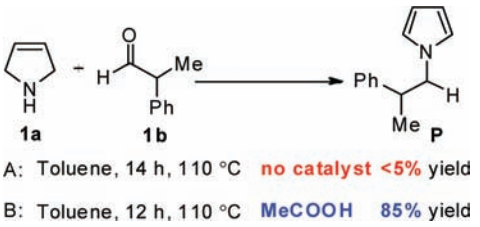
Scheme 2. Redox Neutral Pyrrole Formation and Possible Mechanistic Rationales



Our interests in the computational resolution of complex reaction mechanisms prompted us to carry out an in-depth computational study of the acid catalyzed redox amination. Here we present a clear elucidation of the reaction mechanism of the Brønsted acid catalyzed redox isomerization and a detailed understanding of the energy surfaces and structures of the intermediates and transition states involved in these transformations. It is believed that the important findings in the present work should be helpful to synthetic chemists in the design of new catalytic reactions.

All calculations were carried out with the GAUSSIAN 03 packages[11] mounted on the NKStar Supercomputer. The MP2 and DFT computational details and the corresponding data are listed in the Supporting Information. Since the acetic acid and benzoic acid were found to have similar catalytic effects for this type of transformation and can be used interchangeably,[8] we chose, for convenience, the acidic acid catalyzed reaction of 3-pyrroline (**1a**) with

Scheme 3. Tunge's Redox Neutral Pyrrole Formation in the Absence/Presence of an Acetic Acid Catalyst



2-phenylpropanal (**1b**) (Scheme 3) as a model reaction in this study. The computed potential-energy surfaces for this model reaction are given in Figures 1 and 2.

The first step is the nucleophilic addition of amine to the carbonyl group. In the absence of catalyst, the reaction of 3-pyrroline (**1a**) with 2-phenylpropanal (**1b**) via a four-membered transition state (**TS1a**) yielding a carbinolamine intermediate (**IN1**) required an activation free energy of 32.5 kcal/mol at the MP2 level in toluene (Figure 1). In the presence of acetic acid, the formation of **IN1** was found to proceed via an acid assisted transition state (**TS1b**) transferring a proton, which required an activation barrier of only 9.2 kcal/mol (Figure 1), 23.3 kcal/mol lower than that for the uncatalyzed process. This should be the reason that acetic acid is indispensable for this transformation.[8]

The intrinsic reaction coordinate (IRC) calculation shows that the dehydration of **IN1** catalyzed by acetic acid passes through **TS2** which leads to a complex with a barrier of 17.3 kcal/mol in toluene (**Complex 1**, Figure 1). The complete removal of water yields the isolated **IN2**, but NOT a free iminium ion as proposed in literature,[8,9] which is 3.7 kcal/mol higher in free energy than the reactants.

Extrusion of the acetic acid molecule from **IN2** via a seven-membered transition state (**TS4**) leads to the formation of ylide intermediate **IN3**, which requires an activation

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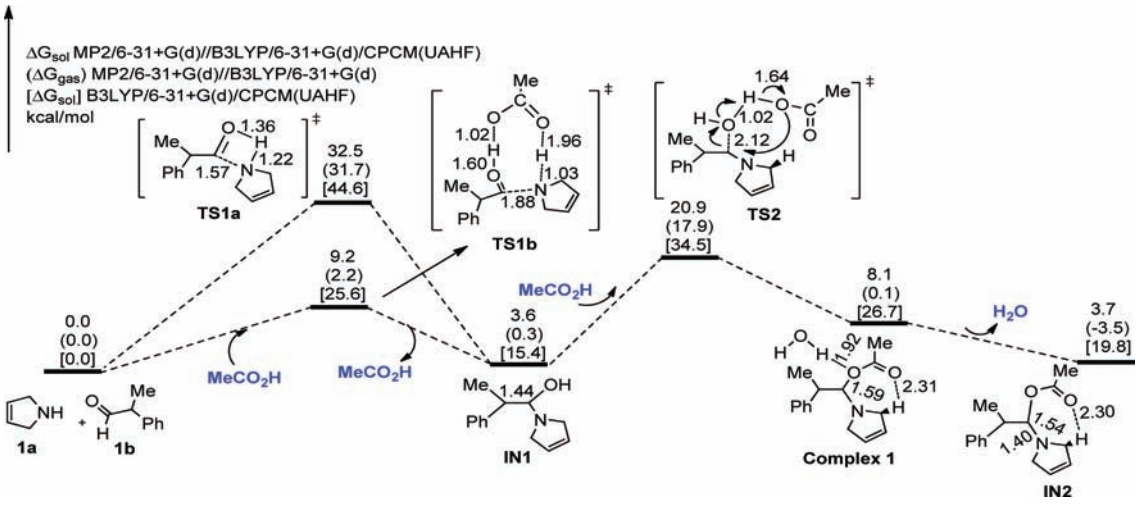

Figure 1. MP2 and DFT computed energy surface for the reaction of 3-pyrroline with 2-phenylpropanal in the presence of an acetic acid catalyst yielding **IN1** and **IN2**.

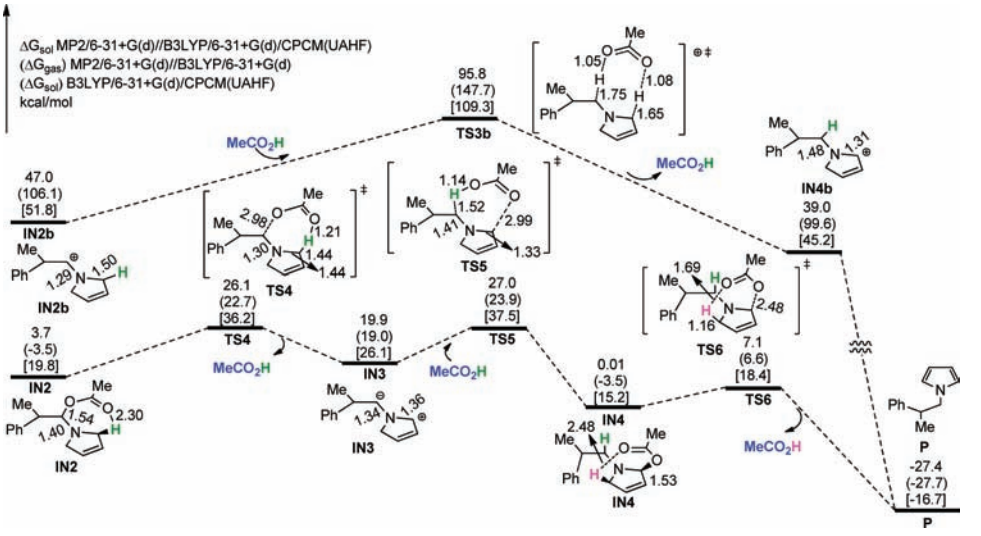

Figure 2. MP2 and DFT computed energy surface for the reaction of 3-pyrroline with 2-phenylpropanal in the presence of an acetic acid catalyst from **IN2** to the final pyrrole (**P**).

free energy of 22.4 kcal/mol in toluene (Figure 2). The hyperconjugative interaction of the lone-pair electrons of N1 with the σ^* C2−O3 orbital and σ^* C4−H5 orbital in **IN2** would weaken and polarize the C−O and C−H bond (LpN1→σ^* C2−O3 = 31.2 kcal/mol, LpN1→σ^* C4−H5 = 5.3 kcal/mol), thus facilitating this process (Figure 3).[12,13] Subsequently, the protonation of the ylide intermediate **IN3** results in a new intermediate **IN4**, requiring an activation free energy of 7.1 kcal/mol via **TS5** in toluene (Figure 2). The final step is to transform the intermediate **IN4** to the final pyrrole (**P**) and to regenerate the acetic acid catalyst. This process via a seven-membered transition state (**TS6**) requires only 7.1 kcal/mol of activation free energy. This process would also be facilitated by the hyperconjugative interaction of the lone-pair electrons of N1 with the σ^* C4−O6 orbital and σ^* C7−H8 orbital in **IN4** (LpN1→σ^* C4−O6 = 24.2 kcal/mol, LpN1→σ^* C7−H8 = 6.2 kcal/mol) (Figure 3). The whole

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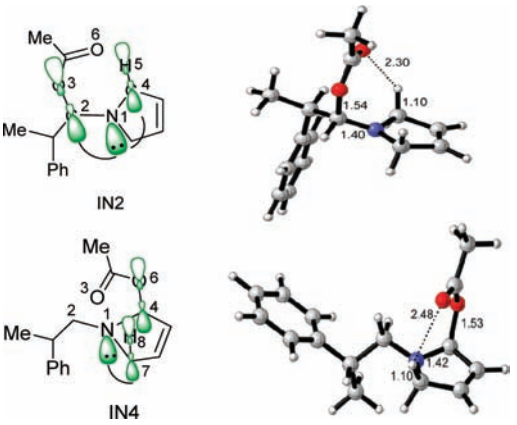

Figure 3. Hyperconjugative interaction of the lone-pair electrons of N with the σ^* C−O orbital and σ^* C−H orbital in **IN2** and **IN4**.

reaction is exergonic with 27.4 kcal/mol (Figure 2). The thermodynamic preference of an aromatic pyrrole would be the driving force for the redox isomerization reaction.

A free iminium ion intermediate was proposed in this rearrangement previously.[8,9] But, we were unable to locate a transition structure connecting **IN1** (or **IN2**) and the free iminium ion intermediate **IN2b**. Moreover, the computational energy of **IN2b** is about 20 kcal/mol higher than that of **TS4** or **TS5** (Figure 2), indicating that the free iminium ion was not likely to exist in the rearrangement coordinate in the presence of an acetic acid catalyst. Furthermore, the located transition state structure (**TS3**) (see Supproting Information Figure 2S) which corresponds to the direct 1,3-hydride transfer process has a free energy of 61.2 kcal/mol in the potential energy surface. Even the transition state (**TS3b**) corresponding to the acid assisted 1,3-hydrogen shift process also has an energy of 48.8 kcal/mol, which is much higher than that of our proposed process (Figure 2). So the direct 1,3-hydrogen transfer process is kinetically unfeasible and can be ruled out.[14]

Reviewing the MP2 energy profile of the overall reaction pathway (Figures 1 and 2), we find that the protonation of ylide intermediate **IN3** is the rate-limiting step, with an activation free energy of 27.0 kcal/mol in toluene. This is in accordance with the experimental observation that the ylide intermediate can be trapped by a dipolarophile group.[9b] On the other hand, by careful checking of the details of potential energy surfaces, one is able to find a remarkable result that the acetic acid catalyst actually plays a crucial role in every step of the overall reaction pathway. This implies that the synthesis reaction might be more efficient by judicious selection of a Brønsted acid catalyst.

In summary, the present computational study on the detailed processes of *N*-alkylpyrrole formation via the acid catalyzed reaction of 3-pyrroline and aldehydes has given important mechanistic insight into this redox isomerization reaction. It reveals that the one-step direct 1,3-hydrogen shift process proposed previously seems not to be valid owing to its very high activation energy requirement, although it is still the often assumed process for some redox isomerization reactions.[15] Our MP2 and DFT computation results suggest that the process involving formation of the acetic acid assisted azomethine ylide intermediate should be the most likely process and the free imimium ion intermediate should not likely be involved in the rearrangement pathway. This indicated that the stepwise 1,3-hydrogen shift process via an acid assisted intermolecule process involving free imimium ion intermediates should also be impossible. On the basis of our calculation results, it is clear that the acid catalyst plays a crucial role in redox amination reactions.

Acknowledgment. This work was supported by the Natural Science Foundation (Grant No. 51173083).

Supporting Information Available. The computational method, Cartesian coordinates and energies for the computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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