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The Coupling of Isonitriles and Carboxylic Acids Occurring By Sequential Concerted Rearrangement Mechanisms

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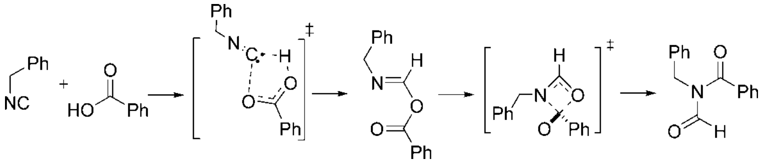
ABSTRACT



Mechanisms for the recently described reactions of isonitriles with carboxylic acids (Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* 2008, *130*, 5446) are explored with the B3LYP density functional method. The mechanism involves the formation of a carboxylate mixed formimidic anhydride intermediate via a concerted mechanism. This intermediate is then transformed to an *N*-formylamide by a concerted pseudopericyclic [1,3]-acyl shift. Mechanisms involving zwitterions or diradicals are discounted.

The coupling of isonitriles with carbonyl compounds in multicomponent reactions such as the Passerini and Ugi reactions is well documented.[1] While these transformations are typically three- and four-component reactions, we have recently shown that the combination of just two of these components is effective in generating new compounds. Therefore, benzylisonitrile (**1**) and benzoic acid (**2**) react under microwave conditions to give *N*-formylamide **4** in 83% yield (Scheme 1).[2] This reaction can be applied to a number of isonitrile and carboxylic acid coupling partners with yields ranging from 50 to 85%. A mixed anhydride intermediate **3**, which was not isolated is presumably formed during this process, then immediately rearranges to form the *N*-formylamide. Notably, Rebek and co-workers have recently demonstrated that encapsulation of similar reactants inside a self-assembled molecular cavitand results in a remarkable acceleration in the rate of reaction.[3] In this case, it was possible to observe the formation of the mixed anhydride intermediate.

Scheme 1 shows three possible pathways for the rearrangement of intermediate **3** via (a) the formation of a

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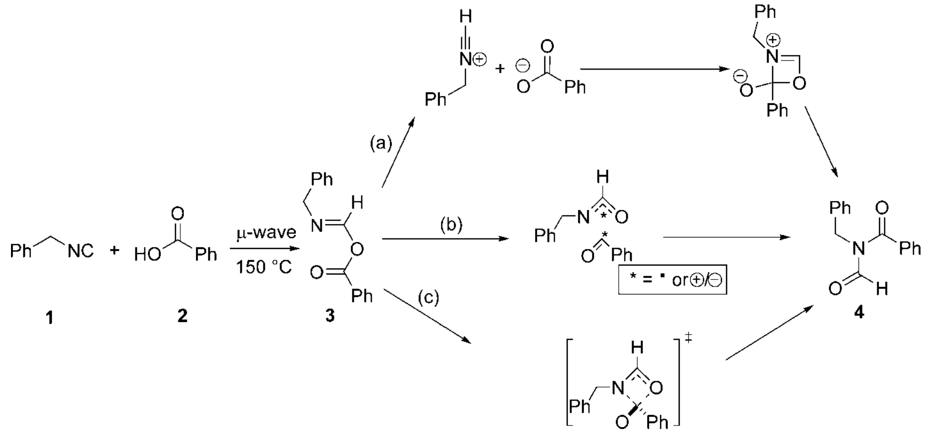
Scheme 1. Possible Mechanisms for the Rearrangement of **3** to **4**



zwitterionic oxazete intermediate via [2 + 2] cycloaddition of the benzylisonitrilium cation and the benzoate anion[4] or (b) a stepwise mechanism involving the formation of either a radical pair or polar intermediates. We have discovered that a third possibility, involving a concerted [1,3]-acyl shift (Scheme 1c),[5] is the operative mechanism in this transformation.

Calculations were performed with the B3LYP[6,7] density functional method and the 6-31+G(d,p) basis set using the Gaussian03[8] suite of programs to elucidate the most likely mechanism for the formation of the *N*-formylamide **4** by the reaction of benzylisonitrile, **1** (R_1 = Bn), with benzoic acid, **2** (R_2 = Ph). Energies of stationary points were corrected with single-point energies in chloroform calculated with the conductor-like polarizable continuum model (CPCM) using HF/6-31+G(d,p).[9]

The formation of the carboxylate mixed formimidic anhydride **3** by the reaction of **1** with **2** is exothermic by 13 kcal/mol in the gas phase ($\Delta H_{\mathrm{rxn}} = -8.4$ kcal/mol in chloroform). This intermediate could be formed by the direct insertion of the carbenoid form of the isonitrile into the O−H bond of the carboxylic acid or by a stepwise process involving the protonation of the isonitrile by the carboxylic acid prior to nucleophilic attack by the formed benzoate anion. In fact, only a single transition structure leading to **3** could be located involving the reaction between the isonitrile and carboxylic acid (Figure 1). In a mechanism reminiscent of both the Alder-ene[10−12] and cheletropic reactions,[13] this rearrangement involves the transfer of the proton from the O−H bond of benzoic acid to the terminal carbon of the isonitrile concomitant with "nucleophilic" attack by the carbonyl oxygen on the terminal carbon atom. This transition structure (TS) is five-centered and is distinct from the three-centered TS that would be involved in the direct insertion mechanism. The activation energy of this process is only 20 kcal/mol. The observed reactivity is presumably influenced by the carbenoid properties of the isonitrile reactant.

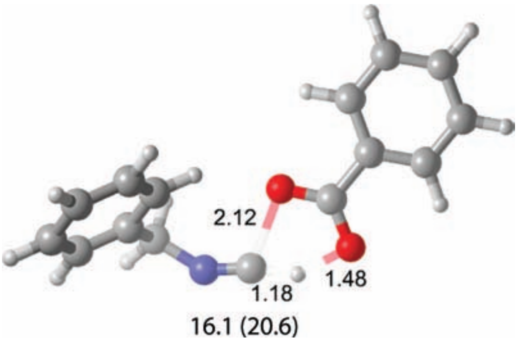


Figure 1. Transition structure for the formation of formimidic anhydride **3**. Activation enthalpies in the gas phase and chloroform (in parentheses) are shown.

The mechanisms postulated for the rearrangement of **3** to **4** were all investigated computationally. Notably, protonation of the terminal carbon of the isonitrile by benzoic acid to form the separated benzoate anion and the isonitrilium cation is endothermic by 55 kcal/mol in chloroform. This is 34 kcal/mol greater in energy than

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(4) Note that these two ionic intermediates could be directly formed from the starting materials, benzoic acid and benzylisonitrile.

(5) Both the formation of the oxazete intermediate and a mechanism similar to the [1,3]-acyl shift proposed herein have been suggested for the Mumm rearrangement, although the actual mechanism is not established. For details, see: (a) Brady, K.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2* **1980**, 121. (b) Schwarz, J. S. P. *J. Org. Chem.* **1972**, *37*, 2906. (c) Hoy, D. J.; Poziomek, E. J. *J. Org. Chem.* **1968**, *33*, 4050. (d) Curtin, D. Y.; Miller, L L. *J. Am. Chem. Soc.* **1967**, *89*, 637. (e) Curtin, D. Y.; Miller, L. L. *Tetrahedron Lett.* **1965**, 1869.

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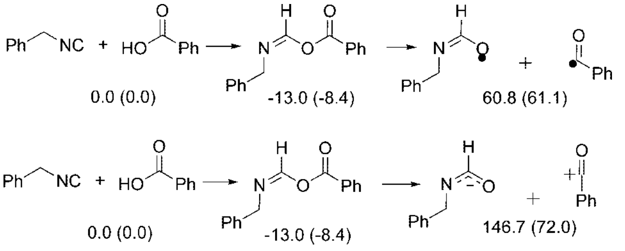
the concerted rearrangement in the same solvent, suggesting that the formation of **4** by a stepwise pathway is unlikely. All attempts to optimize the structure corresponding to a zwitterionic oxazete intermediate (Scheme 1, path a) resulted in the spontaneous formation of the carboxylate mixed formimidic anhydride **3**. Moreover, a transition structure corresponding to the formation of the zwitterionic oxazete via [2 + 2] cycloaddition could not be located. Instead, the benzyl anion was protonated by the isonitrilium cation, thereby leading to the regeneration of the carboxylic acid and isonitrile reactants.

Similarly, polar and radical pair intermediates formed by putative stepwise rearrangement pathways could not be located. In fact, the formation of the completely separated acyl and benzylformimidate radicals by the homolytic cleavage of the C−O bond of **3** is endothermic by 61 kcal/mol (Scheme 2). Notably, heterolytic cleavage to form the completely separated acyl cation and the benzylformimidate anion is endothermic by 72 kcal/mol in chloroform. One would expect that any radical pair or ionic intermediate formed in a stepwise process would have energies that are almost isoenergetic with these fragmentation processes. The large endothermicities of these fragmentations suggest that these processes are unlikely.

Scheme 2. Enthalpies for the Homolytic and Heterolytic Cleavage of the Mixed Anhydride Intermediate **3**[a]



[a] Energies in chloroform are shown in parentheses.

Only 14 kcal/mol is required for the concerted [1,3]-acyl rearrangement of **3** to **4** in chloroform. This process is clearly more favorable than alternative pathways involving stepwise rearrangements. This transition structure (Figure 2a) is concerted but slightly asynchronous: the forming C−N bond has a distance of 1.80 Å, while the forming C−O bond has a distance of 1.89 Å. Mulliken charge analysis indicates that the formimidate fragment transfers 0.21*e* to the acyl fragments, suggesting that there is appreciable charge separation in the transition state. There is no evidence of diradical character in the transition structure ($S^2 = 0$).

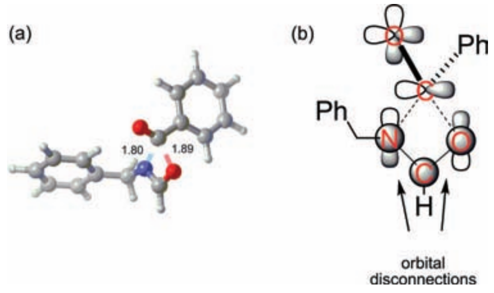
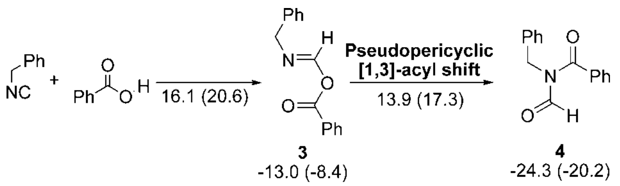


Figure 2. (a) Transition structure for the concerted [1,3]-acyl rearrangement of mixed anhydride **3** to *N*-formylamide **4**. (b) Orbital interactions in the transition state for the [1,3]-acyl rearrangement. Circles show the projection of p orbitals that are perpendicular to the molecular plane.

Sigmatropic [1,3]-rearrangements with pericyclic transition structures are forbidden according to Woodward−Hoffmann symmetry rules.[14] In contrast, the [1,3]-acyl rearrangement observed here is pseudopericyclic,[15] as evidenced by the planarity of the transition state as well as by the fact that it possesses regions where orthogonal sets of orbitals meet but do not overlap (Figure 2b). That is, the interacting orbitals are not in a closed loop, the common feature of pericyclic transition states.

Scheme 3. Preferred Mechanistic Pathway in the Transformation of Benzylisonitrile, **1**, and Benzoic Acid, **2**, to *N*-Formylamide, **4**[a]



[a] Activation enthalpies in the gas phase and chloroform (in parentheses) are shown.

In summary, B3LYP indicates that the coupling of isonitriles with carboxylic acids forms *N*-formylamides by a series of concerted rearrangement mechanisms (Scheme 3). The first step is rate-determining and involves the concertedreaction of the carboxylic acid with the isonitrile reactant. This reaction forms a carboxylate mixed formimidic

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anhydride intermediate **3**. The formation of the *N*-formylamide **4** from intermediate **3** occurs in a single step involving a concerted pseudopericyclic [1,3]-acyl rearrangement. This sequence is preferred to a series of radical or ionic stepwise rearrangement mechanisms.

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Supporting Information Available: B3LYP Cartesian coordinates and full citation for reference 8. This material is available free of charge via the Internet at http://pubs.acs.org.

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