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N-Heterocyclic Carbene Catalyzed Addition of Aldehydes to Diazo Compounds: Stereoselective Synthesis of *N*-Acylhydrazones

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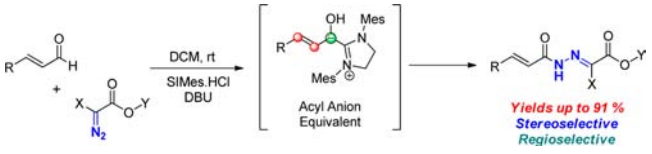
ABSTRACT



An innovative stereoselective synthesis of *N*-acylhydrazones *via* an unprecedented *N*-heterocyclic carbene catalyzed addition of aldehydes to diazo compounds is presented. Enals exclusively afforded *N*-acylhydrazones, in yields up to 91%. The observed regioselectivity was traced back to the reaction of the vinylogous Breslow intermediate *via* the acyl anion pathway over competing homoenolate, enol, and acyl azolium pathways. This unusual reaction profile was studied based on DFT calculations, which revealed that the reaction is under orbital control, rather than being ruled by charge.

The dual life of *N*-heterocyclic carbenes (NHCs) as efficient ligands for metallic centers and as active organocatalysts, granted this unique family of compounds a prominent place in the catalysis scene.[1] In terms of organocatalysis, NHCs are probably best known for their ability to reverse the polarity (umpolung) of aldehydes, generating acyl anion equivalents that have proven their utility in classical benzoin and Stetter-type reactions.[2] In 2004, Bode and Glorious independently reported that extended Breslow intermediates could be generated from α,β-unsaturated aldehydes and NHCs.[3] This has led to the discovery of a collection of new transformations based on unique reaction pathways that stem mostly from the reactivity of three different catalytic intermediates: the extended Breslow intermediate, acting as nucleophilic homoenolate equivalent **A**; the nucleophilic enolate **B**, resulting from internal proton transfer; and the electrophilic acyl azolium **C**, from protonation of **B** or after oxidation. Differently, the chemistry of extended Breslow intermediates reacting as acyl anion

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(1) Selected examples: (a) González, S. D.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3621. (b) Hahn, F. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 1348. (c) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (d) N-Heterocyclic Carbenes in Transition Metal Catalysis. *Topics in Organometallic Chemistry*, Vol. 21; Glorius, F., Ed.; Springer: Berlin/Heidelberg, 2007. (e) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, 2006. (f) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem.* **2008**, *47*, 3317. (g) Marion, N.; González S. D., S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (h) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

(2) (a) Read, J.; Rovis, T. *Synlett* **2009**, *8*, 1189. (b) Grossmann, A.; Enders, D. *Angew. Chem.* **2012**, *51*, 314. (c) Bugaut, X.; Glorious, F. *Chem. Soc. Rev.* **2012**, *41*, 3511.

(3) (a) Burstein, C.; Glorious, F. *Angew. Chem.* **2004**, *43*, 6205. (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370.

(4) (a) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. (b) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617. (c) Douglas, J.; Churchill, G.; Smith, A. D. *Synthesis* **2012**, *44*, 2295.

(5) (a) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402. (b) Fang, X.; Chen, X.; Lv, H.; Chi, Y. R. *Angew. Chem.* **2011**, *50*, 11782. (c) Singh, S.; Singh, P.; Rai, V. K.; Kappor, R.; Yadav, L. D. *Tetrahedron Lett.* **2011**, *52*, 125.

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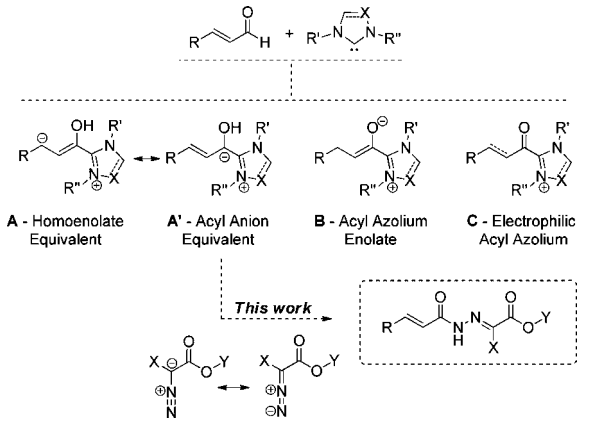
equivalents **A′** has been largely unexplored due to the difficulty of suppressing the aforementioned competing pathways (Scheme 1).[4] Of the very few reports following path **A′**,[5] the groups of Rovis and Chi reported the intermolecular Stetter reaction of enals with nitroalkenes and modified chalcones respectively. In both cases good yields and selectivities were obtained due to a delicate balance of the stereoelectronic properties of both reactants and additives.

Recently Feng et al. reported that α-diazoesters could be very efficiently exploited as electrophiles in a catalytic asymmetric α-functionalization of ketones.[6] Inspired by this transformation, we envisioned the possibility of performing the direct alkylation of diazo compounds with aldehydes catalyzed by NHCs as shown in Scheme 1. Considering the possible reaction pathways, we were particularly interested in the selective acylation of the diazo unit via acyl anion equivalent **A′**, as this would enable an unprecedented simple synthesis of *N*-acylhydrazones which are important biologically active scaffolds.[7]

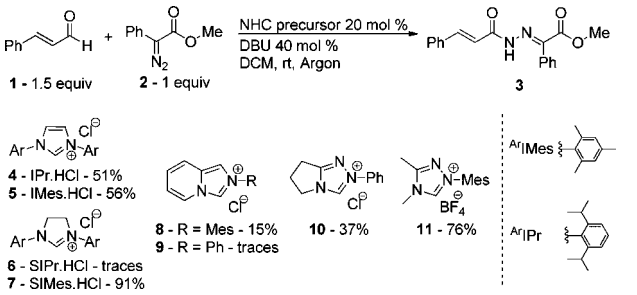
Scheme 1. Intermediates Generated from the NHC and Enals



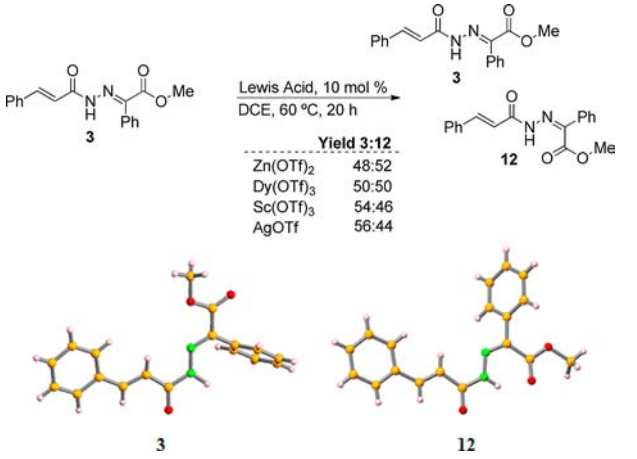
We initiated our study by performing the reaction between cinnamaldehyde and 2-diazo-2-phenylacetate **2** in the presence of NHC precursors **4**–**11**. Very gratifyingly, after extensive optimization of the reaction conditions (see Supporting Information (SI)), SIMes·HCl **7** in the presence of DBU led to the formation of the *N*-acylhydrazone **3** in 91% isolated yield (Scheme 2).

This unexpected efficiency was acompained by a high level of stereoselectivity, as no other product apart from **3** was detected in the reaction mixture, although as shown in Scheme 3, by exposing **3** to different Lewis acids, a 1:1 mixture of stereoisomers is readily obtained. The structures of both stereoisomers were determined based on X-ray analysis of suitable crystals and are presented in Scheme 3.

Scheme 2. Diazo-Ester Acylation: Screening of NHC Catalysts



Scheme 3. X-ray Crystal Structures of Reaction Product **3** and Isomerization Product **12**[a]



[a] For X-ray details, see SI.

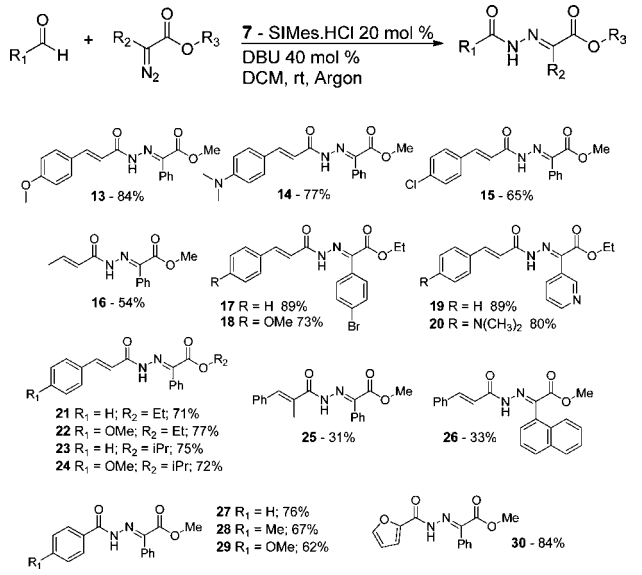
Once the reaction conditions were optimized, the protocol was evaluated in the presence of a number of aldehydes and diazo compounds. As shown in Scheme 4, cinnamaldehyde derivatives reacted smoothly with 2-diazo-2-phenylacetate **2** to afford *N*-acylhydrazones **13**–**15** in up to 84% yield. In addition to this, a moderate yield of **16** was also obtained when using a *β*-alkyl enal. Good to excellent yields were obtained with different aromatic diazoesters (**17**–**24**), although the reaction was quite sensitive to steric effects imposed both by the α-substituent of the enal (**25**, 31%) and the aromatic moiety of the diazo compound (**26**, 33%). Finally, aromatic aldehydes also proved to be suitable substrates for this transformation, affording the expected *N*-acylhydrazones (**27**–**30**) in moderate to good yields (Scheme 4).

Having established the reaction scope, the mechanism was investigated by means of DFT calculations[8] using cinnamaldehyde (**1**), 2-diazo-2-phenylacetate (**2**), and the NHC derived from precursor **7** (SIMes). Calculations start at the nucleophilic attack of the Breslow intermediate (**1′**), and the

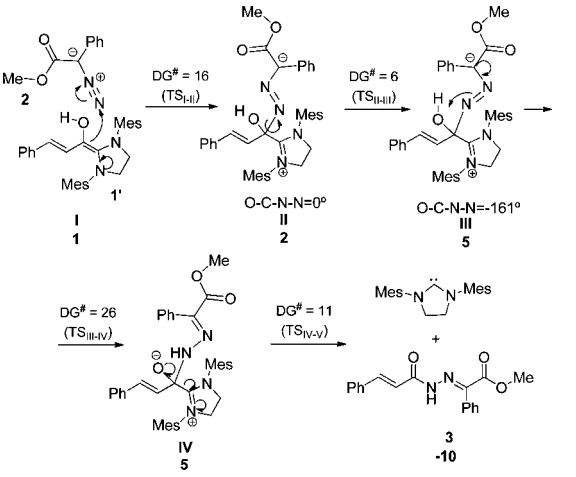
(6) Li, W.; Liu, X.; Hao, X.; Hu, X.; Chu, Y.; Cao, W.; Qin, S.; Hu, C.; Lin, L.; Feng, X. *J. Am. Chem. Soc.* **2011**, *133*, 15268.

(7) Selected examples: (a) Carvalho, S. A.; Feitosa, L. O.; Soares, M.; Costa, T. E. M. M.; Henriques, M. G.; Salomão, K.; Castro, S. L.; Kaiser, M.; Brun, R.; Wardell, J. L.; Wardell, S. M. S. V.; Trossini, G. H. G.; Andricopulo, A. D.; Silva, E. F.; Fraga, C. A. M. *Eur. J. Med. Chem.* **2012**, *54*, 512. (b) Kümmerle, A. E.; Schmitt, M.; Cardozo, S. V. S.; Lugnier, C.; Villa, P.; Lopes, A. B.; Romeiro, N. C.; Justiniano, H.; Martins, M. A.; Fraga, C. A. M.; Bourguignon, J.-J.; Barreiro, E. J. *J. Med. Chem.* **2012**, *55*, 7525.

Scheme 4. Scope of the Acylation of Diazo Compounds with Aldehydes Catalyzed by NHCs



Scheme 5. Calculated Mechanism (DFT)[a]



[a] Free energy values (kcal/mol) referred to the separated reagents (**1′** and **2**).

mechanism obtained comprises four steps (Scheme 5). The full free energy profile obtained is presented in Figure S1 (see SI).

In the first step, the formation of the C−N bond occurs between the pair of reagents. In the corresponding transition state, $\mathbf{TS_{I-II}}$, formation of the new C−N bond is only incipient, as shown by a distance (2.00 Å), still far from the value observed in intermediate **II** (1.50 Å). The bending of C−N−N is also quite evident in $\mathbf{TS_{I-II}}$ with an angle of 141°, significantly different from the linear frame observed in the diazo compound. This reflects the change of the second N-atom from *sp* in the reagent to sp^2 in **II**. The free energy barrier calculated for this step (16 kcal/mol) is consistent with a reaction that occurs at room temperature.

In the second step rotation of the newly formed C−N bond occurs, from **II** to **III**. This rearrangement occurs over $\mathbf{TS_{II-III}}$ with a negligible barrier of 6 kcal/mol and brings both the N-atom and the neighboring OH group to the right relative conformation, necessary for the following proton transfer process. This occurs in the third step, from **III** to **IV**, with protonation of the N-atom and leaving the adjacent oxygen atom with a formal negative charge, in intermediate **IV**. The free energy barrier calculated for this step (26 kcal/mol) is most probably overestimated due to the absence of base in the model used in the calculations. In fact, the DBU present in the reaction medium likely assists the proton transfer step.[9]

The final step includes the loss of NHC **7** (SIMes) and regeneration of the C=O double bond in the carbonyl group of the product. In the transition state, $\mathbf{TS_{IV-V}}$, the $C_{CO}-C_{NHC}$ bond is practically broken (d = 2.05 Å), being elongated by 0.49 Å with respect to the corresponding one in **IV**. The free energy barrier calculated for this step (11 kcal/mol) indicates a facile process.

It should be noted that the two isomers of the product, **3** and **12**, are equally stable with a calculated ΔG of only 1 kcal/mol. This corroborates the 1:1 ratio obtained when **3** is exposed to different Lewis acids (Scheme 3). However, in the absence of acid, the reaction is totally stereoselective with sole formation of product **3**, with an *E* conformation of the imine C=N bond.

The stereoselectivity of the reaction is directly related to the first step of the mechanism, i.e., the nucleophilic attack of the Breslow intermediate to the diazo compound. The product obtained experimentally, **3**, corresponds to the path shown in Scheme 5 and goes over $\mathbf{TS_{I-II}}$ in the first step. The corresponding transition states calculated for the four possible relative orientations of the two reactants are represented in Figure 1, and the corresponding free energy profiles are presented as SI (Figures S2−S4). In fact, the bending of the C−N−N frame in the diazo molecule determines the relative orientation of the two reagents in the corresponding transition state and dictates the configuration of the C=N bond in the final product. There are two possible orientations for the diazo moiety with respect to the Breslow intermediate. In one case, the C−N−N bending brings the second N-atom close to the OH group in the Breslow intermediate ($\mathbf{TS_{I-II}}$ and $\mathbf{TS_{VI-VII}}$), or alternatively, that bending moves the second N-atom of the diazo fragment away from the OH group ($\mathbf{TS_{VIII-IX}}$ and $\mathbf{TS_{X-XI}}$). In addition, there are two conformations of the C−N bond in the diazo compound, namely, with the $C-C_{CO}$ bond on the same side ($\mathbf{TS_{VI-VII}}$ and $\mathbf{TS_{VIII-IX}}$) or opposite to the N−N bond ($\mathbf{TS_{I-II}}$ and $\mathbf{TS_{X-XI}}$). In total, there are four possible conformations for the first transition state of the reaction (Figure 1).

(8) (a) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. (b) Calculations perfomed at the M06-2X/6-311++G(d,p)(PCM, CH_2Cl_2)//PBE0/6-31G(d, p) level using the Gaussian 09 package. A complete account of the computational details and the corresponding list of references are provided in the SI.

(9) (a) This same effect was observed in the 1,2 H-shift, from C to O, in the formation of the Breslow intermediate. (b) Domingo, L. R.; Zaragozá, R. J.; Arnó, M. *Tetrahedron* **2009**, *65*, 3432.

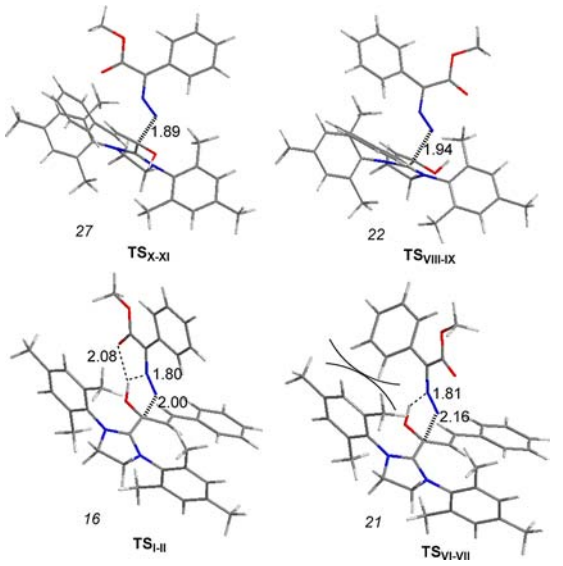


Figure 1. Alternative transition states for the first step of the mechanism. Free energy values (italics, kcal/mol) referred to the separated reagents (**1′** and **2**) and relevant distances in Å.

The establishment of an intramolecular H-bond N--H−O stabilizes the two transition states where that interaction is possible ($\mathbf{TS_{I-II}}$ and $\mathbf{TS_{VI-VII}}$). But in $\mathbf{TS_{I-II}}$ there is one extra H-bond between OH and the O-atom in the carbonyl group of the diazo fragment, further stabilizing this transition state with respect to $\mathbf{TS_{VI-VII}}$. In fact, the H-bond C═O--H—O between the two molecules is maintained along the step, being already evident in the pair of reactants (d = 1.88 Å in **I**; see Figure S1) and guiding the two molecules toward the orientation of the transition state. In addition, $\mathbf{TS_{VI-VII}}$ is further destabilized, with respect to $\mathbf{TS_{I-II}}$ by the stereochemical repulsion between the phenyl ring of the diazo molecule and one mesityl group in the Breslow intermediate (see Figure 1).

The regioselectivity of the reaction was also addressed with the study of the mechanism for nucleophilic attack of C3 in the Breslow intermediate (homoenolate pathway **A** in Scheme 1). The corresponding profile is represented in Figure S5 (SI). The energy barrier calculated for that reaction (25 kcal/mol) indicates that it is less favorable than the C1 attack intermediate (acyl anion pathway **A′** in Scheme 1), in good agreement with the experimental findings. The reason for that regioselectivity can be tracked to the relevant frontier orbitals of the reactants (Figure 2). The results indicate that the reaction is under orbital control, rather than being ruled by charge, as the enol C═C bond in the Breslow intermediate has the greater part of the electron density of the HOMO (34%) of that molecule, and the attack is directed to the terminal N-atom in the diazo moiety, corresponding to the part of this reagent with greater participation in the composition of the respective LUMO (52%).

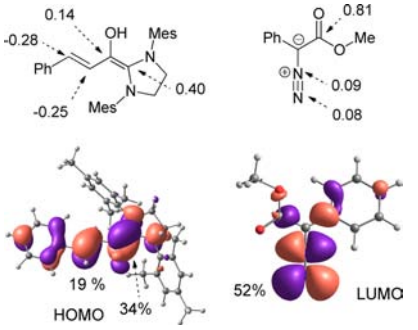


Figure 2. Frontier orbitals and atomic charges (NPA) of the reagents **1′** (left) and **2** (right).

In summary we have developed an unprecedented NHC catalyzed addition of aldehydes to α-diazoesters. This transformation readily afforded *N*-acylhydrazones stereoselectively in yields up to 91%. Interestingly when using enals, the reaction is fully regioselective and the only observed product results from umpolung attack of the carbonyl atom to the terminal nitrogen in the diazo moiety. This unusual substrate controlled pathway was rationalized on the basis of DFT calculations which revealed the reaction to be under orbital control, rather than being ruled by charge, which would result in typical homoenolate chemistry.

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Supporting Information Available. Experimental procedures, spectral data, and DFT data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.