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Metal-Free N–H Insertions of Donor/Acceptor Carbenes

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ABSTRACT

Synthetically useful transformations arise from the thermal decomposition of aryldiazoacetates in the presence of primary and secondary amines without the use of a metal catalyst. Thermally generated, free donor/acceptor carbenes directly undergo N–H insertion with amines through selective aza-ylide formation to afford a variety of α-amino esters in 53–96% yields.

Diazo compounds are versatile reagents in organic synthesis[1] and, in particular, are utilized as precursors for the generation of metal carbenoid intermediates. These reactive species can undergo a myriad of powerful synthetic transformations such as C–H insertions,[2] cyclopropanations,[3] and ylide formations.[4] We and others have conducted extensive studies on the chemistry of metal-bound carbenoids derived from aryldiazoacetates.[5] However, we recently disclosed that these diazo compounds can also be decomposed in a controlled manner under thermal conditions without the use of a metal catalyst to provide free carbenes and effect selective cycloaddition processes with alkenes.[6]

The metal-catalyzed N–H insertion of diazocarbonyls has been developed as a rapid, general, and convergent route to amino ketones, *N*-heterocycles, and amino esters. These products are important precursors to amino acids as well as other natural products and pharmaceutical compounds.[4,7] A range of metals, most notably copper and rhodium, have been studied as catalysts to effect the N–H insertion process. However, the amino component of these reactions is typically limited to amides, carbamates, and anilines. The corresponding reactions of amines are much less developed[8] as the nucleophilic amines can bind to and, consequently, poison the metal catalysts.[8a–c]

In 1996 Moody and co-workers described a thermal N–H insertion into *N*,*N*-diethylamine with phenyldiazoacetate although the desired product was isolated in only 30–40% yield.[8a] Our recent observation of selective thermal carbene cycloaddition reactions led us to hypothesize that a general N–H insertion process could be feasible under thermal conditions without the use of a metal

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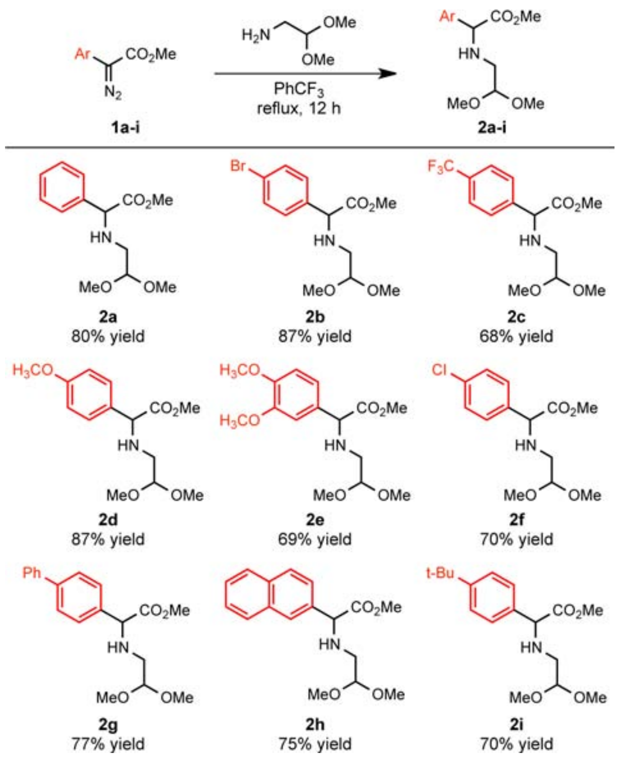
catalyst. Herein, we disclose that free donor/acceptor carbenes, derived from the thermal decomposition of aryldiazoacetates, can readily undergo N−H insertion reactions with a wide range of amines to directly generate α-arylamino esters in good yield.

We initiated our evaluation of this reaction by inducing the thermal decomposition of methyl phenyldiazoacetate (**1a**) in the presence of 2,2-dimethoxyethylamine (Scheme 1, entry 1). The reaction was conducted by slow addition of a solution of the diazo compound to a refluxing solution of the amine in trifluorotoluene.[9] Under these conditions the desired N−H insertion product, **2a**, was isolated in 80% yield. We next conducted a series of experiments to evaluate the scope of the diazo component in this transformation. As shown in Scheme 1, a wide array of aryl diazoacetates, including those with electron-rich and -poor substituents, can function as suitable carbene precursors to provide the desired α-arylamino esters in good yield (68−87% yield).

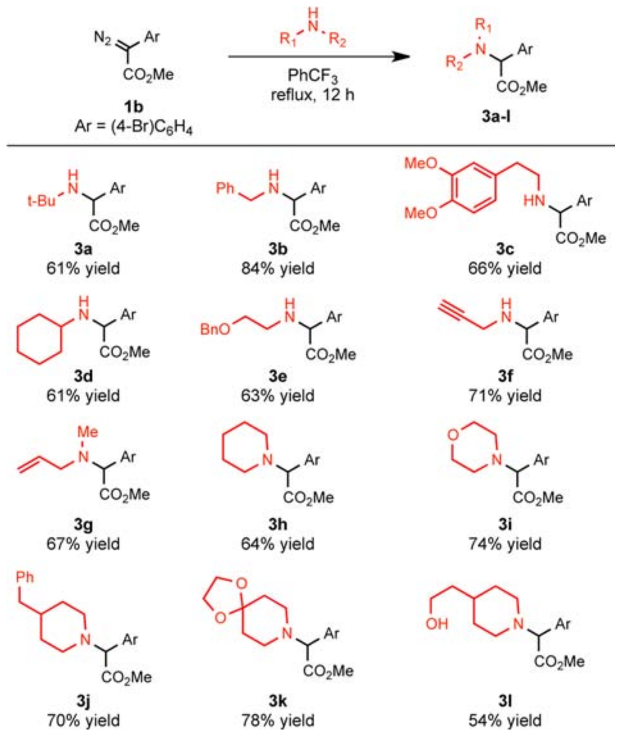
Scheme 1. Thermal N−H Insertions of Aryl Diazoacetates



[a] A dry round-bottom flask was charged with amine (2.0−5.0 equiv) and dry trifluorotoluene. The reaction mixture was heated to reflux, and the diazo compound (1.0 equiv) was added by syringe pump over a period of 3 h and then stirred at reflux for an additional 9 h.

Having established effective conditions for the thermal N−H insertion reaction we proceeded to explore the scope of the amine substrate. Thus, the reactivity of aryldiazoacetate **1b** with a variety of aliphatic amines was examined.

Scheme 2. Thermal N−H Insertions of Primary and Secondary Amines



As shown in Scheme 2, primary amines with quaternary, secondary, and primary α-positions readily undergo N−H insertion in moderate to good yields (**3a**−**f**, 61−84% yield). In all cases selective monoinsertion at the amine is observed. We attribute this selectivity to both steric and electronic deactivation of the secondary amine products **3a**−**f**, which would decrease the rate of a subsequent N−H insertion. In addition, secondary amines are viable substrates and afford the desired tertiary amine products (**3g**−**l**, 54−78% yield). The mild reaction conditions of this transformation are compatible with a variety of functional groups including electron-rich aromatic rings, ethers, acetals, and alkynes (Scheme 2). Interestingly, the use of an allylic amine provides only the N−H insertion product **3g**; the possible byproducts derived from cyclopropanation or a (2,3)-ylide rearrangement are not formed. Furthermore, in the presence of a free hydroxyl group, insertion is observed exclusively at nitrogen, suggesting that this system is highly selective for N−H insertion over O−H insertion (Scheme 2, entry **3l**).

Aromatic and heteroaromatic amines are important motifs in bioactive compounds. Consequently, the reactivity of aromatic and heteroaromatic amines in the N−H insertion reaction was also evaluated. As highlighted in Scheme 3, a range of anilines with both electron-rich and -poor substituents readily undergo N−H insertion to provide the corresponding α-arylamino ester products in moderate to good yields (**4a**−**d**, 54−75% yield). The reaction also was found to be compatible with heteroarylamines

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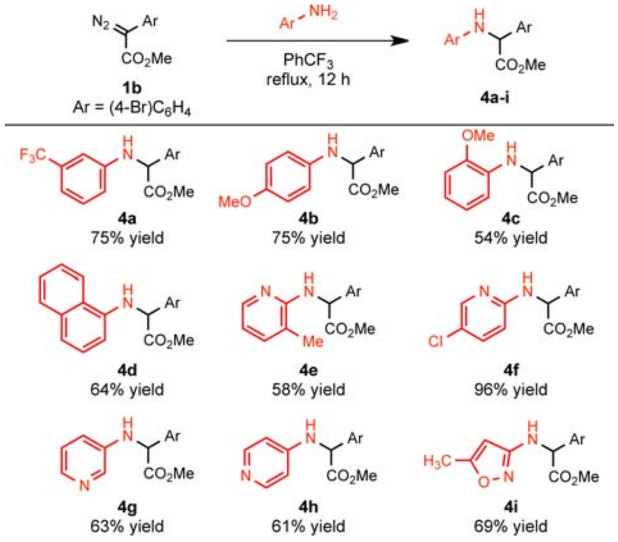
(9) Trifluorotoluene was utilized as the solvent because of its high boiling point and inertness towards reactive carbene intermediates.

and provided a variety of substituted pyridines and isoxazole products in good yields (Scheme 3, entries **4e**–**i**, 58–96% yield). More hindered substrates with *ortho*-substitution can be utilized in this reaction, although the isolated yields are slightly diminished (Scheme 3, entries **4c**–**e**, 54–64% yield).

Scheme 3. Thermal N–H Insertions with Aryl- and Heteroarylamines



The success of the thermal carbene reactions disclosed herein and in previous work[6] prompted us to conduct a computational study to analyze the mechanistic details of the transformation. These studies were performed at the B3LYP/6-311+G(d,p) level of theory[10] with the reaction between **1a** and methylamine as a model system. As shown in Figure 1 the reaction initiates with the thermal extrusion of nitrogen gas from **1a** through **TS-I**, which was found to have a free energy activation barrier of 30.3 kcal/mol. When solvent effects from trifluorotoluene were included[11] the barrier was lowered to 28.3 kcal/mol. Our previous kinetic studies on thermal reactions with **1a** showed a first-order decomposition with $k = 1.92\ \mathrm{h}^{-1}$.[6] Using Transition State Theory, this corresponds to an experimental free energy activation barrier of 27.7 kcal/mol, which is very good agreement between theory and experiment (see Supporting Information for details). Although the triplet carbene **I-*T*** was more stable than the singlet **I-*S*** by approximately 2.9 kcal/mol, a Curtin–Hammett situation can arise because addition of methylamine to the singlet carbene is enthalpically barrierless.[12] This addition generates the ylide **II** which is stable by −20.3 kcal/mol. Rapid intramolecular proton transfer through a five-membered transition state (**TS-II**) generates enol **III** (−24.0 kcal/mol), which can rapidly tautomerize to the α-amino ester product **IV**. The N–H insertion reaction is found to be highly exergonic (−43.9 kcal/mol).[13]

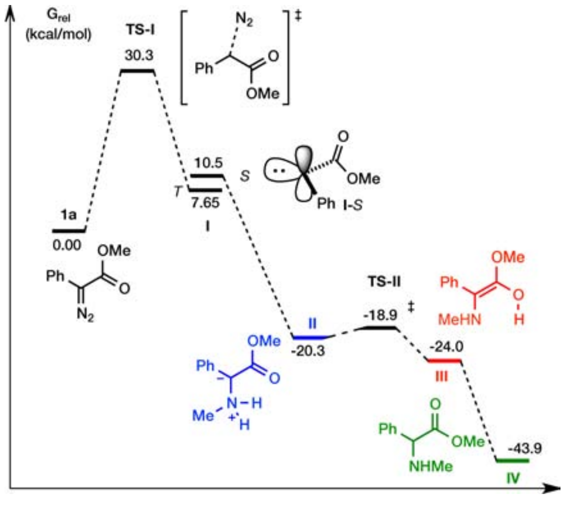


Figure 1. Gas-phase free-energy reaction coordinate diagram for gas-phase reaction between **1a** and methylamine at the B3LYP/6-311+G(d,p) level of theory.

In contrast to other substrates, the reaction of the 1,1-dimethylbenzylamine **5** with aryldiazoacetate **1b** gave an unanticipated result (Scheme 4a). While the desired N–H insertion product **6** was obtained in 66% yield, a second product, the highly congested α-quaternary amino ester **7**, was also obtained in 16% yield. This unexpected product appears to arise *via* a formal [1,2]-alkyl shift of an aza-ylide intermediate in a Stevens-type rearrangement process. We anticipate that both products, **6** and **7**, arise *via* formation of an initial aza-ylide species. A subsequent proton transfer would provide the N–H insertion product (Figure 1). However, this zwitterionic intermediate can also fragment to provide a radical pair with two stabilized carbon-centered radicals. Rapid recombination would provide the formal [1,2]-alkyl shift product. We reason that the augmented stability of the tertiary benzylic radical facilitates this transformation and dictates the selectivity of the [1,2]-alkyl shift.

The use of carbenes to access ammonium ylides with a subsequent [1,2]-alkyl shift was first observed by Stevens in 1952 while heating 9-diazofluorene in the presence of

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(10) (a) Frisch, M. J.; et al. *Gaussian 09*. See Supporting Information for full reference. (b) Becke, A. D. J. *Chem. Phys.* **1993**, *98*, 5648–5652. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (d) For a computational study of these particular types of free carbenes, see: Geise, C. M.; Wang, Y. H.; Mykhaylova, O.; Frink, B. T.; Toscano, J. P.; Hadad, C. M. *J. Org. Chem.* **2002**, *67*, 3079–3088.

(11) Using the default IEFPCM model in Gaussian 09. See Supporting Information for details.

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(13) The observed mechanism is consistent with other computational studies on carbene X–H insertions: (a) Ramasami, K.; Ramalingam, M.; Venuvanalingam, P. *Int. J. Quantum Chem.* **2010**, *110*, 1310–1316. (b) Ramasami, K.; Ramalingam, M.; Venuvanalingam, P. *J. Theor. Comput. Chem.* **2009**, *8*, 1143–1153.

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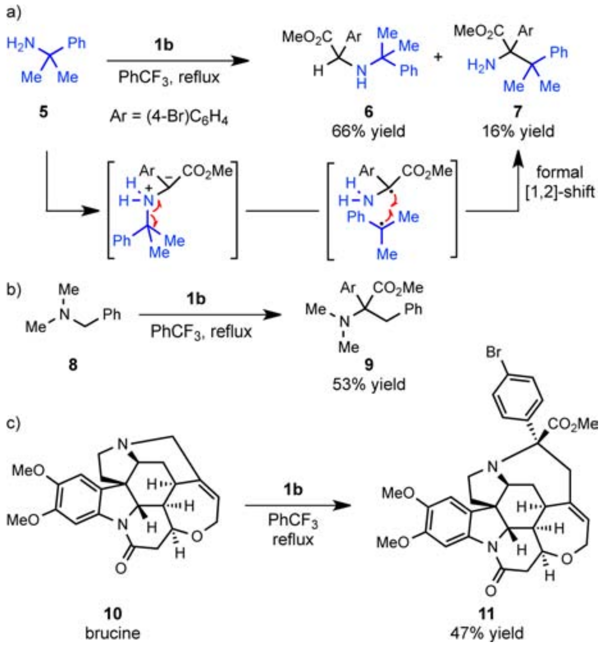
(15) (a) For a review, see: Vanecko, J. A.; Wan, H.; West, F. G. *Tetrahedron* **2006**, *62*, 1043–1062. (b) For an example of a Stevens rearrangement of a tertiary amines, see: West, F. G.; Glaeske, B. N.; Naidu, B. N. *Synthesis* **1993**, *10*, 977–980.

N,*N*-dimethylbenzylamine.[14] Despite this early example, only metal-bound (rhodium and copper) carbenes have found synthetic utility in the Stevens rearrangement.[15,16] Recently, Lacour and co-workers demonstrated the regioselective ring expansion of Tröger bases with donor/acceptor carbenoids using $Rh_2(OAc)_4$ as a catalyst.[17]

Scheme 4. Thermal Stevens-like Rearrangement of Benzylic and Allylic Amines



Formation of the Stevens rearrangement product **7** with a primary amine substrate (**5**) prompted us to evaluate the thermal Stevens rearrangement of free donor/acceptor carbenes with tertiary amines. As anticipated, heating diazo **1b** in the presence of *N*,*N*-dimethyl benzylamine **8** provided the [1,2]-rearrangement product **9** in a 53% isolated yield (Scheme 4b). We further found that we could achieve ring expansion of an extremely complex alkaloid, brucine (**10**), with diazo **1b** under thermal conditions, providing the [1,2]-rearrangement product in modest yield (Scheme 4c). The regiochemistry of the ring expansion was established by 2D-NMR analysis, and the stereochemistry at the newly formed quaternary stereogenic center was tentatively assigned by NOE correlations (see Supporting Information).[18] This reaction occurs selectively at the more electron-rich amine in the presence of multiple reactive functional groups including an alkene and electron-rich aromatic ring. In accordance with our proposed mechanism, both substrates **8** and **10** undergo a selective [1,2]-alkyl shift at the substituent that is more capable of stabilizing a radical intermediate.

The studies presented herein demonstrate that the thermal N–H insertion of aryldiazoacetates in the absence of a metal catalyst can be a high-yielding process. A variety of aliphatic, aromatic, and heteroaromatic amines are compatible with these reaction conditions and give rise to a range of α-arylamino esters. Mechanistic DFT studies were in very good agreement with experimental kinetics and show that the reaction proceeds through ylide formation with the singlet carbene intermediate. Further studies to utilize the highly selective aza-ylide formation of free donor/acceptor carbenes are underway.

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

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(16) The formation of aza-ylide intermediates *via* the photochemical decomposition of diazo compounds in the presence of tertiary amines has been previously described: Tomioka, H.; Suzuki, K. *Tetrahedron Lett*. **1989**, *30*, 6353–6356.

(17) Sharma, A.; Guénée, L.; Naubron, J.-V.; Lacour, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3677–3680.

(18) Approximatly 10% of a mixture of two other regioisomeric or stereoisomeric products was also isolated from this reaction. However, we could not separate these compounds chromatographically and, therefore, could not confidently assign their structure. Attempts to obtain an X-ray quality crystal of **11** to support the structural assignment were unsucessful.

The authors declare no competing financial interest.