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Preparation of Pyrazine Carboxamides: A Reaction Involving *N*-Heterocyclic Carbene (NHC) Intermediates

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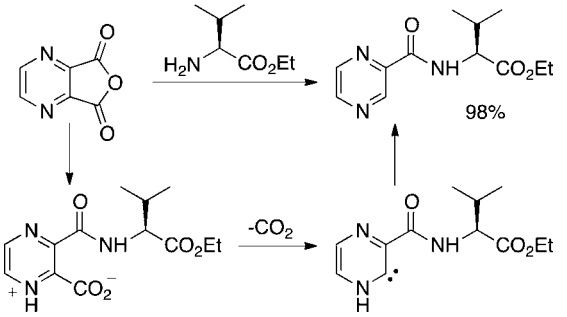
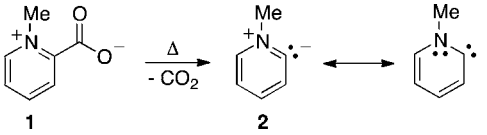
ABSTRACT



In the reactions of 2,3-pyrazinedicarboxylic anhydride with amines and anilines, pyrazine carboxamides are formed in good to excellent yields. A mechanism is proposed involving ring opening of the anhydride and decarboxylation of the heterocyclic ring. Based on other similar heterocyclic decarboxylations, this suggests the involvement of an *N*-heterocyclic carbene intermediate leading to the product.

Since Breslow proposed the involvement of a stable *N*-heterocyclic carbene (NHC) in biosynthetic reactions,[1] this area of chemistry has seen extensive growth. This pioneering work was soon followed by Wanzlick's preparation of an imidazole-2-ylidene carbene,[2] Arduengo's isolation of a stable NHC,[3] and the development of numerous NHC scaffolds.[4] The NHCs have been the subject of many recent studies, research largely driven by the use of NHCs as organocatalysts and ligands in metal complexes.[4] Other than the organocatalytic conversions with NHCs however, there are very few examples of synthetic chemical reactions that occur through NHCs as one of the primary reactive intermediates. In the following Letter, we describe an efficient route to pyrazine carboxamides and a mechanism is proposed which involves an NHC as a key reactive intermediate.

Among the known routes to NHC structures, one is the decarboxylation of pyridinium carboxylates and related heterocyclic betaine species.[5] For example, it has been shown that *N*-methylpyridinum 2-carboxylate **1** (*homarine*, a marine natural product found in the tissues of shellfish and invertebrates) undergoes thermal decarboxylation to give the corresponding NHC **2** (eq 1).[5a] Subsequent trapping reactions by electrophiles or



1 2 (1)

transition metals provide respective routes to pyridinium salts and NHC−metal complexes.[5b,6,7] In a similar

(1) Breslow, R. *J. Am. Chem. Soc.* **1957**, *79*, 1762–1763.
(2) Wanzlick, H.-W.; Schikora, E. *Chem. Ber.* **1960**, *72*, 494.
(3) Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361–363.
(4) (a) Fevre, M.; Pinaud, J.; Gnanou, Y.; Vignolle, J.; Taton, D. *Chem. Soc. Rev.* **2013**, *42*, 2142–2172. (b) Crabtree, R. H. *Coord. Chem. Rev.* **2013**, *257*, 755–766. (c) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686–11698. (d) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511–3522.
(5) (a) Haake, P.; Mantecon, J. *J. Am. Chem. Soc.* **1964**, *86*, 5230–5234. (b) Katritsky, A. R.; Awartani, R.; Patel, R. C. *J. Org. Chem.* **1982**, *47*, 498–502. (c) Lavorato, D.; Terlouw, J. K.; Dargel, T. K.; Koch, W.; McGibbon, G. A.; Schwarz, H. *J. Am. Chem. Soc.* **1996**, *118*, 11898–11904. (d) Schmidt, A.; Snovydovych, B.; Habeck, T.; Dröttboom, P.; Gjikaj, M.; Adam, A. *Eur. J. Org. Chem.* **2007**, 4909–4916.
(6) Katritzky, A. R.; Faid-Allah, H. M. *Synthesis* **1983**, 149–151.
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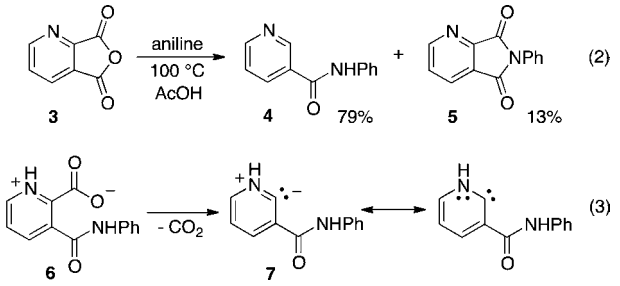
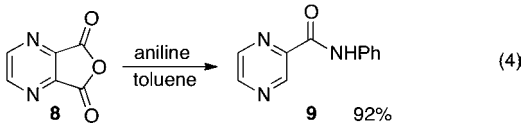
process, Harrington described the synthesis of nicotinamides from 2,3-pyridinedicarboxylic anhydride **3** (eq 2).[8] The conversions involve heating anhydride **3** with anilines in



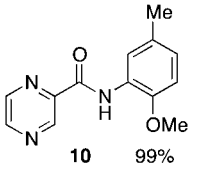
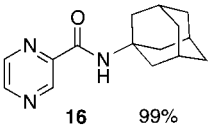
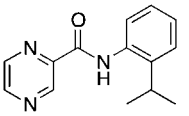
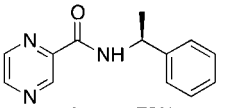
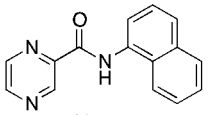
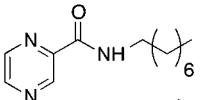
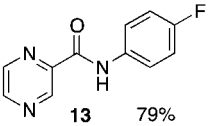
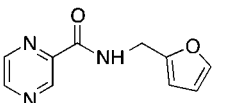
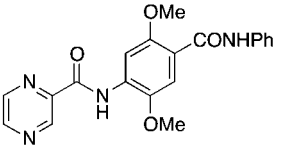
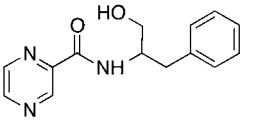
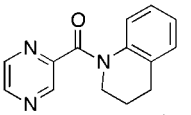
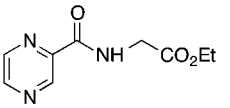
acetic acid. Nicotinamides (i.e., **4**) and pyridine-2,3-dicarboximides (i.e., **5**) are formed as products. Product **4** is clearly the result of a decarboxylation reaction, suggesting the cleavage of **6** to the NHC intermediate **7** (eq 3). Protonation at the ring carbon then leads to the nicotinamide **4**. As a synthetic route to nicotinamides, Harrington's study was limited to only anilines.

Given the value of heterocyclic amides and the importance of NHC species, we have sought to extend this decarboxylation chemistry to reactions involving 2,3-pyrazinedicarboxylic anhydride (**8**). Pyrazinecarboxylic acids are known to undergo thermal decarboxylations,[9] suggesting the possibility of forming pyrazine carboxamides by reactions with the anhydride with amines and anilines. As a class of compounds showing varied biological activities,[10] pyrazine carboxamides are desirable synthetic targets. Our studies began with the reaction of aniline with 2,3-pyrazinedicarboxylic anhydride (**8**, eq 4). An optimized procedure involved the



reaction in refluxing toluene (or xylene) and the expected pyrazine carboxamide (**9**) is formed in excellent yield. Other anilines were converted to the respective pyrazine carboxamides (Table 1). Pyrazine carboxamides **10**–**15** were formed in good to excellent yields by reactions with anhydride **8** and the respective anilines. With primary aliphatic amines, the product amides (**16**–**21**) were isolated in low to excellent yield. In some cases, significant quantities of the

Table 1. Products and Yields from the Reactions of Anilines and Amines with 2,3-Pyrazinedicarboxylic Anhydride (**8**)[a]

product/yield[b]	product/yield[b]
 **10** 99%	 **16** 99%
 **11** 90%	 **17** 73%
 **12** 95%	 **18** 11%[c]
 **13** 79%	 **19** 31%[c]
 **14** 99%	 **20** 22%[c]
 **15** 53%	 **21** 25%[c]

[a] Reaction conditions: 1.0 mmol of anhydride **8**, 1.0 mmol of the amine, 15 mL of toluene refluxed for 12 h. [b] Isolated yield of pure product. [c] Amide product accompanied by pyrazine-2,3-dicarboximide byproduct (see Supporting Information).

pyrazine-2,3-dicarboximides were also isolated from the product mixtures (see Supporting Information). Several amino acids are also shown to give the pyrazine carboxamides. Thus, valine, proline, methionine, and leucine derivatives give the respective heterocyclic amides (**22**–**25**) in fair to excellent yields (Figure 1). The highest yields have been obtained with valine and leucine derivatives, suggesting a possible link between reaction yield and the relative size or bulk of the amino acid nucleophile.

The conversion of anhydride **8** to the pyrazine carboxamides occurs in a reaction accompanied by decarboxylation. By analogy to the decarboxylation of *homarine* and related systems, carboxamide formation likely involves a pyrazine-based carbene (Scheme 1). Thus, a mechanism is proposed in which the amine reacts with the anhydride (**8**) to initially give the zwitterionic species **26**. Ring opening of

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(9) (a) Heinisch, G.; Loetsch, G. *Synthesis* **1988**, 119–121. (b) Rao, A. V. R.; Yadav, J. S.; Ravichandran, K.; Sahasrabudhe, A. B.; Chaurassia, S. S. *Ind. J. Chem., Sec. B: Org. Chem. Incl. Med. Chem.* **1984**, *23B*, 850.

(10) (a) Berg, S.; Bergh, M.; Hellberg, S.; Hoegdin, K.; Lo-Alfredsson, Y.; Soederman, P.; von Berg, S.; Weigelt, T.; Ormoe, M.; Xue, Y.; Tucker, J.; Neelissen, J.; Jerning, E.; Nilsson, Y.; Bhat, R. *J. Med. Chem.* **2012**, *55*, 9107–9119. (b) Scanio, M. J. C.; Shi, L.; Drizin, I.; Gregg, R. J.; Atkinson, R. N.; Thomas, J. B.; Johnson, M. S.; Chapman, M. L.; Liu, D.; Krambis, M. J.; Liu, Y.; Shieh, C.-C.; Zhang, X. F.; Simler, G. H.; Joshi, S.; Honore, P.; Marsh, K. C.; Knox, A.; Werness, S.; Antonio, B.; Krafte, D. S.; Jarvis, M. F.; Faltynek, C. R.; Marron, B. E.; Kort, M. E. *Bioorg. Med. Chem.* **2010**, *18*, 7816–7825. (c) Chiurato, M.; Boulahjar, R.; Routier, S.; Troin, Y.; Guillaumet, G. *Tetrahedron* **2010**, *66*, 4647–4653.

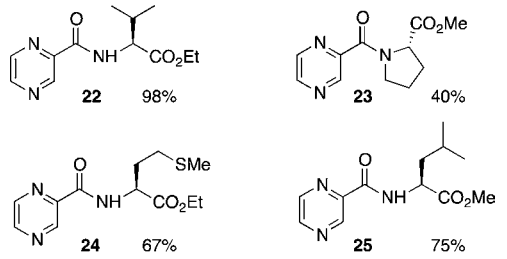
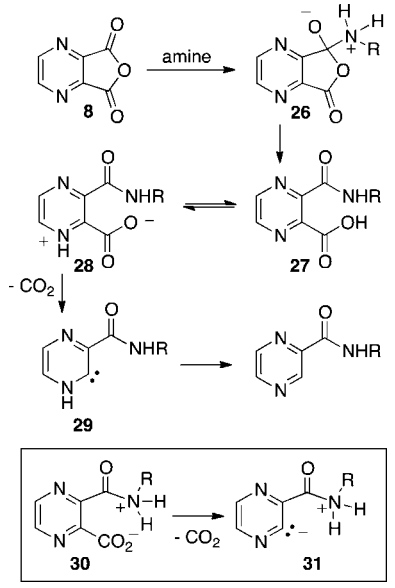


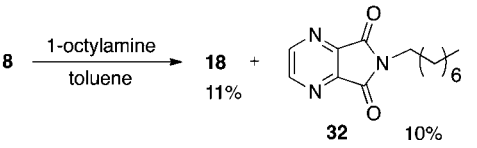
Figure 1. Products and yields for the reactions of 2,3-pyrazinedicarboxylic anhydride (**8**) with amino acids.

Scheme 1. Proposed and Alternative Mechanisms



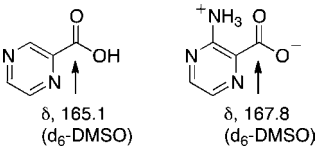
the tetrahedral intermediate provides the pyrazine carboxylic acid **27**. In some case, the intermediate pyrazine carboxylic acids undergo dehydration to give pyrazine-2,3-dicarboximides (*vide supra*). Subsequent formation of the zwitterion **28** then leads to the decarboxylation step. The resulting pyrazine-based carbene (**29**) gives the carboxamide product by a final proton transfer or migration. Several attempts were made to trap the NHC intermediates (i.e., **29**) in organometallic complexes, but these efforts were unsuccessful.[11]

An alternative mechanism can be imagined in which decarboxylation of zwitterion **30** directly provides the carbanion **31** and proton transfer then gives the observed pyrazine carboxamide. While this mechanism is appealing by considering the principle of least motion,[12] there are several factors that argue against it. First, decarboxylation of **30** would need to occur faster than proton transfer leading to the carboxylic acid intermediate (**27**). This seems unlikely considering the very high acidity of the N−H protons on the protonated amide. Second, rapid decarboxylation of **30** would also preclude formation of the pyrazine-2,3-dicarboximide byproducts (eq 5). Although the carboxylic acid intermediate **27** was not isolated from our product mixtures, similar products have been isolated as major products in the reactions of 2,3-pyridinedicarboxylic anhydride (**3**).[8]



(5)

In order to test our mechanistic proposal, we conducted NMR experiments with 2,3-pyrazinedicarboxylic anhydride (**8**) and 1-adamantylamine. The reaction between these two compounds was shown to be an exceptionally efficient route to the amide (**16**, Table 1). The amine and anhydride (**8**) were dissolved in d_8-toluene, and the solution was heated to 90 °C. Acquisition of ^{13}C spectra was done at regular intervals, and the results are consistent with the proposed mechanism (Figure 2). Thus, anhydride **8** has three ^{13}C resonances (spectrum A): δ, 157.5 (C=O), 149.6 (CH), and 145.3 (C). Upon heating the mixture (spectrum B), two prominent new carbonyl resonances appear at δ, 163.8 and 162.6. A smaller carbonyl resonance also begins to appear at about δ, 161.3. We believe that these peaks arise from the formation of primarily the carboxylic acid **27** and a small amount of the final amide product **16**. Thus, intermediate **27** shows peaks in the aromatic region at δ, 147.4 (C), 145.4 (CH), 143.3 (C), 142.2 (CH). The remaining peaks in the aromatic region can be assigned to the final amide product (**16**), based on comparison with the ^{13}C NMR spectrum of the purified amide **16** (spectrum F). It could also be argued that the two carbonyl resonances at δ, 163.8 and 162.6, might arise from the zwitterionic intermediate **30**. However, this seems unlikely given that the carboxylate anion ^{13}C resonance generally occurs downfield from analogous carboxylic acid signals. While acetic acid exhibits a carbonyl resonance at δ, 178.1 (D_2O), a tetramethylammonium acetate resonance is found at δ, 182.6 (D_2O).[13] In the case of pyrazines, pyrazinecarboxylic acid and the zwitterionic amino acid exhibit respective ^{13}C resonances at δ, 165.1 and 167.8 (DMSO).[14] These data suggest intermediate **30**, if formed,



would exhibit a ^{13}C resonance further downfield than the observed δ, 163.8 and 162.6.

(11) Under varied conditions, the reactions were done in the presence of $[Cu(MeCN)_4]BF_4$ and $[IrClCOD]_2$ in an effort to trap the NHC intermediate.

(12) Hine, J. *Adv. Phys. Org. Chem.* **1978**, *15*, 1–61.

(13) Hagen, R.; Roberts, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 4504–4506.

(14) *The Aldrich/ACD Library of FT NMR Spectra*; Sigma-Aldrich.

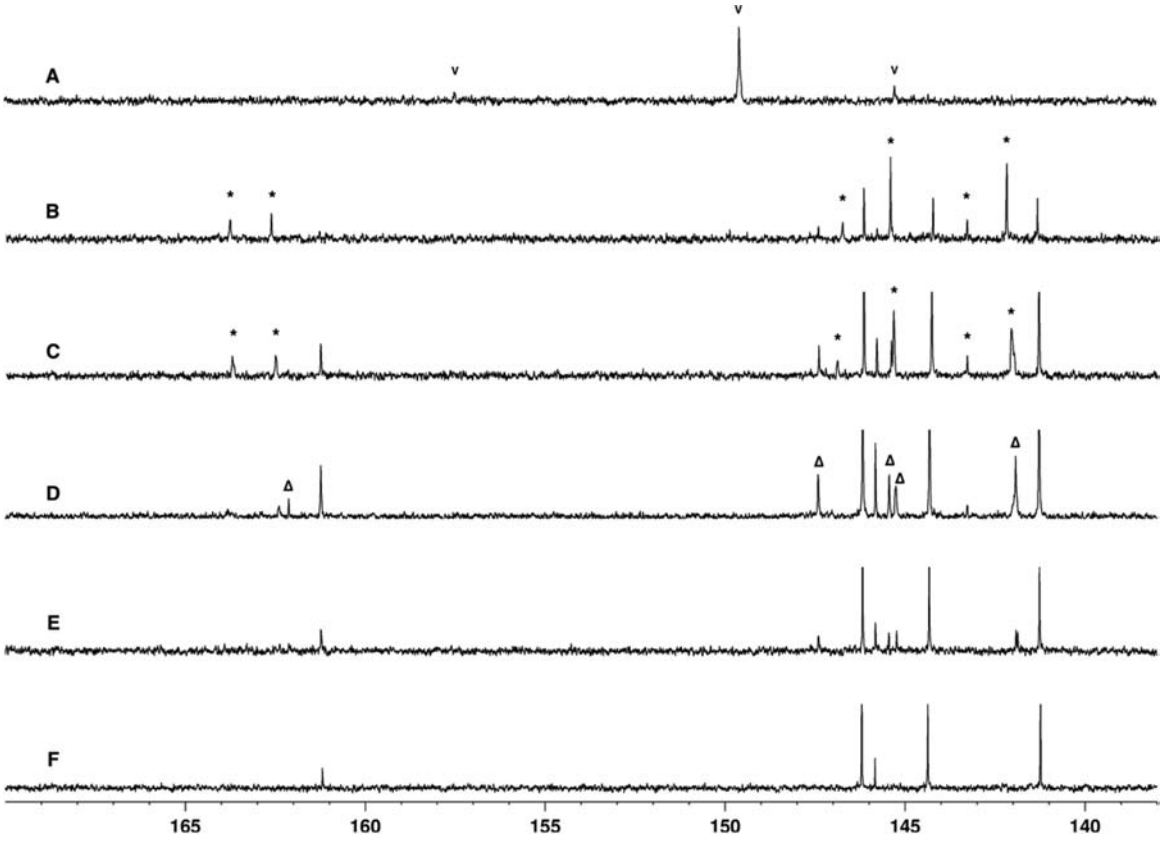


Figure 2. ^{13}C NMR spectra (d_8-toluene) of 2,3-pyrazinedicarboxylic anhydride (spectrum A), purified amide **16** (spectrum F), and reaction mixtures of 2,3-pyrazinedicarboxylic anhydride with 1-adamantylamine. Reactions were done at 90 °C, and analyses were taken at 105 min (spectrum B), 180 min (spectrum C), 360 min (spectrum D), and 540 min (spectrum E). 2,3-Pyrazinedicarboxylic anhydride (v); proposed intermediates: carboxylic acid **27** (*) and NHC **29** or unknown intermediate (Δ); amide **16** is unmarked.

With more time, the signals assigned to compound **27** dissipate and an increasing amount of the final product **16** is seen (spectra D and E). Interestingly, a new set of peaks arise from a low concentration intermediate. This species is found to have a single carbonyl resonance at δ, 162.1 and four other peaks in the aromatic region of the spectrum. These signals are consistent with the proposed NHC structure **29**, although the presence of an unknown intermediate cannot be rigorously excluded. As expected, the peaks assigned to **29** also dissipate and the final product **16** is the main component of the mixture (spectrum E).

In summary, we have found that the pyrazine carboxamides may be prepared in fair to excellent yields by the reactions of anilines and amines with 2,3-pyrazinedicarboxylic anhydride. The conversions involve a novel decarboxylation step, and a mechanism is proposed which invokes the formation of an *N*-heterocyclic carbene intermediate. This chemistry represents a rare example of an NHC as a primary reactive intermediate in a synthetic conversion.

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Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of new compounds. Full NMR spectra from Figure 2. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.