J|A|C|S COMMUNICATIONS

Published on Web 09/11/2008

On the Two-Component Microwave-Mediated Reaction of Isonitriles with Carboxylic Acids: Regarding Alleged Formimidate Carboxylate Mixed Anhydrides

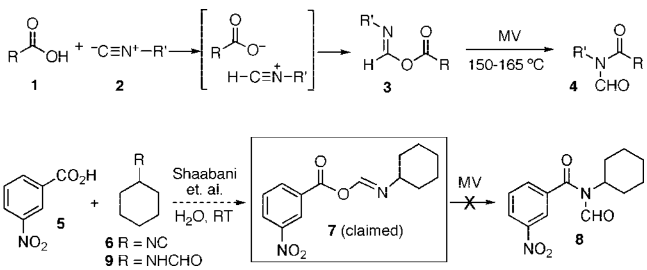
Xuechen Li,† Yu Yuan,† William F. Berkowitz,†,# Louis J. Todaro,‡ and Samuel J. Danishefsky*,†,§

Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10065, Department of Chemistry, Hunter College of City University of New York, 695 Park Avenue, New York, New York 10065, and Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027

Received June 30, 2008; E-mail: s-danishefsky@ski.mskcc.org

Recently we reported on the microwave-induced coupling of carboxylic acids with isonitriles, giving rise to various *N*-formylamides (cf. **4**, Scheme 1).[1] We suggested the term two-component coupling (2CC) to differentiate this work from earlier studies.[2] As we discussed previously, one likely mechanistic interpretation of the 2CC reaction is that **4** arises from a 1,3-O→N acyl transfer within **3**.[3,4] The latter comes about from a protonation-addition sequence in the joining of **1** and **2**. To the best of our knowledge, no structure corresponding to a formimidate carboxylate mixed anhydride **3** (hereafter referred to in this paper as a FCMA), had been documented in a convincing way, let alone fully characterized.[5−7] Our thoughts and experiences in this area led us to suppose that a generic FCMA, **3**, would be a highly reactive acyl donor. Accordingly, a recent report[5a] to the effect that FCMA **7** is produced at room temperature as a crystalline product from the reaction of acid **5** and isonitrile **6** in water provoked our curiosity. Moreover, we noted that the spectroscopic properties of the alleged **7** (particularly its reported IR spectrum)[8] do not correspond to what would be expected from such a structure.[9]

Scheme 1



In our hands, the reaction of **5** and **6** in water did indeed produce, as reported by the authors,[5a] a crystalline product, mp 69−71 °C. Surprisingly at the time, microwave heating of this solid in chloroform failed to produce any discernible amounts of what would have been the expected product, **8**, given the claimed structure **7**.[1] Adding to the puzzle, it was found that the crystalline product could not be retrieved after it had been dissolved in chloroform, even without thermolysis (i.e., at room temperature). Instead, evaporation of the solvent leaves a residue which does not have the properties of its precursor, allegedly **7**. The residue from chloroform could be separated into components **5** and **9** by exploiting their differing acidic and neutral solubility properties, respectively.

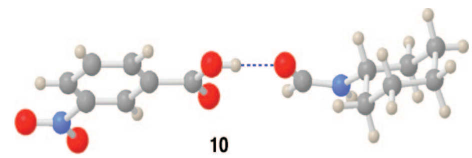
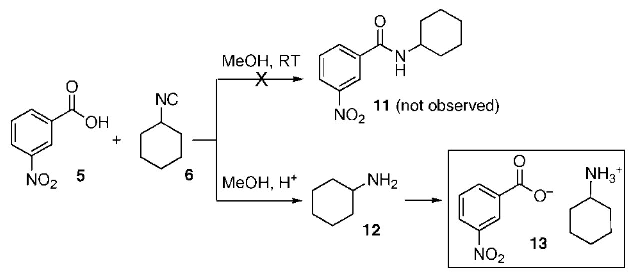


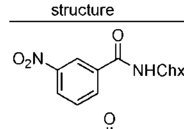
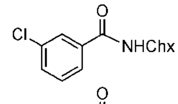
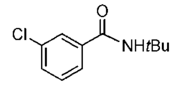
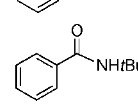
Figure 1

Fortunately, it proved possible to obtain some diffraction-worthy crystals from the product of the reaction of **5** and **6**. Crystallographic analysis of the sample revealed the structure to be **10**, a stable complex (*fascinating in its own right!*) between *N*-formylcyclohexylamine **9** and *m*-nitrobenzoic acid **5** (see Figure 1).[10] Apparently, the fragile molecular association between **5** and **9** unravels upon dissolution in chloroform. Thus, the claim that the reaction of **5** and **6** produces FCMA **7** is not correct.

Also noteworthy was a report, in the same paper, describing a high yielding formation of amides (cf. **11**, Scheme 2) from reactions of various benzoic acids (cf. **5**) and isonitriles (cf. **6)** conducted in methanol at room temperature.[5a] Our previous work,[1] admittedly conducted in chloroform, showed virtually no reaction between acids and isonitriles at room temperature. Moreover we suspected

Scheme 2

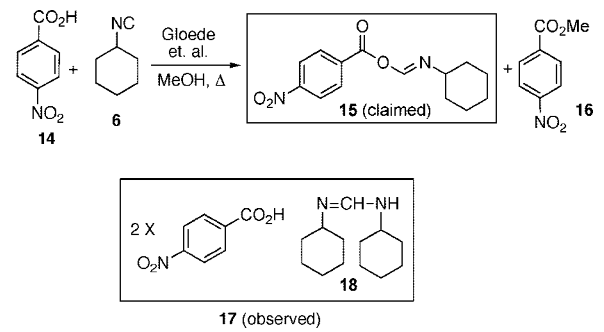


claimed structure	Shaabani's mp (°C)	Literature mp (°C)
	218-220 °C	146 °C (Cooley) 166 °C (Rahman)
	184-186 °C	121 °C (Cooley)
	228-230 °C	125 °C (Femholz)
	223-224 °C	133 °C (Katritzky)

† Sloan-Kettering Institute for Cancer Research.
‡ City University of New York.
§ Columbia University.
# Professor Emeritus, Queen's College, City University of New York.

10.1021/ja8047078 CCC: $40.75

Scheme 3

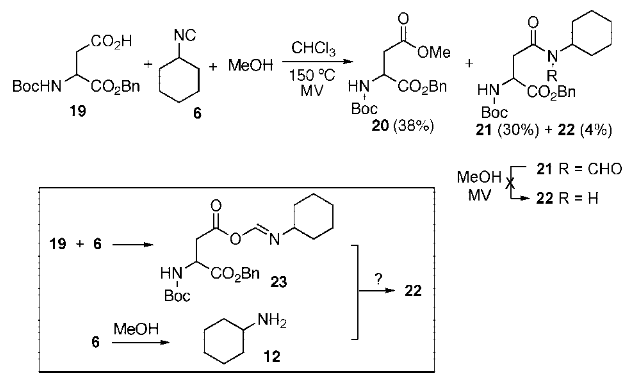


that if a FCMA (cf. **3**) intermediate were produced, it would have suffered conversion to the corresponding methyl ester. Accordingly, we repeated the reaction under the authors' conditions, that is, methanol as the solvent, at room temperature. As before, we had no difficulty in duplicating the published gross observations but we were not in agreement on the assignments. However, the assignments of simple amidic structures to the resultant crystalline products are not correct. First, several of the alleged amides had actually been previously reported in the literature.[11] In each case that could be checked, there was a large discrepancy in melting points between the alleged "amides" reported from the isonitrile-based coupling reactions and those previously reported. In each case the melting points of the purported amides reported[5a] were much higher than those previously reported for the authentic amides. Furthermore, in several cases, we prepared authentic amide samples ourselves by standard (cf. DCC) coupling methods. The NMR spectra of the authentic amides were very different from those of the amides claimed as arising from the isonitrile method.[5a]

In pursuing the matter, it became clear that the product of the reaction of **5** + **6** in methanol is not the amide **11** but rather the salt **13**, arising from the neutralization of the acid **5** and cyclohexyl amine **12**. Indeed, the same material as that synthesized by the authors (cf. **13**) was generated by simply mixing equivalent amounts of **5** and **12**. It is likely that **12** arises from a well-precedented, though mechanistically unclear, methanol-mediated conversion of isonitriles to amines.[12] Neutralization of the amine **12** provides the actual product, salt **13**.

Another earlier paper by Gloede et al. on the reaction of isonitriles and carboxylic acids (Scheme 3) provoked skepticism on our part.[5b,c] It was reported that the reaction of *p*-nitrobenzoic acid **14** and cyclohexylisonitrile **6**, when conducted in methanol under reflux, gave rise to FCMA **15**, mp 174−176 °C. Again, for obvious reasons,[13] we wondered whether such a FCMA could have persisted in methanol. Accordingly, we repeated the experiment and obtained, exactly as reported, a crystalline compound, mp 173−175 °C (in addition to varying quantities of methyl ester **16**). However, it was soon found that the high melting product is actually **17**, the *p*-nitrobenzoic acid salt of 1,3-dicyclohexylamidine **18**.[14] This structure was confirmed by spectroscopic analysis of the product formed from mixing 2 equiv **14** and 1 equiv **18**.[15] Furthermore, removal of *p*-nitrobenzoic acid by basic workup afforded amidine **18** as the product. While the definition of a specific pathway for formation of **17** from among several obvious possibilities is not available from our data, qualitatively, it must involve, in some form, the methanolytic progression of **6** toward cyclohexylamine **12** as discussed above. The formation of the amidine **18** may well reflect an addition reaction of cyclohexylamine with **6**[16] or an acid−mediated condensation between *N*-cyclohexylformamide **9** (or its equivalent) and cyclohexylamine **12** (or its functional equivalent).[17]

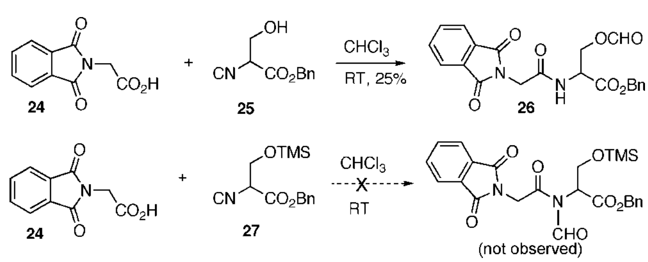
Scheme 4



While this uncertainty remains to be sorted out, it is clear that the published assertions which claimed the formation and survival of labile FCMA systems in the presence of putative acyl acceptors (for instance, methanol or water as solvents) are not correct.[18] In addition to the cases studied above, there may well be other instances where such claims warrant re-examination.[5e]

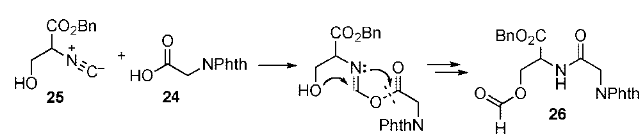
Motivated by the results described above, we asked whether a relatively weak nucleophile, such as methanol, could compete with 1,3-O→N acyl transfer in the context of a microwave mediated 2CC experiment (Scheme 4). Under these near stoichiometric conditions, substantial methanol-induced conversion of isonitrile to amine[12] would hopefully be attenuated. We started by studying the reaction of ca. 1:1:1 equiv of acid **19**, isonitrile **6**, and methanol under the usual microwave-mediated thermolysis. In the event, there was obtained ca. 38% yield of methyl ester **20**, the expected two-component coupling product **21** (30%), and traces of the amide **22** (4%). Separately, it was demonstrated that amide **22** does not arise from methanolytic deformylation of **21** under closely simulated methanol conditions. It is likely that **22** comes about from small amounts of cyclohexylamine (**12**) or its equivalent arising from **6**. Thus, acylation of **12** by FCMA **23** could lead to **22**.

Scheme 5



Finally, it was of interest to study the possibility of a 2CC reaction between phthaloyl glycine **24** and serine isonitrile benzyl ester **25** as a model for interdiction by an intramolecular hydroxyl group (Scheme 5). Remarkably, even at room temperature, the 2CC reaction does occur, giving rise to **26**, although in only ca. 25% yield. In an important control experiment, it was shown that hydroxyl protected serine isonitrile derivative **27**[19] seemingly does not react with **24** at all at room temperature.

Scheme 6



Our data do not allow us to distinguish between several obvious variations of the general scheme suggested in Scheme 6. Globally, the teaching seems to be that an otherwise unfavorable formation of a FCMA can be driven to product **26** through neighboring hydroxyl participation to enable the 1,3-O→N acyl transfer at room temperature.[18]

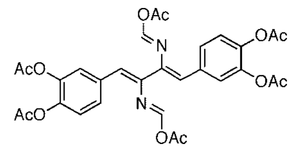
The formation of **26** points to an eventual approach to serine ligation.[20] In the succeeding paper, we probe subtle but important mechanistic issues as well as new directions for the 2CC reaction.

Acknowledgment. Support for this research was provided by the National Institutes of Health (CA28824 to S.J.D.). This investigation was supported by a "Research Centers in Minority Institutions" award, RR-03037 (to L.J.T.), from the National Center for Research Resources, National Institutes of Health. Special thanks go to Rebecca Wilson for editorial consultation and Dana Ryan for assistance with the preparation of the manuscript. We thank Dr. Jianglong Zhu and Dr. Brendan Crowley for their helpful discussions. We thank Dr. George Sukenick for NMR spectroscopic assistance, and Ms. Hui Fang and Ms. Sylvi Rusli for mass spectrometric assistance. We also thank Prof. Shaabani for supplying experimental details regarding ref 5a and Dr. Isaka for a personal communication regarding ref 5e.

Supporting Information Available: Detailed experimental procedures, copies of all spectral data, full characterization, and a cif file of X-ray for compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 5446. (b) Jones, G. O.; Li, X.; Hayden, A. D.; Houk, K. N.; Danishefsky, S. J. *Org. Lett.* Published online August 16, 2008, http://dx.doi.org/10.1021/ol8016287.
(2) (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181. (b) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386. For reviews, see: (c) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1. (d) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (e) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
(3) The reaction described here is a special instance of a Mumm rearrangement which involves a 1,3-O→N acyl transfer not in the formimidate series. However, the formimidate context reported here renders this reaction unique. For literature access to the Mumm reaction, see: (a) Mumm, O.; Hesse, H.; Volquartz, H. *Ber.* **1915**, *48*, 379. (b) Curtin, D. Y.; Miller, L. L. *J. Am. Chem. Soc.* **1967**, *89*, 637. (c) Sheehan, J. C.; Corey, E. J. *J. Am. Chem. Soc.* **1952**, *74*, 4555. (d) Schwarz, J. S. P. *J. Org. Chem.* **1972**, *37*, 2906. (e) Darbeau, R. W.; White, E. H.; Nunez, N.; Coit, B.; Daigle, M. *J. Org. Chem.* **2000**, *65*, 1115.
(4) In our first paper in this series (ref 1), we described a direct pathway to **4**, *via* a formal cycloaddition pathway, which does not pass through **3**. In this paper, we focus on the presumed pathway from **3** to **4**. However, involvement of the direct cycloaddition pathway to reach **4** is not ruled out.
(5) (a) Shaabani, A.; Soleimani, E.; Rezayan, A. H. *Tetrahedron Lett.* **2007**, *48*, 6137. (b) Gloede, J.; Gross, H. *Z. Chem.* **1968**, *8*, 219. (c) Gloede, J. *J. Prakt. Chem.* **1982**, *324*, 667. (d) Shono, T.; Kimura, M.; Ito, Y.; Nishida, K.; Oda, R. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 635. The structure was presumed on the basis of its infrared spectrum. (e) Isaka, M.; Boonkhao, B.; Rachtawee, P.; Auncharoen, P. *J. Nat. Prod.* **2007**, *70*, 656. Actually, it is not clear whether the FCMA structure claimed in the paper is correct (see figure below) (personal communication from Dr. M. Isaka).



For cyclic structures of formimidate-carboxylate mixed anhydride, see: (f) Black, D. S. C.; Boscacci, A. B. *Aus. J. Chem.* **1977**, *30*, 1109. (g) Kobayashi, S.; Tsukamoto, Y.; Saegusa, T. *Macromolecules* **1990**, *23*, 2608. (h) Reed, P. E.; Katzenellenbogen, J. A. *J. Med. Chem.* **1991**, *34*, 1162. (i) Gomory, A.; Somogyi, A.; Tamas, J.; Stajer, G.; Bernath, G.; Komaromi, I. *Int. J. Mass Spec. Ion Proc.* **1991**, *107*, 225.
(6) In some instances, spectroscopic suggestion of such an intermediate has been described, for example: (a) Hou, J-L.; Ajami, D.; Rebek, J., Jr *J. Am. Chem. Soc.* **2008**, *130*, 7810. (b) Restorp, P.; Rebek, J., Jr *J. Am. Soc. Chem.* **2008**, *130*, 11850.
(7) Greater progress in characterization has been achieved with related mixed anhydrides which are not in the formimidate series. cf. inter alia: (a) Kawasaki, K.; Tsumura, S.; Katsuki, T. *Synlett.* **1995**, *12*, 1245. (b) Schwarz, J. S. P. *J. Org. Chem.* **1972**, *37*, 2906. (c) Cambie, R. C.; Hayward, R. C.; Roberts, J. L.; Rutledge, P. S. *J. Chem. Soc., Perkin Transc. 1* **1974**, *15*, 1858.
(8) The authors reported absorptions at 1687 and 1598 cm^{-1} for the alleged mixed anhydride **7**.
(9) Typical IR absorptions reported for a nonformimidate mixed anhydride of the type **7** are ca. 1710−1660 cm^{-1}; see ref 7.
(10) The NMR spectrum of the diffraction worthy crystal is the same as that of the bulk material. For a crystal structure based on a hydrogen-bonded complex between two "small molecules", see: Leiserowitz, L.; Nader, F. *Acta Crystallogr.* **1977**, *B33*, 2719.
(11) (a) Atta-ur-Rahman; Basha, A.; Waheed, N. *Tetrahedron Lett.* **1976**, *3*, 219. (b) Cooley, J. H.; Stone, D. M.; Oguri, H. *J. Org. Chem.* **1977**, *42*, 3096. (c) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* **1989**, *54*, 1144. (d) Rigby, J. H.; Laurent, S. *J. Org. Chem.* **1998**, *63*, 6742. (e) Fernholz, H.; Schmidt, H. J. *Angew. Chem., Int. Ed.* **1969**, *8*, 521. (f) Callens, E.; Burton, A. J.; Barrett, A. G. M. *Tetrahedron Lett.* **2006**, *47*, 8699. (g) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210. (h) Shrestha-Dawadi, P. B.; Jochims, J. C. *Synthesis* **1993**, *4*, 426. (i) Siebenmann, C.; Schnitzer, R. J. *J. Am. Chem. Soc.* **1943**, *65*, 2126.
(12) (a) Gassman, P. G.; Haberman, L. M. *Tetrahedron Lett.* **1985**, *26*, 4971. (b) Kotha, S.; Brahmachary, E. *Bioorg. Med. Chem.* **2002**, *10*, 2291. (c) Priestley, E. S.; Decicco, C. P. *Org. Lett.* **2000**, *2*, 3095. (d) Kotha, S.; Screenivasachary, N.; Mohanraja, K.; Durani, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1421.
(13) Microwave heating of Gloede's product (purported **15**) in chloroform again failed to produce the desired *N*-formylamide.
(14) It should be noted that the elemental analysis, "%N = 10.45," (ref 3b) of Gloede's product **15** (calcd % N = 10.14) fits better for compound **17** (calcd. %N = 10.33) than that concluded by Gloede. As reported by the authors, the claimed **15** does not react with methanol under reflux conditions.
(15) Authentic 1,3-dicyclohexylamidine (**18**) was prepared according to a known procedure: Taylor, E. C.; Ehrhart, W. A. *J. Org. Chem.* **1963**, *28*, 1108.
(16) Simon, J. R. *Synthesis* **2001**, *13*, 2011.
(17) (a) Price, C. C.; Roberts, R. M. *J. Am. Chem. Soc.* **1946**, *68*, 1255. (b) Olguín, L. F.; Jiménez-Estrada, M.; Bárzana, E.; Navarro-Ocaña, A. *Synlett* **2005**, *2*, 340.
(18) This concept was suggested to account for the small amount of amide formation at room temperature; see ref 1. For cyclization examples that do not follow Baldwin's rule, see: Astudillo, M. E. A.; Chokotho, N. C. J.; Jarvis, T. C.; Johnson, C. D.; Lewis, C. C.; McDonnel, P. D. *Tetrahedron* **1985**, *41*, 5919.
(19) Both isonitriles **25** and **27** were prepared in racemic form.
(20) Okamoto, R.; Kajihara, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 5402.

JA8047078