Published in final edited form as:

Tetrahedron Lett. 2009 February 4; 50(5): 577–579. doi:10.1016/j.tetlet.2008.11.069.

On the Preparation of Enantiomerically Pure Isonitriles from Amino Acid Esters and Peptides

Jianglong Zhu^a, Xiangyang Wu^a, and Samuel J. Danishefsky^{a,b}

^aLaboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, NY 10065, USA

^bDepartment of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027, USA

Abstract

An improved method for the synthesis of enantiomerically pure isonitriles from amino acid esters and dipeptides is described.

Initially discovered in 1867 by Gautier¹ and Hofmann,² isonitriles have emerged as a synthetically useful class of organic compounds. A number of important isonitrile-based methods had been developed, including the Passerini reaction³ and the Ugi 4-component coupling reaction,⁴ among others.⁵ We recently reported a novel thermally induced two-component coupling reaction between isonitriles and carboxylic acids, which provides ready access to various *N*-formyl imides.⁶ Importantly, this coupling methodology has been extended to the preparation of peptides bearing *N*-formyl imides. We envision that these peptides could be further elongated through iterative isonitrile–carboxylic acid coupling reactions.

The feasibility of such a peptide coupling strategy is predicated on our ability to gain access to enantiomerically pure amino acid- and N-terminal peptide-derived isonitriles. The typical literature-based approach to the preparation of isonitriles involves dehydration of *N*-alkyl or *N*-arylformamides.⁷ A number of reagents (cf. phosgene,^{6,8} diphosgene,⁹ triphosgene,¹⁰ and POCl₃¹¹) and tertiary amine bases (triethylamine and *N*-methyl morpholine [NMM]) have been employed to accomplish such dehydrations. In 1977, Ugi and co-workers described the syntheses of several optically active α -isocyanocarboxylic acid derivatives, including **2**, which was prepared from **1** through exposure to either phosgene/NMM¹² or diphosgene/NMM.⁸ However, under these conditions, we observed significant racemization of the *N*-formyl amino acid esters (Table 1, entries 2 and 3).¹² Others have since reported the preparation of various α -isocyanocarboxylic esters; however, in these cases, either limited or no information on the enantiomeric excess of the α -chiral center was provided.¹³ In some instances, syntheses of racemates were reported.¹⁴ Herein, we describe the development of an effective protocol for the preparation of a variety of enantiomerically pure isonitriles from amino acid esters and N-terminal peptides. With enantiomerically enriched isonitriles in hand, we investigated the conditions required for their racemization.

In our initial studies, we focused on the enantioselective preparation of isonitrile **2** from *N*-formyl phenylalanine methyl ester (**1**). As shown in Table 1, treatment of **1** with POCl₃/Et₃N gave the racemized product **2** in good yield (entry 1). Postulating that racemization may be caused by use of overly strong dehydrating conditions, we turned to the use of milder protocols, with particular emphasis on the maintenance of a neutral or slightly acidic reaction environment. In the event, treatment of a mixture of **1** and NMM (2.0 equiv.) at –40 °C with solid triphosgene (0.35 equiv.) followed by warming to –30 °C furnished **2** in 79%

yield with slight racemization (*er* = 18:1, entry 4). The enantiomeric ratio was further improved when the reaction was conducted at a lower temperature (entry 5).

We next sought to explore the scope of the reaction with respect to the nature of the particular amino acid residue. Thus, as outlined in Table 2 (entries 1-6), a variety of amino ester isonitriles could be prepared in good yield and with high levels of optical purity from the corresponding *N*-formyl amino esters. The synthesis of CN-*L*-Asp-(OBn)₂ was accompanied by slight racemization of the α -chiral center (entry 4). The preparation of methyl α -isocyano-phenylacetate had been previously reported to be very challenging. Under our optimal conditions, this isonitrile was obtained in good yield and in optically active form ($[\alpha]_D = +96.0$); however, the compound was found to be very unstable to chromatography and all attempts to obtain an HPLC-based enantiomeric ratio were unsuccessful (entry 5). Importantly, an α -cyano alanine phenolic ester, bearing the *ortho*-thiophenolic ester moiety used in the coupling of peptides and glycopeptides, was efficiently prepared under our protocol (entry 6).¹⁵

The applicability of this protocol to more complex systems was further demonstrated in the context of preparing isonitrile derivatives of two N-terminal dipeptides.^{12, 16} Happily, under slightly modified conditions (using 2,6-lutidine as a base in lieu of NMM, and at temperatures of $-50\text{ }^{\circ}\text{C}$), we successfully prepared the isonitrile derivatives of Ala-Ala-OBn (entry 7) and Phe-Leu-OMe (entry 8). Both dipeptides were obtained as single diastereomers and in good yields.

In order to gain further insight into the parameters of the racemization problem, we probed conditions under which the optical purity of the α -isocyano amino ester is eroded. We selected two rather readily racemizable isonitrile amino esters – CN-*L*-Phe-OMe (**2**) and CN-*L*-Ala-OBn (**3**) – and subjected them to a variety of conditions which might induce racemization. As shown in Table 3, we found that, while treatment of these two isonitriles with 1.0 equiv. NMM at $-30\text{ }^{\circ}\text{C}$ for one hour did not lead to detectable racemization (entries 3 and 7), exposure to 1.0 equiv. NMM at room temperature resulted in partial racemization (entry 4 and 8). Furthermore, treatment with triethylamine led to significant levels of racemization (entries 1, 2, 5, and 6), indicating that the choice of base is indeed very crucial.

In summary, we have described herein an improved method for the preparation of enantiomerically pure isonitriles from the corresponding α -amino acid esters and N-terminal dipeptide substrates. This coupling method could potentially be utilized in the preparation of peptides through our newly developed two-component isonitrile–carboxylic acid coupling chemistry. Such applications have been realized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the NIH (CA28824 to S.J.D.). Special thanks go to Rebecca Wilson for editorial consultation and Dana Ryan for assistance with the preparation of the manuscript. We thank Dr. Xuechen Li, Dr. Yu Yuan and Dr. Cindy Kan for their helpful discussions. We thank Dr. George Sukenick, Ms. Hui Fang, and Ms. Sylvi Rusli of the Sloan-Kettering Institute's NMR core facility for mass spectral and NMR spectroscopic analysis.

References

1. Gautier A. Liebigs Ann Chem. 1867; 142:289.
2. Hofmann AW. Liebigs Ann Chem. 1867; 144:114.

3. (a) Passerini M, Simone L. *Gazz Chim Ital.* 1921; 51:126–129. (b) Passerini M, Ragni G. *Gazz Chim Ital.* 1931; 61:964–969.
4. Ugi, I.; Lohberger, S.; Karl, R. The Passerini and Ugi Reactions, Chapter 4.6, *Comprehensive Organic Synthesis*. Vol. 2. 1991. p. 1083
5. Gokel G. *Isonitrile Chem.* 1971:235.
6. (a) Li X, Danishefsky SJ. *J Am Chem Soc.* 2008; 130:5446. [PubMed: 18370392] (b) Li X, Yuan Y, Berkowitz WF, Todaro LJ, Danishefsky SJ. *J Am Chem Soc.* 2008; 130:13222. [PubMed: 18783224] (c) Li X, Yuan Y, Kan C, Danishefsky SJ. *J Am Chem Soc.* 2008; 130:13225. [PubMed: 18783225]
7. Ugi I, Fetrer U, Eholzer U, Knupfer H, Offermann K. *Angew Chem.* 1965; 77:492. *Angew Chem, Int Ed.* 1965; 4:472.
8. (a) Ugi I, Befz W, Fetzter U, Offermann K. *Chem Ber.* 1961; 94:2814. (b) Hoffmann P, Gokef G, Marquarding D, Ugi I. *Isonitrile Chem.* 1971:9.
9. Skorna G, Ugi I. *Angew Chem.* 1977; 89:267. *Angew Chem, Int Ed.* 1977; 16:259.
10. Eckert H, Forster B. *Angew Chem.* 1987; 99:922. *Angew Chem, Int Ed.* 1987; 26:894–895.
11. Obrecht R, Herrmann R, Ugi I. *Synthesis.* 1985:400.
12. Urban R, Marquarding D, Seidel P, Ugi I, Weinelt A. *Chem Ber.* 1977; 110:2012.
13. (a) Seebach D, Adam G, Gees T, Schiess M, Weigand W. *Chem Ber.* 1988; 121:507. (b) Horwell DC, Nichols PD, Roberts E. *Tetrahedron Lett.* 1994; 35:939. (c) Piscopio AD, Miller JF, Koch K. *Tetrahedron.* 1999; 55:8189.
14. Elders N, Schmitz RF, De Kanter FJJ, Ruijter E, Groen MB, Orru RVA. *J Org Chem.* 2007; 72:6135. [PubMed: 17628108]
15. Warren JD, Miller JS, Keding SJ, Danishefsky SJ. *J Am Chem Soc.* 2004; 126:6576. [PubMed: 15161285]
16. Preparation of several isocyano dipeptides was reported using $\text{POCl}_3/\text{Et}_3\text{N}$, see Zhao G, Bughin C, Bienayme H, Zhu J. *Synlett.* 2003:1153.

Table 1

Chemical reaction scheme showing the conversion of compound 1 to compound 2. Compound 1 is (S)-2-benzyl-2-oxo-3-phenylpropanal, and compound 2 is (S)-2-benzyl-2-oxo-3-phenylpropanenitrile. The reaction is labeled "conditions".

entry	conditions	yield	er
1	POCl ₃ /Et ₃ N (1.2 eq., 5.0 eq.), -78 to 0 °C	80%	1:1
2	phosgene/NMM (1.2 eq, 3.5 eq), -30 °C ¹²	51%	1.2:1
3	diphosgene/NMM (0.5 eq., 2.1 eq), -30 °C ⁸	75%	NA
4	triphosgene/NMM (0.35 eq., 2.0 eq.), -40 to -30°C	79%	18:1
5	triphosgene/NMM (0.35 eq., 2.0 eq.), -78 to -30°C	82%	>99:1

Table 2

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{H}-\text{C}-\text{NH}-\text{CH}(\text{R})-\text{C}(=\text{O})-\text{X} \\ \text{H} \end{array} \xrightarrow[\text{NMM (2.0 equiv), CH}_2\text{Cl}_2]{\text{triphosgene (0.35 equiv), } -78^\circ\text{C to } -30^\circ\text{C}} \begin{array}{c} \text{O} \\ \parallel \\ \text{CN}-\text{CH}(\text{R})-\text{C}(=\text{O})-\text{X} \end{array} $			
entry	conditions	yield	er
1	3	75%	>99:1
2	4	90%	>99:1
3	5	63%	>99:1
4	6	62%	32:1
5	7	79%	ND
6	8	52%	>99:1
7	9	70% ^a	single diastereomer
8	10	58% ^a	single diastereomer

^a Conditions: 2,6-lutidine, -50 °C.

Table 3

entry	starting isonitrile	racemization conditions	results (<i>er</i>)
1	2	1.0 equiv. Et ₃ N, CH ₂ Cl ₂ , −30 °C, 1.5 h	1.25:1
2	2	1.0 equiv. Et ₃ N, CH ₂ Cl ₂ , RT, 20 min	1:1
3	2	1.0 equiv. NMM, CH ₂ Cl ₂ , −30 °C, 1 h	>99:1
4	2	1.0 equiv. NMM, CH ₂ Cl ₂ , RT, 20 min	7.3:1
5	3	1.0 equiv. Et ₃ N, CH ₂ Cl ₂ , −30 °C, 1 h	4.5:1
6	3	1.0 equiv. Et ₃ N, CH ₂ Cl ₂ , RT, 20 min	1:1
7	3	1.0 equiv. NMM, CH ₂ Cl ₂ , −30 °C, 1 h	>99:1
8	3	1.0 equiv. NMM, CH ₂ Cl ₂ , RT, 20 min	13.5:1