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On the preparation of enantiomerically pure isonitriles from amino acid esters and peptides

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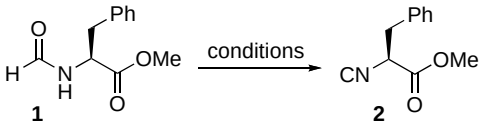
ABSTRACT

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

Initially discovered in 1867 by Gautier[1] 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 reaction[3] 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 $POCl_3$[11]) 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/NMM[12] or diphosgene/NMM.[9] 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-isocyano carboxylic 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.

Table 1



1 **2**

Entry	Conditions	Yield (%)	er
1	$POCl_3/Et_3N$ (1.2 equiv, 5.0 equiv), −78 to 0 °C	80	1:1
2	Phosgene/NMM (1.2 equiv, 3.5 equiv), −30 °C[12]	51	1.2:1
3	Diphosgene/NMM (0.5 equiv, 2.1 equiv), −30 °C[9]	75	NA
4	Triphosgene/NMM (0.35 equiv, 2.0 equiv), −40 to −30 °C	79	18:1
5	Triphosgene/NMM (0.35 equiv, 2.0 equiv), −78 to −30 °C	82	>99:1

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 $POCl_3/Et_3N$ 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-

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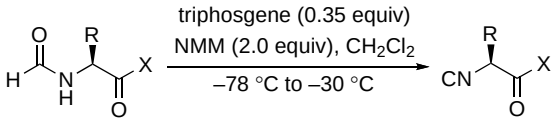
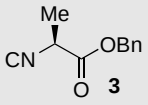
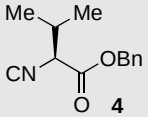
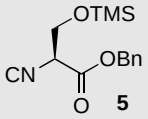
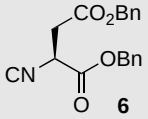
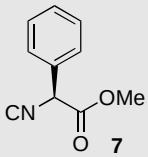
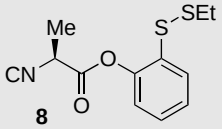
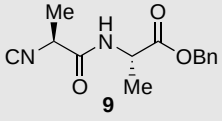
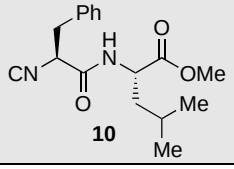
Table 2



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

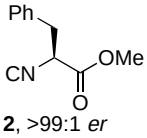
[a] Conditions: 2,6-lutidine, −50 °C.

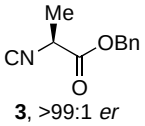
phenylacetate had been previously reported to be very challenging.[15] Under our optimal conditions, this isonitrile was obtained in good yield and in optically active form ($[\alpha]_D$) +96.0; however, the compound was found to be very unstable to chromatography and all attempts to obtain an HPLC-based 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).[16]

The applicability of this protocol to more complex systems was further demonstrated in the context of preparing isonitrile derivatives of two N-terminal dipeptides.[12,17] Happily, under slightly modified conditions (using 2,6-lutidine as a base in lieu of NMM, and at temperatures of −50 °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 °C for 1 h did not lead to detectable racemization (entries 3 and 7), exposure to 1.0 equiv NMM at room temperature resulted in partial racemization (entries 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.

Table 3


2, >99:1 *er*


3, >99:1 *er*

Entry	Starting isonitrile	Racemization conditions	Results (er)
1	**2**	1.0 equiv Et_3N, CH_2Cl_2, −30 °C, 1.5 h	1.25:1
2	**2**	1.0 equiv Et_3N, CH_2Cl_2, rt, 20 min	1:1
3	**2**	1.0 equiv NMM, CH_2Cl_2, −30 °C, 1 h	>99:1
4	**2**	1.0 equiv NMM, CH_2Cl_2, rt, 20 min	7.3:1
5	**3**	1.0 equiv Et_3N, CH_2Cl_2, −30 °C, 1 h	4.5:1
6	**3**	1.0 equiv Et_3N, CH_2Cl_2, rt, 20 min	1:1
7	**3**	1.0 equiv NMM, CH_2Cl_2, −30 °C, 1 h	>99:1
8	**3**	1.0 equiv NMM, CH_2Cl_2, rt, 20 min	13.5:1

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.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.069.

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