Asymmetric Amino Acid Synthesis: Mitsunobu Reaction on Chiral Cyanohydrins

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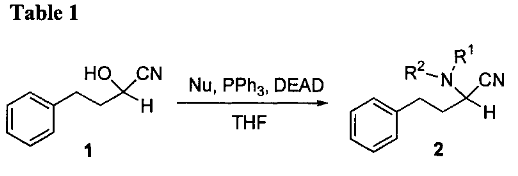
Dedicated, with admiration and respect to Professor E.J. Corey

Abstract: BOC(SES)NH was reacted with chiral cyanohydrins using the Mitsunobu reaction to give good yields of protected α-aminonitriles, which were converted to chiral amino and imino acids.

Amino acids are the basic structural units of proteins and important chiral building blocks for organic synthesis. The centrality of this synthon in both chemistry and biology has inspired an array of synthetic methodology directed toward asymmetric amino acid synthesis.[1] As part of our research effort in the area of peptidomimetics, we are exploring various methods of producing optically active amino acids under mild reaction conditions. Relavent to this study, Davis and co-workers have utilized auxiliary control in the Strecker reaction to produce optically enriched sulfinimines as amino acid precurrsors where the R group is *tert*-butyl or phenyl.[2] In addition, optically active *R*-cyanohydrins have been transformed into α-acetonitriles of opposite configuration under Mitsunobu conditions and subsequently solvolyzed to *S*-cyanohydrins in high chemical and optical yield.[3] We were interested in extending aspects of the Strecker approach to the production of chiral amino acids by using an appropriately protected amine as a Mitsunobu nucleophile. In this communication, we report on the application of the Mitsunobu reaction employed to deliver the amine nitrogen to chiral cyanohydrins, generated via enzyme (oxynitrilase) catalyzed conversion of precursor aldehydes.

To determine the feasibility of this approach, we initially examined a number of "N-delivering" nucleophiles. N,N-disubstituted (electron withdrawing groups) nucleophiles were first surveyed for their utility in the Mitsunobu reaction using the cyanohydrin of dihydro-cinnamaldehyde **1**, as our model system (Table 1). Di-*tert*-butyl imino-dicarboxylate, entry a, did not react with **1** and the corresponding *tert*-butyl(trifluoroethoxy) iminodicarboxylate (entry c) gave only a poor yield of **2c**. Employing a tosyl group did facilitate conversion to **2b** in high chemical yield, however subsequent removal of the tosyl group required harsh conditions incompatible, in our view with a variety of R groups of interest. BOC(SES)NH **1d**, a versatile bis-protected amine first utilized as a Mitsunobu reactant by Hart[4] in an approach to the manzamine alkaloids, was examined and determined to give an excellent yield of **2d**. This reagent was chosen for subsequent study and proved to react effectively under Mitsunobu conditions with a variety of chiral cyanohydrins as shown in Table 2.

Table 1



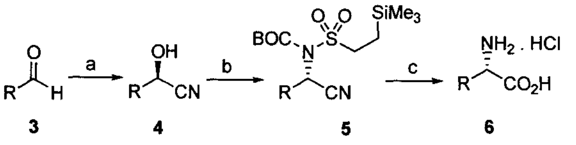
Entry	Nu	2(%)
a	$HNBOC_2$	0
b	HNBOC(Tosyl)	89
c	$HNBOC(CO_2CH_2CF_3)$	28
d	HNBOC(SES)	89

SES = [2-(trimethylsilyl)ethyl]sulfonyl

Optically pure (or enantiomerically enriched) cyanohydrins can be made using a number of recently developed stereoselective synthetic strategies.[5] A convenient preparation complimentary to these synthetic approaches, using oxynitrilase (Almond Meal, Sigma) and acetone cyanohydrin as a transcyanating agent has also been reported.[6] We prepared a number of chiral *R*-cyanohydrins using this procedure.

Table 2 summarizes the results of our 3-step sequence on 7 different substrates to produce chiral amino acids. As reported previously, in most cases, the Almond Meal preparation gave good yields of chiral *R*-cyanohydrins **4** with R = phenyl a notable exception.[7]

Table 2

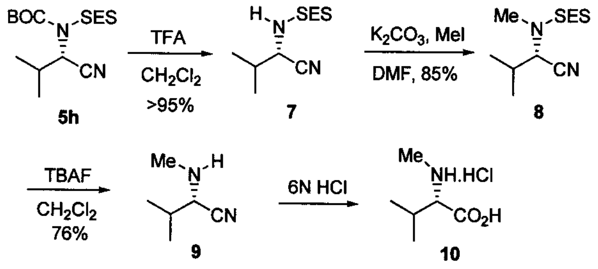


entry	R	4(%)	5(%)	6(%)	6(ee)[d]
a	C_4H_9-	82	90	89	>99
b	$CH_3SCH_2CH_2$-	70	87	88	95
c	$(CH_3)_2CHCH_2$-	53	85	93	>99
d	c-C_6H_{11}-	68	84	87	>99
e	$PhCH_2CH_2$-	55	89	94	60
f	Ph-	27	48	91	0
g	furanyl-	50	10	-	-

Reaction conditions: (a) oxynitrilase, $CH_3C(OH)CNCH_3$, (b) BOC(SES)NH, PPh_3, DEAD, (c) i. 6N HCl, ii. propylene oxide, EtOH, reflux, (d) ee's determined by chiral HPLC comparison to racemic material (CROWNPAK CR, 50 °C, 0.1% $HClO_4$-15% MeOH-85% H_2O, 0.4 ml/min, 210 nm uv detection)

As described above, conversion to the N-protected cyanohydrins **5** using the Mitsunobu reaction was, in general, found to be a high yielding reaction, except for cases when R is an aromatic group (phenyl and furanyl, entries f and g). Hydrolysis with 6N HCl and treatment with propylene oxide gave the corresponding amino acids **6a-f**, which were analysed by chiral HPLC to determine their optical purity. Cases in which R was an aliphatic group gave ee's in the desirable >95% range, even for sterically hindered cases like cyclohexyl. Dihydrocinnamoyl and phenyl gave lower ee's of 60% and 0% respectively. The absolute stereochemistry of the products was determined by HPLC comparison to authentic samples of amino acids. As expected, the Mitsunobu reactions proceeded with inversion of configuration to give the *S*-amino acid products.

Further utility in this methodology was realized with mono-deprotection of the BOC group using TFA and subsequent alkylation to produce an imino acid. As a representative example of this procedure (Scheme 1) the protected aminonitrile **5h** was prepared from isobutyraldehyde, using the previously described procedure. Deprotection of the BOC group with TFA gave a near quantitative yield of SES protected aminonitrile **7**. Deprotonation with carbonate followed by alkylation with methyl iodide proceeded in high yield to give **8**. As described previously by Hart, the SES group can be removed with fluoride, in this case to give the N-methyl aminonitrile **9**. The latter is a versatile synthon, functionalized for subsequent elaboration to heterocyclic peptide mimics, or through treatment with acid, conversion to an N-methyl amino acid **10** as shown in Scheme 1.



Scheme 1

Ee determination by HPLC analysis and spectral comparison to authentic N-methylvaline hydrochloride indicated that product **10** was >95% enantiopure.

In summary, we have applied the Mitsunobu reaction of the BOC(SES)NH reagent to the hydroxy displacement of chiral cyanohydrins generated enzymatically from aldehydes, to provide a mild method of producing optically active amino acids. The reactions have been shown to go with the expected inversion of configuration. We are currently employing this sequence in the preparation of various non-proteinogenic amino acids for incorporation into structures of medicinal interest.

References and Notes

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(7) A modified procedure was recently reported using oxynitrilase from *Hevea brasiliensis* in which several aromatic and heteroaromatic aldehydes, including benzaldehyde and furanal, were converted to cycanohydrins in excellent chemical and optical yields.; Schmidt, M.; Herve, S.; Klempier, N.; Griengl, H. *Tetrahedron*, **1996**, *52*, 7883.