TRIAZOLINES 32. ATTEMPTS AT APPLICATION OF THE STRECKER SYNTHESIS TO HETEROCYCLIC SUBSTITUTED AMINO ACIDS

Pankaja K. Kadaba* and Louis P. Glavinos
Division of Medicinal Chemistry and Pharmaceutics
College of Pharmacy, Albert B. Chandler Medical Center,
University of Kentucky, Lexington, KY 40536-0082, U.S.A.

Abstract

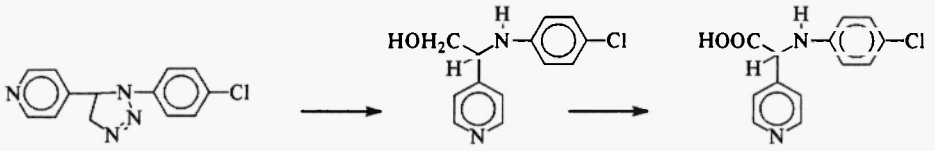
The Strecker synthesis provides a versatile route to the synthesis of both aliphatic and aromatic amino acids. It involves the formation of an α-amino nitrile by the addition of hydrogen cyanide to an aldimine, followed by acid hydrolysis of the nitrile to yield the amino acid. However, the Strecker method fails when applied to the synthesis of a 4-pyridyl substituted heterocyclic amino acid, and yields instead 4-pyridinecarboxanilide as the reaction product. These results indicate that the Strecker synthesis is not a useful route for the preparation of amino acids bearing electron withdrawing groups, such as the 4-pyridyl.

Introduction

Studies on the metabolism of 1-(4-chlorophenyl)-5-(4-pyridyl)-Δ²-1,2,3-triazoline **1**, a unique anticonvulsant agent (1-3), necessitated the synthesis of α-(4-pyridyl)-N-(4-chlorophenyl)glycine **3**, as a potential biotransformation product formed via the amino alcohol **2**. Although the synthesis of α-amino acids may be accomplished through a variety of reaction schemes (4,5), one of the more commonly used methods is the Strecker synthesis (6-8). Basically, the reaction involves heating an amine and an aldehyde in the presence of ammonium cyanide. There is evidence that first an aldimine is formed to which the hydrogen cyanide, generated *in situ* from the ammonium cyanide, adds to yield an α-amino nitrile (6-8) which upon acid hydrolysis yields the α-amino acid (Scheme II). The Strecker synthesis is the most well-studied reaction for amino acid preparation, and provides a versatile route to the synthesis of both aliphatic and aromatic α-amino acids. However, there are no published reports on the application of the Strecker reaction to the synthesis of heterocyclic substituted amino acids.

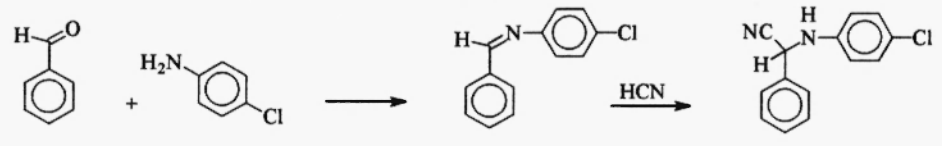
Results and Discussion

The Strecker synthesis with certain modifications was selected for the preparation of the α-(4-(pyridyl)-N-(4-chlorophenyl)glycine **3**. Instead of using a mixture of the aniline and the aldehyde, a purified sample of the aldimine, prepared from the respective aldehyde and aniline was employed. It was



1 **2** **3**

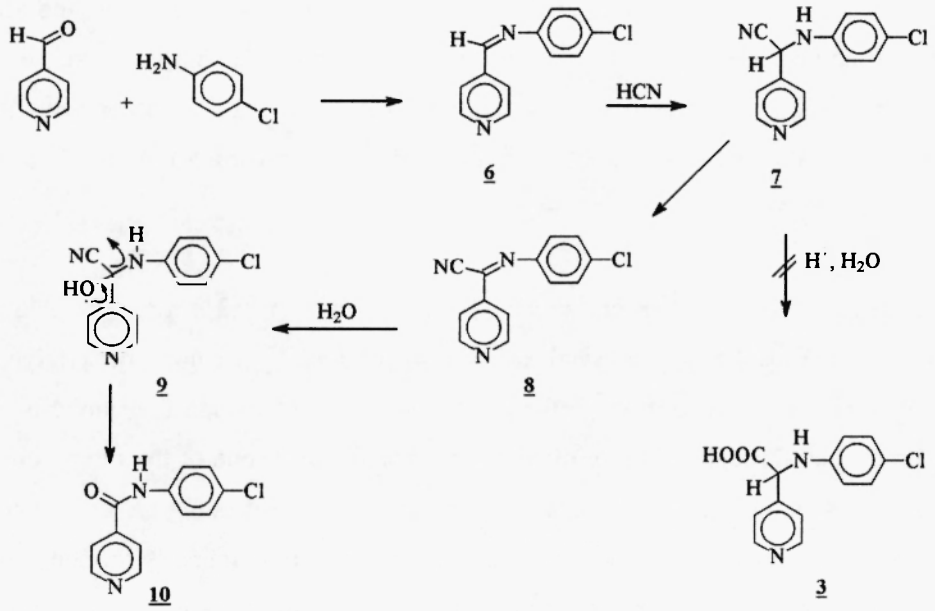
Biotransformation Pathway of Triazoline



4 **5**

Strecker Synthesis of α-Cyanobenzyl-4-chloroaniline

Scheme I



6 **7** **8** **9** **10** **3**

Strecker Synthesis of α-(4-Pyridyl)-N-(4-chlorophenyl)glycine

Scheme II

then reacted with hydrogen cyanide generated *in situ* from ammonium cyanide, formed from a mixture of equivalent amounts of ammonium chloride and sodium cyanide, and the reaction was allowed to run at room temperature. The applicability of these reaction conditions was then tested using the known reaction of benzylidene-4-chloroaniline **4** with hydrogen cyanide (6), which yielded 42% of the pure α-amino nitrile **5** after 96 h (Scheme I). Next, the aldimine **6** prepared from 4-pyridinecarboxaldehyde and 4-chloroaniline (9) was subjected to the same reaction procedure under identical conditions, except a longer reaction period of 120 h was used. This was necessary since studies on substituent effects in the Strecker reaction have

indicated that electron withdrawing substituents decrease the rate of hydrogen cyanide addition to the aldimine (6), and a 4-pyridyl group with the N incorporated on the ring, is electron withdrawing or π-deficient (10). However, no α-amino nitrile was obtained from this reaction.

The product from the reaction of 4-[(4-chlorophenyl)iminomethyl]pyridine **6** and ammonium cyanide, upon fractional crystallization, indicated that it consisted of one major component along with two minor ones. Surprisingly, IR analysis of the major component showed no CN stretch at 2240 cm^{-1}. An NMR spectrum of the product was analyzed to check the presence of a CH (δ 5.3) or NH (δ 4.1) chemical shift, similar to that observed for the hydrogen cyanide addition product from benzylidene-4-chloroaniline. No CH signal was found in the δ 5-6 region, although an NH signal was present. However, it was located too far down field in the δ 8.5 region to be correlated with the NH signal of the amino group of an amino nitrile. On the other hand, the NH signal moved upfield with increasing dilution of the sample, a characteristic of NH signals arising from acid amides (11). Elemental analysis, considered along with the IR and NMR data, indicated the product to be N-(4-chlorophenyl)-4-pyridinecarboxamide **10**; conclusive evidence for the product was obtained from the identical IR and NMR spectra and chromatographic mobility in HPLC, when compared with an authentic sample of N-(4-chlorophenyl)-isonicotinamide.

The formation of amide **10** in the Strecker reaction of the α-iminomethylpyridine **6** with hydrogen cyanide may be rationalized as shown in Scheme II. A key step in the reaction may involve oxidation of the α-amino nitrile **7** bearing the electron withdrawing 4-pyridyl group, to yield an α-imino nitrile **8**. A similar reaction has been previously reported for α-cyano-4-nitrobenzylaniline (6) substituted with the electron withdrawing 4-nitrophenyl group. The α-imino nitriles could be considered as "imidoyl cyanides", very similar to imidoyl chlorides (12). The latter are highly reactive molecules, very sensitive to traces of water, and are known to yield amides via the hydroxy compounds (4). In fact, in the synthesis of tetrazoles from imidoyl chlorides and inorganic azides, amide formation cannot be completely avoided even under anhydrous reaction conditions (13,14). By an analogous reaction path, the α-imino nitriles could be conceived to yield the α-hydroxy compound **9**, which would then rearrange to give the amides, although the α-cyano-4-nitrobenzylideneaniline has been isolated and not reported to yield the 4-nitrobenzamide.

Conclusions

Our results indicate that Strecker synthesis is not a useful route for amino acid synthesis from aldimines substituted with a π-deficient electron withdrawing heterocyclic ring system. However, it may be possible to apply the Strecker reaction to those cases where the heterocyclic substituent is a π-excessive pyrrole ring and should be investigated.

Experimental

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are not corrected. NMR Spectra were determined using a Varian EM-360 60-MHz NMR spectrometer, in $CDCl_3$ with TMS as internal standard. IR spectra were recorded on a Perkin Elmer 1430 Ratio Recording Infrared Spectrophotometer using KBr pellets.

Preparation of Aldimines

The aldimines were synthesized by known methods (9). Equimolar quantities of the oily aldehyde and aniline were mixed directly and the mixture warmed on a steam bath, when it turned into a solid mass, which was then recrystallized from ethanol.

Benzylidene-4-chloroaniline **4** was obtained as very pale yellow crystals, m.p. 62-62.5°C (Lit. m.p. 62-63°C); yield, 77%.

4-[(4-Chlorophenyl)iminomethyl]pyridine **6** was obtained as greenish yellow crystals, m.p. 86-88°C (Lit. m.p. 86-88°C); yield, 92%.

Synthesis of α-Amino Nitriles

a. Addition of HCN to Benzylidene-4-chloroaniline 4

Benzylidene-4-chloroaniline (2.2 g, 0.01 mol) dissolved in MeOH (15 mL) was placed in a 500 mL round bottom flask fitted with a magnetic stirrer. A solution of NaCN (0.74 g, 0.015 mol) and NH_4Cl (0.9 g, 0.017 mol) in water (4 mL) was then added to the methanolic solution of the aldimine. A drying tube with a cotton plug was attached to the mouth of the reaction flask to prevent splashing due to stirring. The reaction was allowed to proceed at room temperature for 96 h with continuous, vigorous stirring. At the end of this period, the reaction mixture was cooled, made basic to litmus with IN NaOH (~ 3 mL), and then diluted with a large excess of water. Upon cooling in an ice bath, a white precipitate separated out, which was filtered under suction, washed well with water and dried.

It was purified by crystallization from diethyl ether-petroleum ether mixture, when the α-cyanobenzyl-4-chloroaniline **5** was obtained as white crystals, m.p. 83-85°C (Lit. m.p. 79.5-81°C), in 42% yield. Its IR spectrum indicated a sharp absorption band at 2230 cm^{-1}, similar to that reported previously (6) and characteristic of the C≡N stretch for nitriles in the 2273-2000 cm^{-1} region (11) and an NH band at 3340 cm^{-1}. Its NMR spectrum showed, in addition to the phenyl protons, two characteristic signals, a broad doublet at δ 4.1 and a sharp doublet at δ 5.3, integrating to one proton each for the NH and CH signals respectively.

b. **Addition of HCN to 4-[(4-Chlorophenyl)iminomethyl]pyridine 6**

The reaction was conducted in essentially the same manner as that described above for benzylidene-4-chloroaniline **4**, except it was allowed to run for five days (120 h).

The reaction mixture was cooled, made basic to litmus with 1N NaOH, and diluted with a large excess of water. Upon further cooling in an ice bath, a brownish yellow precipitate was obtained, which was filtered, washed and dried. It was purified by repeated trituration with a diethyl ether-petroleum ether mixture, which removed most of the brown impurities and gave 1.7 g of a yellow residual product.

It was crystallized from acetone. A small amount (~ 25 mg) of white material, F_1, remained insoluble, m.p. 320-325°C with decomposition to a dark black-red melt. The m.p and mixture m.p. did not correspond to that of pyridine-4-carboxylic acid (m.p. 310-315°C), which could have been formed by hydrolysis of the aldimine followed by conversion of the aldehyde to the acid.

The acetone solution remaining after filtering F_1, was concentrated and cooled, when a bright yellow crystalline product, F_2, was obtained, m.p. 172-174°C with previous softening from 168°C; yield, 0.3 g. Its IR spectrum failed to show any C=N absorbance in the 2273-2000 cm^{-1} region. An analysis by high performance liquid chromatography (HPLC) at 260 nm, using phosphate buffer (0.01 M, pH=6.8)-acetonitrile mixture (50:50 v/v) as mobile phase, indicated the presence of three components in this fraction, the major one being identified as pyridine-4-carboxanilide **10**. An NMR spectrum of F_2 did not indicate the characteristic CH or NH signal of an HCN addition product, although the pyridyl and phenyl protons were present.

The final remaining acetone solution, upon further concentration, yielded an off-white crystalline product, F_3, m.p. 130-135°C; yield, 1.3 g. It was recrystallized from acetone to give a cream colored crystalline product, m.p. 135-136°C. Found: C, 62.04; H, 3.83; N, 12.05. Calcd: C, 61.93; H, 3.87; N, 12.04. Its IR spectrum showed no CN stretch; however, an absorption at 3440 cm^{-1}, indicative of an NH group, and a strong absorption at 1620 cm^{-1}, characteristic of a C=O group, together suggested that F_3 was comprised of the amide **10**.

The NMR spectrum of pure F_3 integrated to a total of nine protons, eight of which accounted for the pyridyl and the phenyl protons. The ninth proton yielded a signal near δ 8.5, only when the sample was highly diluted. At high sample concentration, this peak was not apparent; but, with increasing dilution it became more discrete and showed small upfield movements, a behavior characteristic of the NH proton of acid amides (11). The NMR spectrum of an authentic sample of pyridine-N-(4-chloro)-4-carboxanilide was identical to that of F_3 and showed the same variations of the NH peak with increasing dilution. HPLC analysis of F_3 under the same conditions as that described for F_2, showed a single component with a retention time of 5.94 min and it coeluted with the authentic amide to give a single peak, with identical retention time.

The pyridine-4-carboxanilide **10** was synthesized as described previously (15) by reacting pyridine-4-carboxylic acid with $SOCl_2$ in benzene and treating the resulting acid chloride with 4-chloroaniline in the presence of pyridine.

Two other HCN addition reactions to 4-[(4-chlorophenyl)iminomethyl]pyridine **9**, run in an identical manner but with their reaction periods extended to seven and eight days respectively, yielded the same three component fractions, F_1, F_2 and F_3, but in slightly larger amounts.

Note

This paper was presented at the Thirteenth International Congress of Heterocyclic Chemistry, Oregon, U.S.A., 1991. It is based on the undergraduate research work of LPG and it won first prize in the 1986-87 Oswald Research and Creativity Competition for undergraduate students at the University of Kentucky.

References

(1) P.K. Kadaba, J. Med. Chem. 31, 196 (1988)

(2) P.K. Kadaba and J.T. Slevin, Epilepsia, 29, 330 (1988)

(3) P.K. Kadaba, Drugs of the Future, 15, 1013 (1990)

(4) J. March, Advanced Organic Chemistry, McGraw-Hill, New York, 1977

(5) R.O.C. Norman, Principles of Organic Synthesis, Chapman and Hall, New York, 1978

(6) Y. Ogata and A. Kawasaki, J. Chem. Soc. (B), 325 (1971)

(7) J.W. Stanley, J.G. Beasley and I.W. Mathison, J. Org. Chem. 37, 3746 (1972)

(8) A.S. Walia, S.N. Bannore, J.S. Walia and L. Guillot, Chem. Letters, 1005 (1974)

(9) (a) P.K. Kadaba, Tetrahedron, 22, 2453 (1966)
(b) P.K. Kadaba, J. Heterocycl. Chem. 12, 143 (1975)

(10) (a) A.R. Katritzky and J.M. Lagowski, The Principles of Heterocyclic Chemistry, Methuen & Co. Ltd, London, 1967
(b) A. Albert, in Heterocyclic Chemistry, Oxford University Press, Inc., Essential Books, Fairlawn, N.J., 1959

(11) R.M. Silverstein, G.C. Bassler and T.C. Morrill, Spectrometric Identification of Organic Compounds, John Wiley, New York, 1974

(12) H. Ulrich, The Chemistry of Imidoyl Halides, Plenum Press, New York, 1968

(13) J. Vaughan and P.A.S. Smith, J. Org. Chem. 23. 1909 (1958)

(14) P.K. Kadaba, J. Org. Chem. 41, 1073 (1976)

(15) P.K. Kadaba, Org. Prep. Proc. 2, 309 (1970)

Received March 3, 1995