Pergamon

Tetrahedron Letters, Vol. 38, No. 25, pp. 4359-4362, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00934-9

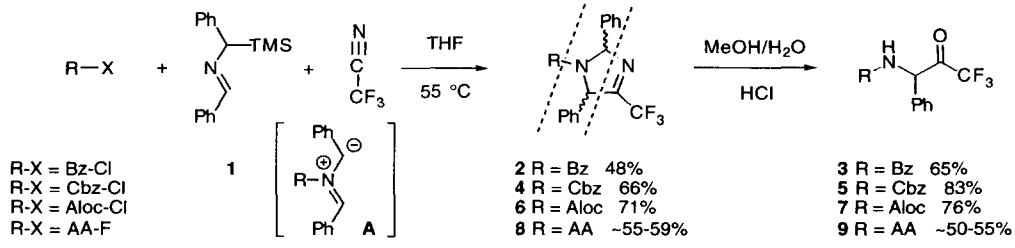
Trifluoromethyl-Substituted Δ^3-Imidazolines: Synthesis and Reactivity

Christopher W. Derstine, David N. Smith and John A. Katzenellenbogen*
Department of Chemistry, University of Illinois, 600 S. Mathews Avenue, Urbana, Illinois 61801

Abstract: We describe the preparation of various 4-trifluoromethyl-substituted Δ^3-imidazolines, which are precursors to amino acid-derived trifluoromethyl ketones. The imidazolines are prepared from α-silylimines and trifluoroacetonitrile by a 3+2 cycloaddition, and they can be hydrolyzed in weak acid to trifluoromethyl ketones. Additionally, we have identified several ring-opened compounds which result from treatment of the imidazolines with acid or base. Attempts to alkylate the imidazolines led to ring-opened products, so that the alkylation sequence ultimately produced N-alkylated amino acid-derived trifluoromethyl ketones.

As part of our efforts to develop new synthetic methodology for the preparation of peptidyl trifluoromethyl ketones, we have examined the use of Δ^3-imidazolines as latent forms of trifluoromethyl ketones. In previous work, we reported a concise synthesis of peptidyl trifluoromethyl ketones which proceeds through 4-trifluoromethyl-substituted Δ^3-imidazolines.[1] The imidazolines were synthesized by a 1,3-dipolar cycloaddition reaction and were incorporated into larger peptides. The imidazolines were then hydrolyzed under mild conditions to afford trifluoromethyl ketones. In this report we describe, in more detail, the synthesis and reactivity of the Δ^3-imidazoline moiety.

As shown in Scheme 1, 4-trifluoromethyl-Δ^3-imidazolines are synthesized by a three-component reaction between an acyl halide, an α-silylimine, and trifluoroacetonitrile. Reaction of the acyl halide with an α-silylimine generates an azomethine ylide (**A**) in situ.[2,3] The ylide then undergoes a 1,3-dipolar cycloaddition reaction with trifluoroacetonitrile to afford 4-trifluoromethyl-Δ^3-imidazolines. In our studies, a number of acylating agents have been used to initiate azomethine ylide formation. These include benzoyl chloride (Bz-Cl), benzyl chloroformate (Cbz-Cl), allyl chloroformate (Aloc-Cl), and amino acid fluorides[4,5] (AA-F). Each of these acylating reagents was allowed to react with **1**[6] and trifluoroacetonitrile in a stainless steel sample cylinder to produce N^1-protected imidazolines **2**, **4**, **6** and **8** in good yield. The acid chlorides and chloroformates initiated the dipolar cycloadditions effectively at 55 °C, whereas the acid fluorides required temperatures around 75 °C. The Aloc and the Cbz protecting groups were very effective in the 1,3-dipolar cycloaddition and demonstrated excellent stability to a wide range of conditions, including acid and strong base (*vide infra*).

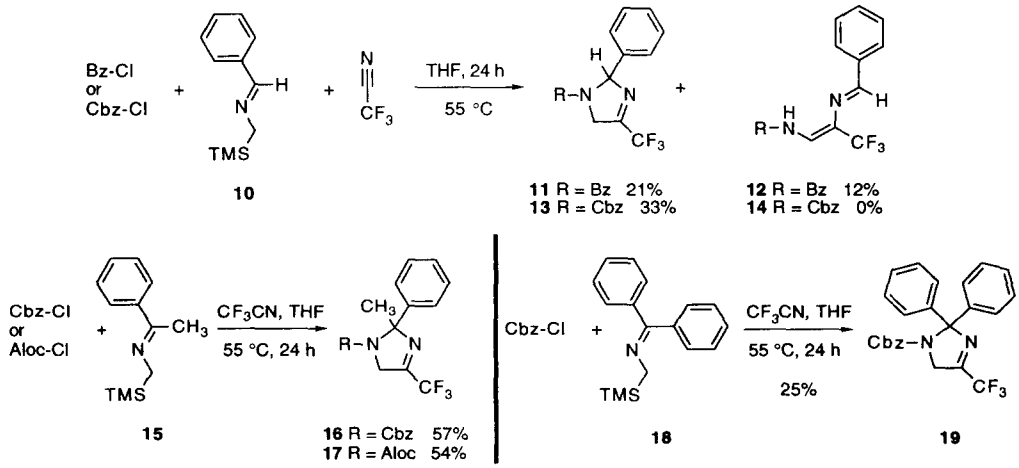


Scheme 1

The dipolar cycloaddition reactions, shown in Scheme 1, resulted in approximately a 1:1 ratio of the two possible diastereomers of the Δ^3-imidazolines (syn and anti isomers of the phenyl substituents at C-2 and C-5). Occasionally these diastereomers could be separated by careful column chromatography. The imidazolines in which the phenyl substituents are syn to one another across the imidazoline ring tended to be colorless oils, whereas the imidazolines with the phenyl substituents anti were white crystalline solids.[7] Also, it is worth noting the complicated NMR spectra arising from rotomeric species of the N^1-protected imidazolines. Hindered rotation around the N-CO bond leads to doubling of most signals in the ^1H, ^{13}C and ^{19}F NMR spectra. At high temperatures these signals coalesced into broad peaks.

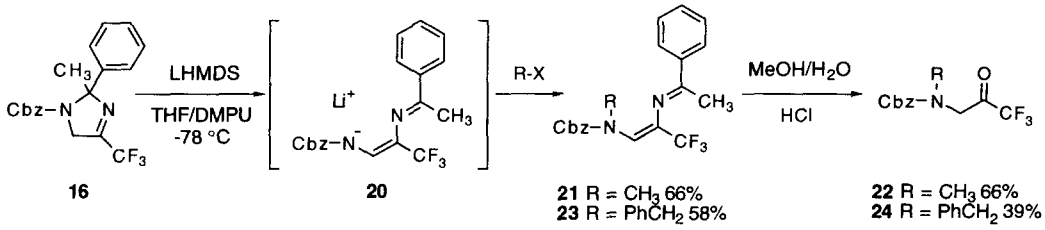
The imidazolines are readily hydrolyzed in methanol or acetonitrile and water in the presence of dilute hydrochloric acid to afford N-protected phenyl glycine-derived trifluoromethyl ketones **3**, **5**, **7** and **9** (Scheme 1). The ketones were best characterized by obtaining NMR spectra in d_6-DMSO/D_2O; in this solvent system the trifluoromethyl ketones are fully hydrated, and the spectra are simplified.

To study imidazolines with different substitution patterns at the C-2 and C-5 positions, we used other α-silyl imines (shown in Scheme 2) in the dipolar cycloaddition. Imines **10**, **15**, and **18** were readily prepared by condensation reactions between trimethylsilylmethyl amine and the appropriate aldehyde or ketone.[8] Reaction of imine **10** with benzoyl chloride and trifluoroacetonitrile afforded a mixture of imidazoline **11** and the ring-opened enediamine imine derivative **12**.[9] Imine **10** proved to be a fairly poor substrate for the cycloaddition reactions, as shown by the low yield of **11** and the tendency for **11** to undergo ring opening to **12**. Reaction of Cbz-Cl with **10** did not produce any ring opened compound (**14**), but the yield of desired imidazoline (**13**) was still low. In contrast to **10**, imine **15** afforded 2-methyl-2-phenyl substituted imidazolines **16** and **17** in considerably improved yield and with excellent regioselectivity. The cycloaddition reaction also tolerated the significant bulk from two germinal phenyl substituents of imine **18** and afforded a modest yield of **19**. Each of the imidazolines **11**, **13**, **16**, **17**, and **19** were hydrolyzed to the N^1-protected glycine-derived trifluoromethyl ketones, lending further support to the structural assignments.



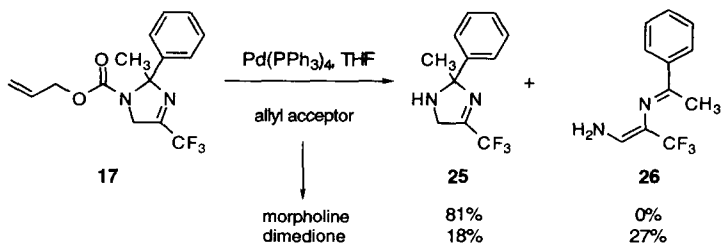
Scheme 2

Since we were interested in trifluoromethyl ketones derived from a variety of amino acids, we attempted to introduce substitution into the C-5 position of the imidazoline by alkylation. Imidazoline **16** was studied because the only acidic protons available are at the C-5 position. When **16** (Scheme 3) was treated with lithium hexamethyldisilazide at –78 °C, a deep red to purple color developed. The alkylating agent was added to this colored solution at –78 °C, and the color slowly disappeared as the reaction was warmed to room temperature. The product isolated from the reaction with methyl iodide was not a C-5 methylated imidazoline, but a ring-opened Cbz enediamine imine **21**[9] which had been methylated on N^1. Presumably, deprotonation took place at C-5, generating an unstable anion which underwent an electrocyclic ring opening to form the more stable conjugated anion **20**. This species was then alkylated upon warming to produce **21**. As further proof of the structure of **21**, it was hydrolyzed in dilute acid to afford the carbamate protected *N*-alkylated trifluoromethyl ketone of glycine (**22**). This sequence of steps was also repeated using benzyl bromide as the alkylating reagent, producing **23** and then **24**. The carbamate protection of the imidazolines appears to be necessary for this reaction, as other N^1-protected imidazolines (amide protected) appeared to undergo complete decomposition in the presence of strong base.



Scheme 3

Also of interest to us was the possibility of deprotecting the N^1 position of an imidazoline and then coupling the free heterocycle to a peptide. This would provide an additional route for the introduction of a trifluoromethyl ketone into a peptide, besides the use of amino acid fluorides.[1] The Aloc protecting group of **17** was cleanly removed by treatment with palladium tetrakistriphenylphosphine, affording the free imidazoline **25**, as shown in Scheme 4. When **17** was used in conjunction with the basic allyl acceptor morpholine, **25** was produced in 81% yield with very few by-products. Imidazoline **25** is a stable molecule and can be isolated by column chromatography.[10] Interestingly, when an acidic allyl acceptor, such as



Scheme 4

dimedone, was used as an allyl acceptor under anhydrous conditions, **25** was isolated in only 18% yield, along with larger amouns of the free enediamine imine **26**, which resulted from deprotection followed by ring opening.[9] The isolation of **25** provided the first NMR spectrum of a 4-trifluoromethyl-substituted imidazoline devoid of carboxamide rotomeric species. Incorporation of **25** into a peptide through standard peptide coupling methods proved unsuccessful, however. This was not surprising, since **25** is an α-disubstituted secondary amine and is probably too hindered to undergo effective peptide coupling.

In summary, synthesis of the 4-trifluoromethyl-substituted Δ^3-imidazolines from a variety of α-silylimines and acylating agents proceeds in good yield. The imidazolines can be alkylated at N^1, after undergoing an electrocyclic ring opening of the corresponding anion; acid hydrolysis ultimately produces *N*-alkylated trifluoromethyl ketones. Appropriately protected Δ^3-imidazolines can be hydrolyzed to the trifluoromethyl ketones or deprotected to afford imidazolines such as **25** and other ring-opened compounds (enediamine imines). Unfortunately, the use of free imidazolines like **25** to incorporate a trifluoromethyl ketone into a larger peptide is limited by its unreactivity toward standard peptide coupling reactions. Therefore, alternate approaches to the preparation of C-5–substituted 5-trifluoromethyl-Δ^3-imidazolines and C-α–substituted peptidyl trifluoromethyl ketones are being pursued.

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7. The syn and anti relationships have been assigned based on NOE signals measured between the 2-H and the 5-H of selected molecules.
8. The α-silyl imines were prepared by stirring trimethylsilylmethylamine and the appropriate ketone or aldehyde in diethyl ether, over activated of 4 Å molecular sieves, for 24 h or more. The imines were isolated by filtration and concentration of the resulting filtrate by rotary evaporation. The unstable imines were used as isolated, as they could not be purified further by distillation or chromatography.
9. The ring opening of the Δ^3-imidazoline to give the enediamine imines (**12**, **14**, **21**, **23**, and **26**) may proceed via an electrocyclic ring opening reaction of the corresponding anion. The stereochemistry of the ring opened product is not readily evident from the NMR spectra and is presumed to have a *cis*-enediamine unit (from the Δ^3-imidazoline precursor) and to have the smaller imine substituent cis to the chain (steric considerations).
10. Flash column chromatography (silica, 20% EtOAc:hexanes) afforded **25** as a colorless oil. R_f = 0.21 (20% EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.57 (m, 2H), 7.38-7.26 (m, 3H), 4.02 (AB quartets, $\Delta\nu$ = 0.72, J = 17.6 Hz, 2H), 2.10 (bs, 1H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (q, $^2J_{C\text{-}F}$ = 36.6 Hz), 143.7, 128.5, 127.8, 125.4, 119.7 (q, $^1J_{C\text{-}F}$ = 274.7 Hz), 96.3, 53.7, 29.3; ^{19}F NMR (396 MHz, $CDCl_3$) δ -69.5; FABMS (M.B.) *m/z* 229 (M+1), 135, 119 (base); FABHRMS calcd for $C_{11}H_{12}N_2F_3$ 229.0953, found 229.0954; IR ($CDCl_3$) 1445 (w), 1423 (w), 1373, 1363, 1303, 1193, 118, 1058 cm^{-1}.

(*Received in USA* 16 *April* 1997; *accepted* 8 *May* 1997)