Tetrahedron Letters,Vol.23,No.27,pp 2741-2744,1982 0040-4039/82/272741-04$03.00/0
Printed in Great Britain

THE CYANOMETHYL GROUP FOR NITROGEN PROTECTION AND IMINIUM ION GENERATION IN RING-ENLARGING PYRROLIDINE ANNULATIONS. A SHORT SYNTHESIS OF THE AMARYLLIDACEAE ALKALOID d,l-CRININE[1]

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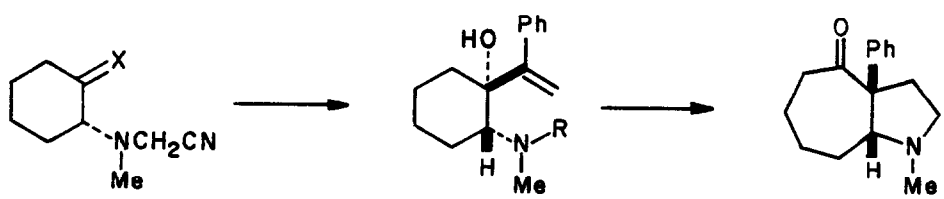
Summary: The preparation of cis-3a-aryl-4-oxo-decahydrocyclohepta[b]pyrroles and cis-3a-aryl-4-oxo-octahydroindoles is facilitated by using a cyanomethyl group to both protect nitrogen and serve as a precursor for a formaldehyde iminium ion.

Recent publications from our laboratory have described the efficient formation of 3a-aryl-4-oxo-octahydroindoles[2] and 3a-aryl-4-oxo-decahydrocylohepta-[b]pyrroles[3] from 2-amino-1-(1-arylvinyl)-cyclopentanols and -cyclohexanols. In this Letter, we report that the synthesis of these important bicyclics[4] can be further simplified by using a cyanomethyl group to both protect the basic nitrogen of a 2-aminoketone starting material and to serve subsequently as a source for a formaldehyde iminium ion intermediate.[5] The use of this chemistry to achieve a short formal total synthesis of the Amaryllidaceae alkaloid dl-crinine is also described.

Treatment of an aqueous solution of trans-2-(methylamino)cyclohexanol[6] with HCl, KCN, and paraformaldehyde (1 equiv of each, rt, 12 h)[7] afforded the N-cyanomethyl derivative 1[8] (75%; ^{1}H NMR δ 3.58, s, CH_2CN), which was cleanly oxidized to ketone 2[8] (88%; IR 1725 cm^{-1}, CCl_4) under the Swern conditions.[9]



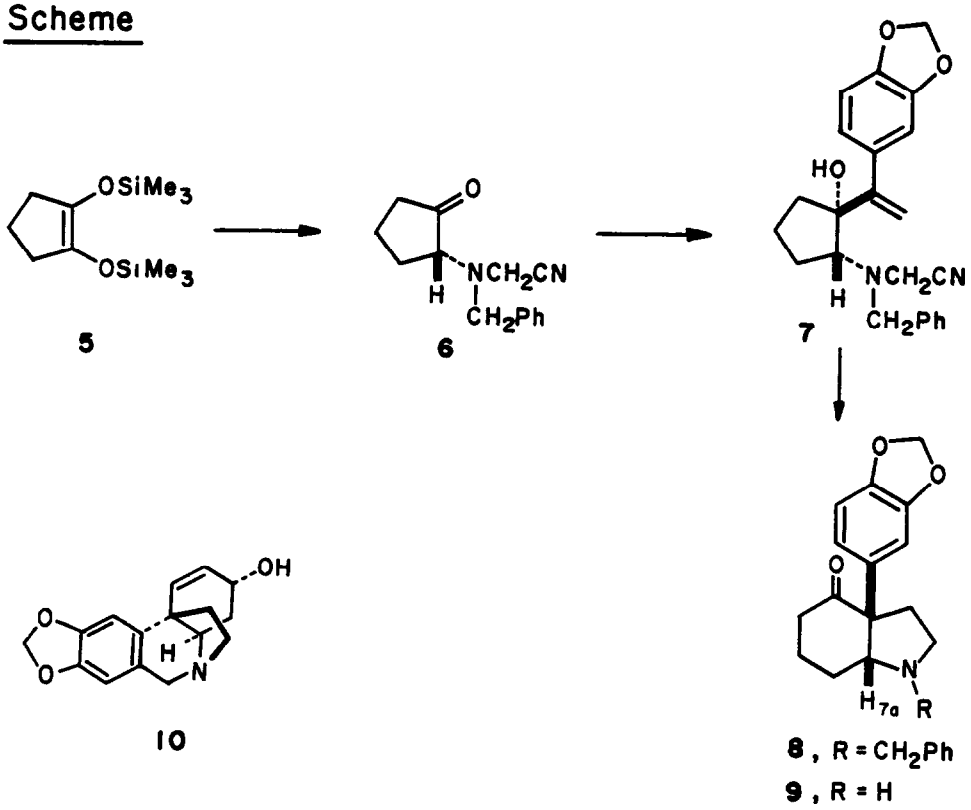
1, X = OH, H
2, X = O
3, R = CH_2CN
4

Dropwise addition of a THF solution of (1-phenylvinyl)lithium[2a] to 2 (THF, -78°C; quenched after 40 min at -78°C by adding wet THF) gave a single adduct 3[8,10] (^{1}H NMR δ 3.71, ABq, CH_2CN; δ 2.45-2.60, m, CHN), which was isolated in 50% yield after chromatography on silica gel. Treatment of 3 with 1.1 equiv of d-10-camphorsulfonic acid in refluxing benzene for 11 h, or with 1.1 equiv of $AgNO_3$ at room temperature in ethanol for 1 h, gave the known[3] cis-3a-phenyl-4-oxo-decahydrocyclohepta[b]pyrrole 4[8] as the sole product (isolated in 60-70% yield after silica gel chromatography).

A related sequence can be utilized to prepare cis-3a-aryl-4-oxo-octahydroindoles in three steps from 1,2-bis(trimethylsilyloxy)cyclopentene (5).[11] For example, reaction[12] of 5 with 1.2 equiv of benzyl(cyanomethyl)amine (prepared in 86% yield from benzylamine, HCl, KCN, and paraformaldehyde)[7] in refluxing methanol for 28 h gave aminocyclopentanone 6[8] (IR 1750 cm^{-1}, CCl_4; ^{1}H NMR AB quartets centered at δ 3.78 and 3.65 for CH_2CN and CH_2Ph; δ 3.25-3.35, m, CHN) in 72% yield. The reaction of [1-[3,4-(methylenedioxy)phenyl]vinyl]lithium[2a] with ketone 6 occurred predominantly (9:1 preference in THF at -78°C) from the side opposite the dialkylamino group to give alcohol 7 as a chromatographically homogeneous oil in 74% yield after purification on silica gel. Aminoalcohol 7 showed characteristic AB quartets in the ^{1}H NMR for the benzyl and cyanomethyl methylene hydrogens at δ 3.83 and 3.40 and an intramolecular hydrogen-bonded OH absorption[2a,13] at 3418 cm^{-1} (CCl_4) in the infrared spectrum. Treatment of 7 with 1.1 equiv of $AgNO_3$ in ethanol for 2 h at 50°C gave 8 in 93% yield after purification on silica gel. cis-Decahydroquinoline 8 (mp 102-103°C after crystallization from hexane) showed a characteristic[2a,14] narrow multiplet (half-height width = 5.2 Hz) for H_{7a} at δ 3.39 in the ^{1}H NMR spectrum and an AB quartet for the benzyl methylene centered at δ 3.62 (J_{AB} = 13.3 Hz, $\Delta\nu_{AB}$ = 232 Hz at 250 MHz). Debenzylation (Pd/C, cyclohexene, ethanol, 1 N HCl)[2a] of 8 was accomplished in 95% yield to give hydroindolone 9, which was identical (250 MHz ^{1}H NMR, 63 MHz ^{13}C NMR, TLC) with an authentic sample.[2a,15b] Since cis-octahydroindolone 9 has been previously converted in six steps to dl-crinine (10),[15b] the sequence described here constitutes a concise formal total synthesis of this alkaloid.[15]

Hydroindolone 8 was assembled as summarized in the Scheme with complete stereocontrol in three steps and 47% overall yield from 1,2-bis(trimethylsilyloxy)cyclopentene. This sequence achieves the most practical entry to the widely occurring[4] cis-3a-aryloctahydroindole ring system to be described to date, and provides another illustration of the utility of "directed" aza-Cope rearrangements in organic synthesis.

Scheme



Acknowledgment. Financial support from the National Institutes of Health (NS-12389) and the Camille and Henry Dreyfus Foundation (teacher-scholar award to L.E.O.) is gratefully acknowledged. NMR and mass spectra were determined at Irvine with spectrometers purchased with the assistance of NSF departmental instrumentation grants, and high resolution mass spectra at the NSF-sponsored Midwest Center for Mass Spectroscopy at the University of Nebraska-Lincoln.

References and Notes:

1. Part 9 in the series "Synthesis Applications of Aza-Cope Rearrangements". For part 8, see preceding paper.

2. (a) Overman, L.E.; Mendelson, L.T. J. Am. Chem. Soc. 1981, 103, 5579. (b) Overman, L.E.; Mendelson, L.T.; Flippin, L.A. Tetrahedron Lett. 1982 in press.

3. Overman, L.E.; Jacobsen, E.J. Tetrahedron Lett. 1982, preceding paper.

4. See footnotes 3 and 4 of reference 2a, and reference 3.

5. 2-Cyanoamines have been often used as iminium ion precursors. For a recent example and leading references see: Grierson, D.S.; Harris, M.; Husson, H.-P. J. Am. Chem. Soc. 1980, 102, 1064.

6. Kovář, J.; Blaha, K. Chem. Listy 1958, 52, 283.

7. Cf. Kuffner, F.; Koechlin, W. Monatsh. 1962, 93, 476.

8. New compounds showed IR, 250 MHz ^{1}H NMR, 63 MHz ^{13}C NMR, and mass spectra consistent with their assigned structures.

9. Mancuso, A.J.; Huang, S.; Swern, D. J. Org. Chem. 1978, 43, 2480.

10. (a) The addition is much less clean if the reaction is conducted at a higher temperature, or if the reaction mixture is allowed to warm to room temperature before quenching. We assume that the cyanomethylamine functionality is reactive under these conditions. (b) The stereochemistry of 3 follows from our expectation[2a] that addition to a cyclohexanone of this type should occur from the face opposite the dialkylamino group. Alcohol 3 has been chemically correlated with the major product resulting from the reaction (1-phenylvinyl)lithium with 2-(dimethylamino)cyclohexanone.

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14. Cf. Stevens, R.V.; Dupree, L.E., Jr.; Lowenstien, R.L. J. Org. Chem. 1972, 37, 977.

15. For previous total syntheses of dl-crinine, see: (a) Muxfeldt, H.; Schneider, R.S.; Mooberry, J.B. J. Am. Chem. Soc. 1966, 88, 3670. (b) Whitlock, H.W., Jr.; Smith G.L. Ibid. 1967, 89, 3600. For a recent review of the synthesis of other closely related 5,10b-ethanophenathridine alkaloids, see: Tsuda, Y. Heterocycles 1978, 10, 555.

(Received in USA 2 April 1982)