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HYDROBORATION-CARBONYLATION OF BISOLEFINIC AMINES: A FACILE SYNTHESIS OF δ-CONICEINE

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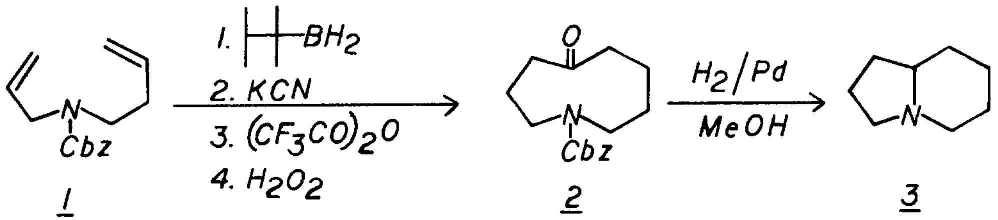
Abstract: Treatment of N-allyl-N-3-butenyl-N-Cbz-amine (1) with thexyl borane followed by cyanidation affords an azacyclononanone 2 in 35% yield which can be transformed into δ-coniceine (3) by catalytic reduction.

We wish to report the total synthesis of the indolizidine alkaloid δ-coniceine (3)[1] via transannular reductive closure of azacyclononanone 2. The key step in this short synthesis is the efficient cyclization of an acyclic, bisolefinic carbamate to yield the medium-sized ring ketone 2 using hydroboration-carbonylation.[2] This aminoketone preparation is the first example of any ketone synthesis using hydroboration to be effected in the presence of a reducible functional group and illustrates a general method for production of these compounds.



Previous syntheses of azacyclanones related to 2 have included high dilution Dieckmann or acyloin cyclizations[4] of acyclic precursors and ring expansion reactions of appropriate cyclic ketones.[1] The cyclization described herein utilizing thexyl borane[3] followed by the Pelter[2] cyanidation protocol offers four practical advantages for the preparation of medium sized rings such as 2: the olefinic amine precursors (1) are readily obtained; the hydroboration with thexyl borane and the carbonylation sequence involve easily manipulated reagents; the one-pot ring closure sequence yields the desired ketone without high dilution; and all of the side products (primarily alcohols) are removed by sequential Jones oxidation and base extraction. Ketone 2 is formed without substantial competitive reduction of the electrophilic carbamate by thexyl borane. Enolate reactions of 2 offer the potential for additional elaboration. The only drawback of this sequence is the modest 35% yield. Reductive ring closure of 2 provided δ-coniceine (3) in 65% yield.

The isomeric integrity of the ketone 2 derived from 1 is much greater than that observed from simple α,ω-dienes. For example, Brown[5] reports that 1,7 heptadiene yields cyclooctanone, 2-methylcycloheptanone 2-ethylcyclohexanone in a 5:1:1 ratio. Since hydroboration of 1 has occurred in the normal sense, the intermediate organoborane must have increased kinetic or thermodynamic stability. Replacement of a methylene by a carbamate nitrogen decreases transannular ring interactions and may effect a boron-nitrogen attraction. The carbamate decreases internal rotation in 1 minimizing the entropy loss upon formation of 2. Experiments to define these effects are in progress.

In the course of our studies on pyrrolizidine alkaloid synthesis,[6] we have investigated other hydroboration-carbonylation reactions related to this transformation, the full details of which will be reported shortly.[7] To underscore the simplicity of this sequence a detailed preparation of 2 is included.

Ketone (2): A solution of 0.022 mol of thexyl borane at 0 °C under nitrogen was prepared according to Brown[9] and treated with 0.020 mol (4.90 g) of diene[10] in 15 ml of THF over 20 min. The resulting mixture was stirred for 3 hr at room temperature, treated with 0.023 mol (1.50 g) of KCN, and stirred for 4 hr. After dissolution of the KCN, the mixture was cooled to -78 °C and treated with 0.020 mol (3.40 ml) of $(CF_3CO)_2O$. The resulting solid was warmed to room temperature, stirred for 2.5 hr and oxidized by sequential addition of 60 ml of aqueous NaOAc and 60 ml of 30% H_2O_2. After 2 hr, the standard work-up left a viscous oil which was directly oxidized by Jones reagent in the standard fashion. Work-up including bicarbonate extraction and filtration through Florisil with ether afforded 2.05 g (35%) of 2[9] in greater than 95% purity.

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References:

1. For recent syntheses see: Weinreb, S. M., Khatri, N. A., and Shringarpure, J., J. Am. Chem. Soc., 1979, 101, 5073 and ref. 5 therein.
2. Pelter, A., Hutchings, M. G., and Smith, K., J.C.S. Chem. Comm., 1970, 1528 and 1971, 1048.
3. Brown, H. C. and Negishi, E., J. Am. Chem. Soc., 1967, 89, 5477.
4. Leonard, N. J. and Sato, T., J. Org. Chem., 1969, 34, 1066.
5. Brown, H. C. et al., J. Am. Chem. Soc., 1976, 98, 4917 and J. Org. Chem., 1979, 44, 2417.
6. Garst, M. E. et al., J. Org. Chem., 1980, 45, 2307 and M. E. Garst and D. Lukton, submitted
7. Garst, M. E., Bonfiglio, J. N., and Marks, J., work in progress. N-Cbz-4-azacycloöctanone has been prepared in ca. 40% yield from N-Cbz-diallylamine using this chemistry.
8. Negishi, E. and Brown, H. C., Synthesis, 1979, 77.
9. Characterized by ir, nmr, and high resolution ms.

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