Studies on the Synthesis of *Strychnos* Indole Alkaloids. Synthesis of (±)-Dehydrotubifoline†

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The synthesis of *Strychnos* indole alkaloids has become an area of renewed interest during the last few years.[1] The considerable synthetic efforts made in this field[2] have culminated in five new total syntheses of the heptacyclic alkaloid strychnine in only 3 years (Figure 1).[3]

Several of the most recent approaches to the *Strychnos* alkaloids involve the construction of the pentacyclic ABCDE core of these alkaloids by closure of the piperidine ring by formation of the crucial C_{15}–C_{20} bond in the key step,[4] either by conjugate nucleophilic addition[3e] or by intramolecular Heck reaction[2b,3d] or radical cyclization.[2g] In this context, we have recently reported[2a] a synthetic pathway to *Strychnos* indole alkaloids. Its most important features are (i) the closure of the piperidine ring (bond formed, C_{15}−C_{20}) by an intramolecular Michael addition from an appropriately substituted 3a-arylhexahydroindol-4-one and (ii) the formation of the indoline nucleus by reductive cyclization in the last step.

We report here an alternative procedure for formation of the C_{15}−C_{20} bond of *Strychnos* alkaloids from 3a-arylhexahydroindol-4-ones based on the nickel(0)-promoted cyclization of vinyl halides with alkenes. The required *N*-substituted 3a-arylhexahydroindol-4-one **2**[5] was prepared by alkylation of the known intermediate **1**[2a] (Scheme 1) with (*Z*)-1-bromo-2-iodo-2-butene.[6] Initial attempts to induce the closure of the piperidine ring by either a radical cyclization or an intramolecular Heck reaction failed. Thus, treatment of **2** with Bu_3SnH and AIBN led to the tricyclic compound **5** (15%; 80% of recovered starting material),[7] whereas the Heck cyclization under a variety of conditions (catalytic or stoichiometric on palladium)[8] led only to complex unidentifiable mixtures.

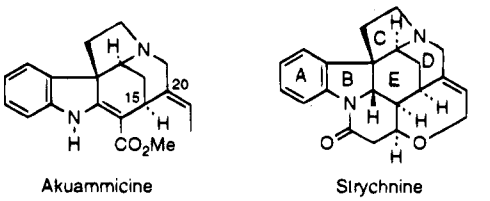
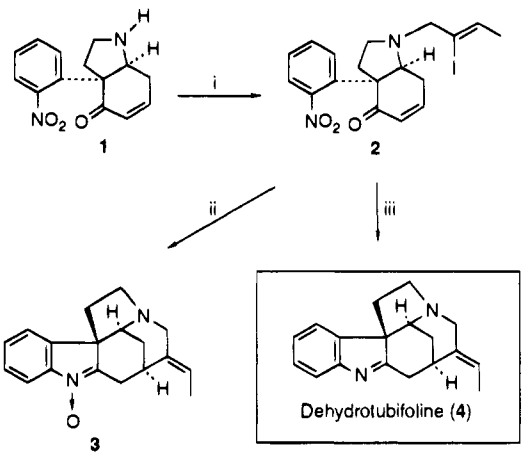


Figure 1.

Scheme 1[a]



[a] (i) (*Z*)-$BrCH_2CI{=}CHCH_3$, anhydrous K_2CO_3, CH_3CN, room temperature, 3 h, 70%. (ii) $Ni(COD)_2$ (6.6 equiv), Et_3N, anhydrous CH_3CN, room temperature, 2.5 h, 40%. (iii) $Ni(COD)_2$ (6.6 equiv), Et_3N, LiCN (10 equiv), 1:1.5 CH_3CN−DMF, room temperature, 2.5 h, 40%.

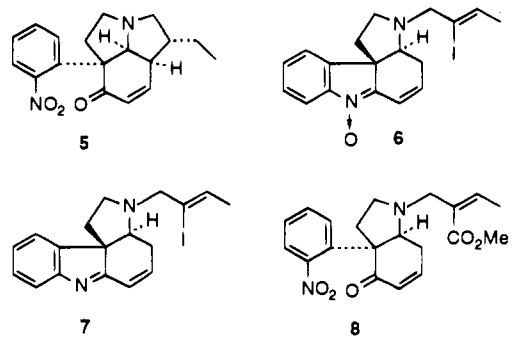


Figure 2.

These discouraging results prompted us to explore nickel(0)-promoted cyclizations of vinyl iodide **2**. To our surprise, treatment of **2** with 6.6 equiv of $Ni(COD)_2$[9] directly afforded the pentacyclic nitrone **3** in 40% yield. This one-pot transformation involves the Ni(0)-promoted cyclization of the vinyl iodide upon the carbon−carbon double bond and the controlled reductive cyclization of the α-(*o*-nitrophenyl) ketone moiety to the nitrone functionality.[10] When the amount of $Ni(COD)_2$ was reduced to 2.5 equiv, the tetracyclic nitrone **6** (Figure 2) was obtained as the only isolable product (50%).[11] This result seems

† Dedicated to the memory of the late Professor Fèlix Serratosa, who was a pioneer of organic synthesis in our country.

(1) For recent reviews, see: (a) Sapi, J.; Massiot, G. Indoles: The Monoterpenoid Indole Alkaloids (Saxton, J. E., Ed.). In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: New York, 1994; Supplement to Vol. 25, Part IV, pp 279−355. (b) Bosch, J.; Bonjoch, J.; Amat, M. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1995; Vol. 48 (in press).

(2) For recent total syntheses, see: (a) Bonjoch, J.; Solé, D.; Bosch, J. *J. Am. Chem. Soc.* **1993**, *115*, 2064−2065. (b) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030−3031. (c) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966−3977. (d) Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939−3951. (e) Kuehne, M. E.; Brook, C. S.; Frasier, D. A.; Xu, F. *J. Org. Chem.* **1994**, *59*, 5977−5982. (f) Kuehne, M. E.; Xu, F.; Brook, C. S. *J. Org. Chem.* **1994**, *59*, 7803−7806. (g) Kuehne, M. E.; Wang, T.; Seraphin, D. *Synlett* **1995**, 557−558.

(3) (a) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116−8129. (b) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776−5788. (c) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490−7497. (d) Rawal, V. H.; Iwasa, S.; Michoud, C. *J. Org. Chem.* **1994**, *59*, 2685−2686. (e) Stork, G. Presented at the Ischia Advanced School of Organic Chemistry. Ischia Porto, Italy. Sept 21, 1992. We thank Professor Gilbert Stork for sending us a detailed scheme of his synthesis of strychnine.

(4) Biogenetic numbering and ring labeling is used throughout this paper: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508−510.

(5) All yields are after purification by chromatography. New compounds were characterized by IR, ^1H NMR, ^{13}C NMR, HRMS, and/or microanalysis.

(6) Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404−408. Corey, E. J.; Kirst, H. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 6314−6319.

(7) The pyrrolidine ring is formed by a 1,5-hydrogen shift from the initially formed vinylic radical, followed by a 5-exo-trig cyclization of the resulting allylic radical: Lathbury, D. C.; Parson, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81−82.

(8) For a recent review on the Heck reaction, see: Heck, R. F. Vinyl Substitution with Organopalladium Intermediates. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 4, pp 833−863.

(9) For the use of $Ni(COD)_2$ in cyclizations of vinyl halides with alkenes, see: Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133−12134.

(10) Formation of **3** requires the protolysis of the transient alkylnickel intermediate. For a related example from an alkylpalladium intermediate in which syn elimination of a hydridopalladium species is not possible, see: Benhaddou, R.; Czernecki, S.; Ville, G. *J. Org. Chem.* **1992**, *57*, 4612−4616.

(11) For the formation of nitrones by reductive cyclization of γ-nitro ketones, see: Benchekroun-Mounir, N.; Dugat, D.; Gramain, J.-C.; Husson, H.-P. *J. Org. Chem.* **1993**, *58*, 6457−6465.

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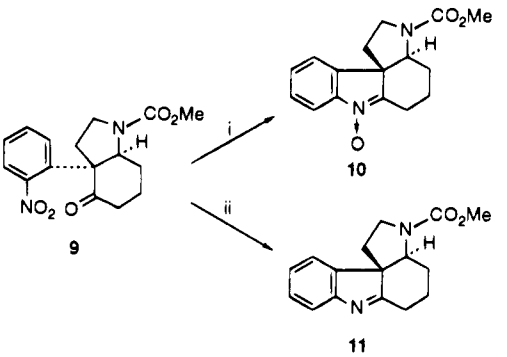
to indicate that reduction of the nitro aromatic group occurs prior to the nickel-induced C−C bond formation. The outcome of the reductive cyclization was slightly different when the process was carried out [6.6 equiv of $Ni(COD)_2$] in the presence of LiCN and DMF as the cosolvent: dehydrotubifoline (**4**),[12] an akummicine degradation product, was obtained in a single step in 40% yield.[13] Formation of cyanonickelate(0) species,[14] for instance dicyano(cyclooctadiene) nickelate(0) ($[(COD)Ni(CN)_2]^{2-}$) or tricyanonickelate(0) ($[Ni(CN)_3]^{3-}$), when LiCN is present in the medium could account for the different course of the above reductive cyclizations.

Although the use of $Ni(CO)_4$ to promote the tandem cyclization−carbonylation process has recently been described,[15] treatment of vinyl iodide **2** with $Ni(CO)_4$ (Et_3N, MeOH, anhydrous CH_3CN, argon, 37 °C, 18 h) did not afford cyclized products bearing the C-16 methoxycarbonyl group; only starting material (37%) and the uncyclized carbonylated compound **8** (27%) could be detected. Unfortunately, under the above conditions, cyclization was not fast enough to compete with direct carbonylation.

The controlled reductive cyclization of α-(*o*-nitrophenyl) ketones using $Ni(COD)_2$ is unprecedented and seems to be quite general. It can be exploited for assembling the partially reduced pyrrolo[2,3-*d*]carbazole unit, which is present in several groups of indole alkaloids. Thus, treatment of octahydroindol-4-one **9** with $Ni(COD)_2$ under the above conditions led to either nitrone **10** (50% yield) or indolenine **11** (51% yield), depending on the absence or the presence of LiCN in the reaction mixture (Scheme 2). The formation of more reduced products, i.e., indolines, was not detected. The above reductive cyclizations, associated with the coupling of vinyl halides with alkenes, expand the potencial of 3a-arylhexahydroindol-4-ones as building blocks for indole alkaloid synthesis.[2a,16]

Scheme 2[a]



[a] (i) $Ni(COD)_2$ (6.6 equiv), Et_3N, anhydrous CH_3CN, room temperature, 2.5 h, 50%. (ii) $Ni(COD)_2$ (6.6 equiv), Et_3N, LiCN (10 equiv), 1:1.5 CH_3CN−DMF, room temperature, 2.5 h, 51%.

The procedure reported here provide new solutions for the formation of the crucial C_{15}−C_{20} bond of *Strychnos* alkaloids that can be applied to the synthesis of the most complex alkaloids of this group.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **2**−**11** and characterization data for new compounds **2, 3, 5**−**11** (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(12) The ^1H and ^{13}C NMR spectra of dehydrotubifoline were identical with those reported in the literature.[2b,c] For previous syntheses, see: (a) Harley-Mason, J.; Crawley, G. C. *J. Chem. Soc., Chem. Commun.* **1971**, 685. (b) Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 881−884. (c) See also refs 2b,c.

(13) The reaction conditions are very critical, and decreasing the amount of $Ni(COD)_2$ led to mixtures of tetracyclic and pentacyclic products. In some runs, the tetracyclic indolenine **7** was obtained as a minor product. A typical experimental procedure is as follows: a solution of vinyl iodide **2** (47 mg, 0.107 mmol), LiCN in DMF (2.14 mL, 0.5 M, 1.07 mmol), and Et_3N (45 μL, 0.322 mmol) in acetonitrile (6 mL) was added at room temperature under Ar to $Ni(COD)_2$ (195 mg, 0.706 mmol). The mixture was stirred at room temperature for 2.5 h and filtered through Celite. The solvent was evaporated, and the residue was dissolved in ether and washed with saturated Na_2CO_3 and brine. Evaporation of the dried organic phase, followed by flash chromatography, gave dehydrotubifoline (**4**) (11 mg, 40%).

(14) Species like these have been postulated as intermediates in some reductions with cyanonickel complexes: (a) Bingham, D.; Burnett, M. G. *J. Chem. Soc. (A)* **1971**, 1782−1788. (b) Bingham, D.; Burnett, M. G. *J. Chem. Soc. (A)* **1970**, 2165−2169.

(15) For reactions of cyclization−carbonylation of vinyl halides promoted by $Ni(CO)_4$, see: (a) Llebaria, A.; Camps, F.; Moretó, J. M. *Tetrahedron Lett.* **1992**, *33*, 3683−3686. (b) Delgado, A.; Llebaria, A.; Camps, F.; Moretó, J. M. *Tetrahedron Lett.* **1994**, *35*, 4011−4014.

(16) Solé, D.; Bonjoch, J. *Tetrahedron Lett.* **1991**, *32*, 5183−5186.