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Nucleophilic Aromatic Substitution via a New Nickel-Catalyzed Process and via the $S_{RN}1$ Reaction. Improved Synthesis of Cephalotaxinone.

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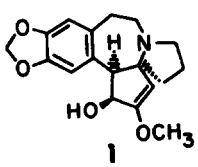
Cephalotaxine (1) forms simple esters which are very active against experimental luekemia, in preliminary testing.[1] Two total syntheses of this relatively rare compound have been recorded[2,3] based on the construction of cephalotaxinone (2)[4] followed by stereospecific reduction to cephalotaxine.[2,3,5] Our earlier approach is relatively short, but suffers from an inefficient ring closure of 3 to cephalotaxinone (2).[3]

The ring closure is a specific example of the classic general problem of nucleophilic aromatic substitution. In unactivated aromatic rings (absence of electron withdrawing substituents) direct displacement of halogen by nucleophiles requires high temperatures. A general alternative to nucleophilic displacement, involving nucleophilic attack on a transient benzyne derivative, has been applied in many simple systems[6] and in one other natural product synthesis.[7] The best yield we have achieved by exposing 3 (also the chloro and bromo analogs) to conditions expected to generate a benzyne is 15%.[3] Recent studies in our laboratory pointed to a mild method of ring closure via an aryl nickel species, while Bunnett and Rossi have shown that aryl iodides are attacked by carbon anions during alkali metal reduction[8] and during irradiation.[9] We wish to report that each of these methods is superior to the benzyne route for the synthesis of cephalotaxinone.

The iodoketone 3 was prepared by a direct route. Hydride reduction of 3,4-methylenedioxyphenylacetic acid gave an alcohol (4, 95%)[3] which was treated with iodine and silver trifluoroacetate to produce the crude iodoalcohol 5 which, in turn, reacted with p-nitrobenzenesulfonyl chloride (excess pyridine, ether, 25°) to afford the p-nitrobenzenesulfonate ester 6[10] (mp 126-127°, from carbon tetrachloride) in 52% yield overall from 4. In the presence of diisopropyl ethyl amine in acetonitrile at 25°, 6 combines with the spirocycle 7[3] to produce 3[10] in 61% yield, mp 119.0-119.5 (corr); pmr ($CDCl_3$): δ 1.7-2.1 (m, 4H, CH_2CH_2 - in pyrrolidine ring); 2.3 (ABq, 2H, J=14.0 Hz, $-CH_2CO-$); 2.3-3.2 (m, 6H); 3.70 (s, 3H, $-OCH_3$); 5.98 (s, 2H, $-OCH_2O-$); 6.04 (s, 1H, -C=CH-); 6.74 (s, 1H, aryl H); 7.24 (s, 1H, aryl H).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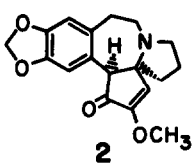
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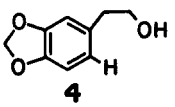
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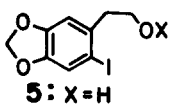
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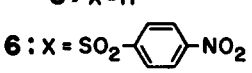
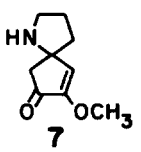

6: X = SO_2-NO_2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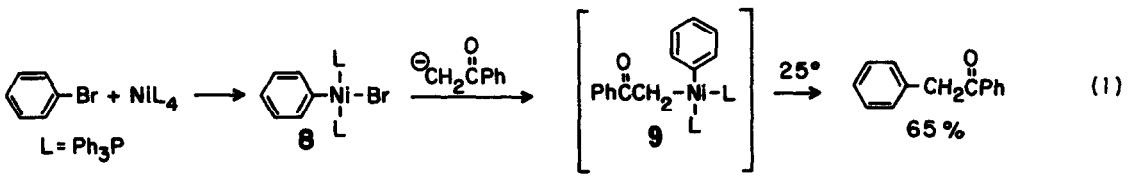
The unique reactivity of aryl halides and vinyl halides in oxidative-addition to low-valent transition metals[11,12] suggested to us a means of activating aryl halides toward carbon-carbon

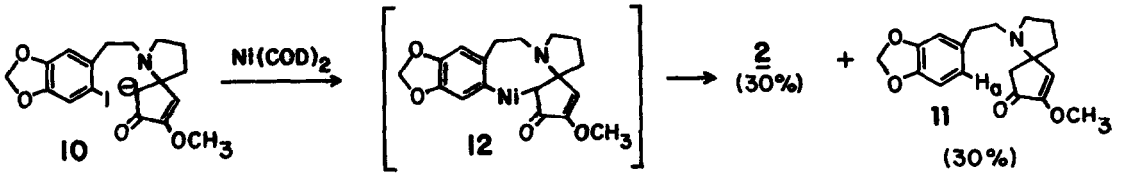
coupling. The scope of the method is under active investigation, but we report here a simple example and an application in the desired ring closure. The reaction of bromobenzene with tetrakis(triphenylphosphine)nickel(0) produces bis(triphenylphosphine)phenylnickel(II)bromide (8) in high yield.[13] The complex decomposes rapidly in solution, producing biphenyl in 99% yield after 22 hr at 45° in dimethylformamide. However, if the enolate anion of acetophenone (one molar equivalent) is added to a mixture of 8 and dimethylformamide at -78°, reaction occurs upon warming to give a 1:1 mixture of biphenyl and benzylphenyl ketone, the product of formal nucleophilic substitution. The phenylnickel complex 8 need not be prepared at first; simply stirring together iodobenzene (or bromobenzene), tetrakis(triphenylphosphine)nickel(0), and the lithium salt of acetophenone produces



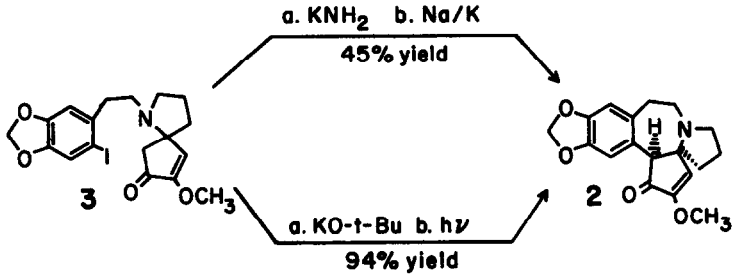
(1)

similar results. As written in equation 1, the process is expected to involve complex 9 (not isolated) and to be formally catalytic overall. Inefficient catalysis is observed: using 0.14 molar equivalents of tetrakis(triphenylphosphine)nickel(0), the yield of phenylbenzyl ketone is 250% based on nickel catalyst, and ca. 65% based on iodobenzene not recovered (ca. 50% conversion). Further details and examples will be reported later.

Application of this procedure in the crucial ring closure 3 → 2 provided results distinctly better than the benzyne reaction.[14] In the best case, iodoketone 3 was quantitatively converted to enolate anion 10 with one equivalent of lithium triphenylmethide in tetrahydrofuran. After warming at 25° for 15 hours, the iodoketone could be recovered (80%) after quenching with water. However, with 1.1 mole-equivalents of bis(1,5-cyclooctadiene)nickel, the solution becomes deep brown after 1.0 hr at 25°, and two products are formed in equal amounts: the product (11)[15] from reduction of the aryl iodide, and cephalotaxinone (2). After isolation by preparative layer chromatography, the yield of 2 is 25-30%. In analogy with the simple case (equation 1), the intermediacy of complex 12 is assumed without evidence. The source of the hydrogen atom, H_a, in 11 is under investigation; preliminary results suggest hydrogen atom transfer from the solvent is the main path. For example, treatment of 3 with bis(1,5-cyclooctadiene)nickel in tetrahydrofuran-d_8 produced 11 in 90% yield and 82 ± 5% (pmr) deuterium incorporation at H_a.



A comparable yield of cephalotaxinone (45%) was obtained by an intramolecular aromatic $S_{RN}1$ reaction.[8] The iodoketone was suspended in liquid ammonia at reflux containing excess potassium amide in order to produce anion 10; then sodium-potassium alloy (1:5) was added (ca. 1 mole-equiv.) and the reaction was quenched with excess methyl alcohol after 15 min. Cephalotaxinone was isolated by layer chromatography in 45% yield, based on iodoketone not recovered (65% conversion). The main contaminant is the reduction product, 11.



By far, the best yield of cephalotaxinone (2) has been obtained by irradiation of iodoketone 3 in the presence of base.[16] A mixture of 3 (118 mg) and potassium tert-butoxide (sublimed, 210 mg, 7-fold molar excess) in liquid ammonia at reflux was irradiated[18] for one hr. After evaporation of the ammonia and partitioning the residue between aqueous sodium carbonate solution and methylene chloride, the organic layer was dried and concentrated to leave a yellow oil which solidified. The pmr spectrum of the crude product was superimposable with the spectrum of pure cephalotaxinone,[19] and showed no additional absorption band; the sample showed a single spot of R_f 0.35 (silica gel/ethyl acetate) on tlc analysis, identical with natural material. The yield is 79.2 mg, 94%. Recrystallization from ethyl acetate afforded colorless microcrystals, mp 181 - 184° (no dec); Lit:[4] mp 170 - 178° (dec).

The efficiency of the photochemical reaction is remarkable, and may find important future application in the synthesis of aromatic natural products. With the improved efficiency for the ring closure, the overall yield of cephalotaxine (1) from pyrrolidone[3] is 12 - 13%.[20]

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(10) Satisfactory pmr, ir, mass spectral, and combustion analytical data have been obtained for this compound.

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(14) We are grateful to Dr. Paul Helquist for carrying out preliminary experiments in this series.

(15) The reduction product (11) was identified by comparison of spectral properties and tlc behavior with a sample of 11 prepared from the p-nitrobenzenesulfonate of 4 and spirocycle 7. Compound 11 shows: pmr ($CDCl_3$) δ 1.75-2.12 (m, 4H, $-CH_2CH_2-$ in pyrrolidine ring); 2.12-2.92 (m, 8H, $-CH_2-$); 3.72 (s, 3H, $-OCH_3$); 5.93 (s, 2H, $-OCH_2O-$); 6.01 (s, 1H, -CH=C); 6.70 (m, 3H, aryl H); mass spectral mol wt: 315.

(16) This reaction is based on the concept first exemplified by Rossi and Bunnett.[9,17]

(17) With 1.9 molar-equiv. of potassium tert-butoxide, a 1:1 mixture of cephalotaxinone 2 and the reduction product 11 is obtained. It may be that the smaller quantity of base is insufficient to generate a high concentration of anion 10 and irradiation of 3 leads to 11.

(18) Hanovia 450 watt medium pressure mercury arc, Pyrex filter.

(19) We thank Mr. R. Powell (USDA Laboratories, Peoria, Illinois) for spectra and a sample of cephalotaxinone.

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