CHEMISTRY LETTERS, pp. 2161-2164, 1990.

Bicycloannulation of C=N Double Bonds through Organotin-Aided Three Component Coupling. A Short and Stereoselective Synthesis of (±)-*allo*-Berbane and (±)-*allo*-Yohimbane Systems

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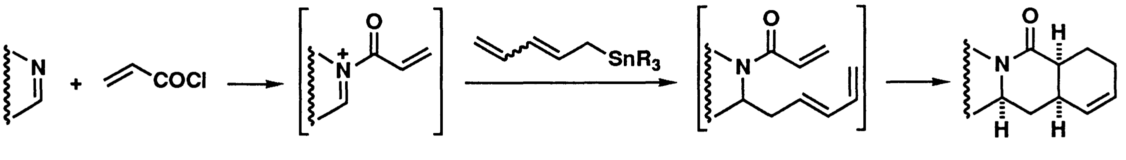
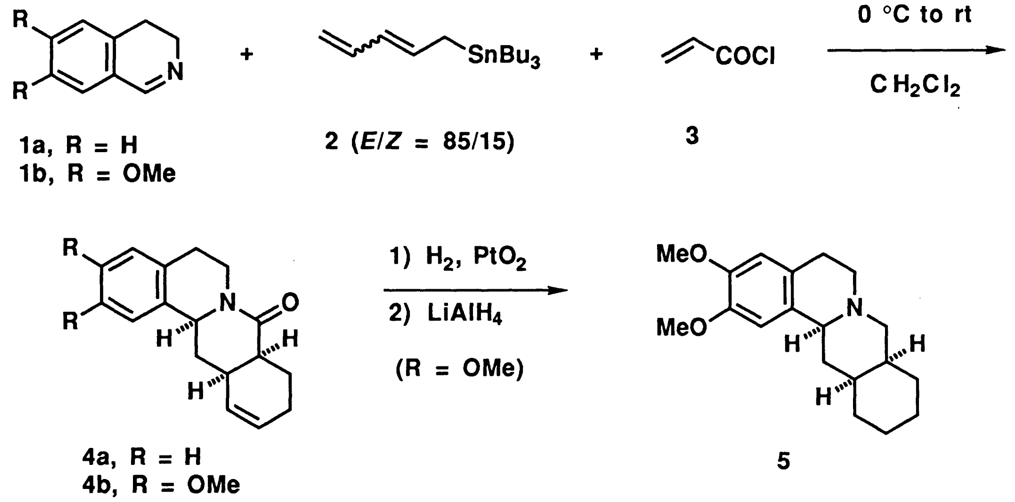
Organotin-aided three component couplings of C=N double bonds with 2,4-pentadienyl and α,β-unsaturated acyl groups followed by intramolecular Diels-Alder reactions result in highly stereoselective bicycloannulation of the C=N double bonds to afford *allo*-berbane and *allo*-yohimbane systems in one-flask operation.

Development of methodology for effective construction of nitrogen polycycles related to yohimbine-type and protoberberine-type alkaloids has attracted considerable attention for a few decades.1) We have reported that some organotin reagents react chemoselectively with cyclic C=N double bonds activated by acyl chlorides, providing an effective method for introduction of several kinds of unsaturated carbon substituents into nitrogen heterocycles.2) We have recently uncovered that allylic tin reagents react with isoquinolines activated by α,β,γ,δ-unsaturated acyl chlorides to give 1,2-adducts and that the subsequent *inverse* electron demand intramolecular Diels-Alder reactions give *pseudo*-berbane derivatives as major products.3,4) In this letter, we wish to report that the organotin methodology makes it possible to couple C=N double bonds with 2,4-pentadienyl and α,β-unsaturated acyl groups and that the subsequent *normal* electron demand intramolecular Diels-Alder reaction proceeds even *at room temperature* to afford bicycloannulated products stereoselectively in one-flask operation (Scheme 1).5,6)



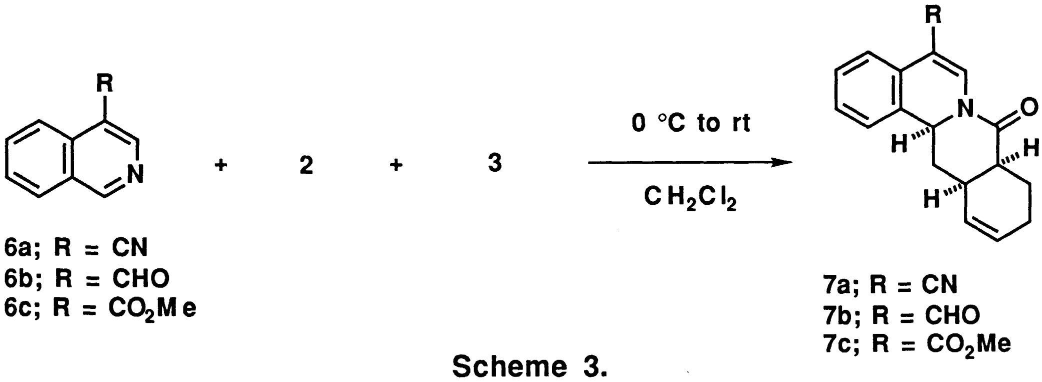
Scheme 1.

When acryloyl chloride (**3**) was added to a solution of 3,4-dihydroisoquinoline (**1a**) and 2,4-pentadienyltributyltin (**2**, *E*/*Z* = 85/15) in dichloromethane, the coupling of the three components followed by the intramolecular Diels-Alder reaction proceeded smoothly to afford a bicycloannulated compound **4a**[7] in 83% isolated yield (Scheme 2). Similarly, the reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline (**1b**) with **2** and **3** gave a bicycloannulated product **4b** in 81% yield. The stereochemistry of the products was determined to be the *allo*-configuration by transforming **2b** to the known *allo*-7,8-dimethoxyberbane (**5**).[8] Thus, the present reaction provides a new, short, and stereoselective method for the synthesis of *allo*-berbane systems. It should be noted that the stereochemistry of the cycloadducts is complementary to that obtained in the *inverse* electron demand cycloadditions where *pseudo*-isomers are major products.[3a,9]



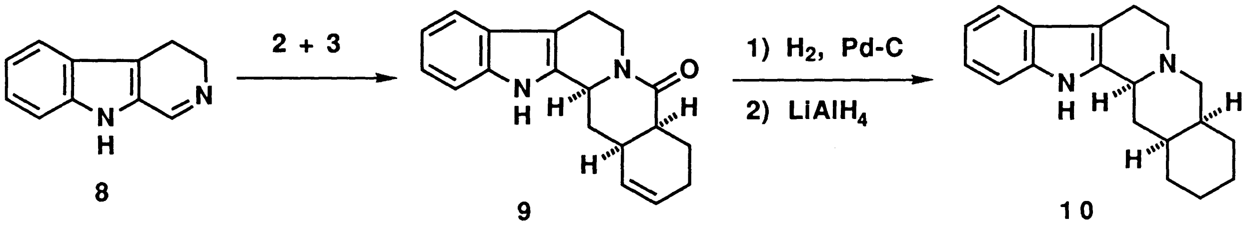
Scheme 2.

Further examples for the reactions of isoquinolines having functional groups are shown in Scheme 3. 4-Cyano-, 4-formyl-, and 4-methoxycarbonylisoquinolines (**6a**—**c**) can be bicycloannulated to give *allo*-berbane derivatives **7a**—**c** in 81, 66, and 64% yields, respectively, indicating the versatility of the reaction.



Scheme 3.

The present methodology is also applicable to synthesis of yohimbane system, a basic skeleton of one of the most studied and physiologically interested alkaloids. The coupling reaction of 3,4-dihydro-β-carboline (**8**) with **2** and **3** followed by the intramolecular cycloaddition gave directly a pentacyclic yohimbane derivative **9** in 68% yield (Scheme 4). The yield rose up to 74% when heated at reflux temperature after benzene was added to the reaction mixture. Eventually, catalytic reduction of **9** followed by hydride reduction afforded *allo*-yohimbane (**10**)$^{10)}$ in 76% overall yield. Thus, the present reaction also provides a new, short, and stereoselective method for the synthesis of the D and E rings of yohimbane system.



Scheme 4.

A typical experimental procedure is as follows: To a solution of **1a** (268 mg, 2.04 mmol) and **2** (728 mg, 2.04 mmol) in dry CH_2Cl_2 (15 mL) is added **3** (0.20 mL, 2.4 mmol) dropwise under ice-cooling. The reaction mixture is gradually warmed to room temperature and stirred for 24 h. The solvent is evaporated and the residue is chromatographed on silica gel to give **4a** (430 mg, 83%); IR (neat) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12—7.30 (m, 4H), 5.54—5.97 (m, 2H), 4.53—4.98 (m, 2H), 2.29—3.07 (m, 6H), 1.99—2.29 (m, 2H), 1.33—1.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 172.4 (s), 137.0 (s), 134.9 (s), 128.8 (d), 128.4 (d), 128.2 (d), 126.6 (d), 126.4 (d), 125.0 (d), 56.5 (d), 40.6 (d), 39.6 (t), 34.3 (t), 32.0 (d), 29.0 (t), 25.3 (t), 23.0 (t); Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; Found: C, 80.34; H, 7.51.

In summary, we have demonstrated a highly effective method for bicycloannulation of cyclic C=N double bonds by means of organotin reagent. The methodology described herein provides a short and stereoselective route to *allo*-berbane and *allo*-yohimbane systems, basic skeletons of important class of alkaloids.

References

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2) R. Yamaguchi, M. Moriyasu, M. Yoshioka, and M. Kawanisi, *J. Org. Chem.*, **50**, 287 (1985); R. Yamaguchi, M. Moriyasu, and M. Kawanisi, *Tetrahedron Lett.*, **27**, 211

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3) a) R. Yamaguchi, A. Otsuji, and K. Utimoto, *J. Am. Chem. Soc.*, **110**, 2186 (1988). See also b) S. F. Martin, B. Benage, and J. E. Hunter, *ibid.*, **110**, 5925 (1988).

4) The inverse electron demand Diels-Alder reaction is usually more sluggish than the normal one and suffers from more limitation. For instance, we have observed that, although allyltributyltin readily reacts with 3,4-dihydro-β-carboline (**8**) activated by 2,4-pentadienoyl chloride to give the corresponding 1,2-adduct, the inverse electron demand intramolecular Diels-Alder reaction of the adduct is very sluggish and the reaction at higher temperature gives a complex mixture.

5) For extensive works on reactions of 2,4-pentadienyltin reagents with carbonyl compounds and tandem Michael/Diels-Alder addition affording anthracycline system, see Y. Naruta, Y. Nishigaichi, and K. Maruyama, *J. Org. Chem.*, **53**, 1192 (1988) and references cited therein.

6) For recent intramolecular Diels-Alder reactions of triene amides, see S. F. Martin and W. Li, *J. Org. Chem.*, **54**, 268 (1989) and references cited therein; S. F. Martin and L. S. Geraci, *Tetrahedron Lett.*, **51**, 6725 (1988); S. F. Martin, H. Rüeger, S. A. Williamson, and S. J. Grzejszczak, *J. Am. Chem. Soc.*, **109**, 6124 (1987); S. Wattanasin, F. G. Kathawala, and R. K. Boeckman, Jr. *J. Org. Chem.*, **50**, 3810 (1985); S. Handa, K. Jones, C. G. Newton, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, **1985**, 1362.

7) All new compounds gave consistent spectral and analytical or high resolution MS data with proposed structures. NMR analyses showed that other stereoisomers, if any, are produced less than 5%.

8) For synthesis of berbane derivatives and their physiological activities, see L. Szabó, K. Honty, I. Tóth, and Cs. Szántay, *Chem. Ber.*, **105**, 3215 (1972); L. Szabó, K. Honty, L. Töke, and Cs. Szántay, *ibid.*, **105**, 3231 (1972); I. Tóth, L. Szabó, G. Bozsár, Cs. Szántay, L. Szekeres, and J. G. Papp, *J. Med. Chem.*, **27**, 1411 (1984); I. Tóth, G. Bozsár, L. Szabó, E. Baitz-Gács, and Cs. Szántay, *Liebigs Ann. Chem.* **1987**, 243.

9) The *allo*-isomers are likely produced via the endo addition of *trans*-2,4-pentadienyl group to acryloyl moiety. This is in contrast with the exo addition of allyl group to 2,4-pentadienoyl moiety in the inverse electron demand Diels-Alder reaction in which *pseudo*-isomers are major products.[3a)]

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(Received August 20, 1990)