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Simultaneous 1,2-Introduction of Allylic and α,β,γ,δ-Unsaturated Acyl Groups into Isoquinoline Systems and Subsequent Intramolecular Diels-Alder Reactions

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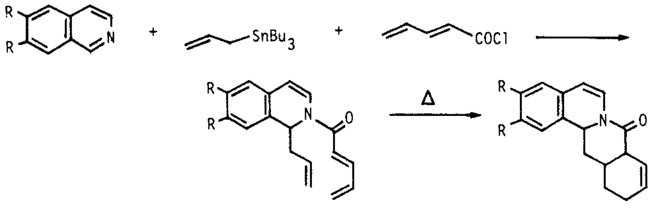
Abstract: The reactions of allyltributyltin with isoquinolines activated by 2,4-pentadienoyl chloride successfully give 1-allyl-2-(2,4-pentadienoyl)-1,2-dihydroisoquinolines in good yields. The subsequent intramolecular Diels-Alder reactions afford nitrogen tetracyclic compounds. The similar reaction of allyltributyltin with 6,7-dimethoxy-3,4-dihydroisoquinoline activated by 2,4-pentadienoyl chloride gives the corresponding 1,2-adduct, the intramolecular Diels-Alder reaction of which furnishes pseudo-7,8-dimethoxyberbane, after catalytic hydrogenation and hydride reduction.

Effective introduction of a variety of useful functionalized carbon substituents into nitrogen heterocycles is important for synthesizing complex naturally occurring heterocycles. We have reported that allyltin reagents attack chemo- and regioselectively on the α-positions of nitrogen heteroaromatics activated by alkyl chloroformates.[1] In view of the high chemoselectivity of this reaction and the substantial potential of the intramolecular Diels-Alder reaction for constructing polycyclic structures,[2,3] we thought that if α,β,γ,δ-unsaturated acyl chlorides could be used as acylating agents in this reaction allylic and polyunsaturated acyl groups could be introduced simultaneously and the subsequent intramolecular Diels-Alder reaction would lead to a nitrogen polycycle. We now report that this idea can be realized in the case of the isoquinoline system (Scheme I). The resulting polycycles may be valuable synthetic intermediates for protoberberine and isoquinoline alkaloids.[4-6] It should be pointed out that the α,β,γ,δ-unsaturated acyl group plays three roles: (1) activation of isoquinoline, (2) stabilization of the resulting enamine, (3) diene partner of the inverse electron demand Diels-Alder reaction.

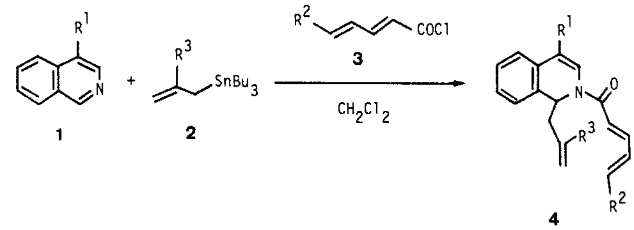
We first examined the reaction with isoquinoline as a model compound. When 2,4-pentadienoyl chloride was added to a mixture of isoquinoline and allyltributyltin in dry dichloromethane, a reaction proceeded smoothly to give the expected 1-allyl-2-(2,4-pentadienoyl)-1,2-dihydroisoquinoline (**4a**) as a relatively labile oil in 68% yield. The results obtained for additional examples are shown in Scheme II and Table I.

As shown in Table I, the yields are good or excellent. The fact that several functional groups on isoquinoline remain intact (entries c-e) demonstrates the versatility of the reaction. Thus, the present reaction provides a straightforward method for the introduction of polyunsaturated substituents, which otherwise appears difficult.[7]

Scheme I



Scheme II



Scheme III

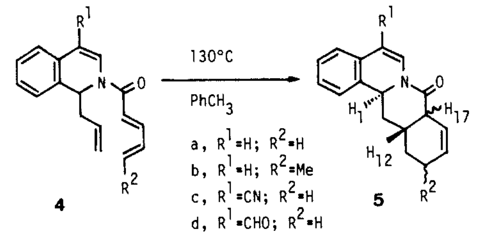


Table I. Reactions of Allyltin Reagents with Isoquinolines Activated by α,β,γ,δ-Unsaturated Acyl Chlorides[a]

entry	R^1	R^2	R^3	product	yield,[b] %
a	H	H	H	**4a**	68
b	H	Me	H	**4b**	94
c	CN	H	H	**4c**	86
d	CHO	H	H	**4d**	93
e	Br	H	H	**4e**	82
f	H	H	Me	**4f**	83

[a] To a solution of isoquinoline (1 equiv) and allyltributyltin (1 equiv) in dichloromethane was added α,β,γ,δ-unsaturated acyl chloride (1 equiv) with ice cooling, and the mixture was stirred at room temperature for a few hours. [b] Isolated yield.

With the desired polyunsaturated compounds in hand, we next examined the intramolecular Diels-Alder reaction. A solution of **4a** in toluene was heated at 130 °C for 24 h to give the cycloadducts **5a** in 76% yield as a mixture of two stereoisomers (91:9

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(1) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem.* **1985** *50*, 287. For our other work on reactions of organotin reagents with nitrogen heteroaromatics activated by alkyl chloroformates, see: Yamaguchi, R.; Moriyasu, M.; Kawanisi, M. *Tetrahedron Lett.* **1986**, *27*, 211. Yamaguchi, R.; Moriyasu, M.; Takase, I.; Kawanisi, M.; Kozima, S. *Chem. Lett.* **1987**, 1519.

(2) For a review of the intrmamolecular Diels-Alder reaction, see: Ciganek, E. *Org. React.* (*N.Y.*) **1984**, *32*, 1.

(3) For recent intramolecular Diels-Alder reactions of triene amides, see: (a) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, A. K. *J. Org. Chem.* **1983**, *48*, 5170. (b) Martin, S. F.; Grzejszczak, S.; Rüeger, H.; Williamson, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 4072. (c) Martin, S. F.; Benage, B.; Williamson, S. A.; Brown, S. P. *Tetrahedron* **1986**, *42*, 2903. (d) Wattanasin, S.; Kathawala, F. G.; Boeckman, R. K., Jr. *J. Org. Chem.* **1985**, *50*, 3810. (e) Handa, S.; Jones, K.; Newton, C. G.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1362.

(4) For the synthesis of berbane derivatives and their physiological activities, see: (a) Szabó, L.; Honty, K.; Tőke, L.; Tőth, I.; Szántay, Cs. *Chem. Ber.* **1972**, *105*, 3215. (b) Szabó, L.; Honty, K.; Tőke, L.; Szántay, Cs. *Ibid.* **1972**, *105*, 3231. (c) Tőth, I.; Szabó, L.; Bozsár, G.; Szántay, Cs.; Szekeres, L.; Papp, J. G. *J. Med. Chem.* **1984**, *27*, 1411.

(5) Brossi, A.; Bruderer, H.; Rachlin, A. I.; Teitel, S. *Tetrahedron* **1968**, *24*, 4277.

(6) Takano, S.; Sasaki, M.; Kanno, H.; Shishido, K.; Ogasawara, K. *J. Org. Chem.* **1978**, *43*, 4169.

(7) Similar reaction of the isoquinolinium salt with allyl Grignard reagent gave a complex reaction mixture.

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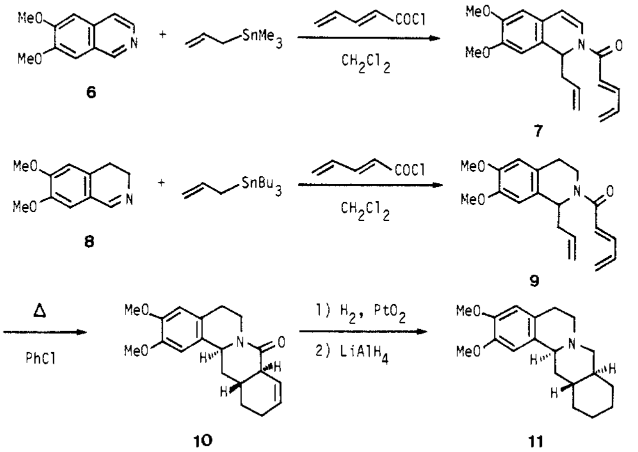
Table II. Intramolecular Diels–Alder Reactions of the 1,2-Adducts **4**

entry	R^1	R^2	yield of **5**,[a] %	isomeric ratio[b]
a	H	H	76	91:9
b	H	Me	84[c]	76:24[d]
c	CN	H	78	>95:5
d	CHO	H	64	82:18

[a] Isolated yield. [b] Determined by ^{1}H NMR (see ref 8). [c] Heated at reflux in *o*-dichlorobenzene. [d] ^{1}H and ^{13}C NMR indicated that the product is a mixture of two stereoisomers. Hence, R^2 (=Me) and H_{17} should be trans by considering the Diels–Alder reaction of the (*E,E*)-2,4-hexadienoyl group with olefin.

Scheme IV



by ^{1}H NMR)[8] (Scheme III). Other examples of the intramolecular Diels–Alder reaction are listed in Table II.

We next turned our attention to the reaction of 6,7-dimethoxyisoquinolines, which are one of the principal partial structures of isoquinoline alkaloids. When **6** was reacted with allyltrimethyltin in the presence of 2,4-pentadienoyl chloride (Scheme IV), the reaction was very sluggish and the yield of the 1,2-adduct **7** was 31%, probably due to the reduced electrophilicity of the isoquinolinium salt by the electron-donating methoxy groups.[10,11] We found, however, that the reaction could be achieved with a cyclic imine[12] with much better results. Thus, the reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline (**8**) with 1 equiv of allyltributyltin in the presence of 2,4-pentadienoyl chloride proceeded very nicely to give the 1,2-adduct **9** in 79% yield after flash chromatography. The subsequent intramolecular Diels–Alder reaction of **9** was carried out in refluxing chlorobenzene to afford the cycloadduct **10** in 86% yield with 95% stereoselectivity. Catalytic hydrogention of **10** over platinum dioxide followed by reduction with lithium aluminum hydride afforded pseudo-7,8-dimethoxyberbane (**11**).

The IR spectrum of **11** shows no Bohlmann band, and the signal due to H_1 of **11** appears at 4.22 ppm in ^{1}H NMR. Comparison of these spectroscopic and physical data with those of normal and allo- and epiallo-7,8-dimethoxyberbanes indicates that **11** is pseudo-7,8-dimethoxyberbane.[4a,b,9]

In summary, we have demonstrated an effective method for the simultaneous 1,2-introduction of unsaturated carbon substituents into isoquinoline systems by means of organotin reagents. The subsequent intramolecular Diels–Alder reaction leads to complex nitrogen polycycles, which may be valuable intermediates for isoquinoline alkaloids.

Experimental Section[13]

As the typical experimental procedures, synthesis of pseudo-7,8-dimethoxyberbane (**11**) is described here.

Reaction of Allyltributyltin with 8 Activated by 2,4-Pentadienoyl Chloride. To a solution of **8** (953 mg, 4.99 mmol) and allyltributyltin (1666 mg, 5.03 mmol) in CH_2Cl_2 (15 mL) was added 2,4-pentadienoyl chloride (588 mg, 5.04 mmol) with ice cooling. The reaction mixture was warmed to room temperature and stirred for 5 h. The solvent was evaporated, and the residue was rapidly chromatographed on silica gel. Elution by hexane-CH_2Cl_2 (7:3) and then hexane–AcOEt (7:3) gave 1-allyl-6,7-dimethoxy-2-(2,4-pentadienoyl)-1,2,3,4-tetrahydroisoquinoline (**9**; 1230 mg, 79%), which was immediately subjected to the next reaction due to its relative instability. **9**: IR (neat) 1640, 1610 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.32 (dd, 1 H, *J* = 15, 10 Hz), 6.31–6.79 (m, 4 H), 4.53–6.25 (m, 8 H), 3.85 (s, 6 H), 2.51–2.98 (m, 4 H); ^{13}C NMR (CDCl$_3$) δ 165.7–165.5 (s), 148.0–147.8 (s), 147.6–147.5 (s), 142.8–142.7 (d), 135.1–135.0 (d), 134.0 (d), 129.1–128.2 (s), 126.6–125.4 (s), 123.8 (t), 122.1–121.6 (d), 117.1 (t), 111.7–111.3 (d), 110.4–109.9 (d), 56.0 (q), 55.9 (q), 52.0 (d), 41.6–41.1 (t), 40.1 (t), 28.9–27.7 (t).

Intramolecular Diels–Alder Reaction of 9, Affording 5,6,8,8a,12,12a,13,13a-Octahydro-2,3-dimethoxy-11*H*-dibenzo[*a*,*g*]-quinolizin-8-one (10). A solution of **9** (1230 mg, 3.92 mmol) and 2,6-di-*tert*-butylphenol (a few milligrams) in chlorobenzene (120 mL) was heated at reflux for 26 h. The solvent was evaporated, and the residue was chromatographed on silica gel. Elution by hexane–AcOEt (7:3) gave **10** (1054 mg, 86%), which included a slight amount (ca. 5% by ^{1}H NMR) of an isomer. **10**: mp 98–102 °C; IR (Nujol) 1630 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.68 (s, 1 H), 6.62 (s, 1 H), 6.14 (dd, 1 H, *J* = 2, 10 Hz), 5.58–5.71 (m, 1 H), 4.52–4.70 (m, 2 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 2.45–2.95 (m, 4 H), 1.32–2.20 (m, 7 H); ^{13}C NMR (CDCl$_3$) δ 171.4 (s), 147.9 (s), 147.6 (s), 129.1 (s), 127.8 (s), 127.6 (d), 124.2 (d), 112.0 (d), 108.3 (d), 56.2 (q), 55.9 (q), 54.4 (d), 44.4 (d), 40.7 (t), 36.4 (t), 31.8 (d), 29.4 (t), 28.3 (t), 25.0 (t). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40. Found: C, 72.58; H. 7.51.

Pseudo-7,8-dimethoxyberbane (11). A mixture of **10** (145 mg, 0.46 mmol) and PtO_2 (23 mg) in MeOH (10 mL) was stirred under a H_2 atmosphere. After the reaction was complete, PtO_2 was filtered off through Celite and the solvent was evaporated. The residue (136 mg) was dissolved in 5 mL of THF–Et$_2$O (1:1) and added to a suspension of LiAlH$_4$ (142 mg) in 8 mL of THF–Et$_2$O (1:1). The mixture was heated at reflux for 4 h. The usual workup and chromatography on alumina eluted by hexane–AcOEt (8:2) gave **11** (75 mg, 54%): mp 109–112 °C; IR (CHCl$_3$) 1610, 1520 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.76 (s, 1 H), 6.60 (s, 1 H), 4.22 (br s, 1 H), 3.89 (s, 6 H), 2.75–3.38 (m, 4 H), 1.75–2.67 (m, 14 H); ^{13}C NMR (CDCl$_3$) δ 147.6 (s), 147.5 (s), 128.6 (s), 127.1 (s), 112.1 (d), 109.3 (d) 56.6 (d), 56.2 (q), 55.8 (q), 51.7 (t), 51.0 (t), 42.2 (d), 35.4 (2t), 33.0 (t), 30.4 (d), 26.4 (t), 26.0 (t), 22.7 (t). Anal. Calcd for $C_{19}H_{27}O_2N$: C, 75.71; H, 9.03. Found: C, 75.51; H, 9.11.

Supplementary Material Available: Physical and spectral data for compounds **4a–f**, **5a–d**, **7**, and **9–12** (4 pages). Ordering information is given on any current masthead page.

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(8) The fact that treatment of the 1:1 mixture (**5a**) with sodium methoxide gives a single α,β-unsaturated amide (**12**) in 95% yield indicates that the cycloadducts are stereoisomeric in the C/D ring junction. The ^{1}H NMR shows that the coupling constant between H_{12} and H_{17} of the major isomer is 11 Hz (trans), while that of the minor one is 5 Hz (cis). Furthermore, H_1 of the major isomer appears as triplet (*J* = 7.5 Hz), while that of the minor one is as doublet of doublet (*J* = 4.5, 10.5 Hz). Therefore, the major isomer possesses the *cis*-benzo[*a*]quinolizidine system and the minor, the trans one.[9] All these spectroscopic data and inspection of the Dreiding model led us to the conclusion that the stereochemistry of the major isomer is trans,trans and that of the minor one is trans,cis in terms of H_1 and H_{12} and H_{12} and H_{17}. This stereochemical assignment was further supported by the formation of pseudo-7,8-dimethoxyberbane (vide infra). It should be noted that the stereochemistry of the major isomer is produced via the exo addition of an equatorial allyl group to an equatorial 2,4-pentadienoyl one, which is thought to be energetically the most favorable transition state.

(9) Uskoković, M.; Bruderer, H.; Planta, C. v.; Williams, T.; Brossi, A. *J. Am. Chem. Soc.* **1964**, *86*, 3364.

(10) An additional difficulty is that **7** is unstable and readily polymerizes unless diluted in a solvent.

(11) The use of 3 equiv of allyltrimethyltin increased the yield up to 67%, while allyltributyltin gave lower yields.

(12) During this research and preparation of the manuscript, two reports on the reaction of *preformed stable* iminium salts with allyltin reagents have appeared. (a) Photochemical addition to 1-methyl-2-phenyl-1-pyrrolium perchlorate in MeOH: Borg, R. M.; Mariano, P. S. *Tetrahedron Lett.* **1986**, *27*, 2821. (b) Addition to the trifluoroacetate salt of dihydro-β-carboline in MeOH-CHCl$_3$: Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 1378. These reactions, however, undergo only allylation of imines. See also for Lewis acid promoted reactions of allylic tin reagents with aldimines: Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146. Yamamoto, Y.; Komatsu, T.; Maruyama, K. *Ibid.* **1985**, *50*, 3115.

(13) All the temperatures were uncorrected. The IR spectra were obtained on a Jasco IR-80 spectrometer. The high-resolution mass spectra were taken by using a Hitachi M-80 mass spectrometer. The ^{1}H and ^{13}C NMR spectra were obtained on Varian EM-390, XL-200, and JEOL FX-90Q spectrometers, Me$_4$Si being chosen as the internal standard. The microanalyses were performed by Kyoto University Elemental Analysis Center. All the reactions were carried out under Ar atmosphere, otherwise noted. CH$_2$Cl$_2$ was distilled from P$_2$O$_5$ before use.