

Bibenzyl is produced by benzyl radicals escaping from the cage and dimerizing.

In short, the reaction of methylenetitanocene (**2**) with alkyl halides exhibits behavior contrary to that expected for either of the two previously defined classes of metal carbenes and to that predicted from reactions with olefins or organic carbonyls. The results presented are best explained by invoking one-electron steps for both the cleavage of the carbon-halogen bond and the formation of the carbon-carbon bond and suggest that instead of two distinct classes of metal carbenes, metal carbenes manifesting a continuum of reactivity behavior may exist. The pathway followed in a particular reaction is dictated by the combination of the characteristics of the metal carbene and the nature of the substrate.

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Registry No. 1, 80122-07-2; 3, 95044-99-8; DMAP, 57951-36-7; $\text{Cp}_2\text{Ti}(\text{Cl})\text{CH}_2\text{CH}=\text{CH}_2$, 90076-38-3; $\text{Cp}_2\text{Ti}(\text{Cl})\text{CH}_2\text{CH}_2\text{Ph}$, 12663-68-2; $\text{Cp}_2\text{Ti}(\text{Cl})\text{CH}_3$, 1278-83-7; PhCH_2Cl , 100-44-7; PhCHDCl , 79449-94-8; $\text{C}_6\text{H}_5\text{CHDCH}_2\text{OH}$, 10606-75-4; allylic chloride, 107-05-1; *tert*-butyl chloride, 507-20-0; methyl iodide, 74-88-4; bibenzyl, 103-29-7; 2-methyl-1-propene, 115-11-7; *p*-methoxybenzyl chloride, 824-94-2; *p*-phenylbenzyl chloride, 1667-11-4; *p*-chlorobenzyl chloride, 104-83-6; *p*-methylbenzyl chloride, 104-82-5.

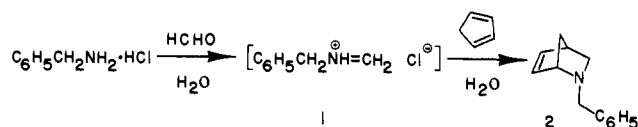
Aza Diels-Alder Reactions in Aqueous Solution: Cyclocondensation of Dienes with Simple Iminium Salts Generated under Mannich Conditions

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Compared to the all-carbon Diels-Alder reaction, the imino variation has received only scant attention, despite the enormous potential it holds for alkaloid synthesis.^{1,2} The vast majority of aza cycloadditions recorded in the literature have employed imines substituted with one or more electron-withdrawing activating groups; however, a few successful examples have been reported that utilize dialkyliminium salts.³ Although simple imines are unreactive toward electron-rich dienes, Danishefsky has recently demonstrated that Lewis acid catalysis is sufficient to promote reaction with a highly reactive diene.⁴ We now wish to report that simple unactivated iminium salts, generated *in situ* under Mannich-like conditions, react with dienes in an exceptionally mild and convenient aqueous aza Diels-Alder reaction.

Preliminary studies focused on the reaction of a variety of dienes with the benzyliminium ion **1** derived from formaldehyde and benzylamine. Addition of neat cyclopentadiene (2.0 equiv) to a 2.5 M aqueous solution of benzylamine hydrochloride (1.0 equiv) and 37% aqueous formaldehyde (1.4 equiv) gave rise to a heterogeneous reaction mixture which was vigorously stirred for 3 h at room temperature. Workup^{5a} provided a near quantitative yield of bicyclic amine **2**. This procedure is applicable to a number



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Table I. Reaction of Iminium Ions with Dienes^a

entry	diene	amine	temp, °C	time	product	% yield ^b
1		BnNH ₂ ·HCl	55	42 h		35 (41)
2		BnNH ₂ ·HCl	35	48 h		64 (69)
3		BnNH ₂ ·HCl	35	70 h		(59)
4		BnNH ₂ ·HCl	55	96 h		62
5		BnNH ₂ ·HCl	25	23 h		45 (49)
6 ^c		MeNH ₂ ·HCl	25	3 h		82
7 ^d		NH ₄ Cl	25	6 h		44
8 ^d		NH ₄ Cl	35	96 h		(40)

^aAll reactions were run with 1.3 equiv of amine hydrochloride and 1.3 equiv of 37% aqueous formaldehyde solution unless otherwise stated. The aqueous solutions were ca. 2.85 M in amine hydrochloride. ^bIsolated yields. Yields in parentheses are based on ¹H NMR. ^cReaction was carried out in 2.6 M monomethylamine hydrochloride with 2.0 equiv of cyclopentadiene and 1.4 equiv of 37% formaldehyde. ^dReaction was conducted in a saturated ammonium chloride solution.

of other dienes (Table I).^{5b} As can be seen from the table, reaction times and temperatures vary according to the reactivity of the diene. With the exception of entry 6, all condensation reactions were carried out in sealed ampules. Yields varied from modest to good. Use of alcoholic solvents inevitably led to a decrease in the reaction rate, however, aqueous tetrahydrofuran mixtures could be employed without any noticeable effect in reaction rate and yield. Entries 3 and 5 address the regioselectivity question. The results shown in Table I are consistent with those reported in previous work on iminium salts.^{3b,d} The formation of a single diastereomer in the reaction of (*E,E*)-2,4-hexadiene with iminium ion **1** (entry 4) is mechanistically significant. The high stereospecificity observed for this reaction is characteristic of a truly concerted cycloaddition rather than an ionic, stepwise process.

The recent surge of interest in asymmetric Diels-Alder cycloaddition reactions⁶ using chiral dienophiles and dienes prompted us to explore the potential for chiral induction employing an optically active iminium ion. In a preliminary study, aqueous formaldehyde was treated at 0 °C with (–)- α -methylbenzylamine hydrochloride in the presence of cyclopentadiene. After 20 h at 0 °C, a 4:1 mixture of separable diastereomers (cf. **3** and **4**) were isolated in 86% yield.



To date use of acetaldehyde in place of formaldehyde has met with only limited success. Reaction of cyclopentadiene with benzylamine hydrochloride and acetaldehyde afforded a 47% isolated yield of a mixture of the *exo* and *endo* adducts **5** and **6**

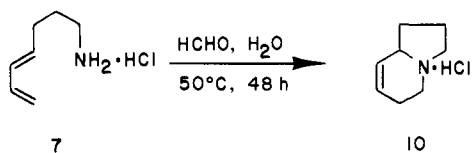


in a 1.5:1 ratio, respectively. The reaction rate was substantially

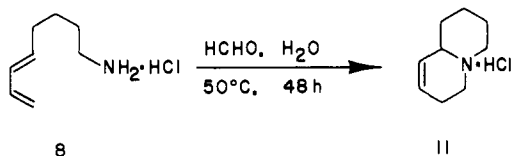
retarded relative to the formaldehyde case (16 h vs. 3 h) and the number of byproducts were significantly increased. Attempts to employ acetone in the aza Diels-Alder reaction led to no reaction whatsoever. Methylamine hydrochloride may be successfully substituted for benzylamine hydrochloride (Table I, entry 6). The yield is lower due only to the greater volatility of the product. Even ammonium chloride may be employed which provides access to the corresponding secondary amines (entries 7 and 8); however, a significant reduction in yield is observed.

The intramolecular imino variation of the Diels-Alder reaction, like its intermolecular counterpart, has also received only limited attention. The first example of an intramolecular imino Diels-Alder reaction, in which an oximino dienophile was condensed with a highly reactive quinone methide, was reported by Oppolzer.⁷ More recently Weinreb has relied on pyrolytically generated *N*-acyl imines as dienophiles.⁸ To date no example of an iminium ion participating in an intramolecular Diels-Alder reaction has been recorded. We detail below the first example of such a reaction.

In order to examine the intramolecular iminium ion variation of the Diels-Alder reaction, we prepared substrates 7-9. Treatment of a 0.2 M solution of (*E*)-4,6-heptadienylamine hydrochloride (7)^{9a} with 37% aqueous formaldehyde (2.0 equiv) at 50 °C for 48 h gave rise to 95% yield of crystalline dehydro- δ -coniciene hydrochloride (10).^{5b} Similar exposure of 8^{9b} (0.2



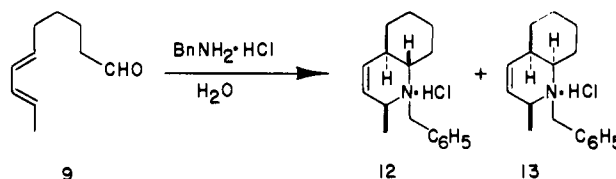
M in H₂O) to aqueous formaldehyde afforded a 65% yield of adduct 11.^{5b} The formation of 10 and 11 via the iminium



Diels-Alder strategy offers a mild and highly practical alternative to the pyrolytic conditions cited above. Moreover, the methodology should prove generally applicable to the synthesis of a number of alkaloids embodying a bridgehead nitrogen.

In order to expand the scope of this reaction we examined the cyclocondensation of dienyl aldehyde 9^{9c} with benzylamine hydrochloride. Slow addition of 9 over 20 h to a 1.0 M solution of benzylamine hydrochloride (5.0 equiv) in water/ethanol, 1:1,

heated at ca. 70 °C provided^{5c} a 63% yield (unoptimized) of adducts 12 and 13 in a ratio of 2.5:1. The extension of the



intramolecular reaction to iminium salts derived from aldehydes other than formaldehyde is very encouraging and may prove useful in alkaloid total synthesis.

Work is currently in progress to further expand the scope of the iminium Diels-Alder reaction and to examine its effectiveness in the construction of naturally occurring alkaloids.

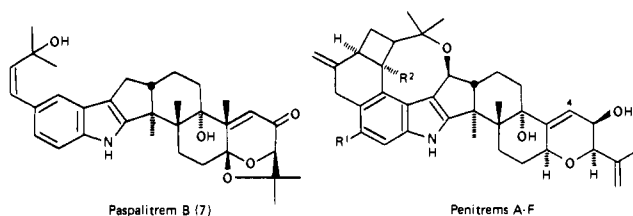
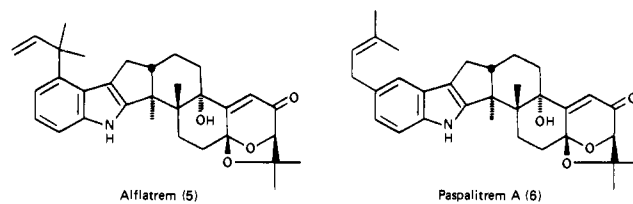
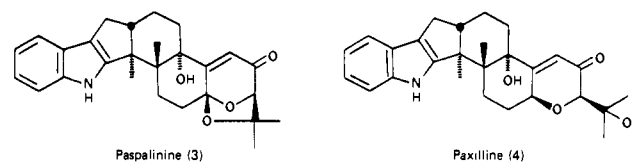
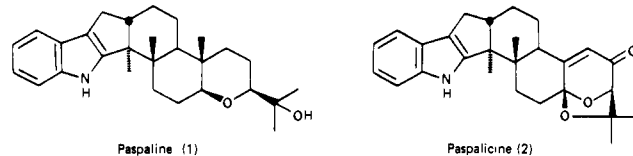
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Total Synthesis of (-)-Paspaline

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In this paper we disclose the *first* total synthesis of (-)-paspaline (1),^{2,3} the simplest member of a rapidly growing class of indole



- (8) A: R¹ = Cl, R² = OH; 4a, 4aa-epoxide
(9) B: R¹ = R² = H; 4a, 4aa-epoxide
(10) C: R¹ = Cl, R² = H
(11) D: R¹ = R² = H
(12) E: R¹ = H, R² = OH; 4a, 4aa-epoxide
(13) F: R¹ = Cl, R² = H; 4a, 4aa-epoxide

(5) (a) The reaction is diluted with an equal volume of water and is washed twice with ether. The aqueous phase is made basic with solid potassium hydroxide. The product is isolated by extraction with ether. (b) In cases where the amine hydrochlorides are isolated, the aqueous phase is evaporated to dryness after washing with ether. The product is isolated by extracting the residue with chloroform. (c) The reaction is diluted with an equal volume of water and is washed twice with an equal volume of ether-hexane (1:1). The products are isolated by extraction with chloroform.

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(9) (a) Reduction (LiAlH₄, Et₂O) of (*E*)-3,5-hexadienoic acid¹⁰ provided (100%) the corresponding alcohol which was converted (95%) [(a) TsCl, Et₃N, DMAP; (b) NaCN, Me₂SO] into 1-cyano-(*E*)-3,5-hexadiene. Reduction (LiAlH₄, Et₂O) and acidification (dry HCl, Et₂O, -44 °C) gave rise to amine hydrochloride 7. (b) Reduction of 1-cyano-(*E*)-4,6-heptadiene,¹¹ followed by acidification as in 5a, provided an 82% overall yield of amine hydrochloride 8. (c) Coupling (THF, Li₂CuCl₄) of the Grignard reagent derived from (4-chlorobutoxy)trimethylsilane with sorbyl acetate and subsequent treatment (reflux) with aqueous ethanol afforded (58% overall) (*E*)-6,8-decadiene, which upon PCC oxidation provided aldehyde 9.

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