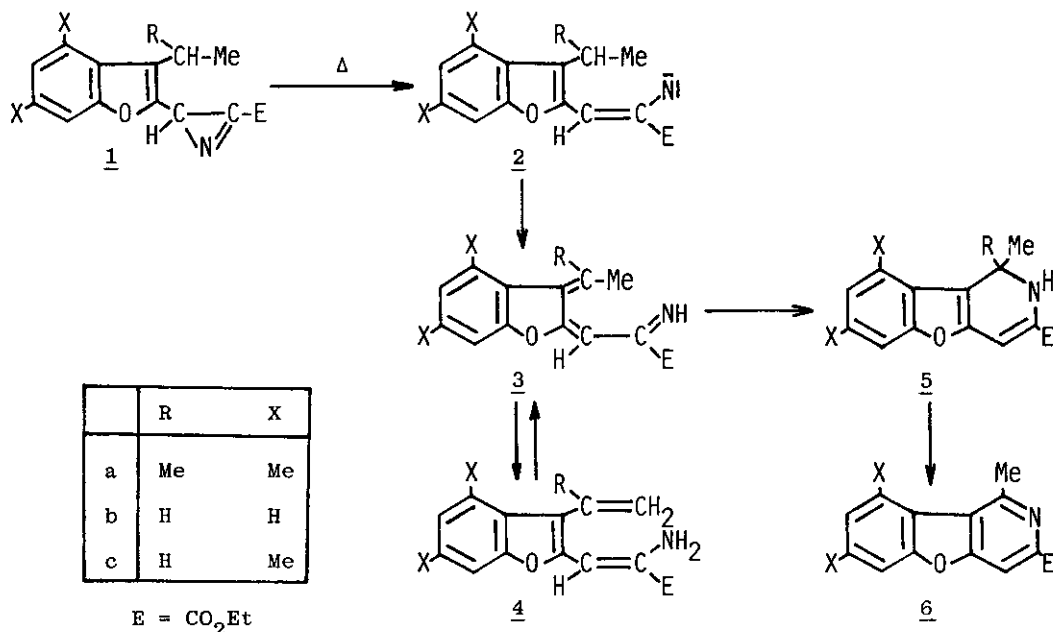


PALLADIUM-PROMOTED FORMATION OF AZEPINES FROM 1-AMINOHEXATRIENYL SYSTEM<sup>†</sup>

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**Abstract**—Treatment of ethyl  $\alpha$ -amino- $\beta$ -(3-alkenylbenzofuran-2-yl)acrylate (1-aminohexatrienyl system) with  $\text{PdCl}_2(\text{PhCN})_2$  in the presence of  $\text{Na}_2\text{CO}_3$  caused a selective cyclization of the amino group to the terminal carbon of the alkenyl group forming azepines.

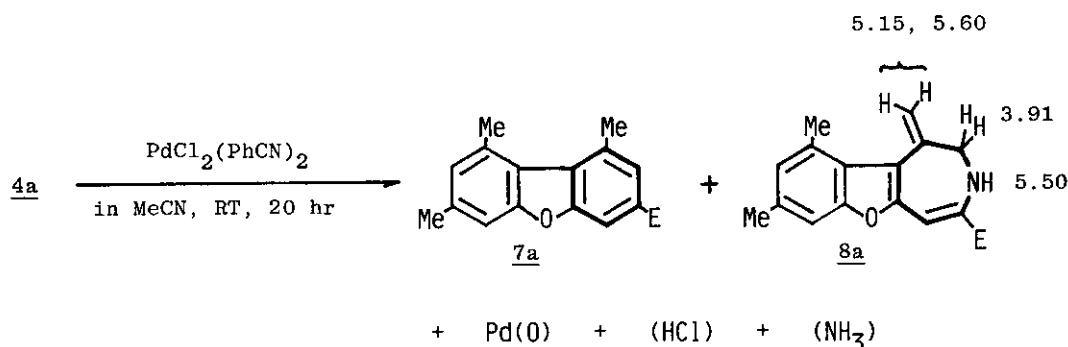
In the course of the investigation on thermal rearrangement of 2H-azirines 1 into 6-membered cyclic compounds 5 and 6, we found a novel intramolecular hydrogen shift of the vinyl nitrene intermediates 2 to form enamines 4 (1-aminohexatrienyl system), which at higher temperatures gave 5 or 6.<sup>1)</sup>



<sup>†</sup> This article is dedicated to professor Tetsuji Kametani on the occasion of the celebration of his retirement from the Chair of Organic Chemistry at the Pharmaceutical Institute of Tohoku University.

These enamines are considered as the suitable candidates for 7-membered ring compounds, azepines, as azepines will be formed by bonding the nitrogen with the terminal carbon of the alkenyl group. Thus, we examined the intramolecular amino-palladation.<sup>2)</sup>

When ethyl  $\alpha$ -amino- $\beta$ -(4,6-dimethyl-3-*i*-propenylbenzofuran-2-yl)acrylate 4a was treated with 1.1 mol eq. of dichlorobis(benzonitrile)palladium(II) in acetonitrile at room temperature under argon for 20 hr, precipitation of Pd-black was observed. Usual work-up and separation by silica gel column chromatography gave colorless granules (28%) and yellow needles (26%). On the basis of spectral results,<sup>3)</sup> and micro analysis, the colorless compound was assigned as ethyl 1,7,9-trimethyldibenzofuran-3-carboxylate 7a. By micro analysis and mass spectrum the molecular formula of the yellow needles was determined to be  $C_{18}H_{19}NO_3$ , which corresponded to a compound formed by elimination of a hydrogen molecule from 4a. The IR spectrum of this compound showed a band at  $3400\text{ cm}^{-1}$  indicating the presence of a secondary amino group. The NMR spectrum showed broad signals at  $\delta$  3.91 (2H), 5.15 (1H), 5.50 (1H), and 5.60 (1H) in addition to the signals of the protons of ethoxycarbonyl group, two methyl groups, aromatic protons, and a vinyl proton. The broad signal at  $\delta$  5.50 was assigned as the amino proton by  $D_2O$  exchange technique. Double resonance by irradiation of the signal at  $\delta$  3.91 reduced two broad signals at  $\delta$  5.15 and 5.60 into two doublets, with a coupling constant of 1.5 Hz. From these results, the yellow compound was assigned as ethyl 8,10-dimethyl-1-methylene-2,3-dihydro-1*H*-benzofuro[2,3-*d*]azepine-4-carboxylate 8a.

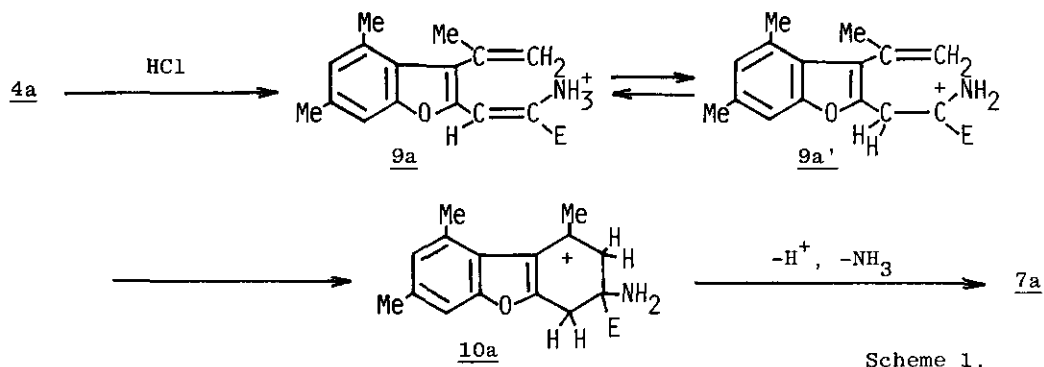


Consideration of the stoichiometric aspect of this reaction suggested elimination of ammonia by the formation of 7a, and production of hydrogen chloride by the formation of 8a and Pd-black. Therefore, this reaction was expected to be influenced by an acid or a base. In the presence of hydrogen chloride, 4a gave 7a

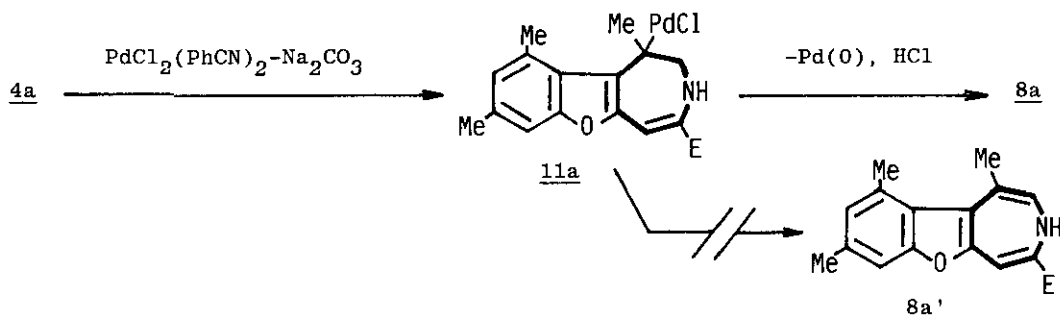
quantitatively, even in the absence of Pd(II). When the reaction was performed in the presence of 1.1 mol eq. of sodium carbonate, 8a was obtained as the sole product (67% isolated yield).

The above results suggested the pathway for the formation of 7a and 8a, as follows.

The dibenzofuran 7a would be formed as shown in Scheme 1. Protonation of 4a gives an ammonium ion 9a which tautomerized to a carbonium ion 9a'. Intramolecular electrophilic addition of the positively charged carbon of 9a' to the *i*-propenyl group to form a stabilized cation 10a would be followed by elimination of proton and ammonia to give 7a.

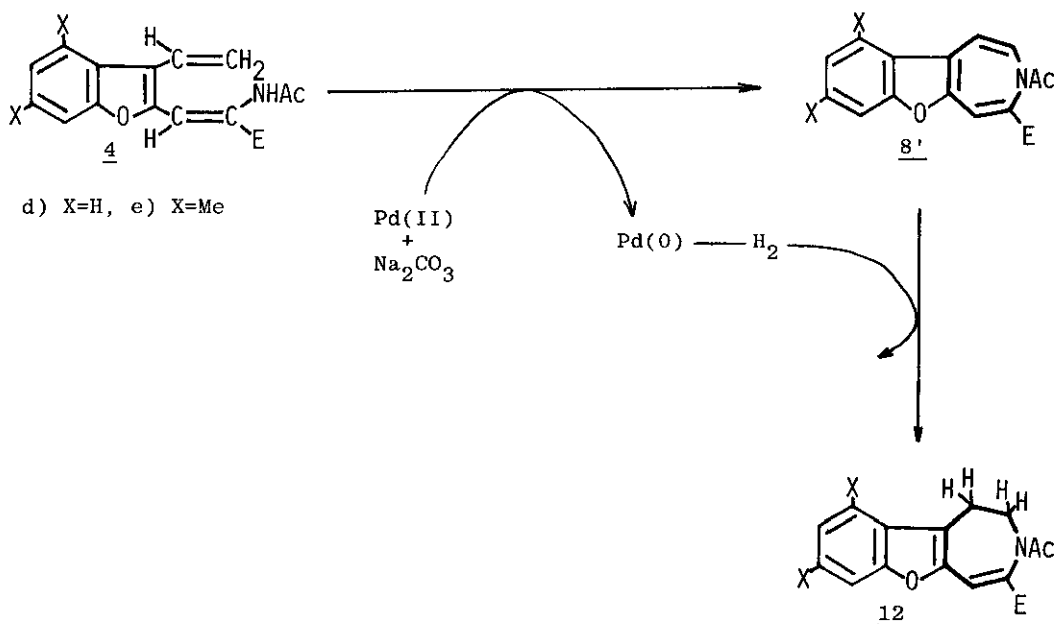


As shown in Scheme 2, formation of the exo-cyclic double bond in 8a implies the intermediacy of the palladium  $\sigma$ -complex 11a, which gives 8a by elimination of Pd-black and hydrogen chloride. Absence of the alternative elimination product 8a', having 1*H*-azepine nucleus, would be ascribed to its instability caused by an  $8\pi$ -cyclic conjugated system.<sup>4)</sup>



We were interested in the amino-palladation reactions of enamines 4b and 4c, which were missing the methyl group to form the exo-cyclic double bond. When 4b and 4c were treated with Pd(II) in the presence of  $\text{Na}_2\text{CO}_3$  expecting the selective azepine formation, precipitation of Pd-black was observed. However, the usual work-up gave tarry products. With a hope of stabilizing the 1*H*-azepine, we examined the reactions of the *N*-acetyl derivatives 4d and 4e, which were easily obtained by the reactions of 4b and 4c with acetyl chloride in the presence of pyridine. But the reactions of these compounds also gave tarry products.

Finally, we tried the catalytic hydrogenation of the product using the Pd-black formed in the course of amino-palladation. When the precipitation of Pd-black seemed to be finished in the reaction of 4d, the atmosphere of the reaction was changed from argon to hydrogen and stirred for 1 day. Work-up and separation by silicagel column chromatography afforded pale yellow granules in 54% yield. This compound was assigned as ethyl 3-acetyl-2,3-dihydro-1*H*-benzofuro[2,3-*d*]-azepine-3-carboxylate 12d on the basis of micro analysis and spectral results.<sup>3)</sup> Especially, most relevant for this assignment is the NMR spectrum, which showed four aliphatic protons of the dihydroazepine nucleus at  $\delta$  2.50 (1H), 3.10 (2H), and 4.90 (1H). By the same way, 4e afforded 12e in 47% yield.



Now, it became clear that azepines could be formed by the intramolecular amino-palladation reaction of 1-aminohexatrienyl system. Considering that 6-membered ring compounds are obtained by thermal reaction,<sup>1)</sup> 1-aminohexatrienyl system is versatile starting material for the synthesis of the nitrogen containing 6- and 7-membered heterocycles.

## ACKNOWLEDGEMENTS

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## References and note

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3. Spectral data of 7a, 8a, 12d, and 12e.
 

7a mp. 134.5-135.0°C. IR (nujol,  $\text{cm}^{-1}$ ); 1703. NMR ( $\text{CDCl}_3$ ,  $\delta$ ); 1.41 (3H, t J 7 Hz), 2.39 (3H, s), 2.78 (3H, s), 2.84 (3H, s), 4.36 (2H, q J 7 Hz), 6.82 (1H, s), 7.10 (1H, s), 7.67 (1H, s), 7.90 (1H, s). MS (m/e); 282 ( $\text{M}^+$ ).

8a mp. 152.6-153.4°C. IR (nujol,  $\text{cm}^{-1}$ ); 3400, 1688, 1608. NMR ( $\text{CDCl}_3$ ,  $\delta$ ), 1.32 (3H, t J 7 Hz), 2.37 (3H, s), 2.52 (3H, s), 3.91 (2H, bs), 4.30 (2H, q J 7 Hz), 5.15 (1H, bs), 5.50 (1H, bs), 5.60 (1H, bs), 6.49 (1H, bs), 6.77 (1H, s), 7.02 (1H, s), MS (m/e); 297 ( $\text{M}^+$ ).

12d mp. 98.5-102.0°C. IR (nujol,  $\text{cm}^{-1}$ ); 1715, 1670. NMR ( $\text{CDCl}_3$ ,  $\delta$ ); 1.37 (3H, t J 7 Hz), 1.96 (3H, s), 2.50 (1H, bs), 3.10 (2H, bs), 4.35 (2H, q J 7 Hz), 4.90 (1H, bs), 7.20-7.60 (6H, m). MS (m/e); 299 ( $\text{M}^+$ ).

12e mp. 186.5-188.0°C. IR (nujol,  $\text{cm}^{-1}$ ); 1715, 1670. NMR ( $\text{CDCl}_3$ ,  $\delta$ ); 1.39 (3H, t J 7 Hz), 1.96 (3H, s), 2.40 (3H, s), 2.50 (1H, bs), 2.59 (4H, bs), 3.30 (2H, bs), 4.32 (2H, q J 7 Hz), 4.90 (1H, bs), 6.79 (1H, s), 7.04 (1H, s), 7.48 (1H, s). MS (m/e); 327 ( $\text{M}^+$ ).
4. According to SCF-MO calculation by Dewar and Trinajestic, 1H-azepine is destabilized by 1.80 Kcal/mol (resonance energy).<sup>5)</sup> The 1H-azepines, 8a,

8d', and 8e', which are fused with electron rich benzofuran ring would be much destabilized.<sup>6)</sup>

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