

SYNTHESIS OF BENZOFURANS AND BENZOTHIOPHENES BY PALLADIUM CATALYZED
CYCLOCARBONYLATION OF 3-FURYLALLYL AND 3-THIENYLALLYL ACETATES¹⁾

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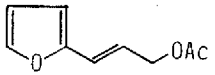
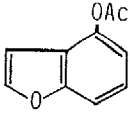
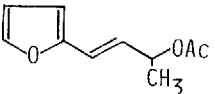
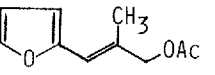
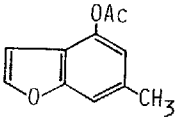
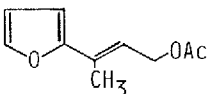
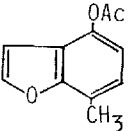
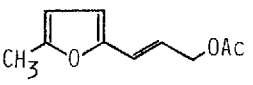
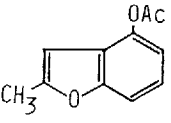
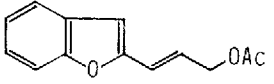
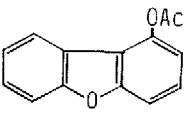
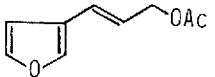
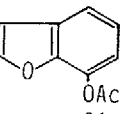
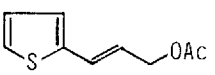
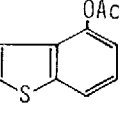
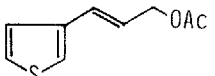
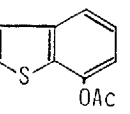
SUMMARY: Acetoxybenzofurans and acetoxybenzothiophenes were obtained in good yields by palladium catalyzed cyclocarbonylation of 3-furylallyl and 3-thienylallyl acetates, respectively.

Transition metal catalyzed cyclocarbonylation of aromatic compounds is one of the promising synthetic methods for fused polycyclic systems, such as indenone, indanone, and anthraquinone.²⁾ However, to date, the cyclocarbonylation has been applied only to substrate having a benzene ring and no such a reaction of heterocyclic compounds has appeared in the literature. Recently we reported a novel synthesis of 1-naphthol derivatives by palladium or platinum catalyzed cyclocarbonylation of cinnamyl compounds, and showed it to be applicable to the synthesis of phenanthrene derivatives.^{3,4)} This reaction is also interesting in that an acyl-metal intermediate is considered to react directly with an aromatic ring to form a carbon-carbon bond. In order to appreciate the versatility of the palladium catalyzed cyclocarbonylation as well as to obtain further information regarding the reaction mechanism, the reactivity of heterocyclic substrates has been investigated. Here we wish to describe the preliminary results.

When 3-(2-furyl)allyl acetate (1a) was carbonylated in the presence of a palladium catalyst, 4-acetoxybenzofuran (2a) was obtained. The typical procedure is as follows. To a 50 ml stainless-steel autoclave was charged a mixture of 1a (10 mmol), PdCl₂(PPh₃)₂ (0.5 mmol), NEt₃ (20 mmol), Ac₂O (20 mmol), and benzene (10 ml). The reactor was pressurized with CO (70 kg/cm² at room temperature), heated to 170°C, and maintained at this temperature for 1.5 h with magnetic stirring. The reaction was terminated by rapid cooling and CO was discharged. The reaction mixture was washed with 10% HCl, 10% aqueous NaHCO₃, and water, dried over MgSO₄, and evaporated. The residual brown oil was chromatographed on silica gel to give 2a in 85% yield, which was characterized by IR and ¹H-NMR.⁵⁾

The representative results are summarized in Table 1. In most cases the cyclocarbonylated products were obtained in good yields. 3-Furylallyl and 3-thienylallyl acetates except 1b were carbonylated smoothly and afforded the corresponding benzofurans and benzothiophenes in high yields. Similarly a benzofuran skeleton was transformed into a dibenzofuran skeleton. A secondary

Table 1. Syntheses of Benzofurans and Benzothiophenes

| Run | Substrate | Reaction condition ^{a)} | Product | Isolated yield ^{b)} / % |
|-----|---|----------------------------------|---|----------------------------------|
| 1 |  1a | A |  2a | 85 |
| 2 |  1b | A | — | — |
| 3 |  1c | A |  2c | 78 |
| 4 |  1d | B |  2d | 56 |
| 5 |  1e | A |  2e | 76 |
| 6 |  1f | B |  2f | 70 |
| 7 |  1g | A |  2g | 89 |
| 8 |  3a | B |  4a | 79 |
| 9 |  3b | B |  4b | 86 |

a) A: Substrate 10 mmol, PdCl₂(PPh₃)₂ 0.5 mmol, Ac₂O 20 mmol, NEt₃ 20 mmol, benzene 10 ml, CO 70 kg/cm² at room temperature, 170°C, 1.5 h.

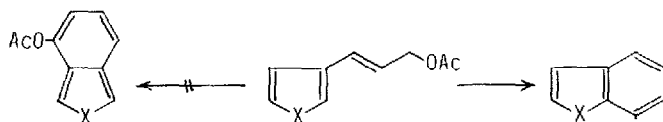
B: Substrate 3 mmol, PdCl₂(PPh₃)₂ 0.15 mmol, Ac₂O 6 mmol, NEt₃ 6 mmol, benzene 2 ml, CO 70 kg/cm² at room temperature, 170°C, 1.5 h.

b) Based on substrate.

allyl acetate, **1b**, gave no isolable carbonylation product probably due to diene formation and polymerization.⁶⁾ It should be noted that 3-(3-furyl)-allyl acetates (**1g**) and 3-(3-thienyl)allyl acetates (**3b**) cyclized selectively at the 2-position to form 7-acetoxybenzofuran (**2g**) and 7-acetoxybenzothiophene (**4b**), respectively, as the only products. 3-Acetoxyisobenzofuran, 3-acetoxyisobenzothiophene, and related compounds which are formed by the cyclization at the 4-position were not detected in the reaction mixture (Scheme 1.).

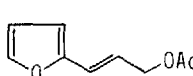
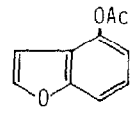
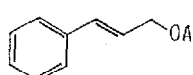
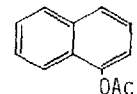
In order to compare the reactivities of furan and benzene rings, the temperature effect on the cyclocarbonylation was examined by using **1a** and cinnamyl acetate as substrates. As shown in Table 2, both substrates gave the cyclocarbonylation products in high yields at 170°C. Reactions at lower temperatures resulted in the decrease of yields because of side reactions affording unidentified high-boiling by-products. At 100°C, cinnamyl acetate gave 1-naphthyl acetate in only 2% yield, while **1a** still gave **2a** in a moderate yield. This result seems to suggest a furan ring is more reactive in the cyclocarbonylation than a benzene ring. In contrast, no isolable cyclocarbonylation product was obtained in the reaction of 3-(3-pyridyl)allyl acetate. Thus the order of the reactivity in the cyclocarbonylation is considered to be furan > benzene > pyridine ring.

It has already been shown that the unsaturated acyl-palladium complexes $(ArCH=CHCH_2CO)Pd(OAc)(PPh_3)_n$ and $(ArCH_2CH=CHCO)Pd(OAc)(PPh_3)_n$ ($n=1$ or 2), formed from the oxidative addition of an allylic acetate and CO insertion, are the intermediates of the cyclocarbonylation.⁷⁾ The subsequent intramolecular



Scheme 1. X=O, S

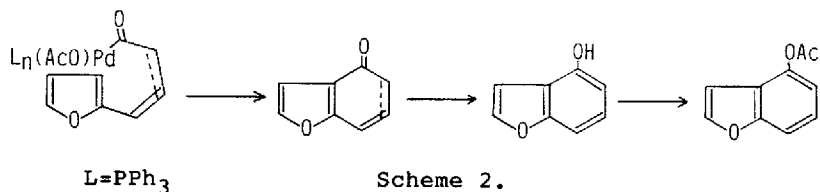
Table 2. Effect of Reaction Temperature on Cyclocarbonylation^{a)}

| Substrate | Reaction Temperature/°C | Conversion ^{b)} /% | Product | Yield ^{c)} /% |
|---|-------------------------|-----------------------------|--|------------------------|
|  | 170 | 100 |  | (85) |
| | 130 | 100 | | 98(83) |
| | 100 | 97 | | 48(41) |
| | 70 | 33 | | 5 |
|  | 170 | 100 |  | 81 |
| | 100 | 99 | | 2 |

a) See text for reaction condition. b) Determined by GLC.

c) Determined by GLC, isolated yield in parentheses.

cyclization produces bicyclic ketones, and their isomerization into hydroxybenzofurans or hydroxybenzothiophenes and acetylation lead to the products (Scheme 2.). In the previous paper it was assumed that the ring closure step involved an intramolecular electrophilic attack of the acyl group on the aromatic ring on the basis that the cyclocarbonylation of 3-(2-naphthyl)allyl acetate occurs selectively at the 1-position of the naphthalene ring to give 4-phenanthryl acetate in spite of the greater steric hindrance. The selective formation of 2g and 4b from 1g and 3b as well as the reaction order of aromatic systems is consistent with that in the aromatic electrophilic substitution reactions, and strongly supports the above assumption.



Scheme 2.

In conclusion, the palladium catalyzed cyclocarbonylation was shown to provide a novel and effective synthetic route to substituted benzofurans and benzothiophenes. Extension of this reaction to other aromatic systems and intermolecular carbonylations is now under investigation.

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