

**PALLADIUM-CATALYZED INDOLE AND BENZOFURAN
RING FORMATION ACCOMPANYING CARBONYLATION**

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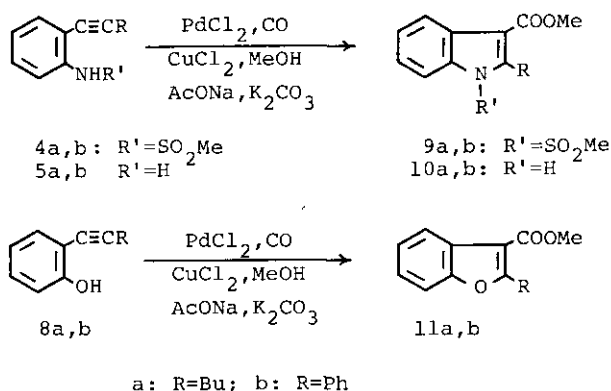
Abstract—— The reaction of 2-(1-hexynyl)aniline with carbon monoxide in methanol under basic conditions is promoted by the catalytic action of palladium dichloride to give methyl 2-butylindole-3-carboxylate. Similarly, the reaction of 2-(1-hexynyl)phenol under the same conditions gives methyl 2-butylbenzofuran-3-carboxylate. The carbonylative cyclization mentioned above is successful with the corresponding 2-phenylethynyl derivatives of aniline and phenol.

Recently, the scope of Reissert-type indole synthesis has been expanded by using palladium-catalyzed carbon-carbon bond forming reaction for the synthesis of key intermediates.¹⁻⁵ For example, the palladium-catalyzed cross-coupling reaction of ethyl 2-bromophenylcarbamate with terminal acetylenes followed by the alkaline cyclization of the resulting ethyl 2-alkynylphenylcarbamate gives 2-substituted indoles.

On the other hand, Utimoto et al.⁶ have reported the indole cyclization of 2-alkynylanilines to be assisted with palladium dichloride. In this reaction, addition of allyl chloride to the reaction mixture gave 3-allylindole derivatives via substitution of the intermediary 3-indolylpalladium species with allyl chloride.

In the present communication, we describe a successive cyclization/carbonylation of 2-ethynylaniline and 2-ethynylphenol derivatives which gives rise to methyl indole-3-carboxylates and benzofuran-3-carboxylates in the presence of palladium dichloride, carbon monoxide, and methanol.

The starting materials employed in the investigation were synthesized as shown in



Scheme 2

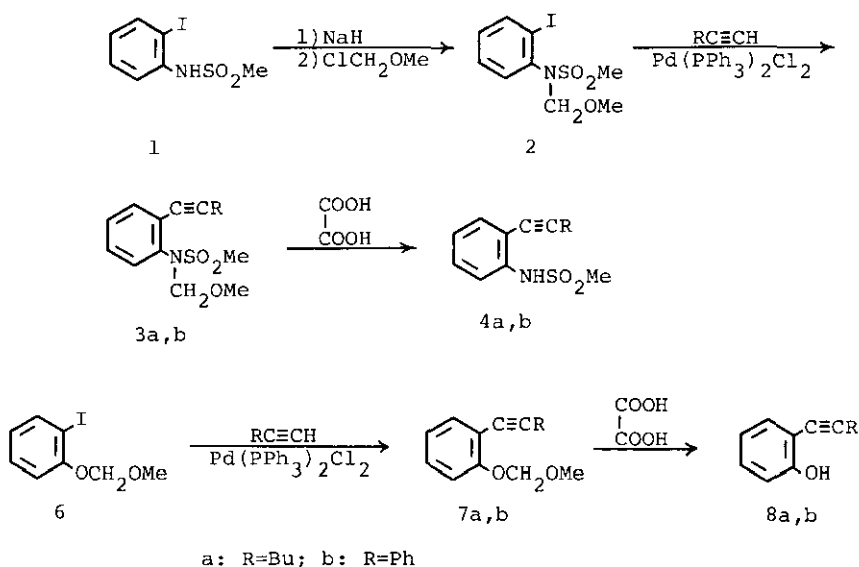
Table I. Carbonylative Cyclization of 2-Alkynylanilines and Phenols

No.	Yield (%)	mp(°C) [bp/mmHg]	¹ H-Nmr δ (ppm) (CDCl ₃)
9a	67	75-76	0.7-2.0 (7H, m), 3.10 (3H, s), 3.3-3.7 (1H, m) 3.96 (3H, s), 7.2-7.5 (2H, m), 8.0-8.2 (3H, m)
9b	76 ^{a)}	143-144	3.05 (3H, s), 3.76 (3H, s), 7.3-7.8 (6H, m) 8.1-8.5 (3H, m)
10a	30	67-68	0.7-2.0 (7H, m), 3.16 (2H, t, J=7 Hz), 3.93 (3H, s) 7.1-7.5 (3H, m), 7.9-8.3 (1H, m), 8.60 (1H, br s)
10b	51	150-151	3.86 (3H, s), 7.1-7.8 (8H, m), 8.0-8.3 (1H, m) 8.80 (1H, br s)
11a	66	[145-150/3]	0.7-2.0 (7H, m), 3.20 (2H, t, J=7 Hz), 3.95 (3H, s) 7.2-7.5 (3H, m), 7.8-8.1 (1H, m)
11b	79	77-78	3.92 (3H, s), 7.2-7.7 (6H, m), 7.9-8.2 (3H, m)

a) Acetonitrile was used as a cosolvent.

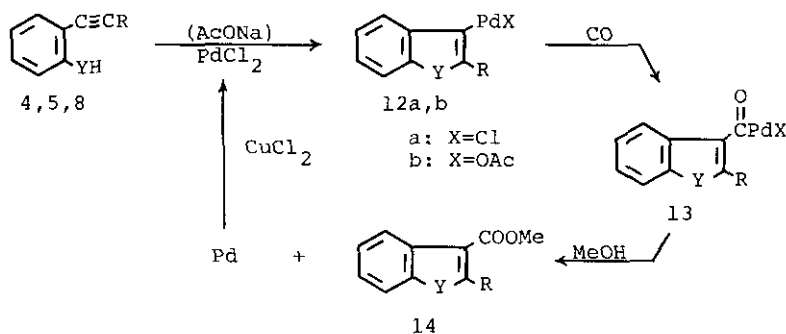
The pathway of this carbonylative ring formation is conceivable as follows. The palladated intermediates (12) generated during the palladium-catalyzed cyclization subsequently react with carbon monoxide to form the acylpalladium species (13) which change to the final product. The palladium(0) species formed in this step are oxidized fairly with cupric chloride to palladium dichloride. But, the use of 1,4-benzoquinone, disodium peroxydisulfate, or molecular oxygen as an oxidant of the palladium(0) species was ineffective for the regeneration of the palladium(II) species. In addition to the above, it was found that the addition of sodium acetate into the reaction mixture improved the yields of the products. This result suggests that the arylpalladium acetate (12b) is much smoothly carbonylated than the arylpalladium chloride (12a).

Scheme 1. The palladium-catalyzed cross-coupling reaction⁷ of *N*-(2-iodophenyl)-*N*-(methoxymethyl)methanesulfonamide (2) derived from *N*-(2-iodophenyl)methanesulfonamide (1) with 1-hexyne followed by the hydrolysis of the cross-coupling products (3a) with aqueous oxalic acid gave *N*-[2-(1-hexynyl)phenyl]methanesulfonamide (4a). 2-(1-Hexynyl)phenol (8a) was synthesized from 2-iodo-*O*-(methoxymethyl)phenol (6) via the acetylenic compound (7a) in a similar manner. Compound 2 and 6 reacted also with phenylacetylene under the same conditions, and the desired 2-substituted diphenylacetylene derivatives (4b and 8b) were obtained in good yields.



Scheme 1

When 2-(1-hexynyl)aniline (4a) was allowed to react with carbon monoxide in methanol under the conditions described in General Procedure,⁸ methyl 2-butylindole-3-carboxylate (9a) was obtained in considerable yield. It should be mentioned that in the case of aniline derivatives with a free amino group, the indole formation with carbonylation seemed not to proceed smoothly. Namely, the yields of the 2-substituted methyl indole-2-carboxylates (10a,b) through the reactions of the 2-ethynylanilines (5a,b)⁹ under the same conditions were relatively low as shown in Table I. In addition to the above, 4b and 8a,b reacted with carbon monoxide, accompanying with cyclization, to give the corresponding methyl indole- and benzofuran-3-carboxylates (9b, and 11a,b) in yields ranging from 66 to 79 %, the results of which are listed in Table I.



Scheme 3

In conclusion, our results together with Utimoto's results may provide a new method for the one-step synthesis of condensed heteroaromatics with a functional group.

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8. General Procedure: A mixture of a 2-substituted arylacetylenes (2 mmol), palladium dichloride (20 mg), copper dichloride dihydrate (1.02 g, 6 mmol), sodium acetate (0.33 g, 4 mmol), potassium carbonate (0.55 g, 4 mmol), and methanol (20 ml) was vigorously stirred under carbon monoxide atmosphere at room temperature for 3 h. After removal of the solvent under reduced pressure, the residue was diluted with water and extracted with chloroform. The chloroform extract was purified by silica gel column chromatography to give the product.
9. Compounds **5a,b** were synthesized from the corresponding nitro compounds by the reduction with stannous chloride in ethanol or iron in hydrochloric acid.

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