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Synthesis of 3-Substituted Indoles by a Palladium-Assisted Reaction

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Synopsis. In the presence of palladium(II) chloride, 2-bromoanilines readily react with the methyl vinyl ketone and the ethyl acrylate to produce vinylogous arylamino ketones and esters. A palladium(0)-assisted cyclization of the arylamino ketones and the esters leads to a formation of 3-substituted indoles.

Beginning with the classical Fisher and Reissert methods, many reports on the synthesis of indoles have appeared from practical and theoretical points of view. Specifically, many 3-substituted indoles were well known to have a biological function, either as biochemical intermediates (aurin, tryptophan, tryptamine, serotonin) or as natural drugs (gramine, bufotenine, psilocine).

A variety of heterocyclic compounds can be synthesized using a palladium-catalyzed intramolecular functionalization of olefins as the ring-forming step.[1] Hegedus et al. have recently reported the synthesis of indoles from 2-allylanilines,[2] 2-vinylanilines,[2] and *N*-(3-bromo-2-vinylphenyl)-*p*-toluenesulfoamides[3] by a palladium-assisted cyclization reaction. Independent of their work, we present a new and efficient method for synthesizing 3-substituted indoles in two steps from 2-bromoanilines, based on a palladium-catalyzed reaction.

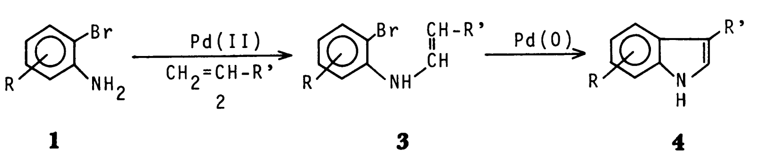
Table 1. The Reaction of 2-Bromoanilines and Olefins

2-Bromoaniline	Olefin	Product	Yield/%	Mp(θ_m/°C)
1a	**2a**	**3a**	76	46—47
1a	**2b**	**3b**	79	oil
1b	**2a**	**3c**	85	79—81
1b	**2b**	**3d**	78	67—68
1c	**2a**	**3e**	72	83—84
1c	**2b**	**3f**	74	80—81
1d	**2a**	**3g**	84	82—84
1d	**2b**	**3h**	68	113—114
1e	**2a**	**3i**	83	146—147
1e	**2b**	**3j**	85	112—113

Bozell and Hegedus[4] reported previously that palladium(II) chloride catalyzed the reaction of anilines with methyl vinyl ketone and methyl acrylate to produce vinylogous arylamino ketones and esters. According to the method, 2-bromoaniline (**1a**), 2-bromo-5-methoxyaniline (**1b**), 2-bromo-3-methoxycarbonylaniline (**1c**), 2-bromo-4-methoxycarbonylaniline (**1d**), and 2-bromo-5-methoxycarbonylaniline (**1e**) reacted with conjugated olefins such as methyl vinyl ketone (**2a**) and ethyl acrylate (**2b**) to vinylogous arylamino ketones and esters (**3**) in good yield (Table 1). Nonconjugated olefins such as 1-hexene, styrene, and ethyl 2-acetamino-4-pentenoate, however, fail to undergo the amination. The structures of the products were determined on the basis of IR, ^{1}H-NMR, and mass spectral measurements and elemental analyses.

A possible reaction course of **1** to **3** is shown in Eq 1. The catalytic palladium(II) species coordinates an olefin **2** which undergoes a nucleophilic attack by the amine to generate the σ-alkylpalladium complex. The σ-complex then decomposes by β-elimination to give an unstable palladium hydride complex and the observed product **3**. The palladium hydride complex ultimately forms palladium(0), which is reoxidized to palladium(II) by benzoquinone to complete the catalytic cycle.

In acetonitrile, the arylaminated olefins **3** were



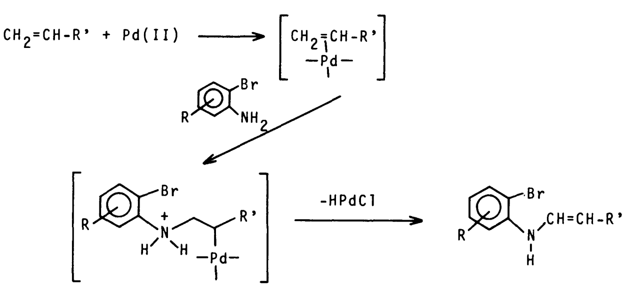
1 **3** **4**

2a: R′=$COCH_3$
2b: R′=COOEt

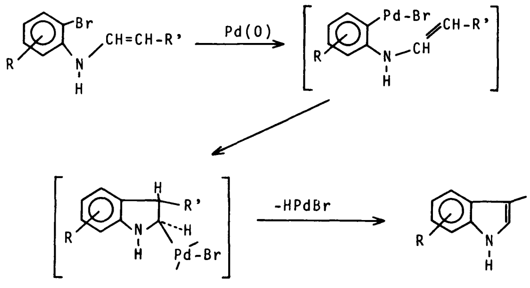
1a, **3a**: R=H, R′=$COCH_3$
1b, **3b**: R=H, R′=COOEt
1c, **3c**: R=5-OMe, R′=$COCH_3$
1d, **3d**: R=5-OMe, R′=COOEt
1e, **3e**: R=3-COOMe, R′=$COCH_3$
1f, **3f**: R=3-COOMe, R′=COOEt
1g, **3g**: R=4-COOMe, R=$COCH_3$
1h, **3h**: R=4-COOMe, R′=COOEt
1i, **3i**: R=5-COOMe, R′=$COCH_3$
1j, **3j**: R=5-COOMe, R′=COOEt

4a: R=H, R′=$COCH_3$
4b: R=H, R′=COOEt
4c: R=6-OMe, R=$COCH_3$
4d: R=6-OMe, R′=COOEt
4e: R=4-COOMe, R′=$COCH_3$
4f: R=4-COOMe, R′=COOEt
4g: R=5-COOMe, R′=$COCH_3$
4h: R=5-COOMe, R′=COOEt
4i: R=6-COOMe, R′=$COCH_3$
4j: R=6-COOMe, R′=COOEt

Scheme 1.



(1)



(2)

Table 2. The Palladium-Assisted Cyclization Reaction of the Arylaminated Olefins

Starting material	Product	Yield/%	Mp(θ_m/°C(lit. mp))
3a	**4a**	95	192—194(194[a])
3b	**4b**	96	118—119(118—119[b])
3c	**4c**	80	208—209
3d	**4d**	82	141—142(142—142.5[c])
3e	**4e**	95	143—144
3f	**4f**	93	93—94
3g	**4g**	84	223—224
3h	**4h**	85	186—188
3i	**4i**	86	213 (decomp)
3j	**4j**	90	160—161

a) J. W. Baker, *J. Chem. Soc.*, **1964**, 461. b) R. Majima, and M. Kotake, *Chem. Ber.*, **55**, 3865 (1922). c) Roussel-UCLAF, *Chem. Abst.*, **60**, 2899 (1964).

warmed with a catalytic amount of palladium(II) acetate and tri-*o*-tolylphosphine to afford the expected 3-substituted indoles (**4**) in high yield (Table 2). The reaction **3** to **4** is thought to proceed by an oxidative addition of an aromatic halide **3** to the palladium(0) complex, followed by an intramolecular olefin insertion and a β-hydride elimination (Eq 2).

Experimental

All melting points are uncorrected. The IR spectra were measured on KBr disks with a Hitachi 260-10 spectrometer and ^{1}H-NMR spectra were obtained using a Hitachi R-22 spectrometer in $CDCl_3$. TMS was used as internal standard. The mass spectra were obtained on a Hitachi RMU-6M mass spectrometer, using a direct-insertion probe at an ionization energy of 70 eV.

General Procedure for the Palladium-Catalyzed Reaction of 2-Bromoanilines (1) with Olefins (2). Dichlorobis(acetonitrile)palladium(II) (778 mg, 3 mmol), benzoquinone (3.24 g, 30 mmol), lithium chloride (12.70 g, 300 mmol), and olefin **2** (30 mmol) were mixed in THF (100 cm^3) at room temperature. After stirring for 15 min, **1** (30 mmol) in THF (20 cm^3) was added. The resulting mixture was stirred for 24 h at room temperature and the solvent was removed under a reduced pressure. The residue was stirred with ether and filtered; the ether solution was repeatedly washed with 1 M sodium hydroxide(1 M=1 mol dm^{-3}) solution and water. The organic layer was dried over $MgSO_4$ and filtered and the solvent was removed to give the crude product which was purified by column chromatography using silica gel and hexane–benzene (2:1). The results are presented in Table 1.

General Procedure for the Palladium-Assisted Cyclization Reaction Vinylogous Arylamino Compounds (3) to Indoles (4). A mixture of **3** (14.9 mmol), palladium(II) acetate (0.167 g, 0.745 mmol), tri-*o*-tolylphosphine (0.906 g, 2.98 mmol), and triethylamine (1.88 g, 18.6 mmol) in acetonitrile (20 cm^3) was heated in a sealed tube flushed with nitrogen at 100 °C for 20 h. The cooled reaction mixture was diluted with ether and water. The ether layer was separated, washed with water, dried, and concentrated. The remaining residue was chromatographed on silica gel with benzene to give product **4**. The results are presented in Table 2.

The structures of the products were verified by elemental analyses, mass spectrometry, and by their ^{1}H-NMR and IR spectra. The complete ^{1}H-NMR, IR, and elemental analyses data are deposited at the Office of the Editor of the Bulletin of the Chemical Society of Japan (Document No. 8616).

References

1) J. Tsuji, "Organic Synthesis with Palladium Compounds," Berlin, Springer-Verlag, 1980, p. 13, 21, 33.

2) L. S. Hegedus, G. F. Allen, J. J. Bozell, and E. L. Waterman, *J. Am. Chem. Soc.*, **100**, 5800 (1978).

3) P. J. Harrington and L. S. Hegedus, *J. Org. Chem.*, **49**, 2657 (1984).

4) J. J. Bozell and L. S. Hegedus, *J. Org. Chem.*, **46**, 2561 (1981).