Palladium-Catalyzed Vinylic Substitution Reactions with Heterocyclic Bromides

Walter C. Frank, Yong C. Kim, and Richard F. Heck*

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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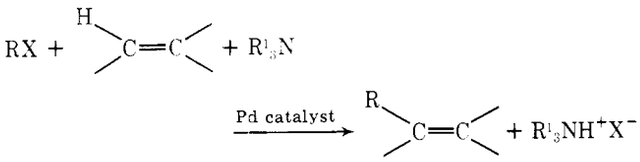
The palladium-catalyzed vinylic substitution reaction of olefins has been shown to proceed in good to excellent yields with a variety of heterocyclic bromides. The reaction was used to prepare nornicotine in four steps from 3-bromopyridine and *N*-3-butenylphthalimide.

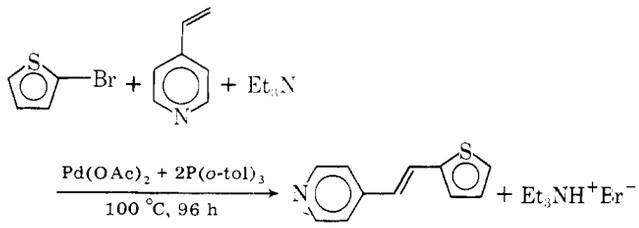
Previous work has shown that aryl,[1] vinylic,[1,2] and benzylic[1] halides reacted readily in the presence of tertiary amines with olefins and palladium catalysts to form vinylic substitution products. Related palladium-catalyzed reactions of organic halides with carbon monoxide and aniline[3] and with



monosubstituted acetylenes[4] also went well with the above types of halides and also, in two examples, with heterocyclic halides. Since the vinylic substitution reaction with heterocyclic halides could be of considerable synthetic value, we undertook a more complete investigation of it.

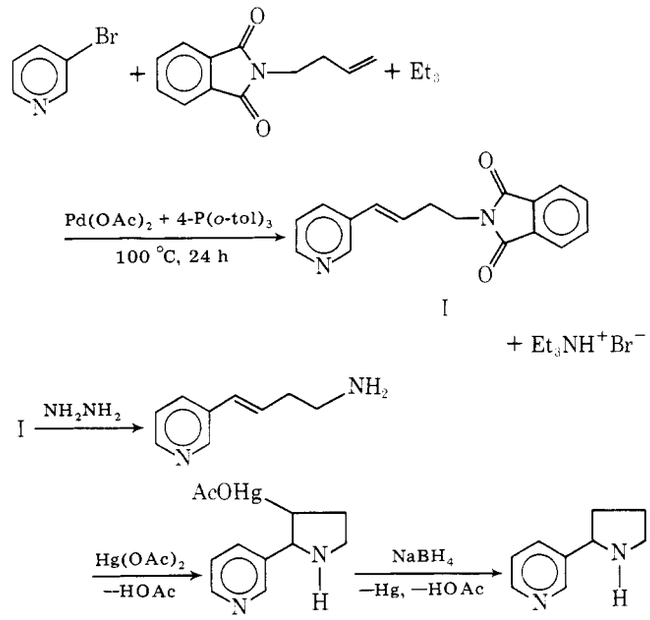
Results and Discussion

A variety of heterocyclic bromides were reacted under our usual conditions[1] with styrene, vinylpyridines, methyl acrylate, or in one case *N*-3-butenylphthalimide. The results obtained are summarized in Table I. In all examples 1 mol % palladium acetate and 2–4 mol % tri-*o*-tolylphosphine based on the organic halide were used as the catalyst at 100 °C. Methyl 5-bromo-2-furanoate and 3-bromopyridine gave high yields of styryl derivatives with styrene. 2-Bromothiophene formed a 57% yield of product with 4-vinylpyridine. The alternative preparation of this product by a Wittig reaction was much less convenient to carry out.[5]



Both 4- and 2-bromopyridines reacted only slowly with styrene at 100 °C and gave low yields of the expected products. We have not determined the reasons for the low yields, but high yields can be obtained simply by switching the functional groups by reacting bromobenzene with the appropriate vinylpyridine. Thus, 4-bromopyridine and styrene in 240 h gave only 41% 4-styrylpyridine, while bromobenzene and 4-vinylpyridine gave the same product in 92% yield in the same time. Similarly, 2-bromopyridine and styrene gave only 6% 2-styrylpyridine in 200 h, while under the same conditions in 136 h bromobenzene and 2-vinylpyridine gave the product in 84% yield. Much higher reaction rates, no doubt, could be obtained by using 125–150 °C reaction temperatures judging by results obtained with related reactions.

A nonconjugated olefin also reacted easily with 3-bromopyridine. The 3-bromopyridine was reacted with *N*-3-butenylphthalimide and the product was converted into nornicotine. This vinylic substitution reaction gave a mixture of products as is characteristic of terminal olefins.[1] Even though the products were solids they could not be separated readily by recrystallization. The crude product, therefore, was hydrolyzed to a mixture of amines. Analyses by GLC showed that the 57% yield of amine mixture obtained contained 68% of the expected 4-(3′-pyridyl)-3-butenylamine. The product could be purified by fractional distillation under reduced pressure, but for conversion into nornicotine this was not necessary. Nornicotine was obtained from the crude amine mixture by reacting it with mercuric acetate, followed by reduction of the intermediate mercurial with sodium borohydride, by a procedure based on the results of Perie et al.[6] Nornicotine was produced in 65% yield in the cyclization as determined by GLC. Pure nornicotine was easily obtained from the crude product by converting it into the dipicrate, recrystallizing, and recovering the amine.



Both 3-bromoquinoline and 4-bromoisoquinoline reacted in high yield with methyl acrylate to produce the predicted heterocyclic derivatives of methyl acrylate. 5-Bromoindole also reacted with methyl acrylate, but the product was ob-

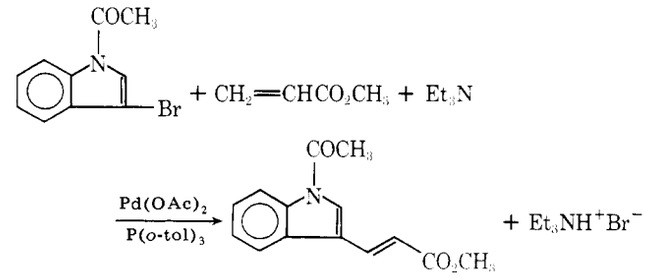


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Table I. Vinylic Substitution Reactions with Heterocyclic Halides and Olefins[a]

organic halide	registry no.	alkene	registry no.	mL of Et_3N	$P(o\text{-tol})_3/(OAc)_2$	reaction time, h, at 100 °C	product (% yield)	registry no.
methyl 5-bromofuranoate	2527-99-3	styrene	100-42-5	6	2	18	(*E*)-methyl 5-styrylfuranoate (61)(90)[b]	66417-74-1
2-bromothiophene	1003-09-4	4-vinylpyridine	100-43-6	5	2	96	(*E*)-2-(4′-pyridylvinyl)thiophene (57)	66417-75-2
3-bromopyridine		styrene		5	4	20	3-stilbazole (78) (~100)[b]	2633-06-9
3-bromopyridine	626-55-1	methallyl alcohol	513-42-8	4	4	17	2-methyl-3-(3′-pyridyl)propanal (64)	66417-76-3
4-bromopyridine hydrochloride	19524-06-2	styrene		6.4	2	240	4-stilbazole (41)[b]	103-31-1
bromobenzene	108-86-1	4-vinylpyridine		5	2	240	4-stilbazole (91)	
2-bromopyridine	109-04-6	styrene		5	2	240	2-stilbazole (19)[b]	714-08-9
2-bromopyridine		styrene		5	4	200	2-stilbazole (6)[b]	
bromobenzene		2-vinylpyridine	100-69-6	6	4	136	2-stilbazole (84)	
3-bromopyridine		*N*-3-butenylphthalimide	52898-32-5	40	4	10	4-(3′-pyridyl)-3-butenylamine (37)[d]	66417-77-4
3-bromoquinoline	5332-24-1	methyl acrylate	96-33-3	5	4	6	(*E*)-methyl 3-(3′-quinolyl)acrylate (83)	66417-78-5
4-bromoisoquinoline	1532-97-4	methyl acrylate		5	4	40	(*E*)-methyl 3-(4′-isoquinolyl)acrylate (88)	66417-79-6
5-bromoindole	10075-50-0	methyl acrylate		5	2	2	(*E*)-methyl 3-(5′-indolyl)acrylate (53)	66417-80-9
N-acetyl-3-bromoindole	66417-73-0	methyl acrylate		4	2	6	(*E*)-methyl 3-(*N*-acetyl-3′-indolyl)-acrylate (50)	19626-93-8

[a] Reaction mixtures consisted of 10 mmol of heterocyclic halide, 12.5 mmol of olefin (except in the *N*-3-butenylphthalimide reaction), and the amount of triethylamine shown. 0.1 mmol of $Pd(OAc)_2$ with the indicated ratio of tri-*o*-tolylphosphine was used as catalyst. [b] GLC yield. [c] Reaction mixture: 0.15 mol of 3-bromopyridine, 0.14 mol of *N*-butenylphthalimide, 40 mL of triethylamine, 50 mL of acetonitrile, 1.4 mmol of $Pd(OAc)_2$, and 5.7 mmol of $P(o\text{-tol})_3$. [d] Product obtained after hydrolysis and fractional distillation.

tained in only 53% yield. 3-Bromoindole gave no identifiable product. However, bromination of *N*-acetylindole gave *N*-acetyl-3-bromoindole, which did react normally with methyl acrylate, although only in 50% yield.

In addition to 3-bromoindole, 2-iodoquinoline, 2-bromothiazole, 5-bromouracil, and 4-bromo-5-phenylimidazole[7] failed to undergo the vinylic substitution reaction with methyl acrylate at 50–150 °C.

In many instances, at least, the vinylic substitution reaction provides a convenient and useful new method for adding side chains to various heterocyclic rings.

Experimental Section

Materials. With two exceptions, all of the heterocyclic halides employed were commercial samples. Methyl 5-bromo-2-furanoate, mp 61–62 °C (reported 62.5–63.5 °C),[8] was obtained by treatment of the acid (Aldrich) with diazomethane. The preparation of *N*-acetyl-3-bromoindole is described below. Other reagents were the same as used previously.[1,9]

General Procedure. All reactions were carried out by the same general procedure described previously.[1,9] Two examples are given below. The melting points, molecular weights, and NMR spectra of the products prepared appear in Table II, which will be found only in the microfilm edition of this journal. (See note on Supplementary Material at the end of this article.)

(*E*)-Methyl 5-Styryl-2-furanoate. A solution of 2.05 g (10 mmol) of methyl 5-bromo-2-furanoate, 1.5 mL (12 mmol) of styrene, 0.022 g (0.10 mmol) of palladium acetate, 0.061 g (0.40 mmol) of tri-*o*-tolylphosphine, and 6 mL (43 mmol) of triethylamine was heated under argon in a heavy-walled Pyrex tube at 100 °C for 18 h. The cooled reaction mixture was diluted with water and methylene chloride. The methylene chloride layer was separated, washed with water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent and recrystallization from heptane gave 1.40 g of product (61%): mp 68–69 °C (reported 69–70.5 °C).[10] Analysis by GLC of the original product solution indicated the yield was 90%. Analytical data appear in Table II.

2-Methyl-3-(3′-pyridyl)propanal. A solution of 1.59 g (10 mmol) of 3-bromopyridine, 1.0 mL (12.5 mmol) of methallyl alcohol, 4 mL of triethylamine, 0.022 g (0.10 mmol) of $Pd(OAc)_2$, and 0.122 g (0.40 mmol) of tri-*o*-tolylphosphine was heated at 100 °C for 17 h in a capped heavy-walled Pyrex tube. The cooled reaction mixture was diluted with water and methylene chloride. After washing with water and drying, the methylene chloride solution was concentrated and the residue distilled under reduced pressure. There was obtained 0.96 g (64%) of colorless liquid product: bp 78–81 °C (0.2 mm). Molecular weight and NMR data are given in Table II.

4-(3′-Pyridyl)-3-butenylamine. *N*-3-Butenylphthalimide was prepared by heating 24.05 g (0.130 mol) of potassium phthalimide and 15.95 g (0.118 mol) of 4-bromo-1-butene in 65 mL of DMF at 75 °C for 12 h with stirring. The cooled reaction mixture was diluted with 65 mL of chloroform and 230 mL of water. The water layer was separated and extracted several times with 25-mL portions of chloroform. The combined extracts were washed four times with 50-mL portions of 1 M sodium hydroxide and once with water. After drying and removal of solvent, 18.1 g (76%) of crude product, mp 51–52 °C, was obtained.

N-[4-(3′-Pyridyl)-3-butenyl]phthalimide was then prepared by reacting 28.6 g (0.142 mol) of the above imide derivative with 23.60 g (0.149 mol) of 3-bromopyridine, 40 mL of triethylamine, 0.335 g (1.42 mmol) of $Pd(OAc)_2$, and 1.82 g (5.69 mmol) of tri-*o*-tolylphosphine in 50 mL of acetonitrile as solvent at 100 °C under argon in a capped bottle for 10 h. After cooling and extraction with methylene chloride

as in the above example, evaporation of the extracts gave 39.0 g (98%) of crude product: mp ~140 °C. The compound can be recrystallized from heptane, but even after several recrystallizations it was still a mixture of isomers as determined by GLC analysis of the amine hydrolysis product. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.53; H, 5.04; N, 10.00.

Hydrolysis of the phthalimide group was achieved by heating 42.0 g (0.151 mol) of the crude *N*-[4-(3′-pyridyl)-3-butenyl]phthalimide with 17.73 g of 85% hydrazine hydrate and 375 mL of methanol. After boiling for 15 h and then cooling, 250 mL of water was added. The methanol was then removed under reduced pressure and 380 mL of concentrated hydrochloric acid was added. The mixture was heated at 100 °C for 5 h and cooled in an ice–salt bath. The crystallized phthalhydrazide was filtered and the filtrate was made strongly basic with sodium hydroxide. The solution was saturated with sodium chloride and the product extracted with five 250-mL portions of methylene chloride. The extracts were dried to give 12.63 g of crude amine. This material contained about 65% 4-(3′-pyridyl)-3-butenylamine (37% yield). Purification could be made by careful fractional distillation, although a completely pure sample could not be isolated. There was obtained 9.2 g, bp 89–90 °C (0.25 mm), 93% pure by GLC.

(±)-Nornicotine. Cyclization of 4-(3′-pyridyl)-3-butenylamine was effected by adding 6.09 g (0.037 mol) of the crude amine to a stirred suspension of 35.34 g (0.111 mol) of mercuric acetate, 70 mL of THF, and 70 mL of water in a 150-mL Pyrex bottle. The solution was heated to 56 °C with stirring for 15 h. The initial orange suspension was now a white suspension. The solution was cooled to room temperature, made basic with 3 N potassium hydroxide, and treated with a solution of 1.95 g (0.051 mmol) of sodium borohydride dissolved in a few milliliters of 3 N potassium hydroxide. After stirring for 30 min, solid sodium chloride was added to saturate the solution, and 50 mL of methylene chloride was added. The black suspension of mercury present was removed by filtration and the extract was separated from the aqueous layer in the filtrate. The aqueous phase was extracted five times more with 40-mL portions of methylene chloride. The combined extracts were dried and flash distilled under aspirator vacuum to give 4.87 g of 83% pure nornicotine (66%).

Further purification was achieved by adding 1.07 g of the mixture to a solution of 3.3 g of picric acid in 20 mL of ethanol. The yellow picrate formed was separated by filtration and recrystallized twice from a large volume of ethanol. There was obtained an 81% yield of the pure dipicrate: mp 191–192 °C (reported 191–192 °C).[11] Nornicotine was recovered from the dipicrate as described by Spath[12] in 80% yield. The pure material had an IR spectrum identical with the published spectrum.[13] Molecular weight (HRMS) 148.088 (calcd 148.099).

***N*-Acetyl-3-bromoindole.** A mixture of 20 g (0.17 mol) of indole and 17.5 mL (0.16 mol) of acetic anhydride with 0.1 g of sodium acetate was heated for 24 h at 145 °C under a reflux condenser. The mixture was then distilled under reduced pressure to give 11.61 g (41%) of *N*-acetylindole.

A solution of 7.34 g (0.05 mol) of the *N*-acetylindole, dissolved in 75 mL of carbon disulfide, was stirred at 0 °C and 2.57 mL (0.05 mol) of bromine was added dropwise. After stirring for 3 h at 25 °C, the solvent was removed under reduced pressure and the product was recrystallized four times from ethanol to form 5.05 g (46%) of long, colorless needles of *N*-acetyl-3-bromoindole: mp 106–108 °C. Molecular weight (HRMS) 236.979 (calcd 236.979). NMR ($CDCl_3$) δ 2.65 (s, 3), 7.60 (m, 4), 8.60 (m, 1).

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Registry No.—*N*-[4-(3′-Pyridyl)-3-butenyl]phthalimide, 66417-81-0; (±)-nornicotine, 5746-86-1; indole, 120-72-9.

Supplementary Material Available: Table II contains melting points, molecular weights, and NMR spectra of the products prepared (2 pages). Ordering information is given on any current masthead page.

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Palladium-Catalyzed Vinylic Substitution Reactions of *N*-Vinyl Amides

Carl B. Ziegler, Jr., and Richard F. Heck*

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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N-Vinyl amides undergo the palladium-catalyzed vinylic substitution reaction readily in many instances. *N*-Vinylpyrrolidinone gives a mixture of two isomers in the reaction with bromobenzene, resulting from additions in both possible directions to the vinyl group. *N*-Vinylphthalimide gives, predominantly, the product with the phenyl group added to the terminal carbon of the double bond. Derivatives with *p*-acetoxyl, 3,4-diacetoxyl, 2-bromo, and 4-nitro groups were prepared similarly in moderate to good yields. Catalytic hydrogenation of these compounds produced phenethylamine derivatives. Epoxides of two of the *N*-styrylphthalimide products were also prepared.

2-Arylethylamine structures occur very commonly in natural products and biologically active compounds. This structure might be produced in a new way by use of the palladium-catalyzed vinylic substitution reaction[1] between aryl halides and *N*-vinyl amides. Initial experiments were promising. Subsequent work reported herein demonstrates the simplicity and advantages of the method for producing various 2-styryl- and 2-arylethylamine derivatives.

Results and Discussion

We first investigated the reaction of bromobenzene with *N*-vinylpyrrolidinone. The reaction, which was catalyzed with 1 mol % of palladium acetate, based on the bromobenzene, and 4 mol % of tri-*o*-tolylphosphine,[2] proceeded rapidly at 100 °C producing a mixture of two products in quantitative yield. The two were formed by the addition of the intermediate phenylpalladium species in both possible directions to the

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