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A Low-Pressure, Palladium-Catalyzed *N,N'*-Diarylurea Synthesis from Nitro Compounds, Amines, and Carbon Monoxide

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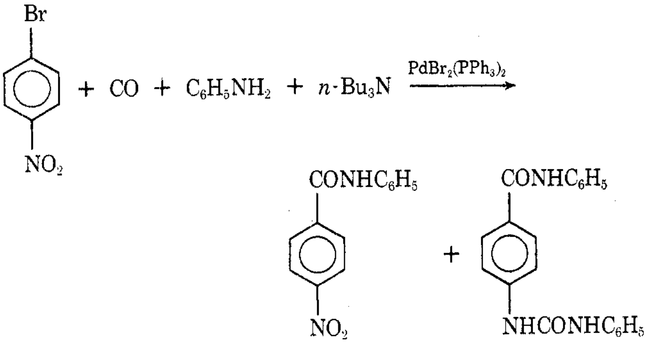
Aromatic primary amines, aromatic nitro compounds, and carbon monoxide react in the presence of catalytic amounts of palladium(II) salts, organic phosphines, a basic tertiary amine, and tetraethylammonium chloride at 90° under 1 atm pressure to form *N,N'*-diarylureas in moderate to good yields.

It was previously noted that the reaction of *p*-bromonitrobenzene, carbon monoxide, aniline, and a tertiary amine with $PdBr_2(PPh_3)_2$ as catalyst at 100° and 1 atm pressure led to the formation of considerable amounts of the *N*-phenylamide of 4-carboxydiphenylurea as well as the expected *N*-phenyl-*p*-nitrobenzamide.[1] We have now investigated the diarylurea formation in more detail.



It is known that aromatic nitro compounds can be treated with carbon monoxide under vigorous conditions to give urea derivatives. For example, nitrobenzene with water and 10,000 psi of carbon monoxide at 180° with a palladium–iron catalyst forms diphenylurea[2] and the same product is obtained in 54% yield when nitrobenzene is treated at 140° under 150 atm pressure with carbon monoxide and hydrogen using $[Ru(CO)_4]_3$ as catalyst.[3] We report in this paper a more versatile synthesis of diarylureas that occurs with only 1 atm pressure of carbon monoxide and at temperatures below 100°.

Results and Discussion

Preliminary experiments investigating the reaction of aniline and nitrobenzene with $Pd(OAc)_2$ plus 2 equiv of triphenylphosphine as catalyst under 1 atm of carbon monoxide revealed that both halide ion and a basic tertiary amine were necessary to cause the reaction to occur in reasonable yields. Without halide ion, the reaction stopped with less than 10% of the theoretical amount of CO being absorbed. It was also necessary to purge the apparatus frequently with fresh CO to remove accumulated CO_2 from the reaction vessel. The optimum reaction rate in xylene solution was achieved at about 90° using 15 mol % tetraethylammonium chloride, ~50 mol % tri-*n*-butylamine, 2 mol % palladium acetate, and 4 mol % triphenylphosphine based upon the aromatic amine used. The nitro compound was present in 10–100% excess of the molar amount of the aromatic amine. The reaction could be carried out in solvents other than xylene such as DMF, Me_2SO, and HMPA, but there appeared to be no rate or yield advantage in doing so. In xylene, the urea derivatives generally crystallized from the solution during the reaction while in DMF, Me_2SO, or HMPA they did not. The tetraethylammonium chloride salt was more effective than the bromide and it in turn was better than the iodide. The reaction rates were not very sensitive to the amount of the chloride added; however, the amount of tertiary amine which gave the greatest rate accelleration was about 1 g per 10 ml of xylene solvent. The reaction is presumed to occur according to the following equation.

$$\mathrm{ArNH_2 + ArNO_2 + 3CO \xrightarrow[n\text{-}Bu_3N]{Pd(PPh_3)_2X_2,\ Et_4N^+Cl^-} ArNHCONHAr + 2CO_2}$$

The data obtained from these and related reactions appear in Table I. Reaction rates were estimated from the time required for half of the theoretical amount of CO required, according to the above equation, to be absorbed.

Various palladium complexes were tried as catalysts. Differences in the anions attached to the metal had only minor effects upon the reaction rates. Major effects were caused by changing the phosphine groups. Triphenylphosphine was the best ligand found. Tri-*o*-tolylphosphine and

Table I
Diarylurea Syntheses[a]

Amine (mmol)	Nitro compd (mmol)	Halide (mmol)	Tertiary amine (mmol)	Catalyst (mmol)	$T_{1/2}$, min[b]	Total CO, % of theory	Products (% yield)
$C_6H_5NH_2$ (10)	$C_6H_5NO_2$ (11)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	158	88	$(C_6H_5NH)_2CO$ (64)
$C_6H_5NH_2$ (10)	$C_6H_5NO_2$ (20)	$Et_4N^+Cl^-$ (0.5)	n-Bu_3N (2.7)	$PdClPh(PPh_3)_2$ (0.2)	170		
$C_6H_5NH_2$ (10)	$C_6H_5NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$PdClPh(PPh_3)_2$ (0.2)	165		
$C_6H_5NH_2$ (10)	$C_6H_5NO_2$ (20)	$Et_4N^+Cl^-$ (3.0)	n-Bu_3N (2.7)	$PdClPh(PPh_3)_2$ (0.2)	169		
p-$CH_3C_6H_4NH_2$ (10)	p-$CH_3C_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	155	85	$(p$-$CH_3C_6H_4NH)_2CO$ (69)
p-$CH_3OCOC_6H_4NH_2$ (10)	p-$CH_3OCOC_6H_4NO_2$ (11)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	99	111	$(p$-$CH_3OCOC_6H_4NH)_2CO$ (81)
p-$ClC_6H_4NH_2$ (10)	p-$ClC_6H_4NO_2$ (11)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	90	97	$(p$-$ClC_6H_4NH)_2CO$ (66)
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (11)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	100	94	p-$ClC_6H_4NHCONHC_6H_5$ p-$ClC_6H_4NH)_2CO$ $(C_6H_5NH)_2CO$ (50)[c,j]
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	56	112	p-$ClC_6H_4NHCONHC_6H_5$ $(p$-$ClC_6H_4NH)_2CO$ $(C_6H_5NH)_2CO$ (~60)[c,j]
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	93	97	
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$PdCl_2(PPh_3)_2$ (0.2)	131	106	
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$Pd(Cl)Ph(PPh_3)_2$ (0.2)	89	106	
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$Pd(Br)Ph(PPh_3)_2$ (0.2)	91	115	
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$Pd(PPh_3)_4$ (0.2)	105		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (4.0)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	62		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	56		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (8.0)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	72		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (11)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	82		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	96		

$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	87^d		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	72^e		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Br^-$ (1.5)	n-Bu_3N (2.7)	$Pd(Br)Ph(PPh_3)_2$ (0.2)	120		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+I^-$ (1.5)	n-Bu_3N (2.7)	$Pd(Br)Ph(PPh_3)_2$ (0.2)	$\sim600^f$		
p-$CH_3C_6H_4NH_2$ (10)	p-$CH_3OCOC_6H_4NO_2$ (11)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	51	87	p-$CH_3C_6H_4NHCONHC_6H_4COOCH_3$ $(28)^g$ $(p$-$CH_3C_6H_4NH)_2CO$ $(21)^h$ $(p$-$CH_3OCOC_6H_4NH)_2CO$ $(6)^h$
p-$CH_3OCOC_6H_4NH_2$ (10)	p-$CH_3C_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	296	58	p-$CH_3C_6H_4NHCONHC_6H_4COOCH_3$ $(22)^i$ $(p$-$CH_3C_6H_4NH)_2CO$ $(5)^h$ $(p$-$CH_3OCOC_6H_4NH)_2CO$ $(10)^h$
p-$CH_3C_6H_4NH_2$ (10)	$C_6H_5NO_2$ (11)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	88	89	p-$CH_3C_6H_4NHCONHC_6H_4$ $(p$-$CH_3C_6H_4NH)_2CO$ $(C_6H_5NH)_2CO$ $(\sim44)^j$
$C_6H_5CH_2NH_2$ (10)	$C_6H_5NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	53	71	$(C_6H_5CH_2NH)_2CO$ $(17)^k$

[a] Carried out at 90° with 1 atm of CO and 10 ml of xylene as solvent. [b] The time required for absorption of 5 mmol of CO. This is approximate since no correction was made for the difference in solubility of CO and CO_2 in the reaction medium. [c] No p-chloroaniline could be detected by VPC in this reaction mixture. [d] Carried out at 80°. [e] Carried out at 100°. [f] Extrapolated value. [g] Methyl p-aminobenzoate was shown to be formed in the reaction by VPC. [h] Based on a theoretical yield of 10 mmol of diarylurea. [i] p-Toluidine was shown to be formed in the reaction by VPC. [j] Composition of mixture was not determined. [k] Other ureas were also present but were not specifically identified.

triphenyl phosphite did not catalyze the reaction significantly under the usual conditions.

Reaction rates and yields varied with the substituents present in the aromatic amine and the nitro compound. With an electron-supplying group in the amine (p-toluidine) the reaction rate increased, while with a withdrawing group (methyl p-aminobenzoate) the rate decreased relative to aniline. The p-chloro group in p-chloraniline, however, had little effect. In the nitro compound the effects were larger and reversed in the few examples investigated. The reaction of p-toluidine with methyl p-nitrobenzoate proceeded nearly six times faster than the reverse combination of methyl p-aminobenzoate with p-nitroaniline. In the last case the reaction stopped with absorption of only 58% of the required amount of CO while the reverse combination absorbed 87%, even with a much smaller excess of the nitro compound.

In most of the instances where amines and nitro compounds with different substituents were reacted, mixtures of the unsymmetrical and symmetrical ureas were formed with the expected, unsymmetrical products predominating. The reaction mixtures also usually contained some of the amine expected from reduction of the nitro compound employed. The urea mixtures obtained were not readily separable by crystallization so analyses were made where possible from the NMR spectra of the mixtures by comparing the areas under the different NH-proton absorptions. The NMR spectral data, melting points, and analyses of the products prepared are listed in Table II.

Control experiments showed that neither methyl p-aminobenzoate nor p-toluidine reacted with diphenylurea significantly under the urea formation reaction conditions, indicating that mixing of aryl groups did not occur by a simple nucleophilic attack of amine on the urea. p-Toluidine and N-phenyl-N'-p-tolylurea likewise did not react in the presence of palladium acetate, triphenylphosphine, tri-n-butylamine, and tetraethylammonium chloride at 90° in xylene solution in 24 hr.

A reaction of p-toluidine with p-nitrotoluene was carried out in the presence of diphenylurea with the result that only a trace of aniline was detected in the reaction mixture. Aniline was found in significant amount when nitrobenzene and p-toluidine were allowed to react. Thus, the mixing of aryl groups must be occurring in some intermediate palladium complex.

The mechanism of the urea formation is obscure. Presumably the catalyst is reduced initially and the nitro compound complexes with it, but attempts to isolate or identify such an intermediate have failed. Heating nitrobenzene with a molar amount of tetrakis(triphenylphosphine)palladium(0) under CO at 90° causes a darkening of the solution to a yellow-brown color but no gas is absorbed and only an intractable dark-colored gum could be obtained from the solution. Analyses by VPC failed to show the presence of free nitrobenzene, nitrosobenzene, or phenyl isocyanate. Intermediate arylnitroso, nitrene, and isocyanate palladium complexes can be imagined, but we have not obtained evidence to indicate that any of these are actually formed.

Experimental Section

General Procedure for the Preparation of Diarylureas. The indicated amounts of the nitro compound, aromatic amine, tri-n-butylamine, tetraethylammonium chloride, and 10 ml of xylene were placed in a 100-ml jacketed flask equipped with a magnetic stirring bar and a stopcock attachment from which was suspended a Teflon cup containing the palladium catalyst. The flask was then attached to a microhydrogenation-type apparatus.[4] The apparatus was evacuated and filled several times with carbon monoxide, then brought to the proper temperature (constant-temperature bath)

Table II
Physical Properties and Analytical Data for *N,N'*-Diarylureas

Compd	Mp, °C (reported)	NMR spectrum, τ, ppm
$(C_6H_5NH)_2CO$	235–236 (235)[a]	(Me_2SO-d_6) s 1.29 (2 H), m 2.25–3.15 (10 H)
$(p$-$ClC_6H_4NH)_2CO$	303–305 (306–307)[b,d]	(polysol) s 1.09 (2 H), d 2.27 (4 H), d 2.53 (4 H) (J = 10 Hz)
$(p$-$CH_3C_6H_4NH)_2CO$	263–264 (264)[c,d]	(Me_2SO-d_6) s 1.39 (2 H), d 2.52 (4 H), d 2.83 (4 H) (J = 8 Hz), s 7.74 (6 H)
$(p$-$CH_3OCOC_6H_4NH)_2CO$	258–258.5[d]	(polysol) s 0.78 (2 H), d 1.93 (4 H), d 2.27 (4 H) (J = 9 Hz), s 6.07 (6 H)

[a] T. L. Davis and K. C. Blanchard, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1964, p 453. [b] M. H. Vittenet, *Bull. Soc. Chim. Fr.*, 21, 302 (1899). [c] T. L. Davis and H. W. Underwood, Jr., *J. Am. Chem. Soc.*, 44, 2595 (1922). [d] Satisfactory analytical values (±0.2% for C, H, N, and Cl when present) were reported for these compounds.

and allowed to come to equilibrium at 1 atm pressure. The Teflon cup containing the palladium catalyst was then dropped into the reaction mixture. Gas volume changes and times were periodically recorded until gas absorption stopped. Because of the formation of carbon dioxide in the reactions, stirring was stopped and the system was evacuated and refilled with carbon monoxide at 50-ml intervals. When gas absorption stopped the reaction mixture was cooled to room temperature, diluted with ca. 300 ml of hexane, and filtered. The solid, insoluble urea was then recrystallized from ethanol.

Attempted Reaction of *N*-Phenyl-*N'*-*p*-tolylurea with *p*-Toluidine. *N*-Phenyl-*N'*-*p*-tolylurea (1.13 g, 5 mmol), 0.59 g (5 mmol) of *p*-toluidine, 1.0 g (5.4 mmol) of tri-*n*-butylamine, 0.249 g (1.5 mmol) of tetraethylammonium chloride, 0.045 g (0.2 mmol) of palladium acetate, 0.104 g (0.4 mmol) of triphenylphosphine, and 10 ml of xylene were mixed at 90° in a CO atmosphere in the same manner described in the general procedure for the preparation of ureas. After stirring for 24 hr at 90° only about 4 ml of CO had been absorbed. The reaction mixture was dissolved in about 400 ml of methylene chloride which was then extracted with two 400-ml portions of 40% hydrochloric acid, washed with 400 ml of water, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was analyzed by NMR. The NMR spectra of the residue showed that it consisted entirely of *N*-phenyl-*N'*-*p*-tolylurea and that no *N,N'*-di-*p*-tolylurea or *N,N'*-diphenylurea was formed.

***N,N'*-Di-*p*-tolylurea Formation in the Presence of *N,N'*-Diphenylurea.** *p*-Nitrotoluene (1.51 g, 11 mmol), 1.07 g (10 mmol) of *p*-toluidine, 0.249 g (1.5 mmol) of tetraethylammonium chloride, 1.0 g (5.4 mmol) of tri-*n*-butylamine, 0.045 g (0.2 mmol) of palladium acetate, 0.104 g (0.4 mmol) of triphenylphosphine, and 10 ml of xylene were allowed to react at 90° as described in the general procedure with 1.84 g (10 mmol) of *N,N'*-diphenylurea also present in the reaction mixture. After 30 hr CO absorption had stopped and about half of the theoretical amount of CO had been absorbed by the system. The reaction mixture was then examined by VPC. Although a trace of aniline was detected, this was not enough to indicate that any appreciable amount of exchange had taken place.

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Registry No.—$C_6H_5NH_2$, 62-53-3; p-$CH_3C_6H_4NH_2$, 106-49-0; p-$CH_3OCOC_6H_4NH_2$, 619-45-4; p-$ClC_6H_4NH_2$, 106-47-8; $C_6H_5CH_2NH_2$, 64-04-0; $C_6H_5NO_2$, 98-95-3; p-$CH_3C_6H_4NO_2$, 99-99-0; p-$CH_3OCOC_6H_4NO_2$, 619-50-1; p-$ClC_6H_4NO_2$, 100-00-5; $Et_4N^+Cl^-$, 56-34-8; n-Bu_3N, 102-82-9; $Pd(OAc)_2$, 3375-31-3; Ph_3P, 603-35-0; $PdClPh(PPh_3)_2$, 22605-84-1; $PdCl_2(PPh_3)_2$, 13965-03-2; $PdBrPh(PPh_3)_2$, 30643-33-5; $Pd(PPh_3)_4$, 14221-01-3; $(C_6H_5NH)_2CO$, 102-07-8; $(p$-$ClC_6H_4NH)_2CO$, 1219-99-4; $(p$-$CH_3C_6H_4NH)_2CO$, 621-00-1; $(p$-$CH_3OCOC_6H_4NH)_2CO$, 56050-99-8; CO, 630-08-0.

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