



Palladium(II)-catalyzed regioselective carbonylative coupling of aniline derivatives with terminal aryl acetylenes to give acrylamides under syngas conditions

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Abstract

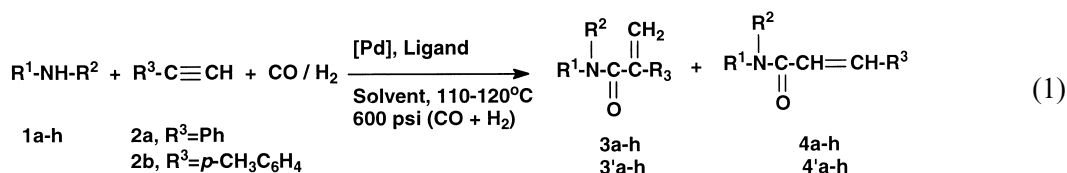
The carbonylative coupling of aniline derivatives (**1a–h**) with terminal aryl acetylenes (**2a, b**) catalyzed by Pd(OAc)₂ and 1,4-bis(diphenylphosphino)butane (dppb) under syngas conditions affords acrylamide derivatives **3** or **3'** in excellent yields and selectivities. © 2000 Published by Elsevier Science Ltd.

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Amides represent an important class of organic compounds for both industrial applications and academic research.¹ The use of transition metal complexes in carbonylation chemistry is an efficient route for the production of carbonyl compounds.^{2,3} The classical synthesis of some *N*-aryl acrylamides is known to be achieved by reacting aromatic amines with methacrylyl chlorides.^{4,12,13} 2-Substituted acrylamides are important intermediates for polymer synthesis⁵ and have been synthesized by palladium-catalyzed carbonylation of terminal alkynes with diethylamine in a strongly acidic medium⁶ or in the presence of organic iodides or amine HI salts.⁷ Recently, the selective synthesis of α,β -unsaturated amides has been achieved via palladium(0)-catalyzed insertion of carbon monoxide into an unactivated carbon–nitrogen bond of propargylamines and 2,3-dienylamines.^{8,9} We now wish to report a direct and highly efficient palladium-catalyzed method of a regioselective carbonylative coupling of aniline derivatives with terminal aryl acetylenes, affording acrylamides under syngas conditions.

The palladium-catalyzed reaction of aniline (**1a**, R¹=Ph, R²=H) with phenylacetylene (**2a**, R³=Ph) and syngas mixture was chosen as a model reaction to determine the optimum reaction conditions (see Eq. (1)).

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The carbonylation of aniline with phenylacetylene was examined by varying the ratio of CO/H₂, in the presence of 1 mol% of Pd(OAc)₂ and 2 mol% of 1,4-bis(diphenylphosphino)butane (dppb) at 600 psi and 110°C in toluene as a solvent. Low total yields (31%) of *N*-2-diphenyl propeneamide (**3a**, R¹=Ph, R²=H, R³=Ph) and *trans*-*N*,3-diphenyl propeneamide (**4a**, R¹=Ph, R²=H, R³=Ph) (ratio of **3a**/**4a**=92/8) were obtained when only carbon monoxide was applied. However, the use of the syngas mixture in the reaction significantly increases the yields of the unsaturated amides, depending on the CO/H₂ ratio. Total yields of 60%, 90%, and 85% of **3a** and **4a** were obtained with the ratios of CO/H₂ of 5/1, 1/1, and 1/5, respectively. Furthermore, the decrease in the total pressure to 200 psi (CO/H₂=1/1) and the reaction time to 24 h decreases the total yield of products to 59% and 60%, respectively. The effect of varying the palladium catalyst and phosphine ligand on the total yield of **3a** and **4a** was also realized at 110°C and in the presence 600 psi of syngas mixture (CO/H₂=1/1). Pd(OAc)₂ gave only traces of **3a** and **4a** in the absence of any phosphine ligand, however, the use of system Pd(OAc)₂/PPh₃ gives a total yield of 75% of products. Furthermore, the use of the bidentate phosphine ligand 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane (dppp), or dppb, gives acrylamide **3a** with total yields of 85%, 82%, and 90%, respectively. In addition, the nature of the solvent greatly affects the yield of acrylamides, for example, the use of dichloromethane in place of toluene with the catalytic system Pd(OAc)₂/dppb/CO/H₂ gave only 40% of products. The use of other palladium complexes, such as PdCl₂, PdCl₂(PPh₃)₂, Pd(dba)₂, and Pd(PPh₃)₄ with dppb gave low yields (10–20%) of acrylamides.

The scope of this new methodology for the catalytic synthesis of acrylamides was demonstrated by the results summarized in Table 1. The carbonylative coupling reaction of a series of aniline derivatives (**1a–h**) with terminal aryl acetylenes (**2a,b**) was performed using 1 mol% of Pd(OAc)₂ and 2 mol% of dppb at 600 psi of a mixture of syngas (CO/H₂=1/1). The unsaturated amides **3a–h** (**3'a–h**) and **4a–h** (**4'a–h**) were isolated in total yields ranging between 67% and 95%. Aniline and *N*-substituted aniline derivatives (**1a–g**) reacted with phenylacetylene (**2a**) or with *p*-tolylacetylene (**2b**) (Table 1, entries 1–7) affording the acrylamides **3** or **3'** as the major products. The reaction exhibits high regioselectivity in favor of the acrylamides **3** or **3'**. The regiochemical outcome is in excellent accord with the related palladium-catalyzed hydrocarboxylation of alkynes.^{10,11} However, the aminophenol derivative (**1h**) reacts with **2a** or **2b** (Table 1, entry 8) forming **3h** or **3'h** as the sole products.

Interestingly, the carbonylative coupling of acetanilide **1i** with phenylacetylene **2a** at 130°C, catalyzed by the system Pd(OAc)₂/dppb/CO/H₂ in toluene, affords an acceptable total yield and excellent regioselectivity of the unsaturated amide **5** (Eq. (2)).

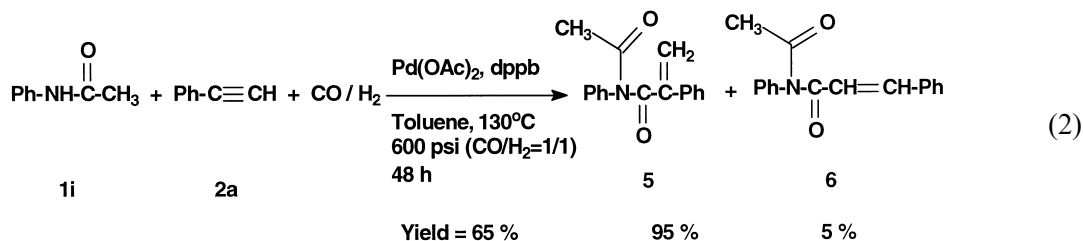
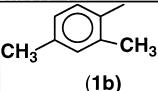
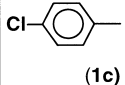
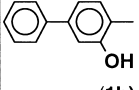


Table 1
Palladium(II)-catalyzed carbonylative coupling of aniline derivatives with terminal aryl acetylenes^a

Entry	Anilines 1 R ¹ R ²	Alkynes 2 2a 2b	T °C	Product Distribution ^b , %				Yield ^c %
				3	3'	4	4'	
1	Ph (1a)	2a	110	92 (3a)		8 (4a)		90
		2b	120		82 (3'a)		18 (4'a)	85
2	 (1b)	2a	110	90 (3b)		10 (4b)		82
		2b	120		85 (3'b)		15 (4'b)	80
3	 (1c)	2a	110	89 (3c)		11 (4c)		82
		2b	110		75 (3'c)		25 (4'c)	67
4	 (1d)	2a	120	93 (3d)		7 (4d)		88
		2b	120		79 (3'd)		21 (4'd)	95
5	Ph (1e)	2a	120	86 (3e)		14 (4e)		88
		2b	120		74 (3'e)		26 (4'e)	95
6	Ph (1f)	2a	120	90 (3f)		10 (4f)		88
		2b	120		82 (3'f)		18 (4'f)	95
7	Ph (1g)	2a	120	87 (3g)		13 (4g)		85
		2b	120		80 (3'g)		20 (4'g)	90
8	 (1h)	2a	120	100 (3h)		-		92
		2b	120		100 (3'h)	-	-	90

^a Reaction conditions: aniline (2.0 mmol), alkyne (2.0 mmol), Pd(OAc)₂ (0.02 mmol), dppb (0.04 mmol), toluene (10 ml), 600 psi, CO/H₂=1/1, 48 h.

^b The products were identified by GC-MS, ¹H and ¹³C NMR. The ratio 3/4 was determined by GC and ¹H NMR.

^c Based on amine employed.

The role of H₂ is probably to stabilize the palladium hydride intermediate 'dppb-Pd-H' formed during the catalytic cycle.

The typical experimental procedure was as follows. To a 45 ml Parr autoclave fitted with a glass liner and stirring bar was added Pd(OAc)₂ (0.02 mmol), dppb (0.04 mmol), phenylacetylene (2.0 mmol), aniline (2.0 mmol), and toluene (10 ml). The autoclave system was vented three times with CO and then pressurized with 300 psi of CO and 300 psi of H₂. The mixture was stirred at 110°C for 48 h. After cooling, the pressure was released, the reaction mixture was filtered and the solvent was removed. The products **3a** and **4a** were separated by recrystallization and preparative thin-layer chromatography (petroleum ether:acetone = 10:1). The products identified by NMR, FT-IR, and GC-MS gave satisfactory spectral data.

The following compounds are known: **4a**,¹² **4d**.¹³ All other unsaturated amides **3** and **4** are new compounds. Representative examples of spectral data of two unsaturated amides are provided:

N,2-Diphenyl propeneamide (**3a**): IR (neat) ν (cm⁻¹) 1652 (CO), 3230 (NH); ¹H NMR δ (ppm): 5.72 (s, 1H, =CH₂), 6.29 (s, 1H, =CH₂), 7.10–7.52 (m, 11H, 2Ph and NH); ¹³C NMR δ (ppm): 119.93, 123.36, 124.63, 128.87, 129.02, 136.67, 137.65, 145.11, 165.20; GC–MS m/z 223 (M⁺). Anal. calcd for C₁₅H₁₃NO: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.75; H, 6.08; N, 6.34. *trans-N*-Phenyl-3-tolyl propeneamide (**4'a**): IR (neat) ν (cm⁻¹) 1656 (CO), 3286 (NH); ¹H NMR δ (ppm): 2.36 (s, 3H, CH₃), 6.53 (d, 1H, J = 15.5 Hz, COCH=), 7.10–7.62 (m, 10H, arom. and NH), 7.72 (d, 1H, J = 15.5 Hz, =CH-tolyl); ¹³C NMR δ (ppm): 21.45, 119.98, 124.40, 127.96, 129.06, 129.61, 131.87, 138.10, 140.32, 142.41, 164.48; GC–MS m/z 237 (M⁺). Anal. calcd for C₁₆H₁₅NO: C, 80.98; H, 6.37; N, 5.90. Found: C, 79.95; H, 6.37; N, 5.85.

In conclusion, the palladium-catalyzed carbonylative coupling of anilines with aryl alkynes and syngas provides a remarkably efficient method for the synthesis of new acrylamides in high isolated yields and regioselectivities. This methodology demonstrates again the efficiency of palladium catalysts in useful carbonylative coupling reactions. We are currently examining the application of this catalytic system to different classes of substances including primary and secondary alkyl amines and diamines with terminal and internal alkyl and aromatic alkynes, diynes, and others.

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