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Regioselective palladium-catalyzed aminations of 3,5-dibromo-2-pyrone with various aryl and alkyl amines

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Abstract—3,5-Dibromo-2-pyrone underwent facile palladium-catalyzed coupling reactions with various primary and secondary alkyl and aryl amines to furnish a variety of the previously unknown 3-arylamino- and 3-alkylamino-5-bromo-2-pyrones with good to excellent regioselectivity and chemical yields. © 2002 Elsevier Science Ltd. All rights reserved.

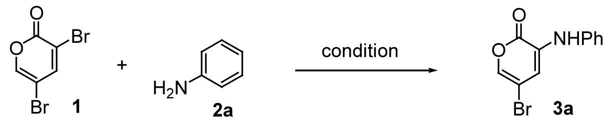
Substituted 2-pyrones are important structural subunits present in a number of naturally occurring products[1] and versatile synthetic building blocks for the production of various structurally and physiologically important molecules, primarily via their Diels–Alder cycloadditions with appropriate dienophiles.[2]

As a part of our ongoing research program on 3,5-dibromo-2-pyrone,[3] we have recently reported that it undergoes regioselective Sonogashira couplings and stannylations to afford 3-alkynyl-5-bromo-2-pyrones and 3-trialkylstannyl-5-bromo-2-pyrones, respectively.[3a] Also reported was the Stille coupling reactions of 3-trimethylstannyl-5-bromo-2-pyrone with various aryl and vinyl halides for the synthesis of various 3-aryl- and 3-vinyl-5-bromo-2-pyrones.[3b]

In this account, we wish to report regioselective amination reactions of 3,5-dibromo-2-pyrone with aryl and alkyl amines for the synthesis of a variety of previously unknown 3-arylamino- and 3-alkylamino-5-bromo-2-pyrones. The amino groups at the C3 position in the resulting 2-pyrones would push the electrons into the pyrone unit. Such electronic perturbation may lead to a substantial change in their dienyl characters. In addition, the resulting stereochemically defined bicyclolactones would be useful synthetic intermediates for various systems including α-amino acids with substituted cyclohexenyl residues.

Palladium-catalyzed amination of 3,5-dibromo-2-pyrone may result in the cleavage of the lactone ring as the reaction requires the presence of a base. In fact, 3,5-dibromo-2-pyrone completely disappeared within a few hours when heated with aniline in the presence of NaO*t*Bu or K_2CO_3. Thus, the reaction conditions must be controlled in order to achieve a successful reaction. With aniline as a model, we studied the aminations of 3,5-dibromo-2-pyrone under various amination conditions reported in the literature.[4] Despite our initial doubt, however, the amination proceeded reasonably well, as can be seen in Table 1.

Table 1. Palladium-catalyzed amination of 3,5-dibromo-2-pyrone with aniline under various conditions



Entry	Condition	Yield
1	$Pd_2(dba)_3$/dppf/NaO*t*Bu/dioxane/110°C/5 h	Trace
2	$Pd(OAc)_2$/BINAP/Cs_2CO_3/toluene/110°C/5 h	Trace
3	$Pd(OAc)_2$/BINAP/K_2CO_3/toluene/110°C/0.5 h	42%
4	$Pd(OAc)_2$/BINAP/K_2CO_3/toluene/120°C/0.5 h	54%
5	$Pd(OAc)_2$/P(*t*Bu)$_3$/Cs_2CO_3/toluene/110°C/2 h	Trace
6	$Pd_2(dba)_3$/xantphos/K_2CO_3/toluene/100°C/4 h	57%
7	$Pd_2(dba)_3$/xantphos/Cs_2CO_3/toluene/100°C/4 h	76%
8	$Pd_2(dba)_3$/xantphos/NaO*t*Bu/toluene/100°C/4 h	Trace
9	$Pd(OAc)_2$/xantphos/Cs_2CO_3/toluene/110°C/0.5 h	82%

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NaO*t*Bu cleaved the lactone ring and was thus ineffective, regardless of the type of palladium catalyst and ligand. $Pd(OAc)_2$ gave better results than $Pd_2(dba)_3$. Only a trace of the product was obtained with the catalytic system of $Pd(OAc)_2/P(tBu)_3$.[5] The results in entries 2 and 3 are quite unusual in that the reaction does proceed with K_2CO_3, but not with Cs_2CO_3. Use of xantphos[6] improved both reaction rate and yield. The best result was obtained under the condition 9, using the $Pd(OAc)_2$/xantphos system. Running the reaction at a slightly elevated temperature (110°C) shortened the reaction time, suppressing the lactone ring cleavage reaction, thus improving the product yield. Further increase of reaction temperature, however, resulted in a decrease of the product yield (55% at 120°C, data not shown in Table 1).

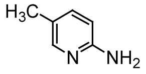
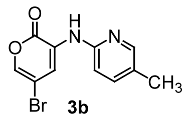
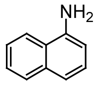
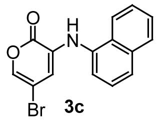
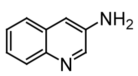
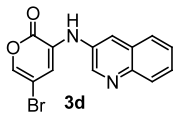
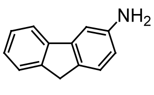
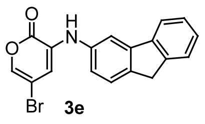
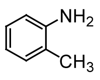
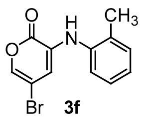
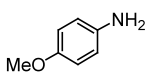
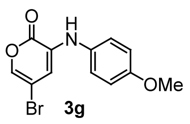
Table 2 summarizes the results of the amination reactions with various other aryl amines under the condition 9.

As shown, various types of aryl amines underwent coupling reactions, providing 3-arylamino-5-bromo-2-pyrones in fair to good isolated yields.[7] No couplings at the C5 position of 3,5-dibromo-2-pyrone were observed.

Unlike the aminations with aromatic amines, however, the catalytic system $Pd(OAc)_2$/xantphos was not effective in the couplings with alkyl amines, providing only a trace of the desired products. We have found that the catalytic system BINAP/$Pd(OAc)_2/K_2CO_3$ is much better suited in this case, affording the corresponding products in reasonable isolated yields. The actual coupling reactions turned out to be highly dependent upon the reaction temperature. Each reaction shown in Table 3 was optimized by running the reactions at various temperatures.[8] Secondary amines gave better results than primary amines, presumably due to their lower nucleophilicity.

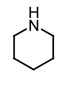
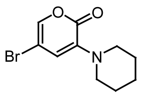
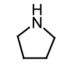
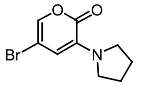
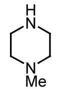
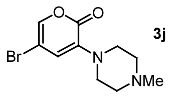
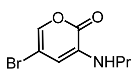
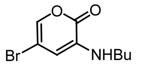
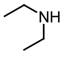
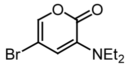
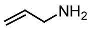
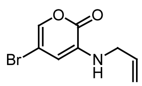
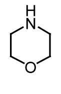
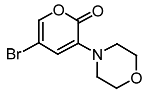
In summary, we have found that 3,5-dibromo-2-pyrone undergoes facile palladium-catalyzed amination reactions with various aryl and alkyl amines, regioselectively at C3, to provide a series of previously unknown 3-aryl- and 3-alkylamino-5-bromo-2-pyrones.[9] Their dienyl properties will be studied and presented in due course.

Table 2. Palladium-catalyzed amination with aniline

entry	amine	time	product	yield
1		0.5 h	 **3b**	42%
2		2h	 **3c**	72%
3		5 h	 **3d**	53%
4		4 h	 **3e**	55%
5		5 h	 **3f**	60%
6		5 h	 **3g**	36%

*Reaction condition: $Pd(OAc)_2$/xantphos/Cs_2CO_3/toluene/110°C

Table 3. Palladium-catalyzed aminations with alkyl amines

entry	amine	temp/time	product		yield
1		110°C/15 min		**3h**	64%
2		80°C/20min		**3i**	77%
3		100°C/40 min		**3j**	43%
4	nPrNH$_2$	80°C/10 min		**3k**	54%
5	nBuNH$_2$	80°C/10 min		**3l**	79%
6		110°C/7 h		**3m**	79%
7		100°C/10 min		**3n**	76%
8		100°C/30 min		**3o**	23%

*Reaction condition: $Pd(OAc)_2$/BINAP/K_2CO_3/toluene

Acknowledgements

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6. Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560.
7. *Representative procedure*: A sealed tube was charged with 50 mg (0.197 mmol) of 3,5-dibromo-2-pyrone, 2 mol% of $Pd(OAc)_2$, 4 mol% of xantphos (ligand/Pd = 2), and cesium carbonate (0.296 mmol). After adding 1 mL of toluene, the mixture was degassed and backfilled with argon whereupon was added aniline (0.236 mmol, 1.2 equiv.), while cooling with an ice bath. After stirring for 30 min at 110°C, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, filtered through a thin layer of Celite, and concentrated. The crude material was purified by using column chromatography (hexanes:EtOAc = 80:1) to give the product **3a** in 82% yield.
8. *Representative procedure*: A sealed tube was charged with 50 mg (0.197 mmol) of 3,5-dibromo-2-pyrone, 3 mol% of $Pd(OAc)_2$, 6 mol% of BINAP(ligand/Pd = 2), and potassium carbonate (0.296 mmol). After adding 1 mL of toluene, the mixture was degassed and backfilled with argon whereupon was added pyrrolidine (0.236 mmol, 1.2 equiv.), while cooling with an ice bath. After stirring for 20 min at 80°C, the reaction mixture was cooled to room temperature, diluted with a mixture of CH_2Cl_2 and methanol (30:1, v/v), filtered through a thin layer of Celite, and concentrated. The crude material was purified using column chromatography (CH_2Cl_2:MeOH = 40:1) to give the product **3i** in 77% yield.
9. All new 3-amino-5-bromo-2-pyrones **3a**–**o** were fully characterized by ^1H and ^{13}C NMR, HRMS, and FT-IR.