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Palladium-Catalyzed Highly Regio- and Stereoselective Synthesis of 4-Alkylidene-4*H*-3,1-benzoxazines from *N*-Acyl-*o*-alkynylanilines

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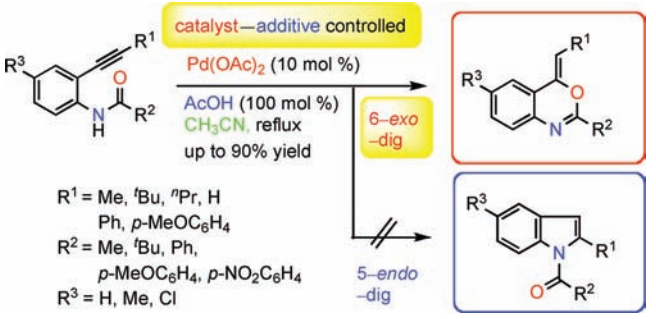
ABSTRACT



The highly regio- and stereoselective 6-*exo*-dig mode cyclization of *N*-acyl-*o*-alkynylanilines producing 4-alkylidene-3,1-benzoxazines occurred unpredictably by use of a proper catalyst [$Pd(OAc)_2$] and an effective additive (acetic acid) under suitable reaction conditions.

3,1-Benzoxazines are attractive targets for medicinal chemists because some 3,1-benzoxazine derivatives are known to show interesting biological activities and have been used as potent progesterone-receptor agonists, DNA-binding antitumor agents,[1] human leukocyte elastase (HLE) inhibitors,[2] and C1r serine protease inhibitors, as well as fungicidal, anti-inflammatory, and anticonvulsant drugs.[3] The indole ring system is among the most important heterocycles owing to its existence in nature and in many pharmaceutical agents,[4] and numerous methods for synthesizing indoles,[5] including functionalization of indoles,[5d,6] have been developed. Recent new methodologies for indole synthesis have involved the catalytic cyclization of a variety of *o*-alkynylaniline derivatives as a key step. When a substrate, for example, of type **I** (*N*-acylated) is employed (Scheme 1), formal cyclization in a 5-*endo*-dig mode yields indoles (**III**), while cyclization in a 6-*exo*-dig mode yields 3,1-benzoxazines (**II**). Therefore, highly effective regiocontrol of the cyclization mode is essential for selective

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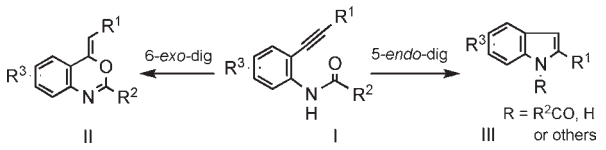
Scheme 1. Cyclizations of 6-*Exo*-dig vs 5-*Endo*-dig Mode

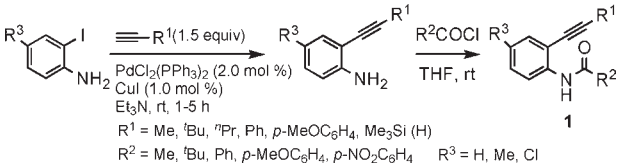


preparation of either indoles (**III**) or 3,1-benzoxazines (**II**). A survey of the literature on SciFinder Scholar (up to December 2010) for both reactions reveals, surprisingly, that there are only 4 reports[7,8] in which the formation of 3,1-benzoxazines (**II** and congeners) from **I** is described, despite 146 reports demonstrating the transformation to indoles (**III** and congeners) and a vast number of examples of indole formation if the *N*-substituent of **I** are not limited to an acyl group ($R^2C{=}O$).[5,9−14]

The development of methodologies for the highly selective synthesis of different products from the same starting materials by simple modification of catalysts/promoters and/or reaction conditions is attractive to chemists.[15] This prompted us to develop a reaction involving the alternative pathway of 6-*endo*-dig mode cyclization of **I**. We have realized a highly regio- and stereoselective synthesis of 4-alkylidene-4*H*-3,1-benzoxazines **II** from *o*-alkynyl-*N*-carboxanilides **I** by seeking a competent catalyst, an effective additive, and appropriate reaction conditions. We report the results herein.

N-Acyl-*o*-alkynylanilines **1**, the key substrates bearing various substituents (R^1, R^2, R^3), were prepared in good yields from 2-iodoanilines via the Sonogashira coupling reaction with 1-alkynes, followed by acylation with acyl chlorides (Scheme 2).

Scheme 2. Preparation of Substrates **1**



Initially, to examine the regioselectivity (6-*exo*-dig vs 5-*endo*-dig cyclization mode) of the reaction to be controlled, we selected palladium catalysts and screened them in a model reaction of 2-(3,3-dimethyl-1-butynyl)phenylacetamide (**1a**) and benzamide (**1c**). The results are shown in Table 1. In the presence of $Pd(dba)_2$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, or $Pd(PPh_3)_4/K_2CO_3$, the reaction proceeded very slowly at room temperature even by use of 20 mol % of the catalyst and appreciable amounts of the starting material **1a** remained (runs 1−3), while at higher temperatures, the formation of indoles **3a**/**c** predominated (runs 4−6). In addition, the $PdCl_2$ catalyst clearly promoted the formation of indoles **3a**/**c** (runs 7 and 8). Interestingly, $Pd(OCOCF_3)_2$ preferentially provided 3,1-benzoxazine **2a** (58% yield) along with a small amount of indole **3a** (6%) (run 9). We finally found that $Pd(OAc)_2$ was most efficient in controlling the regioselectivity of the formation of 3,1-benzoxazines **2a**/**c** in the model reaction in an acetonitrile solution (runs 10−12).

To effectively accelerate the reaction and to obtain **2a** selectively in high yield, the $Pd(OAc)_2$-catalyzed

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(8) In refs 7a−7c, 3,1-benzoxazines having specific substituents were formed as less favored byproduct in the synthesis of indoles[7a,b] or quinolines.[7c] The reaction[7d] is a direct synthetic approach from **I** to 3,1-benzoxazines with the substituent R^2 of an aryl or alkenyl group. However, the method suffered from the demand of relatively high pressure of $[CO + O_2]$ (24 bar) and from that the 3,1-benzoxazines were formed as a mixture of *E*- and *Z*-isomers contaminated with a minor amount of the TMS-eliminated starting materials.

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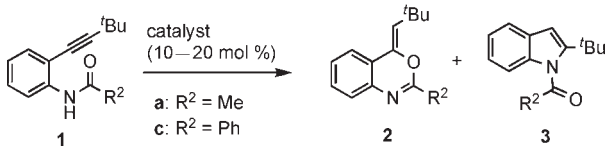
Table 1. Screening of Palladium Catalysts[a]



run	substrate	catalyst (mol %)	conditions	yield,[b] % 1a/c	2a/c	3a/c
1	**1a**	$Pd(dba)_2$ (20)	THF rt, 7 d	98		
2	**1a**	$Pd(PPh_3)_4$ (20)	THF rt, 7 d	96		trace
3	**1a**	$PdCl_2(PPh_3)_2$ (20)	THF rt, 7 d	85		10
4	**1a**	$PdCl_2(PPh_3)_2$ (20)	DMF reflux, 25 h	18		50
5	**1c**	$PdCl_2(PPh_3)_2$ (20)	DMF reflux, 25 h			68
6	**1c**	$Pd(PPh_3)_4$ (10)/K_2CO_3	toluene reflux, 4 d			76
7	**1a**	$PdCl_2$ (20)	THF rt, 2 d			82
8	**1c**	$PdCl_2$ (10)	MeCN rt, 12 h			96
9	**1a**	$Pd(OCOCF_3)_2$ (20)	THF rt, 7 d	27	58	6
10	**1a**	$Pd(OAc)_2$ (20)	THF rt, 3 d		72	
11	**1a**	$Pd(OAc)_2$ (10)	MeCN rt, 3 d		87	
12	**1c**	$Pd(OAc)_2$ (10)	MeCN rt, 2 d		87	

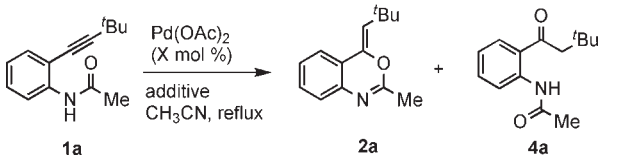
[a] Reaction was carried out in the presence of Pd catalyst in each solvent (1.0 mL) with substrate **1a/c** (0.24 mmol). [b] Yields of isolated **1a**/**c**, **2a**/**c**, and **3a**/**c**.

reaction was further examined in the presence of an additive in refluxing acetonitrile (Table 2). Additives such as MnO_2, CuO, $Cu(OAc)_2$, and AcONa were not sufficiently effective, as the starting material **1a** still remained after 10 h, although benzoxazine **2a** was obtained in appreciable amounts by use of 20 mol % of the catalyst (runs 1−4). Compound **4a** was formed in variable amounts from **2a** by hydrolysis during the reaction and/or separation/purification procedure. Actually, when **2a** was treated with acidic water, **4a** was formed exclusively. AcOH (300 mol %) as an additive clearly accelerated the reaction to produce **2a** in 72% yield and the hydrolyzed form **4a** in 18% yield in 2.5 h with consumption of the starting material **1a** in the presence of 10 mol % of $Pd(OAc)_2$ (run 5). However, the reaction in the absence of $Pd(OAc)_2$ did not yield any product even in the presence of AcOH (300 mol %). Reducing the amount of AcOH to 200 mol % slightly improved the yield of **2a** (75%; run 6). The reaction in the presence of 100 mol % of AcOH for 2.5 h gave the best result; benzoxazine **2a** was exclusively obtained in 83% yield without formation of **4a** (run 7). In the reaction with 50 mol % AcOH (run 8) for 2.5 h, **1a** was not completely consumed, but a prolonged reaction time (10 h) under acidic conditions caused hydrolysis of some of the preformed **2a** to give **4a** (run 9). The reaction in the absence of any additive in refluxing acetonitrile for 12 h produced **2a** exclusively in 92% yield, although 30 mol % of $Pd(OAc)_2$ was required (run 10).

After establishing the optimized reaction conditions (Table 2, run 7), we examined the generality of this interesting 6-*endo*-dig mode cyclization using substrates **1** bearing a variety of alkyl and aryl substituents in R^1 and R^2 (Table 3) and Me and Cl substituents in R^3 (Scheme 3). A tolerable range of the substituted 3,1-benzoxazines **2**[16] was obtained in good-to-excellent yields (62−90%, not thoroughly optimized) within a reasonable reaction time (0.2−5 h). In the reaction of the R^1-unsubstituted substrates **1** (R^1 = H, R^2 = Me, ^{t}Bu, Ph, *p*-$NO_2C_6H_4$), the

(16) The structures of 4-methylene-4*H*-3,1-benzoxazines **2** were determined spectroscopycally (^{1}H NMR, ^{13}C NMR, IR, HRMS) and confirmed by X-ray crystallography of **2d** and **2r**: The crystallographic coordinates for **2r** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 769241. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html. (see the Supporting Information). Noe was also observed between the olefinic-H and the peri-position-H of the benzene ring of **2**, suggesting the *Z*-configuration.

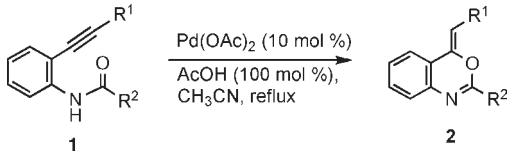
Table 2. Screening of Additives[a]



run	$Pd(OAc)_2$, mol %	additive (mol %)	time, h	yield,[b] % 1a	2a	4a
1	20	MnO_2 (300)	10	9	68	17
2	20	CuO (300)	10	39	42	10
3	20	$Cu(OAc)_2$ (40)	10	58	39	
4	20	AcONa (300)	10	10	62	
5	10	AcOH (300)	2.5		72	18
6	10	AcOH (200)	2.5		75	12
7	10	AcOH (100)	2.5		83	
8	10	AcOH (50)	2.5	28	56	
9	10	AcOH (50)	10		35	55
10	30	none	12		92	

[a] Reaction was carried out in refluxing MeCN (1.0 mL) with substrate **1a** (0.24 mmol) in the presence of 10−30 mol % of $Pd(OAc)_2$ and 50−300 mol % of AcOH. [b] Yields of isolated **1a**, **2a**, and **4a**.

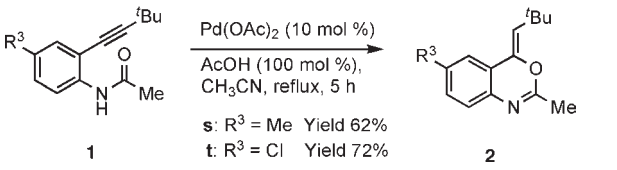
Table 3. Palladium-Catalyzed Regioselective Cyclization of Various *N*-Acyl-*o*-alkynylanilines **1** to Produce 3,1-Benzoxazines **2**[a]



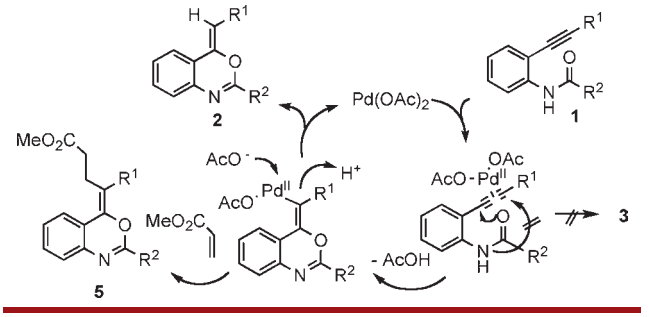
run	R^1	R^2	1	time, h	product	yield,[b] %
1	^{t}Bu	Me	**1a**	2.5	**2a**	83
2		^{t}Bu	**1b**	0.5	**2b**	70
3		Ph	**1c**	0.5	**2c**	75
4		p-$NO_2C_6H_4$	**1d**	1	**2d**	90
5	Me	Me	**1e**	0.5	**2e**	77
6		^{t}Bu	**1f**	0.5	**2f**	70
7		Ph	**1g**	0.2	**2g**	77
8		p-$NO_2C_6H_4$	**1h**	0.5	**2h**	72
9	^{n}Pr	Me	**1i**	0.5	**2i**	65
10		^{t}Bu	**1j**	0.5	**2j**	89
11		Ph	**1k**	1	**2k**	74
12		p-$MeOC_6H_4$	**1l**	1	**2l**	65
13	Ph	Me	**1m**	3	**2m**	65
14		^{t}Bu	**1n**	0.5	**2n**	89
15		Ph	**1o**	1	**2o**	79
16		p-$NO_2C_6H_4$	**1p**	1.5	**2p**	72
17	p-$MeOC_6H_4$	Me	**1q**	3	**2q**	67
18		p-$NO_2C_6H_4$	**1r**	10	**2r**	72

[a] Reaction was carried out in refluxing MeCN (1.0 mL) with substrate **1** (0.24 mmol) in the presence of 10 mol % of $Pd(OAc)_2$ and 100 mol % of AcOH. [b] Yields of isolated **2**.

Scheme 3. Palladium-Catalyzed Cyclization of **1** To Yield **2**



Scheme 4. A Possible Mechanism for the Palladium Acetate-Catalyzed Cyclization of **1** To Produce **2**



3,1-benzoxazines **2** formed tended to hydrolyze to afford compounds **4** (R^1 = H), and only 3,1-benzoxazine **2u** (R^2 = p-$NO_2C_6H_4$) was isolated, albeit in 25% yield, when the reaction was carried out in the absence of AcOH under the conditions of Table 1, run 11, for 7 d.

Although the precise mechanism for this reaction is not clear, a plausible mechanism is illustrated in Scheme 4. Initially, the catalyst $Pd(OAc)_2$ attacks the alkyne π-bond of **1** to form a palladium π-complex. The 6-*exo*-dig mode cyclization by the intramolecular nucleophilic attack of the relatively harder carbonyl oxygen rather than the nitrogen at the alkyne carbon (the former is harder than the latter) occurs preferentially, together with elimination of AcOH to form a palladium σ-complex. The AcOH added in adjusted amounts (100 mol %) promotes the catalytic cycle by accelerating the formation of **2** and regeneration of the $Pd(OAc)_2$ catalyst from the σ-complex without hydrolysis of **2** formed under the optimized conditions. The existence of the σ-complex is supported by the observation that in the presence of methyl acrylate the reaction yielded the Michael addition product **5**.

In conclusion, we have developed a $Pd(OAc)_2$-catalyzed new, straightforward and highly regio- and stereoselective synthetic method for 4-alkylidene-4*H*-3,1-benzoxazines from readily available *o*-alkynyl-*N*-carboxanilides. A further investigation directed toward the utilization of this reaction and elucidation of the regioselectivity is in progress.

Supporting Information Available. Typical experimental procedure, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.