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A Simple Synthesis of 2-Substituted-4*H*-3,1-benzoxazin-4-ones by Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines with Acid Chlorides

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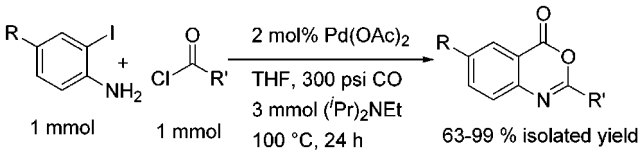
ABSTRACT



One-pot reaction of *o*-iodoanilines with acid chlorides and carbon monoxide, in the presence of a palladium catalyst and diisopropylethylamine, regioselectively affords 2-substituted-4*H*-3,1-benzoxazin-4-ones in good to excellent yields. The reaction is believed to proceed via in situ amide formation from an *o*-iodoaniline and an acid chloride, followed by oxidative addition to Pd(0), CO insertion, and intramolecular cyclization to form the 2-substituted-4*H*-3,1-benzoxazin-4-one derivatives.

4*H*-3,1-Benzoxazin-4-ones (acylanthranils) are a class of fused heterocycles of considerable interest owing to their biological activity.[1] Indeed some of these compounds act as chymotrypsin inactivators,[1a] inhibitors of human leukocyte elastase,[1b,c] serine protease,[1d] and 2-aryl derivatives have the ability to lower the concentration of plasma cholesterol and triglyceride.[1e] Moreover, 2-substituted-4*H*-3,1-benzoxazin-4-ones were reported to be used as precursors for the preparation of pharmaceutically active compounds such as antimicrobial agents (*N*-substituted-quinazolin-4-one derivatives)[2] and analgesics (4-hydroxy-3-quinoline-carboxamides).[3] Several methods have been reported for the preparation of 2-substituted-4*H*-3,1-benzoxazin-4-ones.[4] The most popular synthetic pathways involve the use of anthranilic acid or its derivatives,[5] *N*-acylanthranilic acids,[6] or isatonic anhydride.[7] Other synthetic methods such as oxidation of indoles,[8] [4 + 2] cycloaddition of 1,2,3-benzotriazin-

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(6) (a) Zentmyer, D. T.; Wagner, E. C. *J. Org. Chem.* **1949**, *14*, 967. (b) Balsubramaniyan, V.; Argade, N. P. *Tetrahedron Lett.* **1986**, *27*, 2487. (c) Papadopoulos, E. P.; Torres, C. D. *Heterocycles* **1982**, *19*, 1039. (d) Papadopoulos, E. P.; Torres, C. D. *J. Heterocycl. Chem.* **1982**, *19*, 269.

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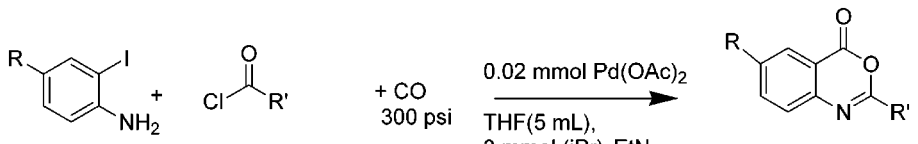
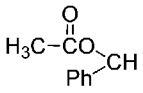
Table 1. Cyclocarbonylation of *o*-Iodoanilines (**1**) with Acid Chlorides (**2**) Catalyzed by Palladium Acetate[a]



1, 1 mmol
1a, R =H, **1b**, R = Cl
1c, R =CH_3, **1d**, R = OH
1e, R =CN

2, 1 mmol

3

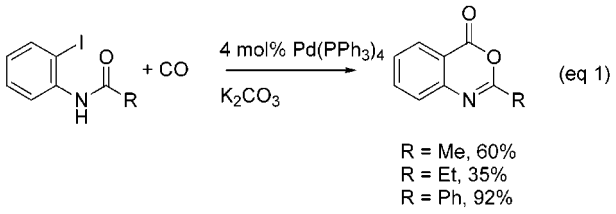
entry	**1**	R'COCl, **2**, R' =		product	isolated yield[b] (%)
1	**1a**	CH_3	**2a**	**3a**	99[c]
2	**1a**	$(Ph)_2CH$	**2b**	**3b**	90
3	**1b**		**2b**	**3c**	96
4	**1c**		**2b**	**3d**	94
5	**1d**		**2b**	**3e**	94
6	**1e**		**2b**	**3f**	80
7	**1a**	$PhCH_2$	**2c**	**3g**	63
8	**1c**		**2c**	**3h**	81
9	**1b**	*p*-$ClC_6H_4CH_2$	**2d**	**3i**	67
10	**1c**		**2d**	**3j**	71
11	**1a**	$Ph(CH_3CH_2)CH$	**2e**	**3k**	95
12	**1b**		**2e**	**3l**	94
13	**1e**		**2e**	**3m**	86
14	**1b**		**2f**	**3n**	95
15	**1c**		**2f**	**3o**	91
16	**1a**	$PhSCH_2$	**2g**	**3p**	80
17	**1c**		**2g**	**3q**	91
18	**1a**	Ph	**2h**	**3r**	98
19	**1c**	o-$CH_3OC_6H_4$	**2i**	**3s**	89
20	**1a**	PhCH=CH	**2j**	**3t**	98
21	**1a**	t-Bu	**2k**	**3u**	98

[a] All reactions were conducted in THF (5 mL) using **1** (1 mmol), **2** (1 mmol), $(i\text{-Pr})_2NEt$ (3 mmol), $Pd(OAc)_2$ (0.02 mmol), and 300 psi of CO, at 100 °C for 24 h. [b] Isolated yield following silica gel column chromatography. [c] 0.02 mmol of dppf was used in this reaction.

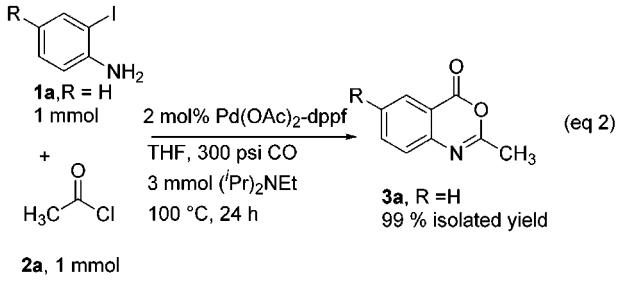
4-ones with benzaldehydes,[9] electrochemical cyclization of *o*-trichloroacetylanilides,[10] and solid-phase synthesis[11] were described.

Two papers have reported the use of palladium-catalyzed carbonylation methodology for the preparation of 2-substituted-4*H*-3,1-benzoxazin-4-ones. For example, thallation and subsequent palladium-catalyzed carbonylation of *N*-acetylaniline[12] and Pd(0)-catalyzed carbonylation of *o*-iodoanilines

with unsaturated halides or triflates have been reported for the synthesis of 2-substituted-4*H*-3,1-benzoxazin-4-ones.[13] In the latter publication, the authors observed that *o*-acylamidoiodobenzene can undergo annulation to give 2-substituted-4*H*-3,1-benzoxazin-4-ones in the presence of K_2CO_3 and 4 mol % of $Pd(PPh_3)_4$ under an atmosphere of carbon monoxide (eq 1).



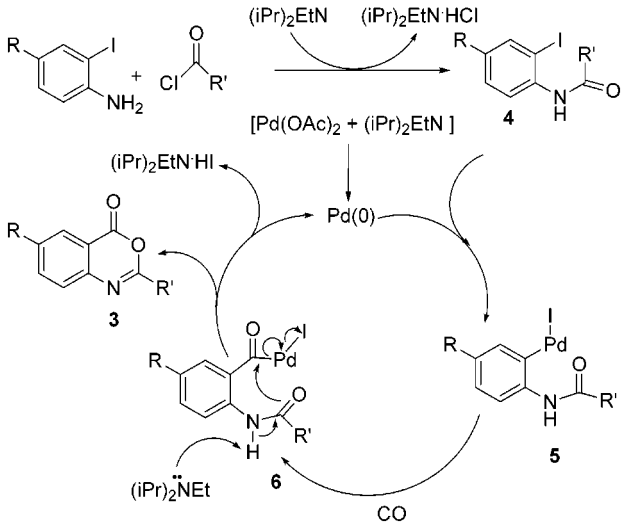
We envisioned that the cyclocarbonylation would be accessible by directly using *o*-iodoaniline and acid chlorides in the reaction under carbon monoxide pressure in the presence of base and palladium catalyst. Therefore, we initiated our investigation by using a mixture of *o*-iodoaniline (**1a,** R = H), 1 equiv of acetyl chloride (**2a**), 300 psi of CO, 3 equiv of $(^iPr)_2NEt$, and 2 mol % of $Pd(OAc)_2$-1,1′-bis-(diphenylphosphino)ferrocene (dppf) in THF, and after 24 h at 100 °C **3a** was isolated in 99% yield (eq 2). This encouraging result led us to examine the one-pot three-component reaction for the formation of the pharmaceutically interesting 2-substituted-4*H*-3,1-benzoxazin-4-ones (**3**) by palladium-catalyzed cyclocarbonylation reactions of *o*-iodoanilines (**1**) with a variety of acid chlorides (**2**). Herein we wish to report the results from this investigation.



Treatment of *o*-iodoanilines (**1**) with carbon monoxide and a variety of acid chlorides (**2**) in the presence of 2 mol % of $Pd(OAc)_2$ in THF at 100 °C afforded 2-substituted-4*H*-3,1-benzoxazin-4-ones (**3**) in good to excellent yields (Table 1).[14] A phosphine ligand is not necessary for this reaction, e.g., reactions of *o*-iodoanilines (**1a**−**c**) with diphenylacetyl chloride using 2 mol % of $Pd(OAc)_2$ and dppf in THF at 100 °C under 300 psi of CO for 24 h resulted in the formation of **3b**, **3c**, and **3d** in 88, 94, and 90% yields, respectively. Without dppf, the yields were 90, 96, and 94% (entries 2−4). The palladium catalyst is needed to form the desired product as the corresponding amide was formed in 96% yield from the reaction of **1a** with **2b** in THF under 300 psi of CO in the absence of $Pd(OAc)_2$. Both electron rich and electron poor *o*-iodoanilines reacted with acid chlorides to form 2-substituted-4*H*-3,1-benzoxazin-4-ones in fine yields. This annulation process tolerates nitrile as well as hydroxyl substituents on the *o*-iodoaniline (entries 5, 6, and 13). In general using α-di- or trisubstituted acid chlorides affords better product yields (entries 2−6, 11−15, 18, 19, and 21) compared to those of the α-monosubstituted analogues (entries 7−10, 16, and 17). When cinnamoyl chloride (**2j**) was used for the palladium-catalyzed cyclocarbonylation reaction with **1a**, 2-styryl-4*H*-3,1-benzoxazin-4-one **3t** having the *E* configuration was isolated in excellent yield (entry 20). These results demonstrate the superiority of this method in comparison to previously reported Pd-based syntheses of **3,** e.g., **3a** was formed in 99% while 40 and 60% yields of **3a** were obtained from the thallation−palladium carbonylation of *N*-acetylaniline[12] and Pd(0)-catalyzed carbonylation of *N*-acetyl-*o*-iodoaniline,[13] respectively. In addition, **3s** was isolated in 89% yield while the yield of a similar compound, 2-(*o*-methoxyphenyl)-4*H*-3,1-benzoxazin-4-one, was 29% by Pd(0)-catalyzed carbonylation of *o*-methoxyiodobenzene with *o*-iodoaniline; also **3t** was obtained in 98% yield by following the reaction described herein while the yields were only 41 and 47% when *β*-bromostyrene and *o*-iodoaniline were subjected to carbonylation.[13]

The cyclocarbonylation reaction appears to proceed via in situ formation of amide (**4**) from the reaction of *o*-iodoanilines with acid chlorides in the presence of base. Oxidative addition of **4** to the in situ generated palladium-(0) species[15] leads to complex **5**. Carbon monoxide insertion into the aryl carbon−palladium bond of **5** would afford the aroylpalladium iodide complex **6**. Cyclization is presumably facilitated by a deprotonation of the amide proton (or the

Scheme 1



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proton of the enol tautomer of **6**) by diisopropylethylamine to give the desired product with regeneration of palladium(0) (Scheme 1).

In conclusion, we have demonstrated that 2-substituted-4*H*-3,1-benzoxazin-4-one derivatives can be easily synthesized by reaction of *o*-iodoanilines, acid chlorides, and carbon monoxide in the presence of a palladium catalyst and diisopropylethylamine. The present methodology is a versatile synthetic approach for the one-pot three-component reaction leading to 2-substituted-4*H*-3,1-benzoxazin-4-ones.

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Supporting Information Available: General experimental procedures for the carbonylation reactions and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The following general procedure was used: a mixture of **1** (1 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.02 mmol), $(i\text{-}Pr)_2NEt$ (3.0 mmol), and dry THF (5.0 mL) was reacted in an autoclave at 300 psi of carbon monoxide for 24 h at 100 °C. The reaction mixture was cooled to room temperature, and excess carbon monoxide was released. The reaction mixture was filtered, and the filtrate was concentrated by rotary evaporation. The residue was purified by silica gel column chromatography using 1:1 ether:*n*-pentane as the eluant.

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