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COPPER-CATALYZED *N*-ARYLATION OF 2-OXAZOLIDINONES. AN EXPEDITIOUS ROUTE TO TOLOXATONE

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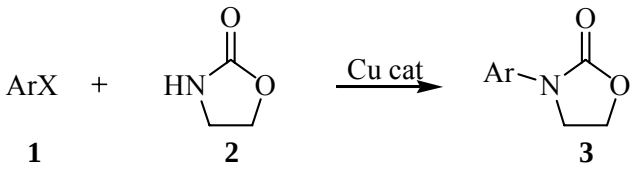
Abstract – 3-Aryl-2-oxazolidinones are obtained in excellent yields through the copper-catalyzed *N*-arylation of 2-oxazolidinones with a variety of aryl iodides. With aryl halides containing both iodo and bromo substituents, a high C-I/C-Br selectivity can be achieved. The procedure has been successfully applied to the preparation of a key intermediate in the synthesis of linezolid and to develop an expeditious route to toloxatone.

3-Aryl- and heteroaryl-2-oxazolidinones are important pharmacologically active compounds and because of this they have attracted much attention of late. For example, 5-acetamidomethyl-3-aryl-2-oxazolidinones have been shown to exhibit a potent antibacterial activity,[1] 3-(1*H*-pyrrol-1-yl)-2-oxazolidinones are reversible, highly potent, and selective inhibitors of monoamine oxidase type A,[2] and 5-hydroxymethyl-3-(3-methylphenyl)-2-oxazolidinone is a drug used as antidepressant.[3]

Recently, we reported a simple and versatile synthesis of this class of compounds[4] that compares well with known procedures.[1e,5] Indeed, 3-aryl-2-oxazolidinones are prepared, usually in good to high yields, through the palladium-catalyzed reaction of a variety of neutral, electron-poor and electron-rich aryl bromides with 2-oxazolidinones.

The reaction, however, appears to be influenced by steric effects. For example, low yields or trace amounts of the desired products were obtained with aryl bromides containing substituents close to the oxidative addition site. To remove this drawback and widen the scope of our procedure, we decided to explore new reaction conditions. In particular, encouraged by the recent renewed interest in copper-catalyzed reactions[6] and by the work of Buchwald using amine ligands to facilitate the *N*-arylation of amides,[6l] we investigated the copper-catalyzed coupling of 2-oxazolidinone with aryl halides (Scheme 1). We report here the results of this study.



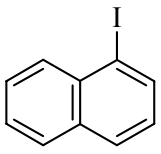
1 **2** **3**

Scheme 1

Initial attempts were made by using *m*-bromoanisole and 1.2 equiv of 2-oxazolidinone (**2**) as the model system in the presence of commercially available CuI and (±)-*trans*-cyclohexanediamine with a variety of carbonate bases and K_3PO_4 in dioxane at 110 °C. However, unsatisfactory results were always obtained. Only after switching to *m*-iodoanisole did the reaction produced the desired product in 94 % isolated yield in 2 h [CuI (5 mol %), (±)-*trans*- cyclohexanediamine (10 mol %), K_3PO_4 (2 equiv), dioxane, 110 °C]. Therefore, these conditions were subsequently applied to a variety of aryl iodides.

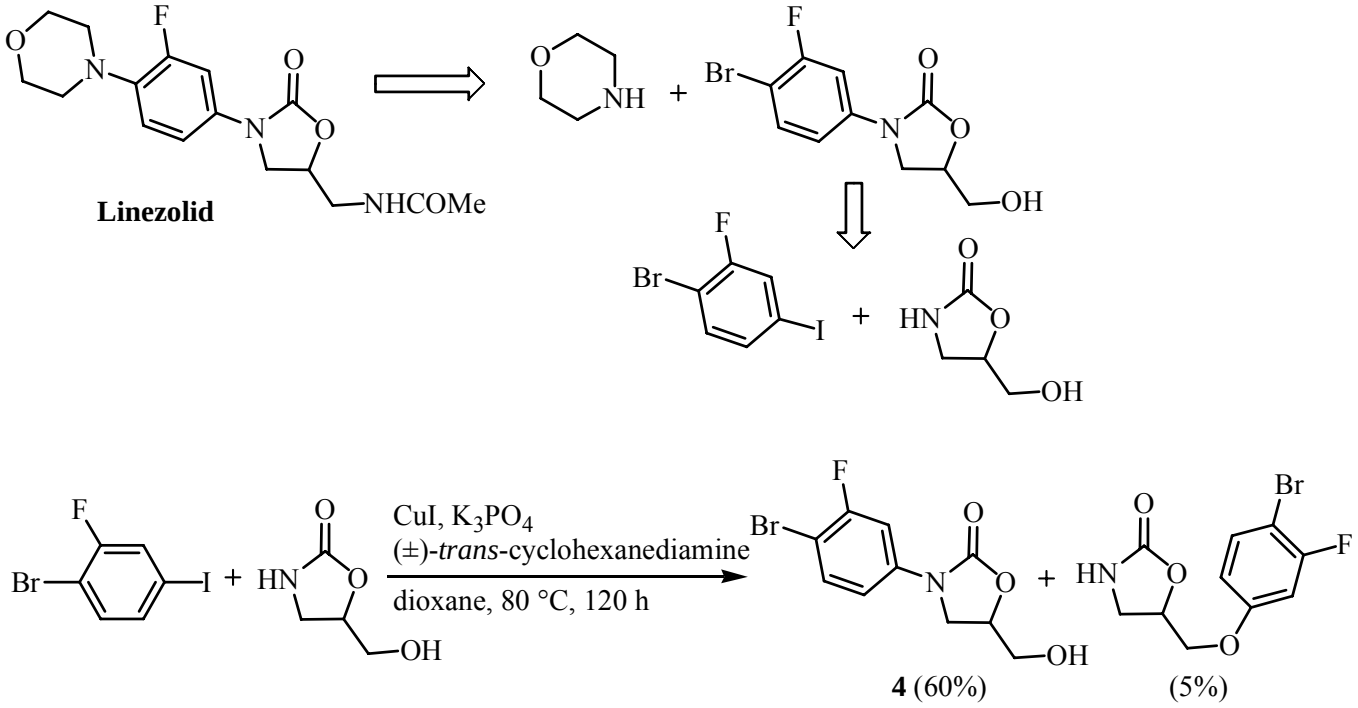
As shown in Table 1, 3-aryl-2-oxazolidinones were isolated in excellent yields with neutral, electron-rich and electron-poor aryl iodides. The presence of substituents close to the carbon-iodo bond does not hamper the reaction (our original task) (Table 1, entries 3, 4, 5, 11, 15). With aryl iodides containing bromo substituents, competitive *N*-arylation involving the C-Br bond may be observed. For example, 1-bromo-4-iodobenzene produced 9 % of 3-(*p*-iodophenyl)-2-oxazolidinone (Table 1, entry 6). Lowering the reaction temperature to 80 °C, however, led to a high C-I/C-Br selectivity and, though longer reaction times were observed, none of this product was observed (Table 1, entry 7).

Table 1. Copper-Catalyzed *N*-Arylation of 2-Oxazolidinone (**2**).[a]

entry	aryl iodide (**1**)	t (h)	yield% of (**3**)		entry	aryl iodide (**1**)	t (h)	yield% of **3**	
1	*p*-MeO-C_6H_4-I	2.5	97	**3a**	8	*p*-Cl-C_6H_4-I	5	96	**3g**
2	*m*-MeO-C_6H_4-I	2	94	**3b**	9	*p*-F-C_6H_4-I	4	90	**3h**
3	*o*-MeO-C_6H_4-I	10	93	**3c**	10	*m*-F-C_6H_4-I	6	89	**3i**
4	*o*-Me-C_6H_4-I[b]	48	86	**3d**	11	*o*-F-C_6H_4-I	3.5	91	**3j**
					12	*m*-CF_3-C_6H_4-I	4.5	92	**3k**
5		24	90	**3e**	13	*p*-MeOC-C_6H_4-I	5	92	**3l**
					14	*p*-EtOOC-C_6H_4-I	3	95	**3m**
6	*p*-Br-C_6H_4-I	8	67[c]	**3f**	15	*o*-MeOOC-C_6H_4-I	4.5	70	**3n**
7	*p*-Br-C_6H_4-I[d]	120	88	**3f**	16	*p*-NO_2-C_6H_4-I	5	93	**3o**

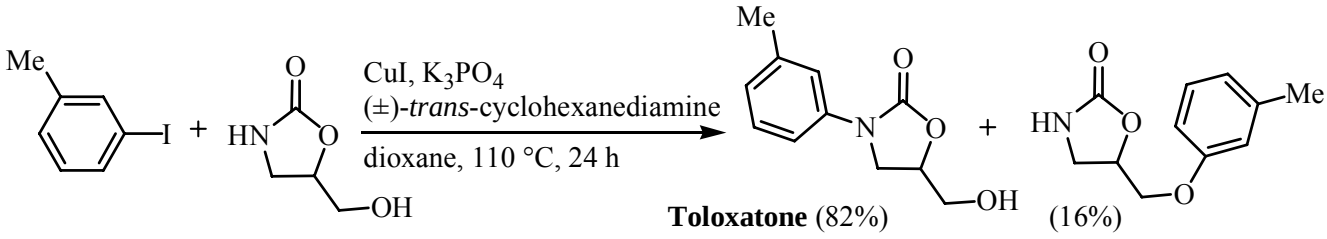
[a] Unless otherwise stated, reactions were carried out by using 1 equiv. of aryl iodide, 1.2 equiv. of 2-oxazolidinone, 5 mol % of CuI, 10 mol % of (±)-*trans*-cyclohexanediamine, 2 equiv. of K_3PO_4 in dioxane at 110 °C. [b] 10 mol % of CuI, 120 °C. [c] 3-(*p*-iodophenyl)oxazolidinone was isolated in 9% yield. [d] 80 °C.

The high C-I/C-Br selectivity achieved with 1-bromo-4-iodobenzene prompted us to develop an expeditious approach to the synthesis of the *N*-aryl derivative (**4**), a strategic intermediate in the synthesis of linezolid (a member of a new class of antibiotics),[7] from racemic 5-hydroxymethyl-2-oxazolidinone[8] and commercially available 1-bromo-2-fluoro-4-iodobenzene (Scheme 2). The alcohol was not protected and compound (**4**) was isolated in good yield under unoptimized conditions.



Scheme 2. Synthesis of a Linezolid Intermediate.

This protocol was also applied to the synthesis of toloxatone (Scheme 3).



Scheme 3

While this manuscript was in preparation, a similar synthesis of 3-aryl-2-oxazolidinones appeared that uses recrystallized CuI.[9] Under these conditions, aryl bromides can be used as aryl donors. However, the syntheses of toloxatone and linezolid require a protection/deprotection protocol for the alcohol that may lead to lower yields. For example, toloxatone was isolated in 40% overall yield in two 2 steps from *m*-bromotoluene and the tetrahydropyran derivative of 5-hydroxymethyl-2-oxazolidinone.

To sum up, we have developed a convenient and straightforward procedure for the preparation of 3-aryl-2-oxazolidinones. The method shows a high substrate generality: excellent yields are obtained with neutral, electron-rich and electron-poor aryl iodides and the presence of substituents close to the carbon-iodo bond does not hamper the reaction. A high C-I/C-Br selectivity can be achieved with aryl halides containing both iodo and bromo substituents. The preparation of a key intermediate in the synthesis of linezolid and the synthesis of toloxatone from 5-hydroxymethyl-2-oxazolidinone according to the procedure developed do not require the protection and deprotection of the alcohol.

EXPERIMENTAL

Melting points are uncorrected. Aryl iodides, dioxane, CuI, K_3PO_4, and (±)-*trans*-cyclohexanediamine are commercially available and were used as purchased, without further purification. Racemic 5-hydroxymethyl-2-oxazolidinone was prepared according to ref. 8. Reaction products were purified on axially compressed columns, packed with SiO_2 25-40 μm, connected to a solvent delivery system and to a refractive index detector, and eluting with n-hexane/ethyl acetate mixtures. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 100.6 MHz (in $CDCl_3$, unless otherwise stated).

Typical Procedure for the Preparation of 3-Aryl-2-oxazolidinones (3): In a Carousel Tube Reaction (Radley Discovery), to a solution of 2-iodoanisole (175.5 mg, 0.750 mmol) and 2-oxazolidinone (78.4 mg, 0.9 mmol) in 2 mL of 1,4-dioxane, CuI (7.1 mg, 0.038 mmol), (±)-*trans*-cyclohexanediamine (9 μL, 0.075 mmol), K_3PO_4 (318.4 mg, 0.15 mmol) were added. The mixture was warmed under argon at 110 °C and stirred for 10 h. After cooling, the reaction mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified by chromatography (silica gel, 35 g; *n*-hexane/ethylacetate 60/40 v/v) to give 135.7 mg (93 %) of **3c**: oil; IR (neat) 1734 cm^{-1}; ^{1}H NMR δ 7.38 (dd, J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1 H), 7.31-7.27 (m, 1 H), 7.03-6.96 (m, 2 H), 4.52-4.47 (m, 2 H), 4.02-3.97(m, 2 H), 3.9 (s, 3 H); ^{13}C NMR δ 157.5, 155.0, 129.0, 128.5, 126.1, 121.1, 112.1, 62.5, 55.7, 47.1; Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7,25. Found: C, 62.3; H, 5.8; N, 7.3.

3a: mp 107-108 °C (methanol); IR (KBr) 1721 cm^{-1}; ^{1}H NMR δ 7.43 (d, J = 9.1 Hz, 2 H), 6.91 (d J = 9.1 Hz, 2 H), 4.48-4.42 (m, 2 H), 4.03-3.99 (m, 2 H), 3.80 (s, 3 H); ^{13}C NMR δ 156. 8, 156.0, 131.9, 120.7, 114.7, 61.7, 55.9, 46.1; Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.2; H, 5.8; N, 7.1.

3b: mp 73-74 °C (*n*-hexane/dichloromethane); lit.,[4] mp 73-74°C.

3c: oil; IR (neat) 1734 cm^{-1}; ^{1}H NMR δ 7.38 (dd, J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1 H), 7.31-7.27 (m, 1 H),

7.03-6.96 (m, 2 H), 4.52-4.47 (m, 2 H), 4.02-3.97(m, 2 H), 3.9 (s, 3 H); ^{13}C NMR δ 157.5, 155.0, 129.0, 128.5, 126.1, 121.1, 112.1, 62.5, 55.7, 47.1; Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.3; H, 5.8; N, 7.3.

3d: oil; IR (neat) 1728 cm^{-1}; ^{1}H NMR δ 7.30-7.23 (m, 4 H), 4.55-4.48 (m, 2 H), 3.97-3.91 (m, 2 H), 2.33 (s, 3 H); ^{13}C NMR δ 156.9, 136.1, 131.5, 128.3, 127.1, 126.6, 62.4, 48.0, 18.0; Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.9; H, 6.3 ; N, 7.8.

3e: 233-234 °C (methanol); lit.,[4] mp 233-234 °C.

3f: mp 132-133 °C (methanol); IR (KBr) 1741 cm^{-1}; ^{1}H NMR δ 7.50-7.27 (m, 4 H), 4.51-4.46 (m, 2 H), 4.05-4.00 (m, 2 H); ^{13}C NMR δ 155.1, 137.5, 132.1, 119.7, 116.9, 61.3, 45.1; Anal. Calcd for $C_9H_8NO_2Br$: C, 44.66; H, 3.33; N, 5.79. Found: C, 44.7; H, 5.6; N, 7.3.

3g: mp 117-118 °C (methanol); IR (KBr) 1744 cm^{-1}; ^{1}H NMR δ 7.50 (d, *J* = 9.1 Hz, 2 H), 7.34 (d, *J* = 9.1 Hz, 2 H), 4.52-4.46 (m, 2 H), 4.06-4.00 (m, 2 H); ^{13}C NMR δ 155.2, 137.0, 129.3, 129.1, 119.4, 61.4, 45.2; Anal. Calcd for $C_9H_8NO_2Cl$: C, 54.70; H, 4.08; N, 7.09. Found: C, 54.6; H, 4.2; N, 7.0.

3h: mp 71-72 °C (*n*-hexane/dichloromethane); lit.,[4] mp 71-72 °C.

3i: mp 87-88 °C (*n*-hexane/dichloromethane); lit.,[4] mp 87-88 °C.

3j: mp 84-85 °C (*n*-hexane/dichloromethane); IR (KBr) 1746 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.53 (dt, J = 7.5 Hz, J_2 = 1.6 Hz, 1 H), 7.29-7.11 (m, 3 H), 4.52-4.48 (m, 2 H), 4.09-4.04 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 157.0 (d, *J* =250.5 Hz), 156.6, 128.4 (d, *J* = 8 Hz), 127.2 (d, *J* = 1.4 Hz), 125.5 (d, *J* = 11.0), 124.8 (d, *J* = 3.6 Hz), 116.7 (d, *J* = 19.9 Hz), 62.6, 47.1; ^{19}F NMR {H}(DMSO-d_6) δ -121.43; Anal. Calcd for $C_9H_8NO_2F$: C, 59.67; H, 4.45; N, 7.73. Found: C, 59.5; H, 4.5; N, 7.6.

3k: mp 52-53 °C (*n*-hexane/dichloromethane); lit.,[4] mp 52-53 °C.

3l: mp 146-147 °C (methanol); lit.,[4] mp 146-147 °C.

3m: mp114-115 °C (ethanol); IR (KBr) 1743, 1697 cm^{-1}; ^{1}H NMR δ 8.06 (d, *J* = 9.4 Hz, 2 H), 7.63 (d, *J* = 9.4 Hz, 2 H),4.6-4.49 (m, 2 H), 4.38 (q, *J* = 7.1 Hz, 2 H9, 4.13-4.07 (m, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR δ 166.1, 155.3, 142.2, 130.8, 125.8, 117.2, 61.4, 61.0, 45.0, 14.4; Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.3; H, 5.6; N, 6.0.

3n: oil; IR (neat) 1753, cm^{-1}; ^{1}H NMR δ 7.96-7.92 (m, 1 H) 7.56-7.52 (m, 1 H), 7.39-7.36 (m, 1 H), 7.32-7.29 (m, 1 H), 4.53-4.48 (m, 2 H) 4.05-4.00 (m, 2 H), 3.88 (s, 3 H); ^{13}C NMR δ 166.2, 157.2, 137.5, 133.1, 131.5, 127.9, 127.6, 127.5, 62.6, 52.4, 48.1; Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found C, 59.8; H, 5.0; N, 6.4.

3o: mp 153-154 °C (ethanol); lit.,[4] mp 153-154 °C.

4: mp 108-109 °C (ethanol); IR (KBr) 3394, 1724 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.82-7.65 (m, 2 H), 7.36 (dd, J_1 = 8.9 Hz, J_2 = 2.6 Hz, 1 H), 5.22 (t, *J* = 5.59 Hz, 1 H), 4.74-4.70 (m, 1 H), 3.86-3.81 (m, 1 H),

3.72-3.65 (m, 1 H), 3.60-3.53 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 158.8 (d, J = 242.5), 154.8, 140.3 (d, J = 10.0 Hz), 134.0, 115.6 (d, J = 3.0 Hz), 106.6 (d, J = 27.9 Hz), 101.6 (d, J = 21.0 Hz), 74.0, 62.1, 46.5; ^{19}F NMR {H} (DMSO-d_6) δ -107.3. Anal Calcd for $C_{10}H_9NO_3BrF$: C, 41.40; H, 3.13; N, 4.83. Found C, 41.3; H, 3.0; N, 4.7.

Toloxatone: mp 75-76 °C (methanol); lit.,[3a] mp 76 °C.

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