Chemoselective Access to π-Conjugated Heterocycles by Stille and Sonogashira Reactions on 2-Substituted 4H-pyrido[e][1,3]oxazin-4-ones

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Abstract: Site-selective Pd(II) catalyzed cross-coupling reactions have been developed on 2-substituted-4*H*-pyrido[*e*][1,3]oxazin-4-ones. C^4- and C^5-alkynylated pyridooxazinones have been thus obtained *via* Sonogashira reaction while the efficient incorporation at C^5 position of (hetero)aryl, ethenyl substituents have been achieved *via* Stille reaction. Finally one example of a one pot sequential multiple Sonogashira reaction with different alkynes has been realized. The strategy developed herein provides a rapid access to polyfunctionnalized precursors with extended π-conjugation for further application as fluorescent material.

Introduction

In the past two decades, many heteroaroamatic scaffolds functionalized with alkynyl or alkenyl groups have been reported to provide synthetically useful precursors for biologically active compounds,[1] fluorescent functional materials[2] and electronic and optoelectronic devices.[3] Among them, π-conjugated systems containing a triazine or a triazole central core have been reported to possess high luminescence and photoluminescence properties providing powerful molecules for nonlinear optics applications. (Figure 1).[4]
In the meantime, we have recently reported the first synthesis[5] of 2-substituted 4*H*-pyrido[*e*][1,3]oxazin-4-ones **1** which have been identified in 2009[6] from a calculation study within a list of hundred virtually generated heteroaromatic bicyclic ring systems as a new and original chemical series with potential medicinal interest.[7] We have also reported full studies on the preparation of halogen-containing 4*H*-pyrido[*e*][1,3]oxazin-4-ones and their transformations into original hydroxypyridinyl-substituted 1,2,4-oxadiazoles, 1,2,4-triazoles and 1,3,5 triazines (Scheme 1).[8] The synthesis of π-conjugated molecules containing these new classes of compounds may represent an attractive way for the development of new fluorescent dyes for bioanalysis and material sciences

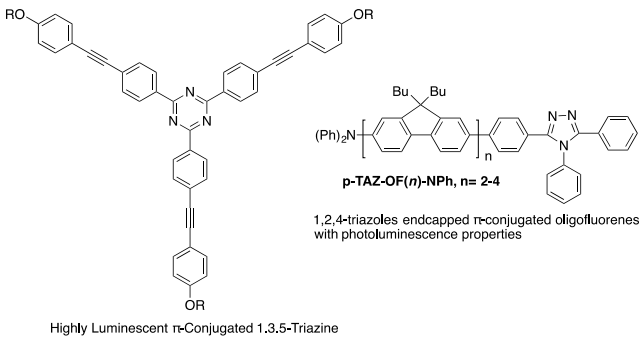
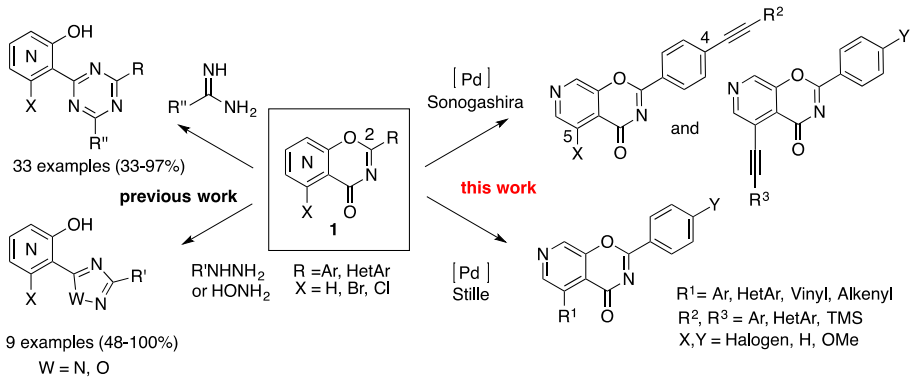


Figure 1. Examples of reported π-conjugated heteroaromatic scaffolds with luminescence or optical properties.

The 4*H*-pyrido[*e*][1,3]oxazin-4-ones **1** with extended π-conjugation systems could be considered as potential original precursors for the preparation of fluorescent probes. Organometallic cross coupling reactions such as Stille, Sonogashira or Suzuki reactions are the most straightforward methods to introduce alkynyl or/ and alkenyl functions onto (hetero)aromatic scaffolds.[9] Furthermore, chemoselective cross coupling reactions involving different halide in a molecule may be considered as the most powerful tools for the access to polyunsaturated heterocycles.[10] Consequently, the development of efficient and selective strategies for the installation of different sp^2-substituents on the pyridooxazinones to extend π-conjugation has attracted our attention.



Scheme 1. Previous and current works on the transformations of 4*H*-pyrido[*e*][1,3]oxazin-4-ones.

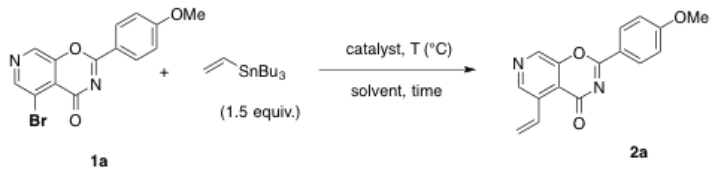
Herein, we report chemoselective examples of C-C bond formation on 4*H*-pyrido[*e*][1,3]oxazin-4-ones at C^5 on the pyridine ring and C^4 on the phenyl group using standard Sonogashira and Stille reaction conditions (Scheme 1).

Results and Discussion

First, arylation and alkenylation on pyridooxazinones using both the Suzuki-Miyaura or Heck reaction conditions with various boronic acids or with ethyl acrylate as a coupling partners failed to give the expected coupling products either at the C^5 or C^4 halogenated sites. In these conditions, poor reaction conversion and/or degradation of the starting pyridooxazinones were observed. (See supporting informations for the investigations concerning Suzuki reactions Table S1 and Heck reactions Table S2). Then, we successfully

investigated the Stille reaction conditions[11] using vinyltributyltin with 5-bromopyridooxazinone **1a** as a model.[12] Initial attempts with 10 mol % of $Pd(PPh_3)_4$ as catalyst gave moderate yields (10-37%) in DMF or toluene, even after additional time (Table 1, entry 1-4). Better yields and lower catalytic loading were attained with $PdCl_2(PPh_3)_2$ as precatalyst. Complete conversion was observed after 21 h and the coupling product **2a** was isolated in 60% yield (entry 7).

Table 1. Optimization of Stille reaction with 5-bromopyridooxazinone **1a**.

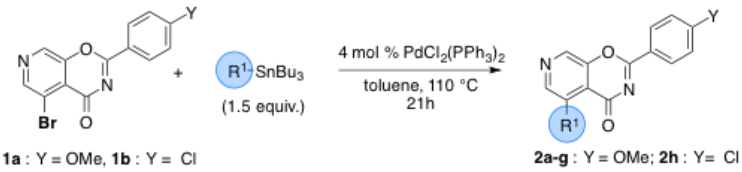


Entry	Catalyst (Mol %)	Solvent	Time (h)	Temp. (°C)	Yield (%)
1	$Pd(PPh_3)_4$ (10)	DMF	2	85	10[a]
2	$Pd(PPh_3)_4$ (10)	DMF	15	85	37[a]
3	$Pd(PPh_3)_4$ (10)	toluene	2	100	21[a]
4	$Pd(PPh_3)_4$ (10)	toluene	15	100	24[a]
5	$PdCl_2(PPh_3)_2$ (4)	toluene	2,5	110	17
6	$PdCl_2(PPh_3)_2$ (4)	toluene	21	110	60

[a].1 equiv. of vinyl$SnBu_3$ was used.

With these optimized conditions in hand, we explored the scope and limitation of this method with 5-bromo-2-(4-methoxyphenyl) pyridooxazinone **1a** using vinyl, aryl (with electron-donating group) and heteroaryl tin derivatives as summarized in Table 2. Excepted for the allyltin derivative producing product **2c** in only 7% yield (Table 2, entry 3), the resulting coupling products **2a-h** were isolated successfully in yields ranging from 55 to 84 % (Table 2, entries 1-8). These moderate yields could be explained by the instability of the final compounds toward potential ring opening during purification steps.

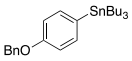
Table 2. Scope of the Stille reaction



1a : Y = OMe, **1b** : Y = Cl

2a-g : Y = OMe; **2h** : Y= Cl

.

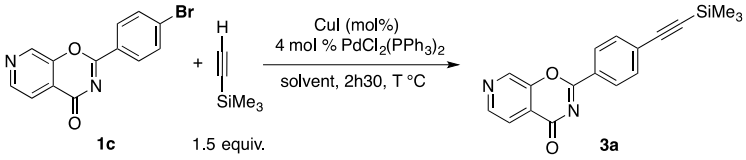
Entry	Y	R^1-$SnBu_3$	**2**	yield (%)[a]
1	OMe		**2a**	60
2	OMe	 (Z,E)	**2b**	67 (Z/E, 82/18)
3	OMe		**2c**	7
4	OMe		**2d**	71
5	OMe		**2e**	84
6	OMe		**2f**	55
7	OMe		**2g**	56
8	Cl		**2h**	54[b]

[a] Total conversion of the reaction, modest yields were due to degradation during the purification [b] The reaction was performed in 11h.

On the other hand, a chemoselective Stille coupling example was achieved starting from a bromo chloro pyridooxazinone precursor **1b**. After 11h, we observed 100% in selectivity for the monosubstituted compound **2h** with 54% isolated yield (Table 2, entry 8). This result may be explained by a lower bond dissociation energy (BDE) of the C-Halogen bond on the pyridine ring (2-8 kcal/mol) than the usual C-Halogen BDE's of six membered ring.[10]

In the second part of our work, we focused on determining the optimized conditions for the Sonogashira reaction with the 2-(4-bromophenyl)pyridooxazinone **1c** as a model. Using 1.5 equivalents of trimethylsilylacetylene, we tested classical reported catalytic system with different amount of CuI and 4 mol% of $Pd(PPh_3)_2Cl_2$, triethylamine as a base, various solvent and temperature.[9a] The results are presented in Table 3. The best conditions were found to be 3 mol % CuI, 4 mol % $Pd(PPh_3)_2Cl_2$, in toluene/ triethylamine: 2/1 as a solvent mixture, at 80°C for 2h30 providing the product **3a** in 74% yield (Table 3, entry 4).

Table 3. Sonogashira reaction of 4-bromophenyl pyridooxazinone **1c** and trimethylsilylacetylene.



Entry	solvent	CuI (mol%)	T (°C)	**3a** (yield %)
1	THF / NEt_3: 2/1	1	120[a]	trace
2	NEt_3	1	80	--[b]
3	Toluene / NEt_3 : 2/1	1	80	42
4	Toluene/ NEt_3 : 2/1	3	80	74

[a] 30 min. under microwave irradiation. [b] Only decomposition of the starting material was observed.

Under the optimized conditions, we next examined the coupling reaction of **1c** with various aryl-, heteroaryl- and alkylacetylenes (Table 4).

Table 4. Sonogashira reaction with terminal acetylenes.

Entry	R^2	**3**	yield (%)
1	TMS	**3a**	74
2	Ph	**3b**	93
3	*p*-NMe_2-Ph	**3c**	quant
4	*p*-F-Ph	**3d**	68
5	CO_2Et	**3e**	--[a]
6	3-pyridyl	**3f**	84

[a] No product was observed only starting material was recovered.

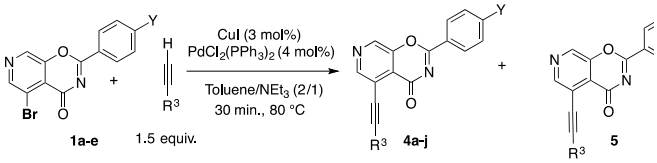
In the selected examples, the coupling reaction with aryl acetylenes bearing no substituents (R^2 = Ph, **3b**), electron donating (R^2 = *p*-NMe_2-Ph, **3c**) or -withdrawing groups (R^2 = *p*-F-Ph, **3d**) on the phenyl ring proceeded in good to excellent yield whatever the nature of the substituent (Table 4, entries 2-4).

Thus, 2-(4-bromophenyl) pyridooxazinone **1c** react efficiently under Sonogashira reaction conditions to afford functionalized pyridoxazinones with various ethynyl substituents at C^4 on the phenyl group. On the contrary, with acetylene bearing ethylpropiolate group, only degradation was observed (Table 4, entry 5).

Finally, coupling reaction with 3-pyridylacetylene provided the corresponding alkynylated product **3f** in 84% isolated yield (Table 4, entry 6).

We next focused our attention on the Sonogashira reaction at C^5 on the pyridine ring of pyridooxazinone. Using the optimized reaction conditions, we examined the reaction with various substituted ethynyl compounds and a range of 5-bromo-2-(4-substituted phenyl)-pyridooxazinones **1** bearing electron donating (*p*-OMe-Ph) as well as withdrawing groups (*p*-F-Ph or *p*-Cl-Ph) (Table 5).

Table 5. Sonogashira reactions of 5-bromo pyridooxazinones derivatives **1a-e**.



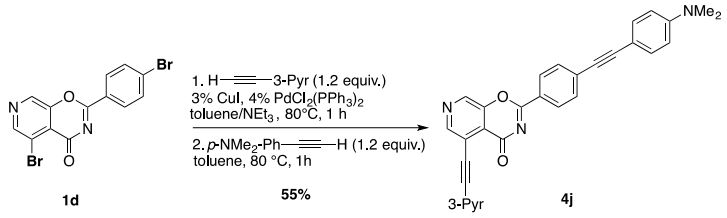
Entry	**1**	Y	R^3	**4** (Yield %)	ratio (**4**:**5**)[a]
1	**1a**	OMe	Ph	**4a** (91)	
2	**1a**	OMe	Me_3Si	**4b** (53)[b]	
3	**1a**	OMe	3-pyridyl	**4c** (82)	
4	**1b**	F	Ph	**4d** (83)	
5	**1b**	F	Me_3Si	**4e** (41)[b]	
6	**1b**	F	3-pyridyl	**4f** (70)	
7	**1d**[c]	Br	Ph	**4g** (nd)[d]	77:23
8	**1d**[e]	Br	Ph	**4g** (nd)[d]	64:36
9	**1d**[e]	Br	Ph	**4g** (nd)[d]	70:30
10	**1d**[f]	Br	Ph	**4g** (nd)[d]	82:18
11	**1e**[e]	Cl	Ph	**4h** (78)	100:0
12	**1e**	Cl	Hexyl	**4i** (64)	100:0

[a] Total conversion, ratio of **4**:**5** determined by crude 1H NMR for entries 7-12. [b] Low yield due to the purification problems [c] Run 5h at 30°C. [d] Inseparable mixture of **4**:**5**, yield not determined but complete conversion observed by NMR. [e] Run 30 min. at 50°C. [f] Run 30 min. at 40°C.

The cross-coupling reaction on the pyridine ring was achieved in 30 min at 80°C. The observed short reaction time was rationalized considering the low value of BDE of the C-Halogen bond on the pyridine ring.[10] In all the cases, complete conversion of the starting material was observed. The best yields of coupling product were obtained with phenylacetylene (Table 5, entries 1, 4 and 11). C^5 alkynylation with trimethylsilyl substituents on the terminal alkynes with both electron-donating (OMe-, Table 5, entries 2) or electron-withdrawing groups (F-, Table 5, entries 5) on the pyridooxazinone scaffold furnished the expected products with lower yields due to the partial degradation of the final products to silica gel during chromatography. As expected, a total chemoselective cross coupling reaction was obtained with the 5-

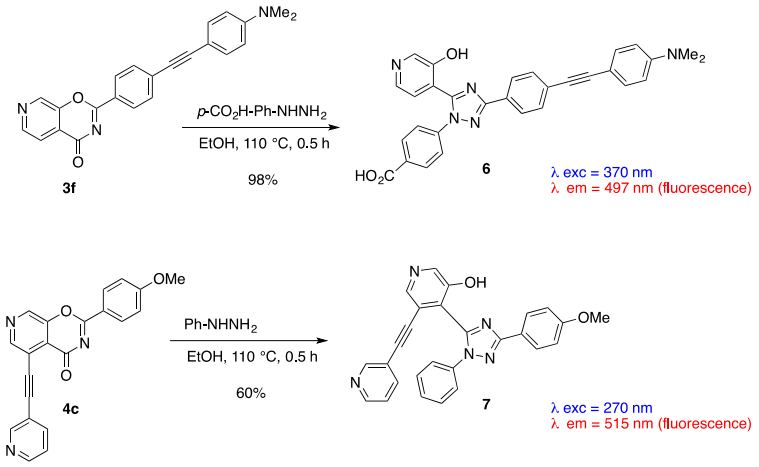
bromo-2-(4-chlorophenyl) pyridooxazinone **1e** (Y = Cl, entries 11 and 12). Based on our understanding of the above results, we considered we were able to discriminate both position even if the same halogen atom was present on the C^5 on pyridine ring and the C^4 on the phenyl ring.

By running the reaction at 30 °C for 5h with phenylacetylene and 5-bromo-2-(4-bromo-phenyl)-pyridooxazinone **1d** as a model system, a mixture of the monosubstituted **4g** and the disubstituted products **5** was obtained with, as expected, a preference for the monosubstitution at the C^5 on the pyridine ring over the C^4 position giving product **4g** as a major product with a ratio of 77:23 (Table 5, entry 7). We conducted investigation to optimize the reaction conditions by varying temperature and time of reaction (Table 5, entries 8-10). Finally, a reaction temperature of 40°C and a reaction time of 30 min. were found to be the best conditions allowing the formation of the monosubstituted product **4g** over the disubstituted product **5** with a ratio of 82/18 **(**Table 5, entry 10). Encouraged by these results, we further realized one pot sequential multiple reactions to functionalize both positions of the pyridooxazinone **1d** with two different alkynes (Scheme 2).[13] Using 1.2 equivalents of 3-ethynyl pyridine at 80 °C for 1h followed by the sequential addition of 1.2 equivalents of 4-dimethylaminophenylacetylene to the reaction mixture, we obtained the bifunctionnalized product **4j** with 55% isolated yield. Traces of disubstituted product **5** (with two 3-pyridylacetylene substituents, See Table 5) were observed and discarded during purification.



Scheme 2. One-pot sequential multiple Sonogashira reactions of dibromo pyridooxazinone 1d with two different alkynes.

With some π-conjugated pyridoxazinones in hand, we have examined their photophysical properties. Unfortunately, none of these structures provided acceptable data to be used as fluorescent dyes. Consequently, to expand the cross coupling reaction utility on pyridooxazinones and developed an easy way to access push-pull systems with fluorescent properties, we have converted following our recent published procedure, [8b] **3f** and **4c** into 2-hydroxy-1-pyridyl substituted 1,2,4-triazoles **6** and **7** respectively, a new type of aza-analogs of reported 1,2,4-triazoles with electroluminescence properties (Scheme 3).[14] The UV-visible absorption and fluorescence spectra were recorded and showed promising fluorescence data in DMSO with a large stoke shift: (λ exc = 370 nm, λ em = 493 nm for triazole **6**, λ exc = 270 nm, λ em = 515 nm for triazole **7**). The development and the evaluation of the fluorescence properties of this class of molecules are now in progress (Scheme 3).



Scheme 3. First fluorescence properties of two specimens of trisubstituted triazoles.

Conclusions

In conclusion, the protocol described in this publication allows the chemoselective incorporation of aryl, heteroaryl, ethenyl and ethynyl substituents into pyridooxazinone rings using classical Sonogashira and Stille reactions conditions. In addition, efficient example of a one-pot sequential multiple reaction via Sonogashira reaction of the dibromo pyridooxazinone **1d** with two different alkynes has been developed. Finally, two specimens of π-conjugated 2-hydroxypyridyl triazoles with promising fluorescent properties have been synthetized from pyridooxazinone scaffold demonstrating the high potential of this original compound to be used as precursors for fluorescent probes.

Experimental Section

Experimental *General method for Stille coupling.*

*2-(4-methoxyphenyl)-5-vinyl-4H-pyrido [4,3-e][1,3] oxazin-4-one **2a***

In a sealed tube, a mixture of 5-Bromo-2-(4-methoxyphenyl)-4H-pyrido[4,3-e][1,3]oxazin-4-one **1a** (89 mg, 0.26 mg, 0.26 mmol), vinyltributytin (127 mg, 117 µL, 0.39 mmol), $PdCl_2(PPh_3)_2$ (7.3 mg, 0.011 mmol) in toluene (3 mL) were degassed for 10 minutes and refluxed for 21h at 110 °C. Upon completion the reaction mixture was transferred in a separating funnel containing 10 mL of a saturated aqueous solution of NH_4Cl and 10 mL of ethylacetate. The two phases were decanted and separated. The aqueous layer was extracted with EtOAc (2x10 mL). The combined organic layers were washed 3 times with 1M KF aqueous solution, followed by water (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified on silica gel (petroleum ether/ EtOAc : 4/6) and triturated with ether, filtered and dried under vacuum to provide the desired compound **2a** in 56% yield (0.042g) ; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.81 (bs, 1H), 8.79 (bs, 1H), 8.30 (d, *J*= 6.8, 2H), 7.90 (dd, *J*= 17.6, 10.8, 1H), 7.00 (d, *J*= 8.8, 2H), 5.84 (dd, *J*= 17.6, 1.2, 1H), 5.57 (dd, J= 10.8, 1.2, 1H), 3.85 (s, 3H); JMOD ^{13}C NMR (100MHz, $CDCl_3$) δ 165.9, 165.2, 163.2, 150.6, 145.3, 139.3, 133.3, 132.0 (2C), 121.0, 120.4 (2C), 119.7, 114.6 (2C), 55.8; IR (film, cm^{-1}) 1691, 1598, 1570, 1548, 1512, 1465, 1427, 1338, 1303, 1271, 1238, 1207, 1168, 1060, 1010, 977, 939, 837, 748; mass spectrum ESI+ m/z 303.0751 [$C_{16}H_{12}NaN_2O_3$ (M+Na) require 303.0740]; mp 201-203°C

General method for Sonogashira coupling

*2-(4-trimethylsilanylethynyl-phenyl)-pyrido[4,3-e][1,3] oxazin-4-one (**3a**)*

In a microwave tube, under Argon, were added CuI (1.7 mg, 3 mol%), $PdCl_2PPh_3$ (9 mg, 4 mol%), 2-(4-bromophenyl)-4H-pyrido [4,3-e][1,3]oxazin-4-one **1c** (91 mg, 0.3 mmol), toluene (1.2 mL) and NEt_3 (0.6 mL) previously degassed. The reaction mixture was degassed for 10 min and trimethylsilylacetylene (63 µL, 0.45 mmol) was added. The vial was sealed and heated at 80 °C until completion of the reaction followed

by ^{1}H NMR. The resulting mixture was filtered on celite and washed with AcOEt (3x2 mL) and CH_2Cl_2 (2 mL). The organic filtrate was washed with water (3x6 mL) and dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was solubilized in CH_2Cl_2, precipated in pentane and filtered. The title compound was more specifically purified on silica gel eluting with EtOAc/ petroleum ether : 60/40 to yield to 71 mg (74%) of the corresponding final compound **3a** as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1 H), 8.77 (d, *J* = 5.2 Hz, 1 H), 8.34 (d, *J* = 8.7 Hz, 2 H), 7.99 (d, *J* = 5.2 Hz, 1 H), 7.63 (d, *J* = 8.7 Hz, 2 H), 0.27 (s, 9H); JMOD ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 163.6, 150.3, 147.8, 140.9, 132.6 (2 C), 129.9, 129.6 (2 C), 128.7, 123.4, 119.7, 103.8, 100.1, -0.09 (3C); IR (film, cm^{-1}) 2955 (bs), 2897, 2159, 1683, 1600, 1561, 1543, 1423, 1346, 1245, 842, 796, 757, 751; mass spectrum ESI+ *m/z* 343.0870 [$C_{18}H_{16}N_2O_2SiNa$ (M+Na) requires 343.0873]; mp 216-218 °C.

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Keywords: Cross-coupling • Fluorescent probes • Heterocycles • Homogeneous catalysis • Palladium

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