Tetrahedron Letters 52 (2011) 523–525

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Reactivity and regioselectivity in Stille couplings of 3-substituted 2,4-dichloropyridines

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ARTICLE INFO

Article history:
Received 28 September 2010
Revised 11 November 2010
Accepted 19 November 2010
Available online 24 November 2010

Keywords:
Pyridine
Regioselectivity
Substituent effect
Stille coupling

ABSTRACT

The influence of substituents at C-3 of 2,4-dichloropyridines on their reactivity and regioselectivity in Pd-catalyzed cross-couplings is studied. As a model reaction, the $(Ph_3P)_2PdCl_2$-catalyzed Stille coupling between 2-furyl(tributyl)tin and pyridines is chosen. Increased electron-withdrawing ability of a substituent at the pyridine 3-position improves the overall reactivity. Absolute selectivity for coupling at C-2 is achieved with an amino group at C-3, and the selectivity is totally reversed when the amino group is exchanged for a nitro substituent.

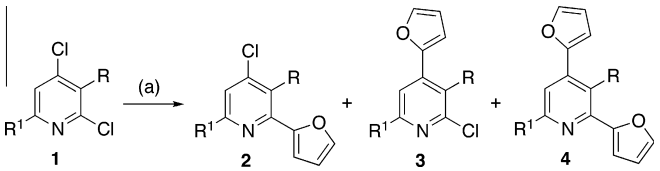
The pyridine ring is present in numerous natural products, drugs, and other molecules of interest in both physical and life sciences. Hence selective and efficient functionalization of pyridines is of synthetic importance.[1] A number of halopyridines are readily available and these may serve as important synthetic intermediates, especially in substitution and coupling reactions. It is still regarded as difficult to predict *a priori* the regioselectivity in nucleophilic displacement reactions performed on di- or trihalopyridines when the halogens are located at the activated 2-, 4-, and 6-positions.[2] Palladium-catalyzed cross-coupling reactions are important for functionalization of haloaryls or heteroaryls.[3] Except for one example of a Suzuki coupling on 2,4-dichloro-3-cyanopyridine,[4] Pd-catalyzed couplings on 2,4-dichloropyridines tend to give the 2-substituted product as the major isomer.[5] 2,4,6-Tribromopyridines react preferably at the α-positions in Sonogashira couplings, and this has been explained due to 'a directing role by the ring nitrogen'.[6] However, there are relatively few examples of couplings on such substrates, and no systematic study of reactivity and selectivity has been reported.

We herein describe a study examining the influence of substituents at the 3-position of 2,4-dichloropyridines in cross-couplings. The $(Ph_3P)_2PdCl_2$-catalyzed Stille couplings between 2-furyl(tributyl)tin and pyridines **1a**–**h** were investigated (Scheme 1, Table 1).[7] Compound **1a** was commercially available and pyridines **1b**,[5d] **1c**,[4] **1g**,[5d] **1h**,[8] and **1i**[9] were readily available by literature methods. The syntheses of pyridines **1d**, **1e**, and **1f** are shown in Scheme 2. The structures of the products **2**–**4** were determined by NMR spectroscopy, especially HMBC and/or selective NOE spectroscopy (Fig. 1).

Conversion of 2,4-dichloropyridine (**1a**) at ambient temperature was slow and the major coupling product was the 2-furylpyridine **2a**. No regioisomer **3a** was observed, but some disubstituted product **4a** was formed. When the temperature was raised to 55 °C or even 90 °C, the conversion and the formation of disubstituted product **4a** were increased.

Compound **1b**, which contains an electron-donating amino group at the pyridine 3-position, required an elevated temperature in order to react, and the coupling occurred with complete conversion and selectivity at 90 °C to give the 2-furylpyridine **2b**.

Good selectivity was difficult to achieve in the couplings of amide **1c**, aldehyde **1d**, ester **1e**, and nitrile **1f**. The 2-substituted isomers **2** were the major products, but (except for the nitrile **1f**) conversion at ambient temperature was relatively slow, especially for the amide, and the regioisomer **3** and/or the dicoupled product **4** were generally observed. The nitrile **1f** reacted with fairly good selectivity at ambient temperature. Unfortunately, selectivity was not improved when the reaction temperature was reduced. A Suzuki coupling of the nitrile **1f** was previously reported to take place mainly at C-4.[4]



Scheme 1. (a) 2-(Bu_3Sn)furan, $(Ph_3P)_2PdCl_2$, DMF; see also Table 1.

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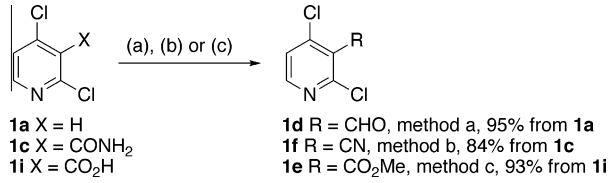
doi:10.1016/j.tetlet.2010.11.108

Table 1
Stille coupling between pyridines **1** and 2-furyltri(butyl)tin

Substrate	R	R^1	Temp (°C)	Time (h)	Product ratio[a]				Isolated yield (%)
					% **1**	% **2**	% **3**	% **4**	
1a	H	H	rt	18	54	37	0	9	22, **2a**
1a	H	H	55	18	42	39	0	19	—[b]
1a	H	H	90	18	39	45	0	16	—[b]
1b	NH_2	H	90	1	0	100	0	0	70, **2b**
1c	$CONH_2$	H	rt	18	87	13	0	0	—[b]
1c	$CONH_2$	H	55	18	12	56	22	10	—[b]
1d	CHO	H	rt	18	13	65	11	11	64,[c] **2d**
1d	CHO	H	0	7	17	47	12	24	—[b]
1e	CO_2Me	H	rt	18	22	54	0	24	35, **2e** 18, **4e**
1e	CO_2Me	H	0	7	25	50	0	25	—[b]
1f	CN	H	rt	18	0	82	13	5	61, **2f** 12, **3f**
1f	CN	H	0	7	19	53	20	8	—[b]
1g	NO_2	H	rt	1	0	13	76	11	—[b]
1g	NO_2	H	0	4	0	6	92	2	76,[d] **3g**
1h	NO_2	Cl	0	2.5	0	2	87	11[e]	73, **3h**

[a] Determined from the ^1H NMR spectra of the crude products.
[b] No product isolated in pure form.
[c] Contained 9% of **3d**.
[d] Contained 4% of **2g**.
[e] The structure of the difurylpyridine could not be determined with absolute certainty.



Scheme 2. Reagents and conditions: (a) (1) LDA, (2) DMF, THF, −78 °C; (b) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 0 °C; (c) MeI, DBU, MeCN.

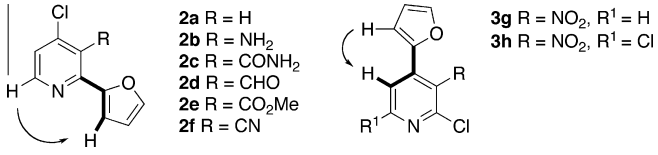


Figure 1. Structure elucidation of compounds **2** and **3**. The highlighted bonds show the most important HMBC correlations and the curly arrow the most important enhancement observed from selective NOE.

The most interesting finding in this study was that the regioselectivity was completely reversed for the 3-nitropyridines **1g** and **1h**. Herein coupling took place at C-4 almost exclusively, even with compound **1h** where exchangeable chlorides are present at both α-positions. The reason for this reversed selectivity is not fully understood, but the nitro group is the most electron-withdrawing C-3 substituent included in this study based on substituent constants (σ_p, σ_m or *F*).[10] It would appear that the important effect from the NO_2 group is activation of the C-4 position rather than deactivation of the 2-position, since there are many examples of successful Pd-catalyzed couplings on 2-chloro-3-nitropyridine.[11] Also Pd-catalyzed coupling on 2,6-dichloro-3-nitropyridine readily occurs, although with low regioselectvity.[12]

Nucleophilic substitutions by amines take place at C-4 of pyridine in both 2,4-dichloropyridine (**1a**)[13] and the 3-nitro analog **1g**,[14] although good selectivity is dependent on solvent and temperature, at least in the case of compound **1a**.[13b] One reason for the formation of the regioisomer **3**, especially from the most electron-deficient pyridines **1** examined in this study, could have been due to the fact that the isomers **3** were formed by direct nucleophilic substitution[15] rather than a Pd-catalyzed cross-coupling. However the nitropyridine **1g** did not react at all with 2-furyl(tributyl)tin alone.[16]

In summary, the increased electron-withdrawing ability of a substituent at the 3-position of 2,4-dichloropyridines increases the overall reactivity in Pd-catalyzed Stille couplings. The nature of the C-3 substituent strongly influences the regioselective outcome of the reaction. Complete selectivity for the 2-position can be achieved with an amine group at the pyridine 3-position, and the selectivity is completely reversed if the amine group is exchanged for a nitro substituent. When a substituent with electron-withdrawing ability other than a nitro group is attached to C-3, there is a preference for coupling at C-2, but extensive fine-tuning of the reaction conditions would be required to achieve complete regioselectivity, which is beyond the scope of this initial study.

Acknowledgments

The Norwegian Research Council is gratefully acknowledged for a grant to A.D.K. (KOSK II, project number 177368) as well as for partial financing of the Bruker Avance instruments used in this study.

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16. The reaction was performed as described above,[7] but without $(PPh_3)_2PdCl_2$. The reaction mixture was stirred at ambient temperature for 18 h.