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Pd-catalyzed C-N coupling of primary (het)arylamines with 5-substituted 3-chloro-4*H*-1,2,6-thiadiazin-4-ones

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ABSTRACT

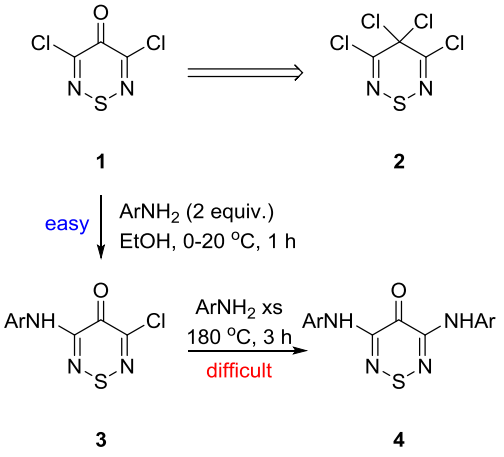
The Buchwald-Hartwig Pd-catalyzed C-N coupling reaction of 5-substituted 3-chloro-4*H*-1,2,6-thiadiazin-4-ones with primary (het)arylamines is described, affording twenty new 3,5-disubstituted 4*H*-1,2,6-thiadiazin-4-ones in 56–99% yield. The protocol enables the mild preparation of difficult to access 3,5-dianilino-1,2,6-4*H*-thiadiazin-4-ones. The reaction scope and limitations are discussed.

Introduction

Non S-oxidized 4*H*-1,2,6-thiadiazines have been known for over 40 years. Selected 3-chloro-4*H*-1,2,6-thiadiazin-4-ones are plant antifungals,[1] while other derivatives have been studied as "extreme quinoids",[2] liquid crystals or near-infrared dyes.[3] More recently, 4*H*-1,2,6-thiadiazines were proposed as precursors to radical anions for molecule-based magnetic and conducting materials,[4] and small molecules containing 4*H*-1,2,6-thiadiazin-4-one were studied as electron donors in solution-processed bulk heterojunction solar cells.[5] In spite of these useful properties, work on this heterocycle remains limited.

Most syntheses of non S-oxidized 4*H*-1,2,6-thiadiazines involve either 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**1**) or 3,4,4,5-tetrachloro-1,2,6-thiadiazine (**2**), both of which can be readily prepared from malononitrile and SCl_2 (Scheme 1).[6]

As part of our ongoing studies into rare heterocycles, we have expanded the synthetic scope of 3,5-dichlorothiadiazinone **1**, by systematically developing protocols for difficult to achieve chemistry such as various condensation reactions at the C4 carbonyl.[7] Another difficult to achieve reaction is the double displacement of the chlorides by anilines: the first chloride can be readily displaced by anilines using stoichiometric amounts of aniline (2 equiv.) in EtOH, at *ca.* 0–20 °C.[6] Nevertheless, owing to electron release from the new anilino group, the electrophilicity of the new 3-anilino-5-chloro-1,2,6-4*H*-thiadiazin-4-one **3** is significantly reduced. Consequently, the second displacement of the remaining chloride by aniline requires forcing conditions: *i.e.* excess aniline in the absence of solvent at *ca.* 150–180 °C. These conditions are incompatible with sensitive functionality that cannot tolerate high



Scheme 1. Chemistry of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**1**).

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temperatures, or expensive anilines that cannot be used in large excess. As such, we investigated Pd-catalyzed Buchwald-Hartwig coupling[8] protocols to introduce the second aniline under milder conditions to enable a more versatile method of preparing symmetric and asymmetric 3,5-dianilino-4*H*-1,2,6-thiadiazin-4-ones **4**. While the use of Pd catalysts in the presence of a weakly aromatic dichlorothiadiazinone had initially been avoided over fears that sulfur would poison the catalyst, studies have since revealed the tolerance of the ring system to Pd-catalyzed Suzuki-Miyaura,[9a] Stille[9a,b] and Sonogashira[9a] couplings.

Results and discussion

Treatment of dichlorothiadiazinone **1** with aniline (2 equiv.) in EtOH at *ca.* 20 °C for 1 h gave 3-chloro-5-(phenyl-amino)-4*H*-1,2,6-thiadiazin-4-one (**3a**) in 95% yield *via* a chromatography free literature procedure.[6] Anilinothiadiazine **3a** was subsequently used as the starting point for identifying suitable Buchwald-Hartwig reaction conditions for the preparation of 3,5-bis(phenylamino)-4*H*-1,2,6-thiadiazin-4-one (**4a**). Initially, we confirmed the known preparation of bisanilinothiadiazine **4a** by treating anilinothiadiazine **3a** with neat aniline (8 equiv.) at *ca.* 180 °C, which in our hands was complete in 45 min and gave the desired product **4a** in 84% yield.[6] The reaction temperature can be lowered to *ca.* 150 °C to give the product in a similar 83% yield; however at *ca.* 100 °C or when EtOH was used as a solvent at *ca.* 78 °C, no reaction occurred.

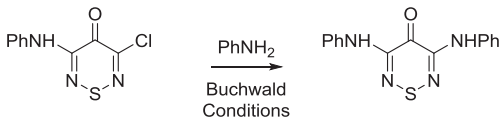
The search for suitable Buchwald-Hartwig reaction conditions focused on the reaction of anilines with 2-chloropyridines,[10] which are somewhat similar to chlorothiadiazines in that they are both electron deficient hetarenes bearing chlorine groups. As such, treatment of anilinothiadiazine with aniline (1.2 equiv.), using Pd(OAc)$_2$ (4 mol%), [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] (BINAP) (4 mol%) and powdered Cs_2CO_3 (3 equiv.), in anhydrous PhMe at *ca.* 110 °C for 1.5 h under an argon atmosphere, gratifyingly gave the desired dianilinothiadiazine **4a** in 63% yield (Table 1, entry 1). By changing both the solvent and base to anhydrous 1,4-dioxane and powdered K_2CO_3 (2.4 equiv.), respectively, the catalyst loading and reaction temperature could be lowered to 1.25 mol% and ~102 °C, respectively, and the product yield improved to 88% (Table 1, entry 2). A subsequent bidentate ligand screen to investigate the influence of bite angle[11] revealed that the reaction times were significantly slower (24 h) with the use of 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xanthphos) (104.6°), marginally faster (2 h) with the use of 1,4-bis(diphenylphosphino)butane (dppb) (97.0°) and significantly faster (0.5 h) with bis[(2-diphenylphosphino)phenyl] ether (DPEPhos) (101.5°) (Table 1, entries 3, 4 and 5, respectively) *cf.* BINAP (92.8°). The use of DPEPhos not only shortened the reaction time but also led to a near quantitative yield of 98%. It is noteworthy that the use of bidentate ligands with large bite angles favors the coupling of anilines with aryl halides by promoting the reductive elimination step.[12]

While the latter conditions (Table 1, entry 5) worked well for the Buchwald-Hartwig coupling of anilinothiadiazine **3a** with aniline, a preliminary screen of other anilines revealed that the use of electron rich 2-methoxy and 2-methylanilines failed to proceed to completion (data not shown). Fortunately, replacing Pd(OAc)$_2$ by Pd{[3,5-(F$_3$C)$_2$C$_6$H$_3$]$_3$P}$_3$ [aka Superstable Pd(0)], also led to equally fast and near quantitative reactions of aniline with 3-anilino-5-chloro-1,2,6-thiadiazine **3a** (Table 1, entry 6) and under these new conditions the reactions with electron rich anilines worked well (Table 2, entries 2 and 7).

Nevertheless, while Superstable Pd(0) worked well with DPEPhos as the ligand (Table 1, entry 6), the analogous reaction with Xantphos as the ligand was significantly slower (20 h) and gave product **4a** in lower yield (72%) (Table 1, entry 7). Interestingly, the use of Superstable Pd(0) to support C-N coupling chemistry is not common, but we have successfully used this catalyst for the Buchwald-Hartwig coupling of (het)arylamines with 5,5′-dibromo-2,2′-bithiazoles.[13] Repeating the reaction of anilinothiadiazine **3a** and aniline using the optimized reaction conditions but in the absence of a Pd catalyst (Table 1, entry 8) led to no reaction supporting the need for Pd-catalysis. It is also worthy to note that in the absence of a bidentate ligand the reaction failed to proceed to completion within 24 h (Table 1, entry 9).

Under the optimized Buchwald-Hartwig coupling conditions: Superstable Pd(0) (1.25 mol%), DPEPhos (5 mol%), K_2CO_3 (2.4 equiv.), anhydrous 1,4-dioxane, 102 °C, under an argon atmosphere, we systematically examined the scope of this (het)arylamination protocol (Table 2). *ortho*-Substituted anilines were selected to illustrate the effect of both steric and electronic effects. In most cases, the reaction of 3-anilino-5-chloro-1,2,6-thiadiazinone **3a** with primary anilines bearing either electron donating (Table 2,

Table 1
Reaction of 3-chloro-5-(phenylamino)-4*H*-1,2,6-thiadiazin-4-one (**3a**) with aniline (1.2 equiv.) under an argon atmosphere.



3a **4a**

Entry	Solvent	Catalyst (mol%)	Ligand (mol%)	Base (equiv.)	Temp. (°C)	Time (h)	Yield **4a** (%)[a]
1	PhMe	Pd(OAc)$_2$ (4)	BINAP (4)	Cs_2CO_3 (3)	110	1.5	63
2	1,4-dioxane	Pd(OAc)$_2$ (1.25)	BINAP (5)	K_2CO_3 (2.4)	102	4	88
3	1,4-dioxane	Pd(OAc)$_2$ (1.25)	Xanthphos (5)	K_2CO_3 (2.4)	102	24	92
4	1,4-dioxane	Pd(OAc)$_2$ (1.25)	dppb (5)	K_2CO_3 (2.4)	102	2	90
5	1,4-dioxane	Pd(OAc)$_2$ (1.25)	DPEPhos (5)	K_2CO_3 (2.4)	102	0.5	98
6	1,4-dioxane	Superstable Pd(0) (1.25)	DPEPhos (5)	K_2CO_3 (2.4)	102	0.5	99
7	1,4-dioxane	Superstable Pd(0) (1.25)	Xanthphos (5)	K_2CO_3 (2.4)	102	20	72
8	1,4-dioxane	–	DPEPhos (5)	K_2CO_3 (2.4)	102	24	–[b]
9	1,4-dioxane	Superstable Pd(0) (1.25)	–	K_2CO_3 (2.4)	102	24	–[c]

[a] Isolated yields.
[b] No reaction.
[c] Incomplete reaction.