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Desulfitative Cross-Coupling of Protecting Group-Free 2-Thiouracil Derivatives with Organostannanes

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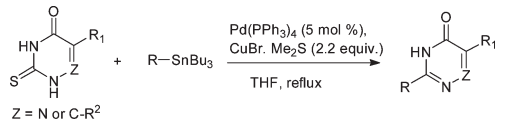
Received February 24, 2010



We here report a unique and efficient copper bromide mediated pallado-catalyzed coupling of protecting group-free 2-thiouracil derivatives with organostannanes. The nature of the copper appears to be crucial for successful cross coupling.

Heterocycle structures have played an important role in lead discovery and biological activities in the pharmaceutical industry and academic research.[1] Metal-catalyzed coupling protocols have developed into powerful tools for synthetic chemists and have proved highly successful in the construction and functionalization of heteroaromatic series over the past two decades.[2] However, the ability to selectively form site specific covalent bonds within a sensitive molecule under mild conditions and without the need for protection−deprotection remains an attractive challenge for organic chemists.

Most transition metal cross-coupling procedures involve the interaction of an electrophilic organohalide (or related substrate) with a nucleophilic organometallic reagent. The limited stability and/or accessibility of the corresponding heteroaromatic derivatives appears somewhat problematic and led Liebeskind and Srogl to develop a new efficient palladium-catalyzed cross-coupling reaction involving thiol ester[3] and thioether[4] type species. This method requires a stoichiometric amount of a copper(I) carboxylate for efficient coupling with boronic acids,[4,5] organostannanes,[6] or arylsiloxanes[7] and allows access to original, and previously unobtained, functionalizations.[8] The scope of this novel base free reaction has been extended considerably to enable the coupling reaction between organosulfur and organometallic reagents to overcome the failure encountered by the traditional C−C bond formation method.[9] In independent studies, our group has shown that the carboxylate counterion is not essential for the catalytic cycle to proceed with stannane derivatives, and can be efficiently replaced by the readily accessible copper(I) bromide−dimethyl sulfide complex ($CuBr \cdot Me_2S$).[10] This approach has been recently successfully applied to various substrates.[11]

In the context of the synthesis of combinatorial libraries of 2-aryl-1,4-dihydropyrimidines as potential non-nucleosidic inhibitors of hepatitis B virus replication, Kappe and coworkers developed a direct C−C cross-coupling of cyclic thioureas containing a latent free-thiol functionality under microwave conditions in high yields.[12] This promising desulfitative coupling was successfully applied to thioamide fragments[13] and oxazolinethiones[14] with boronic acids and stannanes, and extended to arylsiloxanes for the former and a variety of terminal alkynes for the latter.[15]

2-Thiouracil (**1**) and related modified pyrimidine nucleobases are important reagents for the synthesis of different kinds of heterocycles with potential biological activity. Their special structures have also emerged as a building block in natural or synthetic molecules. Furthermore, uracil has been proposed as the central scaffold in the butterfly strategies for the synthesis of original non-nucleoside reverse transcriptase inhibitors (NNRTIs).[16] Therefore the acyl thiourea moiety (−NH−C(S)−NH−C(O)−), which can also be found in many easily accessible modified pyrimidines, appeared to be an interesting function in order to access various substituted pyrimidin-4-ones. In this paper, we report a unique and efficient copper bromide mediated pallado-catalyzed coupling of protecting group-free 2-thiouracil derivatives with organostannanes.

Encouraged by the success of Kappe's work,[12,13] we explored the Liebeskind−Srogl cross-coupling between the C═S of 2-thiouracil **1** with phenylboronic acid **2**. Unfortunately,

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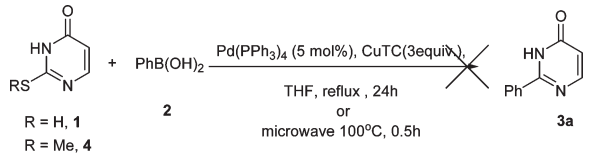
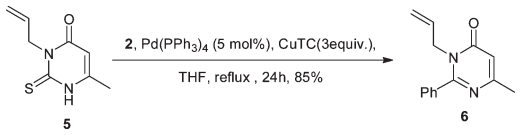
DOI: 10.1021/jo1003482 Published on Web 04/01/2010

SCHEME 1. Liebeskind−Srogl Reaction on Thiouracil 1 and SMe-Thiouracil 4



SCHEME 2. Liebeskind-Srogl Reaction on N-Protected Thiouracil 5



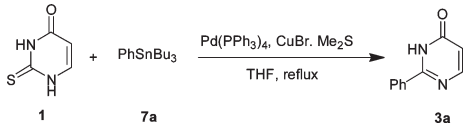
attempts to isolate the desired coupled compound **3a** under microwave irradiation or conventional reflux conditions with 3 equiv of copper(I) thiophene-2-carboxylate (CuTC) failed (Scheme 1).

We first surmised that in this particular case, a thioether function was essential for the success of the reaction and therefore synthesized the methylthioether **4** by reaction of **1** with sodium hydroxide and methyl iodide.[17] Compound **4** was then refluxed with **2** in the presence of $Pd(PPh_3)_4$ (5 mol %) and CuTC (3 equiv). However, yet again, the reaction did not proceed (Scheme 1).

This result led us to consider more closely the modular synthesis of functionalized pyrimidinones via sulfide cross-coupling chemistry recently reported in the literature.[18] For all the examples reported, the reaction was carried out starting from an N-3 protected (alkylated) pyrimidone. To assess the crucial impact of this protection, we introduced an allyl group on N-3 according to Mizutani's protocol,[19] to provide the desired N-substituted product **5** in 65% yield. Refluxing a solution of **5** with phenylboronic acid **2**, $Pd(PPh_3)_4$ (5 mol %), and 3 equiv of CuTC in THF provided the desired coupling product **6** in 85% yield (Scheme 2).

At this stage, experimental results indicated that classic Liebeskind−Srogl reaction conditions were not suitable for cross-coupling with a protecting group-free acyl thiourea moiety (−NH−C(S)−NH−C(O)−) present in 2-thiouracil derivatives for example. Considering a probable interaction between the carboxylate moiety of the CuTC cofactor and the free NH of the thiouracil scaffold, we were intrigued by the interest of using the initial copper source, i.e. CuBr, that we had found for the Pd-catalyzed cross-coupling reactions of heteroaromatic thioethers with organostannanes.[10] Initially, we examined the cross-coupling reaction of 2-thiouracil **1** with the commercially available phenyltri-*n*-butyltin **7a** catalyzed by $Pd(PPh_3)_4$ (10 mol %) in the presence of 2.2 equiv of $CuBr \cdot Me_2S$. After 14 h of reflux in THF, we were delighted to isolate product **3a** in 66% yield (Table 1, entry 1). The structure

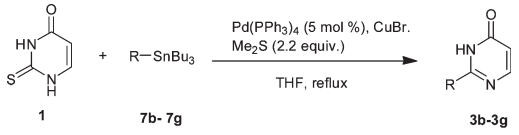
TABLE 1. Optimization of Reaction Conditions



entry	$PhSnBu_3$ (equiv)	$Pd(PPh_3)_4$ (equiv)	$CuBr \cdot Me_2S$ (equiv)	time (h)	yield [a] (%)
1	2.2	0.1	2.2	14	68
2	2.2	0.05	2.2	14	62
3	2.2	0.03	2.2	14	41
4	2.2		2.2	14	0
5	2.2	0.05		14	0
6	2.2	0.05	1.2	14	40
7	1.2	0.05	2.2	14	47

[a] Isolated yield after column chromatography.

TABLE 2. Copper(I)-Promoted Palladium-Catalyzed Cross-Coupling of 2-Thiouracil 1 with Organostannanes



entry	organostannane R	time (h)	product	yield[a] (%)
1	3-nitrophenyl (**7b**)	24	**3b**	63
2	4-methoxyphenyl (**7c**)	24	**3c**	52
3	2-furyl (**7d**)	14	**3d**	64
4	2-thienyl (**7e**)	14	**3e**	62
5	3-pyridinyl (**7f**)	24	**3f**	53
6	PhCH=CH− (**7g**)	48	**3g**	36

[a] Isolated yield after column chromatography.

and in particular the C−C bond formation was confirmed by careful analysis of the $^1H/^{13}C$ NMR spectra and MS data.

A series of experiments were then performed to optimize the experimental conditions. Loading down the palladium catalyst to 5 mol % gave a similar yield (Table 1, entry 2) while 3 mol % afforded poorer results (Table 1, entry 3). The palladium catalyst as well as the copper(I) cofactor appear to be essential for the reaction to proceed (Table 1, entries 4 and 5). Decreasing the amount of $CuBr \cdot Me_2S$ or $PhSnBu_3$ to 1.2 equiv also had a detrimental effect on productivity (Table 1, entries 6 and 7). Finally, longer reaction times did not improve the yields, and shorter reaction times or microwave activation for 0.5 h at 100 °C were not conclusive.

We then explored the possibility of generalizing this cross-coupling reaction to various organostannanes using the previously optimized experimental conditions. The results are depicted in Table 2. 2-Thiouracil **1** was reacted with electron-poor (**7b**) or electron-rich aryltributylstannanes (**7c**) to provide the corresponding products in good yields (entries 1 and 2). Different heteroarylstannanes as well as π-deficient 3-stannylpyridine proved to be consistent with this cross-coupling and afforded the desired products **3d**, **3e**, and **3f**, in 64%, 62%, and 53% yields, respectively (entries 3, 4, and 5). Vinyltributyltin derivative **7g** was also cross-coupled with **1** in moderate yields (entry 6).

The extension of these direct Pd-catalyzed, Cu(I)-mediated reactions to modified bases appears particularly interesting especially for medicinal chemists, and was therefore investigated.

(17) See the Supporting Information.

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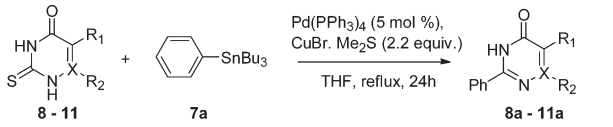
TABLE 3. Copper(I)-Promoted Palladium-Catalyzed Cross-Coupling of 2-Thiouracil Derivatives with Phenylstannane 7a

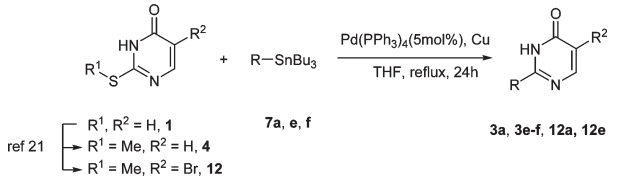


8 - 11 7a 8a - 11a

entry	R^1	$X-R^2$	product	yield[a] (%)
1	Me (**8**)	C−H	**8a**	58
2	H (**9**)	$C-CH_3$	**9a**	65
3	$CO_2C_2H_5$ (**10**)	C−H	**10a**	59
4	Me (**11**)	N	**11a**	67

[a]Isolated yield after column chromatography.

TABLE 4. Copper Sources and Chemoselectivity of the Palladium-Catalyzed Cross-Coupling of Thiouracil Derivatives



entry	R^1, R^2	$R-SnBu_3$	copper	product	yield[b] (%)
1	H, H (**1**)	**7a**	CuTC (2.2 equiv)	**3a**	0
2	H, H (**1**)	**7a**	CuMeSal (2.2 equiv)	**3a**	0
3	Me, H (**4**)[a]	**7a**	CuTC (2.2 equiv)	**3a**	0
4	Me, H (**4**)	**7a**	CuMeSal (2.2 equiv)	**3a**	0
5	Me, H (**4**)	**7a**	$CuBr\cdot Me_2S$ (2.2 equiv)	**3a**	63
6	Me, H (**4**)	**7e**	$CuBr\cdot Me_2S$ (2.2 equiv)	**3e**	84
7	Me, H (**4**)	**7f**	$CuBr\cdot Me_2S$ (2.2 equiv)	**3f**	57
8	Me, Br (**12**)[a]	**7a**	$CuBr\cdot Me_2S$ (2.2 equiv)	**12a**	70
9	Me, Br (**12**)	**7e**	$CuBr\cdot Me_2S$ (2.2 equiv)	**12e**	58

[a]See ref 21 for the synthesis of compounds **4** and **12**. [b]Isolated yield after column chromatography.

The results are reported in Table 3. 2-Thiouracil derivatives **8**, **9**, and **10** substituted with methyl in position 5 or 6 or with an ester group in position 6 were reacted with phenytributylstannane **7a** to produce the corresponding products in good yields (Table 3, entries 1−3). Finally, 6-aza-2-thiothymine **11** also proved to be an excellent coupling substrate, since **11a** was isolated in 67% yield after column chromatography (Table 3, entry 4).

This specific reactivity of the $RSnBu_3$/CuBr reactant couple was highly unexpected.

To check whether it was the boronic acid or the CuTC that was responsible for the absence of reactivity in the Liebeskind−Srogl conditions, we engaged the cross coupling between stannane **7a** and 2-thiouracil **1** in the presence of $Pd(PPh_3)_4$ and 2.2 equiv of CuTC or CuMeSal[20] in accordance with Liebeskind conditions[6] (Table 4, entries 1 and 2). The absence of any coupled product **3a** (Table 4, entry 1) shows that the nature of the copper(I) source appears to be crucial for successful coupling. This absence of reactivity in the presence of copper carboxylate was confirmed starting from the NH-free 2-methysulfanylpyrimidin-2-one **4** (Table 4, entries 3 and 4), while using CuBr, the desired product **3a** was isolated in 63% yields (Table 4, entry 5). This reactivity was confirmed with stannanes **7e** and **7f** (Table 4, entries 6 and 7). This led us to assess the selective sulfide over halide cross-coupling chemistry[18a] on the protecting group-free pyrimidinone **12**. Phenyl and hetaryl stannanes **7a** and **7e** were therefore reacted with the 2-methylsulfanyl-3-bromopyridin-2-one **12** and bromo derivatives **12a** and **12e** were isolated with very high chemoselectivity (Table 4, entries 8 and 9).

In summary, the hitherto unprecedented efficient reaction of 2-thiouracil derivatives with organostannanes has been reported in moderate to good yields. This approach avoids the need for protection−deprotection of the acyl thiourea moiety (−NH−C(S)−NH−C(O)−) present in numerous scaffolds of biological interest. Interestingly, the nature of the copper(I) source appears to be crucial for successful coupling and also provides complementary coupling conditions versus those previously published.

Experimental Section

Typical Procedure for the Palladium-Catalyzed Modified Liebeskind−Srogl Cross-Coupling Reaction. 2-Thiouracil **1** (0.4 mmol), tributyltin derivative (0.88 mmol), and $CuBr\cdot Me_2S$ (0.88 mmol) were added into dry THF (5 mL) under Ar. The solution was stirred at rt for 10 min and $Pd(PPh_3)_4$ (0.02 mmol) was added. The resulting mixture was refluxed for 24 h. The reaction mixture was then filtrated on Celite and washed with EtOAc (10 mL). After evaporation, the product was purified by column chromatography to give the desired product.

2-Phenyl-3*H*-pyrimidin-4-one (3a).[22] Eluent: PE:EA (1:1), then (1:2). Yield: 68%; white needle solid, mp 204−206 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 13.12 (1H, s), 8.18−8.22 (2H, m), 8.12 (1H, d, J = 6.5 Hz), 7.54−7.57 (3H, m), 6.44 (1H, d, J = 6.5 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.3, 158.1, 156.1, 132.6, 132.4, 129.5, 128.1, 114.1. IR (cm^{-1}): 3070, 2956, 1644, 1602, 1532, 1500. MS: 173.0 $[M + 1]^+$.

2-(3-Nitrophenyl)-3*H*-pyrimidin-4-one (3b).[23] Eluent: EA. Yield: 63%, light yellow solid, mp 265 °C dec. ^{1}H NMR (250 MHz, DMSO-MeOD): δ 9.04 (1H, s), 8.54 (1H, d, J = 8.25 Hz), 8.47 (1H, dd, J = 1 Hz, 8.25 Hz), 8.24 (1H, d, J = 6.5 Hz), 7.85 (1H, d, J = 8.25 Hz), 6.53 (1H, d, J = 6.5 Hz). ^{13}C NMR (62.5 MHz, DMSO-MeOD + TFA): δ 165.4, {$C(O)_{TFA}$: 159.6, 158.9, 158.3, 157.7}, 158.0, 155.6, 148.4, 135.7, 134.3, 130.7, 126.2, 122.9, 112.1. IR (cm^{-1}): 3070, 1675, 1620, 1597, 1524, 1353, 1330. MS: 218.0 $[M + 1]^+$.

2-(4-Methoxyphenyl)-3*H*-pyrimidin-4-one (3c). Eluent: EA. Yield: 52%, white solid, mp 208−209 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 13.01 (1H, s), 8.18 (2H, d, J = 9 Hz), 8.09 (1H, d, J = 6.5 Hz), 7.03 (2H, d, J = 9 Hz), 6.39 (1H, d, J = 6.75 Hz), 3.89 (3H, s). ^{13}C NMR (62.5 MHz): δ 165.3, 163.3, 157.8, 156.2, 129.9, 124.7, 114.9, 113.1, 55.9. IR (cm^{-1}): 2840, 1646, 1607, 1538, 1509, 1253. MS: 203.0 $[M + 1]^+$. HRMS (ESI): m/z calcd for $C_{11}H_{10}N_2O_2Na$ $[M + Na]^+$ 225.0640, found 225.0648.

5-Methyl-2-phenyl-3*H*-pyrimidin-4-one (8a).[23] Eluent: PE:EA (3:1), then (1:1). Yield: 58%, white solid, mp 190−192 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 12.91 (1H, s), 8.19−8.23 (2H, m), 8.01 (1H, s), 7.51−7.54 (3H, m), 2.14 (3H, s). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.7, 155.8, 153.1, 132.6, 132.1, 129.3, 127.8, 123.3, 13.3. IR (cm^{-1}): 3064, 2920, 1639, 1605, 1547, 1508, 1475, 1313. MS: 187.5 $[M + 1]^+$.

6-Methyl-2-phenyl-3*H*-pyrimidin-4-one (9a).[22] Eluent: PE:EA (3:1), then (1:1). Yield: 65%, white solid, mp 215−216 °C. ^{1}H

(20) CuMeSal = copper(I) 3-methylsalicylate.

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NMR (250 MHz, $CDCl_3$): δ 13.16 (1H, s), 8.17−8.21 (2H, m), 7.50−7.54 (3H, m), 6.30 (1H, d, J = 0.75 Hz), 2.39 (3H, d, J = 0.75 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.8, 165.8, 156.9, 132.6, 132.3, 129.4, 128.2, 111.3, 24.7. IR (cm^{-1}): 2950, 1653, 1603, 1571, 1538, 1502. MS: 187.0 $[M + 1]^+$.

Ethyl 4-oxo-2-phenyl-3,4-dihydropyrimidine-5-carboxylic acid ester (10a).[24] Eluent: PE:EA (3:1), then (1:1), then EA. Yield: 59%, white solid, mp 210 °C. ^{1}H NMR (250 MHz, DMSO): δ 13.17 (1H, br s), 8.61 (1H, s), 8.15 (2H, d, J = 7.5 Hz), 7.58 (3H, m), 4.21 (2H, q, J = 7.25 Hz), 1.25 (3H, t, J = 7.25 Hz). ^{13}C NMR (62.5 MHz, DMSO): δ 163.9, 161.3, 160.1, 159.0, 133.0, 131.9, 129.1, 128.8, 115.0, 60.8, 14.5. IR (cm^{-1}): 2976, 1707, 1655, 1567, 1538, 1509, 1446. MS: 245.0 $[M + 1]^+$.

6-Methyl-3-phenyl-4*H*-[1,2,4]triazin-5-one (11a).[25] Eluent: PE:EA (3:1), then EA. Yield: 67%, light yellow solid, mp 238−239 °C. ^{1}H NMR (250 MHz, DMSO): δ 13.87 (1H, br s), 8.01−8.05 (2H, m), 7.54−7.68 (3H, m), 2.22 (3H, s). ^{13}C NMR (62.5 MHz, DMSO + TFA): δ 163.1, {$C(O)_{TFA}$: 160.2, 159.6, 159.0, 158.3}, 158.8, 153.2, 133.4, 131.3, 129.8, 128.5, {F_3C_{TFA}: 112.8, 118.2, 113.7, 109.1}, 18.0. IR (cm^{-1}): 2847, 1604, 1543, 1488, 1436, 1373. MS: 188.0 $[M + 1]^+$.

5-Bromo-2-phenyl-3*H*-pyrimidin-4-one (12a).[26] Eluent: PE:EA (2:1). Yield: 70%, light yellow solid, mp 250−252 °C. ^{1}H NMR (250 MHz, DMSO): δ 13.26 (1H, br s), 8.45 (1H, s), 8.08−8.10 (2H, m), 7.50−7.63 (3H, m). ^{13}C NMR (62.5 MHz, DMSO + TFA): δ 160.0, 158.0, 155.1, 132.9, 132.5, 129.6, 128.8, 112.1. IR (cm^{-1}): 3042, 2952, 1648, 1603, 1559, 1535, 1498, 1466, 1016. MS: 251.0 $[M + 1, Br^{79}]^+$, 253.0 $[M + 1, Br^{81}]^+$.

5-Bromo-2-thiophen-2-yl-3*H*-pyrimidin-4-one (12e). Eluent: PE:EA (4:1). Yield: 58%, yellow solid, mp 227 °C dec. ^{1}H NMR (250 MHz, DMSO + TFA) δ 9.24 (1H, br s), 8.32 (1H, s), 8.19 (1H, dd, J = 1 Hz, 4 Hz), 7.88 (1H, dd, J = 1 Hz, 5 Hz), 7.22 (1H, dd, J = 4 Hz, 5 Hz). ^{13}C NMR (62.5 MHz, DMSO + TFA) δ 159.0, 154.7, 152.8, 136.4, 133.5, 130.6, 129.2, 110.4. IR (cm^{-1}): 1644, 1568, 1546, 1510, 1468, 1366, 1317, 897. MS: 321.0 $[M + Cu, Br^{79}]^+$, 323.0 $[M + Cu, Br^{81}]^+$. HRMS (ESI): m/z calcd for $C_8H_5N_2ONaSBr$ $[M + Na]^+$ 278.9204, found 278.9215.

Acknowledgment. We thank the French Chinese Foundation for Science and Applications (FFCSA) and the China Scholars Council (CSC) for financial support.

Supporting Information Available: Experimental procedures and/or literature references for compounds **3d**−**g**, **4**, **5**, **6**, **7b**, **7c**, **7g**, and **12** and ^{1}H NMR and ^{13}C NMR spectra for compounds **3a**−**g**, **6**, **8a**−**12a**, and **12e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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