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A DIRECT APPROACH TO THE SYNTHESIS OF 5-ARYL-4-CHLOROPYRIDAZINONE: FROM MICROWAVE ASSISTED CATALYST SCREEN TO ROOM TEMPERATURE REGIO- AND CHEMOSELECTIVE SUZUKI ARYLATION

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Abstract – Suzuki coupling of 4,5-dichloropyridazinone with phenylboronic acid yielded the desired 4-chloro-5-phenylpyridazinone along with 4-aryl and 4,5-diaryl derivatives. An extensive microwave-assisted screen led to the identification of $Pd(PEt_3)_2Cl_2$ as an ideal catalyst with superior rate and selectivity. Further optimizations provided an effective, regioselective and chemoselective arylation method at room temperature.

3-(2*H*)-Pyridazinone is a versatile heterocyclic pharmacophore. Its early derivatives have been commercialized as herbicides and insecticides. Recently, the 3-(2*H*)-pyridazinone core has been utilized as a key template in the search of new medicines that may prove to be useful for treating many diseases such as inflammation, thrombosis, and hypertension.[1] However, selective and effective functionalization of the ring in some instances still poses great challenges for the synthesis of substituted 3-(2*H*)-pyridazinones. In principle, some of the 4,5-disubstituted pyridazinones could be synthesized by selective and tandem Suzuki reactions on easily accessible 4,5-dihalopyridazinone precursors, but such a direct approach was complicated by the poor regioselectivity and the uncontrollable, subsequent double Suzuki coupling under the coupling conditions.[2a] In the presence of excess arylboronic acids, 4,5-dihalopyridazinones were completely converted to 4,5-diarylpyridazinones with two identical aryl groups.[2b-c,4] 4,5-Disubstituted pyridazinones with two different aryl groups were impossible to be synthesized under commonly used Suzuki reaction conditions. Consequently, such direct approach is widely accepted as unfavorable or impractical, and is often abandoned in favor of alternative syntheses. For example, 5-aryl-4-halopyridazinones (and their equivalents) are the key intermediates in the synthesis

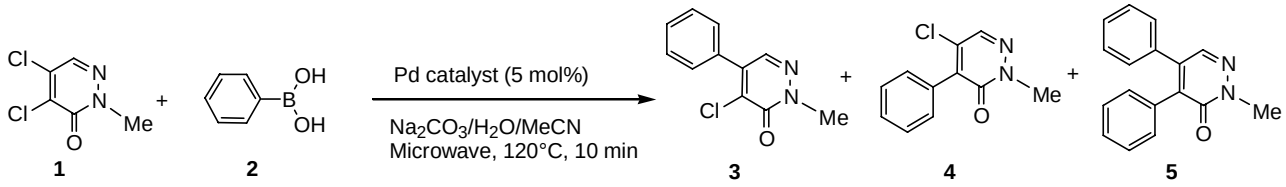
of 4,5-disubstituted analogs,[2] including asymmetrical 4,5-diarylpyridazinones as a new class of orally active COX-2 inhibitors.[3] Three alternative routes were recently developed to circumvent the selectivity issues. The first approach required a 7- step synthesis from 4-bromofuran-2-one, involving arylation, bromination and ring transformation.[3] The second method took advantages of the coupling difference between bromide and triflate functional groups of a 4-Br-5-TfO-pyridazinone, which itself required a three-step synthesis. In addition, the selectivity was still an issue since a mixture of mono- and diarylated products was obtained.[2a] The third approach improved selectivity by substituting 4-chloro in a 4,5-dichloropyridazinone with a methoxy group prior to the first Suzuki coupling and then converting the methoxy group to a hydroxyl group then to the corresponding triflate for the second Suzuki coupling.[2a]

In a research effort, we need a convergent and practical method for the synthesis of structurally diversified pyridazinone, rather than making each pyridazinone derivative in multiple steps one at a time. We envision that such goal can be achieved by a direct synthesis with selective Suzuki coupling. Regioselective Suzuki coupling has been reported in certain dihalogenated systems, where reactivity between two halogens was well defined.[5] In pyridazinone system, however, it appeared that halogens were so activated and became much less distinguishable.[2a] Previously, we reported our success with a microwave-assisted method to utilize the Suzuki coupling for the synthesis of 4-arylphenylalanines.[6] The microwave instruments can be readily automated and programmed for screening reaction conditions, as well as for high throughput synthesis in a very short period of time. Once again, we decided to take advantages of our microwave instruments to explore the direct synthesis of 5-aryl-4-halopyridazinones involving 4,5-dihalopyridazinone. We recognized that the failure with previous direct synthesis is perhaps due to the fact that not enough reaction conditions (different catalysts, reaction temperatures, time and solvents) have been fully explored. Herein, we report a method of the direct synthesis with 4,5-dichloropyridazinones for the preparation of symmetrical and asymmetrical substituted pyridazinones.

Commercially available and inexpensive 4,5-dichloro-2-methylpyridazin-3-(2*H*)-one (**1**) was selected as the substrate for our initial study. Compound (**1**) was found to be efficient for non-selective diarylation under typical Suzuki conditions.[2c] Its lower reactivity, compared to the corresponding dibromo counterpart, could be beneficial to the selectivity for a controlled monoarylation. A diverse collection of commercially available palladium catalysts was used to screen the coupling reaction between 4,5-dichloropyridazinone (**1**) and phenylboronic acid (**2**) under microwave irradiations. Two equivalent of **1** was used initially to reduce the potential diarylation statistically. In a typical screen, a mixture of **1** and **2** in aqueous acetonitrile (1:1) was heated under microwave at 120 °C for 10 minutes in the presence of

two equivalent of sodium carbonate and a 5 mol% palladium catalyst. The reactions were analyzed by HPLC and LC/MS.[7]

Table 1. Catalyst Screen on the Suzuki Coupling of **1** with **2**[a]



entry	catalyst[b]	convn. (%)[c]	**3**/**4**/**5** ratio[d]
1	$Pd(PPh_3)_2Cl_2$	100	1.7/2.0/1
2	$Pd(PPh_3)_4$	61	2.6/4.5/1
3	$Pd(dppf)_2Cl_2$	100	2.7/5.1/1
4	$Pd(BINAP)_2Cl_2$	100	2.1/2.9/1
5	$PdClBn(PPh_3)_2$	100	2.7/4.9/1
6	$Pd(PPh_2CH_2)_2$	100	2.9/4.7/1
7	$Pd[(PPh_2)_2CH_2]Cl_2$	100	1.8/2.5/1
8	$Pd(PPhMe_2)_2Cl_2$	100	4.2/2.3/1
9	$Pd(P\text{-}t\text{-}Bu_3)_2$	100[e]	1.7/2.6/1
10	$Pd(PCy_3)_2$	92[e]	1.6/1.4/1
11	$Pd(PCy_3)_2Cl_2$	100	1.5/1.8/1
12	$Pd(PEt_3)_2Cl_2$	100	7.7/1.4/1
13	$Pd[t\text{-}Bu_2P(OH)_2]_2Cl_2$	100	2.1/0.5/1
14	$Pd(NMe_2CH_2)_2Cl_2$	100	10/3.0/1
15	$[PdCl(dmamp)]_2$[f]	100	3.8/1.7/1
16	$[allylPdCl]_2$	75[g]	33/5.3/1
17	$Pd_2(dba)_3$	53[g]	25/7.5/1

[a] Under microwave heating with 2 equiv of **1**, except noted. [b] Pd/C, $Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$, $Pd(MeCN)_2Cl_2$ showed < 20% conversion. [c] Based on the loss of phenylboronic acid **2** and determined by HPLC at 214 nm. [d] Determined by HPLC at 214 nm. [e] Room temperature, 15 h. [f] Di-μ-chlorobis[2-[(dimethylamino)methyl]-phenyl-*C*,*N*]-dipalladium. [g] With significant amount of homo-coupling byproduct-biphenyl.

Among the catalysts screened in Table 1, ligands played essential role in both reactivity and selectivity. Consistent with previous findings by others,[2] commonly used palladium complexes of arylphosphine ligands (entries 1-7) afforded a mixture of 4-, 5- monosubstituted and 4,5-disubstituted products with a

very close range of selectivity. Partially replacement of phenyl groups in $Pd(PPh_3)_2Cl_2$ (entry 1) with methyl groups in $Pd(PPhMe_2)_2Cl_2$ (entry 8) altered regioselectivity towards 5-arylation product (**3**), and reduced diarylation. Highly reactive catalysts[10] with bulky P-*t*-Bu_3 and PCy_3 groups (entries 9-11), however, did not improve selectivity. On the other hand the catalyst with less hindered PEt_3 groups (entry 12) offered excellent selectivity for **3**, which might imply the steric control on the reaction. Catalysts with phosphine oxide ligand[11] (entry 13), nitrogen ligand (entry 14), and palladacycle (entry 15) all showed selectivity favored **3** but still with significant amount of product (**4**). Less reactive catalysts $[allylPdCl]_2$ and $Pd_2(dba)_3$ (entries 16-17) demonstrated impressive selectivity, but proved to be less useful due to significant, competitive homo-coupling of **2** to biphenyl as observed. Catalysts with weak ligands like $Pd(PhCN)_2Cl_2$, $Pd(MeCN)_2Cl_2$, and ligand-free palladium Pd/C, $Pd(OAc)_2$ showed poor reactivity under screen conditions (data not shown).

Table 2. Solvent and Temperature Effects on the $Pd(PEt_3)_2Cl_2$ (5 mol%) Catalyzed Suzuki Coupling of **1** with **2**

entry	T (°C)[a]	co-solvent	time (h)[b]	Convn. (%)	**1**/**2** ratio	**3**/**4**/**5** ratio[c]
1	90	MeCN	1/6	100	2/1	12/1.6/1
2	90	DMF	1/6	100	2/1	14/0.7/1
3	90	dioxane	1/6	100	2/1	12/3.0/1
4	90	DME	1/6	100	2/1	11/2.8/1
5	90	toluene	1/6	<20	2/1	5.0/3.2/1
6	90	H_2O	1/6	100	2/1	12/3.6/1
7	rt	MeCN	8	100	2/1	25/2.0/1
8	rt	DMF	5	100	2/1	330/<1/1
9	rt	DMF	8	100	1/1	170/<0.5/1

[a] Preheated oil-bath or room temperature. [b] Time required for the completed conversion, except noted. [c] Determined by HPLC at 214 nm.

$Pd(PEt_3)_2Cl_2$,[12] an old and rarely used catalyst, stood out as the catalyst of choice. Further experiment (entry 1 in Table 2) showed that the reaction could also proceed at lower temperature with traditional thermal heating, i.e. 90 °C oil bath, within 10 min, with improved selectivity. Screen of co-solvents revealed that DMF provided better selectivity (entry 2). Other co-solvents, dioxane (entry 3), dimethoxyethane (DME) (entry 4), toluene (entry 5), and water itself (entry 6), turned out to be less selective. Additional enhancement of selectivity was accomplished with reactions carried at room temperature with extended reaction time (entries 7 and 8), especially with DMF as solvent. The method in

entry 8 produced the desired product (**3**) with a selectivity of greater than 300-fold over products (**4**) and (**5**), which is a dramatically improvement over known procedures. Reducing the amount of **1** to one equivalent resulted in an increase of byproduct (**5**) (entry 9) as well as reaction time from 5 hours to 8 hours. Therefore, the optimized conditions, as identified by entry 8 in Table 2, were selected for the preparation of compound (**3**) with a 77% isolated yield as described.[13] Compound (**3**) is a key synthetic intermediate and can be easily converted to other versatile derivatives *via* a second Suzuki coupling or chlorine atom displacement.

The limitation and scope of the direct synthesis is currently under investigation, as well as the further transformation of the key intermediate (**3**). The findings of these efforts will be reported in due course. Nevertheless, we have achieved a direct, single step synthesis of 5-aryl-4-chloropyridazinone utilizing the Suzuki coupling from 4,5-dicholoropyridazinone with acceptable selectivity and isolated yield. The fact that optimized reaction conditions at room temperature result from initial catalyst screening with automated microwave instruments indicates such new technology will have more impact on organic syntheses than ever before.

REFERENCES AND NOTES

1. (a) M. P. Giovannoni, C. Vergelli, C. Ghelardini, N. Galeotti, A. Bartolini, and V. Dal Piaz, *J. Med. Chem.*, 2003, **46**, 1055. (b) E. Sotelo, N. Fraiz, M. Yanez, V. Terrades, R. Laguna, E. Cano, and E. Ravina, *Bioorg. Med. Chem.*, 2002, **10**, 2873. (c) L. Betti, M. Floridi, G. Giannaccini, F. Manetti, G. Strappaghetti, A. Tafi, and M. Botta, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 171.
2. (a) B. U. W. Maes, K. Monsieurs, K. T. J. Loones, G. L. F. Lemiere, R. Dommisse, P. Matyus, Z. Riedl, and G. Hajos, *Tetrahedron*, 2002, **58**, 9713. (b) B. U. W. Maes, J. Kosmrlj, and G. L. F. Lemiere, *J. Heterocycl. Chem.*, 2002, **39**, 535. (c) B. U. W. Maes, O. R'kyek, J. Kosmrlj, G. L. F. Lemiere, E. Esmans, J. Rozenski, R. A. Dommisse, and A. Haemers, *Tetrahedron*, 2001, **57**, 1323. (d) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457. (e) S. Kotha, K. Lhiri, and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633.
3. C. S. Li, C. Brideau, C. C. Chan, C. Savoie, D. Claveau, S. Charleson, R. Gordon, G. Greig, J. Y. Gauthier, C. K. Lau, D. Riendeau, M. Therien, E. Wong, and P. Prasit, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 597.
4. (a) L. Botella and C. Najera, *Angew. Chem., Int. Ed.*, 2002, **41**, 179. (b) L. Botella and C. Najera, *J. Organomet. Chem.*, 2002, **663**, 46. (c) D. A. Alonso, C. Najera, and M. C. Pacheco, *J. Org. Chem.*, 2002, **67**, 5588. (d) E. Sotelo, C. Coelho, and E. Ravina, *Tetrahedron Lett.*, 2003, **44**, 4459.

5. (a) Y. Gong and H. W. Pauls, *Synlett*, 2000, 829. (b) E. Sotelo and E. Ravina, *Synlett*, 2002, 223. (c) C.-G. Yang, G. Liu, and B. Jiang, *J. Org. Chem.*, 2002, **67**, 9392. (d) J. Zhang, P. G. Blazecka, D. Belmont, and J. G. Davidson, *Org. Lett.*, 2002, **4**, 4559. (e) A. Heynderickx, A. Samat, and R. Guglielmetti, *Synthesis*, 2002, 213.
6. Y. Gong and W. He, *Org. Lett.*, 2002, **4**, 3803.
7. Two regioisomers (**3** and **4**) can be determined by either NOE experiment[8] or the coupling constants in dehalogenated derivatives.[9] They can also be easily distinguished based on their HPLC area ratios under different wavelengths. For example, the area ratio of **3** between 214 nm and 254 nm (5.3) is smaller (2-fold) than that of **4** (11.2) since phenyl group in **3** is at β position to the carbonyl group in pyridazinone, which has longer conjugation and bathochromic shift in UV spectrum. Therefore, by using analytical HPLC with double wavelength display, we can not only monitor the progress of the reaction, but also obtain the structure information right away. 4-Aryl isomers (**4**) can serve as internal references to verify the structure of 5-aryl products (**3**). Compound (**4**), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (s, 1H), 7.45 (s, 5H), 3.81 (s, 3H); MS *m*/*z*: 221, 223 ($M+H^+$). Compound (**5**), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87 (s, 1H), 7.28-7.21 (m, 8H), 7.12-7.10 (m, 2H), 3.88 (s, 3H); MS *m*/*z*: 263 ($M+H^+$).
8. P. Matyus, E. Zara-Kacsian, and S. Boros, *J. Heterocycl. Chem.*, 1996, **33**, 583.
9. D-H. Kweon, Y-J. Kang, H-A. Chung, and Y-J. Yoon, *J. Heterocycl. Chem.*, 1998, **35**, 819.
10. (a) A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176. (b) S. Kotha, K. Lahiri, and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633.
11. G. Y. Li, *J. Org. Chem.*, 2002, **67**, 3643.
12. P. L. Goggin and R. J. Goodfellow, *J. Chem. Soc. (A)*, 1966, 1462.
13. Optimized procedure for the synthesis of **3**: Phenylboronic acid (**2**) (61 mg, 0.50 mmol) was dissolved in 1 M Na_2CO_3 (1 mL) and then mixed with 4,5-dichloro-2-methylpyridazin-3-(2*H*)-one (**1**) (180 mg, 1.0 mmol) in DMF (1 mL). Catalyst $Pd(PEt_3)_2Cl_2$ (10 mg, 0.024 mmol) was added and the resulting slurry was stirred at room temperature. The reaction was completed within 5 h, as monitored by HPLC. After the solvents were removed, the solid was treated with water (2 mL) and extracted with dichloromethane (3 x 2 mL). The crude mixture, upon concentration of dichloromethane, was purified by reverse phase HPLC (eluted with 0.1% TFA H_2O/MeCN gradient). Compound (**3**) was obtained as a white solid (85 mg, 77%), mp 131-133°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (s, 1H), 7.50 (s, 5H), 3.89 (s, 3H); MS *m*/*z*: 221, 223 ($M+H^+$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.18, 136.64, 133.02, 129.84, 128.84, 128.62, 41.10. HRMS (FAB) *m*/*z* 221.0476 ($M+H^+$), calcd for $C_{11}H_{10}N_2OCl$: 221.0481.