Hydroxymethylations of Aryl Halides by Pd-Catalyzed Cross-Couplings with (Benzoyloxy)methylzinc Iodide – Scope and Limitations of the Reaction

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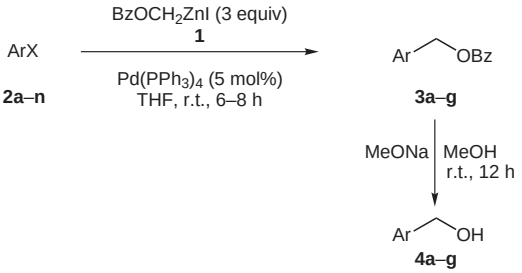
Abstract: Palladium-catalyzed cross-coupling reactions of (benzoyloxymethyl)zinc iodide with diverse (het)aryl halides leading to (benzoyloxymethyl)(het)arenes were studied to define the scope of this reaction. It has been found that this reaction is only applicable for electron-deficient aryl halides and the most efficient it is for 2-halopyridines and 4-halopyrimidines. Deprotection of the intermediates gives (hydroxymethyl)pyridines and -pyrimidines in high yields.

Key words: cross-coupling, organozinc reagents, pyridines, pyrimidines, palladium, hydroxymethylations



Scheme 1 Cross-coupling reaction

Hydroxymethyl groups attached to an aromatic or heteroaromatic ring is a very frequent structural motif in many natural and/or bioactive molecules. Introduction of the hydroxymethyl function to the aromatic ring could be achieved in several ways: (i) direct electrophilic hydroxymethylations,[1] (ii) electrophilic formylations[2] followed by reduction,[3] (iii) generation of arylmetal species and their reactions with formaldehyde or its equivalents,[4] (iv) metalation and oxidation of methylaromatic derivatives.[5] None of them is generally applicable since the electrophilic substitution is efficient only for electron-rich aromatics and may lead to regioisomers, generation of organometallics may not tolerate functional groups and also may form regioisomers due to migration of the metal (especially in the case of aryllithium species) and also the redox reactions are not always efficient, selective, and compatible with other functional groups. So far, no general direct nucleophilic hydroxymethylation of aryl halides has been developed.

Recently, we have developed an efficient hydroxymethylation of halopurines by the Pd-catalyzed cross-coupling reactions with (acyloxymethyl)zinc iodides.[6,7] This type of reagents was developed by Knochel[8] and used for transmetalation to cuprate and conjugate additions or Ullmann coupling with vinyl halides. Our hydroxymethylation of purines was the first example of their use in a Pd-catalyzed cross-coupling. Three acyl protecting groups have been tested[6] to show that the acetyl group is too labile, pivaloyl group is too stable for final deprotection, while the benzoyl group is just perfectly stable enough for efficient cross-coupling and labile enough for efficient deprotection either with ammonia or NaOMe. Though we have further used this reaction for regioselective synthesis[7,9] of either 2- or 6-(hydroxymethyl)purine bases and nucleosides and it was used by us[9] and others[10] for preparation of other hydroxymethylated nucleosides, the scope and limitations of the method remained to be explored and this communication reports on these results.

At first we have tested the reactivity of a set of 15 diverse aryl halides **2a**–**n** with (benzoyloxymethyl)zinc iodide **1** under standard conditions used for hydroxymathylation of purines. The reactions were performed at ambient temperature using three equivalents of the organozinc **1** and $Pd(PPh_3)_4$ in THF (Scheme 1). In general, only some electron-deficient aryl halides **2a**–**g** were good substrates for this reaction giving the desired (benzoyloxymethyl)arenes **3a**–**g** (Table 1), while electron-rich aryl bromides or iodides **2h**,**j**,**m**,**n**, as well as 4-iodobenzonitrile (**2i**), 3-iodopyridine (**2k**) and 3-bromoquinoline (**2l**) were totally unreactive (Figure 1). The best reactivity was observed in 2-chloroazine derivatives **2d**–**f**. Surprisingly, aryl bromides and iodides were less reactive than aryl chlorides. In the case of 2-iodo-5-bromopyrimidine (**2g**) the reaction occurred exclusively in position 2 to give 2-(benzoyloxymethyl)-5-bromopyrimidine (**3g**) in quantitative yield. In order to evaluate the influence of ligand, we have tried the reaction of poorly reactive 2-iodopyridine (**2bb**), as well as unreactive 2-bromonaphthalene (**2j**) with organozinc **1** in the presence of Pd_2dba_3 in combination with Buchwald-type ligands (2-biphenyl)di-*tert*-butylphosphine (bpdbp),[11] (2-biphenyl)dicyclohexylphosphine (bdCyp),[12] or with tri-*tert*-butylphosphonium tetrafluoroborate[13] (in our previous study[14] of cross-coupling reactions of 6-halopurines with the Reformatsky reagent, we have observed a strong increase in reactivity using this type of ligands). While the reaction of 2-iodopyridine (**2bb**) was strongly influenced by the ligand (yields when

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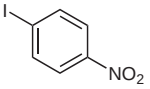
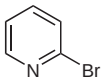
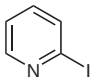
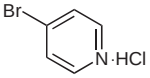
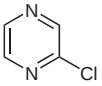
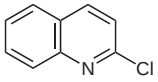
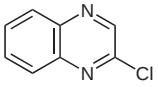
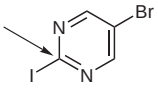
Table 1 Cross-Coupling Reaction

Entry	ArX	Coupling (yield, %)	Deprotection[a] (yield, %)
1	**2a** 	**3a** (69)	**4a** (95)
2	**2ba** 	**3b** (76)	**4b** (73)
3	**2bb** 	**3b** (17) **3b** (72)[b]	
4	**2c** 	**3c** (55)	**4c** (81)
5	**2d** 	**3d** (96)	**4d** (96)
6	**2e** 	**3e** (95)	**4e** (97)
7	**2f** 	**3f** (68)	**4f** (72)
8	**2g** 	**3g** (96)	**4g** (75)

[a] 1 M NaOMe in MeOH (0.1 equiv).
[b] Catalyst: 2% Pd_2dba_3, 8% (2-biphenyl)dicyclohexylphosphine.

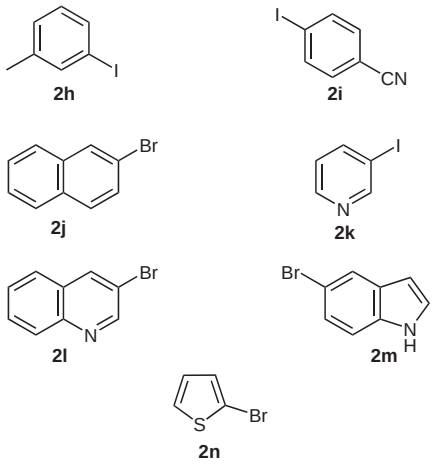
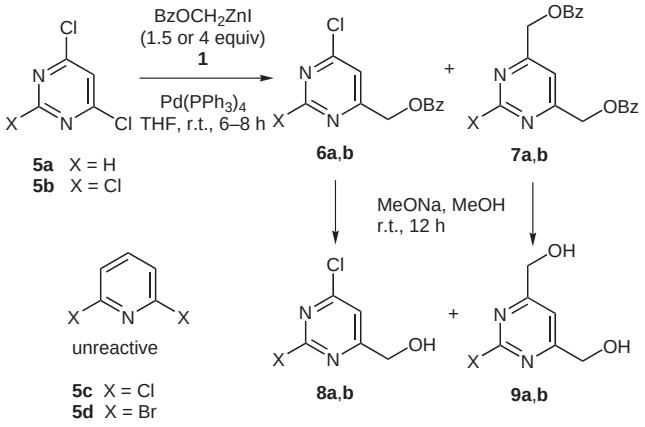


Figure 1 List of unreactive aryl halides

using *t*-$Bu_3P{\cdot}HBF_4$: 32%, bpdbp: 41%, and bdCyp: 72%), 2-bromonaphthalene was entirely unreactive irrespective of the ligand used even when increasing the reaction temperature up to 50 °C.

All the resulting (benzoyloxymethyl)arenes **3a**–**g** were successfully deprotected by cleaving the ester groups using NaOMe in methanol at room temperature giving the desired benzylic alcohols **4a**–**g** in high yields (Scheme 1; Table 1, last column).



Scheme 2 Cross-coupling reaction of compounds **5a**,**b** with subsequent deprotection

Table 2 Cross-Coupling Reaction of Compounds **5a**,**b** with Subsequent Deprotection

Entry	Starting compound	**1** (equiv)	Product (yield, %)	Deprotection[c] (yield, %)
1	**5a**	1.5	**6a** (43) **7a** (35)	**8a** (72)
2	**5a**	4[a]	**6a** (37) **7a** (30)	
3	**5a**	4[b]	**6a** (38) **7a** (54)	**9a** (76)
4	**5b**	1.5	**6b** (69)	**8b** (35)
5	**5b**	4[a]	**6b** (72) **7b** (21)	
6	**5b**	4[b]	**6b** (64) **7b** (24)	**9b** (74)

[a] 10% $Pd(PPh_3)_4$.
[b] 5% + 5% $Pd(PPh_3)_4$.
[c] For **6a** and **7a**,**b**: 1 M NaOMe in MeOH (0.1 equiv), 0 °C; for **6b**: 1 M NaOMe in MeOH (0.1 equiv), r.t.

Further we were interested in the hydroxymethylation of di- and trihalopyridines and -pyrimidines **5a**–**d**. In our previous study on dihalopurines, we have found[7] useful regioselectivity of the hydroxymethylations. While the 4,6-dichloro- and 2,4,6-trichloropyrimidine (**5a**,**b**) were good substrates for the reaction with organozinc **1**, 2,6-dichloro- and 2,6-dibromopyridine (**5c**,**d**) were totally unreactive. Reaction of 4,6-dichloropyrimidine **5a** with 1.5 equivalents of **1** was poorly regioselective giving the mono- and disubstituted products **6a** and **7a** in 43% and 35% yields, respectively. The use of excess (4 equiv) of **1** with 10 mol% of $Pd(PPh_3)_4$ gave almost the same results and only small increase in the yield of the disubstituted derivative **7a** (54%) was observed when the second portion of the catalyst was added after six hours. On the other hand, reaction of 2,4,6-trichloropyrimidine (**5b**) with 1.5 equivalents of **1** gave only monosubstituted product **6b** (69%) accompanied by unreacted starting compound. Re-

action of **5b** with 4 equivalents of **1** gave still preferentially monosubstituted product **6b** (72%) and only small amount of the disubstituted compound **7b** (21–24%).

Also the mono- and di(benzoyloxymethyl)pyrimidines **6** and **7** were deprotected to the desired hydroxymethylpyrimidines using NaOMe in methanol. The deprotection on pyrimidines **6a** and **7a**,**b** proceeded at 0 °C to avoid nucleophilic substitutions on chloro substituents in a basic media (Scheme 2, Table 2).

In conclusion, we have shown that the (benzoyloxy)methylzinc iodide is a suitable reagent for cross-coupling hydroxymethylation of certain aryl halides. However, the scope of the reaction is quite narrow. The reaction proceeds only in electron-deficient aryl halides and the most efficient it is for hydroxymethylation of 2-haloazines.

General Procedure for Cross-Couplings of 1 with Aryl Halides

A solution of (benzoyloxymethyl)zinc iodide (**1**, 3 mmol) in THF was added at r.t. to a solution of an aryl halide (**2a**–**n**, **5a**–**d**, 1 mmol), $Pd(PPh_3)_4$ (58 mg) in THF (2 mL) and stirred at r.t. for 6–8 h. The reaction was quenched with 1 M NaH_2PO_4 (30 mL) and extracted with $CHCl_3$ (3 × 25 mL). Collected organic phases were dried over $MgSO_4$, filtered, and the solvent was evaporated. The crude oily product was purified by chromatography.

Compound **3d**: yield 96%, yellowish crystals, mp 45.5–47 °C. ^{1}H NMR ($CDCl_3$): δ = 5.53 (s, 2 H), 7.46 (m, 2 H), 7.59 (m, 1 H), 8.11 (m, 2 H), 8.56–8.61 (m, 2 H), 8.79 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 65.09, 128.48, 129.38, 129.79, 133.39, 143.66, 144.07, 144.13, 151.59, 166.03. MS (EI): *m/z* (%) = 105 (100), 77 (65), 51 (30). HRMS (EI): *m/z* calcd for $C_{12}H_{10}N_2O_2$: 214.0742; found: 214.0748.

Compound **3f**: yield 68% as yellowish crystals, mp 76–77 °C. ^{1}H NMR ($CDCl_3$): δ = 5.70 (s, 2 H), 7.47 (m, 2 H), 7.60 (m, 1 H), 7.76–7.84 (m, 2 H), 8.08–8.17 (m, 3 H), 9.05 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 66.03, 128.54, 129.30, 129.37, 129.45, 129.89, 130.16, 130.45, 133.46, 141.84, 142.23, 144.22, 151.01, 166.16. MS (EI): *m/z* (%) = 265 (25), 181 (30), 91 (40). HRMS (EI): *m/z* calcd for $C_{16}H_{13}N_2O_2$: 265.0977; found: 265.0984. IR (CCl_4): 3071, 1730, 1603, 1494, 1452, 1264, 1108 cm^{-1}.

Compound **3g**: yield 96% as yellow oil. ^{1}H NMR ($CDCl_3$): δ = 5.52 (s, 2 H), 7.46 (m, 2 H), 7.58 (m, 1 H), 8.13 (m, 2 H), 8.77 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ = 65.87, 119.04, 128.42, 129.62, 129.91, 133.25, 157.95, 163.43, 166.22. MS (EI): *m/z* (%) = 105 (100), 77 (65), 51 (40). HRMS (EI): *m/z* calcd for $C_{12}H_9N_2O_2Br$: 291.9847; found: 291.9842.

Compound **6a**: yield 43% as beige crystals, mp 79–80 °C. ^{1}H NMR ($CDCl_3$): δ = 5.46 (d, 2 H, *J* = 0.8, CH_2), 7.47 (dt, 1 H), 7.52 (m, 2 H), 7.65 (m, 1 H), 8.14 (m, 2 H), 8.98 (d, 1 H). ^{13}C NMR ($CDCl_3$): δ = 65.07, 118.42, 128.67, 128.95, 129.86, 133.75, 158.63, 162.16, 165.73, 166.83. MS (EI): *m/z* (%) = 105 (100), 77 (50), 51 (30). HRMS (EI): *m/z* calcd for $C_{12}H_9N_2O_2Cl$: 248.0352; found: 248.0360. IR (CCl_4): 3064, 1734, 1569, 1540, 1267, 1112 cm^{-1}.

Compound **7a**: yield 54% as yellowish crystals, mp 109–113 °C. ^{1}H NMR ($CDCl_3$): δ = 5.48 (d, 4 H), 7.42 (m, 4 H), 7.55 (dt, 1 H), 7.60 (m, 2 H), 8.07 (m, 4 H, 2 × H-*o*-Ph), 9.17 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 65.51, 114.24, 128.56, 129.17, 129.72, 133.50, 158.27, 165.75, 165.78. MS (EI): *m/z* (%) = 304 (10), 105 (100), 77 (55), 51 (15). HRMS (EI): *m/z* calcd for $C_{20}H_{16}N_2O_4$: 348.1110; found: 348.1122. IR (CCl_4): 2945, 1734, 1595, 1272, 1111 cm^{-1}.

Compound **6b**: yield 72% as yellowish crystals, mp 69–70 °C. ^{1}H NMR ($CDCl_3$): δ = 5.44 (d, 2 H), 7.38 (t, 1 H), 7.52 (m, 2 H), 7.66 (m, 1 H), 8.13 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ = 64.69, 116.66, 128.70, 128.72, 129.89, 133.89, 160.56, 163.43, 165.57, 169.68. MS (EI): *m/z* (%) = 105 (100), 77 (50), 51 (30). HRMS (EI): *m/z* calcd for $C_{12}H_8N_2O_2Cl_2$: 281.9962; found: 281.9953. IR (CCl_4): 2942, 1737, 1561, 1535, 1264, 1109 cm^{-1}. Anal. Calcd (%) for $C_{12}H_8N_2O_2Cl_2$ (283.1): C, 50.91; H, 2.72; N, 9.89. Found: C, 50.63; H, 2.72; N, 9.89.

Compound **7b**: yield 24% as yellowish crystals, mp 53–55 °C. ^{1}H NMR ($CDCl_3$): δ = 5.44 (d, 4 H), 7.46 (m, 4 H), 7.46 (t, 1 H), 7.60 (m, 2 H), 8.04 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 65.05, 112.61, 128.60, 128.96, 129.72, 133.62, 165.59, 169.28. MS (EI): *m/z* (%) = 105 (100), 77 (55), 41 (25). HRMS (EI): *m/z* calcd for $C_{20}H_{15}N_2O_4Cl$: 382.0720; found: 382.0724.

General Procedure for Deprotection

A 1 M methanolic NaOMe (50 μL, 0.05 mmol) was added to a solution of a benzoylated compounds **3a**–**g**, **6a**,**b**, and **7a**,**b** (0.25 mmol) in MeOH (15 mL) and the mixture was stirred at ambient temperature. After complete deprotection the solvent was evaporated and the residue was chromatographed ($CHCl_3$–MeOH).

Compound **4d**: yield 96% as yellow oil. ^{1}H NMR ($CDCl_3$): δ = 3.64 (s, 1 H), 4.83 (s, 2 H), 8.47–8.53 (m), 8.64 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 62.77, 142.95, 143.43, 143.45, 154.95. MS (EI): *m/z* (%) = 109 (20), 80 (20), 31 (90).

Compound **4g**: yield 75% as white crystals, mp 93–94 °C. ^{1}H NMR ($CDCl_3$): δ = 3.36 (s, 1 H), 4.81 (s, 2 H), 8.79 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ = 64.23, 118.46, 157.65, 166.60. MS (EI): *m/z* (%) = 187 (35), 158 (50), 52 (45). Anal. Calcd (%) for $C_5H_5BrN_2O$ (189.0): C, 31.77; H, 2.67; N, 14.82. Found: C, 31.78; H, 2.64; N, 14.39.

Compound **8a**: yield 72% as yellow oil. ^{1}H NMR ($CDCl_3$): δ = 3.07 (s, 1 H), 4.78 (s, 2 H), 7.47 (s, 1 H), 8.93 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 63.60, 118.10, 158.20, 161.77, 170.43. MS (EI): *m/z* (%) = 143 (100), 115 (40), 52 (40). HRMS (EI): *m/z* calcd for $C_5H_5N_2OCl$: 144.0090; found: 144.0087.

Compound **9a**: yield 76% as yellow oil. ^{1}H NMR ($CDCl_3$): δ = 4.55 (d, 4 H), 5.67 (t, 2 H), 7.70 (s, 1 H), 8.91 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 63.30, 113.03, 156.65, 171.01. MS (EI): *m/z* (%) = 139 (100), 111 (100), 52 (70). HRMS (EI): *m/z* calcd for $C_6H_8N_2O_2$: 140.0585; found: 140.0582.

Compound **8b**: yield 35% as white solid, mp 94–96 °C. ^{1}H NMR ($CDCl_3$): δ = 2.79 (t, 1 H), 4.77 (dd, 2 H), 7.47 (t, 1 H). ^{13}C NMR ($CDCl_3$): δ = 63.65, 116.42, 160.17, 163.10, 173.77. MS (EI): *m/z* (%) = 177 (100), 148 (45), 113 (55).

Compound **9b**: yield 74% as white solid, mp 165–172 °C. ^{1}H NMR (DMSO-d_6): δ = 4.54 (d, 4 H), 5.79 (t, 2 H), 7.68 (s, 1 H). ^{13}C NMR (DMSO-d_6): δ = 62.94, 112.16, 158.49, 175.38. MS (EI): *m/z* (%) = 173 (60), 145 (50), 32 (95).

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