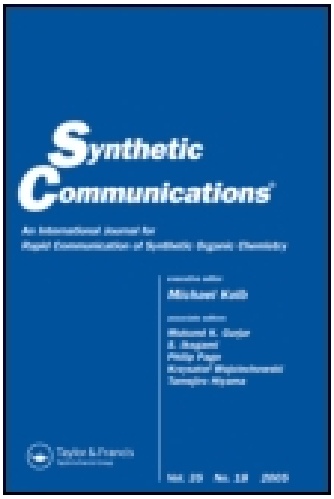

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Palladium-Catalyzed Cross-Coupling Reactions of Potassium N-Methyltrifluoroborate Isoindolin-1-one with Aryl and Heteroaryl Chlorides

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PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS OF POTASSIUM N-METHYLTRIFLUOROBORATE ISOINDOLIN-1-ONE WITH ARYL AND HETEROARYL CHLORIDES

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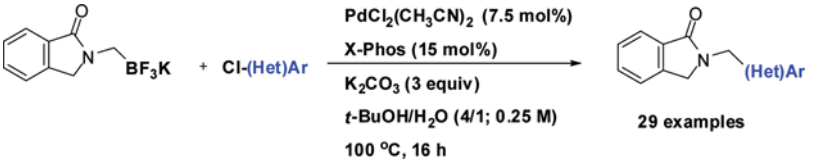
GRAPHICAL ABSTRACT



Abstract *Potassium* N*-methyltrifluoroborate isoindolin-1-one was synthesized and used in Suzuki–Miyaura palladium-catalyzed cross-coupling reactions with aryl and heteroaryl chlorides to prepare 29 examples of substituted* N*-benzyl isoindolin-1-ones. The new approach benefits from mild reaction conditions that tolerate a variety of functional groups. In addition, because of the large number of commercially available aryl and heteroaryl chlorides that can serve as coupling partners, the approach readily provides access to libraries of substituted* N*-benzyl isoindolin-1-ones.*

Keywords Isoindolinone; methylaminotrifluoroborates; organotrifluoroborates; palladium-catalyzed cross-coupling; potassium N-methyltrifluoroborate isoindolin-1-one; Suzuki–Miyaura cross-coupling

INTRODUCTION

Synthesis of isoindolin-1-one derivatives (**1**) (Fig. 1) is important because the isoindolin-1-one substructure is common in a number of natural products and pharmaceuticals.[1–5] The isoindolin-1-one scaffold is of particular interest to medicinal chemistry because of its centrality in a variety of biologically active compounds and pharmaceutical target molecules. In particular, the *N*-benzyl substitution motif is a common structural variation (Fig. 2).[6–10]

Numerous synthetic approaches exist to access isoindolin-1-one target molecules containing *N*-benzyl or substituted *N*-benzyl substructures. These include

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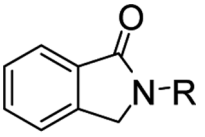


1

Figure 1. *N*-Substituted isoindolin-1-one.

monoreduction of phthalimides before or after *N*-benzylation of the isoindolin-1-one or phthalimide,[5,11,12] addition of benzylamines to phthalaldehyde followed by dehydration,[5] condensation of phthalide or 2-(bromomethyl)benzoate with benzylamines,[11] conversion of benzoylbenzoic acids into the corresponding ψ-acid chlorides followed by condensation with benzylamines,[13] and copper-catalyzed deamidative carbon–carbon coupling of iodoaryl amides.[14] While these and other synthetic approaches have their merits, the increasing demand for high-throughput screening of libraries of potential pharmaceutical molecules has encouraged continual improvements in synthetic efficiencies and diversity of strategies, including functional group tolerance. For example, the isoindolin-1-one scaffold's contribution to potency in the inhibition of MDM2-p53 interaction was studied.[13] These structure–activity relationship (SAR) studies involved the preparation of 33 *N*-substituted 3-hydroxy isoindolin-1-ones. Screening SAR studies such as this offer increasing impetus for complementary synthetic strategies to be developed, strategies that provide easy access to libraries of compounds built on a single scaffold.

Organotrifluoroborate chemistry has widespread utility in Suzuki–Miyaura cross-coupling reactions.[15] In particular, a new and complementary synthetic strategy for the preparation of substituted *N*-benzyl phthalimides (**4**) (Scheme 1) was recently reported.[16] In this study, the authors prepared substituted *N*-benzyl

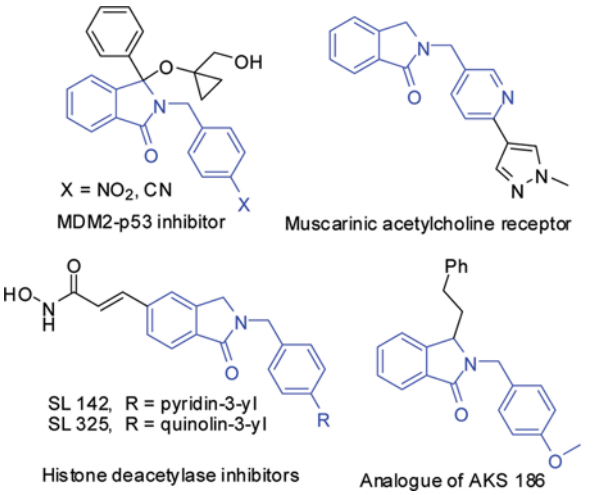
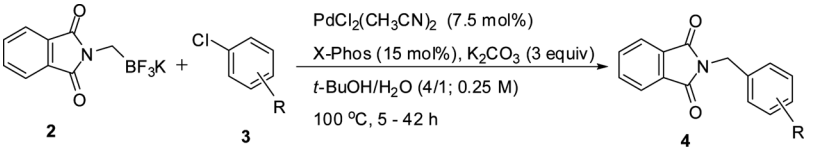


Figure 2. *N*-Substituted isoindolin-1-one drugs.



Scheme 1. Preparation of substituted *N*-benzyl phthalimides **4**.[16]

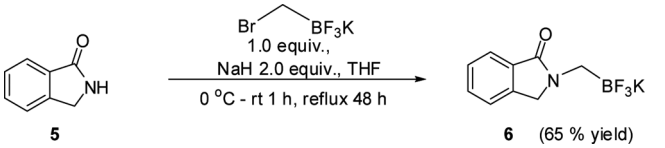
phthalimides by palladium-catalyzed Suzuki–Miyaura cross-coupling between potassium phthalimidomethyltrifluoroborate (**2**) and aryl chlorides (**3**).[16] The authors noted that a key difference is the dissonant carbon–carbon bond-forming reaction that couples an *N*-methyl nucleophile with aryl chloride electrophiles, rather than the traditional nitrogen–carbon bond formation between the nucleophilic nitrogen of deprotonated phthalimide and benzyl halide electrophiles. A significant benefit of this approach is that there are many more commercially available aryl chlorides than benzyl chlorides, thereby supporting easier access to large libraries of compounds. A second advantage is that organotrifluoroborate salts are very stable in air and water, tolerate a wide scope of functionality, and may be introduced early in synthetic strategies. A third advantage is that organotrifluoroborate salts are excellent coupling partners for Suzuki–Miyaura coupling reactions, in part because their coupling reaction conditions are compatible with a variety of functional groups. These methylaminotrifluoroborate nucleophiles have proven to be effective coupling partners in variety of Suzuki–Miyaura coupling reactions.[16–24]

One drawback of methylaminotrifluoroborates is that coupling reaction conditions are usually not general in nature and typically need to be developed for each unique application. Because there are numerous reaction variables (e.g., substrate, solvent mixture, catalyst, ligand, base, temperature, time) screening for reaction protocols often benefits from the use of high-throughput facilities.[25] In light of these previous successes, we set out to determine if the *N*-benzyl isoindolin-1-one scaffold could readily be accessed using organotrifluoroborate chemistry.

In this work, we describe the successful synthesis of potassium *N*-methyltrifluoroborate isoindolin-1-one and demonstrate the scope of its palladium-catalyzed cross-coupling with a range of aryl and heteroaryl halides to prepare substituted *N*-benzyl isoindolin-1-ones.

RESULTS AND DISCUSSION

Isoindolin-1-one (**5**) was prepared by a known procedure involving the monoreduction of phthalimide.[11] Deprotonation of **5** (Scheme 2) with NaH and refluxing in tetrahydrofuran (THF) with commercially available potassium



Scheme 2. Preparation of potassium *N*-methyltriflouro-borate isoindolin-1-one salt (**6**).

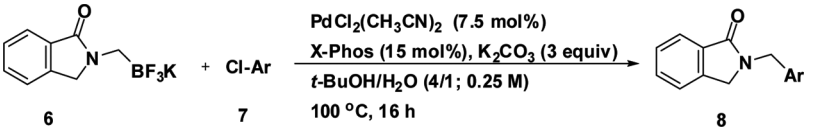
bromomethyltrifluoroborate led to the desired potassium *N*-methyltriflouro-borate isoindolin-1-one salt (**6**) as a white crystalline stable salt in 65% yield.

Cross-coupling reaction conditions for coupling **6** and aryl chlorides were first optimized using 4-chloroanisole (**7a**) (Table 1, entry 1). These conditions were later used without further optimization for all other coupling reactions. Successful coupling conditions were found after 25 combinations of catalyst, ligand, base, and solvent were attempted using a block reactor. $PdCl_2(CH_3CN)_2$ was the best catalyst (93% conversion) with $Pd_2(dba)_2$ nearly as effective (90% conversion). X-Phos proved to be the best ligand (>90% conversion) with Ata-Phos providing modest conversions (40%) as well. Screening for bases showed K_2CO_3 (93% conversion) was slightly better than Na_2CO_3 (90% conversion). *t*-BuOH/H_2O (4:1) was superior to other solvents used. In contrast to our previous experiences with different coupling substrates, and much to our surprise, the optimum conditions for this coupling reaction were found to be the same as those published[16] for potassium phthalimidomethyltrifluoroborate coupling reactions. Potassium *N*-methyltrifluoroborate isoindolin-1-one (**6**) and **7a** were found to optimally couple with the use of $PdCl_2$ $(CH_3CN)_2$ (7.5 mol%), X-Phos (15 mol%), and K_2CO_3 (3 equiv.) in *t*-BuOH/H_2O (4/1) as solvent at 100 °C for 16 h (Table 1, entry 1). Table 1 shows the scope of the coupling potassium *N*-methyltrifluoroborate isoindolin-1-one (**6**) with 17 aryl chlorides (**7a**–**q**). The desired substituted *N*-benzyl isoindolin-1-ones (**8a**–**q**) were obtained in moderate to excellent isolated yields (52–93%). The coupling reaction was compatible with a variety of electron-donating (Table 1, entries 1–4), electron-neutral (Table 1, entries 5–9), and electron-withdrawing groups on aryl chlorides including carbonyl (ketone, aldehyde, and ester), cyano, nitro, methoxy, pyrrolo, and fluoro substituents (Table 1, entries 10–17). Ortho-substituted aryl chlorides (Table 1, entries 7, 9, and 12) consistently gave lower yields, suggesting steric hindrance has an adverse effect.

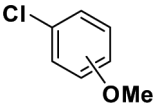
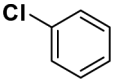
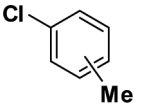
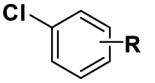
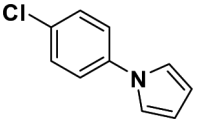
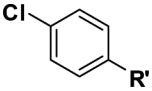
The yields in Table 1 were uniformly generated from 0.25 mmol (Ar-Cl) reactions with 7.5 mol% catalyst loadings and 15 mol% ligand. To make an initial probe into the scalability of these reactions, a larger scale reaction was performed. This scaled-up reaction was run without further optimization efforts and with a reduced catalyst loading because larger scale reactions typically require a smaller percent catalyst loading. When the chlorobenzene reaction (Table 1, entry 5) was run on a larger 4-mmol scale (ca. 1 g) with 1 mol% catalyst loading (2 mol% ligand) and for the same length of time (16 h), the reaction did not go to completion and resulted in only a 57% isolated yield. The comparable small-scale reaction yield was 93%. As only starting materials and product were observed, the reduction in yield upon scaling was attributed to the lack of reaction completion. because reaction rates of organotrifluoroborates are known[26] to depend on catalyst loading and variables such as vessel size and shape or stirring rate, optimum scaled conditions will require additional effort.

Because heteroaryl rings are often desired in screening libraries of pharmaceutical compounds, we also studied the scope of heteroaryl chloride coupling with **6** using the same reaction conditions as those optimized for 4-chloroanisole (**7a**) (Table 1, entry 1). These results are given in Table 2. Relative to aryl chlorides, coupling of **6** with nitrogen-, sulfur-, and oxygen-containing heteroaryl chlorides gave more modest yields (47–69%) of the desired substituted *N*-benzyl isoindolin-1-ones (Table 2, entries 1–7). Successful coupling was achieved with electron-rich and electron-poor chloropyridines (Table 2, entries 1 and 2, respectively), four different chlorothiophenes

Table 1. Scope of cross-coupling compound **6** with aryl chlorides



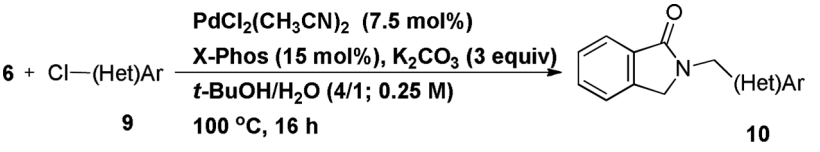
6 7 8

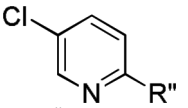
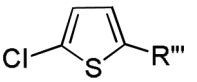
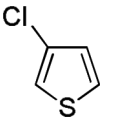
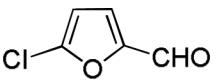
Entry	Ar-Cl	Product **8** (%)[a]
		
1	7a,4-OMe	**8a** (83)
2	7b, 2-OMe	**8b** (79)
3	7c, 3-OMe	**8c** (82)
4	7d,3,5-OMe	**8d** (63)
		
5	7e	**8e** (93)
		
6	7f, 4-Me	**8f** (93)
7	7g, 2-Me	**8g** (61)
8	7h, 3-Me	**8h** (80)
9	7i,2,6-Me	**8i** (63)
		
10	7j, R = 4-CO_2Me	**8j** (89)
11	7k, R = 4-COMe	**8k** (86)
12	71, R = 2-COPh	**81** (60)
		
13	7m	**8m** (71)
		
14	7n, R′ = −CHO	**8n** (56)
15	7o, R′ = −CN	**8o** (63)
16	7p, R′ = −NO_2	**8p** (52)
17	7q, R′ = −F	**8q** (75)

[a]Reaction conditions: 1.0 equiv. of aryl chloride; 1.2 equiv. of trifluoroborate **6**; isolated yields after silica gel column chromatography or preparative TLC.

(Table 2, entries 3–6), and one furan ring (Table 2, entry 7). As was the case with aryl chloride coupling, functional groups such as ketones and aldehydes (entries 3, 4, and 7) were tolerated during the coupling reactions. In comparison to aryl chlorides, the

Table 2. Scope of cross-coupling compound **6** with heteroaryl chlorides



Entry	Ar(Het)-Cl	Product **10** (%)[a]
		
1	9a, R″ = -OMe	**10a** (59)
2	9b, R″ = -F	**10b** (53)
3	 9c, R‴ = -COMe	**10c** (66)
4	9d, R‴ = -CHO	**10d** (47)
5	9e, R‴ = -H	**10e** (61)
6	 9f	**10f** (69)
7	 9 g	**10g** (53)

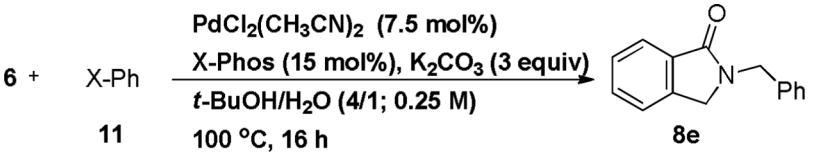
[a]Reaction conditions: 1.0 equiv. of heteroaryl chloride; 1.2 equiv. of trifluoroborate **6**; isolated yields after silica gel column chromatography or preparative TLC.

scope of coupling with **6** was not as broadly successful because no reaction was observed with 2- or 3-chloropyridine, 3-chloroisonicotinaldehyde, 2-chloro-5-methoxypyrimidine, or 5-chloro-1*H*-indole. No further attempt was made to find reaction conditions to support the failed nitrogen heteroaryl coupling reactions.

These same cross-coupling reaction conditions were used to study the scope of cross coupling between **6** and various aromatic electrophiles (Table 3). While the best coupling yield (93%) was obtained with the phenyl chloride (Table 3, entry 1), good to excellent yields (71–91%) were also obtained with phenyl mesylate, tosylate, triflate, and bromide (Table 3, entries 2–5). Only phenyl iodide gave an unsatisfactory yield (27%) (Table 3, entry 6). This demonstrates the versatility of **6** as a Suzuki–Miyaura coupling partner.

In conclusion, potassium *N*-methyltrifluoroborate isoindolin-1-one (**6**) has been synthesized and shown to undergo palladium-catalyzed Suzuki–Miyaura cross-coupling with aryl and heteroaryl chlorides to produce a variety of substituted *N*-benzyl isoindolin-1-ones in moderate to excellent yields. The mild reaction conditions tolerate a wide range of functional groups. In addition, potassium *N*-methyltrifluoroborate isoindolin-1-one was shown to couple with a range of aryl

Table 3. Scope of cross-coupling compound **6** with aromatic electrophiles



Entry	Ph-X	Product **8e** (%)[a]
1	Ph-CI (7e)	(93)
2	Ph-Br(11a)	(71)
3	Ph-OTf(11b)	(83)
4	Ph-OMs(11c)	(91)
5	Ph-OTs(11d)	(86)
6	Ph-I(11e)	(27)

[a]Reaction conditions: 1.0 equiv. of aryl chloride; 1.2 equiv. of trifluoroborate **6**; isolated yields after silica gel column chromatography or preparative TLC.

electrophiles. This new and complementary approach to synthesizing the *N*-benzyl isoindolin-1-one substructure has the advantage over existing methods in that there is an abundance of commercially available aryl and heteroaryl chloride coupling partners, thereby providing easy access to libraries of substituted *N*-benzyl isoindolin-1-ones.

EXPERIMENTAL

Potassium *N*-Methyltrifluoroborate Isoindolin-1-one (6)

Sodium hydride 60% in mineral oil (0.750 mg, 30.0 mmol) and dry THF (150 ml) were added to a two-necked round-bottomed flask. Isoindolin-1-one (**5**) (2.50 g, 18.8 mmol) was added to the suspension at 0 °C under N_2. The reaction mixture was stirred for 30 min at 0 °C, and then potassium bromomethyl trifluoroborate (3.00 g, 15.0 mmol) was added to the reaction mixture in one portion and stirred for 30 min at 0 °C. The reaction mixture was warmed to room temperature and refluxed for 48 h. The reaction mixture was cooled to 0 °C and quenched by KHF_2 (3.0 M) in H_2O (14 mL). The reaction mixture was stirred at room temperature for 2 h. The solvents were removed under vacuum, and residue was dissolved in ethyl acetate (100 mL) and filtered. The solid obtained was triturated with boiling acetone (3 × 50 mL) and the resulting white powder was washed with cold ether (3 × 20 mL) and dried to give the potassium N-methyltrifluoroborate isoindolin-1-one (**6**) as white solid (2.54 g, 65%): mp: 229–234 °C; IR (KBr, neat): 3032, 2936, 2897, 2879, 1658, 1590, 1473, 1455, 1426, 1415, 1306, 1228, 1210, 1099, 1069, 1011, 996, 760, 726, 538 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) $\delta = 7.59$ (d, $J = 8.0$ Hz, 1H), 7.53–7.46 (m, 2H), 7.42–7.39 (m, 1H), 4.38 (s, 2H), 2.47 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) $\delta = 169.9$, 144.0, 131.5, 131.2, 127.5, 123.7, 122.7, 44.8; ^{11}B NMR (DMSO-d_6, 128.37 MHz) $\delta = 3.46$ (br s); ^{19}F NMR (DMSO-d_6, 376.49 MHz): $\delta = -138.67$. HRMS (ESI-TOF) m/z calcd. for $C_9H_8BNOF_3^-$ (M − K) 214.0651; found 214.0661.

General Procedure for the Cross-Coupling Reaction of Potassium *N*-Methyltrifluoroborate Isoindolin-1-one (6) with Aryl and Heteroaryl Electrophiles (7a–q, 9a–l, 11a–e)

In a microwave vial equipped with a stirring bar, potassium *N*-methyltrifluoroborate isoindolin-1-one (**6**) (80.1 mg, 0.316 mmol), potassium carbonate (104 mg, 0.752 mmol), $Pd(MeCN)_2Cl_2$ (4.9 mg, 7.5 mol%), and XPhos (17.9 mg, 15.0 mol%) were successively introduced. The vial was capped and put under inert atmosphere ($3 \times$ vacuum/N_2 cycles). The electrophile was then introduced using a microsyringe (0.25 mmol, 1.0 equiv.) followed by 0.8 mL of degassed *t*-BuOH and 0.2 mL of degassed distilled water. The resulting mixture was then placed in an oil bath or a hotplate-magnetic stirrer system preheated at 100 °C and stirred at this temperature overnight (reactions followed by thin-layer chromatography, TLC). After cooling to room temperature, the vial was uncapped and the reaction mixture was diluted with dichloromethane (DCM) (5 mL) and water (5 mL). The aqueous layer was extracted with dichloromethane (3×15 mL). Organic layers were combined, washed with brine solution, and dried over Na_2SO_4, and the solvent was removed under vacuum to yield the crude product. The crude product was purified by flash column chromatography on silica gel using 30% ethyl acetate/hexane as the eluent.

FUNDING

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SUPPLEMENTARY MATERIAL

Supplementary material (i.e., full experimental details and copies of ^{1}H, ^{13}C, ^{19}F, and ^{11}B spectra for all compounds synthesized) associated with this article can be accessed on the publisher's website.

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