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C-H Arylation of *N*-heteroarenes under Metal-free conditions and its Application towards the Synthesis of Pentabromo- and Pentachloropseudilins

Mukesh Kumar,[a] Shweta Sharma,[a] Parijat Sil,[b] Manoj Kushwaha,[a] Satyajit Mayor,[b] Ram A. Vishwakarma,[a] and Parvinder Pal Singh*[a]

Abstract: Here, we are reporting metal-free conditions for radical initiation and direct C-H arylation of *N*-heteroarenes. Starting from aniline, the corresponding arenediazonium salt generated *in situ* is reduced to an aryl radical in the presence of chloropromazine hydrochloride, a new reagent for this application. The optimized procedures are mild, operationally simple, and also successfully working with more diverse substrates in comparison to reported methods. The optimized method is also employed for the synthesis of marine natural products *Pentabromo- and Pentachloropseudilins (PBP/PCP)*. In the present study, we also validated the potential of the Pentachloropseudilin (PCP), thus synthesized, for inhibition of Myosin1 function in mammalian cells and confirmed that PCP phenocopies Myosin1c depletion in cells.

Introduction

The substituted pyrrole particularly 2-arylated pyrrole ring represent the most fascinating core because of its presence in many drugs, clinical candidates and natural products. The notable examples of 2-arylated pyrroles are atorvastatin (lipid-lowering agents),[1] chlorfenapyr,[2a-b] elopiprazole,[3] lamellarins,[4a-4b] prodigiosins,[5] pentabromo,[6,7,8]/chloropseudilin,[9] pyrrolomycin-E.[10] 2-Arylated pyrroles also have shown interesting optical and electronic properties.[11a-d] Considering the importance of this important core, synthesis of 2-arylated pyrrole has become one of the most important reaction in organic synthesis. The direct arylation of pyrroles *via* C−H bond activation under transition metal and metal-free conditions have been tried by employing diverse coupling partners such as aryl halides, [12,13a-c] and aryl boronic acids.[12,14] In addition to this, Meerwein-type arylation[15] using diazonium salts[16,17] and anilines[18,19] have also been employed (Figure 1). In the recent decade, this approach has attracted the major attraction because of the recent development regarding the exploration of suitable conditions for the *in situ* generation of diazonium salts.[20] Moreover, this approach work *via* aryl radical upon electron addition which has been exploited from metals[18] and photoredox[16] conditions. Recently, small molecules such as ascorbic acid,[19a] polyaniline[17a,19b] hydrazine,[17b] gallic acid,[17c] and hydrogen peroxide[19c] capable of single electron-transfer reactions were also used for the reduction of diazonium salts to generate aryl radicals. However, most of these method works well with an electron-withdrawing group containing pyrroles such as *N*-Boc and *N*-tosyl pyrroles and pose problem with electron-donating group containing pyrroles and *NH*-pyrroles which gave unwanted azo-products instead of 2-arylated pyrroles[18a] except, Gowrisankar and Seayed method.[18b] This method required high temperature, which may pose a problem with sensitive substrates. Considering the importance of 2-arylated pyrrole, a general and effective method is highly required. The reported method suggested that the reagents having the capability of complex formation and single-electron transfer reaction could be highly useful for the diverse scope. In the literature, phenothiazine derivatives are well known for complex forming and single-electron transfer reaction [21,22,23a-c] and considering these properties and our interest in radical chemistry,[24] we hypothesized its use as a novel reagent for complex formation and reduction of diazonium salt to generate phenyl radicals.

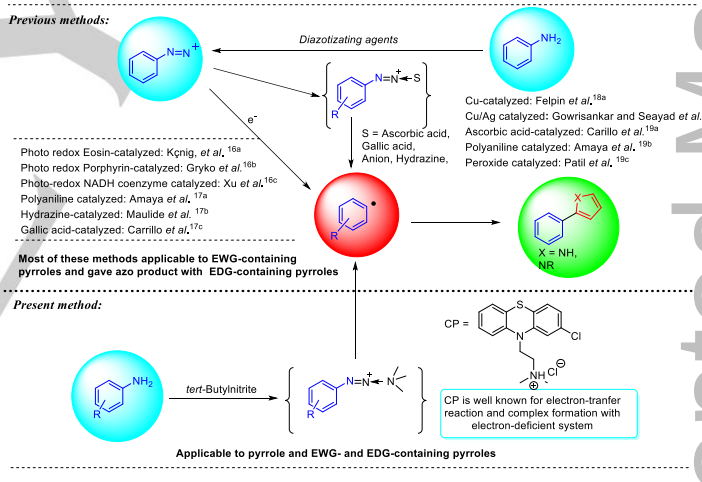

Figure 1. Previous and present approaches

Result and Discussion

We started our investigation by using *p*-chloro aniline **1** and *N*-Bocpyrrole **2** as coupling partners, DMSO as solvent, *tert*-butyl nitrite as diazotizing agent and chlorpromazine hydrochloride (CP salt) as a novel complex forming and reducing agent. Initially, *p*-chloro aniline **1** (1 mmol), was treated with *tert*-butyl nitrite in DMSO to generate diazonium salt, which then treated with *N*-Bocpyrrole **2** (2.5 mmol) and CP salt was (1 mmol), the desired coupled product **3a** was formed in a yield of 53% (entry 1). In further experiments, a range of solvents such as DMF, d_6-DMSO, DCM, ACN and THF were screened (entries 2-6), only DMF afforded the desired product but a comparatively lower yield of 40% (entry 2). When the stoichiometry of *p*-chloro aniline

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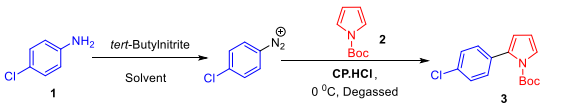
was increased from 1 to 2.5 equivalents, surprisingly, significant suppression was observed (entries 7 and 8). In the next reaction, decrease in the quantity of CP salt also drastically affected the yield of the desired product (entry 9). Increase in the quantity of CP salt along with degassing further increases the yield of desired product **3** upto 60% (entry 10). In the absence of CP salt, no product formation was observed (entry 11). Further, other salts such as DIPEA.HCl, ammonium chloride was also evaluated but no product formation was observed (entries 12-13). Furthermore, the reaction with chlorpromazine and other bases did not produce the coupled product indicated that CP salts played a major role (entries 15-18). After all the control experiments, we found entry 10 as the best reaction conditions and could be exploited for further derivatization.

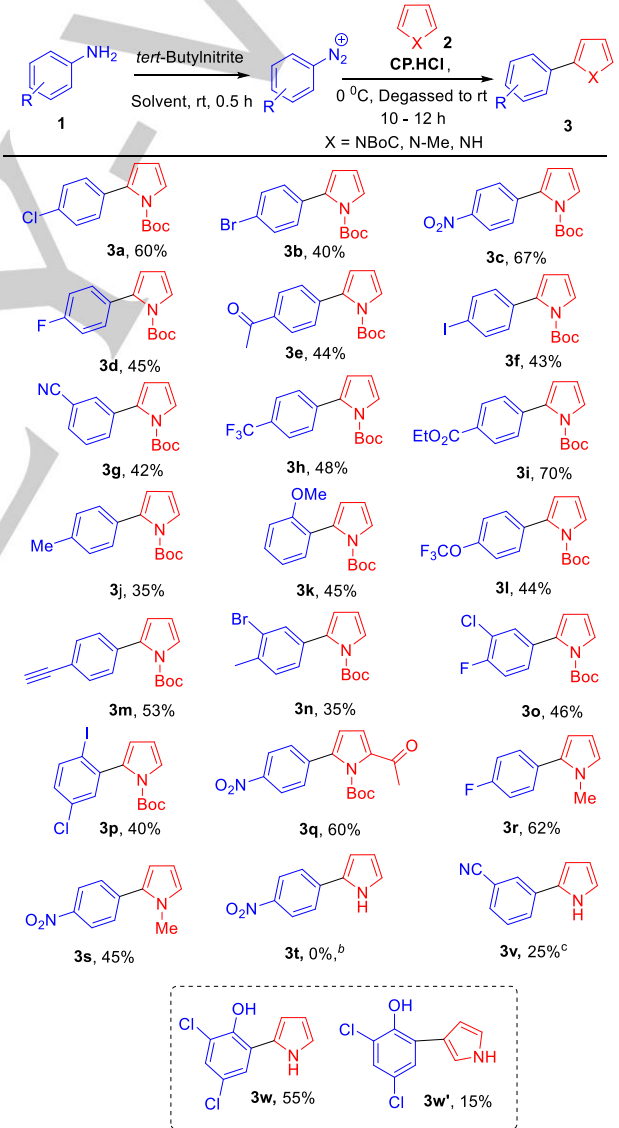


entries	**1** (mmol)	**2** (mmol)	**CP.HCl** (mmol)	Base	Solvent	**3** Yield %[b]
1	1	2.5	1	.....	DMSO	53
2	1	2.5	1	.....	DMF	40
3	1	2.5	1	.....	D_6-DMSO	NR
4	1	2.5	1	.....	DCM	NR
5	1	2.5	1	.....	ACN	NR
6	1	2.5	1	.....	THF	NR
7	2	1	1	.....	DMSO	NR
8	2.5	1	1	.....	DMSO	NR
9	1	2.5	0.5	.....	DMSO	<10
10[c]	**1**	**2.5**	**2**	.....	**DMSO**	**60**
11[c]	1	2.5	...	....	DMSO	NR
12[c]	1	2.5	DIPEA.HCl	.....	DMSO	14
13[c]	1	2.5	NH_4Cl	.....	DMSO	12
15[c]	1	2.5	.....	Chlorpromazine	DMSO	NR
16[c]	1	2.5	.....	Et_3N	DMSO	NR
17[c]	1	2.5		DABCO	DMSO	NR
18[c]	1	2.5	.....	DIPEA	DMSO	NR

Reaction conditions: [a]Reactions were carried out using **1** (1 mmol) in 4 mL of solvent; [b]isolated yields; [c]reaction conducted under Ar after degassing

Table 1. Optimization studies

Equipped with optimized conditions in hand, we further explored the scope of C-2 arylation by investigating the reaction between various anilines and pyrroles (Scheme 1). Electron-withdrawing groups such as 4-bromo, 4-nitro, 4-fluoro, 4-acetyl, 4-iodo, 3-cyano, 4-(trifluoromethyl) and 4-ethoxycarbonyl containing anilines reacted smoothly with *N*-Bocpyrrole **2** and furnished the coupled product **3b-3i** in good to moderate yield (40-70%). Anilines containing electron-donating groups such as 4-methyl, 2-methoxy and 4-(trifluoromethoxy) aniline also reacted smoothly and afforded the desired products **3j-3l** in a moderate to good yields (35-53%). Sensitive substrates which pose a problem under metal-catalyzed conditions such as 4-ethynylaniline when tried under optimized conditions gave the corresponding coupled product in a yield of 53%. Several disubstituted anilines such as 3-bromo-4-methylaniline, 3-chloro-4-fluoroaniline and 3-chloro-2-iodoanline also coupled with *N*-Bocpyrrole and afforded the corresponding products **3n, 3o and 3p** in a yield of 35, 46 and 40%, respectively. Furthermore, the optimized reaction condition was also applied to substituted pyrroles to further expand the scope of the present protocol. 2-Acetyl-*N*-Bocpyrrole underwent reaction with *p*-nitroaniline and gave the coupled products **3q** in a yield of 60%. Unlike a most reported method, the present optimized conditions when tried with *N*-methyl pyrrole, gave the coupled product with good yields (Scheme 1). *N*-Methyl pyrrole on reaction with 4-fluoro and 4-nitroanilines gave the corresponding desired products **3r** and **3s** in a yield of 62 and 45%, respectively. Furthermore, optimized conditions when tried for the coupling of 4-nitroaniline with *NH*-pyrrole, no 2-arylated product **3t** was formed, instead 2-azo product was observed. On the other hand, when 3-cyanoaniline was employed, 2-aryl pyrrole **3v** was observed in a yield of 25% along with a 2-azo product. The position of substitution play an important role to decide the fate of product and it seems the presence of electron-withdrawing group at 3-position favors dediazotization more frequently and could be the reason for providing the coupled product (need more investigation, will be studied in depth). This was further validated when 3,5-dichloro-6-hydoxyaniline (having two electron-withdrawing groups at 3-positions) was used, 2-arylated product **3w** was formed in a yield of **55%** along with some quantity of 3-aryl product **3w'**, no azo product was formed.



Reaction conditions unless otherwise noted: [a]Reactions were carried out using **1** (1 mmol), heteroarene **2** (2.5 mmol, in the case of pyrrole derivatives), and Chlorpromazine hydrochloride (2 mmol) in 4 mL of DMSO under Ar; [b]*azo product was observed with a yield of 74%; [c]azo product was observed with a yield of 50%

Scheme 1. Substrate scope of Boc-Pyrrole.

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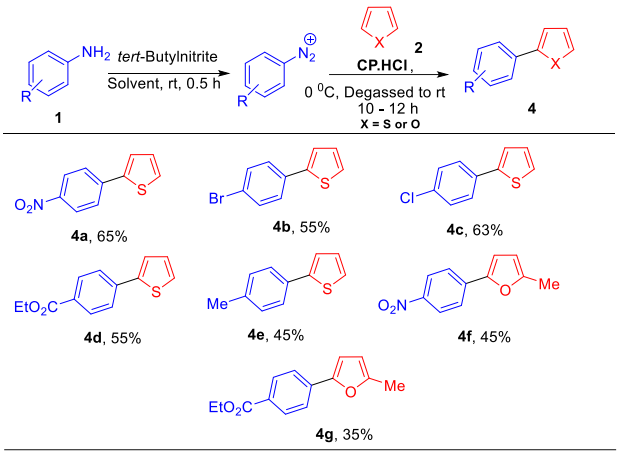
To increase the diversity, other heteroarenes such as thiophene and furan were also tried, and the results are provided in Scheme 2. Thiophene reacted well with both electron-withdrawing and electron-donating groups containing anilines and afforded the desired products (**4a**-**4e**) with a yield of 55-65%. On the other hand, 2-methylfuran when reacted with *p*-nitroaniline and 4-ethoxycarbonyl anilines, coupling happened and afforded the desired products **4f** and **4g** in a yield of 45% and 35 %, respectively.

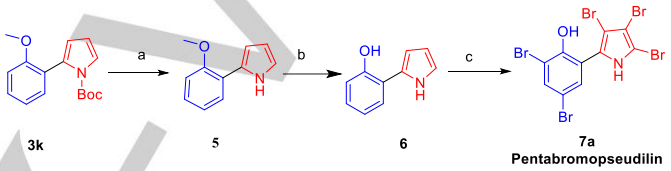


Reaction conditions unless otherwise noted: [a]Reactions were carried out using **1** (1 mmol), heteroarene **2** (2.5 mmol, in the case of furans and 5 mmol in case of thiophenes), and Chlorpromazine hydrochloride (2 mmol) in 4 mL of DMSO.

Scheme 2. Substrate scopes with other heteroarenes.

As mentioned above in the introductory paragraph, 2-arylated pyrrole present in many pharmacologically active molecules and among those, marine natural products namely pentabromopseudilin (PBP) and pentachloropseudilin (PCP) represent an important class, which were first isolated from *Pseudomonas bromoutilis* in 1966[6,7] and later from *Chromobacteria*, *Alteromonas luteoviolaceus*, and other *Pseudoalteromonas* sp.[9] They have attracted the potential because of their role as allosteric inhibitors of Myosin ATPase[25] and Non-mevalonate pathways of Isoprenoid (IspD).[26] Apart from these, pseudilins are also known for potential anti-bacterial and anti-fungal activities.[27] Myosin 1 is an ancient family of motor proteins. Most Myosin 1 motors are a single headed molecular motor that travels on actin tracks, and its functions are poorly understood.[28] Although it is reported to be involved in multiple cellular functions, [29] there are few tools to address its precise role. The discovery of the potential of inhibiting Myosin family proteins via the pseudilin family of molecules has opened up new ways of exploring the role of this important motor class. The availability of new and facile synthetic strategies for pseudilin is an important step towards finding small molecule chemical inhibitors for this family. The strategy of allosteric inhibition that is reported here should provide a potential flexibility of deriving specific inhibitors of this family of molecules.

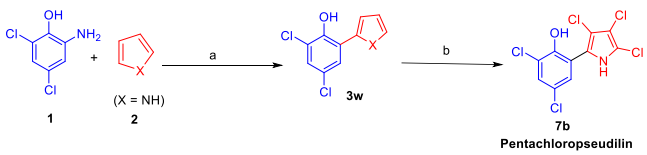
Considering their importance, many groups have attempted their synthesis and till date, four synthetic routes have been developed for the synthesis of pentabromopseudilin (PBP),[30a-b,25,30c] however, on the other hand there is only route towards the synthesis of pentachloropseudilin (PCP).[25] All the literature reported methods (detail provided in Figures S1 and S2 of supporting information (SI)) involves the construction of pyrrole nucleus by using multi-step synthetic strategies starting from aliphatic intermediates already containing the aromatic substituent and none of them have used the direct method of synthesizing 2-arylated pyrrole. This might be because of functionalities such as the hydroxyl group present on the arylated nucleus and offered difficulties during synthesis by direct methods. As the present method has good functional group compatibility with an electron-donating group (2-methoxy) containing anilines, therefore, its corresponding coupled product **3k** is further explored for the synthesis of pentabromopseudilin **7a** (Scheme 3). To synthesized pentabromopseudilin **7a**, the coupled product **3k** was first treated with potassium carbonate for the deprotection of Boc group and then heated with pyridine hydrochloride for demethylation to get key intermediate 2-(2-hydroxyphenyl)pyrrole **6**. The intermediate **6** was then treated with brominating agent (pyridinium tribromide) which furnished the final product *i.e* PBP in a yield of **25%.**



Reagent and Conditions: a) K_2CO_3, MeOH, 24-36 h, 40%; b) Py. HCl, 180 °C, 30%; c) Py.HBr_3 dry, 25% THF

Scheme 3. Synthesis of Pentabromopseudilin (PBP).

In order to get the pentachloropseudilin (PCP, **7b**, the intermediate 2-(2-hydroxypheyl)pyrrole **6** was treated with various chlorinating agents such as boron trichloride and *N*-chorosuccinimide but none gave the desired product, pentachloropseudilin in our hand. In most of the attempts, a mixture of di-and tri-chloro products was observed based on LC-MS analysis. These results suggested that the presence of chloro-groups makes the system deficient and suppressed the formation of required pentachloro product **7b**. Later, we changed the strategy, where 2-arylated product **3w** was taken as substrate and when treated with *N*-chlorosuccinimide, successfully yielded PCP **7b** in a yield of 46% (Scheme 4).

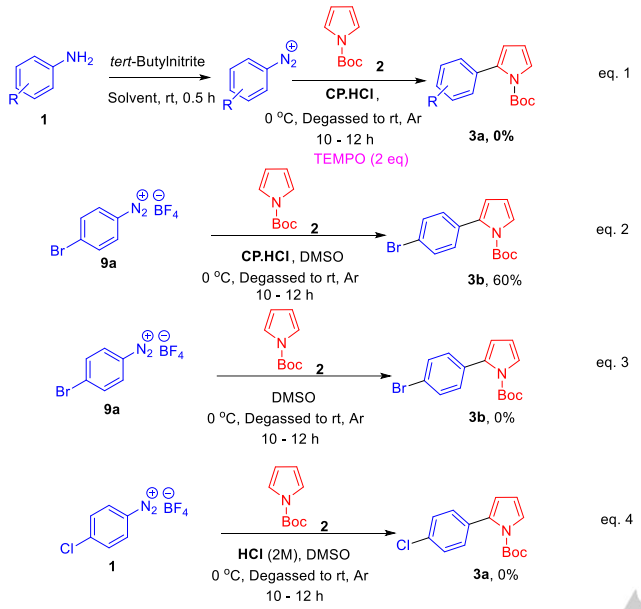


Reagent and Conditions: a) *t*-BuONO, Chloropromazine, DMSO; 8a (55%) and 8a' (15%); b) Recrystallized NCS, -40 to 0 °C, 12-16 h, 46%.

Scheme 4. Synthesis of pentachloropseudiline (PCP).

To gain insight into the reaction mechanism, a series of control experiments were performed (eq. 1-4, Scheme 5). When the reaction was performed in the presence of free radical scavengers such as TEMPO, the formation of the product, **3a**, was significantly suppressed (eq. 1), confirming the involvement of a radical pathway. In another attempt, the preformed

diazonium salt such as 4-bromobenzenediazonium tetrafluoroborate **1a** was tried under optimized conditions, the corresponding coupled product was formed in a yield of 60% (eq. 2). On the other hand, when the same reaction was conducted in the absence of CP salt (eq. 3), no product formation was observed confirming that CP salt plays an important role in the present reaction. The reaction in the presence of CP salt



Scheme 5. Control experiments.

suggested that chloride ion may also play some role in dediazotization step. In order to ruled out this, when the reaction was conducted in the presence of HCl instead of

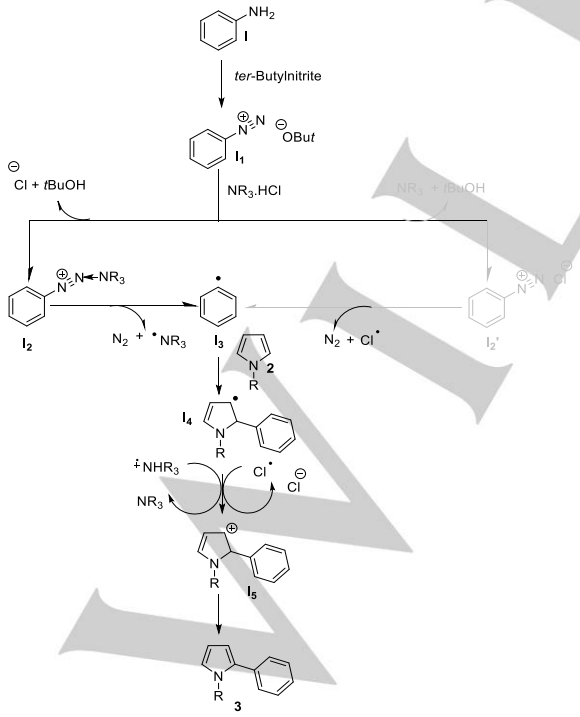


Figure 2. Plausible mechanism.

CP.HCl, no product formation was observed (eq. 4). During the optimization study, when the reaction was conducted in the presence of chlorpromazine (entry 15, Table 1), no desired product was formed suggested that CP.HCl might be balancing the *tert*-butoxide ion and then allowing the diazonium salt to interact with chlorpromazine.

On the basis of the above observation and literature precedents[16,17,18,19] a tentative mechanism is proposed as shown in Figure 2. First, aniline reacts with *tert*-butyl nitrite to yield the diazonium salt[18,19] which undergo an exchange of anion with CP.HCl and generate the intermediate $\mathbf{I_2}$, because of complex forming properties of CP. The intermediate $\mathbf{I_2}$ undergo single-electron transfer reaction lead to the formation of phenyl radical $\mathbf{I_3}$ which was subsequently intercepted by the pyrrole **(2)** to generate the resonance stabilized allyl radical $\mathbf{I_4}$. The radical intermediate $\mathbf{I_4}$ is further oxidized by cation radical followed by the loss of a proton to furnish the expected coupled products **3**.

Here, we have also investigated the effect of the PCP on several reported phenotypes in mammalian cells. We studied the effect of PCP **7b** on the distribution of GFP-tagged GPI anchored proteins (GFP GPI), stably expressed in Chinese hamster ovary (CHO) cells (Figure 3). Myosin 1c depletion has been shown to affect the trafficking of GPI-anchored proteins in earlier studies.[31] Treatment of cell with PCP **7b** for 3.5 h, reduces levels of GPI-anchored protein at the plasma membrane as observed by total internal reflection microscopy (TIRF-M) (Figure 3A and B). Using confocal microscopy, we also observed perinuclear accumulation of GFP GPI (Figure 3C) which has also been reported upon depletion of Myosin 1c in cells.[31] Finally, we examined the effect of PCP **7b** upon cell spreading on fibronectin (Figure 3D and E). We observed that the cells spread to a lesser extent when treated with the drug compared to vehicle-treated cells. This is in agreement with earlier reports on the effect of Myosin1c depletion on spreading of cells.[31] Altogether, our results suggest that the treatment with PCP **7b** phenocopies Myosin1c depletion in cells, providing a strong biological validation of the activity of this compound.

Conclusion

We have developed a general method for the arylation of *N*-heteroarenes under metal-free and mild reaction conditions. In this methodology, CP.HCl has been successfully employed as a radical initiator for the direct C-H arylation of (hetero)arenes. The reaction is mild, operationally simple, and constitutes a good approach for arylation. Remarkably, the present methodology was also utilized for the synthesis of highly important marine based natural products namely pentabromopseudilin and pentachloropseudilin. Pentachloropseudilin (PCP) has been shown to phenocopy the effect of Myosin1c depletion with respect to the accumulation of lysosomal vesicles in HeLa cells,[32] and several other trafficking defects. PCP treatment appears to phenocopy these effects, remarkably faithfully, providing strong justification for the use of PCP as a Myosin 1 inhibitor in cellular studies. The lack of effects on the function of other Myosins[32] indicates that this compound may be used as a specific probe for Myosin 1 function in cells. This study indicates the huge potential application of CP or its derivatives as a radical initiator and opening a new opportunity for its further use as a catalyst in other radical processes.

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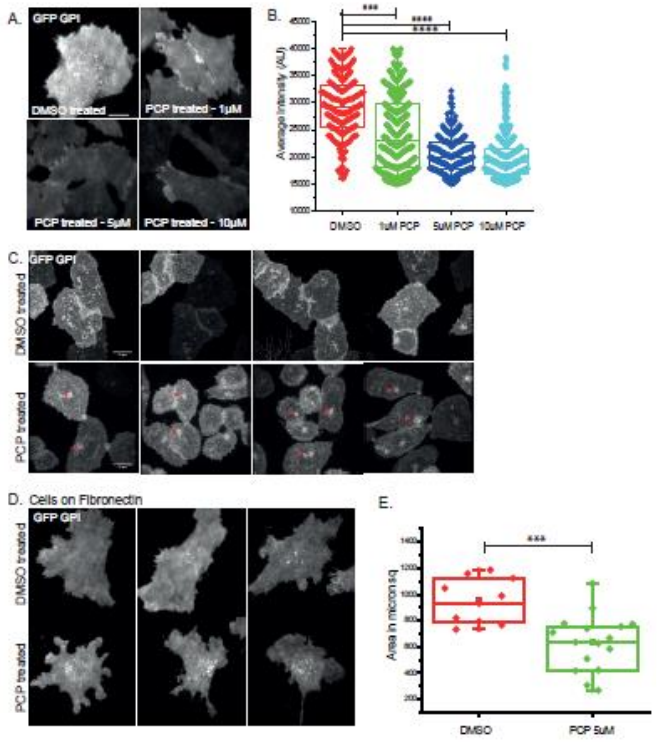

Figure 3. Pentachloropseudilin (PCP, **7b**) phenocopies Myosin1 perturbation in cells: A) Representative TIRF-M images showing cells expressing GFP tagged GPI (GFP GPI) treated overnight with DMSO or 1, 5, 10 µM PCP, exhibiting lowering of surface intensity of GPI anchored proteins; B) Quantification of intensity of regions from TIRF images of cells expressing GFP GPI (C) Maximum intensity projection images depicting accumulation of GFP GPI (arrows) in cells treated with PCP for 3.5 hours; D) Representative images depicting cell spreading on fibronectin-coated surface upon pre-treatment with DMSO/PCP after 150 minutes of plating; E) Quantification of cell area in DMSO versus PCP treated cells depicted in D.

Experimental Section

Appropriate aniline (1 mmole) was dissolved in 4 mL of DMSO followed by the addition of (2 mmol) *tert*-butyl nitrite. Then the reaction mixture was stirred for 30 min for the generation (*in-situ)* of the diazonium salt. The resulting mixture was then degassed by "pump-freeze-thaw" cycles (×2) via a syringe needle After that, the reaction mixture was cooled to 0°C followed by the slow addition of **2** (Boc-Pyrrole, *N*-methyl Pyrrole, *NH*-Pyrrole) and chlorpromazine hydrochloride. After completion, the reaction mixture was diluted with diethyl ether and washed with 30 mL of water. The aqueous layer was washed three times with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to give the crude product which was further purified by using column chromatography.

Cell culture

A Chinese Hamster Ovary (CHO) cell line expressing GFP tagged GPI has been used for our experiments. Cells were cultured in Ham's F12 media from HiMedia and with 10% fetal bovine serum from GIBCO invitrogen.

Experimental methods

Cells were grown on coverslip-bottom dishes for 2 days before imaging. Cells were treated with the drugs for indicated time and concentration either in media for overnight treatment or in Hepes buffer saline (HBS) containing 2mg/ml glucose for acute perturbation. For cell spreading experiments, cells were pre-incubated with the drug and plated on fibronectin coated surface.

Microscopy

Cells were imaged on TIRF using a 100X oil objective, 1.49NA, using an inverted Nikon Ti Eclipse microscope and Cascade 512 cameras. For a perinuclear vesicle identification experiment, cells were imaged using a 100X oil objective mounted on a Spinning disc confocal microscope equipped with a Yokogawa CSU and Andor EMCCD cameras.

Analysis and statistical significance

Intensity was measured by making 20X20 pixel or 30X30 regions on the flat surface of the cell membrane and average intensity from these boxes were calculated for cells imaged on TIRF. The Area was measured by drawing regions along the periphery of the cells using Image J plugin. KS test was performed to compare two distributions and test for statistical significance.

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Keywords: C-H arylation • Aryl Radical • Pentabromopseudilin • Pentachloropseudilin • 2-arylated pyrroles.

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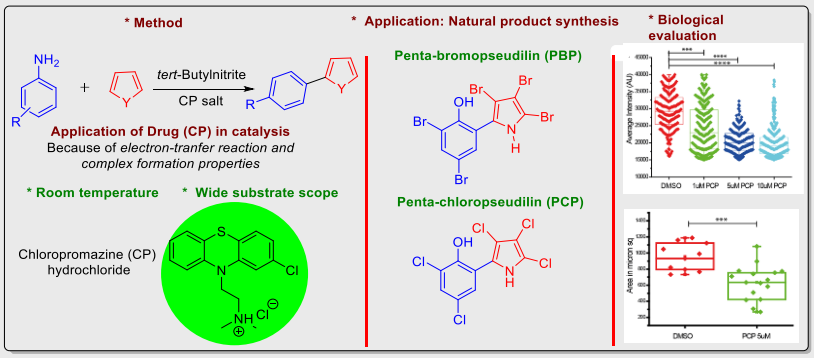
Table of Contents

COMMUNICATION: C-H Arylation and Synthesis of Pentabromo/choropseudilins



Here, we have developed a metal-free and mild condition for the synthesis of 2-arylated heteroarenes. The complex forming property and charge transfer property of phenothiazine expanded its application towards catalysis The optimized condition has been successfully employed for the synthesis important marine natural product namely pentabromo/chloropseudilins (PBP/PCP). The synthesized Pentachloropseudilin (PCP) has been shown to phenocopy the effect of Myosin1c depletion which provides a strong justification for the use of PCP as a specific probe for Myosin 1 function in cells.

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C-H Arylation of N-heteroarenes: Application towards the synthesis of marine natural product