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Direct halogenation of the C1—H bond in pyrrolo[1,2–a]quinoxalines

Huy X. Le [a,b], Tran N.B. Hoang [a,b], Thang H. Tran [a,b], Cao T.D. Nguyen [a,b], Linh N.T. Chiem [a,b], Nam T.S. Phan [a,b], Tung T. Nguyen [a,b,*]

[a] Faculty of Chemical Engineering, Ho Chi Minh City University of Technology (HCMUT), 268 Ly Thuong Kiet, District 10, Ho Chi Minh City, Viet Nam
[b] Vietnam National University, Ho Chi Minh City, Viet Nam

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ABSTRACT

Although pyrrolo[1,2–a]quinoxalines are important in pharmaceutical research and organic synthesis, diversification of these compounds is still limited. Herein we have developed a method for the selective chlorination of the C1—H bond in 4-aryl pyrrolo[1,2–a]quinoxalines. The reactions proceeded in the presence of NCS as a chlorinating agent, a catalytic amount of DMSO, and $CHCl_3$ as the solvent. Various functional groups including fluoro, chloro, and methylthio were compatible with the reaction conditions. Heterocycles located at the C4 positions of pyrrolo[1,2–a]quinoxalines such as furan, thiophene, or pyridine were also compatible with the reaction conditions. The bromination of pyrrolo[1,2–a]quinoxalines was successful in the presence of $CuBr_2$ as a brominating agent, $K_2S_2O_8$ as an oxidant, and toluene as the solvent.

Introduction

Pyrrolo[1,2–a]quinoxalines have found various uses in bio-related studies (Fig. 1) [1]. Such [6,5]fused heterocycles have attracted substantial attention [2]. Most of the known examples utilize three-step synthetic sequences starting from commercially available 2-nitroanilines. Meanwhile, a general method for the direct monofunctionalization of C—H bonds in pyrroloquinoxalines is unknown. 1-Halo-4-arylpyrroloquinoxalines have been obtained *via* a sequence of dihalogenation/C—C cross coupling [2a]. One example of the bromination of *N*-acetyl dihydropyrroloquinoxaline was reported [1b]. Since the direct C—H functionalization of pyrrolo[1,2–a]quinoxalines would facilitate late-stage diversification, the development of such methods is of interest.

The halogenation of aromatic C—H bonds is perhaps the most typical and convenient transformation for the prefunctionalization of substrates toward cross-coupling [3]. Although electrophilic substitution of halogens is well-precedented, the toxic and corrosive reagents utilized represents a major drawback. Additionally, using highly electrophilic reagents often results in the formation of isomeric mixtures. Methods for the direct halogenation of sp^2 C—H bonds under mild conditions have recently been reported [4]. A novel reagent, namely chlorobis(methoxycarbonyl)guanidine, was developed by Baran and co-workers, allowing for the functionalization of challenging substrates [4a]. Jiao and co-workers recently described a notable method for the chlorination of arene C—H bonds at room temperature [5]. The reaction utilized an electrophilic chlorinating agent formed *in situ* from NCS and DMSO. Herein, the synthesis of 1-chloro-4-arylpyrroloquinoxalines directly from its precursors is reported. Bromination of the C1—H bond in 4-aryl pyrrolo[1,2–a]quinoxalines was also feasible, thus providing flexible routes to obtain halogenated [6,5]fused *N*,*N*-heterocycles.

Results and discussion

Our study started with the chlorination of 4-phenyl pyrrolo [1,2–a]quinoxaline **1a**. Different conditions were investigated, and the results are shown in Table 1. Using NCS as a chlorinating source in the presence of a catalytic amount of DMSO and $CHCl_3$ as the solvent, the C1-chlorinated product **2a** was obtained in 59% yield (Entry 1) [6]. Cheeseman previously described a method for the chlorination of pyrrolo[1,2–a]quinoxaline, using NCS in aqueous sulfuric acid [7]. However, only one example, which was obtained as the regioisomeric product, was reported. Omitting DMSO only gave trace amounts of **2a** (Entry 2) [5]. Attempts to use hypervalent iodine reagents were examined, affording the desired product in moderate yields (Entries 3 and 4). The chlorination was successful using Togni's reagent (Entry 5). However, the two-step synthesis of this chloro-benziodoxolone limits the convenience of this method [4b]. Recently, a protocol for selective halogenation was developed using trihaloisocyanuric acids [4d]. Using the reported conditions with pyrrolo[1,2–a]quinoxaline **1a**

* Corresponding author.
E-mail address: tungtn@hcmut.edu.vn (T.T. Nguyen).

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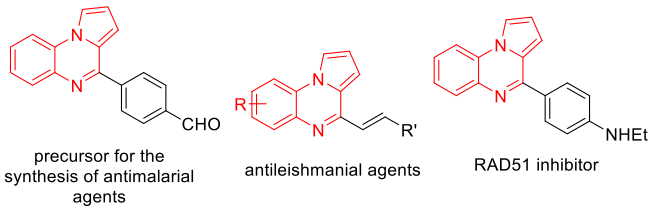
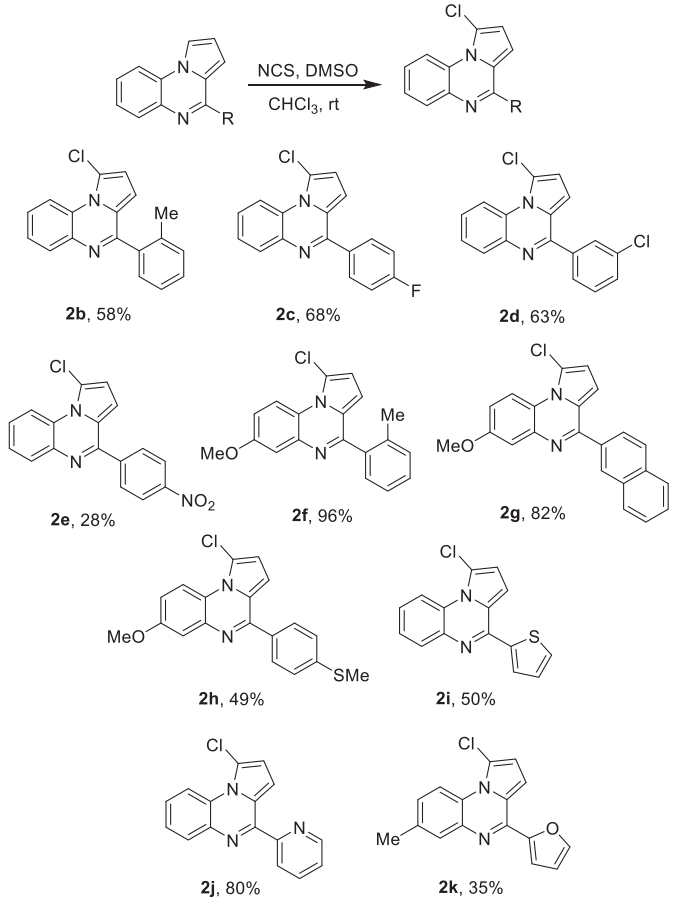


Fig. 1. Bio-related pyrrolo[1,2–a]quinoxalines.

afforded an isomeric, inseparable mixture of chlorinated products (Entry 6). A selective bromination was also considered. In the first attempt, replacing NCS with NBS gave heteroaryl bromide **2b** in 47% yield (Entry 7). After extensive screening, the desired halide **2b** was obtained in good yield (66%) using $CuBr_2$ as a bromide source, $K_2S_2O_8$ as an oxidant, and toluene as the solvent (Entry 8). Notably, using $CuCl_2$ for the chlorination under similar conditions afforded a complex mixture of regioisomers.

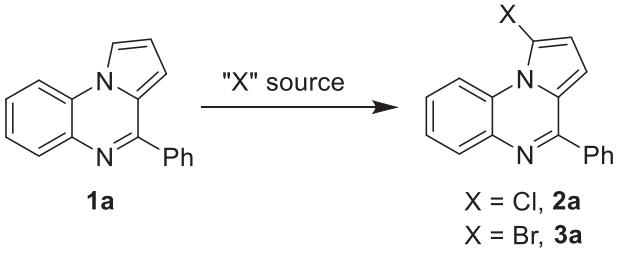
The scope of the selective chlorination is presented in Scheme 1. Benzylic C—H bonds were inert, thus methyl-substituted substrates were obtainable (**2b**, **2f**). Functionalities such as fluoro (**2c**), chloro (**2d**), and methylthio (**2h**) groups were compatible with the reaction conditions, affording the chlorinated heterocycles in moderate yields. Nitro-substituted pyrrolo[1,2–a]quinoxaline could also be used; albeit giving the desired chloride **2e** in low yield. Naphthalene-derived pyrrolo[1,2–a]quinoxaline (**2g**) was obtained in 82% yield. Substrates bearing heteroaryl rings at the C4 positions are potential bidentate ligands. Thus, attempts to chlorinate such pyrrolo[1,2–a]quinoxalines were examined. The corresponding chlorides **2i**-**2k** were obtained in moderate to high yields (35–80%).

Control experiments were carried out to clarify the mechanism of the chlorination (Scheme 2). The addition of radical quenchers such as TEMPO or BHT did not significantly affect the yield of **2a**. This result somewhat eliminated the involvement of radical species during the reaction course. Omitting NCS gave only trace



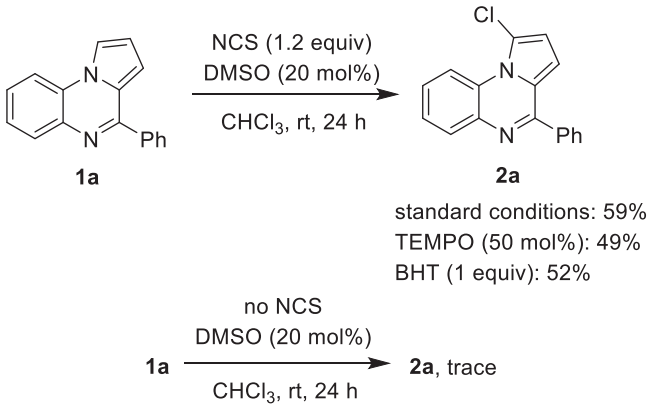
Scheme 1. Chlorination of pyrrolo[1,2–a]quinoxalines. Reagents and conditions: pyrrolo[1,2–a]quinoxaline (0.1 mmol), NCS (0.12 mmol), DMSO (0.02 mmol), $CHCl_3$ (1 mL), room temperature, 24 h. Isolated yields.

Table 1
Reaction optimization for the C1-halogenation of pyrroloquinoxaline 1a.[a]

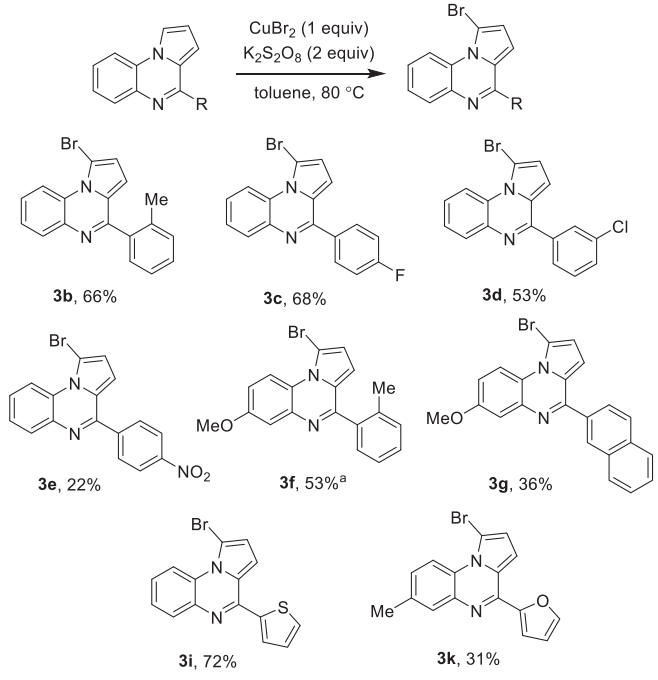


Entry	X	"X" source	Conditions	Yield **2a** or **3a** (%)[b]
1[c]	Cl	NCS	DMSO, $CHCl_3$, rt	59
2[d]	Cl	NCS	$CHCl_3$, rt	33
3[e]	Cl	Bu_4NCl	$PhI(OAc)_2$, DCE, 50 °C	51
4[f]	Cl	TMSCl	$PhI(OTFA)_2$, CH_2Cl_2, rt	54
5[g]	Cl	Togni's reagent	DMF, rt	57
6[h]	Cl	TCICA	EtOH, rt	n.d.
7[i]	Br	NBS	DMSO, $CHCl_3$, rt	47
8[j]	Br	$CuBr_2$	$K_2S_2O_8$, toluene, 80 °C	66
9[k]	Cl	$CuBr_2$	$K_2S_2O_8$, toluene, 80 °C	n.d.

[a] **1a** (0.1 mmol). [b]Isolated yields. [c]NCS (0.12 mmol), DMSO (0.02 mmol), $CHCl_3$ (1 mL), room temperature, 24 h. [d]NCS (0.12 mmol), $CHCl_3$ (1 mL), room temperature, 24 h. [e]Bu_4NCl (0.5 mmol), $PhI(OAc)_2$ (0.15 mmol), 1,2-dichloroethane (2 mL), 50 °C, 1 h. [f]TMSCl (0.2 mmol), $PhI(OTFA)_2$ (0.1 mmol), CH_2Cl_2 (0.5 mL), room temperature, 18 h. [g]Togni's reagent (1-chloro-1,2-benziodoxol-3-one, 0.12 mmol), DMF (2 mL), room temperature, 12 h. [h]Trichloroisocyanuric acid (TCICA, 0.04 mmol), EtOH (1 mL), room temperature, 1 h; a mixture of chlorinated products was obtained. [i]NBS (0.12 mmol) instead of NCS. [j]$CuBr_2$ (0.1 mmol), $K_2S_2O_8$ (0.2 mmol), toluene (1 mL), 80 °C, 24 h. [k]$CuCl_2$ (0.1 mmol) instead of $CuBr_2$. Abbreviation: n.d. = not determined.



Scheme 2. Control experiments for the chlorination reaction.



Scheme 3. Bromination of pyrrolo[1,2–a]quinoxalines. Reagents and conditions: pyrrolo[1,2–a]quinoxaline (0.1 mmol), $CuBr_2$ (0.1 mmol), $K_2S_2O_8$ (0.2 mmol), toluene (1 mL), 80 °C, 24 h. Isolated yields. [a]A dibrominated product observed by GC–MS was also isolated in 7% yield.

amounts of the chlorination product, thus confirming the crucial role of NCS as the major chloride source [5].

The scope of the bromination of pyrrolo[1,2–a]quinoxalines is presented in Scheme 3. The conditions did not affect benzylic C—H bonds (**3b**, **3f**). Halogenated pyrrolo[1,2–a]quinoxalines were brominated in moderate yields (**3c**, **3d**). Unfortunately, nitro-substituted pyrrolo[1,2–a]quinoxaline was only obtained in 22% yield (**3e**). A dibrominated product was obtained when an electron rich pyrrolo[1,2–a]quinoxaline was used (**3f**). The synthesis of polyaromatic molecules such as **3g** was also possible. The pyrrolo[1,2–a]quinoxaline containing a thiophene ring at the C4 position was also a competent substrate for bromination (**3i**). A low yield was obtained for the pyrrolo[1,2–a]quinoxaline containing a furan moiety at the C4 position (**3k**).

Conclusion

A novel method has been developed for the selective chlorination and bromination of sp [2] C—H bonds in 4-aryl pyrrolo[1,2–a]quinoxalines. The conditions are mild and simple, and thus compatible with functionalities such as halogen, methylthio, nitro and heterocyclic groups. Our approach represents a feasible route for the late-stage functionalization of complex pyrrolo[1,2–a]quinoxalines.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152879.

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