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ARTICLE TYPE

Palladium catalyzed *ortho*-halogenation of 2-arylbenzothiazole and 2,3-diarylquinoxaline†

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A palladium catalysed *ortho*-halogenation strategy has been developed using benzothiazoles and quinoxalines as the directing substrates. This method provides mono-*o*-halogenated product at the other available *ortho* site of a mono-*ortho* substituted 2-arylbenzothiazole. However, *ortho*-unsubstituted 2-arylbenzothiazole afforded di-*ortho* halogenated product exclusively. The preformed (or installed) *ortho*-group is towards the sulphur side of benzothiazoles as arrived from energy minimised calculation. Thus the selective formation of di-*ortho*-halogenated products is due to favourable exposure of second *ortho* site for subsequent halogenation. However the phenyl ring in 2,3-diarylquinoxalines can be selectively mono *ortho* halogenated. A plausible reaction mechanism has been proposed for this halogenation process.

Introduction

Transition metal-catalysed directed[1] and non directed[2] C–H functionalisation has emerged as an atom and step economic strategy for developing synthetically versatile intermediates *via* unprecedented disconnections. Besides other transition metals, the use of palladium catalyst in chelation-directed C–H activation reactions are of interest due to its better efficacy and high turnover numbers.[3] Of late a plethora of Pd-catalysed *ortho* C–H functionalisations have appeared in the literature using various rigid and flexible directing substrates.[4] Although a number of transition metal-catalysed C–H functionalisation strategies are reported for the formation of carbon–carbon (C–C) bonds,[5] formation of carbon–heteroatom (C–X) bonds, in particular carbon–halogen bonds, are relatively less explored. Aryl halides (Ar–X) are useful intermediates for synthetic organic chemistry and are valuable precursors for nucleophilic substitution reactions as well as for the synthesis of various organometallic reagents.[6] Aryl halides are also used in transition metal-catalysed cross-coupling reactions such as Suzuki, Negishi and Heck type couplings to construct complex structures.[7] However, preparation of aryl halides *via* classical halogenation suffer from some drawbacks such as poor regioselectivity and polyhalogenations, particularly for activated aromatics.[8] As a solution to these problems, substantial endeavours have been made recently for the regioselective *o*-halogenation of arenes catalysed by transition metals. A few Pd-catalysed protocols have emerged recently for the selective installation of halo groups at the *ortho* site of various directing groups *via* arene sp^2 C–H activation.[9] 2-Arylbenzothiazoles and 2,3-diarylquinoxalines bearing *o*-chelating moieties may provide cyclometallation at their proximal sites *via* the assistance of their nitrogen donor atoms and therefore could be employed for *o*-functionalisations. Recently our group and others have developed strategies for the *ortho* selective C–C and C–X bond formation using benzothiazole and quinoxaline as directing arenes.[10] In continuation to these reports we envisaged that these two directing arenes *viz.* benzothiazole and quinoxaline could similarly be *ortho* halogenated. 2-Arylbenzothiazoles and 2,3-diarylquinoxalines are both privileged motifs present in many naturally occurring molecules and pharmaceuticals.[11] Thus, further functionalisations of these important scaffolds may provide useful intermediates which may find potential applications. Herein, we describe a Pd-catalysed *o*-halogenation of 2-arylbenzothiazoles and 2,3-diarylquinoxalines using *N*-halosuccinamides NXS (X = Cl, Br and I) as halogen sources.

Results and Discussion

From the crystal-structure of 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1**) it was found that the ester group in 2-aryl ring is towards the sulfur side of benzothiazole and the two aromatic moieties are periplanar.[12] This periplanar orientation with further assistance from *N*-atom of benzothiazole is favaouable for cyclopalladation. Thus, 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1**) was chosen as the model substrate for *ortho*-bromination using *N*-bromosuccinimide as the source of bromine and $Pd(OAc)_2$ as the catalyst. When (**1**) (1 equiv.) was reacted with *N*-bromosuccinimide (**a**) (1.2 equiv.) in the presence of $Pd(OAc)_2$ (5 mol%) in toluene at 90 °C, mono-*o*-bromo product (**1a**) was obtained in 39% yield. Absence of any *meta* or *para*-bromo products suggest a substrate-directed regioselective *o*-bromination. Encouraged by this success, other reaction parameters such as solvents, catalysts, additives and their quantities were varied to maximise the product yield. Polar aprotic solvents such as DMF or DMSO (Table 1, entries 2 and 3)

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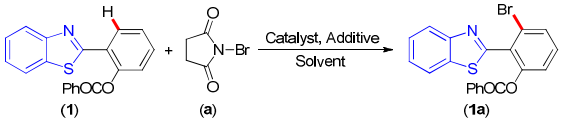
failed to give any trace of product whereas non polar solvents such as cyclohexane, *o*-xylene (Table 1, entries 4 and 5) provided very low yield of the product. Interestingly, by switching the solvent from toluene to 1,2-dichloroethane (DCE) (Table 1, entry 6) the product yield improved up to 58% under otherwise identical conditions. Other palladium salts such as $Pd(TFA)_2$, $PdCl_2$ and $PdBr_2$ (Table 1, entries 7–9), were relatively less potent compared to $Pd(OAc)_2$. In the absence of catalyst ($Pd(OAc)_2$) no *o*-bromination occured (Table 1, entry 10). No significant improvement in the product yield was observed even when the catalyst loading was increased from 5 to 10 mol %, (Table 1, entry 11). In a pursuit to further improve the yield, acid additives such as pivallic acid (PivOH), *para*-toluenesulfonic acid (PTSA), CF_3COOH (TFA) and CH_3COOH (AcOH) were used during the reaction. After screening the reaction with these acid additives, it was found that the use of 50 mol% PTSA under otherwise identical conditions provided an improved yield (79%) of the desired *o*-brominated product (**1a**) (Table 1, entry 12). In the presence of other acid additives such as TFA, AcOH cleavage of ester group in (**1**) was observed alongwith the formation of *o*-bromo product (**1a**) (Table 1, entry 13–14) thereby effectively lowering the yield. The ester group survived when PivOH was used as the additive but was not so effective toward desired *o*-bromination (Table 1, entry 15). Thus, after a series of experimentations, 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1**) (1 equiv.), catalyst $Pd(OAc)_2$ (5 mol %), additive PTSA (50 mol %) and *N*-bromosuccinimide (**a**) (1.2 equiv.) in 1,2 dichloroethane (2 mL) at 90 °C and a reaction time of 7 h was found to be the best conditions for this transformation (Table 1, entry 12).

Table 1 Screening of reaction conditions for *o*-bromination.[a,b]



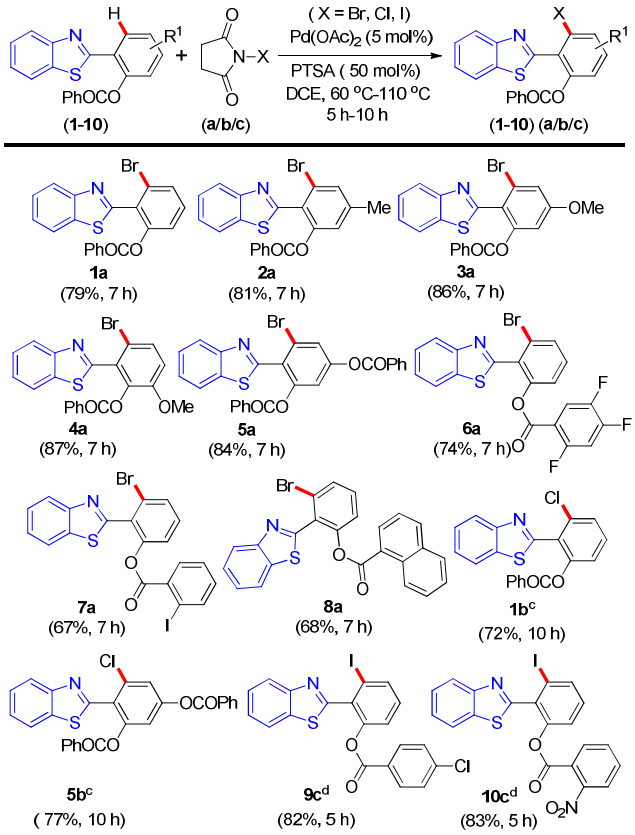
Entry	Catalyst (mol%)	Solvent	Oxidant	Yield (%)
1	$Pd(OAc)_2$ (5)	Toluene	NBS	39
2	$Pd(OAc)_2$ (5)	DMF	NBS	00
3	$Pd(OAc)_2$ (5)	DMSO	NBS	00
4	$Pd(OAc)_2$ (5)	C_6H_{12}	NBS	trace
5	$Pd(OAc)_2$ (5)	*o*-Xylene	NBS	trace
6	$Pd(OAc)_2$ (5)	DCE	NBS	58
7	$Pd(TFA)_2$ (5)	DCE	NBS	46
8	$PdCl_2$ (5)	DCE	NBS	44
9	$PdBr_2$ (5)	DCE	NBS	43
10	-	DCE	NBS	00
11	$Pd(OAc)_2$ (10)	DCE	NBS	62
12	**$Pd(OAc)_2$ (5)**	**DCE**	**NBS/PTSA**	**79[c]**
13	$Pd(OAc)_2$ (5)	DCE	NBS/TFA	68[c]
14	$Pd(OAc)_2$ (5)	DCE	NBS/AcOH	66[c]
15	$Pd(OAc)_2$ (5)	DCE	NBS/PivOH	63[c]

[a]Reaction conditions: **1** (0.25 mmol), NBS (0.3 mmol) at 90 °C for 7 h. [b]Isolated yield. [c]Additive (0.13 mmol).

Keeping the above optimised conditions in mind, this methodology was further applied to various substituted 2-(benzo[*d*]thiazol-2-yl)phenyl carboxylate with *N*-bromosuccinamide (**a**). 2-(Benzo[*d*]thiazol-2-yl)aryl benzoate containing various substituents at the 2-aryl ring such as *p*-Me (**2**), *p*-OMe (**3**), *m*-OMe (**4**) and *p*-OCOPh (**5**) gave their corresponding *o*-brominated products (**2a**), (**3a**), (**4a**) and (**5a**) in excellent yields (81–87%) (Scheme 1). It is clear from substrates (**1-5**) that no loss of regioselectivity and product yields were observed even with different substitution patterns on the aryl ring. Conversely, for substrates (**6**) and (**7**) the yields of their desired *o*-bromo products (**6a**) and (**7a**) were dropped marginally when substituents are present in the phenyl rings possessing the ester group (Scheme 1). Naphthylester bearing benzothiazole (**8**) also provided moderated yield of its corresponding *o*-bromo product (**8a**) (Scheme 1).

When analogous chlorination reaction of (**1**) with *N*-chlorosuccinimide (**b**) was carried out using the above optimised conditions, only 33% yield of *o*-chloro product (**1b**) was obtained. However by increasing the reaction temperature from 90 °C to 110 °C and prolonging the reaction time from 7 to 10 h provided the *o*-chlorinated product (**1b**) in an improved yield of 72%. Benzothiazole (**5**) having *ortho* and *para* di-OCOPh group in its 2-aryl ring gave 77% of *o*-chlorinated product (**5b**). Then the strategy was further extended toward *o*-iodination of mono-*o*-protected benzothiazole (**1**) using *N*-iodosuccinamide. Substrates (**9**) and (**10**) bearing *p*-Cl and *o*-NO_2 groups in their phenyl rings of the ester provided mono-*o*-iodo products (**9c**) and (**10c**) in 82% and 83% yields respectively. Interestingly, no substantial change in the product yield was observed even when the reaction was performed at lower temperature (60 °C). However, only trace amount of desired *o*-iodo product was formed when the reaction was carried out at 40 °C. From these observations it is evident that the rates of halogenation follow the order: iodination > bromination > chlorination.

Scheme 1 Scope of *o*-halogenation of 2-arylbenzothiazoles.[a,b]



[a]Reaction conditions: 2-arylbenzothiazole (**1-10**) (0.25 mmol), NXS (**a-c**) (0.30 mmol) and PTSA (0.13 mmol) in DCE (2.0 mL) at 90 °C, 7 h. [b]Yields of isolated product. [c]Temperature: 110 °C, 10 h. [d]Temperature: 60 °C, 5 h.

To verify whether this selective mono-*o*-bromination strategy can be applied to 2-arylbenzothiazole in the absence of *o*-ester functionality, substrate (**11**) with two available *ortho* sites was reacted under the above optimised conditions. When 2-phenylbenzothiazole (**11**) (1 equiv.) was treated with NBS (1.2 equiv.) under otherwise identical conditions surprisingly rather than the expected mono-*o*-brominated product only *ortho*-di-bromo product (**11a**) was obtained in 41% yield. Typically substrate-directed *o*-halogenation provides mono-halogenated as the major product with trace of di-*ortho*-halogenated product in few cases.[9(a-c),(f-h),13] In the present case exclusive formation of *ortho*-di-bromo product (**11a**) was rather surprising to us. After the initial *o*-mono bromination the benzothiazole and the 2-phenyl ring possibly adopt a similar periplanar orientation to that of substrate (**1**) exposing the other *ortho* site for subsequent bromination. Even the use of 2 equiv. of (NBS) provided no traces of mono-*o*-bromo product rather the yield of *ortho*-di-bromo product (**11a**) was enhanced to 53%.

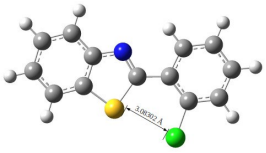


Fig. 1(**a**)

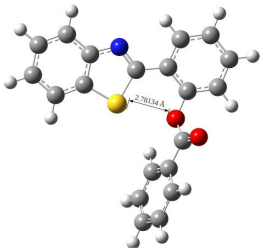
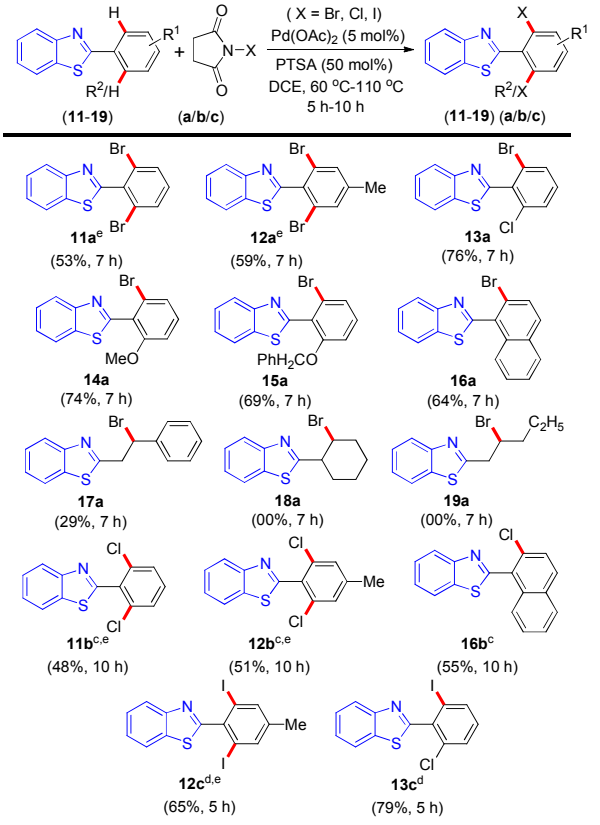


Fig. 1(**b**)

2-Arylbenzothiazole having moderately electron-donating group *p*-Me (**12**) in its 2-aryl ring gave 59% yield of di-*o*-brominated product (**12a**) again giving no trace of mono-*o*-bromo product. If our assumption on periplanar orientation of benzothiazole and 2-aryl ring after first bromination is true then preformed mono *ortho* substituted benzothiazoles should react to provide better yields of *bis-ortho* substituted products. To verify our assumption *o*-Cl (**13**), *o*-OMe (**14**) and *o*-OCH_2Ph (**15**) substituted 2-arylbenzothiazoles were employed for *ortho* bromination. All three substrates provided *o*-brominated products (**13a**), (**14a**) and (**15a**) in far better yields as shown in Scheme 2. Energy calculation performed using Gaussian 09 package[14] at B3LYP-D3/6-31G (d,p) level of substrate 2-(2-chlorophenyl)benzo[*d*]thiazole (**13**) revealed the periplanar orientation of benzothiazole and 2-chloro phenyl ring to be the most stable conformer with the chloro group orienting toward the sulphur side (Fig. 1(a)). The extra stability of this conformer is due to sulphur (S)···chlorine (Cl) interaction. Similar chloro (halo) and sulphur atom interaction is reported in various organic and inorganic moieties.[15] Such periplanar arrangement with the oxygen atom of the ester group orienting toward sulphur side is also observed in the energy minimised structure of 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1**) (Fig. 1(b)). Apparently, the energy minimised structure of (**1**) (Fig. 1(b)) matches exactly with its X-ray crystal structure.[12] Thus this type of periplanar orientation is the most favourable for *o*-palladation leading to *o*-halogenation. These results demonstrate the conformational predominance of the substrates over their steric and electronic effects during directed bromination. In case of substrate 2-(naphthalen-1-yl)benzo[*d*]thiazole (**16**) possessing both *ortho* and *peri* C–H bonds, bromination occurred selectively at the *ortho* site giving product (**16a**) in 64% yield. When *o*-bromination strategy was applied to 2-phenethylbenzo[*d*]thiazole (**17**), interestingly bromination occurred at the β C_{sp3}–H bond which happened to be a benzylic carbon as well. Now the query arises whether the bromination is due to classical radical benzylic bromination or a substrate directed metal-catalysed sp^3 C–H fucntionalisation. When the reaction was performed in absence of a Pd-catalyst under otherwise identical conditions, no bromination was observed thereby suggesting the later possibility. The lower yield (29%) obtained for (**17a**) is possibly due to the free rotation of C_{sp3}–C_{sp3} containing benzylic and its adjacent carbon thereby lowering the possibility of cyclopalladation. However other β C_{sp3}–H bearing alkane substrates such as (**18**) and (**19**) failed to provide desired brominated products (Scheme 2). Thus, for substrate (**17**) due to the presence of an acidic benzylic β C_{sp3}–H's the bromination was favourable compared to substrates (**18**) and (**19**). The success of this bromination strategy was then extended towards *o*-chlorination of substrates (**11**) and (**12**) using *N*-chlorosuccinimide (**b**) following the previous optimised conditions for chlorination, which provided *o*-di-chloro products (**11b**) and (**12b**) respectively in moderate yields (Scheme 2). Here again substrate (**16**) possessing both *ortho* and *peri* C–H bonds, the chlorination occurred regioselectively at the *ortho* site giving product (**16b**) in 55% yield. Analogous *o*-iodination of (**12**) and (**13**) using *N*-iodosuccinamide (**c**) gave *o*-di-iodo products (**12c**) and (**13c**) in 65% and 79% yields respectively under identical conditions for iodination. Here also the rates of *o*-di-halogenation (Scheme 2) follow the same order (iodination > bromination > chlorination) to that of mono-*o*-halogenation (Scheme 1).

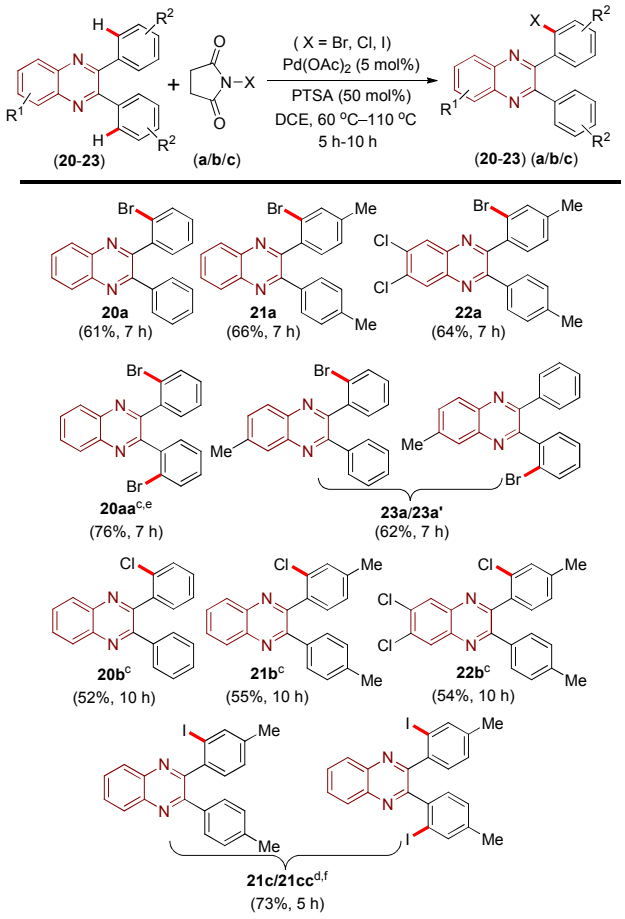
Scheme 2 Scope of *o*-halogenation of 2-arylbenzothiazoles.[a,b]



[a]Reaction conditions: 2-arylbenzothiazole (**11-19**), (0.25 mmol), NXS (**a-c**) (0.30 mmol) and PTSA (0.13 mmol) in DCE (2.0 mL) at 90 °C, 7 h. [b]Yields of isolated product. [c]Temperature: 110 °C, 10 h. [d]Temperature: 60 °C, 5 h. [e]NXS (**a-c**) (0.50 mmol).

Unlike in 2-aryl benzothiazoles, 2,3-diarylquinoxaline moiety has four *ortho* sites for possible directed halogenations. Thus, it would be interesting to see during halogenation which of the following products would be formed selectively under a particular condition. A mono-halogenation in one of the phenyl ring, mono-halogenation in each of the phenyl ring; dihalogenation in one of the ring or a dihalogenation in both the rings are some of the possibilities. Thus the above optimised haloganation conditions were applied to 2,3-diarylquinoxalines for bromination, chlorination and iodination respectively. 2,3-Diphenyl quinoxaline (**20**), when reacted with NBS (**a**) (1.2 equiv.) at 90 °C, mono-*o*-bromo product (**20a**) was obtained in 61% yield along with a trace (< 5%) of di-bromo (mono-bromination in each of the phenyl ring) product (**20aa**). However increasing the quantity of (NBS) to 2 equiv. the yield of the di-bromo product (**20aa**) was improved to 12%. Maintaining the (NBS) quantity to 2 equiv. and increasing the reaction temperature to 110 °C substantial improvement in the yield (76%) of the di-bromo product (**20aa**) was observed

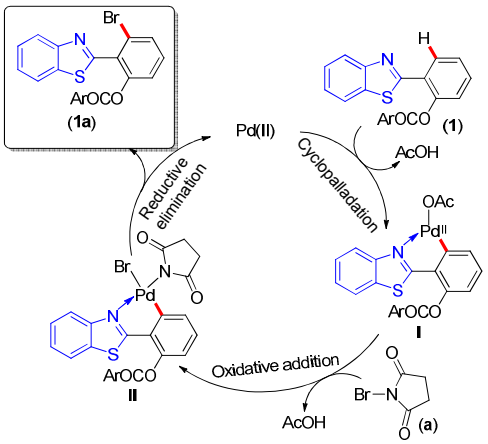
Scheme 3 Scope of *o*-halogenation of 2,3-diarylquinoxalines.[a,b]



[a]Reaction conditions: 2,3-Diarylquinoxaline (**20-23**), (0.25 mmol), NXS (**a-c**) (0.30 mmol) and PTSA (0.13 mmol) in DCE (2.0 mL) at 90 °C, 7 h. [b]Yields of isolated product. [c]Temperature:110 °C, 10 h. [d]Temperature:60 °C, 5 h.[e]NBS (**a**) (0.50 mmol). [f]Yield calculated with respect to recovered of starting material.

Presently, however we concentrate on achieving selective mono-bromination. 2,3-Diphenylquinoxaline (**21**) containing electron-donating group (-Me) in its aryl rings gave 66% of the mono-*o*-bromo product (**21a**). The substrate 6,7-dichloro-2,3-diphenylquinoxaline (**22**) on treatment with NBS (**a**) afforded moderate yield (64%) of the mono-*o*-bromo product (**22a**). Unsymmetrical 2,3-diphenylquinoxaline (**23**) having a -Me group at its 6th position when reacted with NBS provided an inseparable regioisomeric mono-*o*-bromo products **23a/23a′** in the ratio of 55 : 45 (as judged from its ^{1}H and ^{13}C NMR spectra) in 62% yield. So far chlorination is concerned under the optimised conditions various unsubstituted and substituted 2,3-diphenylquinoxaline such as (**20**), (**21**) and (**22**) all provided exclusive mono *ortho*-brominated products (**20b**), (**21b**) and (**22b**) respectively in good yields. Like previous cases iodination of substrate (**21**) provided an inseparable mixture of mono (**21c**) and di-iodo (**21cc**) products in a combined yield of 73%. In this system also the same reactivity trend (iodination > bromination > chlorination) to that of mono-*o*-halogenation was observed.

A possible mechanism has been proposed for this palladium catalysed *ortho*-halogenation reaction as shown in Scheme 4. For *o*-bromination process initial cyclopalladation of substrate (**1**) leads to the formation of intermediate (**I**). This intermediate further undergoes oxidative addition with *N*-bromosuccinamide (NBS) forming either a dimeric Pd(III)[16] or a monomeric Pd(IV)[9b,17] intermediate (**II**). During the mass spectral analysis of the reaction mixture some of the monomeric Pd(IV) species have been detected (see [SI], Fig. S1). However, the formation of a dimeric. Pd(III) during the reaction cannot be ruledout[16] Subsequent reductive elimination of intermediate (**II**) leads to *o*-bromo product (**1a**) *via* C–Br bond formation and regenerating Pd(II) catalyst for the next cycle. The mono-*ortho* bromo product so formed orient favourably for subsequent bromination following similar mechanistic path leading to the formation of di-bromo product. Similar mechanism can be proposed for chlorination and iodination of 2-aryl benzothiazole and 2,3-diarylquinoaline.



Scheme 4. Plausible mechanism for *o*-bromination.

Conclusion

In conclusion we have developed an *ortho*-halogenation strategy using palladium as the catalyst and *N*-halosuccinamide as the halogen source using benzothiazoles and quinoxalines as the directing substrates. This method provides mono-*o*-halogenated product at the other available *ortho* site of a mono-*ortho* substituted 2-arylbenzothiazole. Although *ortho*-unsubstituted 2-arylbenzothiazole afforded di-*ortho* halogenated product exclusively while *ortho*-unsubstituted 2,3-diarylquinoxaline

afforded mono-*o*-halogenated products under identical reaction conditions.

General procedure for the synthesis of 2-(benzo[*d*]thiazol-2-yl)-3-bromophenyl benzoate (1a) from 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (1) and *N*-bromosuccinamide (a):

To an oven-dried 25 mL round bottom flask were added 2-(benzo[*d*]thiazol-2-yl)phenyl benzoate (**1**) (0.083g, 0.25 mmol), *N*-bromosuccinamide (0.053g, 0.3 mmol), $Pd(OAc)_2$ (0.003g, 0.013 mmol), *p*-toluenesulfonic acid (0.024g, 0.13 mmol) and 1,2-dichloroethane (2.0 mL). Then the reaction mixture was refluxed in an oil bath preheated to 90 ^{o}C. After completion of the reaction (7 h) excess solvent was evaporated under reduced pressure. The product was extracted with ethyl acetate (3 x 10 mL) and the combined organic layer was washed carefully with saturated sodium bicarbonate solution (2 x 5 mL), dried over anhydrous sodium sulphate, and evaporated under reduced pressure. The crude product so obtained was purified by silica gel column chromatography (hexane / ethyl acetate, 10:0.3) to give pure 2-(benzo[*d*]thiazol-2-yl)-3-bromophenyl benzoate (**1a**) (0.081g, yield 79%). The identity and purity of the product was confirmed by spectroscopic analysis.

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