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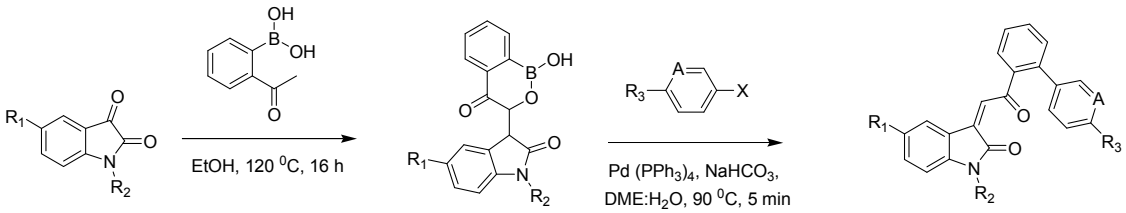

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Synthesis of Novel Benzoxaborinin-4-ones and its Application in Indolin-2-ones Synthesis Using Suzuki-Miyaura Reaction Protocol

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Abstract: We herein discuss the synthesis of novel benzoxaborinin-4-one from substituted isatins and 2-acetyl phenylboronic acid. One of the diastereoisomers was separated from mixture of diastereoisomers. Furthermore, we have demonstrated the application of these boronic acids to synthesize indolin-2-ones (Z isomer) regioselectively using Suzuki-Miyaura reaction.

Introduction:

The unique structural features of boron has allowed this classes of compounds to have medicinal application in the development of antiviral, antibacterial and anticancer therapy.[1] Recently, boron containing compounds such as Tavaborole and Bortezomib were approved by FDA for diverse indications such as fungal infection and cancer.[2] In organic synthesis, boronic acids are used as a synthetic intermediates in different metal catalysed cross coupling reactions to construct complex molecules.[3]

Spiro cyclic compounds are finding increasing application in drug discovery, owing to their conformational restriction and structural novelty.[4] Specifically, cyclic spiro 2-oxindole derivatives obtained from isatin, occur in many natural products such as spirotryprostatins A, horsfiline, etc.[5] The synthetic spiro 2-oxindole derivative such as NITD605 is currently in clinical development for malaria (Fig. 1).[6] In the course of our research, we became interested in the synthesis of a novel spiro boronic acid and its application in the area of medicinal and synthetic organic chemistry.

We used isatin as the key building block due to its presence in many fused bioactive heterocyclic compounds.[7] Benzoxaborole, an important class of boronic acids was synthesized from 2-formylphenylboronic acid.[8]

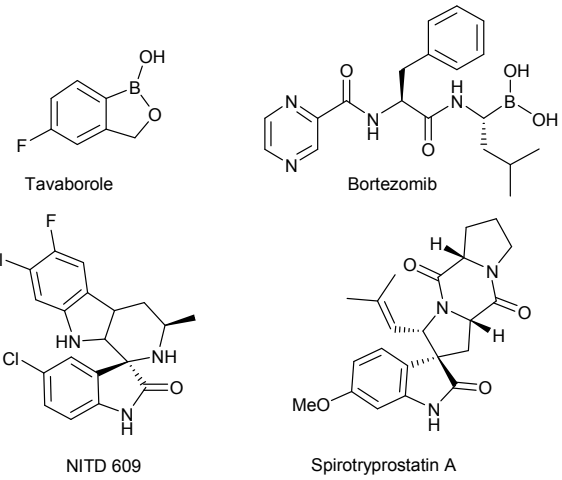

Fig. 1 Biologically active boron derivative and spiro 2-oxindole derivatives

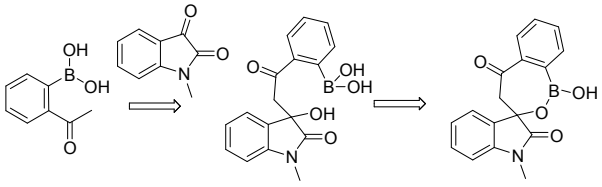

Fig. 2 Design of spirocyclic boron compounds

The benzoxaborole derivatives were synthesised by reducing the aldehyde group with sodium borohydride and followed by condensation (Fig. 2). We envisioned that spirocyclic boron compounds could be synthesized by the condensation of isatin with acetyl phenyl boronic acid.

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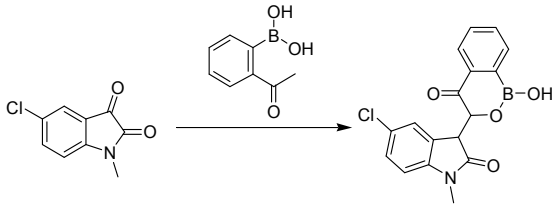
Results and discussion

We carried out the condensation of equimolar quantities of 2-acetyl phenyl boronic acid with 5-chloro-1-methylindoline-2,3-dione in ethanol at 90 ^{0}C for 16 hr (Table 1). We expected a spirocyclic boron compound, but interestingly the reaction exclusively yielded the diastereoisomeric mixture of benzoxaborinin-4-ones (**1a**) in 20 % yield. We isolated both diastereoisomers (**1aa** and **1ab**) using column chromatography and confirmed their structure by NMR spectroscopy. In the ^{1}H NMR spectrum of diastereoisomer **1aa**, the proton of C3 in 2-oxaindole and the carbon alpha to the ketone group appear at δ = 4.47 and 5.59 ppm. Further, the structure was confirmed by COSY and HSQC spectra which exhibits ring junction protons attached to two adjacent carbon atoms. Encouraged by the discovery of this reaction that affords a novel benzoxaborinin-4-one, we began optimisation of reaction conditions to improve the yield of distereoisomers. We screened an array of solvents, pH and temperature condition. Ethanol was found to be the best solvent, methanol and hexanol provided low yields while other solvents yielded no product (Entry **1-7**). We optimized for reaction condition and found that 120 ^{0}C in sealed vials provided the best yields (Entry **8-10**). Addition of acid or base yielded no product (Entry **11-13**). This indicated the essentiality of neutral conditions. Next, we explored the scope of this reaction with other isatin substrates (Table 2). 1-Methylisatin and NH-isatin gave the corresponding product **1b** and **1c** in 56 % and 42 % yield respectively. Variation of halogen groups at C-5 position of isatin afforded the respective products in the yield order 5-F > 5-Cl > 5-Br (**1d**, **1a** and **1e**). Methyl group at the C5 position gave the corresponding product **1f** in 45 % yield. Varying the substitution in isatin had no effect on diastereoselectivity of these isomers. We isolated portion of major diastereoisomers (Yield 6-9 %) from the mixture using column chromatography.

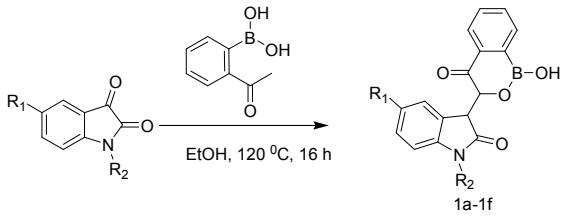
Table 1 Optimization of reaction condition[a]



Entry	Solvent	Reagent	Temp (^{0}C)	Time(Hrs)	Yield (%)[(b)]
1	EtOH	-	90	16	20
2	EtOH	-	90	24	35
3	MeOH	-	90	24	15
4	Hexanol	-	120	16	10
5	THF	-	70	16	0
6	DMF	-	120	16	0
7	Toluene	-	110	16	0
8	EtOH	-	r.t	16	0
9	EtOH	-	100	16	56
10	EtOH	-	120	16	63
11	EtOH	TEA	120	16	0
12	EtOH	AcOH	120	16	0
13	EtOH	PTSA	120	16	0

(a) 5-chloro-1-methylindoline-2,3-dione (1 mmol), 2-acetylphenylboronic acid (1.1 mmol) and solvent (4 ml) in supelco vial. (b) Isolated yield after column chromatography

Table 2 Synthesis of benzoxaborinin-4-one derivatives



Entry	R1	R2	Product	Yield(%)[a]	Ratio of Diastereoisomers[b]
1	Cl	Me	1a	63	49:51
2	H	Me	1b	56	38:62
3	H	H	1c	42	42:58
4	F	Me	1d	70	47:53
5	Br	Me	1e	52	44:56
6	Me	Me	1f	45	39:61

[a] Isolated yield of mixture [b] Ratio of diasteroisomers based on H NMR

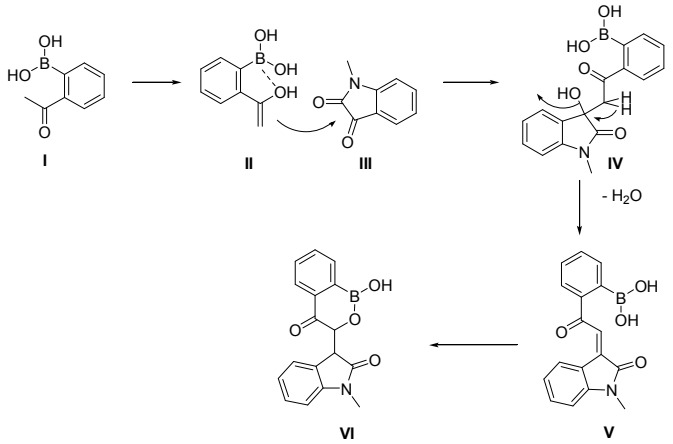


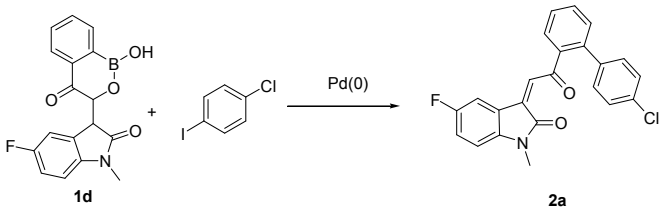
Fig. 3 Proposed mechanism for synthesis of benzoxaborinin-4-one derivatives

Mechanistically, we believe that the reaction begins with the nucleophilic attack of 2-acetyl boronic acid on isatin resulting in the formation of tertiary alcohol intermediate (**IV**) which upon dehydration affords the intermediate (**V**). Cyclisation of the boronic acid onto the activated double bond yielded a diastereoisomeric mixture of products (**VI**). 3-Acetyl boronic acid yielded no product under these conditions, suggesting that boron group at 2 position promotes enolization of the acetyl group.

To explore the applicability of the synthesized boronic acids, we attempted a cross coupling reaction under Suzuki-Miyaura conditions. Initially, we examined the Suzuki coupling reaction of compound **1d** with 4-iodochlorobenzene in presence of 2% $Pd(PPh_3)_4$, $NaHCO_3$ and DME/Water solvent mixture (5:1) at 90 °C (Table **3**, Entry **1**). Gratifyingly, the reaction afforded the indolin-2-one product **2a** in 20 % yield. The structure of the coupled product was established by spectroscopic analysis and single crystal XRD

study. The structure and conformation (Z isomer) of product **2a** were unambiguously determined by single crystal X-ray analysis (Fig. **4**). Indolin-2-one compounds have demonstrated useful biological activity as tyrosine kinase inhibitor,[9] selective plasmodial CDK inhibitors,[10] human transglutaminase-2 inhibitors[11] and antifouling/antibacterial agent.[12] Interestingly on omission of water, the reaction did not yield any product (Entry **2**). The best yield was observed using 10% Pd catalysts at 90 °C in DME/water for 5 min (Entry **3**). DME/water proved to be the best solvent (Entry **3**-**6**) and optimum base was $NaHCO_3$ (Entry **3, 7** and **8**).

Table 3 Optimisation of Suzuki-Miyaura reaction[a]



1d 2a

Entry	Catalyst	Base	Solvent	Temp (^{0}C)/ Time (mins)	Yield (%)[b]
1	5% $Pd(PPh_3)_4$	$NaHCO_3$	DME:H_2O	90/15	45
2	5% $Pd(PPh_3)_4$	$NaHCO_3$	DME	90/120	0
3	10% $Pd(PPh_3)_4$	$NaHCO_3$	DME:H_2O	90/5	65
4	10% $Pd(PPh_3)_4$	$NaHCO_3$	Ethanol:H_2O	90/5	27
5	10% $Pd(PPh_3)_4$	$NaHCO_3$	THF:H_2O	65/5	10
6	10% $Pd(PPh_3)_4$	$NaHCO_3$	Dioxane:H_2O	100/5	50
7	10% $Pd(PPh_3)_4$	Na_2CO_3	DME:H_2O	90/5	55
8	10% $Pd(PPh_3)_4$	K_2CO_3	DME:H_2O	90/5	48

[a] All reaction were performed with **1d** (1 mmol), 4-iodochlorobenzene (1.3 mmol) and base (1.5 mmol) and solvents (5:1). [b] Yield of isolated product.

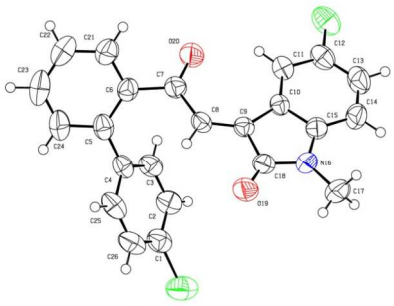


Fig. 4 Crystal structure of compound **2a**

All cyclic boronic acid derivatives were successfully transformed into the respective products in moderate yields. We found that only the Z isomer was formed in the reaction indicating high regioselectivity. Mechanistically, we believe that the reaction first undergoes Suzuki-Miyaura reaction resulting in a boronic acid intermediate that further undergoes E2 elimination reaction leading to indolin-2-one product (Fig. **5**). The regioselectivity can be understood from the geometries for E2 elimination reaction. The Z isomer resulting from the less hindered transition state of boronic acid intermediate is the more favoured isomer.

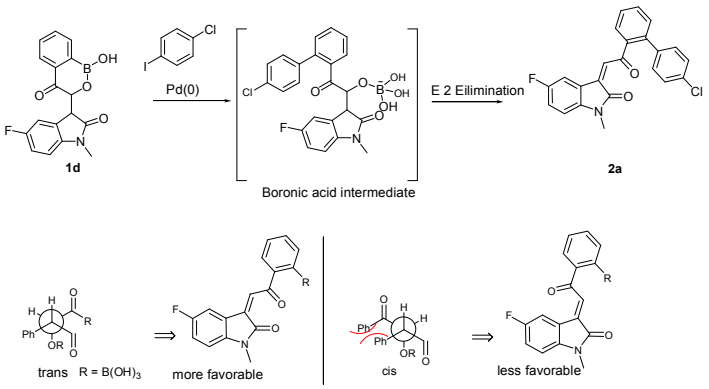
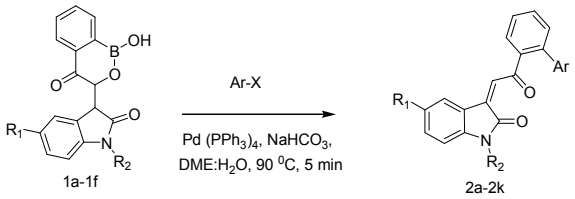
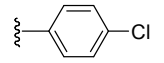
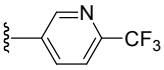
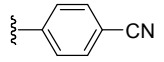
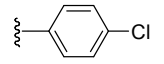
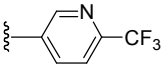
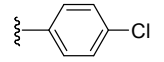
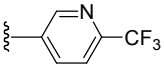
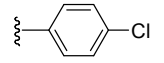
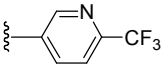
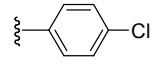
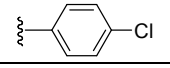


Fig. 5 Plausible conformation for the elimination reaction in Suzuki Miyaura condition

Table 4 Example of Suzuki-Miyaura products[a]



Entry	R1	R2	Ar	Product	Yield (%)[b]
1	F	CH_3		2a	65
2	F	CH_3		2b	57
3	F	CH_3		2c	46
4	H	H		2d	62
5	H	H		2e	35
6	H	CH_3		2f	65
7	H	CH_3		2g	43
8	Cl	CH_3		2h	55
9	Cl	CH_3		2i	41
10	Br	CH_3		2j	42
11	CH_3	CH_3		2k	51

[a] All reaction were performed with benzoxaborinin-4-one (1 mmol), Ar-X (1.3 mmol) and base (1.5 mmol) and solvents (5:1). [b] Yield of isolated product

Conclusions

In summary, we have synthesized novel cyclic boronic acids from substituted isatins and 2-acetyl boronic acid in good yields. Further, we have demonstrated the application of these boronic acids to regioselectively synthesize (Z) indolin-2-one derivatives in moderate yields.

Acknowledgements

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