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Synthesis of the biaryl moiety of the proteasome inhibitors TMC-95 via a ligandless $Pd(OAc)_2$-catalyzed Suzuki-coupling reaction

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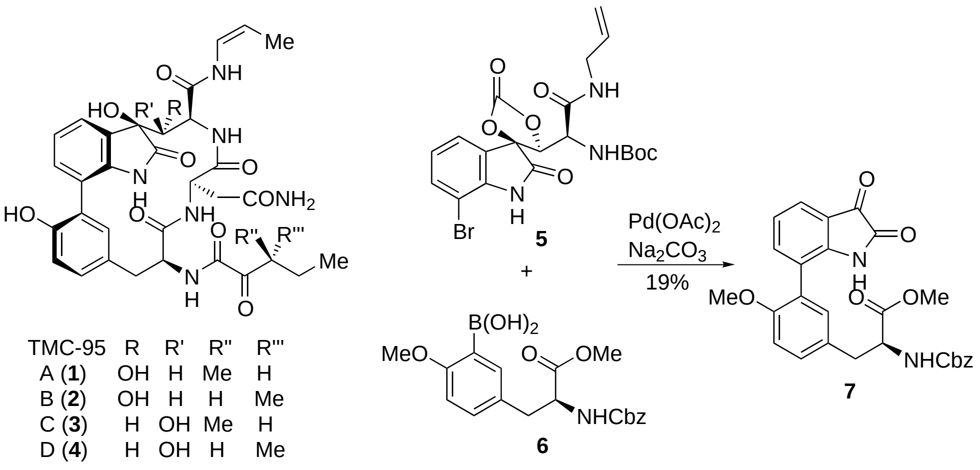
Abstract—The biaryl moiety of proteasome inhibitors TMC-95 was synthesized via a $Pd(OAc)_2$-catalyzed Suzuki-coupling reaction of 7-iodoisatin and a tyrosine-derived arylboronic acid in the absence of phosphine ligands using potassium fluoride as a base. © 2001 Elsevier Science Ltd. All rights reserved.

Recently, we reported our efforts[1] on the construction of an oxidized tryptophan analogue **5**, a proposed intermediate for synthesizing the proteasome inhibitors TMC-95A and TMC-95B.[2] When we attempted to couple **5** with arylboronic acid **6** derived from (*S*)-tyrosine under various Suzuki-coupling reaction conditions,[3] we found that no desired coupling product was isolated. The best result we observed was that the biaryl compound **7** was obtained in 19% yield by refluxing a mixture of **5** and **6**, palladium acetate and sodium carbonate in ethanol (Scheme 1).

The formation of **7** implied that the highly oxidized tryptophan moiety could not survive under typical Suzuki-coupling reaction conditions, which promoted us to study the coupling reaction of 7-iodoisatin with a suitable arylboronic acid derived from (*S*)-tyrosine. Once we obtained this coupling product, we could do further conversions to TMC-95A and TMC-95B using the same reaction sequence reported earlier.[1] The investigation thus undertaken is described here.[4]

We first synthesized 7-iodoisatin **8** from 2-iodoaniline



TMC-95	R	R'	R''	R'''
A (**1**)	OH	H	Me	H
B (**2**)	OH	H	H	Me
C (**3**)	H	OH	Me	H
D (**4**)	H	OH	H	Me

Scheme 1.

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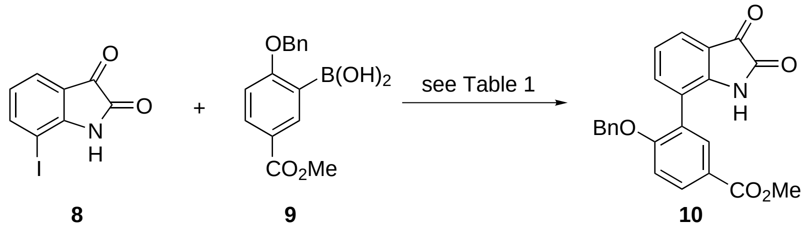
through the known procedure.[5] Recently, many groups have disclosed their efforts on the development of new and more efficient catalytic systems for the Suzuki-coupling reaction.[6] However, few reports were concerned with 7-iodoisatin or even *o*-iodoaniline as coupling reagents.[6] In order to find suitable reaction conditions for our case, we did a model coupling reaction between **8** and arylboronic acid **9**. The results are summarized in Table 1.

Initially, we tried to carry out the reaction in DME/H_2O using $Pd(PPh_3)_4$ as the catalyst and $NaHCO_3$ as a base, because it was reported recently that under these conditions **8** coupled with simple arylboronic acids to give the corresponding coupled products with 55–70% yield.[6d] However, only 18% yield was observed (entry 1), which might result from the steric hindrance of **9**. So, we attempted to employ Buchwald's[6a] and Fu's[6b] catalytic systems that were reported to be effective for highly sterically hindered substrates. Under their conditions, little or no coupling product was delivered (entries 2 and 4). Finally, we found that this reaction worked in methanol using $Pd(OAc)_2$ as a catalyst to give the desired coupling product **10** in 45% yield (entries 5 and 6).[7] Changing the base from alkali metal carbonates to potassium fluoride gave the best result (entry 7). A ligandless Pd catalyst was necessary for this reaction, because phosphine-containing palladium such as $PdCl_2(dppf)$, $Pd_2(dba)_2/P(t\text{-}Bu)_3$ were found inactive for this coupling reaction even when potassium fluoride was used as the base (entries 8–10).

After we had developed suitable reaction conditions for a model reaction, we planned to run the coupling reaction of **8** with arylboronic acid **14** which was synthesized from (*S*)-tyrosine as outlined in Scheme 2. Protection of the amino group of (*S*)-tyrosine with *N*-ethoxycarbonylphthalimide followed by esterification provided **11** in 76% yield. Treatment of **11** with benzyl bromide/potassium carbonate in DMF afforded the benzyl ether, which was subjected to iodination mediated by silver trifluoroacetate to give iodide **12**. As compound **12** contains functional groups sensitive to strong bases, we employed Masuda's method[8] to convert **12** to the arylboronic acid **14**. Accordingly, $PdCl_2(dppf)$-catalyzed coupling reaction of **12** with pinacolborane produced boronate **13**, which was treated with diethanolamine followed by acidification to afford **14** in 67% yield. The coupling reaction of **14** with **8** was attempted under several conditions and the results are summarized in Table 2. Heating a mixture of **8**, **14**, 3 mol% $Pd(OAc)_2$ and KF in methanol for 8 h gave **15** in 55% yield (entry 1). Neither increasing the amount of catalyst nor changing bases could improve the reaction yield (entries 2–4). However, when the reaction was carried out at 20°C and prolonging the reaction time, a better yield was observed (entry 5). This reaction was also performed in other solvents such as acetonitrile, DME or a mixed solvent, but with lower yields (entries 6–9).

In summary, we have obtained the biaryl fragment for synthesizing TMC-95 via a ligandless $Pd(OAc)_2$-catalyzed Suzuki-coupling reaction of 7-iodoisatin **8** with sterically hindered arylboronic acid **14** in reasonable yield. The reaction conditions for Suzuki coupling discussed here should be of benefit for synthesizing biaryl compounds with an *o*-amino moiety. Studies towards the total synthesis of TMC-95 using **15** as the key intermediate are underway in our laboratory.

Table 1. Pd-catalyzed cross coupling of **8** and **9** under various conditions



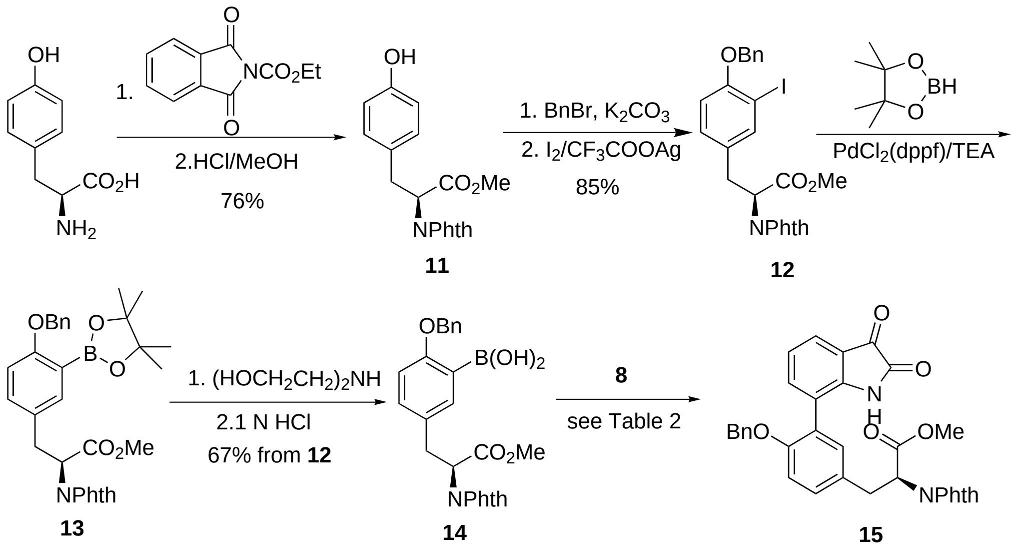
Entry[a]	Catalyst	Base	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	$Pd(PPh_3)_4$	$NaHCO_3$	DME/H_2O	90	5	18
2	$Pd(OAc)_2$-L[c,d]	K_3PO_4	toluene	90	24	Trace
3	$Pd(OAc)_2$-PPh_3[d]	K_3PO_4	DMF	60	72	0
4	$Pd_2(dba)_2/P(t\text{-}Bu)_3$[d]	K_3PO_4	DMF	75	24	0
5	$Pd(OAc)_2$	Na_2CO_3	MeOH	50	24	45
6	$Pd(OAc)_2$	K_2CO_3	MeOH	60	36	52
7	$Pd(OAc)_2$	KF	MeOH	60	24	75
8	$Pd(OAc)_2$-PPh_3[d]	KF	DMF	60	72	0
9	$Pd_2(dba)_2/P(t\text{-}Bu)_3$[d]	KF	DMF	75	24	0
10	$PdCl_2(dppf)$	KF	MeOH	60	24	0

[a] The reactions were carried out utilizing 3 mol% of Pd catalyst, 1.0 equiv. of **8** and 1.5 equiv. of **9** in corresponding solvent under argon.

[b] Isolated yield.

[c] L = *o*-(dicyclohexylphosphino)biphenyl.

[d] The ratio for [Pd] and phosphine ligand was 1:2.



Scheme 2.

Table 2. $Pd(OAc)_2$-catalyzed coupling reaction of **8** with **14**

Entry[a]	Solvent	Base	Temp. (°C)	Time (h)	Yield (%)[b]
1	MeOH	KF	60	8	55
2[c]	MeOH	KF	60	8	51
3	MeOH	$NaHCO_3$	60	20	41
4	MeOH	Bu_4NF	60	20	45
5	MeOH	KF	20	72	64
6	CH_3CN	KF	60	8	25
7	MeOH/CH_3CN	KF	60	8	35
8	DME	KF	60	8	40
9	MeOH/DME	KF	60	8	45

[a] The reactions were carried out utilizing 3 mol% of $Pd(OAc)_2$, 1.0 equiv. of **8**, 1.2 equiv. of **14** and 3 equiv. of base in the corresponding solvent under argon.

[b] Isolated yield.

[c] 10 mol% $Pd(OAc)_2$ was used.

Acknowledgements

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