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Synthesis of imidazoisoindol-3-ones by a palladium-catalyzed intramolecular C–H insertion reaction

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ABSTRACT

A simple protocol for the synthesis of various imidazoisoindol-3-ones is described by employing a palladium-catalyzed intramolecular C–H insertion reaction of substituted 2-haloaryl imidazolin-2-ones.

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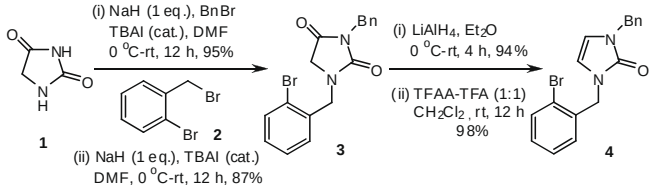
Heterocyclic compounds are commonly used as scaffolds in designing biologically active compounds.[1] Imidazolone-based heterocyclic molecules play an important role in various biochemical processes, and their use as building blocks in developing new drugs such as COX-2 inhibitors,[2a] anti-inflammatory,[2b] anticancer,[2c,d] cardioactive agents,[2e] angiotensin II receptor antagonists,[2f] and others[2g–i] is well documented. Imidazoisoindolones with phenolic subunits have been reported to exhibit high fluorescent properties.[3] Recently, imidazoisoindolone-based orally active drug candidates for the treatment of respiratory syncytial virus were explored.[4]

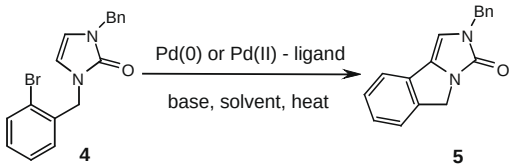
Transition metal-catalyzed C–H activation reactions have gained significant importance over the years.[5] Functional group-directed C–H insertion reactions are widely used for the synthesis of various heterocyclic ring systems.[6] Among these, palladium-catalyzed C-arylation reaction is a valuable synthetic tool for the formation of a wide variety of oxygen and nitrogen heterocycles.[7] Palladium-catalyzed intermolecular C–H functionalization of imidazolin-2-one under ligand-less conditions has been published recently by Chen and co-workers.[8] Herein, we report an intramolecular C–H insertion reaction of 2-haloaryl imidazolinones to synthesize aryl imidazoisoindolones.[9]

Although imidazolin-2-one is commercially available, we have prepared 2-bromobenzyl imidazolinone derivative **4** from commercially cheaply available hydantoin (**1**) in four steps rather than from the quite expensive imidazolin-2-one.[10] Hydantoin (**1**) was first subjected to monobenzylation[11] by treating with NaH, benzyl bromide, and a catalytic amount of tetrabutylammonium iodide (TBAI) in anhydrous DMF, and then reacted with 2-bromobenzyl bromide (**2**) under same conditions to furnish N,N-diarylated hydantoin **3**. Selective reduction of the amide carbonyl of **3** by $LiAlH_4$ (1 equiv) in Et_2O, and the subsequent elimination of aminol by treating with a mixture of trifluoroacetic anhydride (TFAA)[12] and TFA in CH_2Cl_2 furnished 1-benzyl-3-(2-bromobenzyl)-1*H*-imidazol-2(3*H*)-one (**4**) (Scheme 1).



Scheme 1.

Our study began with the cyclization of 1-benzyl-3-(2-bromobenzyl)-1*H*-imidazol-2(3*H*)-one (**4**). In the very first attempt, **4** was treated with $Pd(OAc)_2$, PPh_3, and Cs_2CO_3 in anhydrous DMF at 80 °C. We were delighted to observe the complete consumption of **4** in 12 h to furnish 2-benzyl-2*H*-imidazo[5,1-*a*]isoindol-3(5*H*)-one (**5**) in 66% yield (Scheme 2). In an attempt to improve the yield of **5**, we carried out a series of experiments with different palladium catalysts, ligands, and bases (Table 1). The best observed reaction conditions for C–H insertion reaction were $Pd(OAc)_2$ with bidentate ligand 1,2-bis(diphenylphosphino)ethane (dppe) (Table 1, entry 4) and $Pd(PPh_3)_4$ (Table 1, entry 8) with yields of 79%



Scheme 2.

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Table 1
Optimization of reaction conditions[a]

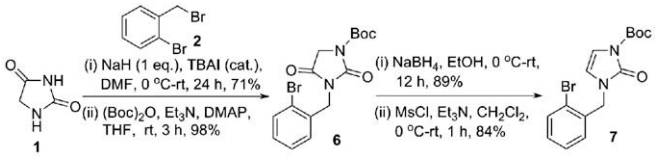
Entry	Catalyst	Ligand	Base	Time (h)	Yield[b] (%)
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	10	66
2	$Pd(OAc)_2$	PPh_3	K_2CO_3	10	60
3	$Pd(OAc)_2$	dppp	Cs_2CO_3	3	53
4	$Pd(OAc)_2$	dppe	Cs_2CO_3	3	80
5	$Pd(OAc)_2$	dppb	Cs_2CO_3	3	72
6	$Pd(OAc)_2$	(±)BINAP	Cs_2CO_3	24	40[c]
7	$Pd(OAc)_2$	Xantophos	Cs_2CO_3	24	40[c]
8	$Pd(PPh_3)_4$	—	Cs_2CO_3	12	79
9	$Pd(OAc)_2$	—	$NaOAc{\cdot}3H_2O$	24	—
10	$Pd(OAc)_2$	—	NaOAc	24	—

[a] Conditions: Pd catalyst (10 mol %), ligand (20 mol %), base (1.5 equiv), DMF (entries 1–8), DMSO (entries 9 and 10), 80 °C.
[b] Isolated yield.
[c] Conversion based on TLC.

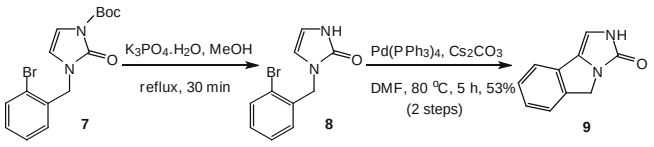
and 80%, respectively. Attempted C–H insertion of **4** under ligand-less conditions[8] using $Pd(OAc)_2$ and NaOAc in DMSO gave multiple products (Table 1, entries 9 and 10).

2-Benzyl-2*H*-imidazo[5,1-*a*]isoindol-3(5*H*)-one (**5**) was characterized by NMR spectroscopy (^1H and ^{13}C) and MS. But to our surprise, **5** decomposed in $CDCl_3$ within an hour resulting in multiple spots. The compound **5** is quite stable in CD_3OD for several days when stored in the freezer, and somewhat stable in acetone-d_6, as we noticed approximately 15% decomposition in 24 h at room temperature.

Owing to the unusual decomposition of **5**, we first sought to replace the benzyl protecting group with a Boc group. Thus, the 2-bromobenzyl group was first introduced onto hydantoin (**1**) by reacting with 2-bromobenzyl bromide (**2**) and NaH, and then transformed it to the Boc protected 2-bromobenzyl derivative **6**. Selective reduction of the amide carbonyl with $NaBH_4$ in EtOH and elimination of the resulted aminol by MsCl and excess of Et_3N in CH_2Cl_2 afforded the *tert*-butyl 3-(2-bromobenzyl)-2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxylate (**7**) (Scheme 3). When



Scheme 3.



Scheme 4.

compound **7** was allowed to react, only a 26% yield of cyclized product **7a** was obtained.[13]

We next decided to attempt the C–H insertion reaction while retaining the free hydrogen on the imidazolin-2-one. Recently, we have developed a mild and efficient method for the *N*-Boc deprotection under basic conditions in boiling MeOH.[14] The *N*-Boc moiety on **7** was cleaved under mild basic conditions using $K_3PO_4{\cdot}H_2O$ in refluxing MeOH within a short reaction time of 30 min to afford 1-(2-bromobenzyl)-1*H*-imidazol-2(3*H*)-one (**8**) (Scheme 4). With suitable reaction conditions in hand, we examined the palladium-catalyzed intramolecular C–H insertion reaction on **8**. When **8** was treated with 20 mol % of $Pd(PPh_3)_4$ and Cs_2CO_3 in DMF, we obtained 2*H*-imidazo[5,1-*a*]isoindol-3(5*H*)-one (**9**) in 53% yield for 2 steps (Scheme 4).[15]

As an extension of this methodology, we decided to elaborate this for differentially substituted 2-haloaryl imidazolone derivatives. Accordingly, we have prepared 2-iodobenzyl imidazolone derivative **10** (Table 2, entry 2) by adopting the same reaction sequence from hydantoin (**1**) and 2-iodobenzyl bromide. *N*-Boc moiety in **10** was deprotected with $K_3PO_4{\cdot}H_2O$ in refluxing MeOH, and the resulted compound was then treated with 20 mol % of $Pd(PPh_3)_4$ and Cs_2CO_3 in DMF to give 2*H*-imidazo[5,1-*a*]isoindol-3(5*H*)-one (**9**) in an improved yield of 84% (Table 2, entry 2). Replacement of bromine with iodine increased the reaction rate and the yield of C–H insertion product.

Our next objective was to study the scope of this protocol for differentially substituted 2-bromoaryl imidazolone derivatives. Hence, we have prepared various substituted 2-bromoaryl-imidazolone derivatives with both electron-deficient aryl bromides and electron-rich aryl bromides by employing the appropriate synthetic sequences. Palladium-catalyzed intramolecular C–H insertion reactions of the substituted 2-bromoaryl-imidazolone derivatives were carried out and they produced various imidazoisoindol-3-ones (Table 2).[16] The reaction tolerated a variety of different aryl substitution. As shown in Table 2, the nature as well as the position of the substituents on the aromatic ring affects the yields of the reaction. Substitution with electron-

Table 2

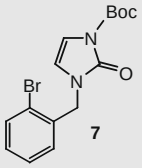
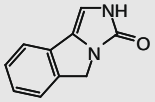
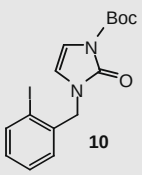
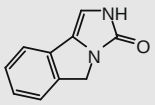
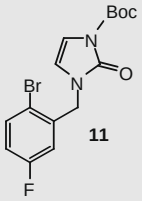
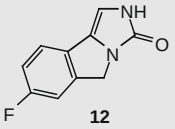
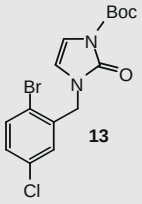
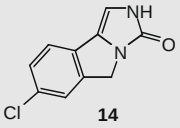
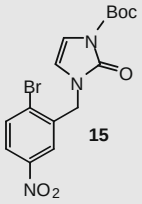
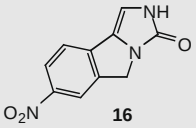
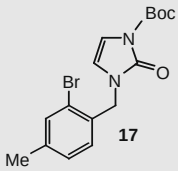
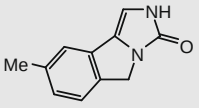
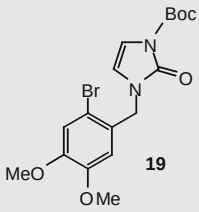
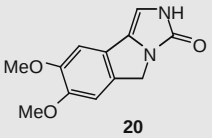
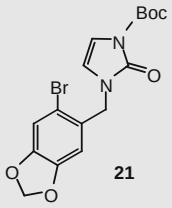
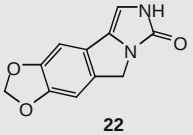
Entry	Substrate[a]	C–H insertion reaction time (h)	Product	Yield[b] (%)
1	 **7**	5	 **9**	53
2	 **10**	1	 **9**	84

Table 2 (*continued*)

Entry	Substrate[a]	C–H insertion reaction time (h)	Product	Yield[b] (%)
3	 **11**	5	 **12**	69
4	 **13**	4	 **14**	90
5	 **15**	3	 **16**	60
6	 **17**	4	 **18**	55
7	 **19**	7	 **20**	44
8	 **21**	7	 **22**	28

[a] Conditions: *Boc deprotection:* $K_3PO_4 \cdot H_2O$ (20 mol %), MeOH, reflux, 30 min. *C–H insertion:* $Pd(PPh_3)_4$ (20 mol %), Cs_2CO_3 (1.5 equiv), DMF, 80 °C.
[b] Isolated yields after 2 steps (Boc deprotection and C–H insertion).

donating groups resulted in lower yields (Table 2, entries 7 and 8). The lower yields appear to be attributed to the decomposition of the cyclized products **20** and **22** during the work-up and/or purification step. Analysis of the reaction by LC/MS showed that, after 7 h, the starting materials were all consumed to give the products **20** and **22,** and there was no detection of any bromo-reduced by-products.[17]

In conclusion, we have developed an efficient methodology for the synthesis of various imadazoisoindol-3-ones by palladium-catalyzed intramolecular C–H insertion reaction. The synthetic utility of this method for the construction of imidazoisoquinolone, aryl imidazoazipinone ring systems, and their application toward natural product synthesis is under investigation, and the results will be published in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.019.

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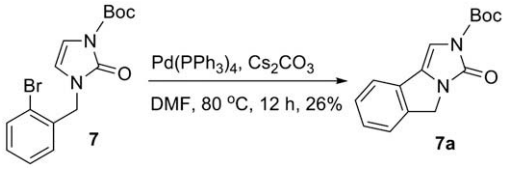
13. Reaction conditions for the cyclization of compound **7**. The low yield is attributed to the decomposition of the product **7a**. Similar to compound **5**, fast decomposition of **7a** was observed in $CDCl_3$. The structure of **7a** was confirmed by ^1H NMR spectroscopy



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15. *Representative procedure for Boc deprotection and C–H insertion reaction:* Step 1: To a solution of *tert*-butyl 3-(2-bromobenzyl)-2-oxo-2,3-dihydro-1*H*-imidazole-1-carboxylate (**7**) (0.2 g, 0.566 mmol) in MeOH (4 mL) was added $K_3PO_4{\cdot}H_2O$ (0.026 g, 0.113 mmol) and heated at reflux for 30 min. Reaction mixture was filtered through a pad of Celite and the filtrate was evaporated under vacuo to give a crude 1-(2-bromobenzyl)-1*H*-imidazol-2(3*H*)-one (**8**), which was carried forward without further purification. Step 2: After dissolving **8** in anhydrous DMF (4 mL) were added $Pd(PPh_3)_4$ (0.131 g, 0.113 mmol) and Cs_2CO_3 (0.277 g, 0.849 mmol), and heated at 80 °C under nitrogen atmosphere for 5 h. After completion of the reaction, solvent was removed under vacuo and the crude mixture was purified by flash silica gel column chromatography by eluting with MeOH–CH_2Cl_2 (1:19) to furnish a pure colorless solid, 2*H*-imidazo[5,1-*a*]isoindol-3(5*H*)-one (**9**) (0.052 g, 53% for 2 steps).
16. *Spectroscopic data of the final imadazoisoindol-3-ones: 2-Benzyl-2H-imidazo[5,1-a]isoindol-3(5H)-one* (**5**): Colorless syrup. ^1H NMR (300 MHz, CD_3OD) δ (ppm) 4.83 (s, 2H), 4.88 (s, 2H), 6.73 (s, 1H), 7.27–7.34 (m, 7H), 7.49 (t, 2H, J = 7.8 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 49.4 (2C), 104.3, 122.0, 126.0, 129.4, 129.6, 129.7, 130.2, 130.7, 131.8, 139.5, 142.4. APCI/ESI-MS: *m/z* 263 $[M+H]^+$. *2H-imidazo[5,1-a]isoindol-3(5H)-one* (**9**): White solid, mp: 224–226 °C. ^1H NMR (300 MHz, CD_3OD) δ (ppm) 4.78 (s, 2H), 6.67 (s, 1H), 7.29 (dt, 1H, J = 1.2, 7.5 Hz), 7.37 (t, 1H, J = 7.5 Hz), 7.47 (d, 1H, J = 7.5 Hz), 7.53 (d, 1H, J = 7.5 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 48.1, 100.6, 121.0, 125.1, 128.3, 129.3, 131.1, 141.8. APCI/ESI-MS: *m/z* 173 $[M+H]^+$. *7-Fluoro-2H-imidazo[5,1-a]isoindol-3(5H)-one* (**12**): Light yellow solid, mp: 241–243 °C. ^1H NMR (300 MHz, CD_3OD+$CDCl_3$) δ (ppm) 4.80 (s, 2H), 6.60 (s, 1H), 7.11 (dt, 1H, J = 2.4, 8.4 Hz), 7.24 (dd, 1H, J = 2.7, 8.4 Hz), 7.51 (dd, 1H, J = 4.8, 8.4 Hz). ^{13}C NMR (75 MHz, CD_3OD+$CDCl_3$) δ (ppm) 47.9 (d), 100.0 (d), 112,4 (d), 116.3 (d), 122.1 (d), 127.2 (d), 143.7 (d), 161.6, 164.9. APCI/ESI-MS: *m/z* 191 $[M+H]^+$. *7-Chloro-2H-imidazo[5,1-a]isoindol-3(5H)-one* (**14**): Light yellow solid, mp: 226–228 °C. ^1H NMR (300 MHz, CD_3OD) δ (ppm) 4.81 (s, 2H), 6.66 (s, 1H), 7.37 (dt, 1H, J = 1.8, 8.1 Hz), 7.47–7.51 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 47.7, 101.0, 121.9, 125.3, 129.4, 133.8, 143.3. APCI/ESI-MS: *m/z* 207 $[M+H]^+$. *7-Nitro-2H-imidazo[5,1-a]isoindol-3(5H)-one* (**16**): Brown solid, mp > 300 °C. ^1H NMR (300 MHz, DMSO-d_6) δ (ppm) 4.87 (s, 2H), 7.07 (d, 1H, J = 2.4 Hz), 7.73 (d, 1H, J = 8.7 Hz), 8.27 (dd, 1H, J = 2.4, 8.7 Hz), 8.36 (s, 1H), 10.50 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 46.7, 104.3, 119.8, 120.0, 124.3, 136.5, 142.0. APCI/ESI-MS: *m/z* 218 $[M+H]^+$. *8-Methyl-2H-imidazo[5,1-a]isoindol-3(5H)-one* (**18**): Light yellow solid, mp: 226–228 °C. ^1H NMR (300 MHz, CD_3OD) δ (ppm) 2.39 (s, 3H), 4.73 (s, 2H), 6.59 (s, 1H), 7.11 (d, 1H, J = 8.1 Hz), 7.30–7.34 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD+$CDCl_3$) δ (ppm) 21.6, 47.7, 100.1, 121.3, 124.5, 129.1, 130.8, 131.0, 138.5, 139.2, 152.5. APCI/ESI-MS: *m/z* 178 $[M+H]^+$. *7,8-Dimethoxy-2H-imidazo[5,1-a]isoindol-3(5H)-one* (**20**): White solid, mp: 234–236 °C. ^1H NMR (300 MHz, CD_3OD) δ (ppm) 3.86 (s, 6H), 4.70 (s, 2H), 6.54 (s, 1H), 7.12 (s, 1H), 7.15 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD) δ (ppm) 46.9, 56.0 (2C), 97.3, 102.8, 106.8, 122.3, 129.9, 132.6, 148.9, 149.4. APCI/ESI-MS: *m/z* 233 $[M+H]^+$. *6H-[1,3]Dioxolo[4,5-f]imidazo[5,1-a]isoindol-7(9H)-one* (**22**): Brown solid, mp > 300 °C. ^1H NMR (300 MHz, CD_3OD+$CDCl_3$) δ (ppm) 4.68 (s, 2H), 6.01 (s, 2H), 6.51 (s, 1H), 6.96 (s, 1H), 6.99 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD+$CDCl_3$) δ (ppm) 47.9, 98.9, 101.4, 103.0, 105.6, 124.6, 135.2, 149.6. APCI/ESI-MS: *m/z* 217 $[M+H]^+$.
17. See Supplementary data for the LC/MS analysis data.