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New formation of 4,5,6,7-tetrahydroisoindoles

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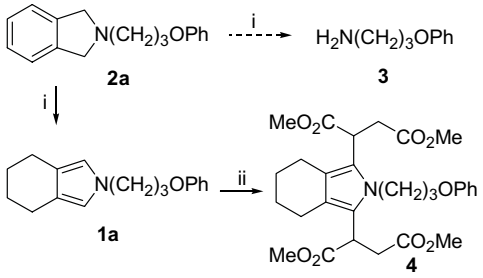
Abstract—The high-yield syntheses of 4,5,6,7-tetrahydro-isoindoles from *N*-substituted isoindolines under palladium catalyzed hydrogenation conditions are reported. Mechanistic study with deuterated and saturated substrates show extensive H/D exchange and the essence of aromaticity in this transformation.

4,5,6,7-Tetrahydroisoindoles (**1**) are popular constitutive factors of porphyrins; some of their derivatives are biologically active.[1,2] The synthetic routes followed to prepare these compounds are generally based on the synthesis of pyrroles and can be placed into the following categories: oxidation of pyrrolidine,[3] condensation of 1,4-dicarbonyl compounds and amines (the Paal–Knorr synthesis),[1a,2a,4] cyclization of α-enamino acids,[1c,2b,5] Diels–Alder reactions of 3-sulfolenes and alkenes,[6] cyclization of isocyanoacetates with vinyl sulfones or nitroalkenes,[7,8] ring contraction of phthalazine,[2c] and samarium-catalyzed reactions of α,β-unsaturated imines with nitroalkane.[9] In this letter, we report an interesting route to 4,5,6,7-tetrahydroisoindoles by hydrogenation of *N*-substituted isoindoline (**2**, Scheme 1).



Scheme 1. Reagents and conditions: (i) ammonium formate (10 equiv), $Pd(OH)_2$ (10 mol %), MeOH, reflux, 14 h, 97%; (ii) Dimethyl maleate, $AlCl_3$, CH_2Cl_2, 57%.

To circumvent a bothersome reductive hydrogenation of dibenzyl amines in our recent syntheses of oncinotines,[10] we believed that the isoindoline **2** might be a good precursor to primary amines. Thus, a model compound, **2a**, was prepared and subjected to the typical hydrogenation conditions—heating under reflux in methanol for 14 h in the presence of Pearlman's catalyst $Pd(OH)_2/C$ and ammonium formate. We did not, however, obtain the expected primary amine **3**. Instead, mass spectrometric analysis indicated that two hydrogen atoms had added to **2a** and no fragmentation product resembling **3** was generated from this reaction. In the ^1H NMR spectrum, we observed new absorptions at 1.74 (m, 4H), 2.54 (m, 4H) and 6.37 (s, 2H) ppm in addition to the original signals of the OPh and three methylene groups between the nitrogen and oxygen atoms. Through ^1H–^{13}C HMQC spectroscopic analysis, these new proton absorptions correlate to two new sp^3-hybridized carbon atoms (δ = 22.1, 24.3) and one new sp^2-hybridized carbon atom (δ = 116.2); in addition, another new quarternary sp^2-hybridized carbon appears at 119.6 ppm. These spectroscopic data suggest the symmetrical structure of 4,5,6,7-tetrahydroisoindole **1a**. The downfielded proton absorption (δ = 6.37) is consistent with the deshielding effect of aromatic pyrrole. The IR spectrum of **1a** also displays characteristic pyrrole absorptions at 1458, 1395 and 1325 cm^{-1}.[9,11] The formation of the pyrrole ring was further confirmed by the reaction of **1a** with dimethyl maleate, which gave the compound **4** derived from the electrophilic aromatic substitution of pyrroles.[12] These data indicate that isoindoline **2a** undergoes partial reduction and forms aromatic pyrrole **1a** under hydrogenation conditions.[13]

To examine the scope and limitations of this process, we synthesized a number of other *N*-substituted isoindolines

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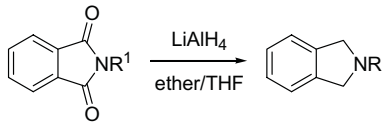
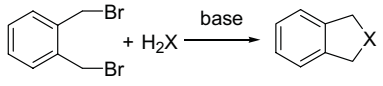


2a, R = R^1 = $(CH_2)_3OPh$, 80%
2b, R = R^1 = $(CH_2)_4OPh$, 79%
2c R = R^1 = CH_3, 96%
2d, R = $CH_2CH_2CH_3$, R^1 = $(CH_2)_3Br$, 99%
2g, R = $(CH_2)_4NH_2$, R^1 = $(CH_2)_4NH_3Cl$, 64%
2h, R = $(CH_2)_4NHBz$, 40%
← BzCl

Scheme 2.

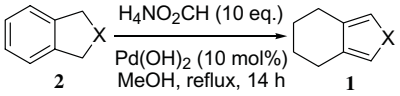


2e, X = $NCH_2CO_2CH_3$, K_2CO_3, 66%
2f, X = $N(CH_2)_2OH$, 94%
2i, X = $N(CH_2)_2O_2C(2,4,6\text{-}C_6H_2Cl_3)$, 40%
2j, X = $NCOCH_3$, NaH, 95%
2k, X = O, NaOH, 47%
2l, X = S, Na_2S, 85%
← LAH
← $(2,4,6\text{-}C_6H_2Cl_3)CCl$

Scheme 3.

(**2b–j**) using two efficient methods: the reduction of *N*-substituted phthalimides and the alkylation of primary amines with α,α′-dibromo-*o*-xylene (Schemes 2 and 3).

Table 1 summarizes the results we obtained after subjecting these isoindolines to the hydrogenation conditions (Eq. 1). Usually, 10 equiv of ammonium formate and 10 mol % of catalyst were required to complete the reactions (entries 1 and 2). Palladium on charcoal was also practical in this reaction, but it gave a slightly lower yield (entry 3). Reducing the reaction time led to a lower yield (entry 4). Simple *N*-methyl and propyl isoindolines, **2c** and **2d**, were good substrates for this reaction (entry 6 and 7). No interference was caused by various functional groups on the *N*-substituted chain, such as phenyl ether (**2a** and **2b**), ester (**2e**), alcohol (**2f**) and amide (**2h**) units, during the formation of pyrroles **1** and we obtained reasonable to excellent yields (entries 8–11). The presence of a free amino group (**2g**) slowed down the reaction and led to the formation of impurities. In addition to the formation of tetrahydroisoindole, the trichlorinated benzoate moiety of **2i** was also reduced to benzoate (entry 12).[16] This result implies that halogen-substituted isoindolines should also be reduced and form the pyrrole moiety under this condition. Unfortunately, *N*-acetyl isoindoline (**2j**), failed to give the corresponding product **1j** (entry 13). This finding suggests that delocalization of the nitrogen atom's lone pair of electrons into the acyl group of **2j** inhibits the reaction.[17] Attempts to extend this reaction to other heterocycles, that is, thiophene and furan derivatives, were unsuccessful (entries 14 and 15); the starting materials were recovered intact. Because, the resonance energies of pyrrole, furan, thiophene and benzene are 21, 16, 29 and 34 kcal/mol, respectively,[18] factors other than resonance energies must play a role in this unique pyrrole formation.



(1)

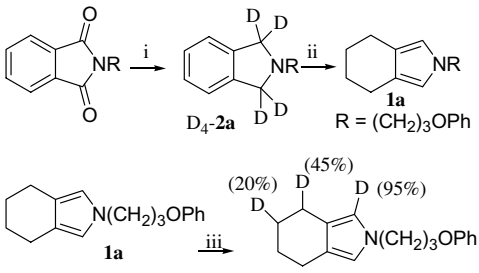
Table 1. Formation of 4,5,6,7-tetrahydroisoindoles

Entry	Reactants	X	Products	Yield (%)[a]
1	**2a**	$N(CH_2)_3OPh$	**1a**	97
2[b]	**2a**	$N(CH_2)_3Oph$	**1a**	35
3[c]	**2a**	$N(CH_2)_3OPh$	**1a**	90
4[d]	**2a**	$N(CH_2)_3OPh$	**1a**	63
5	**2b**	$N(CH_2)_4OPh$	**1b**	98
6	**2c**	NCH_3	**1c**	77
7	**2d**	$NCH_2CH_2CH_3$	**1d**	84
8	**2e**	$NCH_2CO_2CH_3$	**1e**	80
9	**2f**	$N(CH_2)_2OH$	**1f**	85
10	**2g**	$N(CH_2)_4NH_2$	**1g**	9
11	**2h**	$N(CH_2)_4NHBz$	**1h**	88
12	**2i**	$N(CH_2)_2O_2C(2,4,6\text{-}C_6H_2Cl_3)$	**1i**[e]	80
13	**2j**	$NCOCH_3$	**1j**	N.D.[f]
14	**2k**	O	**1k**	N.D.[f]
15	**2l**	S	**1l**	N.D.[f]

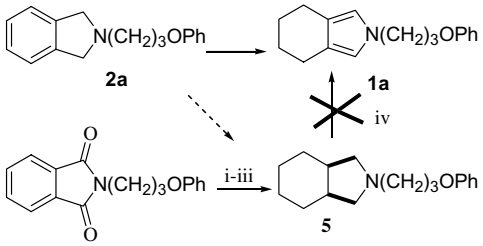
[a] Isolated yields.
[b] 3 mol % of $Pd(OH)_2$ was used.
[c] 10 mol% of Pd/C was used.
[d] Reaction time = 4 h.
[e] X = $N(CH_2)_2O_2CPh$.
[f] No product detected; the starting material was recovered.

The question of whether the benzylic hydrogen atoms of **2** were transferred to the cyclohexyl ring of **1** prompted us to prepare an isotope-labeled congener, D_4-**2a**. The reaction of D_4-**2a** under the hydrogenation conditions gave product **1a** that lacks the deuterium atoms. The loss of all the deuterium atoms indicates that intensive H/D exchange occurs during the reaction. Indeed, heating the product **1a** with $Pd(OH)_2$/C in NH_4O_2CD/CD_3OD under reflux provided a deuterated version of **1a** (Scheme 4). Sajiki et al. have also reported recently such an efficient C–H/C–D exchange of substituted benzenes catalyzed by Pd/C in D_2O.[19]

One possible mechanistic explanation for the transformation of **2** to **1** is the formation of octahydroisoindole intermediate **5**, and then dehydrogenation to form



Scheme 4. Reagents and conditions: (i) $LiAlD_4$, 92%; (ii) ammonium formate (10 equiv), $Pd(OH)_2$ (10 mol %), MeOH, reflux, 14 h; (iii) $Pd(OH)_2$ (10 mol %), NH_4O_2CD (5 equiv), CD_3OD, reflux, 14 h. The percentage of deuterium is provided in parentheses.



Scheme 5. Reagents and conditions: (i) H_2NNH_2, EtOH, 59%; (ii) *cis*-1,2-cyclohexanedicarboxylic anhydride, 68%; (iii) $LiAlH_4$, 67%; (iv) $Pd(OH)_2$ (10 mol %), NH_4O_2CH (5 equiv), CH_3OH, reflux, 14 h.

pyrroles (Scheme 5). To test this hypothesis, compound **5** was prepared independently and subjected to the reaction condition. Only the starting material **5** was recovered and no detectable **1a** could be observed from the NMR spectroscopy. Therefore, compound **5** as the reaction intermediate is unlikely. This result and the above isotope tracking experiments suggest that this reaction may start from the benzylic C–H activation of isoindoline by palladium, and then the formation of pyrrole is accompanied with partial reduction of the benzene moiety. Through the process, the aromaticity is essential and intriguingly transferred to pyrrole at the end. Unlike deprotection of dibenzyl amines,[20] the C–N bonds of isoindolines **2** are not cleaved by palladium catalyzed hydrogenation.

In summary, we report here a simple and efficient method for preparing 4,5,6,7-tetrahydroisoindoles that utilizes a novel pathway to form the pyrrole moiety.

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Supplementary data

Experimental details for preparation and characterization of all new compounds can be found, in the online version, at doi:10.1016/j.tetlet.2005.06.118.

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