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SYNTHESIS OF 2-SUBSTITUTED INDOLE WITH HANTZSCH ESTER CATALYZED BY PALLADIUM

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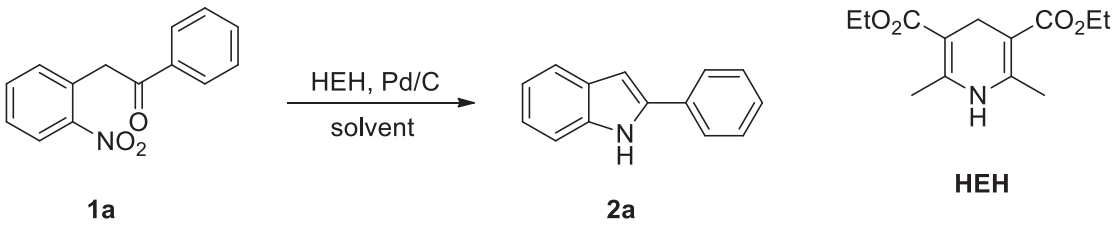
Abstract – An efficient reductive cyclization of *o*-nitrobenzyl ketone compounds was achieved by using a Hantzsch 1,4-dihydropyridine ester as a biomimetic reducing agent in the presence of catalytic palladium on carbon. 2-Substituted indoles were obtained in good yields. Investigation of the mechanism suggests that palladium hydride promotes the reduction of nitro group, and acetic acid was beneficial for the loss of water to produce the intended product. This reaction system can not only broaden the use of Hantzsch 1,4-dihydropyridine ester, but it also provides a novel approach for preparing indole compounds.

Indole ring systems are important heterocyclic compounds due to their unique biological activities. They are widely found in pharmaceuticals, agrochemicals, natural products and materials science,[1] so, organic chemists have been interested in them for well over a century.[2] Among them, 2-substituted indoles represent a subclass of biologically and synthetically useful scaffolds.[3] Traditional methods for the preparation of 2-substituted indoles are mainly based on the Fischer indole synthesis.[4] However, harsh reaction conditions sometimes affect the tolerance of the functional group. To date, many new synthetic methods have been developed for the synthesis of 2-substituted indoles,[5] including annulation reactions of *o*-alkynylanilines[6] or vinylanilines,[7] reductive cyclization reactions of *o*-nitrobenzyl cyanides[8] or *o*-nitrobenzyl ketones,[9] which have received significant attention. Reduction systems, such as Zn/AcOH,[9a] HCO_2NH_4–Pd/C,[9b] $SnCl_2$/HCl[9c] and H_2-Pd/C[9d] have been used for the selective reductive cyclization of *o*-nitrobenzyl ketone. However, some of these methods suffer from relatively low yields, poor regioselectivity, tedious reaction procedures, relatively expensive reagents and/or rather lengthy synthetic sequences. Therefore, the development of new strategies for the efficient reductive cyclization of *o*-nitrobenzyl ketone compounds is urgently needed. Transition-metal-catalyzed transformations of activated nitro compounds play an important role in both synthetic and medicinal chemistry due to their

well-recognized chemical versatility.[10] For our work, we mainly focused on Pd/C-catalyzed intramolecular annulation reactions to construct 2-substituted indoles. Hantzsch 1,4-dihydropyridine (HEH) has been widely used as a model compound for coenzyme NAD(P)H,[11] which plays a pivotal role in biochemical redox processes. Previous studies in our laboratory have shown that the reducibility of HEH is dramatically enhanced in the presence of Pd/C.[12] Previous report showed that HEH could reduce nitroarenes to amino group in the presence of Pd/C,[12c,12e,12f,13] so we suggest using Pd/C-HEH in catalytic-reduction process, to obtain 2-substituted indoles by the reductive cyclization reaction of *o*-nitrobenzyl ketone.

We started our investigations with the easily prepared 2-(2-nitrophenyl)-1-phenylethanone (**1a**) as the substrate. When we refluxed mixture of HEH and **1a** in ethanol for 10 h in the presence of Pd/C, the desired 2-substituted indole compound was obtained with a yield of 60%. In order to improve the reaction efficiency, we studied the effects of reaction temperature, solvent and catalyst (Table 1). No reaction occurred at room temperature using ethanol or acetic acid as a solvent (Table 1, Entries 2 and 5). Initial success was obtained by refluxing an ethanolic solution of **1a** and HEH in the presence of Pd/C (Table 1, Entry 1). To our delight, when the reaction was performed in refluxing acetic acid, 2-substituted indole (**2a**) was obtained in excellent yield (Table 1, Entry 4). The reductive cyclization also proceeded

Table 1. Optimization of the Reaction Conditions



1a **2a** **HEH**

Entry	Conditions[a]	Yield (%)[b]
1	10% Pd/C (5 wt% of HEH), EtOH, reflux, 10 h	60
2	10% Pd/C (5 wt% of HEH), EtOH, rt, 10 h	0
3	10% Pd/C (5 wt% of HEH), toluene, reflux, 10 h	60
4	10% Pd/C (5 wt% of HEH), AcOH, reflux, 10 h	85
5	10% Pd/C (5 wt% of HEH), AcOH, rt, 10 h	0
6	10% Pd/C (2 wt% of HEH), AcOH, reflux, 10 h	84
7	no catalyst, AcOH, reflux, 10 h	0

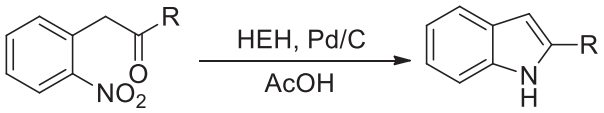
[a] Reactions were performed by using **1a** (1.0 mmol), HEH (3.6 mmol), and the solvent (20 mL).

[b] Yields are isolated yields

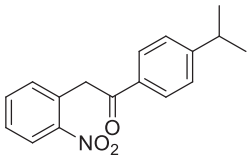
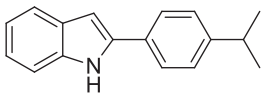
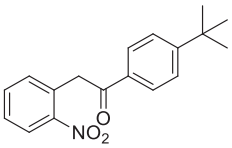
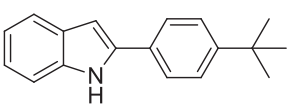
efficiently when the amount of the catalyst was decreased to 2 wt% of HEH (Table 1, Entry 6). A moderate yield was obtained when using toluene as solvent (Table 1, Entry 3). Importantly, there was no yield without the catalyst (Table 1, Entry 7).

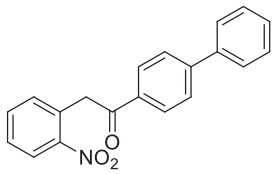
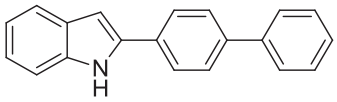
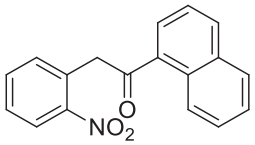
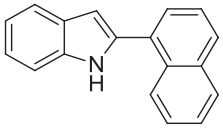
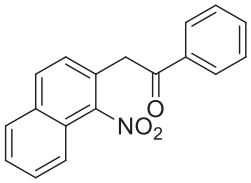
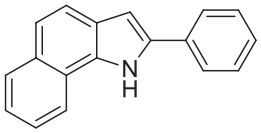
Under the optimized conditions, the scope of the reaction was explored with a variety of substrates. The results are summarized in Table 2. When R was biphenyl or naphthyl, which are both weak electron-withdrawing substituents, we obtained target compounds in excellent yields (Table 2, Entries 8-9). However, when the R substituent was methyl, isopropyl, *tert*-butyl, or methoxy groups on the phenacyl, the yields were lower (Table 2, Entries 2-7). We assume that the electron-withdrawing substituents increase the electron deficiency of the carbonyl group, and make it more reactive. In addition, due to the steric effect, the benzene ring bearing the methoxy group at the *ortho* (**2d**)-, *para* (**2c**)-, and *meta*-position (**2e**) led to yields of 80%, 84%, and 82%, respectively. The substrate with 1-nitronaphthalene derivative led to a lower yield of 80% of the desired product (Table 2, Entry 10) due to the electrophilic effect of the benzene ring.

Table 2. Synthesis of 2-Substituted Indoles[a]



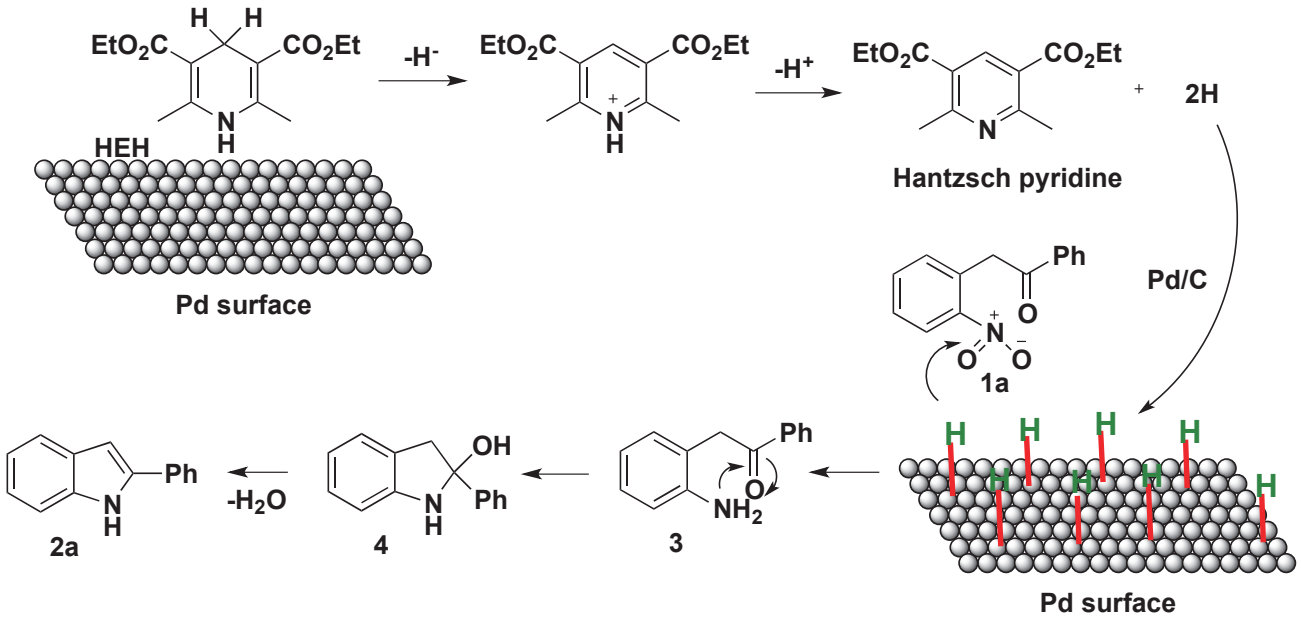
1 **2**

Entry	Substrate	Pruduct	Yield (%)[b]
1	**1a** R = Ph	**2a**	85
2	**1b** R = 4-MeC$_6$H$_4$	**2b**	82
3	**1c** R = 4-MeOC$_6$H$_4$	**2c**	84
4	**1d** R = 2-MeOC$_6$H$_4$	**2d**	80
5	**1e** R = 3-MeOC$_6$H$_4$	**2e**	82
6	 **1f**	 **2f**	85
7	 **1g**	 **2g**	86

8	 **1h**	 **2h**	93
9	 **1i**	 **2i**	89
10	 **1j**	 **2j**	80

[a] Substrate (1.0 mmol), HEH (3.6 mmol), 10% Pd/C (18 mg), AcOH (20 mL), 120 °C, 10 h. [b]Yields are isolated yields. All products are known compounds and were characterized by MS (ESI), ^{1}H and ^{13}C NMR spectroscopies.

The mechanism for the reduction of the nitro group with Hantzsch ester in the presence of Pd/C catalyst has been intensively investigated.[10d-10f] As illustrated in Scheme 1, the hydrogen atom at the 4-position of HEH is easily transferred in the form of a hydride anion in the initial step that is catalyzed by Pd/C, followed by the loss of a hydrogen atom at 1-position, leading to Hantzsch pyridine. Next, the palladium



Scheme 1. Plausible mechanism for the reductive cyclization process

hydride is generated during the aromatization of HEH catalyzed by Pd/C. Subsequently, the nitro group of substrate **1a** is reduced to aniline intermediate **3** by palladium hydride, the nucleophilic addition reaction of the amino group with the carbonyl group leads to the intermediate **4**, and a water molecule is lost in the presence of acetic acid to produce desired product **2a**.

In summary, a novel method for the synthesis of 2-substituted indoles has been developed using Hantzsch ester 1,4-dihydropyridine (HEH) as a biomimetic reducing agent catalyzed by Pd/C. The mechanism for this reaction shows that the palladium hydride played an important role in this reductive cyclization process. This reaction system can not only broaden the application field of HEH, but it provides a new approach for the preparation of indole compounds.

EXPERIMENTAL

Characterization

^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker instrument (400 and 100 MHz, respectively) and internally referenced to the tetramethylsilane signal or residual proto-solvent signals. Mass spectra were recorded by ESI methods. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F254 plates. Silica gel (200-300 mesh) was used for column chromatography. The employed solvents were dried by the standard procedures. Commercially obtained reagents were used without further purification.

Typical prepration of substrate[14]

2-Nitrotoluene (3.54 mL, 30 mmol) reacted with benzaldehyde (3.05 mL, 30 mmol) in DMSO (10 mL) and DBU (4.50 mL, 30 mmol). The reaction was stirred for 3 days. Water (250 mL) was added, followed by extraction with EtOAc (3 x 75 mL). The organics were combined, washed with brine and dried over sodium sulfate. Flash column chromatography (10-30%, EtOAc/Hex) yielded a pale yellow solid (2.14 g, 29%), which was used directly in the next step. Then, the yellow product (2.14 g, 8.6 mmol) was dissoved in DCM (50 mL). PCC (5.58 g, 25.9 mmol) was added portionwise at 0 ^{o}C and stirred overnight at room temperature. The reaction was filtered through silica gel, concentrated under reduced pressure and yielded a pale yellow solid (2.1 g, 99%).

Typical procedure for the synthesis of product

To the AcOH solution (25 mL) of substrate (**1a-1j**, Table 2) (1.0 mmol) were added HEH (904 mg, 3.6 mmol) and 10% Pd/C (18 mg), the mixture was refluxed under argon atmosphere by stirring for 10 h. After completion, the reaction was monitored by TLC, the solution was filtered and the filtrate was concentrated under reduced pressure. The corresponding compounds were isolated by a column chromatography (silica gel).

2-Phenyl-1*H*-indole (2a): mp 188-189 ºC (lit.[5b] mp 187.6-189.3 ºC); ^{1}H NMR ($CDCl_3$, 400 Hz): δ 6.74 (s, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.28-7.35 (m, 3H), 7.55 (d, *J* = 7.2 Hz, 3H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 99.9, 110.9, 120.2, 120.6, 122.3, 125.1, 127.7, 129.0, 129.2, 132.3, 136.8, 137.8

2-*p*-Tolyl-1*H*-indole (2b): mp 211-213 ºC (lit.[15] mp 219.6-220 ºC); ^{1}H NMR ($CDCl_3$, 400 Hz): δ 2.38 (s, 3H), 6.77 (s, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 1H), 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 21.3, 99.4, 110.8, 120.2, 120.5, 122.1, 125.1, 129.3, 129.6, 129.7, 136.7, 137.6, 138.0

2-(4-Methoxyphenyl)-1*H*-indole (2c): mp 222-224 ºC (lit.[5b] mp 228.5-229.7 ºC); ^{1}H NMR ($CDCl_3$, 400Hz): δ 3.86 (s, 3H), 6.72 (s, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.11-7.17 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 3H), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 21.3, 99.4, 110.8, 120.2, 120.5, 122.1, 125.1, 129.3, 129.6, 129.7, 136.7, 137.6, 138.0

2-(2-Methoxyphenyl)-1*H*-indole (2d): mp 82-83 ºC (lit.[16] mp 78-81 ºC); ^{1}H NMR ($CDCl_3$, 400 Hz): δ 3.98 (s, 3H), 6.89 (s, 1H), 6.99-7.28 (m, 5H), 7.40 (d, *J* = 8.0 Hz, 1), 7.63 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 9.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 55.9, 99.8, 110.0, 111.0, 111.9, 119.8, 120.3, 120.6, 121.6, 121.8, 128.1, 128.3, 128.6, 136.1, 155.8

2-(3-Methoxyphenyl)-1*H*-indole (2e): mp 140-141 ºC (lit.[17] mp 139-140 ºC); ^{1}H NMR ($CDCl_3$, 400 Hz): δ 3.88 (s, 3H), 6.83 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.20-7.25 (m, 3H), 7.33-7.40 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 8.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 55.4, 100.2, 110.9, 111.0, 113.1, 117.6, 120.3, 120.7, 122.4, 129.2, 130.1, 133.8, 136.7, 137.7, 160.1

2-(4-Isopropylphenyl)-1*H*-indole (2f): mp 199-203 ºC (lit.[18] mp 208 ºC); ^{1}H NMR ($CDCl_3$, 400 Hz): δ 1.30 (d, *J* = 6.8 Hz, 6H), 2.96 (quint, *J* = 6.8 Hz, 1H), 6.80 (s, 1H), 7.11-7.24 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 1H), 8.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 23.9, 33.9, 99.5, 110.8, 120.2, 120.5, 122.1, 125.2, 127.1, 129.3, 130.0, 136.7, 138.1, 148.6

2-(4-*tert*-Butylphenyl)-1*H*-indole (2g): mp 189-192 ºC (lit.[15] mp 198-199 ºC); ^{1}H NMR ($CDCl_3$, 400 Hz): δ 1.38 (s, 9H), 6.81 (s, 1H), 7.13-7.24 (m, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 8.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 31.3, 34.7, 99.5, 110.8, 120.2, 120.5, 122.1, 124.9, 126.0, 129.3, 129.6, 136.7, 138.0, 150.9

2-(Biphenyl-4-yl)-1*H*-indole (2h): mp 300-302 ºC (lit.[19] mp 296-298 ºC); ^{1}H NMR (DMSO-D_6, 400 Hz): δ 6.96-7.03 (m, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.36-7.55 (m, 5H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H), 11.60 (s, 1H); ^{13}C NMR (aceton-D_6, 100 Hz): δ 100.0, 111.9, 120.4, 121.0, 122.6, 126.2, 127.4, 128.1, 128.2, 129.6, 130.1, 132.5, 138.3, 138.4, 140.5, 141.0

2-(Naphthalen-1-yl)-1*H*-indole (2i): mp 135-137 ºC (lit.[17] mp 130-131 ºC); ^{1}H NMR ($CDCl_3$, 400 Hz):

δ 6.82 (s, 1H), 7.20-7.29 (m, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.51-7.57 (m, 3H), 7.62 (d, *J* = 6.4 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.92 (dd, *J* = 8.4 Hz, *J* = 15.6 Hz, 2H), 8.21 (s, 1H), 8.33 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 103.7, 110.8, 120.2, 120.6, 122.2, 125.3, 125.7, 126.1, 126.7, 127.2, 128.4, 128.6, 128.8, 131.1, 131.5, 133.9, 136.3, 136.7

2-Phenyl-1*H*-benzo[*g*]indole (2j): mp 168-170 °C (lit.[1e] mp 171-172 °C); ^{1}H NMR ($CDCl_3$, 400 Hz): δ 6.98 (s, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.44-7.58 (m, 5H), 7.73 (d, *J* = 8.0 Hz, 3H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 9.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 101.7, 119.3, 120.6, 121.2, 121.6, 124.0, 124.9, 125.3, 125.6, 127.4, 129.0, 129.1, 130.6, 131.3, 132.5, 136.2

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