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Reduction of nitroarenes followed by propanol group transfer from tris(3-hydroxypropyl)-amine and cyclization leading to quinolines under heterogeneous Pd–C catalysis

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Nitroarenes having electron-donating or -withdrawing substituents are reduced to anilines and cyclized with tris(3-hydroxypropyl)amine in the presence of a catalytic amount of Pd–C along with tin(II) chloride and isopropanol in dioxane-H_2O medium to give the corresponding quinolines in good to excellent yields.

Keywords: amine exchange reaction; nitroarenes; palladium catalyst; quinolines; cyclization

Introduction

Transition metal-catalyzed alkyl group transfer between alkylamines is known as amine exchange reaction or amine scrambling reaction.[1] This protocol has been used for the synthesis of unsymmetrical amines and N-heterocycles and for the study of the metabolism of amines.[2–5] During the course of our ongoing studies toward transition metal-catalyzed carbon–carbon and carbon–nitrogen bond forming reactions, we also reported on ruthenium-catalyzed alkanol and alkyl group transfer from alkanol- and alkylamines to N-atom anilines (amine exchange reaction), which eventually led to indoles, quinolines and benzimidazoles.[6–13] Furthermore, in connection with this report, it was disclosed that nitroarenes can be directly used for the synthesis of indoles and quinolines via a ruthenium-catalyzed reductive alkyl and alkanol group transfer from alkyl- and alkanolamines since nitroarenes are precursors of anilines from the viewpoint of industrial organic chemistry.[14–21] Under these circumstances, the reductive alkanol group transfer and cyclization protocol for quinolines[15] led us to seek a catalyst alternative which exhibits a similar catalytic activity. Herein, we describe reduction of nitroarenes into anilines followed by cyclization with tris(3-hydroxypropyl)amine, leading to 2,3,4-unsubstituted quinolines under heterogeneous Pd–C catalysis.

Results and Discussion

The results of several attempted reductive propanol group transfers from tris(3-hydroxypropyl)amine (**2**) to nitrobenzene (**1a**) and cyclization for the optimization of conditions are listed in Table 1. Treatment of **1a** with **2** in H_2O–dioxane in the presence of a catalytic amount of Pd–C along with $SnCl_2$ and isopropanol as hydrogen donor at 120 °C for 20 h afforded quinoline (**3a**) in 40% yield with concomitant formation of aniline (**4**) (entry 1).[22] When the reaction was carried out in the absence of $SnCl_2$, **1a** was not effectively converted into **4** and **3a** was not formed at all (entry 2). This result indicates that $SnCl_2$ plays a decisive role as both the reduction of **1a** to **4** and cyclization toward **3a**. It is known that nitroarenes can be easily converted into anilines in the presence of $SnCl_2$ under aqueous as well as non-aqueous media.[23] The reaction gave no significant change in the quinoline yield for a longer reaction time (entries 1 and 3), whereas the reaction temperature considerably affected the yield of **3a** (entries 3–6). This Pd–C catalyst alternative showed a similar catalytic activity when compared with a known ruthenium catalyst. The result of 111% yield shown in entry 6 indicates that at least two propanol groups out of three in **2** are available for the transfer. Replacing Pd–C with $RuCl_2(PPh_3)_3$ under the conditions shown in entry 5 of Table 1 gave **3a** in 92% yield (entry 7).[15] As has been observed in our recent reports for ruthenium-catalyzed reduction of nitroarenes and subsequent heterocyclization with alkanol- and alkylamines, an aqueous medium is necessary for the effective yield of **3a** and conversion of **1a**.[14–17] Performing the reaction in dioxane under the employed conditions resulted in a lower yield of **3a** with a lower conversion of **1a** (entry 8). Lower reaction rate and yield of **3a** were observed in the absence of isopropanol (entry 9). It appears that isopropanol plays a role as a hydrogen donor under Pd–C catalysis. After further optimization for molar ratio of [**1a**]:[**2**] (entry 10), the best result in terms of both yield of **3a** and conversion of **1a** was accomplished by the standard set of reaction conditions shown in entry 6 of Table 1.

After the reaction conditions had been established, various nitroarenes **1** were subjected to the reaction with **2** in order to investigate the reaction scope and several representative

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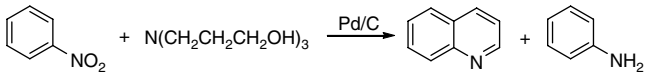
Table 1. Pd–C-catalyzed synthesis of **3a** from **1a** and **2** under various conditions[a]



1a **2** **3a** **4**

Entry	[**1a**] : [**2**]	Temperature (°C)	Time (h)	Conversion (%)[b] of **1a**	Yield %)[b,c] of **3a**	**4** (mmol)[b]
1	4	120	20	100	40	2.95
2[d]	4	120	20	23	0	0.44
3	4	120	40	100	52	2.93
4	4	150	40	100	65	2.58
5	4	180	20	100	98	1.81
6	4	180	40	100	111	1.78
7[e]	4	180	20	100	92	– [f]
8[g]	4	180	24	61	38	0.74
9[h]	4	180	24	98	78	1.46
10	2	180	40	99	82	0.39

[a] All reactions were carried out with **2** (1 mmol), Pd–C (0.05 mmol), $SnCl_2$ (1 mmol) and isopropanol (6 mmol) in H_2O–dioxane (1 ml : 9 ml) under Ar unless otherwise stated.
[b] Determined by GLC.
[c] Based on **2**.
[d] In the absence of $SnCl_2$.
[e] In the presence of $RuCl_2(PPh_3)_3$ (0.05 mmol) in place of Pd–C.[15]
[f] Not determined.
[g] Dioxane (10 ml).
[h] In the absence of isopropanol.

results are summarized in Table 2. Various nitroarenes (**1b–m**) were reductively propanol group transferred from **2** and cyclized to give quinolines (**3b–m**) in the range of 58–137% yields and the product yield varied with the position and electronic nature of the substituent on **1**. The product yield was considerably affected by the position of the substituent. With *para*- and *meta*-substituted nitroarenes (**1b** and **1c**), the quinoline yield was higher than when *ortho*-substituted nitroarenes (**1d** and **1e**) were used. As was expected, in the reaction with 3-nitrotoluene (**1c**), 7-methylquinoline, which was formed via less sterically hindered position, was produced in preference to 5-methylquinoline. However, the electronic nature of the substituent had no exact relevance to the product yield. Except for the reaction with 4-nitrophenol (**1g**), with electron-donating group substituted nitroarenes (**1b** and **1f**), the product yield was generally higher than than when nitroarenes (**1h–j**), having electron-withdrawing substituents such as chloro and acyl, were used. The reaction proceeded likewise with nitroarenes (**1k–m**) having two substituents to give the corresponding quinolines (**3k– m**).

Conclusion

In summary, it has been shown that nitroarenes undergo reduction and cyclization with tris(3-hydroxypropyl)amine in the presence of Pd–C to afford 2,3,4-unsubstituted quinolines in good to excellent yields. The addition of $SnCl_2$ is essential for the formation of quinolines, although an aqueous medium (H_2O–dioxane) is also necessary for the effective formation of quinolines. Further study of synthetic application for N-heterocycles via intrinsic Pd–C-catalyzed amine exchange reaction of this reaction is currently under investigation.

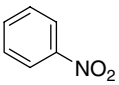
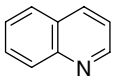
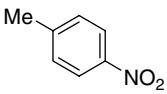
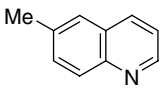
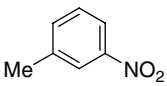
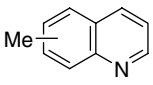
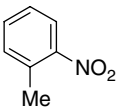
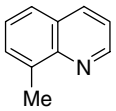
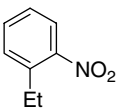
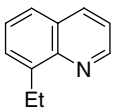
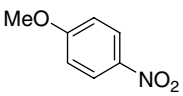
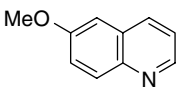
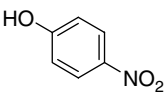
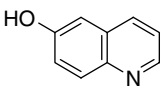
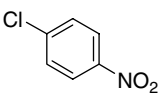
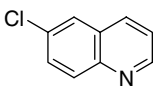
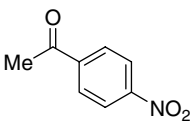
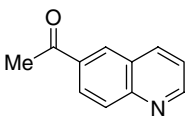
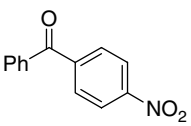
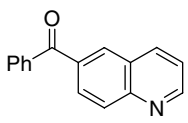
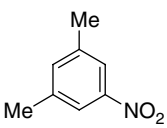
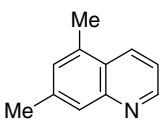
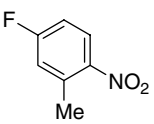
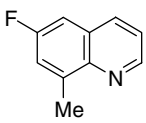
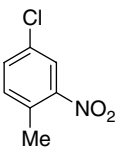
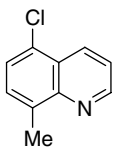
Experimental

^1H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using Me_4Si as an internal standard. Melting points were determined on a Standford Research Inc. MPA100 automated melting point apparatus. GLC analyses were carried out with Shimadzu GC-17A equipped with CBP10-S25-050 column (Shimadzu, a silica fused capillary column, 0.33 mm × 25 m, 0.25 μm film thickness) using N_2 as carrier gas. The isolation of pure products was carried out via thin-layer (silica gel 60 GF_{254}, Merck) chromatography. Commercially available organic and inorganic compounds were used without further purification. Tris(3-hydroxypropyl)amine (**2**) was prepared by the reported method.[24] Palladium, 5 wt% on activated carbon (5% Pd–C) was purchased from Aldrich.

Typical experimental procedure for Pd–C-catalyzed reductive cyclization of nitrobenzene (1a) with tris(3-hydroxypropyl)amine (2) to afford quinoline (3a)

To a 50 ml stainless steel autoclave were added nitrobenzene (**1a**) (0.492 g, 4 mmol), tris(3-hydroxypropyl)amine (**2**) (0.191 g, 1 mmol), isopropanol (0.361 g, 6 mmol), Pd–C (0.05 mmol) and $SnCl_2$ (0.190 g, 1 mmol) in dioxane–H_2O (9 ml : 1 ml). After the system was flushed with argon, the reaction mixture was stirred at 180 °C for 40 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate–chloroform mixture) to eliminate black precipitate. To the extract was added an appropriate amount of undecane as internal standard and analyzed by GLC. Removal of the solvent left a crude mixture, which was separated by thin-layer chromatography (silica gel, ethyl acetate–hexane mixture) to give quinoline (**3a**) (0.132 g, 102%). Except for new compound **3l**, which was characterized spectroscopically as shown below,

Table 2. Pd–C-catalyzed synthesis of quinolines **3** from **1** with **2**[a]

Nitroarene **1**		Quinoline **3**		Yield (%)[b]
	**1a**		**3a**	102
	**1b**		**3b**	137
	**1c**		**3c**	124[c]
	**1d**		**3d**	87
	**1e**		**3e**	91
	**1f**		**3f**	114
	**1g**		**3g**	66
	**1h**		**3h**	82
	**1i**		**3i**	87
	**1j**		**3j**	62
	**1k**		**3k**	106
	**1l**		**3l**	58
	**1m**		**3m**	62

[a] Reaction conditions: **1** (4 mmol), **2** (1 mmol), isopropanol (6 mmol), 5% Pd–C (0.05 mmol), $SnCl_2$ (1 mmol), H_2O-dioxane (1 ml : 9 ml), 180 °C, for 40 h, under Ar.
[b] Isolated yield based on **2**.
[c] Regioisomeric mixture: 5-Me : 7-Me = 1 : 5 (400 MHz ^{1}H NMR).

all quinolines were characterized by GLC and/or spectroscopic comparision with authentic samples synthesized by known methods.[25–29]

*6-Fluoro-8-methylquinoline (**3l**)*

Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (s, 3H, CH_3), 7.20 (dd, J_{HH} = 2.8, J_{HF} = 8.8 Hz, 1H, H7), 7.28–7.29 (m, 1H, H5), 7.35 (dd, J_{HH} = 4.2, 8.2 Hz, 1H, H3), 8.00 (dd, J_{HH} = 1.6, 8.2 Hz, 1H, H4), 8.86 (dd, J_{HH} = 1.6, 4.2 Hz, 1H, H2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.35 (s, CH_3), 108.56 (d, J_{CF} = 21.4 Hz, C5), 119.83 (d, J_{CF} = 24.7 Hz, C7), 121.77 (s, C3), 129.09 (d, J_{CF} = 10.9 Hz, C10), 135.87 (d, J_{CF} = 5.1 Hz, C4), 140.72 (d, J_{CF} = 8.7 Hz, C8), 144.70 (s, C2), 148.57 (d, J_{CF} = 2.9 Hz, C9), 160.12 (d, J_{CF} = 245.9 Hz, C6). Anal. calcd for $C_{10}H_8FN$: C, 74.52; H, 5.00; N, 8.69. Found: C, 74.35; H, 5.39; N, 8.71.

Acknowledgments

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