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Ruthenium-catalyzed reductive cyclization of nitroarenes with trialkylamines leading to quinolines

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Abstract

Nitroarenes react with trialkylamines in the presence of a catalytic amount of a ruthenium catalyst together with tin(II) chloride dihydrate at 180 °C in an aqueous medium (toluene–H_2O) to afford the corresponding quinolines in moderate to good yields. The catalytic pathway seems to be proceeded via a sequence involving initial reduction of nitroarenes to anilines, alkyl group transfer from alkylamines to anilines to form an imine, dimerization of imine, and heterocyclization. © 2002 Published by Elsevier Science B.V.

Keywords: C–N bond activation; Reductive cyclization; Ruthenium catalyst; Nitroarenes; Quinolines; Trialkylamines

1. Introduction

Transition metal-catalyzed alkyl group transfer between alkylamines has been known as amine exchange reaction (amine scrambling reaction) and used for the synthesis of unsymmetrical amines and N-heterocycles and the study of the metabolism of amines [1]. It is known that the alkylamines essentially must have a α-hydrogen for such a carbon–nitrogen bond activation. During the course of our ongoing studies on homogeneous ruthenium catalysis [2–10], we recently centered on an alkyl group transfer from alkylamines to N-atom of anilines [2–7] as well as α-C-atom of ketones [8]. The former transformation eventually leads to indoles [2–4] and quinolines [5–7] in competition with N-alkylations. However, except for our findings, a clear-cut example for the synthesis of N-heterocycles using an alkyl group transfer from alkylamines to both alkylamines and anilines (amine exchange reaction) as yet seems to be limited to palladium-catalyzed synthesis of hydropyrimidines, imidazolidines and imidazoles [11]. Prompted by these circumstances, we have directed our attention to the direct use of nitroarenes instead of anilines for the ruthenium-catalyzed amine exchange reaction leading to N-heterocycles since nitroarenes are precursors of anilines from the viewpoint of industrial organic chemistry [12,13]. Herein we report a ruthenium-catalyzed reductive cyclization of nitroarenes with trialkylamines leading to quinolines via an amine exchange reaction.

2. Results and discussion

When nitrobenzene (**1a**) was treated with tributylamine (**2a**) at 180 °C in the presence of a catalytic amount of a ruthenium-catalyst together with $SnCl_2{\cdot}2H_2O$, the reductive cyclization product 3-ethyl-2-propylquinoline (**3a**) was formed with aniline (Table 1). The reaction proceeded in competition with the intrinsic alkyl group transfer (N-alkylation), in all cases, *N*-butylaniline being produced in the range of 6–55% yields. Among solvents examined, an aqueous medium, toluene–H_2O was turned out to be the most effective toward **3a** (runs 1–4). The presence of $SnCl_2{\cdot}2H_2O$ was necessary for the effective formation of **3a** as has been observed in our recent ruthenium-catalyzed synthesis of indoles and quinolines [2–7], the yield of **3a** being only 8% with incomplete conversion

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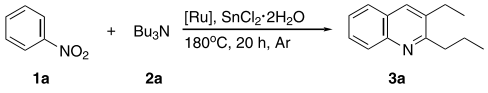
(25%) of **1a** in the absence of $SnCl_2 \cdot 2H_2O$ (run 5) [14]. Among ruthenium catalysts attempted, $RuCl_2(PPh_3)_3$ was the catalyst of choice (runs 6–10). It is noteworthy that much more *N*-butylaniline (55%) was produced under the employment of $RuCl_2(=CHPh)(PCy_3)_2$ (run 8).

With various nitroarenes and trialkylamines the reductive cyclized products were produced in the range of 22–85% yields with the concomitant formation of the corresponding N-alkyl anilines (Table 2). With *meta*- and *para*-substituted nitroarenes **1c** and **1d**, the quinoline yield was higher than that when *ortho*-substituted nitroarene **1b** was used. In the reaction with **1c**, the product quinolines were obtained as a regioisomeric mixture, favoring 7-methyl isomer, which was formed via less sterically hindered position on **1c**. With nitroarenes (**1f**–**h**) having electron-withdrawing substituents such as *p*-chloro, *p*-acetyl, and *p*-benzoyl, the product yield was lower than that when **1d** was employed. As is the case for the ruthenium-catalyzed α-alkylation of ketones with trialkylamines reported by us [8], even if there is a possibility for the α-alkylation of **3g** as well as **1g** by **2a**, no alkylation products were formed from both **1g** and **3g**. In the case of two-methyl substituted nitroarene **1i**, much more product yield was observed when compared with mono-substituted nitroarenes. From the reactions between **1i** and several trialkylamines (**2b**–**e**), the corresponding quinolines were also produced in good yields. On statistical calculation, it is necessary for the two butyl group transfer from **2a** to **1i** to form **3i**. Thus, the result of 85% yield indicates that at least two butyl groups out of three in **2a** are available for the transfer.

Table 1
Ruthenium-catalyzed synthesis of 3-ethyl-2-propylquinoline (**3a**) from nitrobenzene (**1a**) and tributylamine (**2a**) under various conditions



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

Run	[Ru]	Solvent	Conv. Of **1a** (%) [a]	Yield (%) [a,b]
1	$RuCl_2(PPh_3)_3$	THF	100	45
2	$RuCl_2(PPh_3)_3$ [c]	Dioxane	82	24
3	$RuCl_2(PPh_3)_3$	Toluene	95	50
4	$RuCl_2(PPh_3)_3$	Toluene–H_2O [d]	100	63
5 [e]	$RuCl_2(PPh_3)_3$	Toluene–H_2O [d]	25	8
6	$RuCl_3 \cdot nH_2O$–$3PPh_3$	Toluene–H_2O [d]	100	47
7	$RuH_2(PPh_3)_4$	Toluene–H_2O [d]	100	45
8	$RuCl_2(=CHPh)(PCy_3)_2$	Toluene–H_2O [d]	100	46
9	$Cp^*RuCl_2(CO)$	Toluene–H_2O [d]	100	5
10	$Ru_3(CO)_{12}$	Toluene–H_2O [d]	100	40

Reaction conditions: **1a** (2 mmol), **2a** (1 mmol), ruthenium catalyst (0.04 mmol), $SnCl_2 \cdot 2H_2O$ (1 mmol), solvent (10 ml), 180 °C, 20 h, under argon.

[a] Determined by GLC.

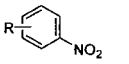
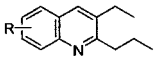
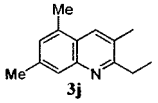
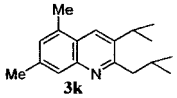
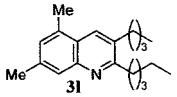
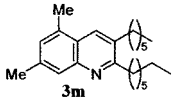
[b] Based on **2**. In all cases, *N*-butylaniline was also formed in 6–55% yields.

[c] 0.02 mmol.

[d] Toluene–H_2O = 9/1 ml.

[e] In the absence of $SnCl_2 \cdot 2H_2O$.

Table 2
Ruthenium-catalyzed synthesis of quinolines from nitroarenes and trialkylamines

Nitroarenes **1**	Trialkylamines **2**	Quinolines **3**	Yield (%) [b]
			
1a R = H	**2a**	**3a** R = H	55
1b R = 2-Me	**2a**	**3b** R = 8-Me	22
1c R = 3-Me	**2a**	**3c** R = 7- and 5-Me	69 [c]
1d R = 4-Me	**2a**	**3d** R = 6-Me	58
1e R = 4-OMe	**2a**	**3e** R = 6-OMe	41
1f R = 4-Cl	**2a**	**3f** R = 6-Cl	40
1g R = 4-acetyl	**2a**	**3g** R = 6-acetyl	40
1h R = 4-benzoyl	**2a**	**3h** R = 6-benzoyl	40
1i R = 3,5-Me_2	**2a**	**3i** R = 5,7-Me_2	85
1i	Pr_3N **2b**	 **3j**	71
1i	$[(CH_3)_2CH(CH_2)_2]_3N$ **2c**	 **3k**	62
1i	$[CH_3(CH_2)_5]_3N$ **2d**	 **3l**	73
1i	$[CH_3(CH_2)_7]_3N$ **2e**	 **3m**	75

[a] Reaction conditions: **1** (2 mmol), **2** (1 mmol), $RuCl_2(PPh_3)_3$ (0.04 mmol), $SnCl_2 \cdot H_2O$ (1 mmol), toluene–H_2O (9 ml/1 ml), 180 °C, 20 h, under argon.

[b] Isolated yield based on **2**.

[c] Regioisomeric distribution was determined by ^{1}H-NMR (400 MHz): 7-Me/5-Me = 5.9/1.

Although the reaction scheme is still obscure, a plausible pathway, consistent with the products formed, is depicted in Scheme 1. Cycle A shows the transfer of butyl moiety from **2a** to aniline. The initial coordination of **2a** to ruthenium followed by oxidative insertion of ruthenium into the adjacent C–H bond forms an alkylruthenium intermediate **4**, which rapidly equilibrates with an iminium ion complex **5**. Nucleophilic attack of aniline to **5** leads to imine **7** via intermediate **6** with concomitant formation of *N*-butylaniline [15,16]. The starting **1a** might be converted into aniline by both $SnCl_2 \cdot 2H_2O$ in an aqueous medium [17] and dihydridoruthenium formed in Cycle A course [18]. Subsequent steps seem to proceed via the known Schiff-base dimerization [19] and cyclization [20] to form intermediates **8** and **10**, respectively, shown in Cycle B. Finally, along with regeneration of ruthenium, the quinoline **3a**

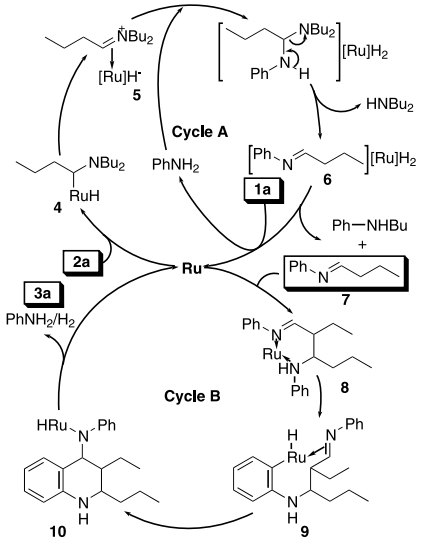
is produced from **10** by several processes such as reductive elimination, deamination, and dehydrogenation. A similar catalytic cycle has also been made by others [20] and in our recent report [7].

3. Conclusion

In summary, we have demonstrated that nitroarenes undergo reductive cyclization with trialkylamines in the presence of a ruthenium catalyst and $SnCl_2{\cdot}2H_2O$ in an aqueous medium to give quinolines in moderate to good yields. The present reaction is a first example for the synthesis of N-heterocycles using amine exchange reaction by the direct use of nitroarenes.

4. Experimental

^{1}H- 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. Infrared spectra were obtained on a Mattson Galaxy 7020A spectrophotometer. Melting points (m.p.) were determined on a Thomas–Hoover capillary melting point apparatus and were uncorrected. The GLC analyses were carried out with Shimadzu GC-17A (FID) 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. Mass spectra were obtained using EI ionization at 70 eV. The isolation of pure products was carried out via column chromatography (silica gel 60, 70-230 mesh, Merck) and thin layer chromatography (silica gel 60 GF_{254}, Merck). All nitroarenes and trialkylamines were used without further purification. Commercially available ruthenium catalysts were introduced except for $Cp^*RuCl_2(CO)$, which was prepared by the reported method [21].



Scheme 1.

4.1. Typical procedure

A mixture of nitrobenzene (**1a**) (0.246 g, 2 mmol), tributylamine (**2a**) (0.185 g, 1 mmol), $RuCl_2(PPh_3)_3$ (0.038 g, 0.04 mmol), $SnCl_2{\cdot}2H_2O$ (0.226 g, 1 mmol) in toluene–H_2O (9/1 ml) was charged in a pressure vessel. The system was flushed with argon and allowed to react at 180 °C for 20 h. The reaction mixture was poured into brine, extracted with chloroform, and dried over anhydrous Na_2SO_4. Removal of the solvent left an oil, which was purified by column chromatography (EtOAc–C_6H_{12} = 1/10) to afford 3-ethyl-2-propylquinoline (**3a**) (0.110 g, 55%).

The compounds **3a**–**f** [6], **3i** [6] and **3j** [5] are known. The new products **3g**, **3h** and **3k**–**m** prepared by the above procedure were characterized spectroscopically as shown below.

4.1.1. 6-Acetyl-3-ethyl-2-propylquinoline (3g)

White solid, m.p. 83–85 °C (from hexane); IR (KBr): 1672 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.08 (t, J = 7.0 Hz, 3H), 1.36 (t, J = 7.0 Hz, 3H), 1.81–1.91 (m, 2H), 2.70 (s, 3H), 2.85 (q, J = 7.0 Hz, 2H), 2.95–2.99 (m, 2H), 7.95 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 8.16 (dd, J = 8.5 and 1.5 Hz, 1H), 8.36 (d, J = 1.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$): δ 14.8, 15.0, 23.2, 25.7, 27.3, 38.5, 127.0, 127.3, 129.6, 129.8, 134.7, 135.6, 137.0, 149.0, 165.4, 198.2 (C=O); MS m/z (relative intensity): 241 ([M]$^+$, 40), 213 (100). Anal. Calc. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.45; H, 7.92; N, 5.81%.

4.1.2. 6-Benzoyl-3-ethyl-2-propylquinoline (3h)

Viscous oil; IR (neat): 1658 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.09 (t, J = 7.0 Hz, 3H), 1.35 (t, J = 7.5 Hz, 3H), 1.82–1.91 (m, 2H), 2.86 (q, J = 7.5 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H), 7.51 (t, J = 7.5 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.84 (d, J = 7.5 Hz, 2H), 7.93 (s, 1H), 8.06–8.11 (m, 2H), 8.18 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 14.9, 15.0, 23.3, 25.8, 38.6, 126.9, 129.0, 129.2, 129.5, 130.7, 131.5, 133.1, 135.1, 135.6, 137.1, 138.5, 148.7, 165.3, 197.0 (C=O); MS m/z (relative intensity): 303 ([M]$^+$, 39), 275 (100). Anal. Calc. for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.23; H, 7.17; N, 4.54%.

4.1.3. 2-Isobutyl-3-isopropyl-5,7-dimethylquinoline (3k)

Pale yellow oil; ^{1}H-NMR ($CDCl_3$): δ 0.90 (d, J = 6.5 Hz, 6H), 1.25 (d, J = 7.0 Hz, 6H), 2.11–2.24 (m, 1H), 2.39 (s, 3H), 2.55 (s, 3H), 2.82 (d, J = 7.0 Hz, 2H), 3.19–3.29 (m, 1H), 7.03 (s, 1H), 7.58 (s, 1H), 7.95 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 17.5, 20.7, 21.6, 23.0, 27.9,

28.4, 43.0, 123.5, 124.8, 126.6, 127.3, 132.3, 136.9, 138.3, 145.6, 159.0; MS m/z (relative intensity): 255 ($[M]^+$, 28), 185 (100). Anal. Calc. for $C_{18}H_{25}N$: C, 84.65; H, 9.87, N, 5.48. Found: C, 84.36; H, 10.23; N, 5.31%.

4.1.4. 3-Butyl-2-pentyl-5,7-dimethylquinoline (**3l**)

Pale yellow oil; ^{1}H-NMR ($CDCl_3$): δ 0.92 (t, $J = 7.5$ Hz, 3H), 0.99 (t, $J = 7.5$ Hz, 3H), 1.35–1.50 (m, 6H), 1.62–1.70 (m, 2H), 1.74–1.82 (m, 2H), 2.47 (s, 3H), 2.60 (s, 3H), 2.78 (t, $J = 8.0$ Hz, 2H), 2.95 (t, $J = 8.0$ Hz, 2H), 7.10 (s, 1H), 7.66 (s, 1H), 7.92 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 14.4, 14.5, 18.9, 22.1, 23.1, 23.2, 30.0, 32.6, 32.8, 33.5, 36.2, 124.9, 126.2, 128.7, 131.7, 133.1, 133.6, 138.3, 147.4, 162.0; MS m/z (relative intensity): 283 ($[M]^+$, 27), 185 (100). Anal. Calc. for $C_{20}H_{29}N$: C, 84.75; H, 10.31, N, 4.94. Found: C, 84.38; H, 10.59; N, 4.87%.

4.1.5. 2-Heptyl-3-hexyl-5,7-dimethylquinoline (**3m**)

Pale yellow oil; ^{1}H-NMR ($CDCl_3$): δ 0.88 (t, $J = 7.0$ Hz, 3H), 0.90 (t, $J = 7.0$ Hz, 3H), 1.28–1.49 (m, 14H), 1.63–1.70 (m, 2H), 1.73–1.81 (m, 2H), 2.47 (s, 3H), 2.60 (s, 3H), 2.77 (t, $J = 8.0$ Hz, 2H), 2.94 (t, $J = 8.0$ Hz, 2H), 7.10 (s, 1H), 7.66 (s, 1H), 7.91 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 14.5, 18.9, 22.1, 23.06, 23.09, 29.68, 29.71, 29.73, 30.30, 30.35, 31.3, 32.1, 32.3, 33.1, 36.2, 124.9, 126.2, 128.7, 131.7, 133.1, 133.6, 138.3, 147.4, 162.0; MS m/z (relative intensity): 339 ($[M]^+$, 4), 84 (100). Anal. Calc. for $C_{24}H_{37}N$: C, 84.89; H, 10.98; N, 4.13. Found: C, 84.69; H, 10.97; N, 3.93%.

Acknowledgements

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