Synthesis of quinolines *via* ruthenium-catalysed amine exchange reaction between anilines and trialkylamines

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Received (in Cambridge, UK) 24th July 2000, Accepted 25th August 2000
First published as an Advance Article on the web 18th September 2000

Anilines react with an array of trialkylamines in the presence of a catalytic amount of $RuCl_3{\cdot}nH_2O$ and bis(diphenylphosphino)methane together with $SnCl_2{\cdot}2H_2O$ and hex-1-ene as hydrogen acceptor in dioxane at 180 °C to afford the corresponding 2,3-disubstituted quinolines in moderate to good yields.

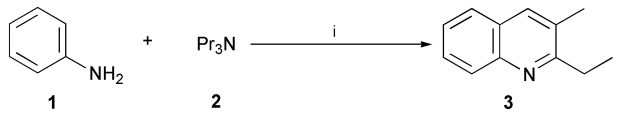
It is well-known that the quinoline skeleton plays an important role as an intermediate for the design of antimalarial compounds. The structural core of quinolines has generally been synthesised by various conventional named routes such as Skraup, Döbner-von Miller, Conrad-Limpach, Friedlaender and Pfitzinger syntheses. In conjunction with the conventional syntheses, transition metal-catalysed versions utilising various substrates have also been attempted because of facility, efficiency and convenience for the formation of quinolines.[1–4] We recently developed and reported a novel ruthenium-catalysed synthetic approach for the formation of indoles[5] and quinolines[6] *via* a mechanistic amine exchange reaction between primary aromatic amines and functionalised aliphatic amines.[7] However, except for the aforementioned indoles and quinolines, a clear-cut example for the synthesis of N-heterocyclic compounds using the amine exchange reaction seems as yet to be limited to palladium-catalysed synthesis of pyrimidines and imidazoles.[7d] In the course of our continuing studies on ruthenium-catalysed synthesis of N-heterocyclic compounds using the amine exchange reaction, we now report another ruthenium-catalysed synthesis of quinolines from an array of primary aromatic amines and trialkylamines *via* an amine exchange reaction.

The results of several attempted ruthenium-catalysed cyclisations between aniline (**1**) and tripropylamine (**2**) are summarised in Table 1 (Scheme 1). Treatment of **1** with **2** in dioxane in the presence of a catalytic amount of $RuCl_3{\cdot}nH_2O$ (8 mol% based on **2**) and dppm (12 mol% based on **2**) together with $SnCl_2{\cdot}2H_2O$ and hex-1-ene as hydrogen acceptor at 180 °C for 20 h afforded 2-ethyl-3-methylquinoline (**3**) in 63% yield along with *N*-propylaniline (**4**) (28%). This reaction condition was eventually revealed to be the best for obtaining **3** (run 1). The absence of both $SnCl_2{\cdot}2H_2O$ and hex-1-ene stopped the reaction almost completely, but **4** was produced in a considerable yield by an alkyl group transfer between **1** and **2** (run 2). The addition of either $SnCl_2{\cdot}2H_2O$ or hex-1-ene was effective for the formation of quinoline **3** compared with the results in the absence of both $SnCl_2{\cdot}2H_2O$ and hex-1-ene (runs 3,4). Thus, the coexistence of $SnCl_2{\cdot}2H_2O$ and hex-1-ene was essential for the effective formation of **3**. Other hydrogen acceptors such as cyclohexene, hex-1-yne, acetone, and nitrobenzene were almost ineffective for the formation of **3** (runs 5–8).

Table 1 Ruthenium-catalysed reaction of **1** with **2** under various conditions[a]

Run	Hydrogen acceptor	Additive	GLC yield (%)[b] **3**	**4**
1	Hex-1-ene	$SnCl_2{\cdot}2H_2O$	63 (49)[c]	28
2	—	—	1	62
3	—	$SnCl_2{\cdot}2H_2O$	48	27
4	Hex-1-ene	—	14	41
5	Cyclohexene	$SnCl_2{\cdot}2H_2O$	40	20
6	Hex-1-yne	$SnCl_2{\cdot}2H_2O$	6	9
7	Acetone	$SnCl_2{\cdot}2H_2O$	16	11
8	Nitrobenzene	$SnCl_2{\cdot}2H_2O$	9	2

[a] All reactions were carried out with **1** (6 mmol), **2** (1 mmol), $RuCl_3{\cdot}nH_2O$ (0.08 mmol), dppm (0.12 mmol), $SnCl_2{\cdot}2H_2$ (1 mmol), and hydrogen acceptor (10 mmol) in dioxane (10 ml) at 180 °C for 20 h. [b] Based on **2**. [c] Isolated yield.

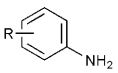
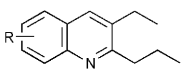
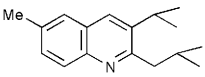
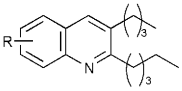
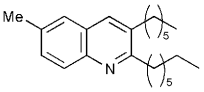


1 2 3

Scheme 1 *Reagents and conditions*: i, $RuCl_3{\cdot}nH_2O$, dppm, dioxane, 180 °C, 20 h.

From the heteroannulation between an array of anilines and trialkylamines under the described controlled reaction conditions above, the corresponding quinolines were also formed in good yields, and several representative results are summarised in Table 2.† The quinoline yield was not decisively affected by the position of the substituent on aniline. With chloroaniline having electron-withdrawing Cl substituent, the product yield

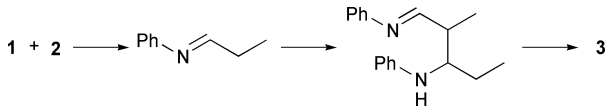
Table 2 Ruthenium-catalysed synthesis of quinolines from anilines and trialkylamines[a]

Anilines	Trialkylamines	Quinolines	Yield (%)[b]
			
R = H	Bu_3N	R = H	51
R = 4-Me	Bu_3N	R = 6-Me	52
R = 3-Me	Bu_3N	R = 7-Me	67
R = 2-Me	Bu_3N	R = 8-Me	47
R = 4-OMe	Bu_3N	R = 6-OMe	46
R = 4-Cl	Bu_3N	R = 6-Cl	21
R = 4-Bu	Bu_3N	R = 6-Bu	77
R = 4-*s*-Bu	Bu_3N	R = 6-*s*-Bu	75
R = 3,5-Me	Bu_3N	R = 5,7-Me	76
R = 4-Me	$[(CH_3)_2CH(CH_2)_2]_3N$		45
			
R = 4-Me	$[CH_3(CH_2)_5]_3N$	R = 6-Me	86
R = 4-*s*-Bu	$[CH_3(CH_2)_5]_3N$	R = 6-*s*-Bu	66
R = 4-Me	$[CH_3(CH_2)_7]_3N$		81

[a] All reactions were carried out with aniline (6 mmol), trialkylamine (1 mmol), $RuCl_3{\bullet}nH_2O$ (0.08 mmol), dppm (0.12 mmol), $SnCl_2{\bullet}sH_2O$ (1 mmol), and hex-1-ene (10 mmol) in dioxane (10 ml) at 180 °C for 20 h. [b] Isolated yield based on trialkylamine.

DOI: 10.1039/b005966h

was lower than that when anilines having electron-donating character were used. However, compared with the cases of anilines having electron-donating character, much more *N*-alkylaniline was produced. This result indicates that the reaction proceeds competitively between heteroannulation and *N*-alkylation and the electronic nature of the substituent on aniline determines relative rate. In the case of *m*-toluidine, the quinolines were obtained as a regioisomeric mixture, favoring predominantly the formation of the 7-substituted isomer.



Scheme 2

Although the details of the present reaction including the role of $SnCl_2{\cdot}2H_2O$ are not fully understood, the initial formation of imines by amine exchange reaction between anilines and trialkylamines seems to be a crucial step. Subsequent steps seem to be followed by the known Schiff-base dimerisation[8] and ruthenium-mediated heteroannulation (Scheme 2).[3c] However, one plausible role of $SnCl_2{\cdot}2H_2O$, as a ruthenium–tin complex formed by the insertion of tin(II) chloride into the ruthenium–chloride bond of $RuCl_3{\cdot}nH_2O$, seems to accelerate the initial amine exchange reaction between anilines and trialkylamines.[9] This can be rationalised by the result of Table 1 (runs 1–4). The statistical sum of **3** and **4** reveals the extent of amine exchange reaction between **1** and **2**.[10] Apparently, as shown in Table 1, the alkyl group transfer was effective for the reaction in the presence of $SnCl_2{\cdot}2H_2O$ (runs 1,3) as compared with the reaction in the absence of $SnCl_2{\cdot}2H_2O$ (runs 2,4).

In summary, we have demonstrated that quinolines can be synthesised by reaction of an array of anilines with easily available trialkylamines in the presence of a ruthenium catalyst. The present heteroannulation is a novel synthetic approach leading to quinolines *via* an amine exchange reaction.

This work was supported by Korea Science & Engineering Foundation (KRF-97-05-01-05-01-3) and grant of Post-Doc. (C. S. C.) Program from Kyungpook National University (1999).

Notes and references

† *General experimental procedure*: a mixture of aniline (6 mmol), trialkylamine (1 mmol), $RuCl_3{\cdot}nH_2O$ (0.08 mmol), dppm (0.12 mmol), hex-1-ene (10 mmol) and $SnCl_2{\cdot}2H_2O$ (1 mmol) in dioxane (10 ml) was placed in a pressure vessel. After the system was flushed with argon, the mixture was stirred at 180 °C for 20 h. The reaction mixture was passed through a short silica gel column ($CHCl_3$), poured into brine, extracted with $CHCl_3$ and dried over anhydrous Na_2SO_4. Removal of the solvent left an oil which was separated by column chromatography (silica gel, ethyl acetate–hexane mixture) to give quinolines.

1 For palladium-catalysed versions, see: N. A. Cortese, C. B. Ziegler, B. J. Hrnjez and R. F. Heck, *J. Org. Chem.*, 1978, **43**, 2952; L. S. Hegedus, G. F. Allen, J. J. Bozell and E. L. Waterman, *J. Am. Chem. Soc.*, 1978, **100**, 5800; R. C. Larock and S. Babu, *Tetrahedron Lett.*, 1987, **28**, 5291; R. C. Larock and M.-Y. Kuo, *Tetrahedron Lett.*, 1991, **32**, 569; N. G. Kundu, J. S. Mahanty, P. Das and B. Das, *Tetrahedron Lett.*, 1993, **34**, 1625; A. Arcadi, S. Cacchi, G. Fabrizi, F. Manna and P. Pace, *Synlett*, 1998, 446; S. Cacchi, G. Fabrizi and F. Marinelli, *Synlett*, 1999, 401.

2 For rhodium-catalysed versions, see: S. E. Diamond, A. Szalkiewicz and F. Mares, *J. Am. Chem. Soc.*, 1979, **101**, 490; Y. Watanabe, M. Yamamoto, S. C. Shim, T. Mitsudo and Y. Takegami, *Chem. Lett.*, 1979, 1025; Y. Watanabe, N. Suzuki, S. C. Shim, M. Yamamoto, T. Mitsudo and Y. Takegami, *Chem. Lett.*, 1980, 429; Y. Watanabe, S. C. Shim and T. Mitsudo, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 3460; W. J. Boyle and F. Mares, *Organometallics*, 1982, **1**, 1003; Y. Watanabe, N. Suzuki, Y. Tsuji, S. C. Shim and T. Mitsudo, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 1116.

3 For ruthenium-catalysed versions, see: (*a*) Y. Watanabe, Y. Tsuji and N. Suzuki, *Chem. Lett.*, 1981, 1067; (*b*) Y. Watanabe, Y. Tsuji and Y. Ohsugi, *Tetrahedron Lett.*, 1981, **22**, 2667; (*c*) Y. Watanabe, Y. Tsuji and Y. Ohsugi and J. Shida, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 2452; (*d*) Y. Watanabe, Y. Tsuji and J. Shida, *Bull. Chem. Soc.*, 1984, **57**, 435; (*e*) Y. Tsuji, H. Nishimura, K.-T. Huh and Y. Watanabe, *J. Organomet. Chem.*, 1985, **286**, C44; (*f*) Y. Tsuji, K.-T. Huh and Y. Watanabe, *J. Org. Chem.*, 1987, **59**, 1673.

4 For iron-catalysed version, see: Y. Watanabe, K. Takatsuki, S. C. Shim, T. Mitsudo and Y. Takegami, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 3397.

5 C. S. Cho, H. K. Lim, S. C. Shim, T. J. Kim and H.-J. Choi, *Chem. Commun.*, 1998, 995; C. S. Cho, J. H. Kim and S. C. Shim, *Tetrahedron Lett.*, 2000, **41**, 1811.

6 C. S. Cho, B. H. Oh and S. C. Shim, *Tetrahedron Lett.*, 1999, **40**, 1499; C. S. Cho, B. H. Oh and S. C. Shim, *J. Heterocycl. Chem.*, 1999, **36**, 1175.

7 For transition metal-catalysed amine exchange reactions, see: (*a*) N. Yoshimura, I. Moritani, T. Shimamura and S.-I. Murahashi, *J. Am. Chem. Soc.*, 1973, **95**, 3038; (*b*) S.-I. Murahashi, T. Hirano and T. Yano, *J. Am. Chem. Soc.*, 1978, **100**, 348; (*c*) Y. Shvo and R. M. Laine, *J. Chem. Soc., Chem. Commun.*, 1980, 753; (*d*) S.-I. Murahashi, K. Kondo and T. Hakata, *Tetrahedron Lett.*, 1982, **23**, 229; (*e*) S.-I. Murahashi, N. Yoshimura, T. Tsumiyama and T. Kojima, *J. Am. Chem. Soc.*, 1983, **105**, 5002.

8 M. S. Kharasch, I. Richlin and F. R. Mayo, *J. Am. Chem. Soc.*, 1940, **62**, 494.

9 For transition metal–tin chemistry, see: M. S. Holt, W. L. Wilson and J. H. Nelson, *Chem. Rev.*, 1989, **89**, 11.

10 One equiv. of **3** corresponds to two equiv. of imine since **3** is formed *via* a dimerisation of imine. The amount of **4** is equal to that of imine since **4** is produced by the hydrogenation of imine under catalysis.