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Microwave-assisted synthesis of 4-quinolylhydrazines followed by nickel boride reduction: a convenient approach to 4-aminoquinolines and derivatives

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Abstract

Nickel(II) chloride/sodium borohydride combination was employed for the reduction of 4-hydrazinoquinoline derivatives to the corresponding anilines. This reductive protocol was efficiently applied for the reductive cleavage of monosubstituted hydrazines. We described herein the microwave-assisted synthesis of 4-hydrazinoquinolines, which furnished a high yielding and rapid two-step procedure for the synthesis, under mild conditions, of 4-aminoquinolines as antimalarial precursors.

Keywords: Nickel boride; Reduction; Hydrazines; Microwave; 4-Aminoquinolines

For more than 50 years, low-cost antimalarial drugs possessing a 4-aminoquinoline scaffold cured billions of infections in poverty stricken malaria-endemic regions of the world.[1] However, these drugs, mainly represented by chloroquine, are no longer efficacious against resistant parasites. Artemisinins are a highly effective alternative to older drugs against resistant parasites, but they are unaffordable for the majority of the affected population; so new and low cost antimalarials are urgently needed.[2]

As a part of our ongoing investigations to develop new antimalarial compounds,[3–5] we recently designed an innovative clotrimazole/chloroquine hybrid pharmacophore, and due to the economic burdens of malaria and the need to develop low-cost drugs, we considered this aspect in all phases of the design and synthetic processes for which 4-aminoquinolines and 9-aminoacridines proved to be key intermediates. To reduce the cost and to improve the yield of these latter, we decided to develop a novel, low-cost and versatile strategy for the synthesis of diversely substituted 4-aminoquinolines and 9-aminoacridines, which represent the aromatic systems of well-known antimalarials such as chloroquine and mepacrine.

4-Aminoquinolines are prepared by ammonolysis of the corresponding 4-halo, 4-alkoxy or 4-aryloxyquinolines under harsh and hazardous conditions. Standard procedures involve the use of gaseous ammonia at high pressure and temperature or the use of ammonia and phenol as the solvent at 180 °C.[6–8] Conversely, the nucleophilic displacement of the halogen of 4-chloroquinolines by means of hydrazine is smoothly accomplished in refluxing ethanol and we exploited this reaction to synthesize a number of 4-quinolynhydrazones with different pharmacological activities.[4,9–13]

4-Hydrazinoquinolines, as well as the corresponding hydrochlorides, are stable compounds and can be readily

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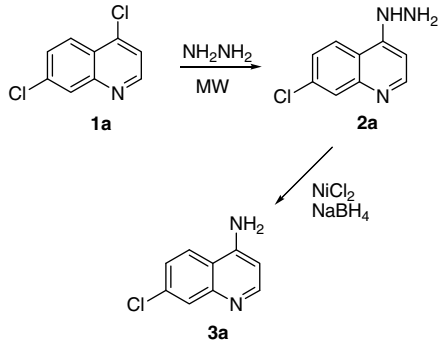


Scheme 1.

purified by crystallization. Thus, we developed a novel nickel boride-based strategy to 4-aminoquinolines starting from the versatile 4-hydrazinoquinolines. At the same time, we highly improved the synthesis of 4-hydrazinoquinolines. Accordingly, starting from 4-chloroquinolines, the novel strategy to 4-aminoquinolines consisted of a two-step sequence involving a microwave assisted synthesis of 4-hydrazinoquinolines followed by the reduction of the hydrazine functionality by nickel boride (Scheme 1).

While the reduction of nitrogen-containing functionalities such as nitro, imines, azides and oximes is a well-established protocol to primary anilines and heteroanilines,[14] there are few reported methods for the reduction of the nitrogen–nitrogen bond of azo- or hydrazo-compounds. N,N′-Disubstituted hydrazines are generally reduced to the corresponding amines by catalytic hydrogenation or using metals in protic solvents, and the conditions required to cleave this bond depend markedly on the substituents attached to it. Lithium aluminium hydride has been used for the reduction of various nitrogen containing functionalities but lacks selectivity. On the other hand, it is known that reductions involving sodium borohydride ($NaBH_4$), a milder, less expensive and easier to handle hydride reducing agent, are greatly accelerated by the addition of certain metal salts, especially cobalt(II) and nickel(II),[15,16] and that $NaBH_4$–transition metal salt systems reduce nitrogen-containing functional groups such as nitro compounds, oximes, symmetric hydrazines and also azo- and azoxy-derivatives.[17,18] In view of our previous experience on nickel boride catalyzed reduction of different functionalities,[19–21] we decided to explore its potential to achieve reductive cleavage of hydrazine functionality in 4-quinolylhydrazines so as to provide a new and alternative route for the synthesis of various 4-aminoquinoline and aniline derivatives.

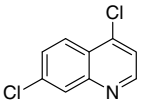
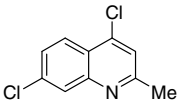
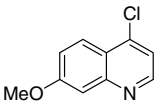
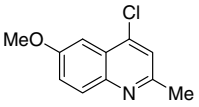
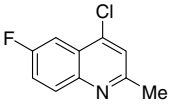
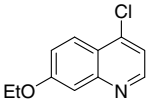
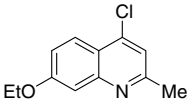
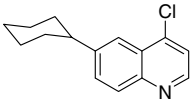
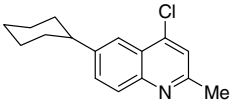
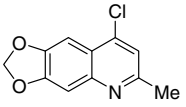
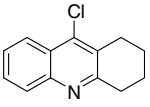
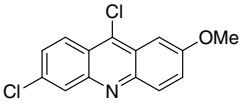
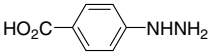
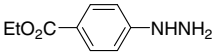
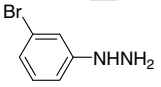
With this purpose, we initially investigated the most appropriate reaction conditions for the nucleophilic displacement of the 4-chloro functionality by hydrazine. This reaction usually proceeds in 60–70% yield by using an excess or equimolar amounts of hydrazine monohydrate in refluxing ethanol for 8–12 h. With the aim to increase the yields while shortening the reaction times, we decided to exploit microwave irradiation as the heating source. Using 4,7-dichloroquinoline (**1a**, Scheme 1) as a model substrate, we tested various reaction conditions to obtain **2a**.

When equimolar amounts of **1a** and hydrazine monohydrate were irradiated at the microwave in an open vessel, only 20% conversion to **2a** was obtained after 2 h. On the other hand, microwave irradiation of the same reaction mixture in a sealed tube for 15 min resulted in the formation of 5% of the target compound **2a** along with an unidentified by-product. Increasing the power to 200 W resulted in the decomposition of the starting material. We therefore decided to use *N*,*N*-dimethylformamide (DMF) as an alternative solvent, but also in this case decomposition of the starting material occurred. Conversely, when a suspension of **1a** in neat hydrazine monohydrate (2 equiv) was irradiated in a sealed tube at 80 W, 30% conversion to **2a** was obtained and the starting material was recovered unreacted. Finally, employing an irradiation power of 150 W resulted in the formation of **2a** in 95% yield after 5 min and the desired compound was isolated simply by filtration of the reaction mixture. The same reaction conditions were successfully applied to synthesize hydrazines **2b**–**l** (Table 1), which were obtained in yields ranging from 65% to 95%, higher than those described in the literature for the same compounds.[22] On the other hand, when at position 8 of the quinoline or the 1,2,3,4-tetrahydroacridine scaffold a nitro group was placed, the microwave-assisted synthesis using 2 equiv of hydrazine did not result in the expected products (8-nitro hydrazine derivatives), but using a large excess of hydrazine monohydrate (4 equiv), the corresponding 8-amino hydrazino-derivatives were detected in 30–40% yield.

7-Chloro-4-hydrazinoquinoline **2a**, synthesized as described above, was in turn used as the model compound for the investigation of the reduction reaction of the hydrazine functionality to the corresponding amino-group catalyzed by the $NiCl_2$ and $NaBH_4$ system (Scheme 1). Treatment of **2a** with 2 M equiv of nickel(II) chloride and 6 M equiv of $NaBH_4$ in MeOH at rt furnished the corresponding amine **3a** in 87% yield and the reaction was complete after 15 min. The same results were obtained by reducing the amounts of both $NiCl_2$ and $NaBH_4$ (1:1:3 substrate/$NiCl_2$/$NaBH_4$). Reductions carried out with $NaBH_4$ alone did not afford the expected product **3a** even after 12 h and unreacted **2a** was also recovered when treated with $NiCl_2$ alone. The reductions are thus undoubtedly proceeding due to the involvement of both reagents, and the reactive species is likely to be nickel boride formed in situ. The reaction of **2a** with nickel boride in THF, acetonitrile and ethanol was incomplete even after 24 h while when DMF was used as the solvent a series of unidentified by-products were immediately formed. We defined methanol or a 1:1 mixture of MeOH and THF, chosen depending upon the solubility of the individual starting materials, as the best solvent system for the nickel boride catalyzed reduction.

The chemoselectivity of this reductive procedure was assayed by reacting differently substituted hydrazines (Table 1) under our optimized reaction conditions resulting

Table 1
Microwave-assisted synthesis of hydrazines **2a–l** and hydrazine reduction by $NiCl_2/NaBH_4$[a] in MeOH[b] at room temperature to anilines **3a–l** and **5a–c**

Compound	Structure	Hydrazine	Yield[d] (%)	Amine	Time[c]	Yield[d] (%)
1a		**2a**	95	**3a**	15	87
1b		**2b**	92	**3b**	30	70
1c		**2c**	89	**3c**	300	55
1d		**2d**	92	**3d**	180	79
1e		**2e**	85	**3e**	60	65
1f		**2f**	83	**3f**	300	62
1g		**2g**	94	**3g**	15	77
1h		**2h**	72	**3h**	15	90
1i		**2i**	65	**3i**	15	74
1j		**2j**	86	**3j**	60	95
1k		**2k**	88	**3k**	30	86
1l		**2l**	92	**3l**	30	86
4a		—	—	**5a**	60	90[e]
4b		—	—	**5b**	120	85
4c		—	—	**5c**	30	65

[a] Molar ratio: substrate/$NiCl_2/NaBH_4$ 1:1:3.
[b] 20 mL of methanol/g of substrate was used.
[c] Time (min) for the disappearance of starting material.
[d] Yields refer to purified compounds.
[e] Not isolated.

in the selective reduction of the 4-hydrazinoquinoline group in the presence of halo (fluoro and chloro), alkoxy and methylendioxy groups.[23] To further explore the compatibility of this reduction procedure with different functional groups, we used the commercially available 4-hydrazinobenzoic acid, its corresponding ethyl ester and the bromophenyl hydrazine (**4a–c**) as a substrate. Following the same protocol, the reduction reaction smoothly took place to afford the corresponding anilines **5a–c** (Table 1) in high yield.

Concluding, we have developed a convenient and rapid method for the conversion of 4-chloroquinolines, 9-chloroacridines and 9-chloro-1,2,3,4-tetrahydroacridine derivatives to the corresponding 4-amino- and 9-amino-analogues through a two-step sequence involving the microwave-assisted formation of 4-hydrazino intermediates followed by their reduction with nickel boride. To the best of our knowledge, this is the first nickel boride catalyzed reduction of monosubstituted hydrazines. Moreover, the entire protocol provides a rapid and efficient access to 4-aminoquinolines, while avoiding the use of harsh and hazardous conditions previously used to synthesize this class of compounds. When developing antimalarial quinolines, this synthetic strategy may reduce costs and reaction time.

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References and notes

1. For reviews, see: (a) Wiesner, J.; Ortmann, R.; Hassan Jomaa, H.; Schlitzer, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5274–5293; (b) Ursos, L. M. B.; Roepe, P. D. *Med. Res. Rev.* **2002**, *22*, 465–491.
2. Fidock, D. A.; Rosenthal, P. J.; Croft, S. L.; Brun, R.; Nwaka, S. *Nat. Rev. Drug Disc.* **2004**, *3*, 509–520.
3. Gemma, S.; Campiani, G.; Butini, S.; Kukreja, G.; Joshi, B. P.; Persico, M.; Catalanotti, B.; Novellino, E.; Fattorusso, E.; Nacci, V.; Savini, L.; Taramelli, D.; Basilico, N.; Morace, G.; Yardley, V.; Fattorusso, C. *J. Med. Chem.* **2007**, *50*, 595–598.
4. Gemma, S.; Kukreja, G.; Fattorusso, C.; Persico, M.; Romano, M. P.; Altarelli, M.; Savini, L.; Campiani, G.; Fattorusso, E.; Basilico, N.; Taramelli, D.; Yardley, V.; Butini, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5384–5388.
5. Gemma, S.; Kukreja, G.; Campiani, G.; Butini, S.; Bernetti, M.; Joshi, B. P.; Savini, L.; Basilico, N.; Taramelli, D.; Yardley, V.; Bertamino, A.; Novellino, E.; Persico, M.; Catalanotti, B.; Fattorusso, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3535–3539.
6. Vippagunta, S. R.; Dorn, A.; Matile, H.; Bhattacharjee, A. K.; Karle, J. M.; Ellis, W. Y.; Ridley, R. G.; Vennerstrom, J. L. *J. Med. Chem.* **1999**, *42*, 4630–4639.
7. Elderfield, R. C.; Gensler, W. J.; Birstein, O.; Kreysa, F. J.; Maynard, J. T.; Galbreath, J. *J. Am. Chem. Soc.* **1946**, *68*, 1250–1251.
8. Hamer, F. M. *J. Chem. Soc.* **1924**, *125*, 1348–1357.
9. Savini, L.; Chiasserini, L.; Gaeta, A.; Pellerano, C. *Bioorg. Med. Chem.* **2002**, *10*, 2193–2198.
10. Savini, L.; Massarelli, P.; Chiasserini, L.; Nencini, C.; Pellerano, C. *Il Farmaco* **1997**, *52*, 609–613.
11. Savini, L.; Massarelli, P.; Chiasserini, L.; Sega, A.; Pellerano, C.; Barzi, A.; Nocentini, G. *Eur. J. Med. Chem.* **1995**, *30*, 547–552.
12. Bartolucci, C.; Cellai, L.; Di Filippo, P.; Brizzi, V.; Pellerano, C.; Savini, L.; Benedetto, A.; Elia, G. *Il Farmaco* **1992**, *47*, 945–952.
13. Thomas, J.; Berkoff, C. E.; Flagg, W. B.; Gallo, J. J.; Haff, R. F.; Pinto, C. A.; Pellerano, C.; Savini, L. *J. Med. Chem.* **1975**, *18*, 245–250.
14. Hudlický, M. *Reductions in Organic Chemistry*; ACS Monograph: Vol. 188, 1996; pp 91–101.
15. Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763–780.
16. Khurana, J. M.; Gogia, A. *Org. Prep. Proced. Int.* **1997**, *29*, 1–32.
17. Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1981**, *29*, 1159–1161.
18. Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1988**, *36*, 1529–1533.
19. Khurana, J. M.; Kandpal, B. M.; Kukreja, G.; Sharma, P. *Can. J. Chem.* **2006**, *84*, 1019–1023.
20. Khurana, J. M.; Kukreja, G.; Bansal, G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2520–2524.
21. Khurana, J. M.; Kukreja, G. *Synth. Commun.* **2002**, *32*, 1265–1269.
22. Microwave reactions were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. The reaction was performed in glass vessels (capacity 10 mL) sealed with a septum. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. In a typical experiment, a suspension of 4-chloroquinoline-derivative (500 mg) and hydrazine monohydrate (2 equiv) was irradiated in a sealed tube at 150 W for 5 min (ramp time 30 s, $T_{max} = 150$ °C, $P_{max} = 200$ psi, Power max = on). After cooling to rt, the resulting solid was isolated by filtration and crystallized from ethanol. Physical and spectroscopic data of hydrazines **2a–l** are consistent with those reported in the literature.
23. In a typical procedure, to a mixture of 4-hydrazino-derivative (100 mg), nickel(II) chloride hexahydrate (1 equiv) in methanol (4 mL), was added sodium borohydride (3 equiv) very cautiously while stirring the reaction mixture vigourously at room temperature. The progress of the reaction was monitored by TLC (10:1 CH_2Cl_2/MeOH). After the complete disappearance of the starting material, the reaction mixture was filtered through a Celite pad. The filtrate was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude products were purified over neutral alumina column using 0.5% MeOH/CH_2Cl_2 to afford the pure compounds. Spectroscopic data for the new compounds: **3f**: ^{1}H NMR ($CDCl_3$) δ 1.44 (t, $J = 1.4$, 5.6 Hz, 3H); 4.12 (q, $J = 1.5$, 5.6 Hz, 2H); 4.8 (s, 2H); 6.45 (dd, $J = 1.2$, 4.1 Hz, 1H); 7.05 (d, $J = 5.2$ Hz, 1H); 7.28 (d, $J = 2.6$ Hz, 1H); 7.65 (d, $J = 9.1$ Hz, 1H); 8.41 (d, $J = 5.2$ Hz, 1H); **3h**: ^{1}H NMR ($CDCl_3$) δ 1.24–1.56 (m, 5H); 1.74–1.96 (m, 5H); 2.62–2.70 (m, 1H); 4.75 (s, 2H); 6.57 (d, $J = 4.9$ Hz, 1H); 7.52 (s, 1H); 7.55 (d, $J = 1.8$ Hz, 1H); 7.92 (d, $J = 7.3$ Hz, 1H); 8.47 (d, $J = 4.9$ Hz, 1H); **3i**: ^{1}H NMR ($CDCl_3$) δ 1.22–1.53 (m, 5H); 1.74–1.90 (m, 5H); 2.56 (s, 3H); 2.23 (s, 2H); 6.47 (s, 1H); 7.47 (s, 1H); 7.51 (d, $J = 1.8$ Hz, 1H); 7.84 (d, $J = 8.8$ Hz, 1H); **3j**, ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H); 4.35 (s, 2H); 6.06 (s, 2H); 6.43 (s, 1H); 7.25 (s, 1H).