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Convenient synthesis of 1,2,3,4-tetrahydroquinolines via direct intramolecular reductive ring closure

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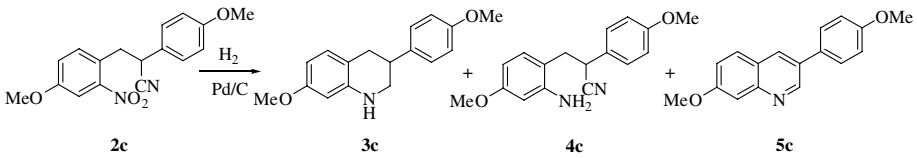
Abstract—A simple and convenient procedure for the synthesis of 3-aryl-1,2,3,4-tetrahydroquinolines is reported. 3-Aryl-1,2,3,4-tetrahydroquinolines are directly obtained by reductive ring closure of 2-phenyl-3-(2-nitrophenyl)-propionitrile derivatives in moderate to high yields.

Tetrahydroquinolines (THQs) are important heterocycles possessing diverse biological activities[1] and multiple applications.[2] They are widely used as antimalarial,[3] antibacterial,[4] antiviral agents,[5] and as key intermediates for the synthesis of photographic couplers.[6]

A number of methods have been reported for the construction of THQ core.[7] However, the application of these methods is limited due to the inadequate diversity of the substrates and/or products. In addition, the 3-monosubstituted THQs have not been well studied and only a few papers described their synthesis,[8a,b] and reduction of 3-substituted quinoline is an ordinary alternative for 3-substituted THQ.[8c,d] The 3-aryl-substituted THQs are aza analogs of isoflavans and isoflavans display promising biological activities.[9] During the course of our drug research we required certain 3-aryl-substituted THQs as intermediates. This prompted us to devise a simple and efficient way to prepare them. Herein, we wish to report our synthesis of THQs by using a direct intramolecular reductive ring closure strategy.

We first attempted to prepare 7-methoxy-3-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline by reductive ring closure of 2-phenyl-3-(2-nitrophenyl)-propionitrile derivative (Scheme 1), which is easily obtained by condensation of 4-methoxy-2-nitro-benzaldehyde with (4-methoxy-phenyl)-acetonitrile followed by reduction with $NaBH_4$. The reaction was carried out in THF and MeOH at ambient temperature. It was found that 3-(2-amino-4-methoxy-phenyl)-2-(4-methoxy-phenyl)-propionitrile (**4c**) was formed as the only product in 95% yield but ring closure did not occur with PtO_2 (10 wt %) as the catalyst. The same result was observed when Pd/C (10 wt %) was used as the catalyst for 10 h. Extension of the reaction time to 48 h yielded the desired ring closure product 7-methoxy-3-(4-methoxy-phenyl)-1,2,3,4-tetrahydroquinoline (**3c**), but the yield was fairly low (26%), accompanied by trace amount of



Scheme 1. Catalytic hydrogenation of 3-(4-methoxy-2-nitrophenyl)-2-(4-methoxy-phenyl)-propionitrile.

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3-(2-aminophenyl)-2-phenylpropionitrile, as well as the dehydrogenated product 7-methoxy-3-(4-methoxyphenyl)-quinoline (**5c**).

We next systematically investigated the effect of the amount of catalyst, temperature, and pressure on the yield of the desired product. When the amount of catalyst was increased to 30 wt %, a significant increase of yield was observed (60%, Table 1, entry 3). Higher yield (74%, Table 1, entry 4) was obtained when the reaction temperature was raised to 40 °C. Changing the pressure was found to have no effect on the reaction. On the basis of these findings, an optimum reaction condition can be reached: 30 wt % of catalyst, 40 °C, and normal pressure.

We then performed this reaction on a series of propionitriles with the optimum reaction conditions (Scheme 2).[10] The results are summarized in Table 2. Reactions of substrates bearing electron-donating (Me and OMe) substituents proceeded smoothly to give the corresponding 1,2,3,4-tetrahydroquinolines in good yields (Table 2, entries 2–10, 14, 15), while reactions of propionitrile derivatives bearing electron-withdrawing groups (CF_3 and CN) gave low to moderate yields (Table 2, entries 16 and 17). The reaction mixture was especially complicated and the yield was remarkably low in the case of cyano-bearing compound (entry 17). A low yield of 21% was also observed with bulky naphthalenyl substituted substrate (entry 19). When the C-3 substituent was thiophenyl, the reaction did not happen, possibly due to poisoning of the palladium catalyst by sulfur.

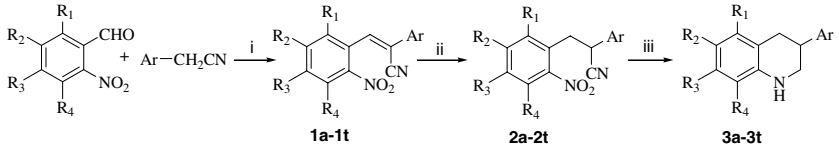
Table 1. Effect of the reaction condition on the reductive ring closure of 3-(4-methoxy-2-nitrophenyl)-2-(4-methoxy-phenyl)-propionitrile

Entry	Pd/C (wt %)	Temp (°C)	**3c** Yield (%)
1	10	rt	26
2	20	rt	53
3	30	rt	60
4	30	40	74

When 3-(2-aminophenyl) propionitrile was used as starting material, we also got the desired ring closure product. The reaction may proceed as Sajiki et al.[11] described.

To explore the possible mechanism for the formation of 1,2,3,4-tetrahydroquinolines, we attempted to apply this procedure to 2-(2-nitrobenzyl)-2-phenyl-butanenitrile. 2-Amino-3-ethyl-3-phenyl-3,4-dihydroquinoline *N*-oxide was obtained as the major product, instead of the expected product, 3-ethyl-3-phenyl-1,2,3,4-tetrahydroquinoline. This result confirmed the early report on the reactions of substrates with variant R-substituents.[12] This could not be explained by Sajiki's postulation.

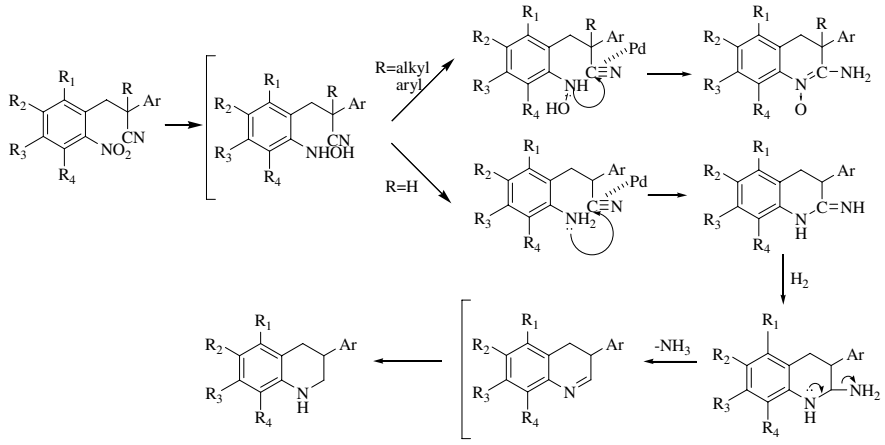
To rationalize these results, we postulate a mechanism as follows (Scheme 3): first, the nitro group is reduced to the corresponding hydroxylamine. On the one hand,



Scheme 2. Synthesis of **3a**–**3t**. Reagents and conditions: (i) Na, C_2H_5OH, 5 h; (ii) $NaBH_4$, THF, CH_3OH; (iii) H_2, Pd/C, THF, CH_3OH.

Table 2. Yields of **3a**–**3t**

Entry	R_1	R_2	R_3	R_4	Ar	**3** Yield (%)
1	H	H	H	H	Phenyl	**3a** (57)
2	H	H	H	H	4-Methoxyphenyl	**3b** (73)
3	H	H	OMe	H	4-Methoxyphenyl	**3c** (74)
4	H	OMe	OMe	H	4-Methoxyphenyl	**3d** (64)
5	H	H	OMe	H	4-Fluorophenyl	**3e** (57)
6	H	H	OMe	H	3-Amino-4-methoxyphenyl	**3f** (62)
7	OMe	OMe	OMe	H	4-Methoxyphenyl	**3g** (64)
8	H	OMe	OMe	H	3,4-Methylenedioxyphenyl	**3h** (63)
9	H	3,4-Methylenedioxyphenyl		H	3,4-Dimethoxyphenyl	**3i** (65)
10	H	OMe	H	H	4-Methoxyphenyl	**3j** (72)
11	H	H	H	OMe	4-Methoxyphenyl	**3k** (47)
12	H	F	H	H	4-Methoxyphenyl	**3l** (45)
13	H	H	OMe	H	3-Fluoro-4-methoxyphenyl	**3m** (50)
14	H	Me	H	Me	4-Methoxyphenyl	**3n** (63)
15	H	H	H	H	4-Methylphenyl	**3o** (60)
16	H	H	H	H	3-Trifluoromethylphenyl	**3p** (48)
17	H	H	H	H	2-Cyanophenyl	**3q** (7)
18	H	H	H	H	Biphenyl	**3r** (57)
19	H	H	H	H	Naphthalen-1-yl	**3s** (21)
20	H	H	H	H	Pyridin-2-yl	**3t** (54)



Scheme 3. Possible mechanism for the formation of 1,2,3,4-tetrahydroquinolines.

the produced hydroxylamine could be further reduced to primary amine and then subjected to the expected ring closure, and on the other hand, the hydroxylamine could directly attack the cyano group and yield the *N*-oxide product. The distance between the hydroxylamine and cyano group may play a determinant role. In fact we detected neither *N*-oxide product nor any hydroxylamine intermediate during the whole procedure when R is hydrogen. The mechanism of the reaction is valuable so as to be investigated further.

In summary, we have developed a simple route for construction of the 3-aryl-substituted 1,2,3,4-tetrahydroquinolines (THQs). Further investigations on the scope of the substrates for construction of other heterocyclic systems are underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.144.

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10. *General procedure for preparation of 1,2,3,4-tetrahydroquinoline derivatives (Table 2).*
After several vacuum/H_2 cycles to remove air from the reaction flask, the stirred mixture of the various propionitriles (200 mg), 10% Pd/C (60 mg, 30 wt % of the propionitrile) in THF (10 mL) and MeOH (2 mL) was hydrogenated at ordinary pressure and at temperature (ca. 40 °C) for 48 h. The reaction mixture was filtrated using a membrane filter and the filtrate was concentrated under reduced pressure. The crude mixture was purified by flash silica gel column chromatography, using petroleum ether/ethyl acetate with different volume proportions as eluent, thus obtaining the desired compounds.
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