Tetrahedron Letters 50 (2009) 2881–2884

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A facile one-pot synthesis of N-substituted tetrahydroquinolines

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ARTICLE INFO

Article history:
Received 5 January 2009
Revised 19 March 2009
Accepted 26 March 2009
Available online 1 April 2009

Keywords:
Quinoline
Hantzsch dihydropyridine
N-Substituted tetrahydroquinoline

ABSTRACT

An uncatalyzed one-pot synthesis of N-substituted tetrahydroquinolines was achieved in good yields by the reaction of quinoline and alkyl/acyl halides with Hantzsch dihydropyridine ester under mild reaction conditions.

The reduced form of the nicotinamide adenine dinucleotide coenzyme [NAD(P)H] plays a vital role in many bioreductions by transferring a hydride ion or an electron to the surrounding substrates.[1] 1-Benzyl-1,4-dihydronicotinamide (BNAH), Hantzsch 1,4-dihydro pyridine (DHP), 10-methyl-9,10-dihydroacridine ($AcrH_2$), and many other 1,4-dihydropyridine derivatives have been widely used as models of NAD(P)H to mimic the reduction of various unsaturated compounds such as quinones,[2] ketones,[3] aldehydes[4], and alkenes[5]. Garden et al.[6] have reported the reduction of certain electron-withdrawing conjugated olefins using Hantzsch 1,4-dihydropyridine ester. Hantzsch esters were also used for the reductive amination of aldehydes and ketones.[7] In recent years, synthetic chemists have made many efforts to develop DHP as a widely used reducing agent and have obtained good to excellent results. Hence the use of NAD(P)H model compounds as a class of mild reducing agent in synthetic organic chemistry is of considerable interest.[8]

1,2,3,4-Tetrahydroquinoline derivatives have attracted considerable interest due to their importance as synthetic intermediates, pesticides, and pharmaceutical products with a broad range of physiological and biological properties.[9,10] Although a number of different methods for the synthesis of tetrahydroquinolines exist, the most direct approach is the regioselective reduction of quinolines, which includes heterogeneous or homogeneous metal-catalyzed hydrogenations, hydroborations, and transfer hydrogenations.[11,12]

On the other hand, only a few reports for the reduction of quinolines to tetrahydroquinolines using dihydropyridines are known in the literature. All these methods involve the use of Bronsted acid,[13] iridium[14] as catalysts. Hence, the development of a simple synthetic method enabling facile access to this heterocycle, is desirable.

As part of our continued interest in the synthesis of tetrahydroquinolines[15] and in the application of Hantzsch dihydropyridine ester in organic synthesis,[16] we herein report the one-pot synthesis of N-substituted tetrahydroquinolines under mild reaction conditions using acyl, benzyl, allyl, and alkyl halides without any catalyst .

In our initial endeavour, we carried out the reaction of quinoline with acetyl chloride in CH_2Cl_2. After forming the quinolinium salt, Hantzsch dihydropyridine was added. The reaction proceeded smoothly at room temperature without any catalyst and was complete within 30 min (Scheme 1).

In order to investigate the scope and generality of this methodology, a variety of acyl/benzyl/allyl/alkyl halides **2** were employed (Scheme 2). It was observed that under optimized reaction conditions,[17] various halides reacted with quinoline forming quinolinium salts, which then underwent reduction with Hantzsch dihydropyridine to afford a series of N-substituted tetrahydroquinolines in good yields. The reaction was amenable to a wide range of halides. The reaction proceeded at a faster rate with acid halides and was slightly slow with allyl/benzyl/alkyl halides with the exception of CH_3I (about 0.5 h), respectively. The results are summarized in Table 1.

We have also carried out the reaction with 2-methyl and 6-methyl quinoline to give the products **4k** and **4l**, respectively. Pyridinium salts do not undergo the reduction with Hantzsch dihydropyridine.

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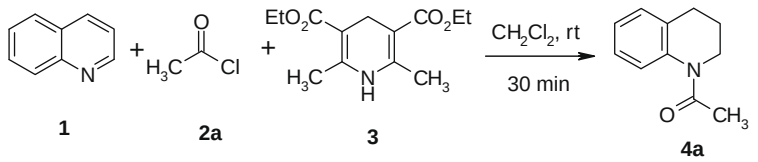
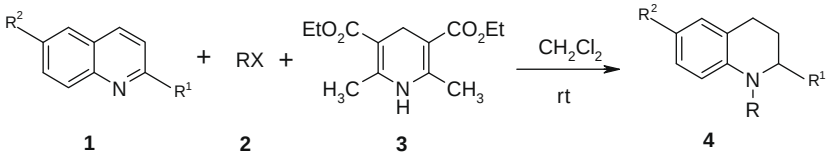
doi:10.1016/j.tetlet.2009.03.181

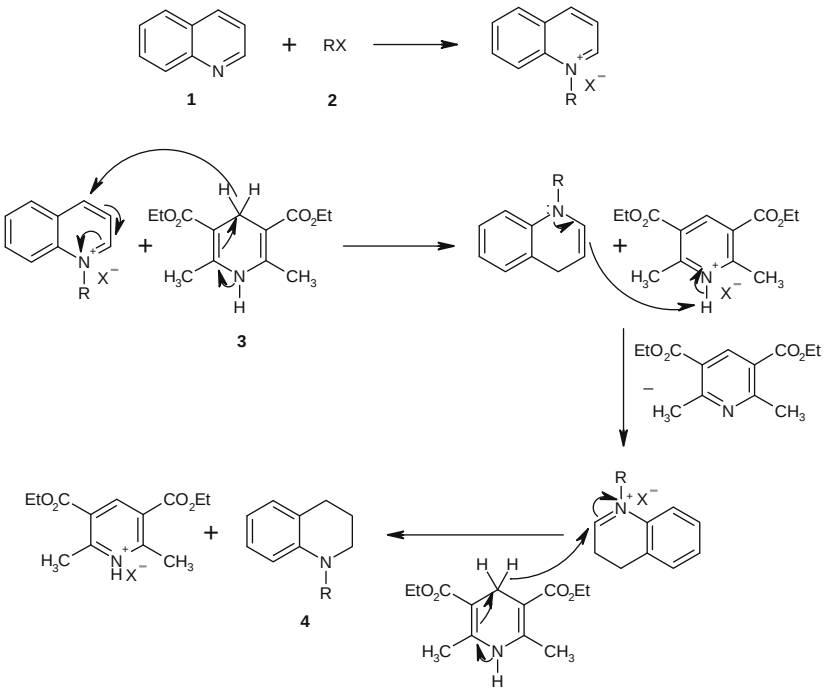


Scheme 1.



R^1=Me, R^2=H (4k), R^1=H, R^2=Me (4l)

Scheme 2.



Scheme 3.

Table 1

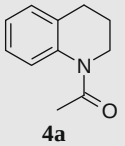
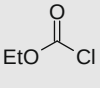
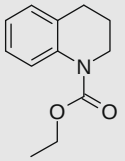
Entry	RX (**2**)	Product (**4**)	Time (h)	Yield[a] (%)
1	CH_3COCl	 **4a**	0.5	73
2		 **4b**	0.5	75

Table 1 (*continued*)

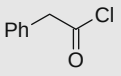
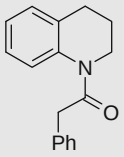
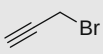
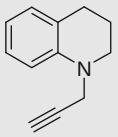
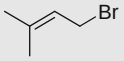
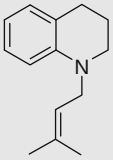
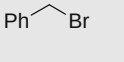
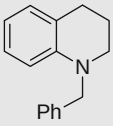
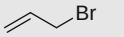
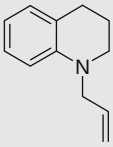
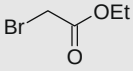
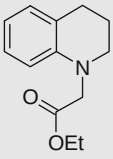
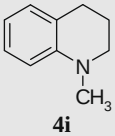
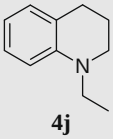
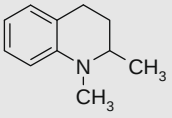
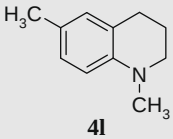
Entry	RX (**2**)	Product (**4**)	Time (h)	Yield[a] (%)
3		 **4c**	0.5	70
4		 **4d**	3.0	75

Table 1 (*continued*)

Entry	RX (**2**)	Product (**4**)	Time (h)	Yield[a] (%)
5		 **4e**	3.0	78
6		 **4f**	2.5	75
7		 **4g**	2.5	74
8		 **4h**	3.0	75
9	CH_3I	 **4i**	0.5	74
10	CH_3CH_2I	 **4j**	6.0	75
11	CH_3I	 **4k**	0.5	70
12	CH_3I	 **4l**	0.5	75

[a] Isolated yield.

We propose a plausible mechanism for the formation of product **4** (Scheme 3).

In conclusion, we have developed a simple method for the synthesis of N-substituted tetrahydroquinolines without any catalyst at room temperature. Further merits of this method are its generality, shorter-reaction time, and easy work-up.

Acknowledgment

One of the authors, T.H. thanks the Council of Scientific and Industrial Research, New Delhi, India for the research fellowship.

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17. *General procedure for the synthesis of N-substituted tetrahydroquinolines* **4a-l**. *Representative experimental procedure for N-acetyl tetrahydroquinoline* **4a**: To a stirred solution of quinoline **1** (1 mmol), acetyl chloride **2a** (1.5 mmol) was added in CH_2Cl_2 (5 mL). To the formed quinolinium salt, Hantzsch dihydropyridine (2.0 mmol) was added and stirred at room temperature. After the completion of the reaction as indicated by TLC, the reaction mixture was washed with water. The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (Merck, 100–200 mesh, ethyl acetate, pet ether, 1:9) to afford 1-(3,4-dihydro-2*H*-quinolin-1-yl)-ethanone.
Spectral data for selected compounds:
1-(3,4-Dihydro-2H-quinolin-1-yl)-ethanone (**4a**)*:* Yellow liquid. Yield: 73%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.94 (q, 2H), 2.20 (s, 3H), 2.70 (t, 2H), 3.78 (t, 2H), 7.15(m 4H,). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.0, 24.0, 26.8, 39.4, 124.3, 125.3, 126.0, 127.6, 128.4, 134.0, 170.1. IR ν_{max}: 2937, 2841, 1728, 1656, 1491, 1379, 1328, 1261, 1204, 760 cm^{-1}. Mass (ESI): 176 (M+1). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.34; H, 7.43; N, 7.96.
3,4-Dihydro-2H-quinoline-1-carboxylic acid ethyl ester (**4b**)*:* pale yellow liquid. Yield: 75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (t, 3H), 1.93 (q, 2H), 2.75 (t, 2H),

3.75 (t, 2H), 4.25 (q, 2H), 6.99 (t, 1H), 7.07 (d, 2H, J = 7.6 Hz), 7.15 (t, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 23.4, 27.3, 44.7, 62.0, 109.0, 116.7, 123.2, 127.3, 129.2, 138.2, 171.0. IR ν_{max}: 2938, 1705, 1493, 1375, 1319, 1258, 1204, 1134, 1055, 760. cm^{-1}. Mass (ESI): 252 (M+2Na). Anal. Calcd for $C_{26}H_{21}N_3O_3$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.02; H, 7.61; N, 8.21.

1-Prop-2-ynyl-1,2,3,4-tetrahydro-quinoline (**4d**)*:* brown liquid. Yield: 75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02 (q, 2H), 2.15 (t, 1H), 2.77 (t, 2H), 3.30 (t, 2H), 4.02 (d, 2H, J = 2.3 Hz), 6.69 (t, 1H), 6.75 (d, 1H, J = 8.4 Hz), 6.99 (d, 1H, J = 6.8 Hz), 7.12 (t, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 27.7, 40.7, 49.2, 71.6, 79.7, 112.0, 117.6, 124.0, 126.9, 129.1, 144.6. IR ν_{max}: 3291, 2928, 2842, 1602, 1500, 1454, 1330, 1239, 1191, 748, 645 cm^{-1}. Mass (ESI): 172 (M+1). Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.02; H, 7.61; N, 8.20.

(3,4-Dihydro-2H-quinolin-1-yl)-acetic acid ethyl ester (**4h**)*:* Brown liquid. Yield: 75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, 3H), 1.99 (q, 2H), 2.79 (t, 2H), 3.40 (t, 2H,) 3.99 (s, 2H), 4.19 (q, 2H,) 6.41 (d, 1H, J = 7.6 Hz), 6.63 (t, 1H) 6.97 (d, 1H, J = 6.8 Hz), 7.02 (t, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.3, 27.9, 50.6, 53.2, 60.8, 110.3, 116.7, 122.8, 127.0, 129.1, 144.8, 171.1. IR ν_{max}: 2933, 2842, 1743, 1602, 1503, 1455, 1336, 1184, 1026, 746 cm^{-1}. Mass (ESI): 220 (M+1). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.05; H, 7.77; N, 6.42.