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TMSCl–NaI-mediated reaction of aryl azides with cyclic enol ethers: An efficient one-pot synthesis of 1,2,3,4-tetrahydroquinolines

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Abstract

The tetrahydroquinoline moiety is an important structural component of a number of natural products. The reaction of aryl azides with 2,3-dihydro-2*H*-furan and 3,4-dihydro-2*H*-pyran in the presence of chlorotrimethylsilane-sodium iodide (TMSCl–NaI) affords the corresponding 1,2,3,4-tetrahydroquinoline derivatives in an efficient manner and most of these compounds exhibited *cis* selectivity. The aza-Diels–Alder reaction may proceed through *in situ* generation of aryl amines followed by the reaction between 2-azadiene and another equivalent of cyclic enol resulting in the formation of 1,2,3,4-tetrahydroquinolines.

Keywords: Aryl azide; Furanoquinolines; Pyranoquinolines; Trimethylsilyl chloride; Sodium iodide

1. Introduction

A number of substituted tetrahydroquinoline derivatives exhibit a wide range of biological properties [1–4] and moreover, this moiety is a component of different natural products. Therefore, it has been considerable interest in the development of new and efficient methodologies for the synthesis of tetrahydroquinoline derivatives [5]. The Lewis acid catalyzed aza-Diels–Alder reaction of *N*-aryl imines with various dienophiles is one of the most powerful tools for constructing 2,3,4-trisubstituted tetrahydroquinoline derivatives [6]. Tricyclic compounds such as pyranoquinoline derivatives are obtained when cyclic enol ethers (3,4-dihydro-2*H*-pyran) are employed as the dienophiles [7–9]. There are also reports of a one-pot procedure for their synthesis based on the three component reaction of substituted aniline, aryl aldehyde and electron-rich olefin in the presence of Lewis acid catalyst [10]. Recently, tetrahydroquinoline derivatives have been synthesized *via* a domino coupling of aniline derivatives and cyclic enol ethers catalyzed by various Lewis acids [11–14]. Iodotrimethylsilane (TMSI) is known to possess remarkable activity as a hard-soft reagent for a wide spectrum of synthetic applications [15]. In the literature [16,17] it is demonstrated that *in situ* generation of TMSI using chlorotrimethylsilane (TMSCl) and sodium iodide (NaI) reagent system is desirable because of its near neutral conditions, more reactivity and commercial viability from practical point of view in comparison to the use of TMSI directly. In continuation to our earlier efforts [17–21] for the synthesis of natural products by exploring mild and versatile methods for the reduction of azido groups, we have developed a new method for the synthesis of furano/pyranoquinolines. Herein, we wish to report an efficient method for the one-pot synthesis of furanoquinolines and pyranoquinolines from aryl azides with 2,3-dihydro-2*H*-furan and 3,4-dihydro-2*H*-pyran by employing TMSCl–NaI reagent system.

2. Experimental

2.1. General

^{1}H NMR spectra were recorded on Gemini varian-VXR-unity (200 MHz) or Bruker UXNMR/XWIN-NMR (300 MHz) instrument. Chemical shifts (δ) are reported in ppm downfield from internal standard TMS. EI mass spectra were recorded on a VG-7070H Micromass mass spectrometer at 200 °C, 70 eV, with a trap current of 200 μA and 4 kV of acceleration voltage. Reactions were monitored by TLC, performed on silica gel glass

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Table 1
Synthesis of 1,2,3,4-tetrahydroquinoline from aryl azides using TMSCl–NaI

Entry	Substrate			*cis*:*trans*	Time (h)	Yield (%)[a]
	R_1	R_2	*n*			
a	H	H	1	90:10	3.0	92
b	H	Cl	1	92:8	3.5	89
c	H	F	1	90:10	3.5	85
d	H	Br	1	85:15	3.5	80
e	H	CH_3	1	90:10	3.0	95
f	H	OCH_3	1	88:12	3.0	94
g	H	CN	1	80:20	4.0	75
h	H	OH	1	85:15	3.5	88
i	CH_3	H	1	93:7	3.0	85
j	F	F	1	80:20	3.5	78
k	H	H	2	92:8	3.5	90
l	H	Cl	2	90:10	4.0	86
m	H	F	2	90:10	4.0	84
n	H	Br	2	85:15	4.0	80
o	H	CH_3	2	95:5	3.5	90
p	H	OCH_3	2	90:10	3.5	92
q	H	CN	2	80:20	4.0	74
r	H	OH	2	90:10	4.0	86
s	CH_3	H	2	90:10	3.0	88
t	F	F	2	82:18	4.0	75

[a] Isolated yields.

plates containing 60 F-254. Visualisation on TLC was achieved by UV light or iodine indicator. Column chromatography was performed with Merck 60–120 mesh silica gel. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Yields reported are based on isolated compounds.

2.2. General procedure for the synthesis of 1,2,3,4-tetrahydroquinolines

To a solution of aryl azide (1 mmol) in acetonitrile (10 ml) was added NaI (9 mmol) followed by TMSCl (1.5 mmol). The resulting mixture was stirred for 10–15 min and to this was added about 1 mL of water and 3,4-dihydro-2*H*-pyran or 2,3-dihydro-2*H*-furan (2.5 mmol). This was stirred at room temperature for the appropriate time (Table 1). After completion of the reaction as indicated by the TLC, the reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$, $Na_2S_2O_3$ and brine. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The products were purified and separated over silica gel (100–200 mesh) with ethyl acetate:hexane (2:8). The resulting products were characterized by ^{1}H NMR, ^{13}C NMR, MS and IR spectra, and comparison with the literature data [11–14].

2.3. Spectral data for selected compounds

cis-Isomer (**3e**): EI MS *m*/*z* 247 M^+; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.10 (d, J = 2.18 Hz, 1H), 6.91 (dd, J = 2.18 Hz, 1H), 6.51 (d, J = 7.62 Hz, 1H), 5.02 (d, J = 7.62 Hz, 1H), 3.82–3.90 (m, 2H), 3.70–3.76 (m, 2H), 3.40–3.46 (m, 1H), 2.82 (br, 1H), 2.55–2.60 (m, 1H), 2.21 (s, 3H), 2.00–2.04 (m, 1H), 1.50–1.90 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.91, 130.48, 129.12, 127.98, 122.85, 115.06, 76.24, 66.88, 62.59, 53.12, 42.76, 31.01, 29.36, 24.32, 20.90; IR (KBr) ν_{max}/cm^{-1}: 3340, 2930, 2896, 1510, 1270, 1060.

trans-Isomer (**4e**): EI MS *m*/*z* 247 M^+; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.15 (d, J = 2.18 Hz, 1H), 6.91 (dd, J = 2.18 Hz, 1H), 6.60 (d, J = 8.50 Hz, 1H), 4.50 (d, J = 5.52 Hz, 1H), 3.90–4.00 (m, 1H), 3.75–3.80 (m, 2H), 3.70–3.75 (m, 2H), 2.80 (br, 1H), 2.75–2.82 (m, 1H), 2.21 (s, 3H), 2.16–2.20 (m, 1H), 1.50–1.90 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.82, 131.50, 129.92, 127.80, 120.80, 115.31, 75.88, 65.82, 62.70, 52.62, 41.69, 30.22, 29.50, 29.85, 20.70; IR (KBr, ν_{max}/cm^{-1}): 3350, 2925, 2890, 1616, 1495, 1292, 1060, 764. Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66%. Found: C, 72.78%; H, 8.54%; N, 5.69%.

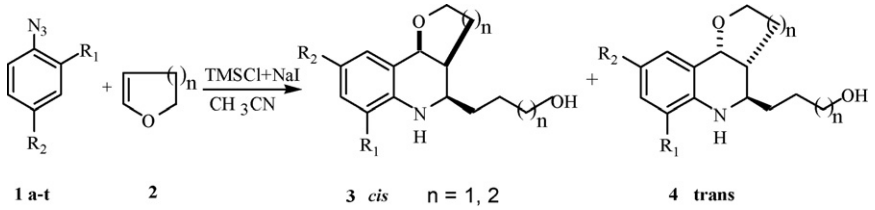
cis-Isomer (**3p**): EI MS *m*/*z* 291 M^+; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.90 (d, J = 2.62 Hz, 1H), 6.65 (dd, J = 2.62, 8.00 Hz, 1H), 6.48 (d, J = 8.00 Hz, 1H), 5.02 (d, J = 5.82 Hz, 1H), 3.75 (s, 3H), 3.68 (t, J = 6.25 Hz, 2H), 3.60–3.65 (m, 1H), 3.40 (dt, J = 2.94, 11.75 Hz, 1H), 3.30 (dt, J = 2.62, 6.64 Hz, 1H), 2.00 (dddd, J = 3.02, 5.41, 7.16, 12.45 Hz, 1H), 1.30–1.70 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.70, 139.32, 121.62, 115.62, 114.96, 111.95, 72.52, 62.50, 61.06, 56.02, 53.92, 35.62, 32.74, 32.40, 25.50, 22.46, 18.02; IR (KBr) ν_{max}/cm^{-1}: 3454, 2930, 2845, 1490, 1280, 1050.

trans-Isomer (**4p**): EI MS *m*/*z* 291 M^+; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.80 (d, J = 2.62 Hz, 1H), 6.68 (dd, J = 2.62, 8.02 Hz, 1H), 6.52 (d, J = 8.02 Hz, 1H), 4.45 (d, J = 2.94 Hz, 1H), 3.90–3.95 (m, 1H), 3.72 (s, 3H), 3.65–3.70 (m, 3H), 3.46–3.52 (m, 1H), 1.96–2.00 (m, 1H), 1.30–1.70 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.18, 139.32, 121.76, 116.75, 115.98, 114.70, 74.30, 67.68, 62.60, 55.22, 51.00, 36.90, 33.28, 33.02, 24.71, 23.30, 21.72; IR (KBr, ν_{max}/cm^{-1}): 3455, 2953, 2845, 1485, 1440, 1280, 1010, 800, 755. Anal. Calcd. for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.64; N, 4.81%. Found: C, 70.20%; H, 8.62%; N, 4.78%.

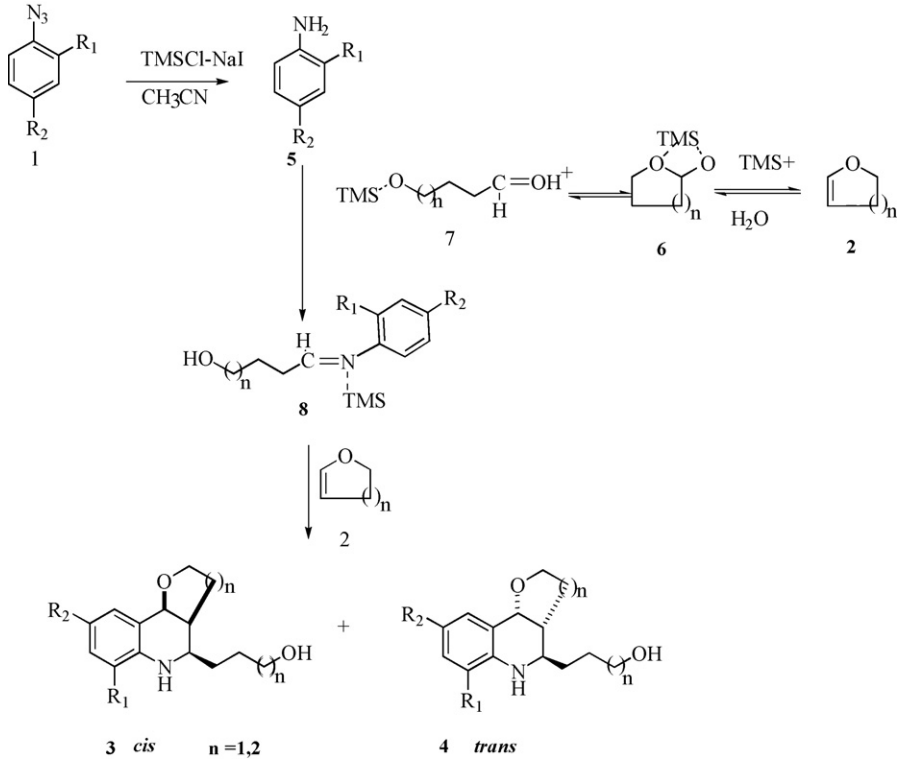
3. Results and discussion

The aza-Diels–Alder reaction for the one-pot synthesis of tetrahydroquinolines from aryl azides (from *in situ* generated aryl amines) has been extensively studied by using different reagents that are usually expensive, whereas addition of aryl azides to cyclic enol ethers has been investigated in this report by the use of TMSCl–NaI. In continuation to our interest in the development of new and practical methods for the reduction of azido functionality [17–21], we reported [17] the reduction of aryl azides to aryl amines employing TMSCl–NaI reagent system. These results have prompted to explore the *in situ* reduction of aryl azides followed by its addition to the cyclic enol ethers to afford tetrahydroquinoline system under mild conditions in high yields. Although we have earlier reported [13] the synthesis of tetrahydroquinolines using $FeCl_3$–NaI, TMSCl–NaI system is milder and we are examining the further aspects of this chemistry.

This methodology has been generalized by reacting a series of substituted aryl azides (**1a**–**t**) with different cyclic enol ethers (**2**) to give 1,2,3,4-tetrahydroquinoline derivatives (**3** and **4**)



Scheme 1. Synthesis of 1,2,3,4-tetrahydroquinolines.



Scheme 2. Proposed mechanism for the TMSCl–NaI-mediated tetrahydroquinoline synthesis.

as illustrated in Table 1 and Scheme 1. The reactions proceeded efficiently in high yields at ambient temperature. As shown in Table 1 electron-rich aryl azides are more reactive than electron deficient aryl azides. The strong deactivating group 4-cyanoaryl azide gave low yield of product (**g** and **q**). In all the cases, the products were obtained as a mixture of *cis*/*trans*-isomer (**3** and **4**), favoring the *cis*-isomer. The ratio of the isomers was determined by the ^{1}H NMR spectra of the crude products. The stereochemistry of the isomers was assigned on the basis of coupling constants and NOE studies in accordance with the literature [12,13]. All the products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy.

The combination of TMSCl–NaI is a suitable reagent system for the efficient synthesis of desired products **3** and **4** in high yields (Scheme 1). The role of NaI is not clear in the process but a plausible explanation can be attributed to the *in situ* generation of TMSI, which is not known to exist in pure state. The mechanism can be rationalized by the *in situ* generation of aniline **5**, while the cyclic enol ether in the presence of protic Lewis acid in water can be hydrated to give **6**, which in the presence of TMSI can undergo a facile ring opening to provide **7**. The condensation reaction between **5** and **7** gives the imine **8**, which is coordinated with trimethyl silyl ion. Finally, an aza-Diels–Alder reaction of the imine **8** with **2** will generate the tetrahydroquinoline derivatives **3** and **4** as shown in Scheme 2. From the results, it is observed that aryl azides bearing electron donating groups are more reactive than the ones with electron withdrawing group.

4. Conclusion

In conclusion, we have reported a highly efficient method for the synthesis of 1,2,3,4-tetrahydroquinolines from aryl azides and cyclic enol ethers using TMSCl–NaI reagent system. The present approach that is carried out under extremely mild and neutral conditions has provided a novel as well as efficient synthesis of tetrahydroquinoline derivatives. The reagent employed for this process is rather inexpensive, non-stinking and non-toxic, hence this is a practical protocol. Further investigations of the scope and limitations of these reactions are in progress in our laboratory to explore its applications in organic synthesis.

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