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$FeCl_3$–NaI mediated reactions of aryl azides with 3,4-dihydro-2*H*-pyran: a convenient synthesis of pyranoquinolines

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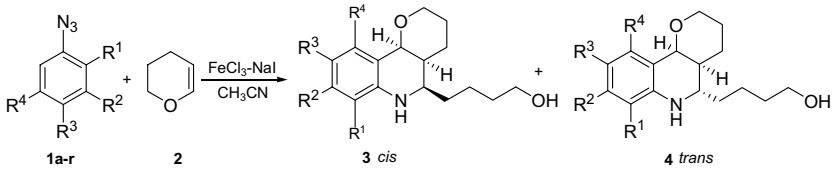
Abstract—The tetrahydroquinoline moiety is an important structural component of a number of natural products. The reaction of aryl azides with 3,4-dihydro-2*H*-pyran in the presence of $FeCl_3$–NaI affords the corresponding tetrahydroquinoline derivatives in an efficient manner. Most of the cyclizations exhibited *cis* selectivity.

A number of tetrahydroquinoline derivatives exhibit a wide range of biological properties,[1,2] and, moreover, this moiety is a component of many natural products. Hence, there has been considerable interest in the development of new and efficient methodologies for the synthesis of tetrahydroquinoline derivatives.[3] The Lewis acid catalyzed aza-Diels–Alder reaction of *N*-arylimines with various dienophiles is one of the most powerful tools for constructing 2,3,4-trisubstituted tetrahydroquinoline derivatives.[4] Tricyclic compounds such as pyranoquinoline derivatives are obtained when cyclic enol ethers (e.g., 3,4-dihydro-2*H*-pyran) are employed as the dienophiles.[5] There are also reports of a one-pot procedure for their synthesis based on the 3-component reaction of a substituted aniline, an aryl aldehyde and an electron rich olefin in the presence of a Lewis acid catalyst.[6] Recently, tetrahydroquinoline derivatives have been synthesized via a domino coupling of aniline derivatives and cyclic enol ethers catalyzed by indium(III) chloride in water[7] or CH_3CN.[8] However, there are no reports on the one-pot synthesis of pyranoquinolines from aryl azides with 3,4-dihydro-2*H*-pyran.

Herein, we wish to report a new and highly efficient method for the synthesis of pyrano[3,2-*c*]quinoline derivatives employing the $FeCl_3$–NaI reagent system. The aza-Diels–Alder reaction for the one-pot synthesis of pyranoquinolines from aryl amines (or from in situ generated aryl amines) has been extensively studied using expensive reagents, whereas the addition of aryl azides to 3,4-dihydro-2*H*-pyran by the use of $FeCl_3$–NaI is reported (Scheme 1).

We have been interested in the development of new and practical methods for the reduction of the azido functionality[9] and in continuation of these findings, we recently reported[10] the reduction of aryl azides to aryl amines employing the $FeCl_3$–NaI reagent system. These



Scheme 1.

Keywords: Aryl azide; Pyranoquinolines; Ferric chloride; Sodium iodide; Reductive cyclization.
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results prompted us to explore the in situ reduction of aryl azides followed by addition to a pyran to afford the pyranoquinoline system under mild conditions in high yields. In the present study aryl azide **1a** (1 mmol) in acetonitrile (10 mL) was treated with sodium iodide (9 mmol) followed by ferric chloride (1.5 mmol) at room temperature. After 10–15 min, a few drops of water (about 1 mL) and 3,4-dihydro-2*H*-pyran **2** (2.5 mmol) were added and the resulting mixture stirred at room temperature.[11] The combination of $FeCl_3$–NaI is a suitable reagent system for the efficient synthesis of the desired products **3** and **4** in high yields (Scheme 1). The role of NaI in this process is not clear but a plausible explanation may involve the participation of in situ generated FeI_3, which is not known to exist in the pure state. The use of an excess of NaI appears to be essential for this conversion as the use of less than 5 equiv not only decreases the amount of the conversion but also the rate of the reaction.

This methodology has been generalized by reacting a series of substituted aryl azides **1b–r** with 3,4-dihydro-2*H*-pyran **2** to give 2-(hydroxyalkyl)tetrahydroquinoline derivatives as illustrated in Table 1.

It was observed that aryl azides bearing electron-donating groups are more reactive than those with electron withdrawing groups. Furthermore by employing aryl azides such as 4-azidopyridine, 2-azidopyridine and 4-nitroarylazide, the desired products could not be obtained upon reaction with 3,4-dihydro-2*H*-pyran under similar conditions.

The stereochemical assignment[12] of product **3f** was carried from coupling constants and NOE studies. The small coupling constant value for the H5 proton $J_{H5–H6} = 5.8$ Hz (δ 5.0 ppm) shows that the two six-membered quinoline and tetrahydropyran rings are *cis* fused; further, the NOE cross peak observation confirms this configuration. The small coupling constant value $J_{H6–H7} = 6.6$ Hz for H7 (δ 3.30 ppm) indicates that the six-membered quinoline ring adopts a twist confirmation. This was also confirmed by the presence of NOE cross peaks between H5–H6 and H6–H7. The six-membered tetrahydropyran ring is in the chair conformation as indicated by the large coupling constant values $J_{H14_{ax}–H13_{ax}} = 11.7$ Hz for $H14_{ax}$ (δ 3.39 ppm) and $J_{H6–H12_{ax}} = 12.4$ Hz for H6 (2.0 ppm). This was also confirmed by the presence of NOE cross peak between H4–H14 and by the absence of an NOE cross peak between H5–H14 as shown in Figure 1.

In the case of the *trans* isomer **4f**, the two six-membered quinoline and tetrahydropyran rings are *cis* fused as shown from the small coupling constant values $J_{H5–H6} = 2.9$ Hz for H5 (δ 4.44 ppm). In addition, the presence of an NOE cross peak between H5–H6 and the absence of an NOE cross peak between H6–H7 further confirms the assigned structure.

In conclusion, we report a highly efficient method that produces more of the *cis* product for the synthesis of

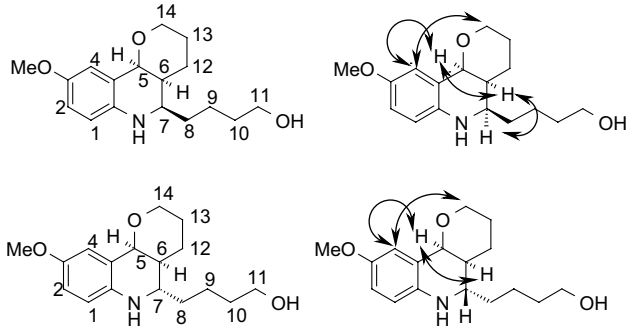

Figure 1. Chemical structure and important NOE's for **3f** (*cis*) and **4f** (*trans*).

Table 1. Synthesis of pyranoquinolines from aryl azides using $FeCl_3$–NaI

Entry	Substrate				Time (h)	*cis*:*trans*	%Yield[a]
	R^1	R^2	R^3	R^4			
a	H	H	H	H	4.5	95:5	85
b	H	H	Cl	H	5.0	93:7	90
c	H	H	F	H	4.0	95:5	90
d	H	H	Br	H	4.5	80:20	85
e	H	H	CH_3	H	3.5	95:5	88
f	H	H	OCH_3	H	3.5	85:15	90
g	H	H	CN	H	6.5	85:15	72
h	H	H	OH	H	5.0	90:10	85
i	CH_3	H	H	H	4.0	95:5	83
j	F	H	F	H	6.0	86:14	76
k	H	NO_2	H	H	6.5	75:25	72
l	CN	H	H	H	5.5	70:30	75
m	Cl	H	H	H	3.5	95:5	84
n	COPh	H	H	H	4.0	80:20	75
o	H	Cl	H	Cl	4.5	90:10	80
p	OH	H	NO_2	H	4.5	80:20	85
q	H	Cl	H	CF_3	3.5	85:15	84
r	H	H	OC_2H_5	H	3.5	90:10	90

[a] Isolated yields are reported.

1,2,3,4-tetrahydroquinolines from aryl azides and 3,4-dihydro-2*H*-pyran using the $FeCl_3$–NaI reagent system.

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11. General procedure for the $FeCl_3$–NaI catalyzed synthesis of tetrahydroquinolines: To a solution of aryl azide (1 mmol) in acetonitrile (10 mL) was added NaI (9 mmol) followed by $FeCl_3$ (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 (2.5 mmol). This was then 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 Na_2SO_4 and concentrated under reduced pressure. The residue was purified over silica gel (100–200 mesh) with ethyl acetate/hexane (2:8) to afford the corresponding product. The resulting products were characterized by ^{1}H NMR, EIMS and IR.
12. Spectral data for compounds **3f** and **4f** IR (KBr): ν_{max} (cm^{-1}): 3455, 2935, 2845, 1485, 1440, 1280, 1010, 800, 755. EIMS: m/z 291[M^+]. ^{1}H NMR and ^{13}CNMR ($CDCl_3$/TMS): *cis*-isomer (**3f**): δ ^{1}H 1.32–1.70 (m, 10H), 2.00 (dddd, $J = 3.0$. 5.4, 7.1, 12.4 Hz, 1H), 3.30 (dt, $J = 2.6$, 6.6 Hz, 1H), 3.39 (dt, $J = 2.9$ Hz, 11.7 Hz, 1H) 3.62 (dt, 1H), 3.68 (t, $J = 6.3$ Hz, 2H), 3.74 (s, 3H), 5.00 (d, $J = 5.8$ Hz, 1H), 6.48 (d, $J = 8.0$ Hz, 1H), 6.66 (dd, $J = 2.6$, 8.0 Hz, 1H), 6.90 (d, $J = 2.6$ Hz, 1H). ^{13}C, 18.06, 22.42, 25.46, 32.30, 32.68, 35.59, 53.96, 55.99, 61.01, 62.42, 72.56, 112.03, 115.02, 115.68, 121.53, 139.34, 152.67.
trans-Isomer (**4f**): δ ^{1}H 1.32–1.70 (m, 10H), 1.96 (m, 1H), 3.48 (m, 1H), 3.68 (m, 3H), 3.72 (s, 3H), 3.92 (m, 1H), 4.44 (d, $J = 2.9$ Hz, 1H), 6.50 (d, $J = 8.0$ Hz, 1H), 6.68 (dd, $J = 2.6$, 8.0 Hz, 1H), 6.80 (d, $J = 2.6$ Hz, 1H). ^{13}C, 21.68, 23.26, 24.67, 33.04, 33.21, 36.84, 50.94, 56.17, 62.54, 67.66, 74.24, 114.73, 116.06, 116.71, 121.72, 139.20, 152.12. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07%; H, 8.65%; N, 4.81%. Found: C, 70.26%; H, 8.72%; N, 4.86%.