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An efficient one-pot synthesis of tetrahydroquinoline derivatives via an aza Diels–Alder reaction mediated by CAN in an aqueous medium and oxidation to heteroaryl quinolines

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Abstract—Various tetrahydroquinoline derivatives have been synthesized by employing ceric ammonium nitrate in an aqueous medium. Subsequently, the tetrahydroquinolines were oxidized to biheterocycles.

Tetrahydroquinoline derivatives are an important class of natural products exhibiting a broad spectrum of biological activity.[1,2] Substituted tetrahydroquinolines are the core structures in many important pharmacological agents and drug molecules such as anti-arrhythmic and cardiovascular agents, anticancer drugs, immunosuppressants and as ligands for 5-HTIA and NMDA receptors.[3] Hence, there has been considerable interest in the development of new and efficient protocols for the synthesis of tetrahydroquinoline derivatives.[4]

The aza Diels–Alder reaction constitutes an attractive strategy for the synthesis of substituted tetrahydroquinoline derivatives[5] due to its efficiency and its potential application in combinatorial synthesis.[6] The appropriate choice of aldehyde in an aza Diels–Alder reaction provides a facile entry to biheterocyclic systems which is an essential moiety in many active pharmaceuticals and in liquid crystals.[7]

Considering the extraordinary biological potential[8] of various heterocyclic moieties such as quinoline, chromone, β-lactams, etc., we decided to prepare these heteroaryl substituted quinolines which are anticipated to be more potent than the parent heterocycle.

In recent times there has been a great deal of interest in developing environmentally benign technologies that provide economical synthetic strategies.[9] Replacing toxic solvents with ionic liquids or with water and minimizing the use of chlorinated hydrocarbons are important. However, ionic liquids are very expensive. Though recycling of ionic liquids justifies the expenditure, their purity can become reduced. Hence, a catalyst that drives the reaction purely in water or in an aqueous medium is preferred.

Recently, the use of ceric ammonium nitrate[10] has received considerable attention as it is an inexpensive, nontoxic catalyst for various organic transformations providing excellent yields. A report on the use of CAN,[10c] for deprotecting ketal groups in an aqueous medium prompted us to explore the catalytic properties of CAN for the synthesis of tetrahydroquinolines in an aqueous medium.

The reaction was first explored by stirring a mixture of **1a**, **2g** and **3** with 5 mol % CAN at rt in water for 20 min. The product was obtained in good yield (92%). Similar conditions were required for the aldehydes **2e** and **2f**. However, for aldehydes **2a**–**d** and **2h**, a water–acetonitrile mixture was used (1:1). Among the various solvents studied, acetonitrile was found to give the highest yield. In all cases, the reaction proceeded smoothly affording tetrahydroquinoline derivatives (Schemes 1 and 2) in good yields with high levels of selectivity and in short reaction times (Table 1).

Tetrahydroquinolines **4a**–**j** were obtained as single regioisomers and diastereoisomers.[11] No other isomers

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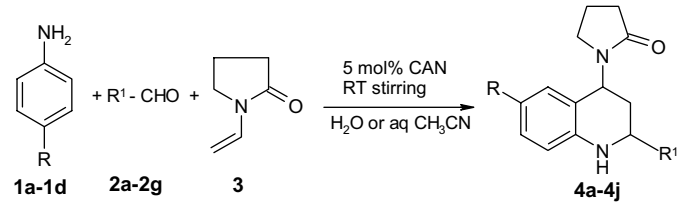
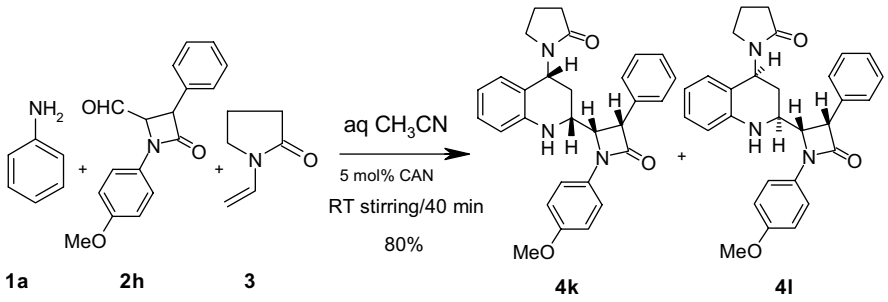
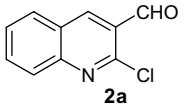
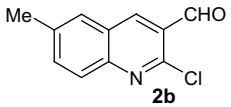
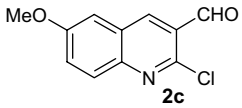
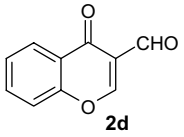
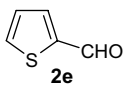
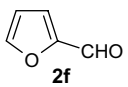
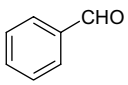


Scheme 1.



Scheme 2.

Table 1. Synthesis of tetrahydroquinoline derivatives

Entry	Aniline	Aldehyde	Product	Time (min)	Yield[a] (%)
1	**1a**	 **2a**	**4a**	45	85
2	**1b**	**2a**	**4b**	50	82
3	**1a**	 **2b**	**4c**	50	87
4	**1a**	 **2c**	**4d**	50	86
5	**1a**	 **2d**	**4e**	40	80
6	**1c**	**2d**	**4f**	35	82
7	**1d**	**2d**	**4g**	35	85
8	**1a**	 **2e**	**4h**[b]	30	90
9	**1a**	 **2f**	**4i**[b]	30	89
10	**1a**	 **2g**	**4j**[b]	20	92

[a] Isolated overall yield.
[b] Reaction carried out in water.

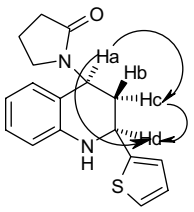
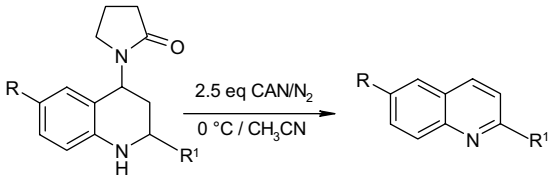


Figure 1. Characteristic NOEs of compound **4h**.



4 **5**

Scheme 3.

could be detected. The relative configuration of the substituents in the tetrahydroquinolines were cis which was confirmed from coupling constants and NOE measurements. In the ^{1}H NMR spectrum of compound **4h**, two doublets of doublets at δ 4.87 and 5.68 were attributed to protons Hd and Ha, respectively. When these protons were irradiated, NOEs (Fig. 1) were observed between protons Ha/Hc and Ha/Hd indicating that the protons Ha, Hc and Hd were on the same side of the ring. Moreover, from the coupling constants of $J_{a,b} = 11.45$ Hz and $J_{d,b} = 11.3$ Hz, an *axial–axial* (*trans*) relationship can be deduced, whereas the coupling constants of $J_{a,c} = 6.3$ Hz and $J_{d,c} = 7.45$ Hz indicated an *axial–equatorial* relationship for these protons.[12]

However, the reaction of **1a**, **2h** and **3** afforded tetrahydroquinolines **4k** and **4l** as a chromatographically separable mixture (60:40) of diastereoisomers (Scheme 2).

The structures of all the compounds were confirmed by ^{1}H and ^{13}C NMR and mass spectroscopy[12] and the stereochemistry of the products were assigned by coupling constants and NOE measurements.

Subsequently, the tetrahydroquinolines were oxidized to the corresponding heteroaryl substituted quinolines by reaction with 2.5 equiv of CAN in MeCN at 0 °C under an N_2 atmosphere for 20 min. The structures of the resulting biheterocycles were confirmed by ^{1}H and ^{13}C NMR and mass spectroscopy (Scheme 3).[13] The results are summarized in Table 2.

In conclusion, we have described a simple, convenient and efficient aza Diels–Alder approach for the synthesis of heteroaryl-substituted tetrahydroquinolines and the oxidation of tetrahydroquinolines into the corresponding heteroaryl substituted quinolines which are anticipated to be biologically active.[7,14] Further studies on these compounds are underway.

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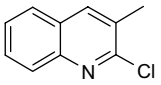
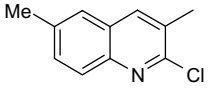
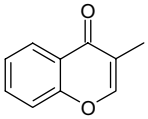
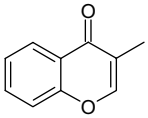
Table 2. Oxidation of tetrahydroquinolines[a]

Entry	Tetrahydroquinoline	R	R^1	Product	Yield (%)
1	**4a**	H		**5a**	92
2	**4c**	H		**5b**	90
3	**4e**	H		**5c**	88
4	**4f**	Me		**5d**	90
5	**4h**	H		**5e**	95
6	**4i**	H		**5f**	93

[a] All reactions were complete within 20 min.

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12. General procedure: Synthesis of tetrahydroquinoline **4b** (Scheme 1). A mixture of **1b** (0.128 g, 1 mmol), **2a** (0.192 g, 1 mmol) and **3** (0.11 g, 1 mmol) was stirred in water (5 mL)–acetonitrile (5 mL) in the presence of CAN (0.027 g, 0.049 mmol, 5 mol %) at rt for 50 min until completion of the reaction as followed by TLC. Water was added to the mixture and the product was extracted into ethyl acetate (2 × 20 mL) and the extract was dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave the crude product, which was further purified by column chromatography on silica gel, ethyl acetate–hexane (6:4) as eluent, to afford the pure product 0.337 g (82%).
    Spectral values for selected compounds. Compound **4b** (Table 1): mp 287 °C; ν_{max} (KBr): 3351, 1660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.89–1.96 (m, 1H), 2.01–2.04 (m, 2H), 2.29–2.34 (m, 1H), 2.43–2.57 (m, 2H), 3.14–3.18 (m, 1H), 3.22–3.27 (dd, 1H, $J_1 = 7.65$ Hz, $J_2 = 16.85$ Hz), 4.58 (br s, 1H, NH), 4.82–4.85 (d, 1H, $J = 10.7$ Hz), 5.67–5.70 (dd, 1H, $J_1 = 6.15$ Hz, $J_2 = 11.45$ Hz), 6.58 (d, 1H, $J = 8.4$ Hz), 6.78 (s, 1H), 6.95–6.97 (d, 1H, $J = 8.4$ Hz), 7.13–7.16 (t, 1H, $J = 7.65$ Hz), 7.35–7.42 (m, 2H), 7.47–7.48 (d, 1H, $J = 7.6$ Hz), 7.87 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.3, 31.3, 42.4, 48.2, 49.7, 49.8, 115.8, 116.9, 119.7, 121.0, 122.8, 123.1, 126.3, 127.9, 128.3, 132.9, 133.2, 135.7, 137.7, 144.7, 163.3, 176.0. MS m/z (%) = 412 M^+. Anal. Calcd for $C_{22}H_{19}Cl_2N_3O$ (412.311): C, 64.09; H, 4.64; N, 10.19. Found: C, 64.18; H, 4.56; N, 10.0.
    Compound **4f** (Table 1): mp 118 °C; ν_{max} (KBr): 3245, 1672, 1642 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.93–2.00 (m, 3H), 2.18 (s, 3H), 2.24–2.30 (m, 1H), 2.39–2.54 (m, 2H), 3.13–3.15 (m, 1H), 3.20–3.22 (m, 1H), 4.47 (br s, 1H, NH), 4.73–4.75 (d, 1H, $J = 9.95$ Hz), 5.65–5.67 (dd, 1H, $J_1 = 6.1$ Hz, $J_2 = 12.25$ Hz), 6.52–6.53 (d, 1H, $J = 8.4$ Hz), 6.63 (s, 1H), 6.82–6.83 (d, 1H, $J = 7.65$ Hz), 7.35–7.38 (t, 1H, $J = 7.65$ Hz), 7.41–7.43 (d, 1H, $J = 8.4$ Hz), 7.62–7.65 (m, 1H), 8.04 (s, 1H), 8.16–8.18 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.3, 20.7, 31.5, 31.5, 42.4, 48.0, 48.1, 116.2, 118.2, 119.6, 123.8, 125.3, 125.4, 125.9, 127.1, 128.2, 129.0, 133.9, 143.4, 153.1, 156.2, 175.8, 177.0. MS m/z (%) = 374 M^+. Anal. Calcd for $C_{23}H_{22}N_2O_3$ (374.432): C, 73.78; H, 5.92; N, 7.48. Found: C, 73.74; H, 5.98; N, 7.50.
    Compound **4h** (Table 1): mp 56 °C; ν_{max} (KBr): 3330, 1670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.96–2.00 (m, 2H), 2.13–2.20 (m, 2H), 2.40–2.50 (m, 2H), 3.13–3.23 (m, 2H), 4.20 (br s, 1H, NH), 4.87 (dd, 1H, $J_1 = 7.45$ Hz, $J_2 = 11.3$ Hz), 5.68 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 11.45$ Hz), 6.56 (d, 1H, $J = 8$ Hz), 6.60–6.70 (t, 1H, $J = 7.45$ Hz), 6.84 (d, 1H, $J = 8.05$ Hz), 6.96 (m, 1H), 7.00 (m, 2H), 7.20 (d, 1H, $J = 5.15$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.3, 31.4, 36.2, 42.4, 48.2, 52.2, 115.3, 118.7, 119.0, 124.2, 124.3, 124.4, 126.8, 126.8, 145.4, 146.9, 175.9. MS

$m/z = 298$ M^+. Anal. Calcd for $C_{17}H_{18}N_2OS$ (298.404): C, 68.42; H, 6.08; N, 9.39. Found: C, 68.47; H, 6.00; N, 9.30.

13. General procedure: Synthesis of biheteroaryl **5f** (Scheme 3). To tetrahydroquinoline **4i** (0.282 g, 1 mmol) in acetonitrile (5 mL), CAN (1.37 g, 2.5 mmol) dissolved in acetonitrile (10 mL) was added dropwise, under a nitrogen atmosphere at 0 °C. The reaction was stirred for 20 min until completion of the reaction as monitored by TLC. Water was added to the mixture and the product was extracted into ethyl acetate (2×20 mL) and the extract was dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave a crude product, which was further purified by column chromatography on silica gel, ethyl acetate–hexane (4:6) as eluent to afford the product 0.181 g (93%).
Spectral data for compound. Compound **5f** (Table 2): mp 110 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60 (m, 1H), 7.24–7.25 (m, 2H), 7.64 (d, 1H, $J = 1.5$ Hz), 7.85–7.87 (d, 1H, $J = 8.4$ Hz), 8.00–8.10 (d, 2H, $J = 7.65$ Hz), 8.22–8.24 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 110.4, 112.4, 118.1, 125.7, 127.4, 129.5, 130.0, 136.9, 138.0, 144.3, 147.7, 149.2, 153.7. MS $m/z = 195$ M^+. Anal. Calcd for $C_{13}H_9NO$ (195.217): C, 79.98; H, 4.65; N, 7.17. Found: C, 79.90; H, 4.50; N, 7.25.

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