# A Facile and Convenient Three-component Coupling Protocol for the Synthesis of Pyrano and Furoquinolines[1]

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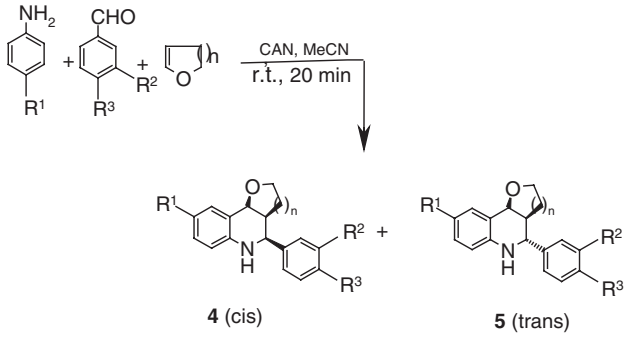
Ceric ammonium nitrate (CAN) catalyzes efficiently the coupling of anilines, benzaldehydes and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran to form the corresponding pyrano or furoquinolines in short reaction times and in high yields.

Pyranoquinoline derivatives are known to possess various biological properties including antiallergic and anti-inflammatory activities.[2] These compounds can be prepared by applying aza-Diels–Alder reactions between imines and 3,4-dihydro-2*H*-pyran (DHP). Generally, Lewis acids[3,4] are employed to catalyze such reactions. However, several Lewis acids are deactivated or decomposed by nitrogen containing substrates.[4c] Some of the Lewis acids are not easily available or expensive, require longer reaction times and form the products with poor yields.

Recently we have discovered an efficient one-pot method for the coupling of anilines, benzaldehydes and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran in the presence of catalytic amount of ceric ammonium nitrate (CAN) to form the corresponding pyrano and furoquinolines (Scheme 1, Table 1).

Several anilines and benzaldehydes were treated with 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran. CAN was found to catalyze the reactions efficiently to afford various quinoline derivatives. The reactions occurred at room temperature in short reaction times.[5] The products were obtained in high yields and high diasteroselectivity. They were formed as a mixture of *exo* and *endo* isomers which could be separated by column chromatography over silica gel. The product ratio was determined by $^1$H NMR spectra of the crude products.




**Scheme 1.**

The reaction proceeded through CAN catalyzed Aza-Diels–Alder reaction between imines (which were formed in situ from anilines and benzaldehydes) and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran. The role of CAN in this reaction is very clear. The imines were found to be produced directly by the reaction between anilines and benzaldehydes without the presence of CAN. However, the imines could not form the products by treatment with 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran in the absence of the catalyst. When the former were separately treated with this pyran or furan derivative using CAN under the present reaction conditions the desired reaction was found to occur smoothly. Thus it is obvious that CAN catalyzed the aza-Diels–Alder reaction between imines and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran to form the corresponding quinolines. CAN has previously been employed[6] for ring opening of epoxides through a radical cation intermediate but in this case pyran or furan ring was not opened. The structures of the products were settled from their spectroscopic data.[5] The spectral properties of the known compounds were in good agreement with those reported earlier (references in the Table).

**Table 1.** CAN catalysed preparation of pyrano and furoquinolines[a]

| Entry | Aniline (**1**) | Benzaldehyde (**2**) | | Olefine (**3**) | Isolated yield/% | Product ratio[b] | Ref |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | *n* | | cis:trans | |
| a | H | H | H | 1 | 81 | 20:70 | 4b |
| b | H | H | Cl | 1 | 84 | 25:75 | |
| c | Cl | H | H | 1 | 89 | 15:85 | 4b |
| d | H | H | H | 2 | 86 | 20:80 | 4b |
| e | H | H | Cl | 2 | 91 | 30:70 | 4c |
| f | H | H | OMe | 2 | 86 | 25:75 | 4c |
| g | H | Cl | Cl | 2 | 93 | 10:90 | 4c |
| h | H | H | Br | 2 | 89 | 15:85 | 4c |
| i | $CH_3$ | H | H | 2 | 86 | 15:85 | 4b |
| j | Cl | H | H | 2 | 89 | 30:70 | 4b |
| k | $CH(CH_3)_2$ | H | Cl | 2 | 80 | 25:75 | |

[a]Product ratios were calculated from crude NMR spectral values. [b]All the products were characterized from their spectral ($^1$H NMR and MS) data.

In conclusion, we have developed an efficient one-pot method for the synthesis of pyrano and furoquinoline derivatives by applying three-component coupling reaction catalyzed by CAN. The mild reaction conditions, utilization of an easily available reagent as catalyst, operational simplicity, short reaction times and high yields and greater diastereoselectivity of the products are the advantages of the present procedure. This is the first report of the application of CAN for the synthesis of tetrahydroquinoline derivatives.

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## References and Notes

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5 Preparation of Pyrano and Furanoquinolines: To a stirred solution of benzaldehyde (1 mmol), aniline (1 mmol) and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran in acetonitrile (10 mL) CAN (0.25 mmol) was added. The mixture was continued to stirr at room temperature for 20 min. On completion the solvent was removed and the mixture was extracted with EtOAc (3 × 20 mL). The concentrated extract was subjected to column chromatography over silica gel and product was eluted with hexane–EtOAc (20:1). Spectral and analytical data of the unknown furoquinolines **4b:** $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.40 (1H, d, $J = 7.8$ Hz), 7.36 (4H, s), 7.05 (1H, t, $J = 7.8$ Hz ), 6.68 (1H, t, $J = 7.8$ Hz ), 6.56 (1H, d, $J = 7.8$ Hz), 5.25 (1H, d, $J = 8$ Hz), 4.65 (1H, d, $J = 3$ Hz), 3.78 (1H, brs), 3.40–3.62 (2H, m), 2.18 (1H, m), 1.56 (2H, m); EIMS ($m/z$): 285 ($M^+$), 206. Anal. Calcd. for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90%. Found: C, 71.28; H, 5.52; N, 4.92%. **5b:** $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.35 (4H, s), 7.14 (1H, d, $J = 7.8$ Hz), 7.05 (1H, t, $J = 7.8$ Hz), 6.64 (1H, d, $J = 8.0$ Hz), 6.42 (1H, d, $J = 8$ Hz ) 4.58 (1H, d, $J = 5.0$ Hz), 4.08 (1H, m), 3.85 (3H, m), 2.45 (1H, m), 2.0 (1H, m), 1.72 (1H, m); EIMS ($m/z$): 285 ($M^+$), Anal. Calcd. for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90%. Found: C, 71.22; H, 5.62; N, 4.82%. Spectral and analytical data of the unknown pyranoquinolines **4k:** $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.38 (4H, m), 7.15 (1H, s), 6.90 (1H, d, $J = 8.0$ Hz), 6.54 (1H, d, $J = 8.2$ Hz), 5.25 (1H, d, $J = 8$ Hz), 4.60 (1H, brs), 3.40–3.68 (3H, m), 2.82 (1H, m), 2.10 (1H, m), 1.50 (4H, m), 1.32 (6H, d); EIMS ($m/z$): 341 ($M^+$). Anal. Calcd. for $C_{21}H_{24}ClNO$: C, 73.77; H, 7.07; N, 4.09%. Found: C, 73.72; H, 7.22; N, 4.22%. **5k**: $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.40 (4H, m), 7.05 (1H, s), 6.95 (1H, d, $J = 8.0$ Hz), 6.44 (1H, d, $J = 8.0$ Hz), 4.68 (1H, d, $J = 5$ Hz), 3.70–4.12 (3H, m), 2.82 (1H, m), 2.04 (1H, m), 1.40–1.82 (4H, m), 1.3 (6H, d) EIMS ($m/z$): ($M^+$) 341. Anal. Calcd. for $C_{21}H_{24}ClNO$: C, 73.77; H, 7.07; N, 4.09%. Found: C, 73.68; H, 7.16; N, 4.18%.
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