# One-Pot Synthesis of Pyrano- and Furanoquinolines Catalyzed by Molten Tetra-*n*-butylphosphonium Bromide Under Solvent-Free Conditions



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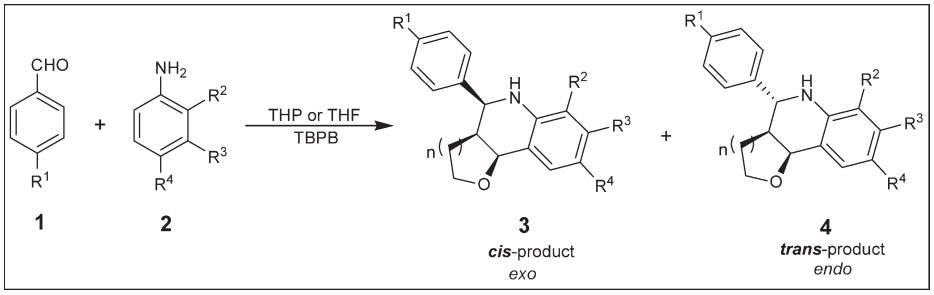


Molten tetra-*n*-butylphosphonium bromide is found to be a practical and inexpensive catalytic media for stereoselective one-pot synthesis of pyranoquinoline and furanoquinoline derivatives in good to excellent yields. Products of undesirable reactions resulting from polymerization are not observed. The use of this catalyst media avoids the use of any cocatalysts or toxic organic solvents.

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## INTRODUCTION

Pyranoquinoline and furanoquinoline derivatives are found abundantly in a variety of natural and synthetic products, which exhibit various physiological properties and are potentially bioactive compounds [1]. These skeletons exist in many alkaloids such as veprisine, oricine, and flindersine [2], which possess a wide rang of biological activity such as antiallergenic [3], antibacterial [4], psychotropic [5], anti-inflammatory [6], and estrogenic activity [7]. Hence, for the preparation of these complex molecules, there has been interest in organic synthesis. One of the most straightforward routs to their synthesis involves imino-Diels–Alder reaction with various dienophiles in the presence of Lewis acids [4,8]. However, the application of these methods suffers from some disadvantages such as the use of expensive or less easily available reagents, vigorous reaction conditions, long reaction times, unsatisfactory yields, low selectivity, or the use of toxic solvents. On the other hand, many Lewis acids are deactivated or sometimes decomposed by nitrogen-containing reactants. Therefore, despite a number of precedents, an efficient, practical, and facile method for these transformations is desired.

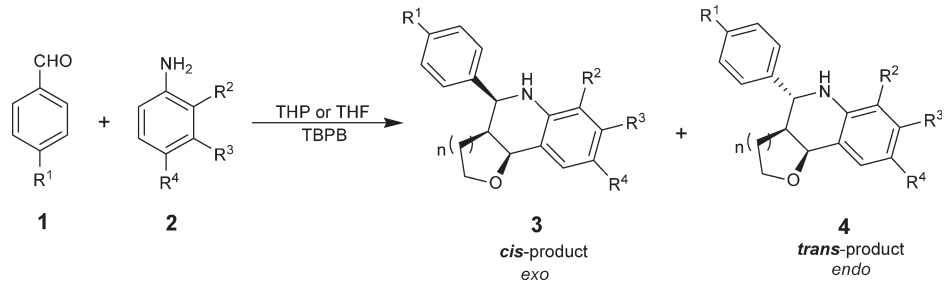
Due to the environmental concerns the use of benign solvents as an alternative to volatile organic solvents are much interest to organic chemists [9]. The use of ionic liquids as reaction media and catalyst can offer a solution to solvent emission and catalyst recycle problems [10]. Ionic liquids possess a number of interesting properties, especially their lack of vapor pressure, a widely accessible temperature range with lack of flammability, and ease of product recovery that reduce environmental emissions [11].

Recently, ionic liquids have been successfully used as solvents with catalytic activity for a variety of reactions but their use as catalyst under solvent-free conditions need to be more attention [12]. However, the high cost of most conventional ionic liquids and apprehension about their toxicity [13] especially imidazolium systems with $PF_4$ and $BF_4$ anions are as toxic as benzene to certain aquatic ecosystems, and also liberate hazardous HF during recycling have led us to explore the use of more benign salts in the molten state as practical alternatives. During our endeavors to explore the utility of ionic liquid in organic transformations, we have recently reported a practical and efficient protocol for thiolysis of epoxides in the presence of tetra-*n*-butylphosphonium bromide (TBPB) as an inexpensive and commercially available ionic liquid [14].

## RESULTS AND DISCUSSION

In further extension of our work in the context of economical chemistry [14], herein, we would like to report

**Scheme 1**




the use of molten tetra-*n*-butylphosphonium bromide (m-TBPB) as an inexpensive ionic liquid for efficient one-pot synthesis of pyrano- and furanoquinoline derivatives under solvent-free conditions (Scheme 1).

Several aldimines (formed *in situ* from aromatic aldehydes and anilines in ionic liquid) and 3,4-dihydro-2*H*-pyran (DHP) or 2,3-dihydrofuran (DHF) were heated in the presence of m-TBPB medium to afford the corresponding pyrano- and furanoquinolines in 72–86% yield. The high-yield transformation did not form any significant amounts of undesirable side products. Among the various ionic liquids such as tetra-*n*-butylammonium bromide, tetra-*n*-butylammonium chloride, tetra-*n*-butylammonium fluoride, and *n*-butylpyridinium tetrachloroferrate ([bpy]$FeCl_4$) which were studied for this reaction, m-TBPB used here gave better yields (also better selectivity) with short reaction times. However, in the absence of ionic liquid, the reaction did not yield any product even after a long reaction time (15–20 h). In all cases, the products were obtained as a mixture of **3** exo- and **4** endo-isomers favoring the endo-diastereomer **4**.

On the other hand, this procedure is highly diastereoselective. The products were formed as a mixture of s-cis and s-trans isomers, which could be separated by column chromatography over silica gel and whose ratio was determined by $^1$H-NMR spectra of the crude products. The results shown in Table 1 clearly indicate the scope and generality of diasteroselective condensation with respect to various aryl aldehydes and anilines with DHP or DHF.

The reaction is fairly general, clear, rapid, and efficient. The experimental procedure for this transformation is remarkably straightforward and unlike previously reported methods, the presence procedure does not require the use of toxic organic solvents or inert atmospheres. The proposed mechanism of formation of quinoline is shown in Scheme 2, being similar to that previously suggested [10c].

## CONCLUSIONS

In conclusion, we have demonstrated a new, straightforward, efficient, and stereoselective method for the one-pot synthesis of pyrano- and furanoquinolines, using m-TBPB as a commercially available ionic liquid. The significant feature of this method include (a) operational simplicity, (b) inexpensive reagent, (c) high yields of product, (d) high diastereoselectivity, and (e) the use of relatively nontoxic catalytic media.

## EXPERIMENTAL

General procedure for one-pot synthesis of pyrano- and furanoquinoline derivatives in the presence of m-TBPB under solvent-free conditions. A mixture of aryl aldehyde (1 mmol), aniline derivative (1 mmol), and DHP or DHF (2 mmol) in m-TBPB (1 mmol) was heated at 50°C under stirring for the appropriate time according to Table 1. The progress of the reaction was monitored by thin layer chromatography (TLC) (4:1, hexane/acetone) and after completion, it was poured into cooled mixture of (1:1) water/ethanol and stirred for 5 min. The solid was suction filtered, washed with cold ethanol (2 × 10 mL), and filtered. The resulting product was directly charged on small silica gel column and eluted with a mixture of acetone/*n*-hexane (1:4) to afford pure products.

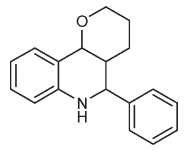
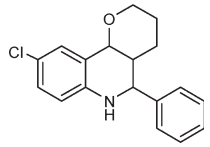
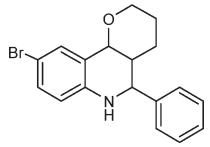
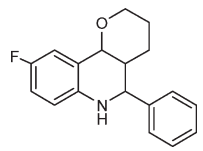
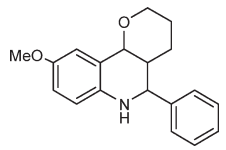
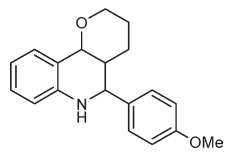
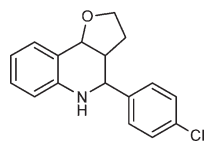
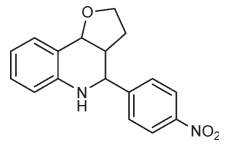
**Analytical data for selected compounds.** ***Product 1.*** Trans: mp: 123–124°C; $^1$H-NMR ($CDCl_3$), δ (ppm): 7.25–7.45 (6H, m), 7.05 (1H, t, $J$ = 7.8 Hz), 6.75 (1H, t, $J$ = 7.8 Hz), 6.55 (1H, d, $J$ = 7.8 Hz), 5.34 (1H, d, $J$ = 5.6 Hz), 4.70 (1H, d, $J$ = 2.8 Hz), 3.35–3.65 (3H, m), 2.15 (1H, m), 1.25–1.55 (4H, m); $^{13}$C-NMR ($CDCl_3$), δ (ppm): 145.2, 141.1, 128.3, 128.0, 127.6, 127.5, 126.8, 119.8, 118.3, 114.4, 72.8, 60.6, 59.3, 38.9, 25.4, 18.0; ir (KBr), ν ($cm^{-1}$): 3378, 2936, 1605, 1485, 1071, 750.

Cis: colorless solid, mp: 94–95°C; $^1$H-NMR ($CDCl_3$), δ (ppm): 7.35–7.45 (5H, m), 7.25 (1H, d, $J$ =7.8 Hz), 7.05 (1H, t, $J$ = 7.8 Hz), 6.80 (1H, t, $J$ = 7.8 Hz), 6.50 (1H, d, $J$ = 7.8 Hz,), 4.75 (1H, d, $J$ = 10.5 Hz), 4.40 (1H, d, $J$ = 2.8 Hz), 3.95 (2H, m), 3.75 (1H, t, $J$ = 11.7 Hz), 2.15 (1H, m), 1.85(1H, m), 1.65 (1H, m), 1.50 (1H, m), 1.25 (1H, m); $^{13}$C-NMR ($CDCl_3$), δ (ppm): 144.1, 141.7, 130.2, 128.7, 128.0, 127.2, 127.1, 120.0, 116.8, 113.5, 73.9, 68.0, 54.1, 38.2, 23.5, 21.4; ir (KBr), ν ($cm^{-1}$): 3374, 2928, 1610, 1489, 1077, 750.

***Product 2.*** Trans: colorless solid, mp: 154–155°C; $^1$H-NMR ($CDCl_3$), δ (ppm): 7.37–7.28 (6H, m), 7.03 (1H, d, $J$ = 8.2 Hz), 6.53 (1H, d, $J$ = 8.3 Hz), 5.24 (1H, brs), 4.64 (1H, brs), 3.89 (1H, brs), 3.61 (1H, d, $J$ = 11.2 Hz), 3.43–3.31 (1H, m), 2.13–2.07 (1H, m), 1.78–1.31 (4H, m); $^{13}$C-NMR ($CDCl_3$), δ (ppm): 145.6, 141.3, 128.1, 128.0, 127.3, 127.1, 126.8, 119.3, 118.0, 114.4, 72.7, 60.5, 59.0, 38.2, 25.4, 18.2; ir (KBr), ν

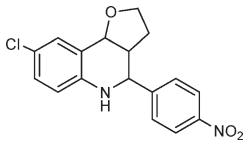
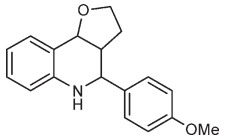
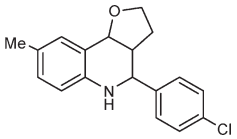
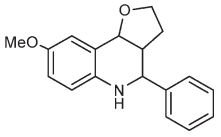
**Table 1**

One-pot synthesis of pyrano- and furanoquinoline in the presence of m-TBPB under solvent-free conditions.

| Entry | Product[a] | Time (h) | Yield (%)[b] | trans/cis[c] | de% |
|---|---|---|---|---|---|
| 1 |  | 1.25 | 79 | 95/5 | 90 |
| 2 |  | 1.30 | 81 | 93/7 | 86 |
| 3 |  | 1.30 | 72 | 92/8 | 84 |
| 4 |  | 1.30 | 78 | 93/7 | 86 |
| 5 |  | 1.15 | 85 | 88/12 | 76 |
| 6 |  | 1.30 | 73 | 85/15 | 70 |
| 7 |  | 1.15 | 83 | 90/10 | 80 |
| 8 |  | 1 | 82 | 96/4 | 92 |

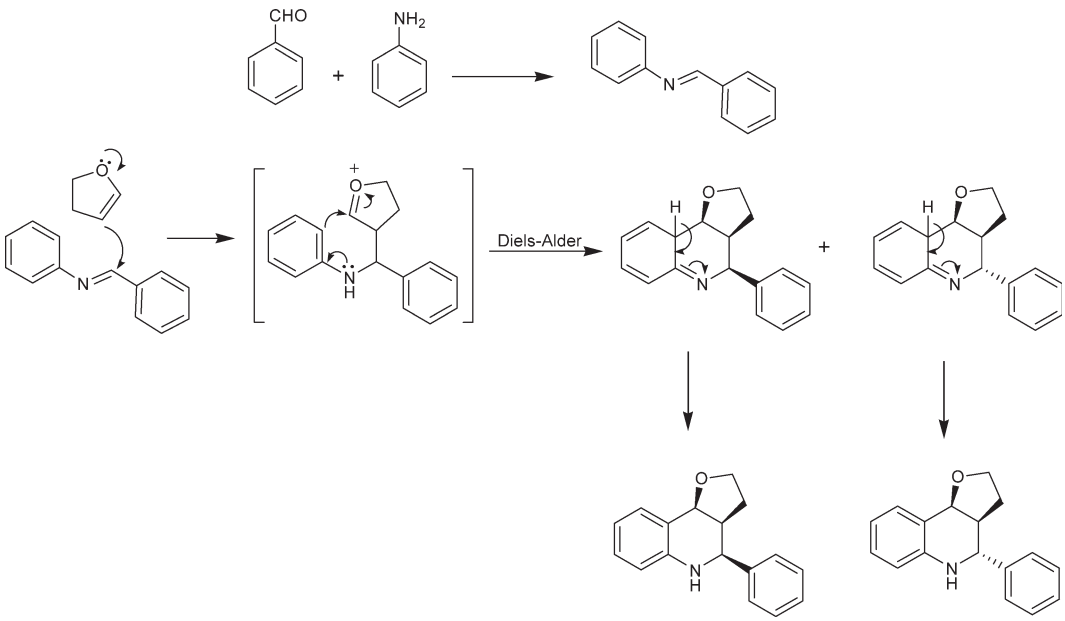
(*Continued*)

**Table 1**
(*Continued*)

| Entry | Product[a] | Time (h) | Yield (%)[b] | trans/cis[c] | de% |
|---|---|---|---|---|---|
| 9 |  | 1.10 | 86 | 90/10 | 80 |
| 10 |  | 1.40 | 80 | 88/12 | 75 |
| 11 |  | 1 | 85 | 90/10 | 90 |
| 12 |  | 1.15 | 85 | 92/8 | 80 |

[a] All products were characterized with $^{1}$H-NMR, $^{13}$C-NMR, IR, and comparison of their physical and spectral data with those samples in the literatures.8
[b] Isolated yields.
[c] The isomeric ratio is based on isolation by column chromatography.

**Scheme 2**



($cm^{-1}$): 3362, 3326, 2937, 1615, 1487, 1071, 920, 820, 800, 750, 700.

Cis: colorless solid, mp 122–123°C; $^1$H-NMR ($CDCl_3$), δ (ppm): 7.37 (5H, m), 7.19 (1H, s), 7.03 (1H, d, $J$ = 8.3 Hz), 6.45 (1H, d, $J$ = 8.3 Hz), 4.67 (1H, d, $J$ = 10.5 Hz), 4.33 (1H, s), 4.08 (2H, m), 3.73 (1H, m), 2.05 (1H, m), 1.83–1.31 (4H, m); $^{13}$C-NMR ($CDCl_3$), δ (ppm): 143.2, 141.8, 130.3, 129.1, 128.6, 127.6, 126.1, 121.8, 121.7, 115.2, 73.8, 68.4, 54.8, 38.6, 23.9, 22.0; ir (KBr), ν ($cm^{-1}$): 3348, 2934, 1494, 1265, 920, 825, 810, 750, 700.

***Product 5.*** Trans: colorless solid, mp: 146–147°C; $^1$H-NMR ($CDCl_3$), δ (ppm): 7.40–7.29 (5H, m), 7.03 (1H, s), 6.73 (1H, d, $J$ = 8.2 Hz), 6.57 (1H, d, $J$ = 8.2 Hz), 5.31 (1H, d, $J$ = 5.4 Hz), 4.61 (1H, s), 3.73 (3H, s), 3.67 (1H, brs), 3.61–3.36 (2H, m), 2.15 (1H, m), 1.54–1.26 (4H, m); $^{13}$C-NMR ($CDCl_3$), δ (ppm): 152.8, 141.3, 139.1, 128.3, 127.4, 126.8, 121.1, 115.7, 115.0, 111.8, 72.9, 60.8, 59.5, 55.8, 39.1, 25.3, 17.9; ir (KBr), ν ($cm^{-1}$): 3295, 2942, 1502, 1262, 1065, 921, 825, 810, 735, 710.

Cis: dense liquid, $^1$H-NMR ($CDCl_3$), δ (ppm): 7.43–7.27 (5H, m), 6.82 (1H, s), 6.75 (1H, d, $J$ = 9.1 Hz), 6.49 (1H, d, $J$ = 8.5 Hz), 4.62 (1H, d, $J$ = 10.5 Hz), 4.38 (1H, s), 4.10 (1H, m), 3.75 (5H, m), 2.10 (1H, m), 1.84–1.30 (4H, m); $^{13}$C-NMR ($CDCl_3$), δ (ppm): 151.9, 142.2, 138.7, 128.1, 127.7, 126.0, 121.3, 116.7, 115.5, 114.7, 74.5, 68.3, 55.7, 55.1, 38.8, 24.0, 21.9; ir (neat), ν ($cm^{-1}$): 3361, 2938, 1504, 1255, 1032, 920, 825, 810, 735, 710.

***Product 6.*** Trans: solid, mp: 146–147°C; $^1$H-NMR ($CDCl_3$), δ (ppm): 7.32 (2H, d, $J$ = 8.0 Hz), 7.18 (1H, d, $J$ = 8.0 Hz), 7.04 (1H, t, $J$ = 8.0 Hz), 6.84 (2H, d, $J$ = 8.0 Hz), 6.64 (1H, t, $J$ = 8.0 Hz), 6.45 (1H, d, $J$ = 8.0 Hz), 4.64 (1H, d, $J$ = 10 Hz), 4.36 (1H, d, $J$ = 2.5 Hz), 4.06 (1H, m), 3.97 (1H, d, $J$ = 3.0 Hz), 3.82 (3H, s), 3.63 (1H, t, $J$ = 10.0 Hz), 2.02 (1H, m), 1.82 (1H, m), 1.64 (1H, m), 1.44 (1H, m), 1.28 (1H, m).

Cis: solid, mp: 154–155°C; $^1$H-NMR ($CDCl_3$), δ (ppm): 7.38 (1H, d, $J$ = 8.0 Hz), 7.30 (2H, d, $J$ = 8.0 Hz), 7.00 (1H, m), 6.82 (2H, d, $J$ = 8.0 Hz), 6.77 (1H, t, $J$ = 8.0 Hz), 6.50 (1H, d, $J$ = 8.0 Hz), 5.26 (1H, d, $J$ = 3.0 Hz), 4.60 (1H, d, $J$ = 3.0 Hz), 3.84 (1H, m), 3.82 (3H, s), 3.58 (1H, m), 3.22 (1H, m), 2.04 (1H, m), 1.58–1.30 (4H, m).

***Product 7.*** Trans: solid, mp: 147–148°C; $^1$H-NMR ($CDCl_3$), δ (ppm): 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, $J$ = 8.0 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); ir (KBr), ν ($cm^{-1}$): 3379, 2940, 1495, 1261, 810, 750.

Cis: solid, mp: 152–153°C; $^1$H-NMR ($CDCl_3$), δ (ppm): 7.4 (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, $J$ = 8.0 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); ir (KBr), ν ($cm^{-1}$): 3345, 2931, 1492, 1265, 815, 750.

***Product 8.*** Trans: solid, mp: 155–156°C; $^1$H-NMR ($CDCl_3$), δ (ppm): 8.31 (2H, d), 7.81 (2H, d), 7.4 (1H, d), 7.2 (1H, t), 6.91 (1H, t), 6.7 (1H, d), 5.4 (1H, d), 4.9 (1H, m), 3.81–3.89 (3H, m), 2.81–2.92 (1H, m), 2.1–2.3 (1H, m), 1.65 (1H, m); $^{13}$C-NMR ($CDCl_3$), δ (ppm): 147.0, 144, 131.0, 129.2, 127.3, 125.4, 124, 122, 120.1, 115, 68, 58, 54, 47, 25; ir (KBr), ν ($cm^{-1}$): 3296, 2940, 1480, 1072, 750, 800.

***Product 9.*** Trans: solide, mp: 160–161°C; $^1$H-NMR ($CDCl_3$), δ (ppm): 8.29 (2H, d), 7.78 (2H, d), 7.41 (1H, d), 7.1 (1H, d), 6.6 (1H, s), 4.65 (1H, d, $J$ = 5.0 Hz), 4.28 (1H, m), 3.75–3.32 (3H, m), 2.25 (1H, m), 2.2 (1H, m), 1.65 (1H, m); $^{13}$C-NMR ($CDCl_3$), δ (ppm): 148, 145, 132.2, 129.3, 128.3, 125.1, 124, 122.3, 117, 115, 63.2, 54, 40.1, 27.3, 21.2; ir (KBr), ν ($cm^{-1}$): 3360,2931,1495,1261, 900, 800,750,700.

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