Synthesis of Benzo[\textit{b}]pyrane Derivatives Using Supported Potassium Fluoride as an Efficient and Reusable Catalytic System

ALIREZA HASANINEJAD\textsuperscript{*}, NASROLAH JAFARPOUR, AND MOHAMMAD MOHAMMADNEJAD

Chemistry Department, Islamic Azad University, Gachsaran Branch, Gachsaran, Iran
ahassaninejad@yahoo.com,

Received 28 September 2011; Accepted 09 November 2011

\textbf{Abstract:} A highly efficient and simple procedure for the synthesis of 4H-benzo[\textit{b}]pyrane derivatives is described. The reaction of 5,5-dimethylcyclohexane-1,3-dione or cyclohexane-1,3-dione with aromatic aldehydes and malononitrile using catalytic amount of alumina supported KF in reflux ethanol affords the title compounds in high to excellent yields and in short reaction times.

\textbf{Keywords:} 4H-benzo[\textit{b}]pyrane, Malononirile, Potassium Fluoride, synthesis.

\textbf{Introduction}

Heterogenization of homogeneous catalysts has been an interesting area of research from the industrial point of view; this could provide an ideal method for combining the advantages of homogeneous catalysts (high activity and selectivity, etc.) with the engineering advantages of heterogeneous catalysts (easy catalyst separation, long catalytic life, easy catalyst regenerability, thermal stability and recycle)\textsuperscript{1}. Therefore, attachments of the catalysts on solid supports have received much attention. One way is to heterogenize soluble catalysts used in liquid-phase reactions by supporting them on high surface-area solids, such as graphite, Al\textsubscript{2}O\textsubscript{3}, SiO\textsubscript{2}, clays, etc. Basically, the support has to be thermally and chemically stable during the reaction process and has to provide accessibility and a good dispersion of the active sites\textsuperscript{1,2}.

The synthesis of heterocycles has become the cornerstone of synthetic organic chemistry. Among heterocyclic compounds 2-Amino-4H-benzo[\textit{b}]pyrane derivatives represent an important class of compounds that are often used in cosmetics and pigments, and utilized as potentially biodegradable agrochemicals\textsuperscript{3}. Polyfunctionalized 4H-benzo[\textit{b}]pyrans also constitute a structural unit of many natural products\textsuperscript{4} and biologically interesting compounds which possess various pharmacological activities\textsuperscript{5}, such as antitumor\textsuperscript{6} and antibacterial\textsuperscript{7-10}. 4H-benzo[\textit{b}]pyrane derivatives are also potential calcium channel antagonists\textsuperscript{11} which are structurally similar to biologically active 1,4-dihydropyridines.
Consequently numerous methods have been reported for the synthesis of 4H-benzo[b]pyranes\textsuperscript{12-19}. Most of these methods suffer from some drawbacks such as low yields, use of expensive reagents and catalyst, tedious work-up and/or need to additional equipments. In the continuation of our studies on the design and application of solid catalysts in organic transformations and synthesis of heterocyclic compounds\textsuperscript{20-27} and by consideration of the importance of 4H-benzo[b]pyranes in pharmacy and medicine, herein, we wish to report the application of alumina-supported potassium fluoride as an efficient catalytic system in a one-pot three component synthesis of 4H-benzo[b]pyranes in reflux ethanol (Scheme 1).

![Scheme 1. Synthesis of benzo[b]pyrane derivatives in the presence of supported-KF.](image)

**Experimental**

All chemicals were purchased from Merck or Fluka Chemical Companies. All products are known and their structures were identified by comparison of their IR and 1H NMR data and melting points with those in the authentic samples. IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. The 1H NMR (500 MHz) and 13C NMR (125 MHz) were run on a Bruker Avance DPX-500 FT-NMR spectrometer. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Stuart Scientific Apparatus SMP3 (UK) in open capillary tubes.

*Procedure for the Preparation of the KF/Al\textsubscript{2}O\textsubscript{3} Catalytic System*

A mixture of KF (0.291 g, 5 mmol) and Al\textsubscript{2}O\textsubscript{3} (0.510, 5 mmol) was ground vigorously to give the KF/Al\textsubscript{2}O\textsubscript{3} catalytic system as a white powder (0.801 g).

*General procedure for the synthesis of benzo[b]pyrane derivatives in the presence of alumina supported-KF*

KF-alumina (0.2 mmol) was added to ethanol (10 mL) and 5,5-dimethylcyclohexane-1,3-dione or cyclohexane-1,3-dione (1 mmol), malononirile (1.2 mmol) and aromatic aldehyde (1 mmol) were added to it. After completion of the reaction, as monitored by TLC, the reaction mixture was transferred to a 25 mL round-bottomed flask connected to a reflux condenser, ethanol (10 mL) was added to it, and heated at 70 °C for 5 min. Afterward, the reaction mixture was filtered to separate the KF-alumina. The supernatant was concentrated to 5 mL, and allowed to stand at room temperature for 4-5 h. During this time, the target molecules were produced, and then collected on a sintered glass funnel, washed with ethanol, and dried. After isolation of the product, the recovered KF-alumina was washed with ethanol, dried and successfully used for the next run under identical reaction conditions.
Selected spectral data of the products

Table 2, Entry 4a:
White powder, $^1$H NMR (DMSO–$d_6$): δ (ppm) = 0.95 (s, 3H), 1.04 (s, 3H), 2.10 (d, $J = 16.0$ Hz, 1H), 2.25 (d, $J = 16.0$ Hz, 1H), 2.49 (brs, 2H), 4.16 (s, 1H), 7.02 (brs, 2H), 7.17 (m, 3H), 7.29 (m, 2H). Anal. Calcd. for C$_{18}$H$_{18}$N$_2$O$_2$: C, 73.45; H, 6.16; N, 9.52; found C, 73.48; H, 6.15; N, 9.51 %.

Table 2, Entry 4b:
White powder, $^1$H NMR (DMSO–$d_6$): δ (ppm) = 0.97 (s, 3H), 1.05 (s, 3H), 2.12 (d, $J = 16.0$ Hz, 1H), 2.22 (d, $J = 16.0$ Hz, 1H), 2.48-2.54 (m, 2H), 4.28 (s, 1H), 7.04 (s, 2H), 7.16 (d, $J = 8.0$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H).

Table 2, Entry 4c:
White powder, $^1$H NMR (DMSO–$d_6$): δ (ppm) = 1.00 (s, 3H), 1.06 (s, 3H), 2.26 (s, 2H), 2.48-2.52 (m, 2H), 4.54 (s, 1H), 5.98 (s, 2H), 7.42-7.96 (m, 4H).

Table 2, Entry 4d:
White powder, $^1$H NMR (DMSO–$d_6$): δ (ppm) = 1.02 (s, 3H), 1.06 (s, 3H), 2.26 (s, 2H), 2.48-2.52 (m, 2H), 4.55 (s, 1H), 6.04 (s, 2H), 7.46-8.06 (m, 4H).

Table 2, Entry 4e:
White powder, $^1$H NMR (DMSO–$d_6$): δ (ppm) = 0.96 (s, 3H), 1.02 (s, 3H), 2.10 (d, $J = 16.0$ Hz, 1H), 2.22 (d, $J = 16.0$ Hz, 1H), 2.46-2.56 (m, 2H), 3.72 (s, 3H), 4.46 (s, 1H), 6.84 (d, $J = 8.0$ Hz, 2H), 6.90 (s, 2H), 7.04 (d, $J = 8.0$ Hz, 2H).

Table 2, Entry 4f:
White powder, $^1$H NMR (DMSO–$d_6$): δ (ppm) = 1.02 (s, 3H), 1.06 (s, 3H), 2.26 (s, 2H), 2.48-2.52 (m, 2H), 4.55 (s, 1H), 6.04 (s, 2H), 7.46-8.06 (m, 4H).

Table 2, Entry 4g:
White powder, $^1$H NMR (DMSO–$d_6$): δ (ppm) = 0.96 (s, 3H), 1.02 (s, 3H), 2.10 (d, $J = 16.0$ Hz, 1H), 2.22 (d, $J = 16.0$ Hz, 1H), 2.26 (s, 3H), 2.46-2.56 (m, 2H), 4.32 (s, 1H), 6.94 (s, 2H), 7.02 (d, $J = 8.0$ Hz, 2H), 7.08 (d, $J = 8.0$ Hz, 2H).

Table 2, Entry 4i:
White powder, $^1$H NMR (DMSO–$d_6$): δ (ppm) = 1.01 (s, 3H), 1.11 (s, 3H), 2.16 (d, $J = 16.0$ Hz, 2H), 2.23 (d, $J = 16.0$ Hz, 2H), 4.20 (s, 1H), 6.11 (s, 2H), 6.63 (m, 3H), 7.05 (t, $J = 7.7$ Hz, 1H), 8.91 (s, 1H).

Table 2, Entry 4j:
White powder, $^1$H NMR (CDCl$_3$, 500 MHz): 1.84-1.88 (m, 1H), 1.92-1.97 (m, 1H), 2.21-2.29 (m, 5H), 2.57-2.61 (m, 2H), 4.15 (s, 1H), 6.95 (s, 2H), 7.04 (d, $J = 8.0$ Hz, 2H), 7.07 (d, $J = 8.0$ Hz, 2H). $^{13}$C NMR (DMSO/CDCl$_3$, 125 MHz): 20.5, 27.3, 33.8, 37.1, 60.3, 114.1, 119.4, 127.4, 128.5, 130.3, 130.5, 133.5, 140.9, 158.6, 164.6, 196.2.
Table 2, Entry 4k:
$^1$H NMR (DMSO-d$_6$, 500 MHz): 1.84–1.88 (m, 1H), 1.92–1.97 (m, 1H), 2.21–2.29 (m, 5H) 2.57–2.61 (m, 2H), 4.15 (s, 1H), 6.95 (s, 2H), 7.04 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): 20.6, 21.4, 27.3, 35.9, 37.2, 59.2, 114.8, 120.6, 127.9, 129.7, 136.4, 142.7, 159.3, 165.1, 196.6.

Table 2, Entry 4l:
$^1$H NMR (CDCl$_3$, 500 MHz): 2.21–2.26 (m, 1H), 2.27–2.32 (m, 1H), 2.41–2.52 (m, 2H), 2.61–2.69 (m, 2H), 4.57 (s, 1H), 4.69 (s, 2H), 7.46 (d, J = 4.4 Hz, 2H), 8.19 (d, J = 4.4 Hz, 2H).

Result and Discussion

Initially, various supports were screened in the condensation reaction between benzoaldehyde, malononitrile and 5,5-dimethylcyclohexane-1,3-dione in ethanol under reflux conditions. After extensive screening, the procedure was optimized by varying reaction time, molar ratio of catalyst/support and solvent for this reaction we found that the optimized best yields and time profiles were obtained with alumina supported KF (20 mol%) in EtOH at reflux conditions, which furnished the corresponding 4H-benzo[b]pyrane 4a in 90% yield within 2 h (Table 1, entry 5). Increasing the amount of KF to more than 25 mol% showed no substantial improvement in the yield, whereas the yield decreased by decreasing the amount of the catalyst to 15 mol%. Moreover, it was observed that the reaction did not proceed efficiently in the absence of KF-alumina after a long time (4 h). Moreover, other supports such as SiO$_2$, K10 and graphite were applied and ineligible results in order to the reaction rate and yield was obtained. The model reaction was also examined in several solvents and ethanol was the best solvent.

Table 1: The effect of different supports on synthesis of benzo[b]pyran (4a) in different solvents under reflux conditions.

| Entry | Support         | Catalyst (mol%) | Solvent | Time (h) | Yield\(^a\) (%) |
|-------|-----------------|-----------------|---------|----------|-----------------|
| 1     | –               | 20              | EtOH    | 3        | 75              |
| 2     | Silica gel      | 20              | EtOH    | 2        | 83              |
| 3     | Neutral Alumina | 20              | EtOH    | 2        | 82              |
| 4     | Acidic Alumina  | 20              | EtOH    | 2        | 72              |
| 5     | Basic Alumina   | 20              | EtOH    | 2        | 90              |
| 6     | Graphite        | 20              | EtOH    | 3        | 70              |
| 7     | K-10            | 20              | EtOH    | 2        | 64              |
| 8     | Basic Alumina   | 15              | EtOH    | 3        | 83              |
| 9     | Basic Alumina   | 25              | EtOH    | 2        | 90              |
| 10    | Basic Alumina   | 20              | H$_2$O  | 2        | 74              |
| 11    | Basic Alumina   | 20              | CHCl$_3$| 3        | 60              |
| 12    | Basic Alumina   | 20              | CH$_3$CN| 3        | 78              |

\(^a\)Isolated yield.
In the next step, scope and efficiency of the KF-alumina was explored under the optimized reaction conditions. For this purpose, a broad range of structurally diverse aldehydes were condensed with malononitrile and 5,5-dimethylcyclohexane-1,3-dione to furnish the corresponding products in high yields and short reaction times. The results are displayed in Table 2.

As it is shown in Table 2, electron withdrawing substituents in aldehydes accelerated the reaction rate (entries 4c and 4h) whereas electron releasing substituents reduced the reaction rate (entries 4e-4g) but nature of substituents did not affect on the yield of product. In order to establish the reusability of catalyst, preparation of compound 4a was examined in the presence of recovered KF-alumina and any lose of activity did not observe for five cycles of reaction.

**Table 2.** Synthesis of 4H-benzo[b]pyran derivatives in the presence of KF-alumina in ethanol at reflux conditions.

| Entry | Ar          | R   | Time (h) | Yield (%) | M.P. (°C) |
|-------|-------------|-----|----------|-----------|-----------|
| 4a    | C₆H₅       | CH₃ | 2        | 90        | 224-227   |
| 4b    | 4-ClC₆H₄   | CH₃ | 2        | 92        | 237-238   |
| 4c    | 3-NO₂C₆H₄  | CH₃ | 1.5      | 90        | 210-212   |
| 4d    | 4-NO₂C₆H₄  | CH₃ | 2        | 89        | 177-179   |
| 4e    | 4-CH₃OC₆H₄ | CH₃ | 3        | 90        | 197-199   |
| 4f    | 4-CH₃C₆H₄  | CH₃ | 2.5      | 92        | 222-225   |
| 4g    | 3-OHC₆H₄   | CH₃ | 3        | 83        | 227-228   |
| 4h    | 4-CF₃-C₆H₄ | CH₃ | 1.5      | 92        | 215-218   |
| 4i    | C₆H₅-CO    | CH₃ | 1        | 92        | 220-221   |
| 4j    | 4-ClC₆H₄   | H   | 2.5      | 90        | 225-227   |
| 4k    | 4-CH₃C₆H₄  | H   | 3        | 81        | 232-234   |

*Isolated yield.*

**Conclusions**

In summary, this new protocol represents a safer, simpler and more environmentally friendly alternative to the usual classical benzo[b]pyran synthesis, avoiding the use of expensive and/or toxic catalyst or solvent. Also, the separation and purification of products is easy.
Synthesis of Benzo[b]pyrane Derivatives using Supported Potassium Fluoride

2005

Acknowledgement
We appreciate Gachsaran branch of Islamic Azad University Research Councils for the financial support of this work.

References
1. Li Z., Ma X., Liu J., Feng X., Tian G., Zhu A., J. Mol. Catal. A: Chem. 2007, 272, 132.
2. Jyothi T.M., Kaliya M.L., Herskowitz M., Landau M. V., Chem. Commun. 2001, 992.
3. Hafez E.A., Elnegdi M.H., Elagamey A. A., El-Taweel F. A. M., Heterocycles 1987, 26, 903.
4. Hatakeyama S., Ochi N., Numata H., Takano S., J. Chem. Soc., Chem. Commun. 1988, 1202.
5. Zamocka J., Misikova E., Durinda J., Pharmazie 1991, 46, 610.
6. Wang J.L., Liu D., Zhang Z.J., Shan S., Han X., Srinivasula S. M., Croce C.M., Alnemri E. S., Huang Z., Proc. Natl. Acad. Sci. U.S.A. 2000, 97, 7124.
7. El-Saghier A.M.M., Naili M.B., Rammash B. K., Saleh N. A., Kreddan K. M., Arkivoc 2007, xi, 83.
8. Kumar R.R., Perumal S., Senthilkumar P., Yogeeswari P., Sriram D., Bioorg. Med. Chem. Lett. 2007, 17, 6459.
9. Fairlamb I.J.S., Marrison L.R., Dickinson J.M., Lu F.J., Schmidt J.P., Bioorg. Med. Chem. 2004, 12, 4285.
10. Kidwai M., Saxena S., Mothsra P., Mohan R., Biswas S., Bioorg. Med. Chem. Lett. 2005, 15, 4295.
11. Suarez M., Salfran E., Verdecia Y., Ochoa E., Alba L., Martin N., Martinez R., Quinteiro M., Secoane C., Novoa H., Balton N., Peeters O. M., De Ranter C., Tetrahedron 2002, 58, 953.
12. Jin T.S., Wang A.Q., Wang X., Zhang J.S., Li T.S., Synlett 2004, 871.
13. Shi D.Q., Zhang S., Zhuang Q. Y., Tu S. J., Hu H. W., Chin. J. Org. Chem. 2003, 23, 877.
14. Wang L.M., Shao J.H., Tian H., Wang Y. H., Liu B., J. Fluorine Chem. 2006, 127, 97.
15. Balalaie S., Bararjanian M., Amani A. M., Movassag B., Synlett 2006, 263.
16. Tu S.J., Gao Y., Guo C., Shi D., Lu, Z. Synth. Commun. 2002, 32, 2137.
17. Peng Y., Song G., Catal. Commun. 2007, 8, 111.
18. Kumar D., Reddy V.B., Sharad S., Dube U., Kapur S., Europ. J. Med. Chem. 2009, 44, 3805.
19. Jin T-S., Zhao R-O., Li T-Sh., Arkivoc 2006, xi, 176.
20. Hasaninejad A., Zare A., Shekouhy M., Ameri Rad J., Green Chem. 2011, 13, 958.
21. Hasaninejad A., Shekouhy M., Golzar N., Zare A., Doroodmand, M. M., Appl. Cat. A: General 2011, 402, 11.
22. Hasaninejad A., Zare A., Shekouhy M., Tetrahedron 2011, 67, 390.
23. Hasaninejad A., Zare A., Shekouhy M., Ameri Rad J., J. Comb. Chem. 2010, 12, 844.
24. Hasaninejad A., Zare A., Zolfigol M. A., Shekouhy M., Synth. Commun. 2009, 39, 569.
25. Hasaninejad A., Zare A., Shekouhy M., Zare A. R. M., E J. Chem. 2009, 6(S1), 5247.
26. Hasaninejad A., Zare A., Jafari F., Zare A. R. M., E J. Chem. 2009, 6(2), 459.
27. Hasaninejad A., Zare A., Sharghi H., Shekouhy M., Arkivoc 2008, xi, 64.
