Environmentally friendly homocoupling reaction of functionalized potassium aryl trifluoroborates salts in aqueous media

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A R T I C L E  I N F O

Article history:
Received 20 July 2011
Accepted 1 August 2011
Available online 7 August 2011

Keywords:
Potassium organotrifluoroborates
Biaryl compounds
Homocoupling reaction

A B S T R A C T

The homocoupling reaction between potassium aryl trifluoroborates containing different functionalities promoted by a catalytic amount of Pd(OAc)_2 is described. The methodology uses water as a solvent under aerobic conditions to give the corresponding biaryl compounds in good yields.

Green technology is a topic, that is, receiving significant attention because of environmental issues.¹ The development of methods focusing on environmentally benign reaction media has been particularly prominent.² Thus, advances in the development of aqueous biphasic catalysis³ and the use of supercritical fluids,⁴ ionic liquids,⁵ and fluorous media⁶ continue to be important areas of investigation. However, the use of water as a solvent seems to be the best option due to its simplicity and very low cost.

There are a wide range of natural products that contain a biaryl bond (Fig. 1).⁷ In addition, the widespread application of biaryl as ligands⁸ and components in new materials⁹ make these compounds interesting synthetic targets.

There are a number of methods developed to synthesize biaryl compounds,¹⁰ being the homo-coupling of aryl boronic acids one of the most important.¹¹ However, the use of boronic acids possess some limitations such as the difficulty to purify and for having some uncertain stoichiometry, due to the formation of boroxines.¹²

Organotrifluoroborates have proven to be a good option to replace boronic acids and boronate esters in Suzuki coupling reactions, providing many advantages over the latter reagents.¹³ In addition, there are many possibilities of functional group interconversion reaction involving these compounds including the syntheses of aldehydes,¹⁴ ketones,¹⁵ alcohols,¹⁶ alkynes¹⁷ and alkenes¹⁸ containing an organotrifluoroborate moiety.

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Figure 1. Biaryl natural products.
The complete characterization of these salts, including heteronuclide NMR analysis, has proven to be possible since better NMR pulse sequences were developed, which allowed the acquisition of new data related to $^{19}$F–$^{11}$B coupling constants.$^{19}$ It’s also important to emphasize the recent interest on biological activities and toxicological data related to these salts. It is already described that organotrifluoroborates may act as serine protease inhibitors,$^{20}$ growth inhibition on human tumor cell lines,$^{21}$ and some of them appear to have antinociceptive activity and low toxicity.$^{22}$

Herein, we wish to describe an environmentally benign reaction for the synthesis of symmetrical biaryl compounds based on the homocoupling reaction of potassium aryl trifluoroborates under aerobic conditions catalyzed by palladium(II).

The potassium organotrifluoroborates $^{2a-o}$ used in this study were prepared from the corresponding boronic acids $^{1a-o}$ using KHF$_2$ in MeOH/H$_2$O in good yields$^{23}$ and their structures were confirmed by $^1$H, $^{13}$C, $^{11}$B, and $^{19}$F NMR analysis (Scheme 1).

Our initial studies focused on the development of an optimum set of reaction conditions. For this purpose, potassium 3-formylphenyl trifluoroborate ($^{2a}$) was used as standard substrate. Thus, $^{2a}$ (0.25 mmol) was treated with a different catalysts and solvents at 25°C using potassium carbonate as a base. The obtained product $^{3a}$ was characterized by $^1$H and $^{13}$C NMR. The results are described in Table 1.

As shown in Table 1, both Pd(OAc)$_2$ and PdCl$_2$ exhibited good catalytic activity (Table 1, entries 1–2), being the desired homocoupling product $^{3a}$ obtained in 82% and 80%, respectively. The use of Cu(OAc)$_2$ and CuCl$_2$ also gave the corresponding homocoupling product but in low yields. All reactions were monitored by $^{19}$F NMR until the disappearance of the starting material which was accomplished after 48 h.

We chose Pd(OAc)$_2$ as the palladium source as a result of its low cost. In the optimization process, the effect of the Pd(OAc)$_2$ amount was investigated, and further experiments showed that the best cost effective results for the coupling reaction were obtained with Pd(OAc)$_2$ (5 mol %). In fact, the yield was slightly enhanced by the use of 15% of Pd(OAc)$_2$ (Table 1, entry 5). However, by using Pd(OAc)$_2$ (5 mol %) a similar result was observed (Table 1, entry 1).

The influence of the solvent in the reaction was also investigated. When the reaction was carried out using only water as a solvent, $^{3a}$ was obtained in 82% yield. The use of THF as a co-solvent gave similar results, where $^{3a}$ was also obtained in 82% yield. When only THF was used as a solvent, no product was observed, probably due to the low solubility of $^{3a}$ in this solvent (Table 1, entry 8). The reaction was also performed without the use of potassium carbonate. However, the product $^{3a}$ was obtained in lower yield (Table 1, entry 9).

Table 1
Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Catalyst (mol %)</th>
<th>Solvent</th>
<th>$^{3a}$ Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pd(OAc)$_2$ (5)</td>
<td>H$_2$O</td>
<td>82</td>
</tr>
<tr>
<td>2 PdCl$_2$ (5)</td>
<td>H$_2$O</td>
<td>80</td>
</tr>
<tr>
<td>3 Cu(OAc)$_2$ (5)</td>
<td>H$_2$O</td>
<td>10</td>
</tr>
<tr>
<td>4 CuCl$_2$ (5)</td>
<td>H$_2$O</td>
<td>15</td>
</tr>
<tr>
<td>5 Pd(OAc)$_2$ (15)</td>
<td>H$_2$O</td>
<td>84</td>
</tr>
<tr>
<td>6 —</td>
<td>H$_2$O</td>
<td>5</td>
</tr>
<tr>
<td>7 Pd(OAc)$_2$ (5)</td>
<td>H$_2$O:THF</td>
<td>82</td>
</tr>
<tr>
<td>8 Pd(OAc)$_2$ (5)</td>
<td>THF</td>
<td>—</td>
</tr>
<tr>
<td>9 Pd(OAc)$_2$ (5)</td>
<td>H$_2$O</td>
<td>50c</td>
</tr>
</tbody>
</table>

a Isolated yield.

b The product was not observed under the reaction conditions.

c The reaction was performed without K$_2$CO$_3$.

Table 2
Ar–Ar (3) prepared from the homocoupling reaction of ArBF$_3$K (2) catalyzed by Pd(OAc)$_2$

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArBF$_3$K, 2</th>
<th>Ar–Ar, 3</th>
<th>Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$^{2a}$</td>
<td>$^{3a}$</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>$^{2b}$</td>
<td>$^{3b}$</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>$^{2c}$</td>
<td>$^{3c}$</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>$^{2d}$</td>
<td>$^{3d}$</td>
<td>75</td>
</tr>
</tbody>
</table>

(continued on next page)
In this way, the optimum set of conditions for the coupling was 2a (0.25 mmol), Pd(OAc)$_2$ (5 mol%), K$_2$CO$_3$ (0.625 mmol), water (4.0 mL) at 25°C for 48 h. By extending the coupling reaction to other potassium aryl trifluoroborates, various biaryls were obtained in moderate to good yields (Table 2). The formation of the products was confirmed by the analysis of the $^1$H and $^{13}$C NMR spectra.

The method is tolerant to a wide range of functional groups. When electron-withdrawing groups were present in the starting potassium aryl trifluoroborate, good yields were observed (Table 2, entries 1–8). In the same way, when the scope of the reaction was extended to electron-donating groups, the corresponding biaryl compounds were also obtained in good yields (Table 2, entries 9 and 10).

It is known that the coupling reaction for the synthesis of biaryls is sensitive to the steric hindrance of substrates and the synthesis of highly hindered biaryls remains a challenge. By the use of the method, meta-, ortho- and para-formyl mono-substituted aryl trifluoroborates gave the corresponding products in similar yields (Table 2, entries 1–3).

However, when the reaction was performed with di-ortho-substituted aryl trifluoroborates, the respective tetra-ortho substituted biaryls were not observed (Table 2, entries 12 and 13). The only exception occurred when 2n was used as the substrate, where the corresponding tetra-ortho substituted biaryl 3n was obtained in good yield (Table 2, entry 14) proving in this case that the reaction is not only sensitive to the steric hindrance, but also to electronic effects.

The applications of binaphthyls in asymmetric synthesis are well known and the development of efficient synthetic methods to prepare this class of compounds is of great interest. In this context, compound 3k was prepared in good yield and high purity using the reaction conditions (Table 2, entry 11).

When potassium 3-thiophenyltrifluoroborate 2o was used, the corresponding product 3o was also obtained in good yield (Table 2, entry 15). Polythiophenes have become the subject of considerable interest due to it applications as conductors, electrode materials, and organic semiconductors.

In summary, we have demonstrated that the potassium aryl trifluoroborates are useful substrates for the synthesis of biaryl...
compounds in good yields under mild conditions. The green methodology is simple, uses water as solvent, low catalyst loading, and is synthetically useful while it could be applied for the synthesis of more complex biaryl compounds.

Acknowledgments

The authors gratefully acknowledge FACEPE (APQ-1402-106/10), CNPq (478333/2009-9), CAPES and INCT-INAMI for financial support. P.H.M. and N.M.M.B. are thankful to CNPq for their fellowships.

Supplementary data

Supplementary data (experimental procedures and spectroscopic characterization data, as well as 1H, 13C, 19F and 11B NMR spectra for all synthesized compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.008.

References and notes


2. (a) Horvath, I. T.; Anastas, P. T.

3. (a) Li, C.-J.

4. Jessop, P. G.; Leitner, W.

5. Kozlowski, M. C.; Morgan, B. J.; Linton, E. C.

6. (a) Kocovsky, P.; Vyskocil, S.; Smrcina, M.

7. (a) Casalbore-Miceli, G.; DegliEspositi, A.; Fattori, V.; Marconi, G.; Sabatini, C.


11. (a) Prastaro, A.; Ceci, P.; Chiancone, E.; Boffi, A.; Fabrizi, G.; Cacchi, S.

12. (a) Grimm, F. A.; Barton, L.; Porter, R. F.

13. (a) Molander, G. A.; Petrillo, D. E.

14. Molander, G. A.; Figueroa, R.

15. (a) Grimm, F. A.; Barton, L.; Porter, R. F.

16. (a) Petullo, D. E.

17. Katona, B. W.; Machrouhi, F.; Molander, G. A.

18. (a) Molander, G. A.; Oliveira, R. A.

19. (a) Molander, G. A.; Petullo, D. E.


28. Representative procedure for the synthesis of 3a: In a flask, at room temperature and under aerobic conditions, was added potassium aryli trifluoroborate 2a (0.25 mmol, 53 mg), Pd(OAc)2 (5 mol %, 3 mg) and K$_2$CO$_3$ (0.40 mmol, 55 mg) followed by H$_2$O (4.0 mL). The contents were stirred for 48 h. After this period, the reaction was extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous MgSO$_4$ and filtered. The solvent was removed in vacuo to yield 22 mg of 3a (82%) sufficiently pure for characterization, m.p 58–100 °C. H NMR (300 MHz, CDCl$_3$), $\delta$ 10.15 (s, 2H), 8.15 (s, 2H), 7.93 (m, 4H), 7.68 (d, 2H, J = 8.1 Hz), $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 192.14, 141.17, 137.5, 133.6, 130.0, 129.5, 128.2.