



# The first synthesis of 4-trifluoromethyl-2*H*-pyrans by palladium-catalyzed cyclization of (*E*)-3-alkynyl-3-trifluoromethyl allylic alcohols

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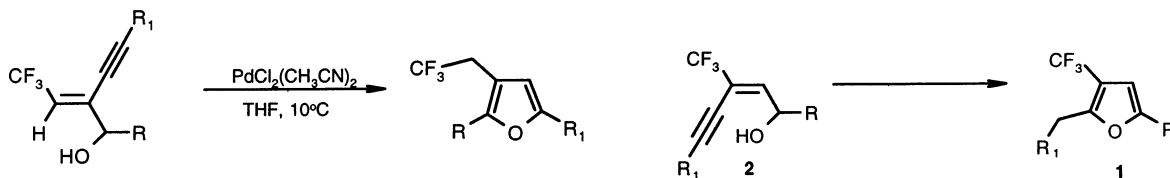
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## Abstract

The cross-coupling of (*Z*)-3-iodo-3-trifluoromethyl allylic alcohols **4** with terminal alkynes **5** in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> and CuI gave conjugated (*E*)-3-alkynyl-3-trifluoromethyl allylic alcohols **2** in high yield. 4-Trifluoromethyl-2*H*-pyrans **7** were prepared from the cyclization of **2** using PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> catalysis. © 2000 Elsevier Science Ltd. All rights reserved.

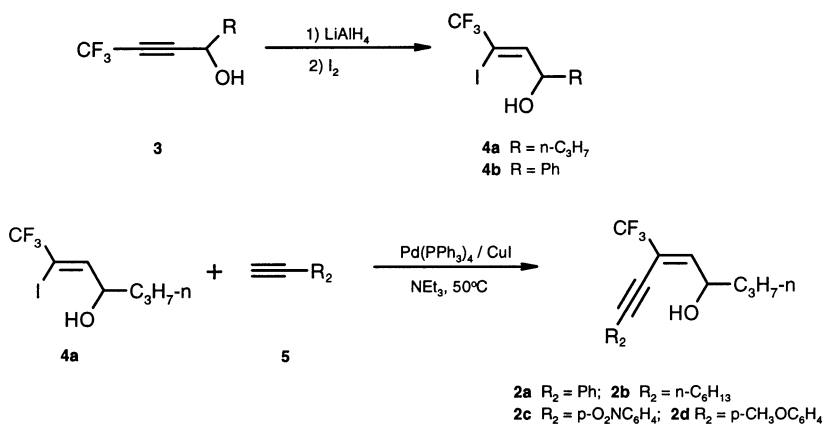
We recently described a novel route to 3-trifluoroethylfurans through palladium-catalyzed cyclization-isomerization of (*Z*)-2-alkynyl-3-trifluoromethyl allylic alcohols (Scheme 1).<sup>1</sup> This reaction proceeds readily and affords a variety of trifluoroethylated furans in high yield. Accordingly, we were interested in testing the feasibility of the synthesis of 3-trifluoromethyl-furans **1** from (*E*)-3-alkynyl-3-trifluoromethyl allylic alcohols **2** (Scheme 1). Recently, cycloisomerization of non-fluorinated 3-alkynyl allylic alcohols to furans was achieved under basic conditions<sup>2</sup> or catalyzed by ruthenium,<sup>3</sup> palladium<sup>4</sup> and silver nitrate.<sup>5</sup>



Scheme 1.

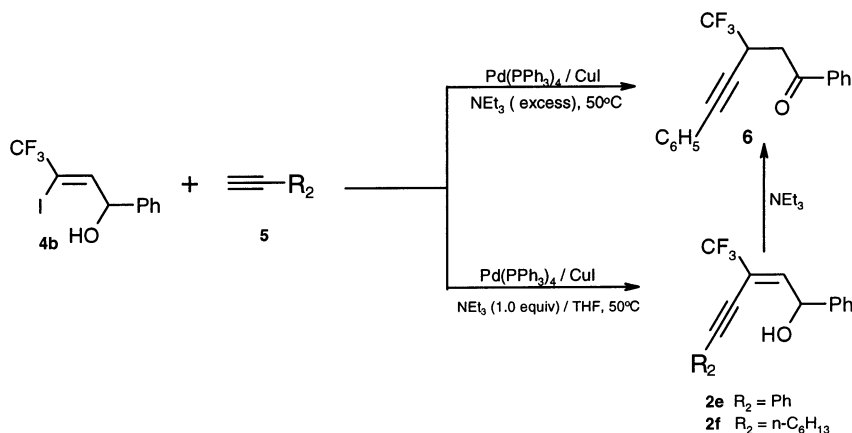
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Trifluoromethyl propargylic alcohols **3** that were easily prepared from 2-bromo-3,3,3-trifluoropropene and aldehydes in the presence of 2 equiv. LDA<sup>6</sup> were used as the starting materials for the syntheses of **2**. Treatment of **3** with LiAlH<sub>4</sub> and then I<sub>2</sub> afforded the (*Z*)-3-iodo-3-trifluoromethyl allylic alcohols **4**.<sup>7</sup> Reaction of **4a** with terminal alkynes **5** in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> and CuI in triethylamine at 50°C gave conjugated (*E*)-3-alkynyl-3-trifluoromethyl allylic alcohols **2** in high yield (Scheme 2).<sup>8</sup>



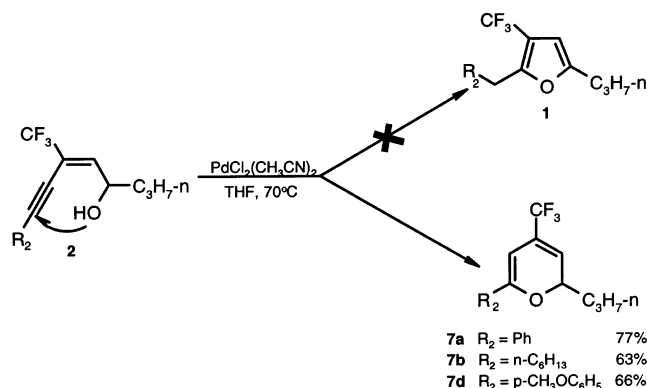
Scheme 2.

The palladium-catalyzed reaction of **4b** with phenylacetylene under the same reaction conditions led not to the expected conjugated (*E*)-3-alkynyl-3-trifluoromethyl allylic alcohol **2e**, but gave the ketone **6** instead. When 1.0 equiv. of triethylamine and THF was used as base and solvent, respectively, in this coupling reaction, the expected product **2e** was isolated in 79% yield. As such, it can be concluded that compound **2e** was formed first, but that it easily rearranged to ketone **6** in the presence of triethylamine (Scheme 3). In the presence of 1.0 equiv. of triethylamine, the palladium-catalyzed cross-coupling of **4b** with 1-octyne gave **2f** in 82% yield.



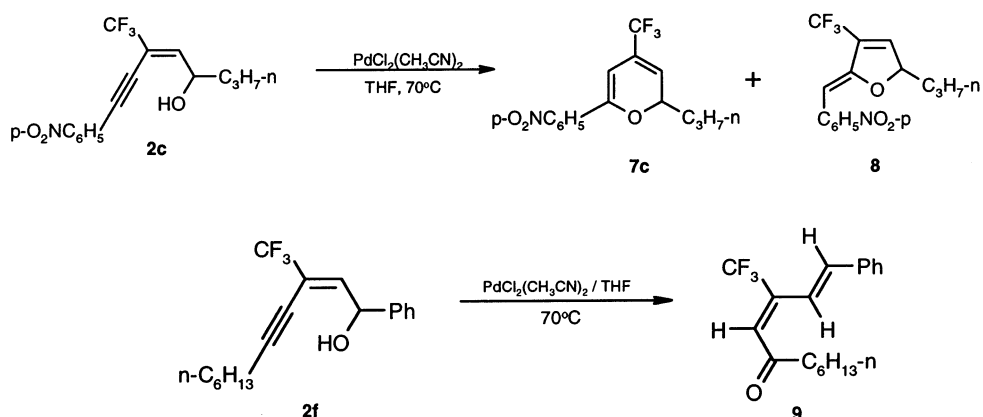
Scheme 3.

With (*E*)-3-alkynyl-3-trifluoromethyl allylic alcohol **2** in hand, we were interested in exploring the feasibility of using **2** in cycloisomerization reactions. The cycloisomerization of **2a** under palladium catalysis was then tested. When **2a** was treated with  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$  (5 mol%) in THF at 70°C for 30 min, compound **2a** was totally converted, affording not the expected product **1**, but the 4-trifluoromethyl-2*H*-pyran **7a** in 77% isolated yield (Scheme 5). A variety of palladium complexes were tested and we found that  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$  and  $\text{PdCl}_2(\text{PhCN})_2$  exhibited similar activities leading to the complete conversion of **2a** to **7a**, while  $\text{Pd}(\text{OAc})_2$ ,  $\text{Pd}(\text{PPh}_3)_4$  and  $\text{PdCl}_2(\text{PPh}_3)_2$  were inactive under similar reaction conditions. Treatment of **2b** and **2d** with a catalytic amount of  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$  effected their smooth conversion to the corresponding 4-trifluoromethyl-2*H*-pyrans **7b** and **7d** (Scheme 4). To the best of our knowledge, this is the first synthesis of 4-trifluoromethyl-2*H*-pyrans. This result was different from the palladium-catalyzed reaction of 3-alkynyl allylic alcohols, which produced substituted furans exclusively.<sup>4c</sup> This is clearly due to the fact the trifluoromethyl group possesses powerful electron-withdrawing properties, so the 6-*endo-dig* cyclization is favored.<sup>9</sup>



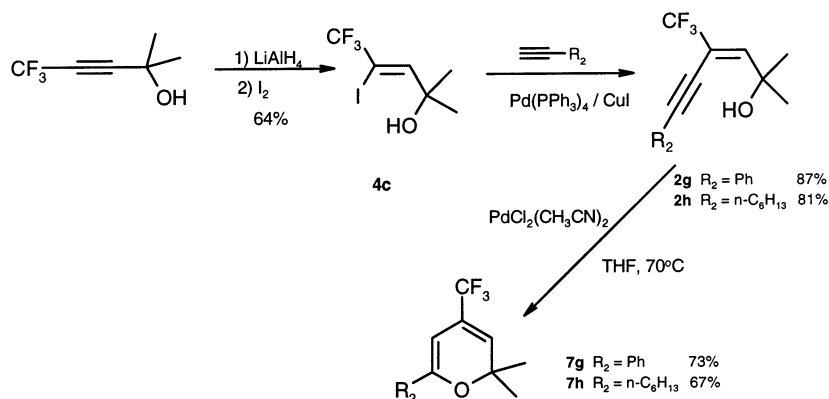
Scheme 4.

Exposure of **2c** to the cyclization conditions afforded the 4-trifluoromethyl-2*H*-pyran **7c** in only 33% yield. This product was accompanied by compound **8** in 32% yield. Interestingly, the reaction of **2f** with catalytic  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$  led to the dienone **9** in 73% yield (Scheme 5).



Scheme 5.

We have also examined the cyclization of the 1,1-dimethyl-3-alkynyl-3-trifluoromethyl allylic alcohols **2g–h** (Scheme 6). Treatment of these alcohols with catalytic  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$  in THF at  $70^\circ\text{C}$  produced the 4-trifluoromethyl-2*H*-pyrans **7g–h**. These results further demonstrate that the 6-*endo-dig* cyclization is a favorable process for (*E*)-3-alkynyl-3-trifluoromethyl allylic alcohols.



Scheme 6.

In summary, we have described the first synthesis of 4-trifluoromethyl-2*H*-pyrans via Pd-catalyzed cyclization of (*E*)-3-alkynyl-3-trifluoromethyl allylic alcohols.

## Acknowledgements

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