Synthesis of substituted phenyl acetic acid and 5-membered heterocycles derivatives.

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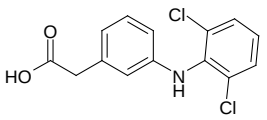
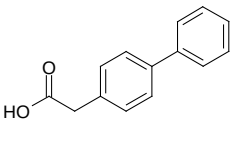
Introduction

Phenyl acetic acid containing molecules, such as those shown below, have proven efficacious in a range of medical treatments[1].



Diclofenac
Anti-inflammatory



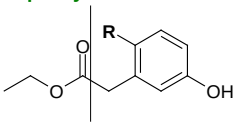
Felbinac
Analgesic

The incorporation of a phenyl acetic acid moiety into therapeutic agents could afford several benefits, such as new biological properties, novelty and thus, potential patentability.

Background

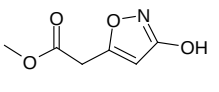
As part of a Hit to Lead campaign, we were interested in the synthesis of ortho-substituted phenyl acetic acid derivatives and of a particular bioisostere, the 3-hydroxy-5-isoxazoleacetic acid building blocks.

ortho-substituted phenyl acetic acid



R= Me, **1**
F, **2**

Bioisostere



3

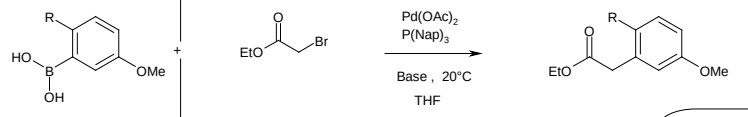
At this stage, the objective of the programm was to identify new molecule within a series with the following properties.

- Retain good potency
- Increase PK profile and selectivity
- Demonstrate in vivo efficacy in relevant disease models at reasonable therapeutic doses

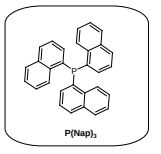
Ortho-substituted phenyl acetic acid preparation

For phenyl acetic acid building blocks, a synthetic strategy using Palladium–catalysed Suzuki coupling reaction was considered. Only few examples of coupling between boronic acid and *alkyl* halides have been reported but a method described by Gooβen appeared to be applicable to our substate[2].

Key step

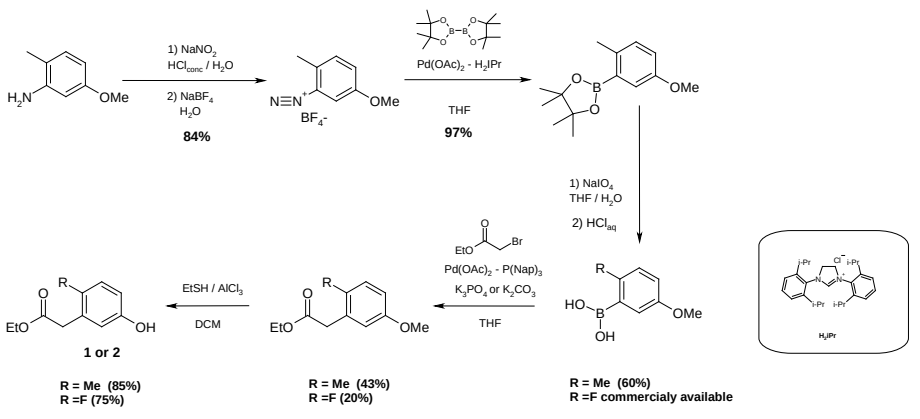


R substituent	Base	Yield
Me	K_3PO_4	43%
F	K_2CO_3	20%



Csp2-Csp3 suzuki coupling gave a moderate yield. In our hands, Suzuki reaction of aryl containing an electro-withdrawing group was found to be less efficient. For this substrate, a base effect was identified. K_2CO_3 gave the best result.

Synthesis of the methyl and fluorine derivatives.



The synthesis of the non commercialy available methyl bearing aryl boronic ester from the aniline was successfully performed using a catalysis method with N-heterocyclic carbene–palladium complexe described by M. Andrus[3].

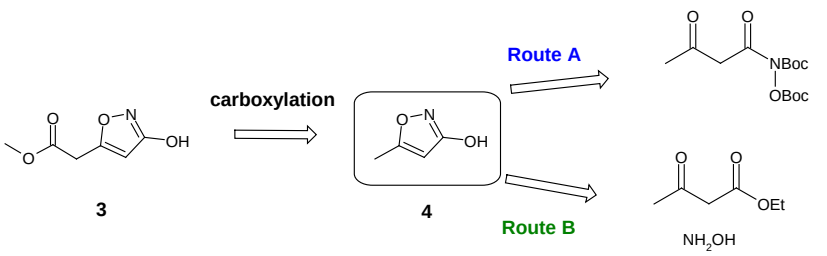
This sequence using boronic acid preparation from aniline followed by this suzuki coupling was easy and efficient (5 steps, 18% overall yield).

The fluoro phenyl acetic acid was obtained directly from the corresponding commercialy available boronic acid.

Synthesis of a phenyl acetic acid bioisostere

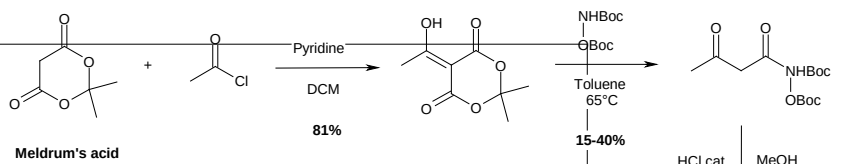
3-hydroxy-5-isoxazoleacetic acid synthesis

Litterature searches for this scaffold have shown that a carboxylation of the 3-hydroxy-5-methylisoxazole (4) at the last step would be an interesting strategy [4].



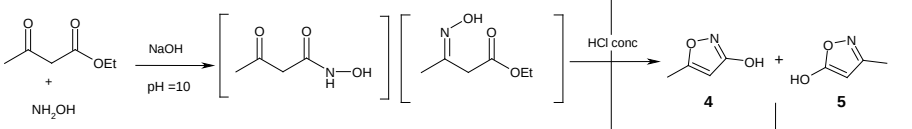
Two synthetic routes of the methyl bearing key intermediate were investigated.

Route A



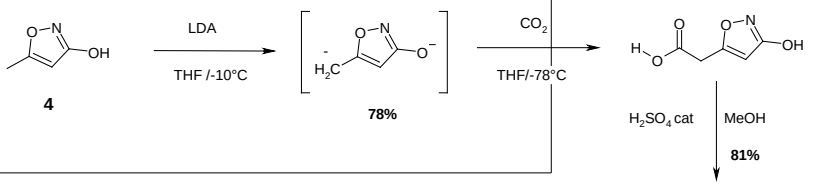
This synthesis has the advantage to form only one regio-isomere, but the aminolyses of the acyl Meldrum's acid with N,O-diboc-protected hydroxylamine was found to be temperamental.

Route B



The obtention of the desired 3-hydroxy-5-methylisoxazole was optimised by careful adjustment of the reaction pH to 10 followed by rapid addition of a large excess of concentrated hydrochloric acid during the quenching. The two isomers were found surprisingly easy to separate by flash column chromatography.

Final steps



The dianion was readily formed with 2 equivalent of LDA. Treatment with carbon dioxide (CO_2 solid) gave exclusively the expected acid.

Conclusion

We described easy and efficient synthesis of 5-Hydroxy-2-methyl phenylacetate (1) and 3-hydroxy-5-isoxazoleacetate (3) key buiding blocks that were used in our medicinal chemistry programm.

Example 1 : ► use of commercialy available aniline
► short reaction sequence

Example 2 : Two routes were explored. Route B which at first glance presented the disadvantage of generating the two isomers, became the route of choice after careful optimisation.

References

1- T.Y. Shen, *Angew. Chem.*, **1972**, 84, 512.
2- L. Gooβen. *Chem. Comm.*, **2001**, 7, 669.
3- M. Andrus and al. *Org. Lett*. **2003**, 5, 4635.
3- T. Harris and al. *J. Org. Chem*. **1983**, 48, 4307.