Expanding of the scope of Castagnoli–Cushman Reaction: trifluoracetaldehyde monohydrate

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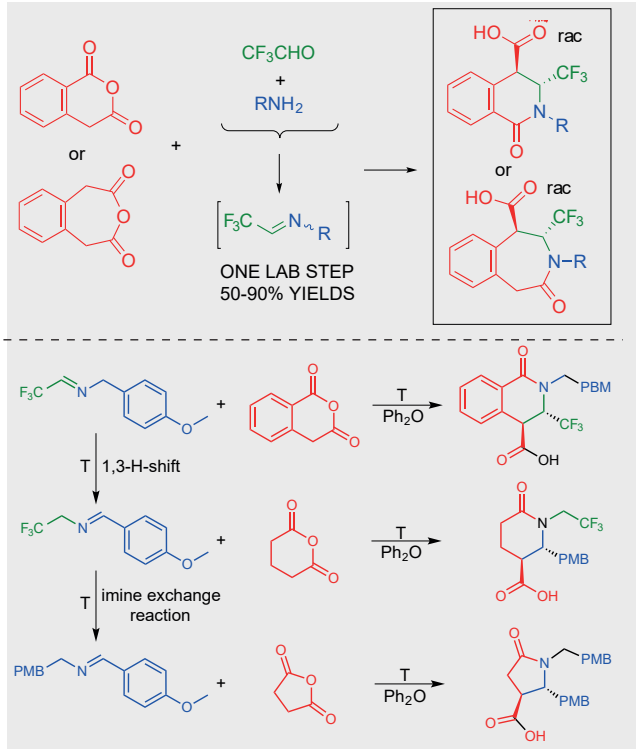
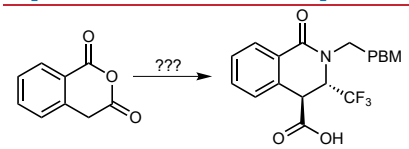
Introduction and Aim

Thorough exploration of chemical space relevant for medicinal chemistry requires synthetic methods, which open access to potential lead compounds in an efficient manner. Multicomponent reactions are especially promising in this view since they provide sufficient diversity of the compound libraries with minimum synthetic efforts required. In particular, Castagnoli-Cushman reaction (CCR), i.e. condensation of imines with cyclic andydrides, has been considered as an efficient tool for synthesis of pyrrolidones and piperidones, as well as their fused and heteroatom-substituted analogues.

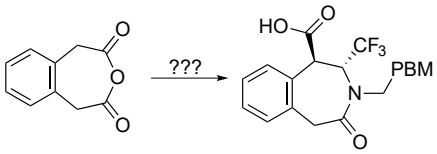
In our ongoing research in discovering of the scope and limitation of this useful reaction the trifluoracetaldehyde monohydrate was utilized. We showed that only most active anhydrydes like homophthalic and benzadipic can be substrates in this reaction. In the case of less active anhydride like glutaric and succinic only products of rearrangements were observed. The structure of the products depends on the ring's size. For 6-membered rings we obtained N-trifluoroethyl substituted products, as a result of 1,3-H-shift in starting imines. For 5-membered rings only products of aromatic imines (result of iminic exchange reaction) were formed. This opened a door for such rare types of benzpiperidones and benzazepinones as 1-oxo-3-(trifluorome-thyl)-1,2,3,4-tetrahydro-isoquinoline-4-carboxylic acids and 4-oxo-2-(trifluoromethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-1-carboxylic acids and their derivatives.



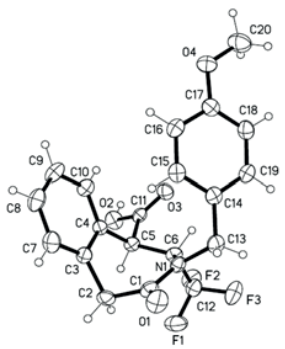
Optimization & Scope



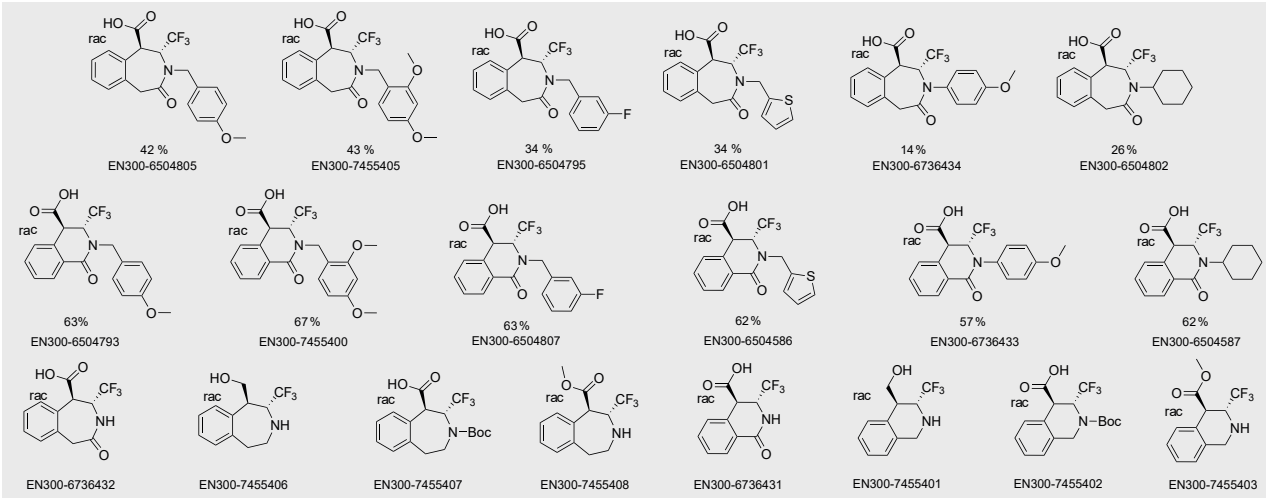
Entry	Solvent	Temperature	Conversion
1	DMA	140 °C	-
2	Xylene	140 °C	73 %
3	$CHCl_3$	RT	67 %
4	MeCN	RT	68 %
5	DCE	80 °C	77 %
6	MeCN	80 °C	54 %
7	Toluene	110 °C	92 %
8	DMA	110 °C	-



Entry	Solvent	Temperature	Conversion
1	Xylene	140 °C	49 %
2	Toluene	110 °C	30 %



Results



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