Hes·so
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Master of Science HES-SO in Life Sciences

α-Halo Ketone Amino Acids
Process Research & Application in Scale-up of Drug Intermediates

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CHEMICAL DEVELOPMENT & PRODUCTION

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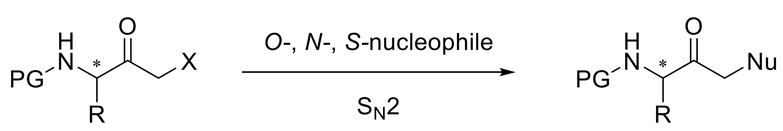
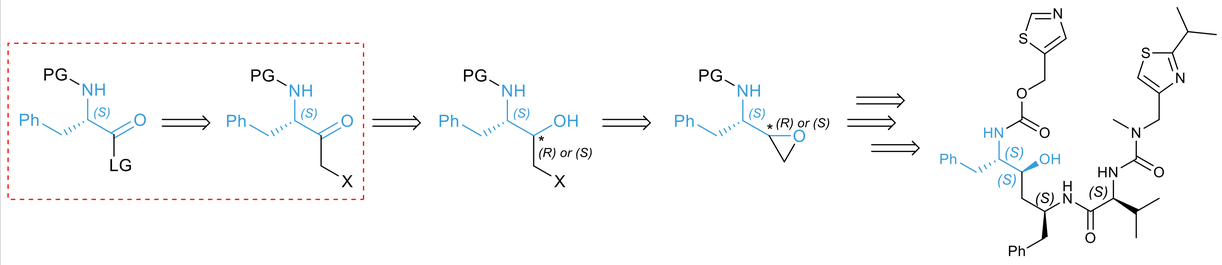
PROJECT DESCRIPTION

α-Halo Ketone Amino Acids are amino acids derivatives which carry a halogen on the α-position of the carbonyl. These compounds can undergo S_N2 reactions with various nucleophiles making them useful for the preparation of larger molecules.

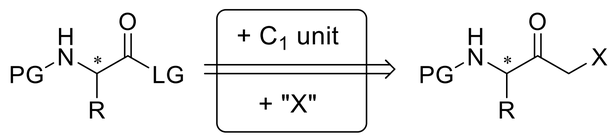


For instance, the preparation of commercially available protease inhibitor drugs for the treatment of HIV are commonly prepared from these intermediates via S_N2 reaction after stereoselective reduction of the ketone.

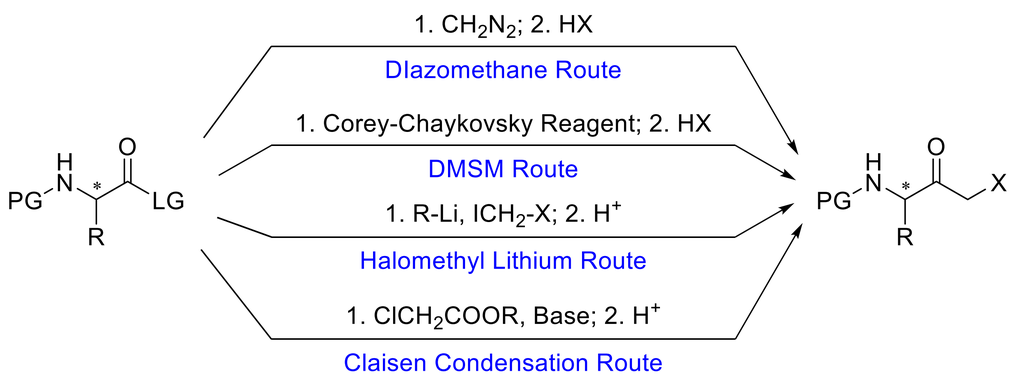


The goal of this project was the development of a reliable process for the preparation of these intermediates; this included drafting a state of the art reviewing different synthetic routes, preliminary investigation, route selection and process optimization, as well as thermal safety assessment and scale-up.

SYNTHETIC PATHS

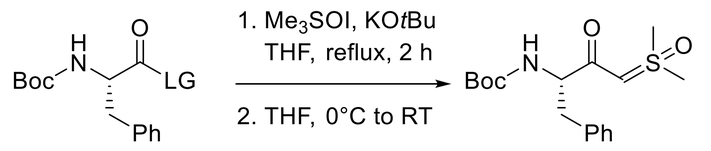


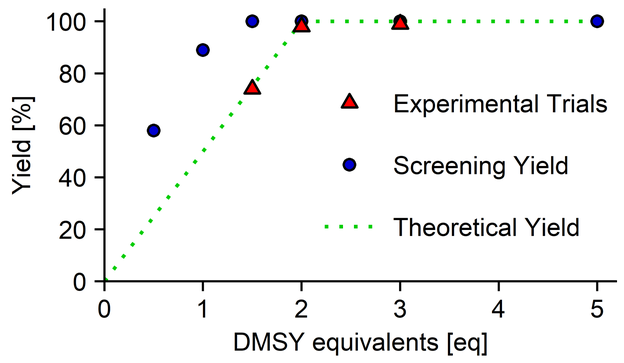
Their synthesis requires the addition of a C_1 unit as well as a halogen. This can be achieved via four different synthetic pathways that are found in literature.

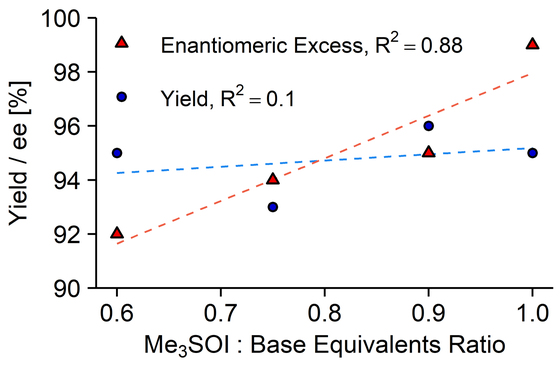


RESULTS

Upon evaluation of the preliminary investigation results of the some previously shown synthetic routes, the Dimethylsulfoxonium Methylide approach (DMSM) was selected and further studied in order to optimize it. Optimization regarding the amount of equivalents, time, temperature and other process metrics were screened.

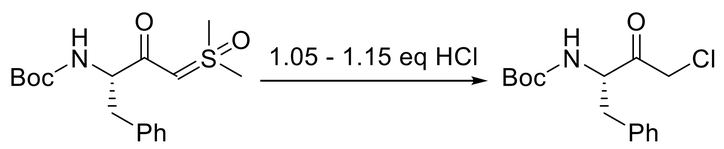






Entry	LG	Crude Aspect	Assay [%]	Yield [%]	ee [%]
1	ONp	Yellow powdery solid	75-85	99	>99
2	OMe	Off-white solid	>95	98	<1
3	OCOOiBu	Yellowish sticky solid	64	38	>99
4	OBn	Wet off-white solid	74	92	<1
5	OSu	Off-white solid	>95	97	>99
6	OPfp	Brownish paste	49	86	-
7	OPiv	White solid	90	73	>99
8	OCOOBn	White solid - oil	53	40	>99

The first reaction step was successfully optimized affording the product in excellent yield and no loss in enantiopurity. The transformation of the sulfoxonium ylide intermediate to the desired chloroketone was then also optimized.



Entry	HCl source	Yield [%]
1	LiCl, MsOH	93
2	LiCl, MsOH[a]	90
3	LiCl, MsOH[b]	47
4	HCl 4 N in dioxane	98
5	HCl 2.36 M in THF	98
6	Aq. HCl 32%	87

a: Addition at reflux; b: 2.0 eq of MsOH

Entry	Solvent	Water [ppm]	Yield [%]
1	THF	775	99
2	EtOAc	58	99
3	DMC	183	98
4	ACN	284	82

Reaction performed with 1.05 eq of HCl in dioxane

CONCLUSION

Investigation, selection and optimization of a synthetic route towards α-haloketone amino acids was achieved. In addition to the optimization of the selected route, thermal safety assessment was carried out and the whole process was assessed as safe. Nevertheless the process could still be optimized by combining the first and second reactions steps in a single one. Additional efforts should be employed for the investigation of the selected process on other amino acids in order to evaluate its applicability to other substrates.