[3+2]-Cycloaddition reaction: Synthesis of Libraries of Drug-Like pyrrolidine scaffolds

Luciane Adeikalam, Karine Bonnet, Gérald Coste, Rachel Guilleux, Caroline Gurcel, Rémy Morgentin, Martin Ohsten, Guillaume Ranty, Anthony Willaume

EDELRIS - Medchem-Oriented Research & Services - 115, Avenue Lacassagne 69003 Lyon - France

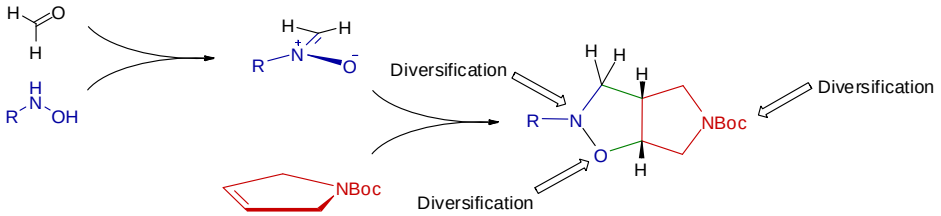
Introduction:

The European Lead Factory (ELF) is a pan-European platform which was set up to foster drug discovery in Europe.[1] In this 5-year programme, academic researchers from prestigious Universities and European CRO SME's have joined their efforts to assemble a new screening collection of 200 000 compounds based on innovative scaffolds. As part of its ~40,000-compounds contribution, Edelris has been considering methodologies, such as the [3+2]-cycloaddition reaction, to achieve the production of a ~500 3D-shaped compound library.[2]

Library Design

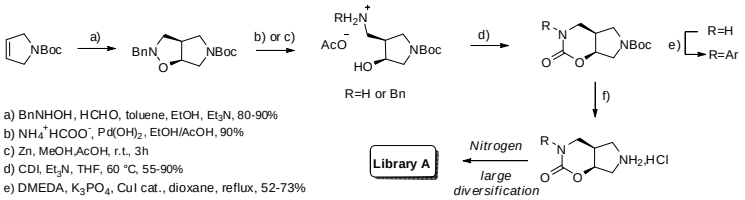
The [3+2]-cycloaddition reaction is a powerful tool to address 3D-rich and highly functionalised scaffolds for chemical library development. The design and the validation of the chemistry routes were carried out before being submitted to the ELF committee for approval and further enumeration, followed by scale-up and final library production.

Two diverse pyrrolidine containing scaffolds (Library A and B) were designed by applying [3+2]-cycloaddition reactions. The 1,3-dipole (a nitrone) was generated *in situ* from an alkyl hydroxylamine and an aldehyde and was reacted with N-Boc 2,5-dihydro-1H-pyrrole (Library A) or an analogue (Library B) as the dipolarophile. For further library elaboration, the obtained isoxazolidine cycloaddition adducts contains multiple entrance point for diversity generation.



Library A

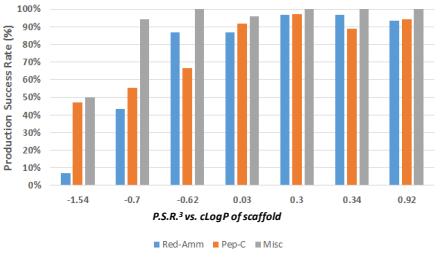
The purpose for this library was to design the smallest and simplest innovative scaffold based on the [3+2] cycloaddition reaction. The use of formaldehyde and N-Boc 2,5-dihydro-1H-pyrrole respectively avoids diastereoselectivity and regioselectivity issues. Benzyl hydroxylamine allows access to further diversification.



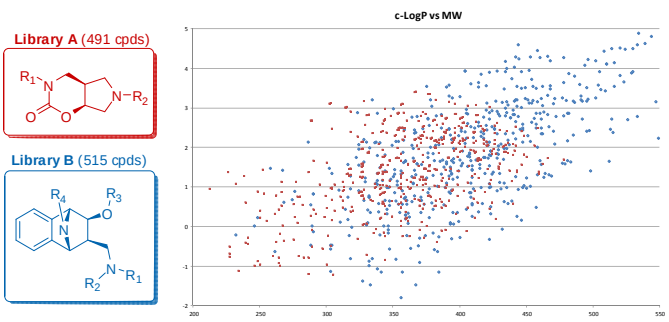
a) BnNHOH, HCHO, toluene, EtOH, Et_3N, 80-90%
b) $NH_4^+HCOO^-$, $Pd(OH)_2$, EtOH/AcOH, 90%
c) Zn, MeOH,AcOH, r.t., 3h
d) CDI, Et_3N, THF, 60 °C, 55-90%
e) DMEDA, K_3PO_4, CuI cat., dioxane, reflux, 52-73%
f) HCl, dioxane, 90-100%

Production & Result

Library production was divided into several production campaigns utilizing from 1 to 4 building blocks performing the same type of capping transformations. Reactions were setup in a standardized way, following well established procedures and final compounds were purified by mass-triggered preparative LCMS.

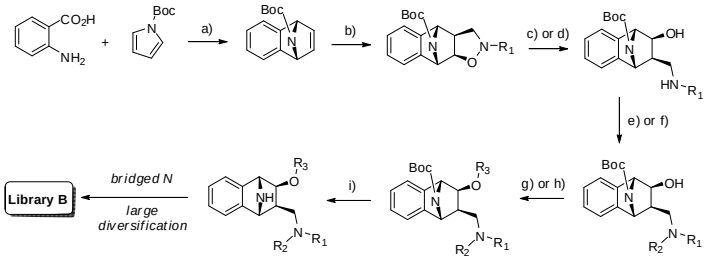


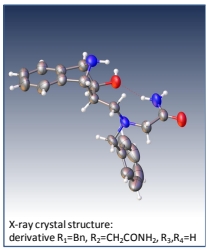
The Production process was designed and formatted to be as fast and reliable as possible to meet the required pace of +10,000 validated compounds per year.



Library B

Successive cycloaddition reactions is an efficient way to introduce 3D. Based on a [4+2] / [3+2] reactions sequence, the bridged scaffold was obtained in 3 steps in a very robust and reproducible synthesis (0.2 mol scale synthesis).





a) iPentylONO, DME, 50°C, 51%
b) R_1NHOH.HCl, (CH2O)n, TEA, EtOH, toluene, 70°C, 55%
c) R_1=Bn: H_2, Pd/C, 10% (H-Cube), 80bar, 80°C, EtOH, 5% AcOH, 75%
d) R_1=Bn, Me, iPr: Zn, AcOH, 70°C, 90%
e) R_2=RCO: RCOCl or RSO_2Cl, DIPEA, DCM, rt, 90%
f) R_2=RCH_2: RCHO, STAB, AcOH, DCE, 80°C, 90%
g) R_3=Me: Me_2SO_4, $BnNEt_3Cl$, NaOH aq; 80°C, 88%
h) R_3=2-Pyridyl: 2-fluoropyridine, NaH, DMF 80°C, 74%
i) HCl, dioxane, rt, quant.

Conclusion

The production of two novel and highly functionalized pyrrolidine-based libraries has been successfully achieved, using the [3+2]-cycloaddition reaction. Owing to the production process that we have developed at EDELRIS, we were able to deliver these two attractive libraries in full compliance with the quality standards defined by the ELF-consortium, and in respect of the defined timelines. We are continuing the adventure by working further towards the development and production of innovative chemical libraries, in respect of the same quality and timeline standards as shown above.

1- The European Lead Factory: Game Changing for Innovative Medicine. Rijnders, T.; Tzalis, D.; Ottow, O.; http://www.europeanleadfactory.eu; Innovative approaches to the design and synthesis of small molecule libraries. Nelson, A.; Roche, D.; *Bioorganic & Medicinal Chemistry*, **2015**, *23*, 2607

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3- **P**roduction **S**uccess **R**ate (P.S.R.)