1. Current literature highlights

1.1. Use of a catalytic Povarov reaction to generate a library of tetrahydroquinolines

The Povarov reaction is a convenient and rapid approach to the preparation of tetrahydroquinolines by the [4 + 2] cycloaddition of N-aryl imines with electron-rich olefins. This reaction, using a chiral urea/Brønsted acid catalyst, is at the heart of a new solid-phase approach to the preparation of a large library of stereochemically and structurally diverse tetrahydroquinolines.  

The study initially embarked on a selection of appropriate partners for the Povarov reaction that provided an alcohol for immobilisation onto a solid support and functionality to allow diversification of the product scaffold. An imine glyoxylate (1) accessible by the condensation of an aniline (2) and ethyl glyoxylate (3) was chosen as the 4-π component. This building block was attractive for its low molecular weight and the presence of an aromatic bromide that provided further diversification through palladium-mediated cross-coupling chemistry. Additionally, the tetrahydroquinoline product would have an epimerisable centre next to the ester that could be used to engender stereochemical diversity.

The dienophile partner selected was a 2,3-dihydropyrrole derivative (4), suitably protected by an Fmoc group that was shown to be compatible with good yields and high levels of diastereoselectivity and enantioselectivity in the production of the Povarov tetrahydroquinoline product (5). The reaction was catalysed by the chiral urea (6) and using anhydrous p-toluenesulphonic acid as the Brønsted acid.

Although the endo diastereoisomer product (5) predominated, treatment with sodium methoxide in methanol solution gave only one epimer as the methyl ester (7) by converting the endo-diestereomeric product into the more thermodynamically favoured exo-product. In fact, careful control of the stereochemistry in this fashion resulted in the production of four diastereoisomers in large quantities to act as the starting point for library generation. Reduc-
tion of the methyl ester using lithium borohydride gave an alcohol that could be immobilised on SynPhase lanterns following methylation of the secondary amine.

This then set the stage for the introduction of diversity at two positions on the scaffold. Capping of the deprotected pyrrolidine secondary amine 8 was undertaken with a number of isocyanates and carboxylic acids, and Sonogashira and Suzuki cross-coupling chemistries on the bromide generated a library of 2328 different tetrahydroquinolines (e.g. 9) suitable for subsequent drug discovery screening.

2. A summary of the papers in this month’s issue

2.1. Polymer supported synthesis

A straightforward solid phase-based strategy for the rapid generation of two small libraries of trans-3-alkyl-substituted β-lactams has been described. For a glycine-derived library, a controlled excess of nonactivated acid chlorides was used to prevent oxazino-one formation. The second library involved the attachment of Fmoc-protected p-aminophenol to Wang resin for the preparation of analogues of known cholesterol absorption inhibitors. This strategy allowed the introduction of diversity in the three variable positions of the β-lactam ring.

A solid-phase methodology to construct aminobenzimidazole tethered sultams and benzothiazepinones from commercial amino acids, amines, carboxylic acids, and sulphonyl chlorides has been described. Coupling of Fmoc-Cys(Trt)-OH to a resin-bound aminobenzimidazole scaffold provided an essential precursor for the construction of a variety of seven membered benzofused cyclic sulphonamides and thiazepinones via palladium catalysed Buchwald–Hartwig type intramolecular cyclization.

2.2. Solution-phase synthesis

A convenient in situ method has been described for the reductive removal of an amino group on an antraquinone system. The reaction proceeds smoothly within a few minutes yielding novel antraquinone derivatives in excellent yields. The method has been applied to a variety of 1-amino-antraquinone derivatives, allowing access to a large library of new compounds with potential as pharmacological tools for studying purinergic signalling.

An efficient and facile L-proline-catalysed three-component coupling of 2-hydroxybenzaldehyde, 5,5-dimethyl-1,3-cyclohexanedione (dimedone), and indole has been accomplished under mild aqueous micellar conditions to deliver a small library of 9-((1H-indol-3-yl)-xanthen-4-(9H)-ones of potential biological relevance. Under optimised conditions, the reaction was highly selective toward the target compounds and essentially free from competitive two-component by-product formation. A synthetic protocol was designed that gave access to a small compound library.

Novel pyrano[2,3-d]pyrimidine-2,4,7-triones have been synthesised in 90–97% yield via a three-component reaction of an aromatic aldehyde, Meldrum’s acid, and barbituric acid in the presence of 10 mol% K2CO3 under microwave irradiation. This is the first protocol to be reported for the synthesis of these compounds and this approach offers utility in the construction of diverse chemical libraries of ‘drug-like’ molecules.

2.3. Scaffolds and synthons for combinatorial libraries

No papers this month.

2.4. Solid-phase supported reagents

A simple, eco-friendly, and versatile method for the selective synthesis of 1,2-disubstituted benzimidazoles and quinoxalines in a water–methanol (1:1) mixture with the aid of resin-bound hexafluorophosphate ion as catalyst has been reported. The method is also effective for the incorporation of quinoxaline nucleus at the A ring of pentacyclic triterpenoid, friedelin. A plausible mechanism for the formation of disubstituted benzimidazole has also been suggested.

CuO nanoflakes bound on polystyrene beads (PS-CuO) have been prepared through the oxidation of copper(I) bromide in a suspension of polystyrene. The use of PS-CuO as a catalyst in the presence of KO8Bu in the coupling reactions of aryl bromides and amines afforded the coupled products with a yield range of 15–89%. This catalytic system also gave access to a key fragment in good yield for the synthesis of Imatinib (Gleevec).

An efficient synthesis of formylacetic esters via ozonolysis of trans-β-hydromiconic esters followed by a solid-supported triphenylphosphine reduction has been developed. In addition, an extension toward formylacetic amides and a one-pot preparation of more stable intermediates which can be used for further transformations were also described.

Organocatalysis has been assessed for the first time in the synthesis of purine and pyrimidine acyclic nucleosides providing high yields and straightforward work-up procedures. Nucleobases containing aldehydes are catalytically ligated (C–C bond formation) to acetone or to phosphate-containing ketones by means of pyrrolidine or silica-immobilised piperazine as amine-based organocatalysts.

Solid supported palladium nano/microparticles were found to be active catalysts to perform mono- and β,β-double-Heck reactions. Different β-unsubstituted and substituted alkenes including acrylate, methacrylate, crotonate, styrene, acrylonitrile, and acrylamide were investigated successfully for mono- and β,β-double-Heck reactions with aryl iodide under milder reaction condition.

2.5. Novel resins, linkers and techniques

A rapid microwave-assisted solution-phase peptide synthesis protocol has been developed. The reaction temperature of 50 °C and short coupling time of 28 min gave racemisation-free synthesis of peptides in 50–80% yield. The method is applicable with equal ease in coupling both side-chain protected and unprotected amino acids indicating reactive-functional group tolerance and high atom-economy.
2.6. Library applications

No papers this month.

References


Further reading

Papers on combinatorial chemistry or solid-phase synthesis from other journals