1. Current literature highlights

1.1. Multicomponent reactions by microwave assisted continuous flow synthesis

In the search for ideal synthetic methodology, chemists seek one step reactions that generate structural complexity in quantitative yields. One of the more effective reactions that offers the promise of ideal chemical conversion is the multicomponent reaction, where several reagents react in the same reaction vessel to give complex products. A recent paper describes a high-yielding and rapid multicomponent approach to heterocycles using microwave assisted flow chemistry that can be scaled to the production of libraries.\(^1\)

The formation of tetrahydropyrazolo[3,4-b]quinolin5(6H)-ones (1) was achieved in seconds and in excellent yields by reacting equal quantities of dimedone (2), aminopyrazole (3) and various substituted benzaldehydes (4) using a microwave-assisted process. The three reagents were introduced into the microwave through three separate capillaries at the same concentration and rate, and were mixed prior to entering the magnetron. Optimisation was achieved by varying the capillary diameter, microwave power, flow rate, reactant concentration and solvent. In particular solvent choice was important as higher-boiling solvents such as DMSO and DMF were found to be ideal due to their high solvating power and ability to absorb microwaves.

Overall, the reactions were found to proceed in seconds in greater than 90% yield. It was found that microwave irradiation was essential for conversion as in the absence of microwaves, only trace amounts of expected products were detected. It was also found possible to increase the output of this system by running the reaction flow for 29 minutes and providing several hundred milligrams of product. In a separate study, microwave-assisted flow chemistry was used to make several furan derivatives from aldehydes, an isonitrile and dimethyl acetylene dicarboxylate.

1.2. Libraries of triazole-containing HIV protease inhibitors

HIV-1 protease has been recognised as a significant target for the treatment of HIV infections and AIDS. A recent report describes the use of the copper (I)-catalysed azide-alkyne cycloaddition as a method of making triazole inhibitors. When using this ‘click’ chemistry in conjunction with the direct screening of crude reaction mixtures, it has rapidly led to the identification of potent protease inhibitors.\(^2\)

Using in silico screening of triazole-containing structures by docking into the active site of HIV-1 protease, and calculating binding energies and the propensity of these structures for further derivitisation, a number of putative leads including compound (5) were chosen for exploration.

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through a synthetic program. It was planned that a number of amino azide core molecules could be cyclised with alkynes and then reacted with acylating reagents to give diverse arrays of potential inhibitors. Preparation of the $\alpha$-amino azide fragments (6) was the most challenging part of the approach, and methods were devised to generate these intermediates from the corresponding $\alpha$-amino acid precursors, using both the syn and anti isomers. The $\alpha$-amino azides (6) were subjected to the copper catalysed cycloadditions with a selection of 69 alkynes to generate a library of triazoles (7).

After reaction was assessed to be complete, as no protecting groups were used and reaction by-products were minimal, the crude reaction mixtures were diluted to 5 μM into 96-well plates and submitted directly to inhibitory assays against HIV-1 protease. Following the identification of compounds with $K_i$ values in the range of 90 nM, optimisation of the structures occurred through the preparation of focused libraries that fine-tuned both the azide and alkyne portions of the structure. It was determined that the triazole ring is an essential fragment for compound activity, and cannot be replaced with a simple amide bond. Of all the compounds synthesised, the triazole (8) was found to be amongst the best HIV protease inhibitors with a $K_i$ value of 8 nM.

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

2.1. Solid-phase synthesis

A systematic study on the asymmetric allylation of aldehydes on solid support has been reported. Different kinds of chiral allylboron reagents with complementary direction of stereoinduction were applied successfully in this reagent-controlled transformation. The homoallylic alcohol products are generated with high levels of stereoselectivity and in high yields. The crotylation of aldehydes on solid support employing (E)- and (Z)-Ipc2crotylborane also proceeded with very high levels of stereoinduction and in high yields. Applications of this methodology for the synthesis of compound collections by subsequent modifications of the allylic moiety have been described. In particular, a collection of $\gamma$- and $\delta$-lactones, including a natural product, has been synthesised by means of a cyclo-release approach. In addition, a procedure for the long-standing problem of the hydrogenation of double bonds on solid support has been reported.

2.2. Solution-phase synthesis

$\alpha$-Phenylenediamines react with an array of ketones in PEG-400 at 60 °C under an atmosphere of air in the presence of KOH to afford the corresponding quinoxalines in good yields.

Mechanistic investigations into the multi-component synthesis of pyridine-3,5-dicarbonitriles has established a reaction pathway, particularly clarifying the role of aerobic oxidation in conversion of the intermediate 1,4-dihydro-pyridines into the final products. Based on such improved understanding of the reaction mechanism, optimised conditions for the preparation of compound libraries based on this core structure have been developed and these represent a significant improvement in yield over existing protocols. In particular, microwave assisted synthesis was found to provide a procedure suitable for high-throughput synthesis of pyridine-3,5-dicarbonitrile libraries.

The chemistry of 1,2,3,4-tetrahydro-1,5-naphthyridines and 2,3,4,5-tetrahydro-1H-pyrido[3,2-b]azepines has been explored with the goal of discovering reactions at N1 suitable for library development. Epoxide openings, Pd-catalyzed N-arylations, DEPBT-promoted acylations, and urea formation through the reaction with isocyanates were all successful. The epoxide opening chemistry using homo-chiral epichlorohydrin followed by epoxide reclosure and a second nucleophilic opening led to the preparation of a small 24-membered library.

The palladium-catalysed highly efficient three component coupling (TCC) reactions between chromones, allylic acetate, and alcohols, which lead to a library of multiply substituted chromones, has been described. The activity of various palladium catalysts, such as Pd(PPh$_3$)$_4$ and Pd$_2$dba$_3$·CHCl$_3$ and their combination with various bisphosphine ligands, was investigated by using THF as a solvent, which revealed that Pd(PPh$_3$)$_4$ catalyst was the best one.
A small tri-β-peptide library has been prepared starting from three enantio- and diastereopure azido acids. Fluorous tagging followed by two cycles of azide reduction, fluororous solid phase extraction (f-SPE), peptide coupling with the original azido acids, and f-SPE provided 27 protected azido peptides. Reduction and HPLC purification provided 25 of the 27 targeted tri-β-peptides in acceptable yields and excellent purities.8

2.3. Scaffolds for combinatorial libraries

The synthesis of 1-(2-nitrophenylethyl) caged O-phosphoro- thioylserine, -threonine, and -tyrosine derivatives has been reported. These amino acid building blocks can be directly incorporated into peptides by Fmoc-based solid phase synthesis as their pentafluorophenyl esters or as symmetric anhydrides. Upon irradiation with UV light, the thiophosphate group, representing a hydrolysis resistant phosphate analogue, has been revealed.9

2.4. Solid-phase supported reagents

The regio- and diastereoselective synthesis of pyrrolidine derivatives through 1,3-dipolar cycloaddition of an azomethine ylide and dipolarophile mediated by KF/Al₂O₃, a versatile solid supported reagent, has been reported. KF/Al₂O₃ is sufficiently basic such that it can deprotonate aziridine esters to generate azomethine ylides and it also functions as a solid supported catalyst leading to the cycloadduct rather than the Michael adduct.10

2.5. Novel resins, linkers and techniques

No papers this month.

2.6. Library applications

FK-228 is a potent histone deacetylase (HDAC) inhibitor with tremendous therapeutic potential against a wide array of human cancers. The development of a library of analogues that share FK-228’s novel mechanism of activation and HDAC inhibition has been described.11

Hairpin pyrrole-imidazole (Py-Im) polyamides are programmable oligomers that bind the DNA minor groove in a sequence-specific manner with affinities comparable to those of natural DNA-binding proteins. These cell-permeable small molecules have been shown to enter the nuclei of live cells and downregulate endogenous gene expression. A library of 27 hairpin Py-Im polyamides, which bind seven-base-pair sequences of the general form 5’-WWGNNNW-3’ (where W = A or T, N = W, G, or C) have been prepared. A table of binding affinities and sequence contexts for this completed 27-member library has been assembled.12

Seven PNA-encoded combinatorial libraries targeting proteases and phosphatases with covalent reversible and irreversible mechanism-based inhibitors have been prepared. The libraries have been synthesised using modified PNA monomers, which dramatically increase the water solubility of the libraries in biologically relevant buffers. The libraries were shown to selectively inhibit targeted enzymes.13

In a search for new leads towards potent antimicrobial agents, an array of novel N-morpholinoacetyl-2,6-diaryl-piperidin-4-ones has been synthesised and their in vitro antibacterial activity against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Salmonella typhi and antifungal activity against Candida albicans, Rhizopus sp., Aspergillus niger and Aspergillus flavus were evaluated.14

The papain-family cathepsins are cysteine proteases that are emerging as promising therapeutic targets for a number of human disease conditions ranging from osteoporosis to cancer. The synthesis of focused libraries of epoxysuccinyl-based inhibitors and their screening in crude tissue extracts has been reported. A number of potent inhibitors that display selectivity for endogenous cathepsin targets both in vitro and in vivo have been identified.15

The potential for the use of Clostridial neurotoxins as bioweapons makes the development of small-molecule inhibitors of these deadly toxins a top priority. Recently, screening of a random hydroxamate library identified a small-molecule inhibitor of C. botulinum Neurotoxin Serotype A Light Chain (BoNT/A-LC), 4-chlorocinnamic hydroxamate, a derivative of which has been shown to have in vivo efficacy in mice and no toxicity. The X-ray crystal structures of BoNT/A-LC in complexes with two potent small-molecule inhibitors has been described.16

Chitinases hydrolyse the β(1,4)-glycosidic bonds of chitin, an essential fungal cell wall component. Specific inhibitors of these enzymes would be useful as tools to study their role in cell wall morphogenesis and could possess antifungal properties. The crystallographic structure of a fungal “plant-type” family 18 chitinase, that of Saccharomyces cerevisiae CTS1 has been described. A library screen against ScCTS1 yielded hits with Ki values as low as 3.2 μM. Crystal structures of ScCTS1 in complex with inhibitors from three series reveal striking mimicry of carbohydrate substrate by small aromatic moieties and a pocket that could be further exploited in optimisation of these inhibitors.17

References

Further reading

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


