1. Current literature highlights

1.1. A new diethylsilylacetylenic linker for solid phase synthesis of steroids

It has been established for some time that the presence of an ethynyl group at the 17-alpha position confers much stability on steroids. The hydroxy group is protected from oxidation and metabolic conjugation in vivo. Consequently a number of pharmaceuticals contain the hydroxy acetylenic group to enhance their stability and biological activity. Examples include the synthetic estrogens such as ethinylestradiol and quinestrol, and progestogens such as norethisterone and levonorgestrel.

Indeed, steroids are used for a wide range of conditions including treatment of autoimmune inflammatory disease and a variety of cancers, and new methods for the introduction of the 17-ethynyl group could have value for the synthesis of novel examples. Traditionally, the acetylene is introduced by addition to the carbonyl at the end of the synthesis. A recent paper describes the use of a novel linker that permits the immobilisation of the acetylene to a solid support and the introduction of molecular diversity elsewhere in the steroidal framework.¹

It was hypothesised that a polystyrene-diethylsilane (PS-DES) resin could be an effective support to link and subsequently release an acetylenic group after structural modification elsewhere in the molecule. The loading and release conditions were first optimised using the ethynyl steroid 1. Formation of an organolithium and reaction with PS-DES-Cl generated the immobilised steroid. Cleavage was found to proceed most effectively using HCl in methanol and dichloromethane. Overall, it was possible to load and cleave the acetylenic steroid from the resin with 55% recovery.

Having demonstrated that the acetylenic steroids could be loaded and released from resin, the study proceeded to design and make a library of 21 diverse 2β-piperazino derivatives (3) anticipated to have antiproliferative activity on HL-60 cancer cells. The library incorporated three amino acids (pyridylalanine, proline and phenylalanine) and was finally capped with seven different carboxylic acids. Compound 4 was made on solid support to check the compatibility of the linker with the sequence of reactions required to make the library compounds. On completion of the synthesis, compounds were isolated in between 80% and 97% purity as assessed by HPLC, and 1H NMR spectra also confirmed successful synthesis.
The diethylsilylacetylenic linker has thus been shown to be an efficient tool for the preparation of hydroxy acetylenic compounds.

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

2.1. Solid-phase synthesis

Phosphodiester-type adenylated (AMPylated) Ser, Thr, and Tyr derivatives have been developed for Fmoc solid-phase peptide synthesis of AMPylated peptides without significant side reactions including dehydroalanine formation.

2.2. Solution-phase synthesis

A library of benzotriazepines has been synthesised employing microwave-mediated synthesis, supported resins and parallel synthesis methodology. The compounds generated may have interesting applications in medicinal chemistry, such as targeted for GPCR receptors.

Multi-component reactions (MCRs) are extremely important owing to their wide range of applications in medicinal chemistry for the production of diversified structural scaffolds and combinatorial synthesis. An intramolecular Ugi reaction of 2-(2-formyl-1H-indol-1-yl)acetic acid with aryl amines and isocyanides has been developed to produce a novel class of N-alkyl-3-oxo-2-aryl-1,2,3,4-tetrahydropyrazino [1,2-alindole-1-carboxamides.

A comprehensive library of N- or 1-substituted indoles has been formed by conjugate additions of indoline with Michael acceptors followed by an oxidation step. Using N-substituted indoles as key Michael donors, the synthesis of 1,3-disubstituted indoles was also accomplished.

A new protocol has been developed for the efficient synthesis of structurally diverse 1H-pyrazolo[1,2-b]phthalazine-1,2-dicarboxylates and 1H-pyrazolo[1,2-a]pyridazine-1,2-dicarboxylates. These compounds have been prepared via a four-component reaction of hydrazine hydrate, dialkyl acetylenedicarboxylates, isocyanides and various cyclic anhydrides such as succinic anhydride, maleic anhydride and phthalic anhydride. Broad substrate scope and mild reaction conditions make this a useful and attractive process for the synthesis of libraries of these important compounds.

2.3. Scaffolds and synthons for combinatorial libraries

No papers this month.

2.4. Solid-phase supported reagents

A novel, simple, and efficient synthetic protocol has been developed for the synthesis of spiro[indoline-3,4'-pyrazolo-[3,4-e][1,4]thiazepine] diones, by using bioglycerol-based sulfonic acid functionalised carbon as a recyclable catalyst. This new protocol produces novel heptacyclic spirooxindole derivatives in good to excellent yields, with operational simplicity and recycling of the catalyst. The catalyst can be prepared by a simple adaptable procedure from an inexpensive and readily available bio-glycerol and found to be recoverable and reusable up to four cycles without any loss of activity.

Nanocrystalline ZnO was found to be a highly efficient heterogeneous catalyst for the guanylation of amines with various carboximides to afford N,N'-trisubstituted guanidines in excellent yields. The catalyst was easy to handle even under atmospheric conditions and can be easily recovered by centrifugation and reused for five cycles with consistent activity.

2.5. Novel resins, linkers and techniques

A straightforward method for creating a bifunctional support possessing pre-defined ratios of amine and chloromethyl groups based upon a controlled conversion of standard Merrifield resin has been presented. This approach avoids extensive optimisation of reactant concentrations and reaction conditions, and will allow for efficient, predictable and reproducible co-immobilisation of molecular species.

2.6. Library applications

As part of an ongoing project to develop new molecular probes for estrogen receptor-alpha, the utility of internally-substituted asymmetric biphenyls as a proteomic scaffold has been explored. Synthetic methods for preparing the requisite substituted-bromophenol precursors, their further elaboration, and the subsequent Suzuki–Miyaura coupling of these sterically-hindered and electronically-rich aromatic systems has recently been described. The results provide an efficient route for the generation of libraries of novel asymmetric biphenyl compounds as potential proteomimetics.

A two-step strategy for the synthesis of arrays of tricyclic tetrazolo-fused benzotriazepines and benzodiazepinones has been investigated. The protocol uses ortho-N-Boc phenyl isocyanides and phenylglyoxaldehydes or ethyl glyoxylate in the four-component Ugi-azide reaction to afford MultiComponent Reaction products. A subsequent acidic treatment allowed a simultaneous deprotection–cyclisation leading to the final products.

P-glycoprotein (P-gp) effluxes a diverse set of drug substrates out of cells in an ATP dependent manner, thereby limiting the effective accumulation of therapeutic agents. The use of click chemistry to rapidly generate bivalent quinine dimers, containing an intervening triazole ring, as potential inhibitors of P-gp mediated efflux has been described. A small library of potent P-gp inhibitors with varying tether lengths has been reported, with the best dimer demonstrating low micromolar efficacy.

The potential use has been investigated of a fluorescent tag system based on the 7-(1H,1,2,3-triazole-4-yl)coumarin fluorophore having a fluorous moiety and a polyethylene glycol (PEG) spacer placed at opposite ends. This system was used as a tool for a step-wise and comparative evaluation of small molecule microarray fabrication process.

References


Further reading

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

