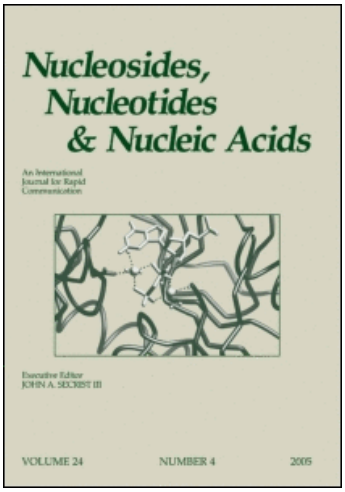

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MCR III[1]. Multicomponent Reactions and Their Libraries, a New Type of Organic Chemistry of the Isocyanides and Phosphorus Derivatives.

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MCR III[1]. MULTICOMPONENT REACTIONS AND THEIR LIBRARIES, A NEW TYPE OF ORGANIC CHEMISTRY OF THE ISOCYANIDES AND PHOSPHORUS DERIVATIVES.*

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ABSTRACT: Various new one-pot multicomponent reactions (MCRs) of C^{II} and P^{III} derivatives and their libraries are described here. The preparation of some nucleobase- and phospholipid compound libraries by MCRs have been carried out.

The recently developed new MCRs and their libraries have several advantages over the traditional preparative organic chemistry. This has profoundly changed many fields of chemistry[1-5]; particularly the production and investigation of large numbers of chemical compounds is much more efficient than any previous methods[6-9]. Such one-pot syntheses can be carried out with less effort, quicker and in most cases with much better yields. Single compounds or simultaneously produced large collections of different chemical products can thus be prepared much better than through usual multistep syntheses.

When a desired product is prepared from three or more starting materials, this usually requires several sequentially performed reactions. One or two components react per step. All intermediate products are isolated and purified before they are combined with the next components.

In principle, all chemical reactions equilibrate, but in practice many proceed irreversibly. Products are thus formed in high yields, if no competing formation of by-products takes place. In a few cases the products can be formed from several different starting materials by 'one-pot' sequences of irreversible procedures[10,11].

* Dedicated to the 70th birthday of T. Mukaiyama

An increasing variety of chemical products can be obtained by MCRs whose starting materials and intermediates can equilibrate, while the final formation of the desired product is formally irreversible and no competing formation of by-products takes place[12].

It is likely that 'one-pot' MCRs have been the basis of various chemical compounds found in living cells[5,16]. It is also quite likely that the relative free energy of the competing equilibria of various cellular MCRs has had a profound influence in setting the pace of the molecular evolution.

Most MCRs take place when pairs of ions or radicals combine with atoms, whose valency increases by two, like $C^{II} \Rightarrow C^{IV}$ or $P^{III} \Rightarrow P^{V}$. In the following we show two examples of libraries, one generated by Ugi reaction and one by programmed phosphorous chemistry.

Unprotected α-amino acids together with isocyanides and nucleobase derived aldehydes in methanol react smoothly to form iminodicarboxylic acid derivatives in more than 90% yield (FIG. 1). With all commercially available α-amino acids, isocyanides and suitable derivatized nucleobases, several hundred thousand compounds with the common iminodicarboxylic acid derivative scaffold can be produced[13]. These compounds promise to be highly active antiviral and anticancer agents.

Searching for highly active five-membered cyclic phosphorylating reagents[14], Chattopadhyaya et al. and our group developed the benzoxazaphosphole, 2-(N-methyl-N-phenyl)-2,3-dihydro-3-methylsulfonyl-1,3,2-benzoxazaphosphole and its 5-chloro- and 5,7-dichloro derivatives which, after acidic activation, can react stepwise with nucleophiles[10]. The most efficient activation reagent turned out to be N-methylanilinium hydrochoride (MAC).

The chemical reactivity of these reagents is based upon the different basicities of the groups attached to the P-atom. The exocyclic N-methyl-N-phenyl-group is protonated first and then replaced by the first added nucleophile. The next step involves a second nucleophilic attack on the phosphorus by either a second alcohol or a phosphate accompanied by cleavage of the endocyclic P-N-bond and thus opening of the five-membered ring. In a third step the aryloxy group can be replaced by a third nucleophile, before the compound finally can be oxidized to give the P^{V}-product. In the case of a binucleophilic reagent , if e.g. a diol or a pyrophosphate derivative is used in the second step, both, the $MeSO_2N$-P-bond cleavage and the displacement of the aryloxy group can take place leading to an triple-displaced cyclic P^{III} intermediate, which then again can easily be oxidized to the P^{V} product (FIG. 2).

These P^{III}-based MCRs are not only useful to generate libraries of modified nucleotides, which for example can be screened for their antiviral activity, they also open the access to

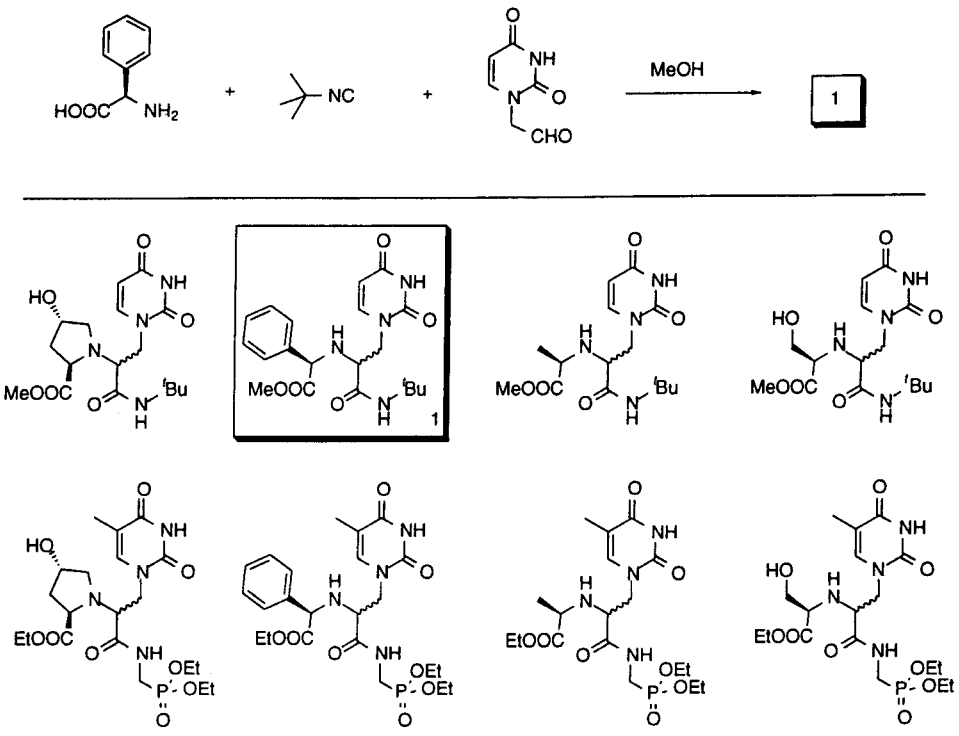

FIG. 1: Part of a nucleobase library generated by Ugi-MCR.

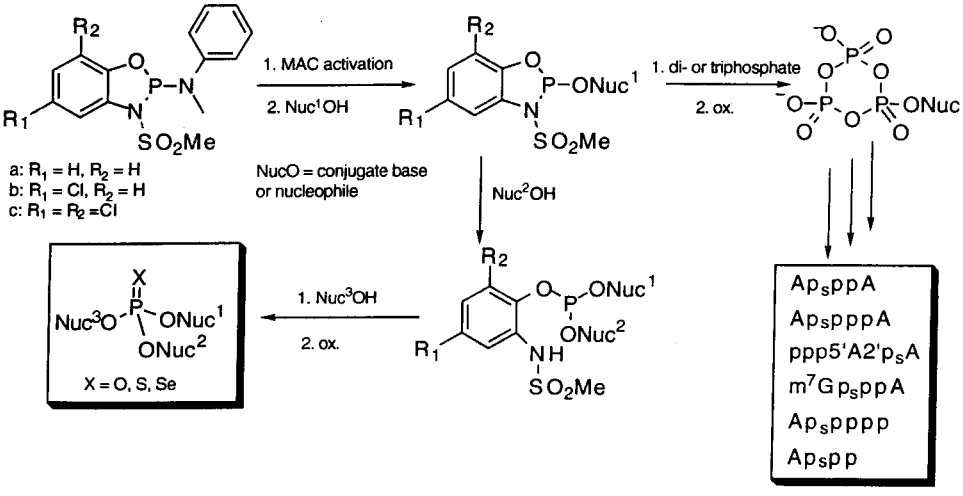

FIG. 2: Synthesis of phosphorus triester by a programmed sequential one pot synthesis.

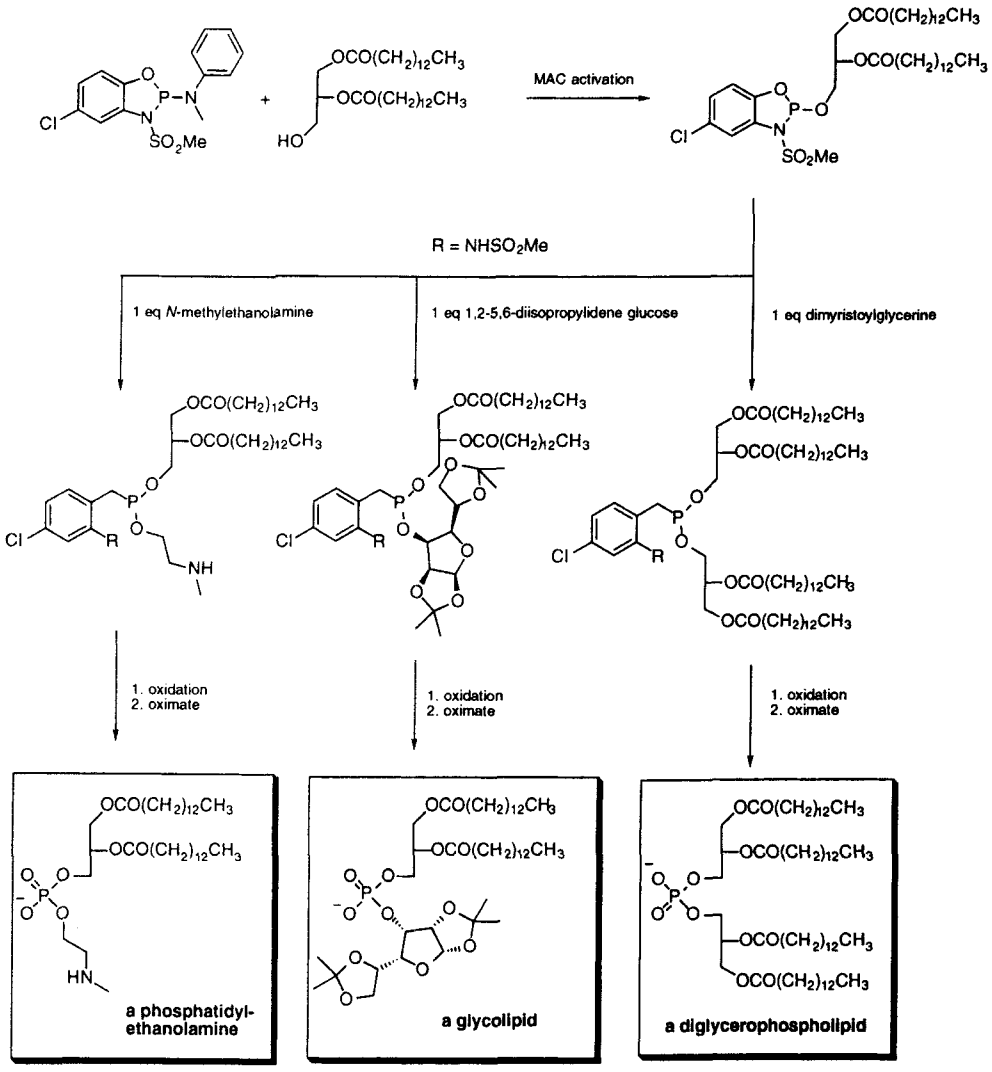

FIG. 3: One pot synthesis of natural product related phosphorus ester libraries.

other classes of interesting and biologically active organo-phosphorus components, e.g. the class of phospholipids[15] and nucleopeptides[16].

In order to synthesize phospholipid derivatives we reacted 2-(N-methyl-N-phenyl)-2,3-dihydro-3-methylsulfonyl-1,3,2-oxazaphosphole with dimyristoylglycerol as the first nucleophile under MAC activation conditions. By addition of another nucleophile, e.g. a second dimyristoylglycerol, an ethanolamine or a sugar compound, cleaving of the

endocyclic P-N-bond occurs. After oxidation and cleavage of the aryloxy group e.g. phosphatidyl choline derivatives or glycolipids can be obtained (FIG. 3).

Currently our group investigates an analogous sequence of reactions in order to synthesize nucleopeptides with the hydroxyl group of serine, threonine or tyrosine as the first added nucleophiles, followed by treatment with a nucleoside.

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