Versatile Synthons and Microwave Dielectric Heating: A combination that Reduces Substance Production Time

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The bottleneck from biology to clinical trials is believed to be chemistry development. It is believed that this bottleneck is somewhat broadened by the use of microwave dielectric heating. The technology has been shown to reduce reaction times and often ameliorate the yields. There is no risk however, that the time gain of the microwave-assisted reaction step drowns in other time-consuming procedures such as preparation of starting materials and reagents and purification of intermediates and final products. In organic chemistry and in medicinal chemistry in particular, the use of versatile synths and scaffolds that trigger cascade or domino reactions are of great interest. They introduce high diversity with minimal effort as the need for work-up and purification between the different reaction steps is eliminated. Three such synths are N,N-dimethylformamide diethylacetal, triphenylphosphorane ethenone and isatoic anhydride.

N,N-dimethylformamide diethylacetal

With N,N-dimethylformamide diethylacetal (1) as starting point a substantial number of pharmacologically interesting heterocycles can be synthesized. The availability of starting materials that can form activated alkylaminopropenones (2) or alkylaminopropenones (2) with (1) is great. In a subsequent step these intermediates were used to form heterocycles of considerable diversity. The intermediates are formed in 53-93% yield based on LC/MS analysis and used without further purification.

Isatoic anhydride

Isatoic anhydrides could be used as versatile synths for the synthesis of a diverse set of heterocycles. It was used for the synthesis of 12 different substance classes. Isatoic anhydrides were reacted with amines, amides, hydrazides, isothiocyanates, diketo substrates, aminocicads, amino-, thio- or hydroxy-anilines and in a three component reaction with aldehydes and amines. Conventionally, the synthesis of the products requires hours to days to accomplish.

Triphenylphosphoranylidene ethenone

Triphenylphosphoranylidene ethenone is a multipurpose reagent that can be used to introduce a carbon-carbonyl building block. This is accomplished by a cascade reaction comprising an addition and a Wittig olefination. Triphenylphosphoranylidene ethenone and aldehydes, esters or ketones with an adjacent hydroxy or amine group in α- or β-position react to form various heterocycles such as tetranoic acids, tetronates, coumarines, benzoxepinones and their N-analogues. The reaction times are conventionally 12-48h under refluxing conditions.

References:


Propenone Chemistry

Propenones (2) are formed by a condensation reaction between (1) and a methylene group of a 2-substituted acetic acid derivative. 5-Dimethylamino propenones react with 1,3-dinucleophiles such as 1,3-dicarbonyl compounds, α-aminoheterocycles and 2-pyridylcarboxamid to form two-ring-systems by a two- or three-step mechanism. In the first step the dimethylamino group is substituted by the dinucleophile, which is followed by the displacement of the ethanol of the ethyl ester.

General reaction conditions:

α, 2 mmol, propenones, 1.2 eq. dinucleophiles, acetic acid/DMF 4:1, 180 °C, 5 min.
Overall yields: 30-90%

Triphenylphosphoranylidene ethenone

Triphenylphosphoranylidene ethenone can also be involved in a three-component, one-pot synthesis of α,β-unsaturated amides. In fact, the mechanism is the same as in the cyclisation of β-keto esters also form isoxazoles and pyrazoles when reacted with hydroxylamine or hydrazine. Overall yields:

21-60%