

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

J. Westman, K. Orrling, A. Franzén, R. Lundin, M. Östbye, A. Hurynowicz
Personal Chemistry, Kungsgatan 76, 753 18 Uppsala, Sweden

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 a 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 synthons and scaffolds that trigger cascade or

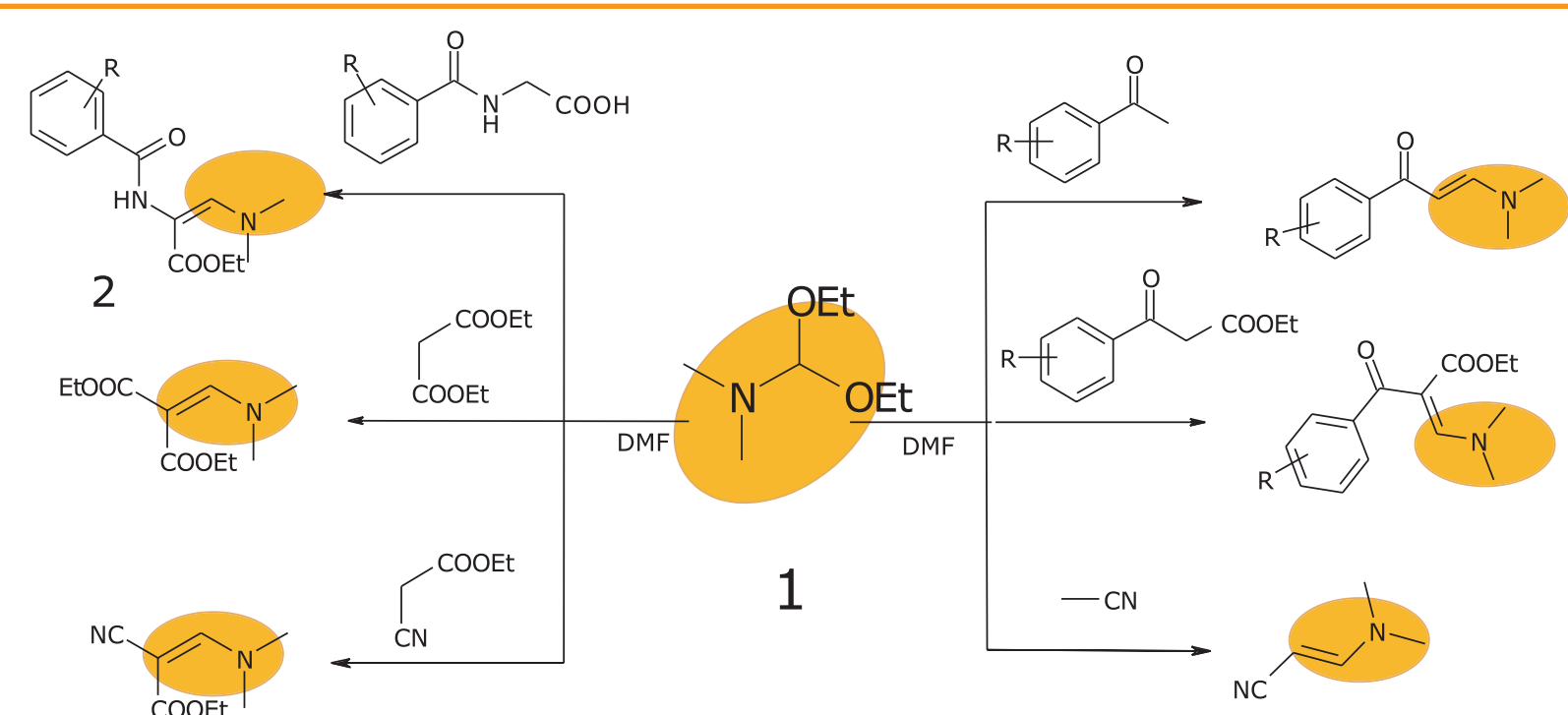
domino reactions are of great interest. They introduce high diversity with minimal effort as the need for work-up and purification between the different reaction steps is eliminated. Three such synthons are N,N-dimethylformamide diethylacetal, triphenylphosphorane ethenone and isatoic anhydride.

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

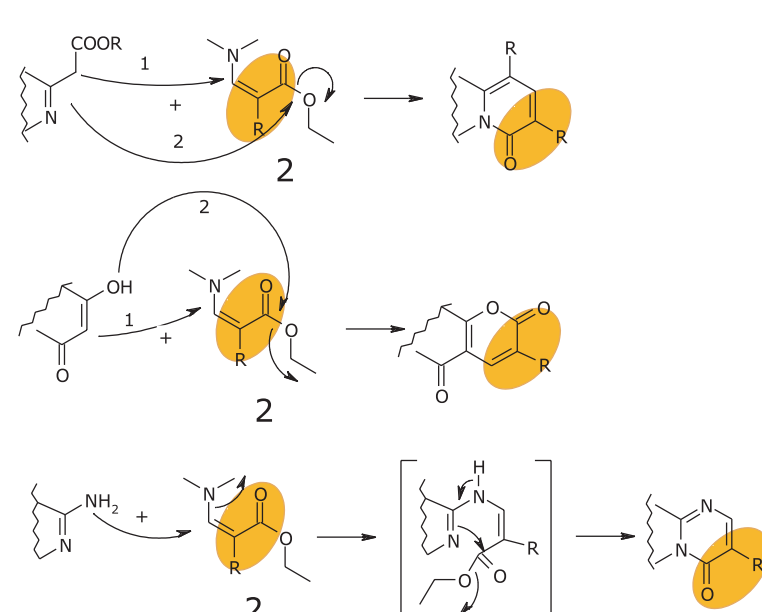
materials that can form activated alkylaminopropenoates (2) or alkylaminopropenones (3) with (1) is great. In a subsequential step these intermediates

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.



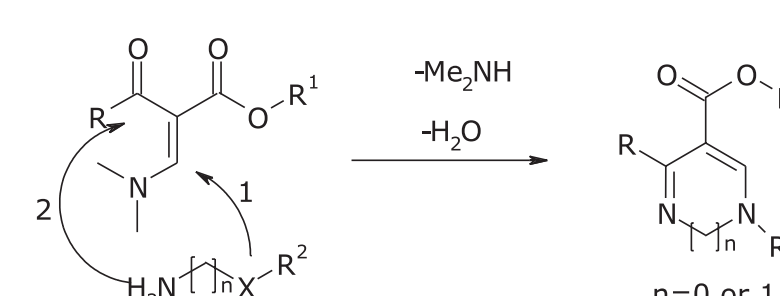
Propenoate Chemistry

Propenoates (2) are formed by condensation reactions between (1) and a methylene group of a 2-substituted acetic acid derivative. 3-Dimethylamino propenoates react with 1,3-dinucleophiles such as β -dicarbonyl compounds, α -amino-heterocycles and 2-pyridylacetonitrile 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.

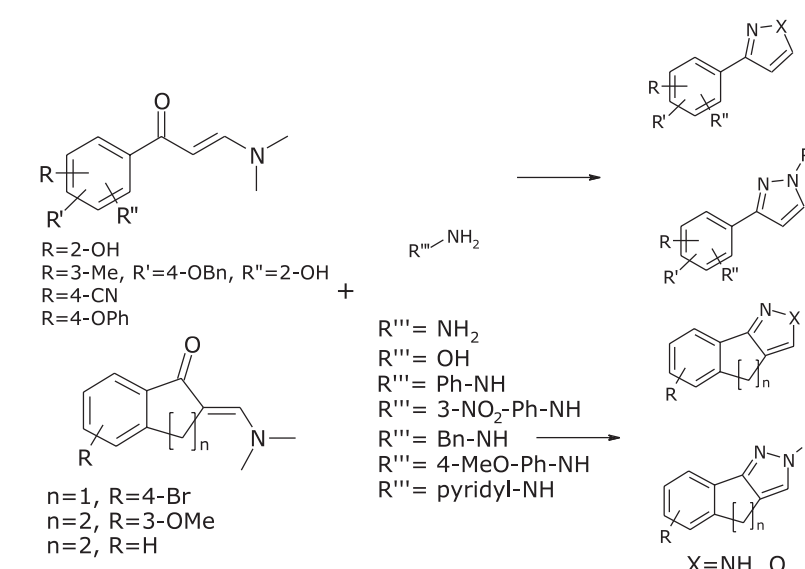


Propenone Chemistry

Propenones (3) are formed by a condensation with a methyl or methylene group adjacent to a keto functionality. Propenones react with dinucleophiles in a two-step reaction where the substitution of the dimethylamino group is followed by a condensation with the keto functionality of the propenone.

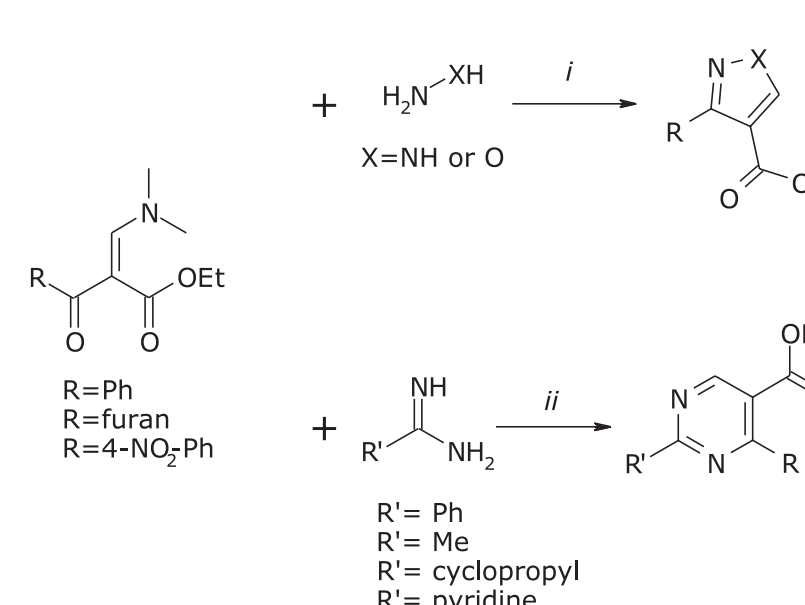


Propenones from (1) and acetophenones give isoxazoles and pyrazoles in 31%-100% and 45%-82% yield respectively when reacted with hydroxylamine or hydrazine.



Reaction conditions:
acetic acid/DMF 4:1,
180 °C, 5 min.
Overall yields: 31-100%

Propenones from (1) and β -keto esters also form isoxazoles and pyrazoles when reacted with hydroxylamine or hydrazine respectively. Substituted pyrimidines were synthesized by reacting the propenones with amidines in DMF with KOH as base.

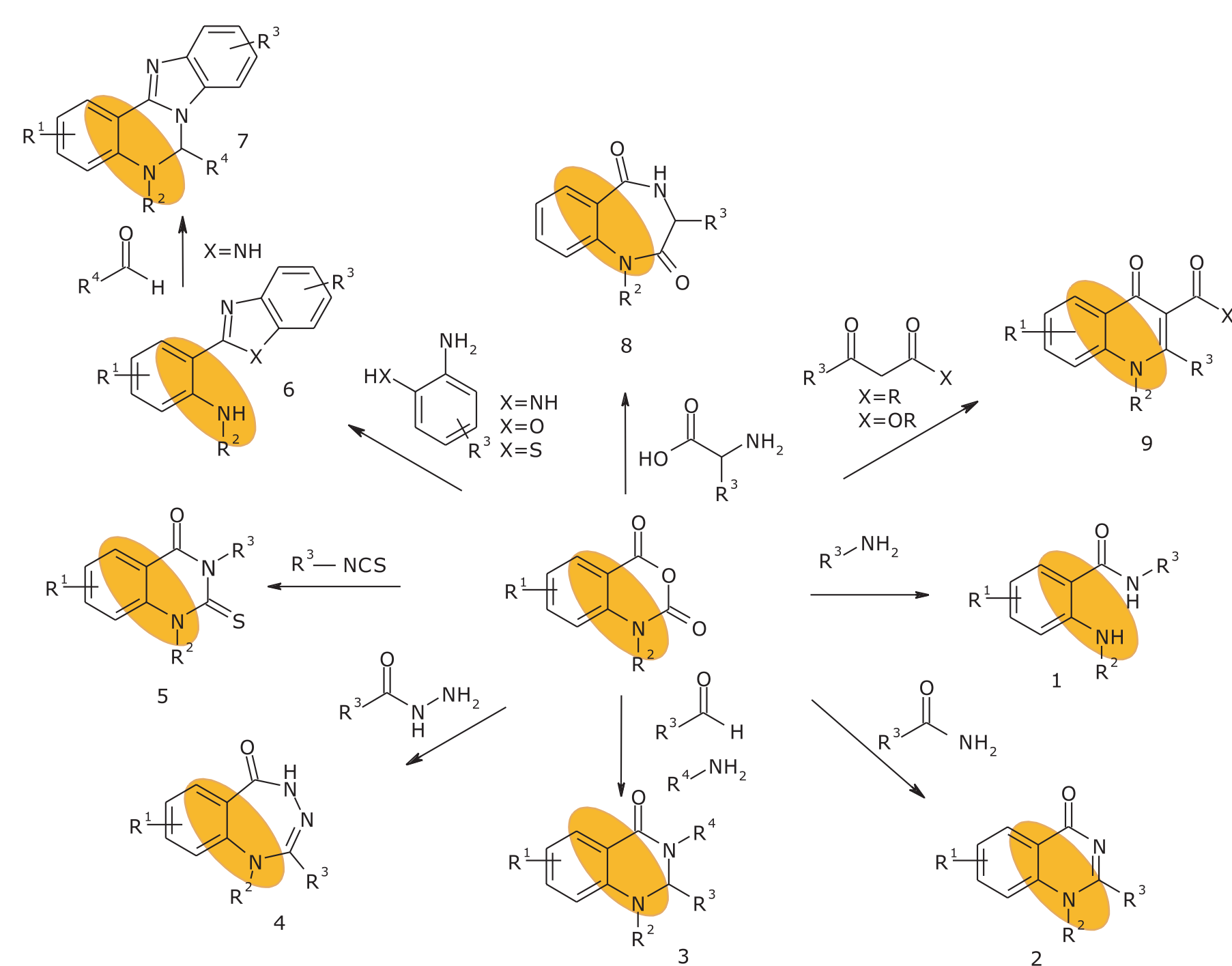


Reaction conditions:
0.2 mmol 2, 1.2 eq. hydrazine
or hydroxylamine or amidine
i, EtOH/DMF 4:1, 160 °C, 5 min.;
ii, KOH, DMF, 180 °C, 5 min.
Overall yields: 21-60%

General reaction conditions:
0.2 mmol, propenoates,
1.2 eq. dinucleophiles,
acetic acid/DMF
4:1, 180 °C, 5 min.
Overall yields: 30-90%

Isatoic anhydride

Isatoic anhydrides could be used as versatile synthons 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, aminoacids, 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.



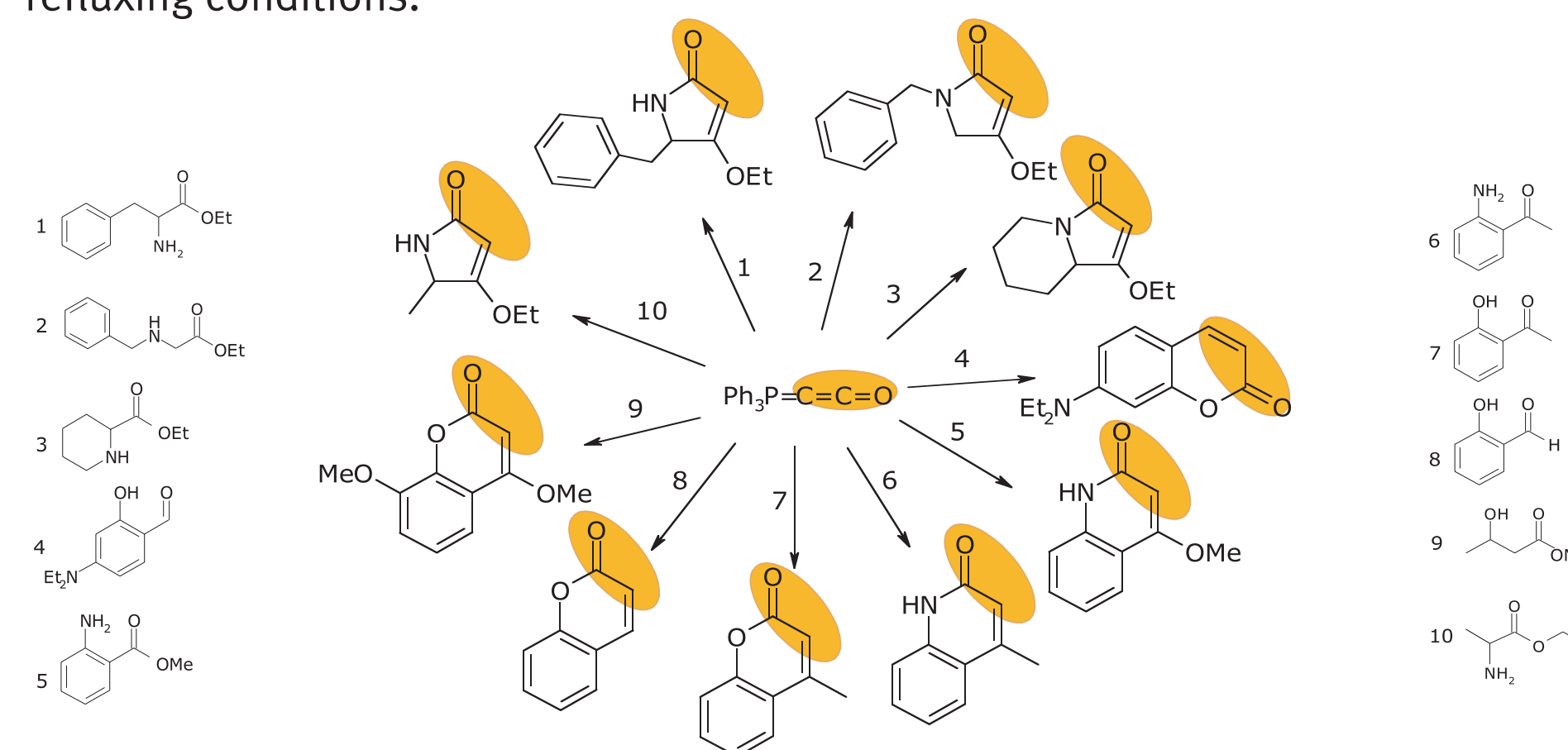
Overall yields: 20-100%

Reaction conditions:

- 1, PS-DMAP, DMF, 200°C, 5min
- 2, neat, 230°C, 15-20min
- 3, 1 eq. AcOH, H₂O, 180°C, 15min
- 4, AcOH, 180°C, 10min
- 5, H₂O, 180°C, 5min
- 6, AcOH, 150°C, 3min
(X=O, S 200°C, 8min)
- 7, AcOH, 150°C, 5min
- 8, AcOH, 200°C, 5min
- 9, K₂CO₃, DMF, 200°C, 5min

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 hydroxyl or amine group in α - or β -position react to form various heterocycles such as tetronic acids, tetronates, coumarines, benzoxepinones and their N-analogues. The reaction times are conventionally 12-48h under refluxing conditions.

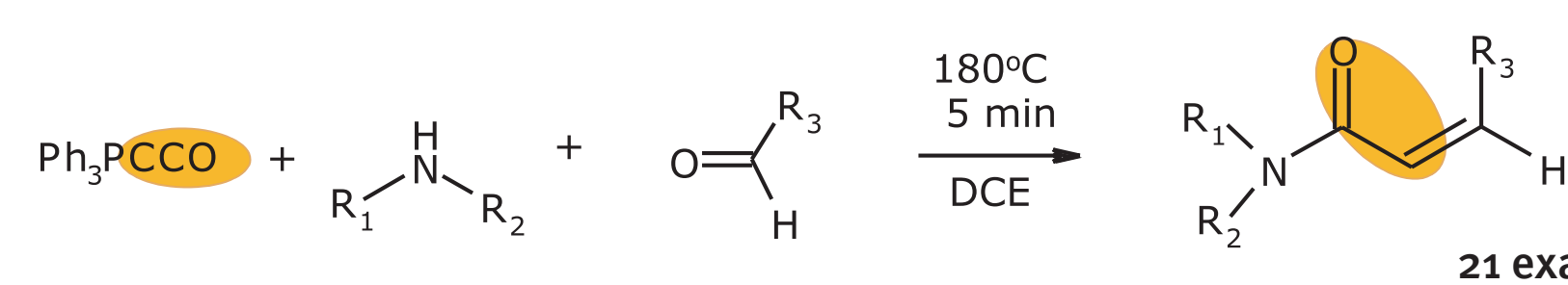


Overall yields: 50-80%

Reaction conditions:

- 1-9: 1.2 eq. Ph₃PCCO, DCE, 180-230 °C, 5-8 min.;
- 10: 1.2 eq. Ph₃PCCO, 1 eq. NEt₃, 180 °C, 8 min

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 reactions, but there is no connection between the reacting amine and carbonyl.



21 examples

Overall yields: 35-100%

References:

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