Reduction of substance production time by the combination of microwave dielectric heating and one-pot synthesis, multi-component synthesis, solid supported reagents or versatile synthons

Jacob Westman
Personal Chemistry, Kungsgatan 76, 753 18 Uppsala, Sweden

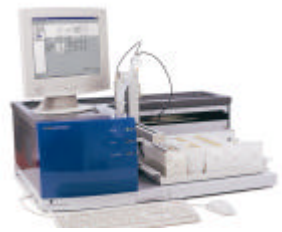
Introduction: **The bottleneck in going from biology to clinical trials is believed to be the chemistry development. The bottleneck is also believed to be a bit broadened by the use of microwave dielectric heating since the technology have been proven to reduce reaction times by several orders of magnitude. Very often increased yields are also found. BUT in the context of producing compounds, short reaction times and high yields are not good enough.**

In order to reduce the overall time for production of substances for biological screening, we have to take several aspects into consideration; time for preparation of starting materials and reagents, purification of intermediates, purification of final products etc. If the reaction time is reduced but the time for purification is still in the same time range as under conventional heating, the value of microwave heating is decreased.

Conventional heating	Microwave heating
Reaction time: 1 day	Reaction time : 1 min
Reaction time reduced 500 times	
Purification time: 1 day	Purification time: 1 day
Total time: 2 days	Total time: 1 days
Total time for production of the compound reduced 2 times	

To overcome some of the problems we will here describe the use of:

- **Solid supported triphenylphosphine for a one-pot synthesis of olefins**
  A three-step reaction is reduced to a one-pot synthesis in order to decrease the number of purification steps. By the use of solid supported triphenylphosphine the by-product triphenylphosphine oxide is easily separated from the reaction mixture by a simple filtration.
- **Keteneylidene phosphorane in heterocyclic chemistry and multicomponent reactions**
  With this reagent we could form heterocyclic compounds and unsaturated amides. The unsaturated amides were synthesized in a three-component reaction, which also reduced the number of purification steps.
- **Dimethylformamide diethylacetal in heterocyclic combinatorial chemistry**
  Dimethylformamide diethylacetal is a reagent, which could act as a versatile synthon since it could form propenones and propenoates. These intermediates could be effectively used in a combinatorial synthesis of a diverse set of heterocycles. The intermediates were synthesized and used in the next step without any purification.
- **A Fast Heterocyclic Three Component Synthesis of Imidazo[1,2-a] Annulated Pyridines, Pyrazines, Pyrimidines and Thiazoles under Microwave Conditions**
  A multicomponent reaction, which forms bicyclic heterocycles. The reaction is a version of the well-known Ugi four-component reaction.
- **One-pot three-step solution phase syntheses of thiohydantoins using microwave heating**
  C-C Suzuki or Negishi reactions followed by reductive aminations and finally a cyclisation reaction with purification only of the final product forms Thiohydantoins with 4 centers of diversity.

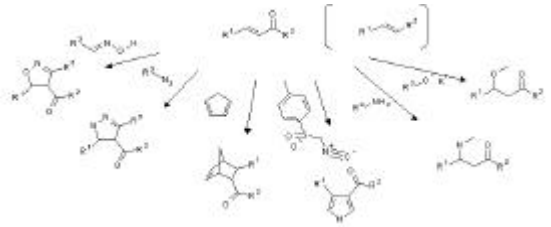


personalchemistry

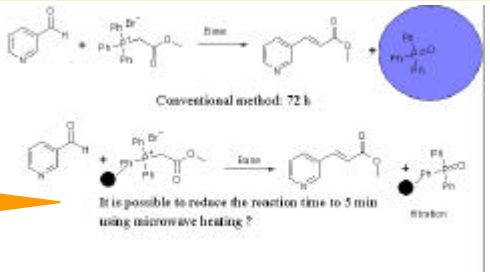
The use of solid supported triphenylphosphine for a one-pot synthesis of olefin

Jacob Westman
(Jacob Westman. *Org. Lett.* (2001), 3, 3745-3747)
Personal Chemistry, Kungsgatan 76, 753 18 Uppsala, Sweden

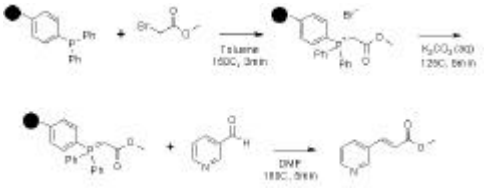
Introduction: For a number of different reactions such as 1,3-dipolar cycloadditio Diels-Alder reactions, pyrrol synthesis and Michael additions, olefins are used as important and useful starting materials and have therefore a large value in the drug development process.

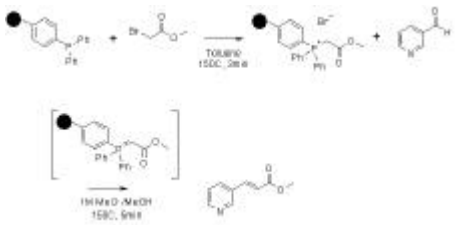


Olefins could be formed under a number of various conditions. Wittig reactions have been known for a long time and used successfully in solution. The reaction has also been described a number of times with the use of solid supported reagents. The major benefit with the solid supported approach is the possibility to separate the byproduct triphenylphosphine oxide by a simple filtration. Obtaining products free from organophosphorous contamination is known to be quite problematic. Since the reaction is very tedious under conventional methods in solution phase the question that have to be address is therefore:

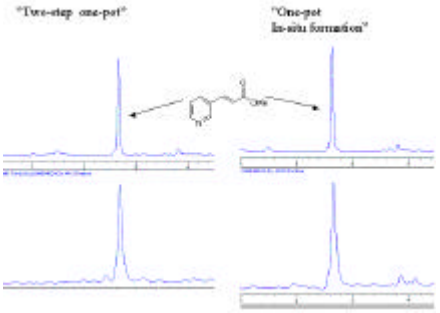


Three step approach:
Polymer supported triphenylphosphine was: 1, treated with methyl bromoacetate in toluene at 150° C for 3 minutes, 2, treated with aqueous potassium carbonate at 125° C for 5 min in order to form the corresponding ylide. 3, treated with pyridine 3-carboxaldehyde in DMF at 180° C for 5 minutes, giving the product in quantitative yield based on LC/MS analysis. As a comparison, Castells *et al* reported the formation of carbomethoxymethyl triphenylphosphonium bromide on solid support in 75% yield after 7 days at room temperature.

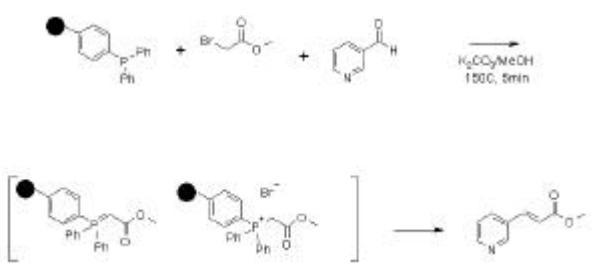


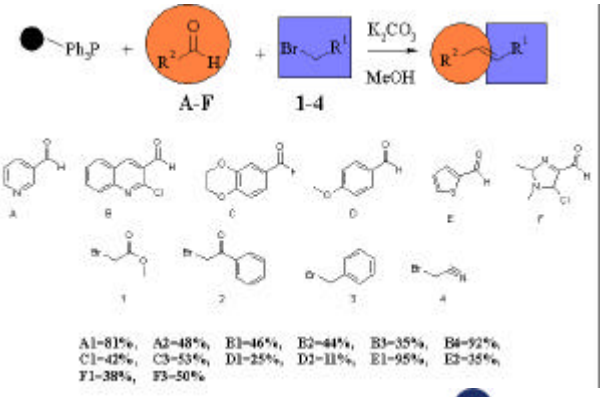


Two-step approach:
In order to find a faster and more convenient way of producing olefins a two-step procedure was adopted. The phosphonium salt resin was treated in the same way as above under basic conditions to form product with excellent yield based on LC/MS analysis.



The next obvious step was to develop a **one-pot reaction protocol**. To the best of our knowledge this has only been presented once by Castell *et al* using conventional methods (reaction time: 3 days at r.t.) We found that the most general protocol was the use of K_2CO_3 and MeOH at 150° C for 5 min. The reaction was verified by synthesizing a number of different olefins from six different aldehydes and four different alkyl halides.



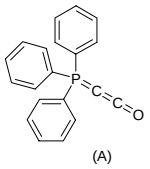


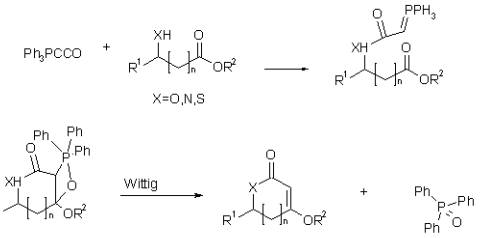
personalchemistry

The use of keteneylidene phosphorane in heterocyclic chemistry and multicomponent reactions

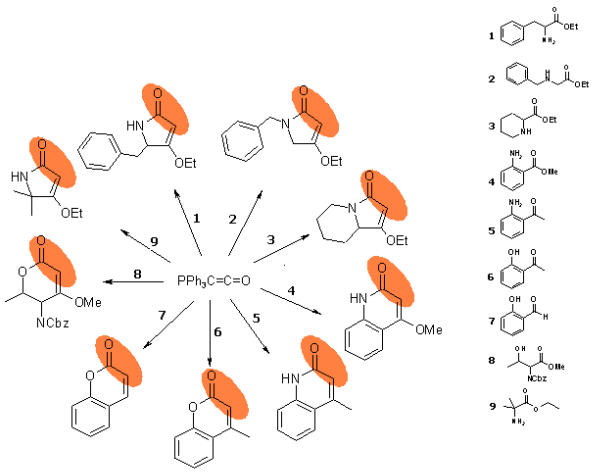
Jacob Westman and Kristina Orrling
(J. Westman and K. Orrling. *Comb. Chem. High Throughput Screen. In press)*
Personal Chemistry, Kungsgatan 76, 753 18 Uppsala, Sweden

Introduction: Cascade reactions signify reactions involving two or more bond forming transformations that take place under unchanged reaction conditions, and in which the subsequent reactions result from the functionality formed in the previous step. These *one-pot multistep* or *domino* reactions eliminate the need for work-up or purification between the different reaction steps. **Keteneylidene phosphorane** (**A**) is an example of a multipurpose reagent that can be used to introduce a carbon-carbonyl building block into the synthesis. This is accomplished by a cascade reaction comprising an addition and a Wittig olefination reaction.

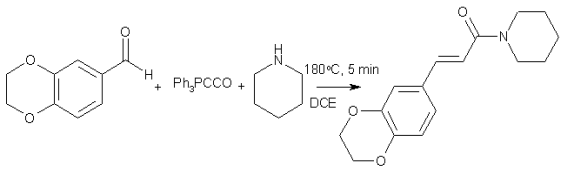




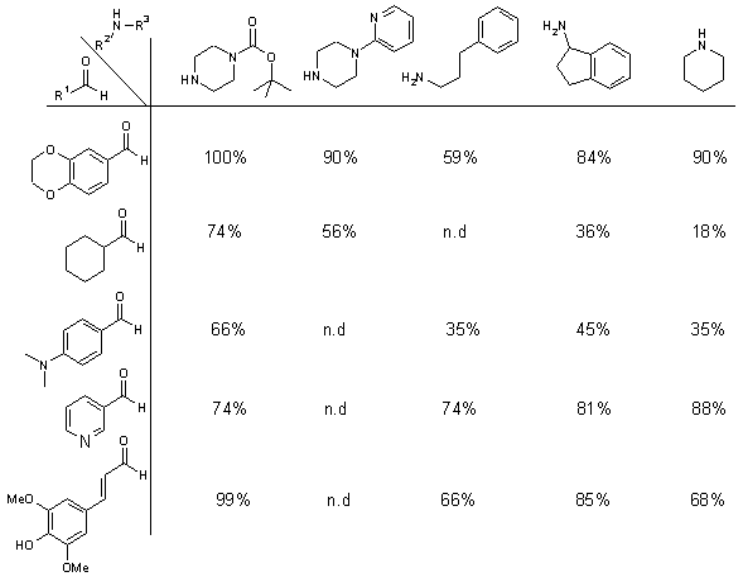
Formation of heterocycles, a two component reaction. With keteneylidene phosphorane, the reaction times are conventionally 12-48 h under refluxing conditions. Keteneylidene phosphorane and aldehydes, carboxylic acid esters or ketones with either an adjacent hydroxyl, amine or thiol group in α or β position can form various heterocycles, such as tetronic acids, tetronates, coumarins, benzoxepinones and their *N*-analogs. The reactions were performed at 180 °C for 5-8 min. The yields were acceptable to good based on crude LC-MS analysis (54-97%).



Formation of unsaturated amides, keteneylidene phosphorane can also be engaged in multi-component reactions when reacting with an aldehyde and an amine or an alcohol in order to form α, β-unsaturated amides or esters respectively. Unsaturated amides can be found in many natural products and these olefins are of great interest since they could be used as intermediates in several important types of reactions, such as 1,3-dipolar cycloadditions, Diels-Alder reactions, pyrrol synthesis and Michael additions.



In order to investigate the methodology in the context of combinatorial chemistry, a small library of unsaturated amides were synthesized. A selection of aldehydes, aromatic as well as aliphatic and five primary and secondary amines were treated with 1.5 eq. of keteneylidene phosphorane in DCE. The reaction times were varied between 5 and 10 min at 180 °C , except for the Boc-protected piperazine. As we have found that Boc-protecting groups could be cleaved at elevated temperatures, the reaction temperature was kept at 150 ºC. Unfortunately some products were not completely separated from triphenylphosphine oxide, thus the yields of these products could not be determined accurately but high yields were indicated by LCMS analysis.



	100%	90%	59%	84%	90%
	74%	56%	n.d	36%	18%
	66%	n.d	35%	45%	35%
	74%	n.d	74%	81%	88%
	99%	n.d	66%	85%	68%

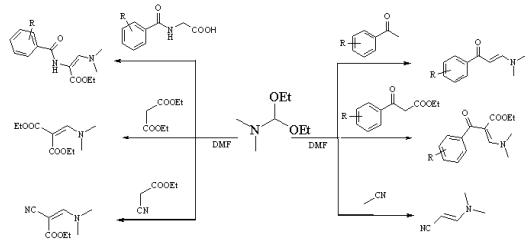
personalchemistry

The use of dimethylformamide diethylacetal in heterocyclic combinatorial chemistry

Jacob Westman, Ronny Lundin, Johan Stålberg, Maria Östbye, Anders Franzén, Adam Hurynowicz
(J.Westman, R. Lundin, J. Stålberg, M. Östbye, A. Franzén, A. Hurynowicz.) *Comb. Chem. High Throughput Screen. In press*).

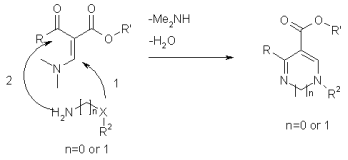
Personal Chemistry, Kungsgatan 76, 753 18 Uppsala, Sweden

Introduction: Highly functionalized heterocycles of various ring sizes, with different heteroatom and substitution patterns are of major interest in the pharmaceutical and agricultural industry due to the many intrinsic biological properties of these substances. In medicinal chemistry in general, and combinatorial chemistry in particular, the use of versatile synthons or versatile scaffolds which are available after just one reaction step are of great interest. One reagent showing this characteristic is *N,N*-dimethylformamide diethyl acetal (DMFDEA). The availability of starting materials, which could form, activated alkylaminopropenones or alkylaminopropenoates with DMFDEA is large and the number of possible heterocycles with large diversity, which are possible to form in a subsequential step from these types of intermediates, is substantial.

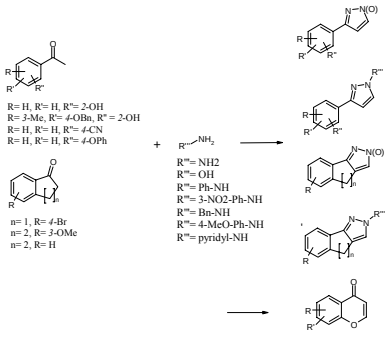


Condensation reactions between a methyl or methylene group adjacent to a keto functionality or a methylene group of a *2*-substituted acetic acid derivative and DMFDEA form alkylaminopropenones or alkylaminopropenoates. The alkylaminopropenones and alkylaminopropenoates were then used for the synthesis of isoxazoles, pyrazoles, chromones, pyrimidines, pyranones, pyrimidones and substituted 4*H*-quinolizin-4-ones. These substance classes are all of them found to be interesting for the pharmaceutical industry due to their potential biologically activities. The intermediates were formed in 53-93% yield based on LC/MS analysis and used without purification.

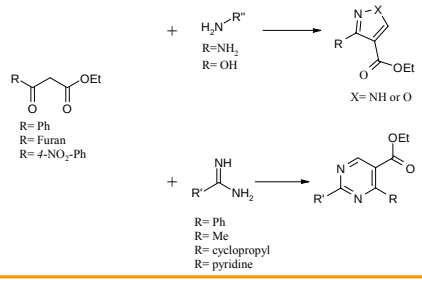
Propenones react with dinucleophiles in a two-step reaction where substitution of the dimethylamino group is followed by a condensation with the keto function.



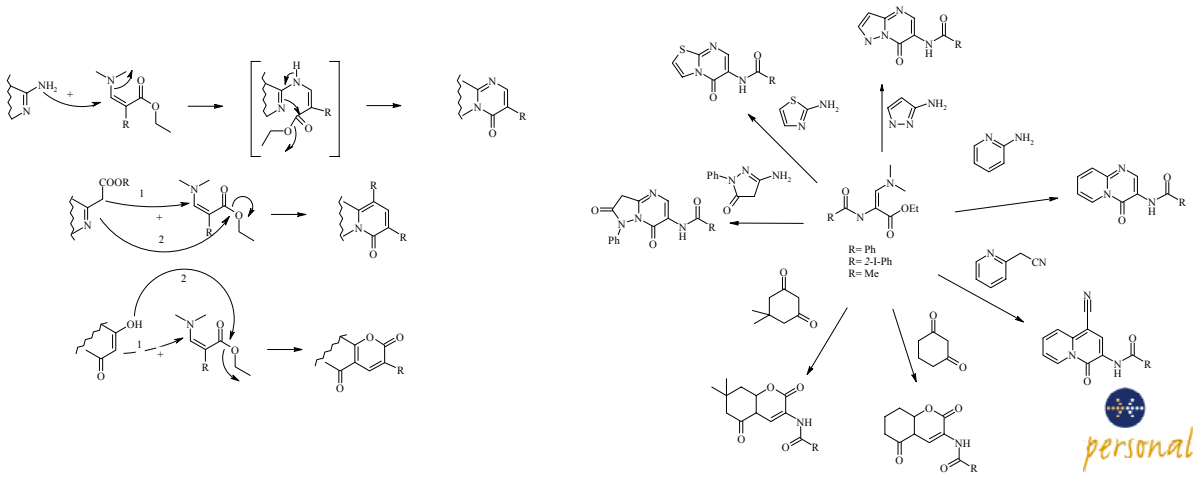
Propenones from acetophenones were reacted with 1.2 eq. of hydroxylamine or hydrazine to give isoxazoles and pyrazoles respectively in 31%-100% and 45%-82% after 5 min. at 180 °C in acetic acid/DMF 4:1. The corresponding substituted pyrazoles were synthesized by treatment with five different substituted hydrazines under the same reaction conditions giving the products in 25%-95% overall yield. Chromones were found as major by-product when propenones with ortho-hydroxyl group was treated under acidic conditions.



Propenones from β-keto esters forms isoxazoles and pyrazoles when reacted with hydroxylamine or hydrazine respectively to give the products in 25%-60% yield after 5 min. at 160 °C (ethanol/DMF 4:1). Substituted pyrimidines were synthesized by reacting the propenones with amidines in DMF with KOH as base. The reactions proceeded well with both aryl and alkyl amidines for 5 min at 180 °C without ester cleavage. Products were formed in 21%-53% yield.



3-Dimethylamino propenoates react with 1,3-dinucleophiles, such as β-dicarbonyl compounds, α-amino-heterocycles and 2-pyridyl-acetonitrile in acetic acid when heated to 180 °C for 5 min. In this case the reactions proceed differently since the substitution of the dimethylamino group is followed by the displacement of ethanol from the ethyl ester. The outcomes of these reactions are generally good giving overall yields between 30% and 90%.

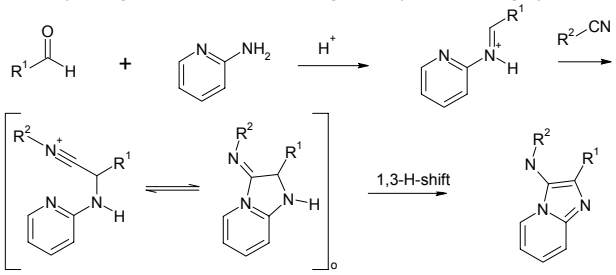


personalchemistry

A fast heterocyclic three component synthesis of imidazo[1,2-a] annulated pyridines, pyrazines, pyrimidines and thiazoles under microwave conditions

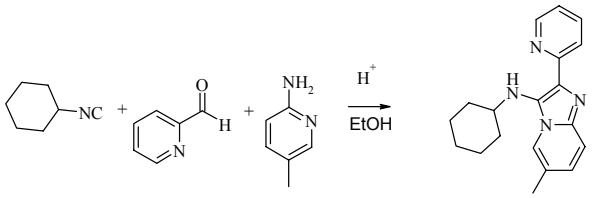
Jacob Westman, Anders Franzén
Personal Chemistry, Kungsgatan 76, 753 18 Uppsala, Sweden

Introduction: Multicomponent reactions are becoming more popular nowadays since they provide a possibility to introduce a large set of diversity to different substance classes in one step.
The imidazo[1,2-a]pyrazines, -pyridines, -pyrimidines and -thiazoles structural moieties can be found in pharmacologically active compounds, such as anti-inflammatory agents, (Miroprofen), calcium channel blockers and antibacterials. In 1998, three different research groups discovered a novel reaction at almost the same time. They found (partly by serendipity!) that when using 2-aminopyridines as the amine component together with isonitriles and aldehydes in the Ugi 4 component reaction (4CR) the formation of imidazo-pyridines was observed. The acid, the fourth component of the Ugi 4CR, is required as a catalyst. Under conventional conditions, the reaction takes 18-72h depending on the method used to give the products in high yield.

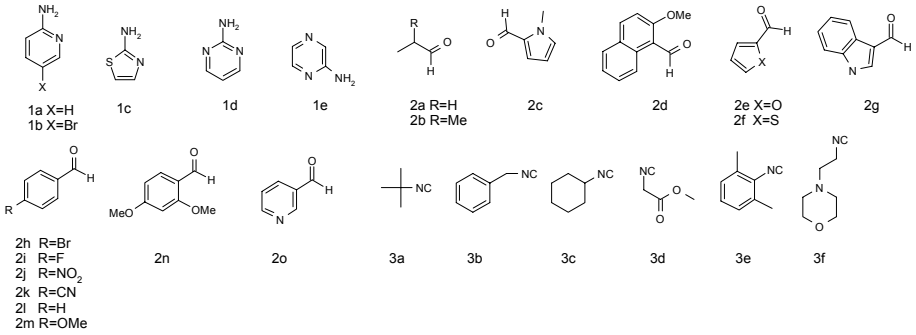


In 1999 Varma *et al.* published this reaction under microwave and solvent-free conditions in a two-step fashion. The two-step procedure introduces a limitation since alkyl iminium ions can be unstable and the solvent free procedure is inconvenient when it comes to library production. Especially when automated liquid handlers are used, but also due to the fact that many products are highly crystalline, making the isolation problematic.

We therefore followed the papers developed by Groebke *et al.* and Bienaymé *et al*. in order to find a solution phase protocol under microwave conditions and short reaction times. First we tried the method by Groebke *et al.* who used 2 eq. of acetic acid as catalyst. After up to 30 min at 170 °C in EtOH we only found traces of product (LC/MS analysis). Bienaymé used perchloric acid as the protic acid needed for the reaction. Perchloric acid may cause an explosion when heated and therefore considered not to be very suitable for microwave heating. But in a closed pressurized vial and in only catalytic amounts we did not find any problems. 170 °C for 5 min was found to be a fairly general protocol .



The table below show the structural variations tolerated by this reaction condition. Both aromatic, aliphatic (even sterically hindered) and heteroaromatic aldehydes were used and gave the corresponding products in acceptable to good yields. The same is true for the different isonitriles and heteroaromatic amidines used. It should be noted though, that the yields presented in the table are based on the product peak area as compared to total peak area of the LC chromatogram (LC purity). As described above some of the products are highly crystalline and in those cases were the products precipitated directly from the reaction mixture the products were isolated by a simple filtration. No further purification was needed. (No recovery from the mother liquor implicit that the total yield could be higher).



Compound	Yield[a]	Compound	Yield[a]	Compound	Yield[a]	Compound	Yield[a]	Compound	Yield[a]
1a2b3a	83	1a2k3c	97	1b2g3a	50	1b2m3a	83	1e2a3d	63 (42)
1a2f3a	60	1a2l3a	82	1b2i3a	76 (71)	1b2j3c	-- (70)	1e2a3f	62 (17)
1a2f3b	57	1a2l3c	97	1b2i3c	23 (58)	1b2n3a	95	1e2d3d	64 (44)
1a2g3a	69	1a2m3a	78	1b2i3e	38	1b2n3c	98	1e2d3f	57 (9)
1a2g3c	69 (37)	1a2m3b	74	1b2j3a	28 (54)	1c2a3d	39	1e2e3f	49
1a2i3a	75	1a2n3c	95	1b2j3e	-- (71)	1c2d3d	42 (21)	1e2h3d	39
1a2i3c	93	1b2b3a	75	1b2k3a	57 (51)	1c2d3f	35	1e2h3f	81 (9)
1a2j3a	82	1b2c3e	76	1b2k3c	16 (66)	1d2c3a	62	1e2o3d	46
1a2j3b	29 (62)	1b2c3a	62	1b2k3e	11 (76)	1d2d3d	42	1e2o3f	55
1a2j3c	27 (66)	1b2g3e	59 (53)	1b2l3a	89 (32)	1d2e3d	36		
1a2k3a	83	1b2f3a	75 (46)	1b2l3c	56 (58)	1d2h3d	20 (9)		
1a2k3b	76 (54)	1b2f3c	8 (60)	1b2l3e	56	1d2o3d	39		

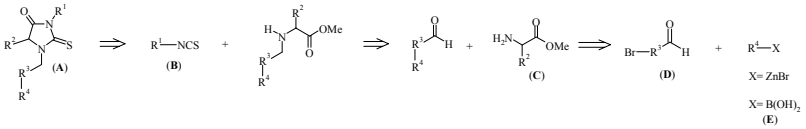
[a]= LC purity, in parentheses: isolated yield after filtration of the precipitated product.

personalchemistry

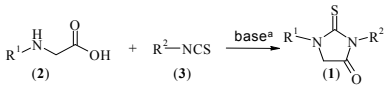
A One-pot Three-step Solution Phase Syntheses of Thiohydantoins using Microwave Heating

Jacob Westman, Liselotte Öhberg
(L. Öhberg, J. Westman. *Synlett* (2001), *12*, 1893-1896.)
Personal Chemistry, Kungsgatan 76, 753 18 Uppsala, Sweden *AstraZeneca AB, 151 85 Södertälje

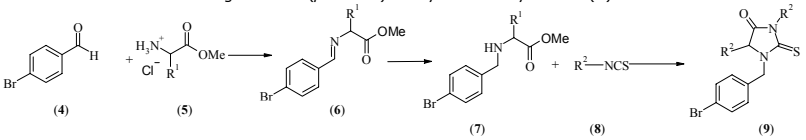
Introduction: High yielding protocols using small excesses of reagent or substrates are of interest in a multistep synthesis in order to avoid purification between the reaction steps. Since only a few number of published papers describes combinatorial synthesis in combination with microwave-assisted heating we decided to examine the use of microwave assisted heating in the context of multi-step solution phase parallel/combinatorial syntheses. The thiohydantoin (**A**) was chosen as a model scaffold, due to the synthetic ease through which a high degree of diversity could be introduced in a short sequence of reactions. A wide range of biological properties such as antiviral, antibacterial, antifungal, antitumor agents have been reported for thiohydantoins.
We herein describe the synthesis of a library with four centres of diversity. In a retrosynthetic approach we planned to introduce R^1 via different alkyl or aryl isothiocyanates (**B**), R^2 from various amino acid esters (**C**), R^3 from halide substituted aryl aldehydes (**D**) and R^4 via Suzuki or Negishi C-C coupling reaction (**E**). All individual reactions steps were optimised in order to develop an efficient library protocol.



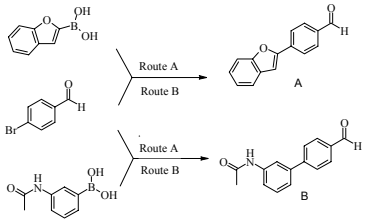
The formation of thiohydantoins (**1**) was optimised from *N*-aryl or *N*-alkyl amino acids (or esters) (**2**) and thioisocyanates (**3**). The cyclisation proceeded as anticipated in high yield and purity when using polystyrene bound dimethylamino pyridine (PS-DMAP) or triethylamine (TEA) as base. 5 min at 170 °C or 180 °C gave satisfactory yields. PS-DMAP as base gave in most cases a slightly lower yield compared to the use of TEA. However, a cleaner reaction mixture, which made the purification easier, was obtained when polymer bound DMAP was used.



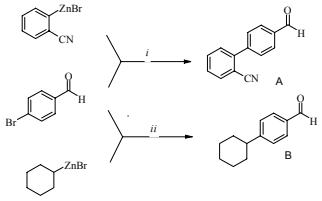
The introduction of R^3 was to be accomplished by reductive amination of the chosen amino acid esters and *p*-bromobenzaldehyde (**4**). With this aldehyde a two step procedure were necessary since $NaBH(OAc)_3$, the reducing agent of choice, was found to reduce the *p*-bromobenzaldehyde at high temperatures. Compound **4** was treated with an amino acid ester hydrochloride (**5**) together with Et_3N at 140º C for 5 min in DCE to form the imine (**6**). $NaBH(OAc)_3$ was then added to the reaction mixture and the mixture was heated at 170 ºC for an additional 9 min to give the *N*-benzylated amino acid ester (**7**). The isothiocyanate (**8**) and TEA were then added and the mixture was heated for another 5 min at 170 ºC to give the *N*-(*p*-bromo) benzylated thiohydantoin (**9**).



To avoid the work-up procedure after the Suzuki reaction, which is necessary when using aqueous conditions with Na_2CO_3 as base, we used EtOH as solvent and TEA as base. The Pd catalyst was separated from the reaction mixture by filtration.The Negishi reaction has the potential to become more popular with the recent increased availability of commercial ZnBr reagents. *p*-Bromobenzaldehyde was reacted with both aryl and alkyl zink bromides to form the product in high yield. Unfortunately, purification of the product before the reductive amination was necessary but the work-up procedure is convenient and rapid.

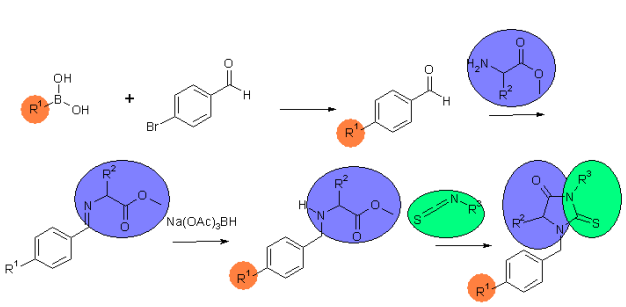


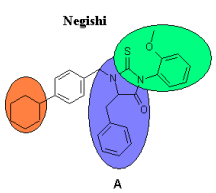
Route A, $(Ph_3P)_2PdCl_2$, Na_2CO_3, DME/EtOH/H_2O 7:2:3, 140 °C, 2 min gave **A** in 82 % yield and **B** in 77% *Route B,* $(Ph_3P)_2PdCl_2$, EtOH, Et_3N, 140 °C, 6 min gave **A** in 86% and **B** in 87% yield .

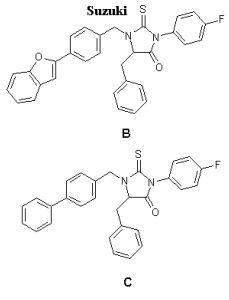


reaction conditions:
i , $(Ph_3P)_2PdCl_2$, THF, 160 °C, 1 min gave **A** in 90% yield
ii, $(Ph_3P)_2PdCl_2$, CuI, THF 160 °C, 10 min. gave **B** in 79 % yield

The developed protocols described above were combined to produce a multi-step protocol, suitable for library production, starting with the carbon-carbon coupling followed by reductive amination and finally cyclisation. The theoretical number of possible compounds attainable with this approach is very large, based on commercially available starting materials (>500,000). The overall yield for the synthesis is between 30-70% based on LC/MS analysis. Three of the products were purified by silica gel chromatography to give compound **A, B** and **C** in 68%, 55% and 31% yield respectively.







personalchemistry