Coherent Synthesis™: Fast and Convenient Approaches for Lead Optimization

Hadi Ghane[1], Edgars Suna[2], Martins Katkevics[2], Vita Ozola[2], and Ilga Mutule[2]

[1]Personal Chemistry AB, Kungsgatan 76, 753 18 Uppsala, SWEDEN, Fax: +46184899200,

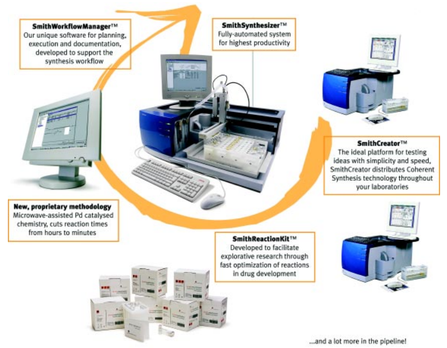
hadi.ghane@personalchemistry.com

[2]Latvian Institute of Organic Synthesis, Aizkraukles 21,LV-1006, Riga, LATVIA

INTRODUCTION

Recent development in genomics and proteomics has moved the bottleneck in drug discovery from target identification to lead optimisation. This has put a tremendous pressure on medicinal/ organic chemists to produce more and higher quality compounds. Coherent Synthesis™ has emerged as a new technology, which permits chemists to fully explore new and unexplored chemistries. Its speed and simplicity allows testing of new and unknown approaches faster, and enables the reaction conditions to be optimised in a matter of hours rather than days. Coherent Synthesis™ is based on microwave dielectric heating and designed to assist scientists and help them in their search for new chemical entities. It also allows for highly controlled process parameters and automated liquid handling for fast synthesis of novel building blocks and production of focused libraries. Here we describe a reaction optimisation of thiohydantoin and a small library production of coumarin derivatives.

Traditionally, with conventional heating, one would pay much less attention to the time spent weighing compounds (a few minutes), compared to the time the reaction would take to complete (hours or even days). Reaction optimization could be tedious and cumber-some if the reaction is slow and if the optimization is done by one variable at a time (OVAT). Decreasing reaction time from hours to minutes by microwave heating creates opportunities in terms of faster synthesis of compounds, faster optimisation of reactions, new approaches and methodologies etc. In order to minimize weighing procedures, liquid handling was implemented. Thus Coherent Synthesis™ offers faster optimisation of reactions resulting often in improved yields.



RESULTS AND DISCUSSION

REACTION OPTIMISATION OF A THIOHYDANTOIN DERIVATIVE USING LIQUID HANDLING AND EXPERIMENTAL DESIGN

As there are many reports in literature describing the synthesis of Thiohydantoin derivatives[1] in detail, the aim of this study was not to show a synthetic approach but to demonstrate how easily the reaction can be optimised in a very short time. Three parameters were of interest in this study, namely: 1) time 2) temperature and 3) concentration. In order to carry out the experiment as profoundly as possible we have utilised experimental design to generate a model for estimating/predicting the optimal conditions. A 3.3 M solution of Sarcosine derivative **I** in water was prepared manually and a stock solution of the thioisocyanide **II** in ethanol was prepared by the SmithSynthesizer™. All the liquid handling and addition of reagents (amount and volume) were automated in order to eliminate human error. The results are presented in **table 1 & 2** and in **plot 1**.

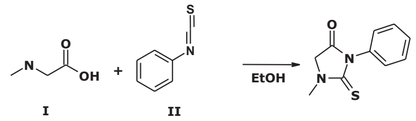


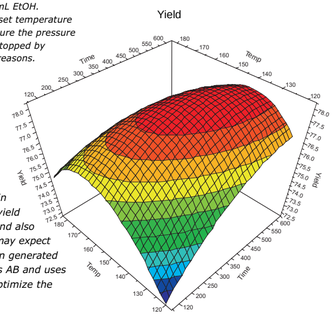
Table 1: *Time estimation for different steps in reaction optimisation of Thiohydantoin.*

Steps	Estimated time/min
Planning SmithWorkflowManager™	10
Preparating and running the reactions (14 runs)	240
Analysis (LC/MS)	140
Sum	**390 (6.5 h)**

Table 2*: Run parameters for the Thiohydantoin reactions and the obtained results.*

Run Order	Time (s)	Temp (°C)	Conc. (mmol)	Yield (LC purity)	SM	BiP1	BiP2
13	120	120	0,22	64,6	10,1	3,4	21,9
2	600	120	0,22	71,5	2,7	10,9	14,9
10	120	180	0,22	73,6	2,5	13,4	10,5
3	600	180	0,22	71,7	2,4	21,7	4,2
1	120	120	1	80,6	3,3	2,8	13,2
12	600	120	1	80,6	1	8,4	10
8	120	180	1	77	0,8	13,4	8,8
4	600	180	1	76,2	0,7	19,2	3,9
5	763,68	150	0,61	77	0,8	18,8	3,4
9	360	99,54	0,61	72,4	4,5	3,1	20
14	**360**	**150**	**1,26598**	**86,9**	**0,7**	**9,3**	**3,1**
11	360	150	0,61	78,3	1,2	13,6	6,9
7	360	150	0,61	77,2	0,8	14,2	7,8

** The reaction was carried out in 2.5 mL EtOH.*
Run number 6 is missing because the set temperature was 200 degrees and at that temperature the pressure went above 20 bars and the run was stopped by the SmithSynthesizer™ due to safety reasons.



Plot 1: *The response surface plot for the outcome of the thiohydantoin reaction. It demonstrates how the yield depends on time and temperature and also predicts under what conditions one may expect even better yields. The plot has been generated using Modde software from Umetrics AB and uses quadratic and/or cubic models to optimize the responses (yield).*

GENERATION OF A SMALL LIBRARY: SYNTHESIS OF COUMARIN DERIVATIVES (PECHMANN REACTION)

Coumarins are common in nature and find their application as fragrances, pharmaceuticals and agrochemicals[2]. They can be utilized as intermediates in syntheses of useful bioactive coumpounds[3]. Coumarins have been synthesized in a domestic microwave oven[4] using concentrated H_2SO_4, or alternatively on solid support (graphite/montmorillonite K10) using a focused monomode microwave system[5].

An alternative synthesis of coumarin derivatives in solution phase using mono-mode microwave system is reported herein. The synthesis of 7-hydroxy-4-methylcoumarin (**3**) from resorcinol (**1a**) and (**2a**) (**Scheme 1, Table3**) has been initially chosen for screening of all reagents and reaction conditions.

Scheme 1

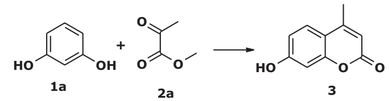


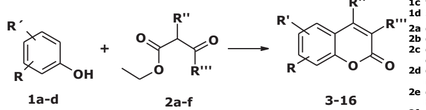
Table 3: *a) reactions were performed in 1.0 mM scale in 0.5 mL of solvent.*

No.	Experimental conditions[a]				HPLC Yield, %
	Catalyst	Solvent	Temp. °C	Time, s	
1	H_2SO_4	H_2SO_4	140	200	4
2	H_2SO_4	H_2SO_4	110	900	13
3	H_2SO_4	H_2SO_4	100	1800	33 (isolated)
4	$AlCl_3$	$PhNO_2$	160	600	16
5	$AlCl_3$	$PhNO_2$	160	200	31
6	$AlCl_3$	$PhNO_2$	120	600	30
7	P_2O_5	toluene	120	900	5
8	P_2O_5	toluene	160	300	5
9	**camphorsulfonic acid**	toluene	120	900	**62**
10	camphorsulfonic acid	toluene	160	300	50
11	CF_3CO_2H	toluene	120	1800	66
12	**CF_3CO_2H**	**CF_3CO_2H**	**100**	**1800**	**78**
13	CF_3CO_2H	CH_2CO_2H	120	1800	0
14	Amberlyst-15	$PhCF_3$	160	600	46
15	Amberlyst-15	toluene	170	600	54
16	Amberlyst-15	toluene	120	600	64
17	Amberlyst-15	toluene	120	1800	73
18	**Amberlyst-15**	**toluene**	**100**	**1800**	**78**
19	H+-montmorillonite	$PhCF_3$	160	600	28
20	H+-montmorillonite	toluene	170	600	35

Concentrated H_2SO_4 gave a poor yield of coumarin (see entry 1-3, **table 3**), as did $AlCl_3$ and P_2O_5. Acceptable results were obtained using camphorsulfonic acid and trifluoroacetic acid, especially if it was used as solvent. On the other hand, use of acetic acid did not provide any coumarin at all. Of the two solid catalysts, Amberlyst-15 afforded better yields than montmorillonite. Longer times and moderate temperature (100°C) was beneficial for synthesis of coumarin (**3**) both using Amberlyst-15 and CF_3CO_2H.

These two reagents were further tested for synthesis of series of oxy-substituted coumarins (**3-16**) (**Scheme 2, Table 4**), because, contrary to camphorsulfonic acid, they are easily separated from the reaction mixture and product. Employing CF_3CO_2H, coumarins were isolated in pure form by pouring reaction mixture into cold water or by removing CF_3CO_2H by aspirator and recrystallization from EtOH/ water or acetone/water. In the case of Amberlyst catalyst, the coumarin solution was separated by decantation.

Scheme 2



1a resorcinol
1b pyrogallol
1c trihydroxybenzene
1d 3-metoxyphenol
2a ethyl acetoacetate
2b ethyl benzoylacetate
2c ethyl 4,4,4-trifluoro-caetoacetate
2d ethyl 2-cyclohexano-necarboxylate
2e ethyl 3,4,5-trimethoxy-benzoylacetate
2f ethyl 4-nitrobenzoyl-acetate

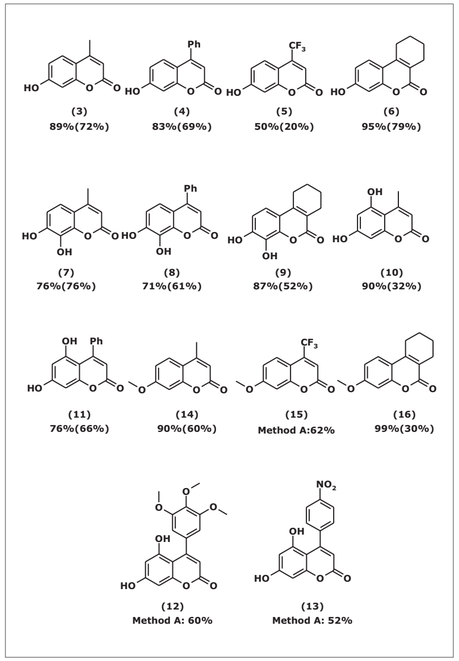


Table 4: *Method **A**: CF_3CO_2H, 100°C, 30 min (10 min for 7). Method **B**: Amberlyst-15, toluene, 100°C, 30 min. reactions were run at 1 mM scale, in 0.5 mL of solvent. Yields shown in brackets were obtained by **method B**.*

Since diverse β-keto esters and phenols can show different reactivity, synthesis of some coumarins has been performed at several temperatures, times and molar ratios of phenol and ketoester. Higher temperatures did not increase the yields of coumarins. For example, if a reaction was performed at 160°C using Amberlyst-15 (Method **B**), compound (**15**) was isolated in 41% yield (vs. 62% at 100°C), and coumarin (**4**) was obtained in 77% yield using Method **A** at 140°C (vs. 83% at 100°C). Shorter reaction times did not improve the yield of coumarins (except **7**) either. Thus, cutting reaction time in method **A** form 30 min to 10 min reduces the yield of (**4**) form 83% to 62%.

Generally, the ratio of phenol and ketoester can have an impact on the outcome of coumarins. If the phenol has good solubility in water, an 0.2 excess would result in a 95% yield of coumarin (**6**) compared to 90% at 1:1 ratio. To the contrary, a better yield of coumarin (**10**), by method **A**, was obtained using a molar ratio of 1:1.2 between phenol and ketoester (90%) than 1.2:1 ratio (73%). Method A in most cases afforded better yields of coumarins than Method **B**.

CONCLUSION

- In summary, a quick and versatile approach to optimize reaction conditions for a thiohydantoin derivative has been described.
- A small library of coumarin derivatives has been generated and the reaction conditions were optimised. The yields have been improved compared to the previously reported literature[4] values (Compound **3**: 89% vs. 72.1% and compound **10**: 90% vs. 68.7%).

REFERENCES

1. a) Öhberg, L.; Westman, *J.; Synlett*, **2001**, 12, 1893-1896. b) Rydberg, P. *et al.*; *Acta. Chem. Scand.*, **1993**, 47 (8), 813-817.
2. a) O'Kennedy, R.; Thornes, R. D. Coumarins: Biology, Application and Mode of Acton. Wiley&Sons, Chichester, **1997**. b) Berger, J.; Batcho A. D.; Antibiotics: Isolation, Separation and Purification, J. Chromatography. Library 15. Elsevier, **1979**,101-156. c) Bartirov, E. Kh.; Yuldashev, M. P.; Malikov, V. M.; *Chem. Nat. Comp.*, **1990**, 26, 489-502.
3. a) Flavin, M. T. *et al.*; *J. Med. Chem.*, **1996**, 36, 1303-1313. b) Bovy, P. R.; Collins, J. T.; McMahon, E. G.; Hutton, W. C. *J. Med. Chem.*, **1991**, 34, 2410-2414. c) Kucherenko, A.; Flavin, M. T.; Boulanger, W. A.; Kholevich, A.; Shone, R. L.; Rizzo, J. D.; Sheinkman, A. K.; Xu, Ze-Qi.; *Tetrahedron Lett.*, **1995**, 36, 5475-5478.
4. Singh, V.; Sivgh, J.; Kaur, K. P.; Kad. G. L.; *J. Chem. Research Synop.*, **1997**, 1, 58-59.
5. Frére, S.; Thièry, V.; Besson, T.; *Tetrahedron Lett.*, **2001**, 42, 2791-2794.

personalchemistry