Reaction Optimization in the mg Range

Johannes Keil, Jörg Rieke-Zapp*
Aventis Pharma Deutschland GmbH, Industriepark Höchst, Building G838, 65926 Frankfurt

Introduction

The use of largely manual processes using reaction blocks have become established as the method of choice for the screening of reaction conditions during chemical development, when 10 to 100 reactions are to be tested. The advantage of this small-volume system with an effective volume of 5-20 mL per reactor is a flexible, block-type approach to the screening phase. This is a time-saving process with the educts often available only in small amounts. Efforts to use these screening systems for optimizing reaction conditions showed that magnetically stirred systems do, in fact, produce internally consistent results in heterogeneous reactions; however, a considerable scale-up effect is often observed later. These effects are attributable to reactor geometry, heat transfer, and above all the grinding effects by the magnetic stirrer. The *Synthesis 1* now offers - apart from reactor geometry - suitably adaptable heating-cooling behavior and accomplishes the mixing by shaking the reaction vessels. After initial positive results with screening, the equipment was then also used for optimizing heterogeneous reactions, in which previously employed magnetically stirred systems have not proven effective thus far. Finally, the screening and optimization phase of a classical racemate resolution is described, which was later also run on the kg scale.

Experimental Work

In the racemate resolution process described here, diastereomeric salt pairs of the starting compound were first formed with a suitable racemate resolving agent. The preferential crystallization of the desired diastereomer from the reaction solution followed and then the release of the target compound from the salt, which had previously been isolated by filtration (**Diagram 1**).

The objective for the reaction step optimized here was to isolate the desired enantiomer from the starting compound in a yield of 75-80% (based on the pure enantiomer) and an optical purity of > 60% *ee*.

Screening of the Reaction Solvent

Selecting the correct solvent for the process was vitally important. In a first block test, 16 reactions (**Diagram 1**) were run simultaneously with different solvents in *Synthesis 1* to determine the best process solvent. Based on the results, 2-propanol was identified as the solvent of choice.

Optimizing the Reaction Conditions

Statistical reaction planning was used in the optimization phase. The procedure again followed **Diagram 1**. The factorial plan was created and evaluated using the software STAVEX (AICOS Technologies AG). The amount of solvent for the first reaction step (see **Diagram 1**), the amount of the racemate resolving agent (based on the starting compound), temperature and time for the second reaction step, and the solvent volume for rewashing the filter residue were used first as the variable parameters. The evaluation of the test series (**Table 1**) led to a factor reduction for further optimization. The volumes for the reaction and rewashing were kept constant in the subsequent optimization step. The time frame for the second reaction step was expanded to 6-30 hours and the amount of added racemate resolving agent was varied between 0.8 and 1.2 equivalents. The tests together with the results are listed in **Table 2**. The validity of the calculated model was tested with two verification tests with regard to yield and the *ee* value (**see Fig. 1**). The experimentally and theoretically obtained data are compared in **Table 3**. As a result, the model was confirmed on the small scale. A scale-up test and the subsequent transfer to the kg scale in the pilot plant showed no scale-up effects. The objective for the process could be easily achieved.

Summary

Both solvent screening and optimization of reaction conditions for the scale-up of a racemate resolution could be performed with the use of *Synthesis 1*. Here, *Synthesis 1* was superior to the conventional screening blocks with magnetic stirring - the obtained results could be applied 1:1 to the scale-up phase. The screening and optimization tests for the studied racemate resolution were successfully completed with < 10 g of starting material in less than a week.

Diagram 1. Procedure of the Screening and Optimization Phase

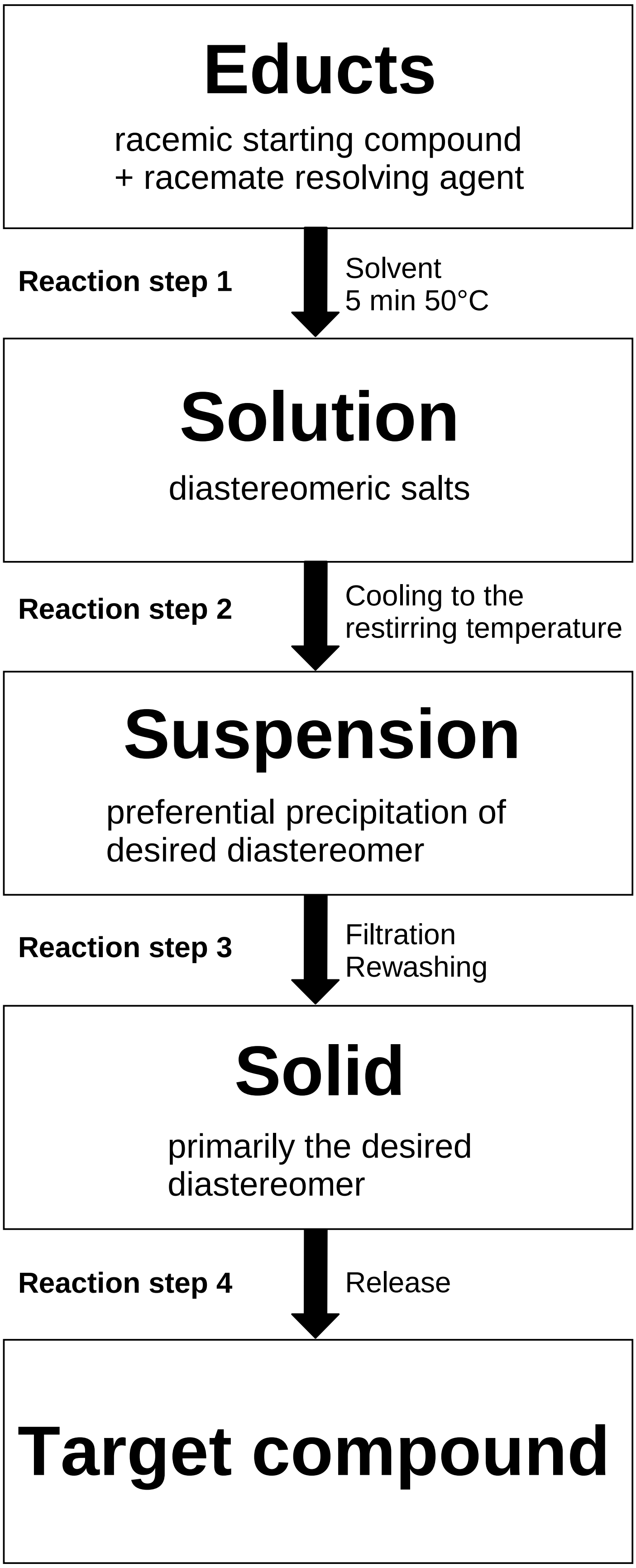


Table 1. First Optimization Block with Statistical Test Planning

Batch No.	RA/[equiv.]	Sol_P/[mL]	Sol_W/[mL]	t/[h]	T/[°C]	*ee* value/[%]	Yield [%]*
1	0.5	4	4	2	10	46	15
2	1.0	4	4	2	30	35	79
3	0.5	10	4	2	30	73	33
4	1.0	10	4	2	10	49	77
5	0.5	4	10	2	30	61	44
6	1.0	4	10	2	10	39	43
7	0.5	10	10	2	10	67	37
8	1.0	10	10	2	30	52	65
9	0.5	4	4	24	30	68	54
10	1.0	4	4	24	10	35	74
11	0.5	10	4	24	10	68	45
12	1.0	10	4	24	30	50	83
13	0.5	4	10	24	10	68	41
14	1.0	4	10	24	30	27	89
15	0.5	10	10	24	30	80	45
16	1.0	10	10	24	10	60	70

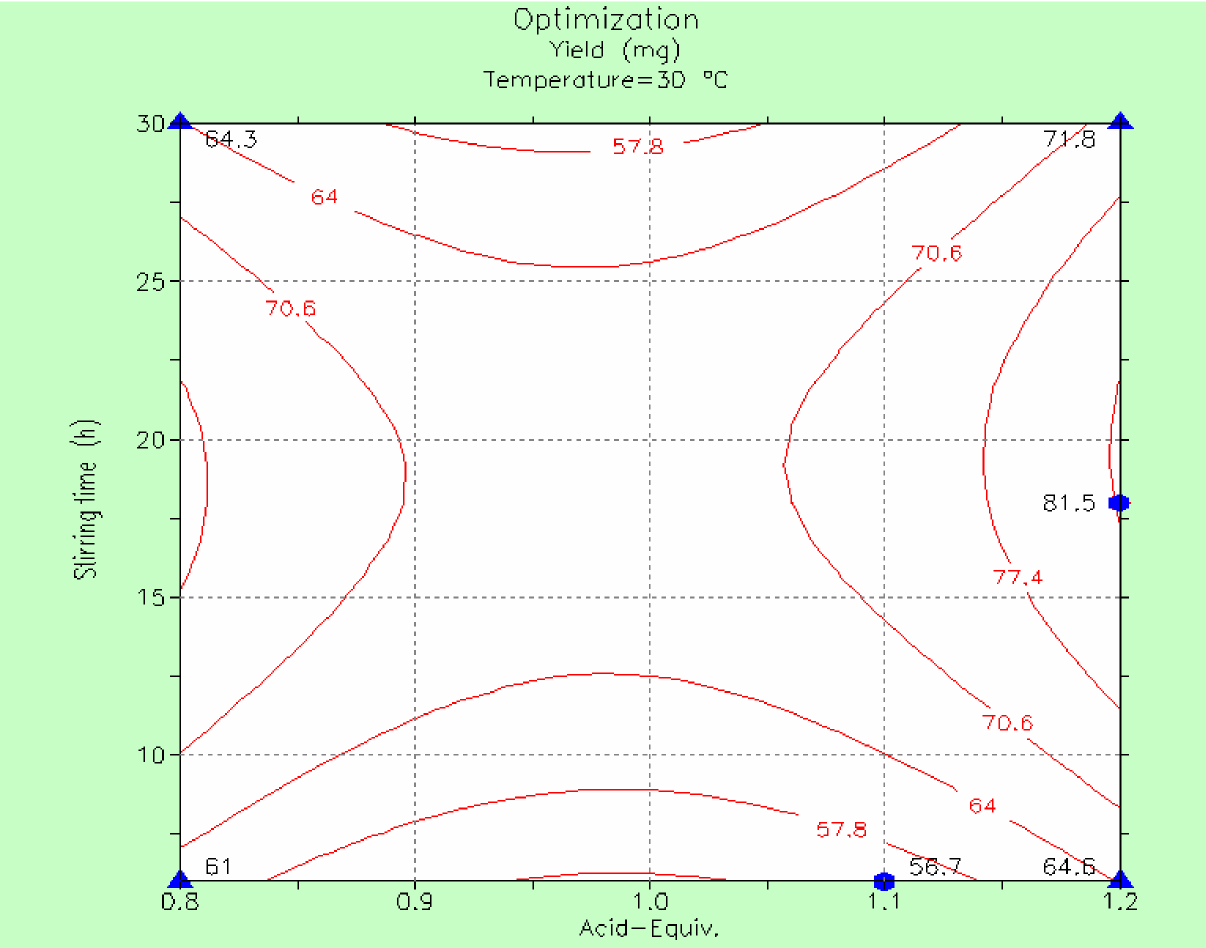
RA: racemate resolving agent; **Sol_p**: solvent (process); **Sol_W**: solvent (washing); **t**: restirring time; **T**: restirring temperature
*isolated yield from reaction step 3 (based on the desired enantiomer)

Table 2. Second Optimization Block after Factor Reduction

Batch No.	RA/[equiv.]	Sol_P/[mL]	Sol_W/[mL]	t/[h]	T/[°C]	*ee* value/[%]	Yield [%]*
1	0.8	4	4	6	10	55	61.5
2	1.2	4	4	6	10	56	54.3
3	0.8	4	4	30	10	51	62.2
4	1.2	4	4	30	10	54	61.2
5	0.8	4	4	6	30	53	61.0
6	1.2	4	4	6	30	62	64.6
7	0.8	4	4	30	30	55	64.3
8	1.2	4	4	30	30	61	71.8
9	1.0	4	4	18	20	51	67.4
10	0.9	4	4	18	20	53	68.1
11	1.1	4	4	18	20	60	69.0
12	1.0	4	4	10	20	65	56.7
13	1.0	4	4	26	20	53	61.1
14	1.0	4	4	18	15	56	62.2
15	1.0	4	4	18	25	59	68.5

RA: racemate resolving agent; **Sol_p**: solvent (process); **Sol_W**: solvent (washing); **t**: restirring time; **T**: restirring temperature
*isolated yield from reaction step 3 (based on the desired enantiomer)

Fig. 1. Contour plot.



--- Contours; ▲ Plan point; ⬢ Plan point (confirmation test)

The observed value of the target parameter is entered next to the plan point. Runs that do not lie within the sectional plane are not shown.

Table 3. Confirmation Tests (90% confidence region)

Confirmation test Yield					
RA/[equiv.]	t/[h]	T/[°C]	Yield [%]* calc. mean	Yield [%]* experimental	*ee* value/[%] experimental
1.2	18	30	85.02	81.5	72.2
Confirmation test *ee* value					
RA/[equiv.]	t/[h]	T/[°C]	*ee* value [%]* calc. mean	*ee* value [%]* experimental	Yield/[%] experimental
1.1	6	30	63.85	62.6	56.7

RA: racemate resolving agent; **t**: restirring time; **T**: restirring temperature
*isolated yield from reaction step 3 (based on the desired enantiomer)