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Rapid Improvement of a Reductive Sulfonylation Using Design of Experiment Methods

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Abstract:

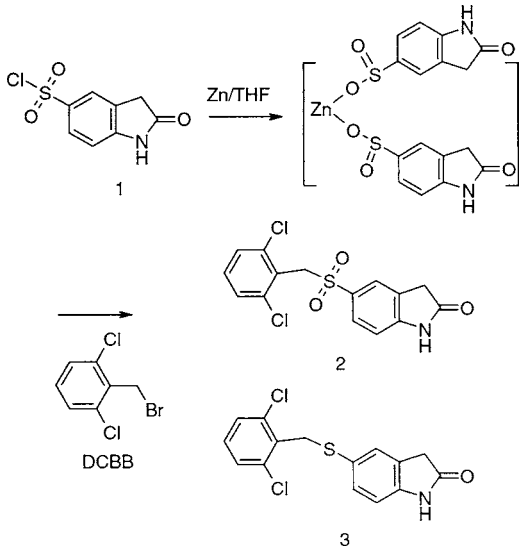
Sulfone 2 was initially prepared using a zinc-mediated one-pot coupling procedure. A traditional sodium sulfite-mediated two-pot procedure was found to eliminate a major impurity, yet modest yields prevailed. Design of experiment methods with the aid of a basic parallel synthesizer rapidly led to a high-yielding one-pot process.

Design of experiment (DoE) has increasingly been applied to the process development of active pharmaceutical ingredients. Process chemists engaged in the preparation of preclinical or early clinical supplies have generally shied away from the use of DoE, due to the perception that DoE is for nominal optimizations and requires a large commitment of time and effort. Furthermore, this view is exacerbated by a general lack of knowledge concerning the fundamentals of DoE and when it should be applied. In this note, we would like to dispel some of these perceptions by disclosing an application of DoE that has had immediate impact on our early development efforts.

The conversion of sulfonyl chlorides to sulfones had been studied extensively prior to the1960s. It was traditionally accomplished via reduction of a sulfonyl chloride, with zinc or sodium sulfite;[1] the resulting sulfinic acid salt[2] was then alkylated to form the sulfone.[1] The procedures usually required two pots, with the sulfinic acid salt as the lone isolated intermediate. Similar one-pot transformations employing various metals have been reported in recent years, e.g., Zn,[3] In,[4] and Fe.[5]

For the preparation of an active pharmaceutical ingredient, we needed quick access to tens of grams and later kilograms of sulfone (**2**). After a literature survey we settled on a Zn-mediated one-pot coupling of a sulfonyl chloride (**1**) and 2,6-dichlorobenzylbromide (DCBB) (Scheme 1). During our initial research, on gram scale, we found that aqueous

Scheme 1



ammonium chloride served well to activate the Zn metal in situ. Simple addition of DMF[6] and the sulfonyl chloride (**1**) to the aqueous Zn medium allowed sulfinic acid salt formation within 30 min; finally addition of DCBB allowed the desired product to form in 6 h. The yields for the one-pot transformation were consistent (40−45%), and a sulfide byproduct (**3**) was always noted in a range of 1.6−2.5 area % (HPLC). While the yield was low, this was offset by the low cost of the starting materials and our immediate need for compound **2**. As a consequence the process was pursued on the tens of grams scale.

However, even on modest scale-up (10−50 g) the yield (10−30%) and purity (sulfide byproduct 5−11 area %) of the isolated sulfone decreased significantly. With our process in question we looked closely at a variety of reaction parameters. Modification of the workup, namely cooling (5 °C) and addition of fewer equivalents of HCl (0.9 equiv, 2.0 N), reduced the sulfide byproduct to the manageable range of 2−5 area % (HPLC).[7] Encouraging as this was, a closer evaluation of the process showed it lacked robustness.

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(5) Saikia, P.; Laskar, D. D.; Prajapati, D.; Sandhu, J. S. *Chem. Lett.* **2001**, 512.

(6) To our knowledge this is the first reported use of DMF for this type of transformation. When the typical solvent THF was employed, ≥1 day was required for complete reaction.

(7) The extreme insolubility of the product **2** and the sulfide **3**, ruled out the use of traditional crystallization scenarios. Ultimately we found that enrichment could be effected by heating the sulfide-rich sulfone in an EtOAc/DMF (2:1) mixture for 15 min at 60 °C, followed by hot filtration. When repeated twice, this allowed a 70 wt % recovery with a 50% reduction in the sulfide content.

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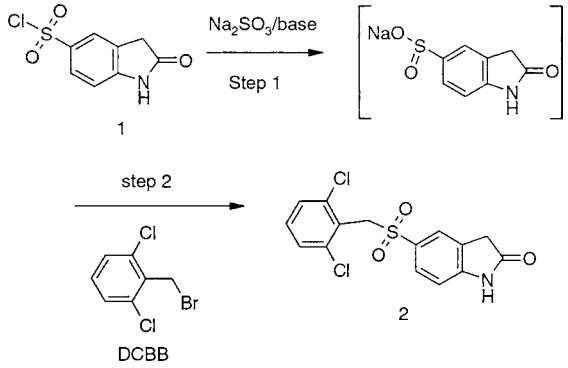
Scheme 2



Seemingly subtle adjustments to a large number of reaction parameters (mode of agitation, slight increases in alkylating agent, concentration of aqueous NH_4Cl, etc.) dramatically lowered the yield and quality of the isolated sulfone. The optimal conditions found at the 40-g scale provided a 39% yield of the sulfone, contaminated with 1.9 area % of the corresponding sulfide when magnetic stirring[8] was employed. At this juncture, we decided to pursue alternative methodology for this coupling.

We turned our attention to the two-pot procedures, particularly the ones using Na_2SO_3.[1] Sodium sulfite is water-soluble and has inherently lower reductive potential than Zn. This was important to us, if the sulfide byproduct was to be mitigated. Using the traditional reaction conditions,[9] the initial trial was quite promising. Treatment of compound **1** with Na_2SO_3 and sodium bicarbonate in water provided the presumed sulfinic acid salt intermediate in 73% yield (Scheme 2). When this intermediate was reacted with DCBB in DMF, compound **2** was isolated in 78% yield. The 53% overall yield was a modest improvement over the Zn procedure, but importantly, no sulfide impurity was observed. However, several problems did exist: (1) extreme foaming was noted when the sulfonyl chloride and sodium bicarbonate were mixed, (2) filtration of the intermediate was very slow, due to its small particle size, and furthermore (3) the one-pot sequence, without intermediate isolation, only resulted in an overall 30% yield.

We still preferred a one-pot procedure for scale-up. However, before initiating a study of the one-pot process, a few concerns needed to be addressed. The use of DMF was undesirable considering the moderate solubility of product in this solvent. A solvent screen for step 2 identified acetone as a convenient and environmentally friendly replacement for DMF. In addition, we replaced $NaHCO_3$ with Na_2HPO_4, thereby avoiding gas evolution. When stronger bases were employed, a side reaction became dominant and resulted in much lower yields of the sulfone. Presumably, the side reaction resulted from reaction at the acid labile 3-position of the oxindole.

Table 1: **Results of 2^3 full factorial design**

	factors			response
standard order	A: sulfite amt (equiv)	B: time (h)	C: temp (°C)	yield[a,b] (%)
1	2	6	60	88
2	4	6	60	42
3	2	24	60	93
4	4	24	60	49
5	2	6	100	87
6	4	6	100	58
7	2	24	100	75
8	4	24	100	31
2*[c]	4	6	60	48

[a] Step 1: All the ingredients (1-mmol scale) were shaken in water (2.0 mL) at the stated temperature and time. [b] Step 2: Mixture from step 1 was cooled to 60 °C, and DCBB (240 mg) and acetone (2 mL) were added and stirred for 1 h. The mixture was then poured into water (14 mL), cooled to room temperature, and filtered to give compound **2**. Yields were corrected for potency. [c] Duplicate of 2. The difference of 6% in yield is considered as the error for these runs.

During our solvent screen for step 2, we also gained further understanding for the alkylation step, noting it was facile and unlikely to be problematic. Thus, step 1, the reduction, would be the focal point for improving the yield. Consequently, it would be possible to use a one-variable-at-time (OVAT) approach. However, the time required to develop a successful process was of critical importance to our overall goals. Furthermore, OVAT may not identify the interdependence of significant reaction factors, i.e., interactions. Therefore, we decided to employ a DoE method with the aid of a parallel synthesizer to accelerate identification of significant factors and the possible interactions between them. The ultimate goal was to define a simple and high-yielding one-pot procedure.

On the basis of our initial data and intuition, we identified three factors likely to have the greatest impact on step 1. They were equivalents of sodium sulfite, reaction temperature, and reaction time. We did not consider the amount of base as a factor, since in theory only 1.0 equiv is required. A total of nine reactions were performed (reaction 9 was a duplicate of reaction 2 to gauge reproducibility) in a parallel synthesizer[10] (Table 1). The resulting yields were entered into the Design Expert software.[11] The software analyzed the data and yielded several key plots. The normal probability plot (Figure 1) and ANOVA[12] showed that factor A (amount of sodium sulfite) and interaction BC were significant. Next, examination of a one-factor plot (Figure 2) revealed that less sodium sulfite (factor A) should allow greater yield. The interaction graph of BC (Figure 3) showed that reactions at

(8) Zinc dust (Aldrich Chemical Co., catalog no. 20, 998-8) aggregation was noted when overhead mechanical stirring was employed as the mode of stirring, and low yields (10−30%) resulted. The agglomeration phenomena observed with the zinc dust is relatively common. Magnetic stir bars have the advantage of physically grinding agglomerates against the face of the glass wall. This is not possible with an overhead stirrer. As a consequence, any reaction requiring physical action to liberate occluded material will not scale well unless something is used to provide this action. On scale-up, depending on the strength of the agglomerate, the use of a recirculating loop with a rotor/stator mill or a grinding sand mill generally corrects the problem. We would like to thank John VanAlsten of Pharmacia for his input regarding these insights.

(9) Field, L.; Clark, R. D. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 674.

(10) We used a parallel synthesizer, LabMate, that is made by Advanced ChemTech Inc. It has four temperature zones, six positions for each zone, and uses shaking for mixing.

(11) *Design Expert*, version 6; DoE software developed by Stat-Ease, Inc. The software is intuitive, but some basic knowledge of DoE is desirable. Our company statisticians provided an overview in a 1-h demonstration.

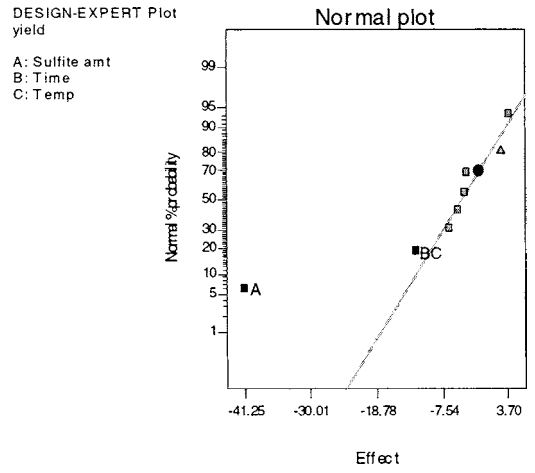


Figure 1.

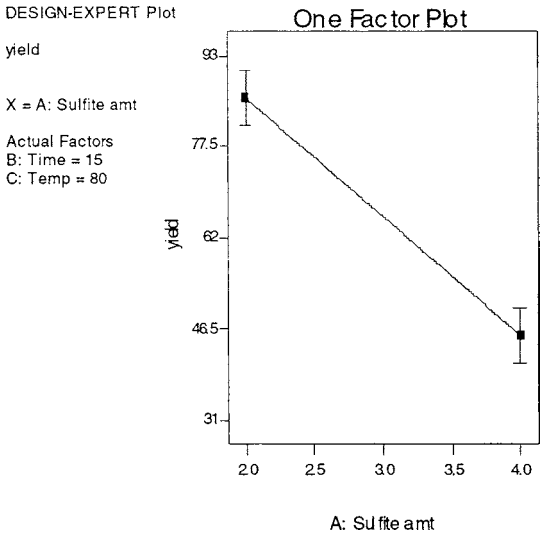


Figure 2.

high temperature required less time than those at lower temperature.

Although an optimization using more advanced DoE methods, such as the response surface method (RSM) may further improve yields, the results from experiments 1 and 3 (Table 1) appeared to be a reasonable starting point from a process chemist's perspective. Thus, experiment 1 was repeated on a 10-mmol scale using normal laboratory glassware and magnetic stirring. It provided sulfone (**2**) in 85% yield. However, a similar 10-mmol scale-up of experiment 3 resulted in a much lower yield (70%), probably as a result of inefficient magnetic stirring. This led us to speculate that mass transfer was an issue for this reaction. We then took a closer look at the solubility of the inorganic salts (Table 2) that were charged and generated during the reaction. It revealed that the aqueous reaction mixture was saturated with inorganic sodium salts. At the same time, the organic layer was a very concentrated acetone solution of DCBB. These facts led us to further speculate that the two saturated phases could generate a biphasic reaction mixture that may have a poor mixing profile. However, the corresponding potassium salts are generally more soluble than the sodium salts (Table 2), and we felt might give superior results in this reaction.

(12) The definition of these terminologies, such as normal probability plot, factor, interaction, etc. may be found in any statistics or experimental design books, such as *DOE Simplified: Practical Tools for Effective Experimentation*, written by the developers of Design Expert. We found a contribution published in this journal very informative: Owen, M. R.; Luscombe, C.; Lai, L.-W.; Godbert, S.; Crooke, D. L.; Emiabata-Smith, D. *Org. Process Res. Dev.* **2001** *5*, 308.

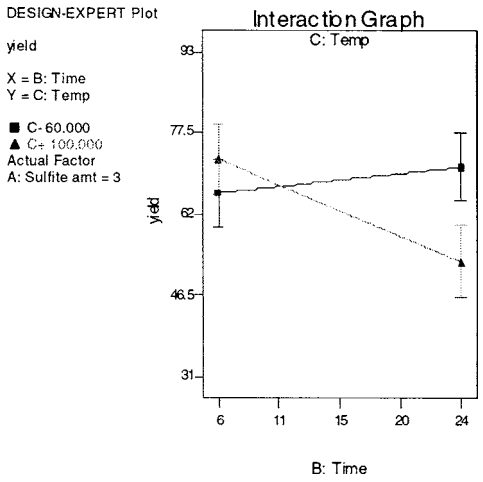


Figure 3.

Table 2: **Solubility of inorganic salts**

salt	equiv at start of reaction	equiv at end of reaction	mol/L (0 °C or 20 °C)	mol/L (100 °C)
NaCl	0	1.0	6.1	6.7
Na_2SO_3	2.0	1.0	1.0	2.2
Na_2SO_4	0	1.0	0.33	2.9
Na_2HPO_4	1.0	0	0.39	0.66
NaH_2PO_4	0	1.0	0.44	3.1
KCl	0	1.0	4.6	7.6
K_2SO_3	2.0	1.0	5.1	5.1
K_2SO_4	0	1.0	0.69	1.4
K_2HPO_4	1.0	0	9.6	>9.6
KH_2PO_4	0	1.0	2.4	6.1

There are a number of factors in step 2 with potential mass-transfer implications, such as reaction concentration, counterion (Na or K), phase-transfer catalyst (PTC), solvent, and reaction time. Time constraints would not allow these parameters to be studied using the one-variable-at-a-time approach. On the other hand, a fractional factorial design could potentially identify at least some significant factors. We decided on a 2^{8-4} study of a one-pot procedure that incorporated most mass-transfer factors plus the factors in the earlier study. We opted to use this low-resolution design due to limited resources. Our goal was to identify if any mass-transfer factors were significant (Table 3).

From the normal probability plot (Figure 4) and ANOVA, the AC interaction is significant (AC is confounded with the BG, DF, and EH interactions). None of the main effects that have mass transfer implications were actually significant, such as concentration (A), counterion (E), presence of phase-transfer catalyst (F), reaction time of step 2 (G), and solvent type (H). The lower yield in one of the 10-mmol scale-ups may be simply because of a poor magnetic stirring in an isolated incident, as we had speculated. This analysis gave us the confidence that mass transfer should not be an

Table 3: **Results of 2^{8-4} fractional factorial design**

	factors								response 1
run	A: concentration (mmol/mL)	B: amount of sulfite (equiv)	C: temperature (°C)	D: time of step 1 (h)	E: Na or K	F: PTC	G: time of step 2 (h)	H: solvent (min)	yield (%)
1	0.25	2	60	6	Na	no	1	Acet	74.2
2	0.5	2	60	6	Na	yes	2	DMF	82.6
3	0.25	2.5	60	6	K	no	2	DMF	60.1
4	0.5	2.5	60	6	K	yes	1	Acet	84.6
5	0.25	2	80	6	K	yes	2	Acet	73.6
6	0.5	2	80	6	K	no	1	DMF	79.8
7	0.25	2.5	80	6	Na	yes	1	DMF	75.8
8	0.5	2.5	80	6	Na	no	2	Acet	78.1
9	0.25	2	60	24	K	yes	1	DMF	72.5
10	0.5	2	60	24	K	no	2	Acet	77
11	0.25	2.5	60	24	Na	yes	2	Acet	71.3
12	0.5	2.5	60	24	Na	no	1	DMF	75.8
13	0.25	2	80	24	Na	no	2	DMF	71.9
14	0.5	2	80	24	Na	yes	1	Acet	68.8
15	0.25	2.5	80	24	K	no	1	Acet	79.8
16	0.5	2.5	80	24	K	yes	2	DMF	65.2
9*	0.25	2	60	24	K	yes	1	DMF	73.6

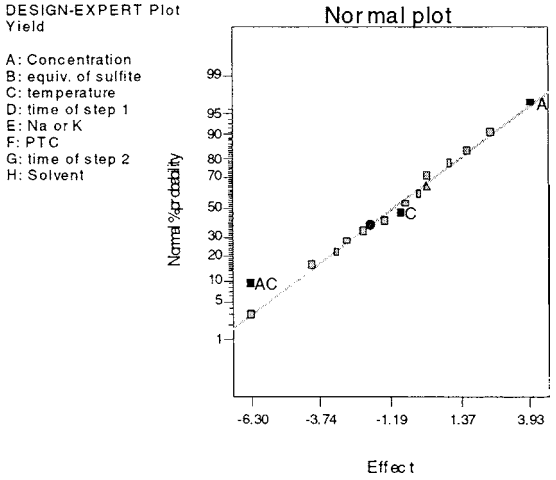


Figure 4.

obstacle. Thus, by simply increasing the reaction time of step 2 and using vigorous mechanical stirring, we were able to achieve a 90% isolated yield with >99% purity on a 30-g scale, with no detectable amount of sulfide impurity **3** noted (HPLC). Finally, a 300-g scale reaction incorporating all our findings resulted in an 88% isolated yield.

In summary, with a basic parallel synthesizer and several simple DoE designs, we were able to develop a reproducible and high-yielding reductive sulfonylation in less than 3 weeks. Moreover, the final process only uses water and acetone as solvents, in addition to a benign reducing agent, sodium sulfite. This study demonstrated that a combination of DoE and parallel synthesizers can be important tools for early process chemists.

Experimental Section

General Procedures. Solvents and reagents were used as received from vendor. 2,3-Dihydro-2-oxo-1H-indole-5-sulfonyl chloride **(1)** (CAS 199328-31-9) was supplied by Austin Chemical Company, Inc. ^{1}H and ^{13}C spectra were obtained using a Bruker Avance 400 in dilute DMSO-d_6 solution. Chemical shifts are reported as δ (ppm) values from Me_4Si as an internal standard. HPLC was analyzed on an Agilent 1100 series system. Elemental analysis was conducted in Analytical Service within Pharmacia Corporation.

Preparation of 5-[(2,6-Dichlorobenzyl)sulfonyl]-1,3-dihydro-2H-indol-2-one (2). *Zn-Mediated Sulfonylation.* Zn dust (11.3 g, 17.3 mmol), was added to DMF (420 mL) and aqueous NH_4Cl (105 mL, 2.0 M) and stirred for 15 min; 2,3-dihydro-2-oxo-1H-indole-5-sulfonyl chloride **(1)** (40.0 g, 17.3 mmol) was then added over 30 min, allowing a controlled exotherm to occur. The heterogeneous solution was then stirred for 45 min followed by the addition of 2,6-dichlorobenzyl bromide (41.4 g, 17.3 mmol) and then heated at 40 °C for 6 h. The reaction mixture was then diluted with 200 mL of water, cooled to 5 °C, quenched with HCl (40 mL, 2.0 N), and stirred for 10 min. Finally the reaction mixture was filtered and the cake washed with water (100 mL × 2), EtOAc (40 mL × 2), and MeOH (30 mL). After air-drying in a large crystallizing dish, 23.50 g of compound **2** (39% yield) was obtained with 1.88 area % of sulfide byproduct **3**. Enrichment of the crude product is possible.[7]

Sulfite-Mediated Sulfonylation. Na_2HPO_4 (142 g, 1.0 mol) and Na_2SO_3 (252 g, 2.0 mol) were dissolved in 2 L of water and heated to 30 °C. This solution was then added to compound **1** (232 g, 1.0 mol). The creamy suspension was heated at 60 °C (became clear, then suspended) for 16 h. 2,6-Dichlorobenzyl bromide (240 g, 1.0 mol) in 1.8 L of acetone was added to the above suspension over 60 min with vigorous stirring at 60 °C followed with an acetone rinse (200 mL). White solids formed immediately. The mixture was stirred at 60 °C for 2 h and then quenched into 5 L of water. The white slurry was stirred at room temperature for 1 h. It was then filtered and washed with water (1 L) and acetone (1 L), and subsequently dried in vacuo at 60 °C overnight to give 314 g of compound **2** as a white powder (88%). ^{1}H NMR (DMSO-d_6) δ 7.55−7.50 (m, 4H), 7.40 (m, 1H), 6.96 (d, 1H, J = 8 Hz), 4.80 (s, 2H), 3.57 (s, 2H).

HPLC: rt = 5.41 min (sampled prepared in ACN:DMF = 9:1, 0.5 mg/mL). HPLC conditions: Zorbax RX-C8, 250 mm × 4.6 mm, UV = 254 nm, flow rate = 1.0 mL/min, inject volume = 5.0 μL, gradient (ACN:0.1 M NH_4OAc): 0 min, 50:50; 7 min, 50:50; 10 min, 100:0; 13 min, 100:0; 15 min, 50:50; 18 min, 50:50. Anal. Calcd for $C_{15}H_{11}Cl_2NO_3S$: C, 50.58; H, 3.11; N, 3.93. Found: C, 50.21; H, 3.06; N, 3.86.

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