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Holistic Route Selection

Ronald B. Leng,* Mark V. M. Emonds, Christopher T. Hamilton, and James W. Ringer

Engineering and Process Sciences, The Dow Chemical Company, Midland, Michigan, United States

ABSTRACT: New agrochemical, fine chemical, and pharmaceutical products often require the development and selection of economical and effective chemical routes to enable commercial success. Atom economy and reaction step minimization are key drivers for low-cost routes. In addition, capital requirements, process operability and robustness, environmental health and safety, supply chain, quality, and intellectual property factors should be considered in the selection process. A holistic evaluation of process route options by a multidiscipline team of chemists and engineers early in the route-selection phase can result in the selection of a better route with a more focused process development research plan. Examples from three Dow AgroSciences projects illustrate route selection criteria.

INTRODUCTION

Inventing, developing, and commercializing new chemistry and products rapidly is a key for sustained profitability in the agrochemical, fine and specialty chemical, and pharmaceutical markets. New products will require the development of efficient synthetic routes and robust manufacturing processes. ***Route Selection*** is a key process development activity and must be made prior to development of a commercial process; thus, an efficient method of selecting the route is imperative.

The selection of the optimal route is much more complex than simply choosing the route with the fewest reaction steps or the lowest raw material cost. Decisions made at this stage of development will impact the project economics, safety, and operability of the process for several years. Some of the factors which should be considered are chemical yields, raw material cost and availability, capital requirements, process operability and robustness, environmental health and safety (EH&S) impact, quality, and intellectual property considerations. A discussion of these factors along with examples from three Dow AgroSciences projects will be included to illustrate these route selection criteria.

It is our hope that these examples will show that the optimum route is not always so obvious at first inspection. It is further offered that many of the approaches used to develop a route for an agrochemical active ingredient is applicable to other organic molecules such as active pharmaceutical ingredients. A holistic evaluation of process route options by a multidiscipline team of chemists and engineers early in the route selection phase can result in a faster selection of a better route with a more focused research plan, which can save time and money both now and in the future.

DISCUSSION AND ANALYSIS

Background. There are many process development aspects related to commercializing a new product which must be prioritized and balanced. Anderson,[1] in his chapter on route selection, points out the need for "expedient" routes to make samples quickly to start clinical studies, and then later "optimal routes" for commercialization. Pisano[2] discusses a strategy of "rapid cycling" where nonoptimized routes are used to enable faster market introduction, but are replaced by ever-evolving, more efficient processes for longer-term manufacture. Sharratt[3] covers the differences in process features and decision criteria between "bulk chemical" and "specialty chemical" processes. Parker and Moseley[4] and Moseley and co-workers[5] recently published papers in which they describe the use of the Kepner–Tregoe decision analysis approach to rapidly evaluate and screen a large number of potential routes to a target compound, ultimately reducing the number of route options to take to the lab for further development. Butters[6] and colleagues present a thorough review of route selection criteria using the acronym SELECT for Safety, Economics, Legal, Environmental, Control, and Throughput.

Process Development Stages. Within Dow, the development of a new agrochemical process proceeds through three major stages; Route Selection, Process Development, and Scale-up and Implementation. Figure 1 shows a typical timeline and slate of activities for a new agrochemical compound from the advancement from "Discovery" through "Commercialization". Typically, a target active ingredient is advanced from the Dow AgroSciences discovery department to our Dow Central R&D process development group after it has met technical performance and financial targets. The acute and chronic toxicology studies are normally on the critical path to registration of a new active ingredient. To enable these studies a large sample of the active ingredient (up to 500 kg) is produced in a pilot plant. This "Tox Sample" is also used for formulation research and field testing studies. The initial process chemistry focus is to ensure that a reasonable and safe route is employed in the pilot plant. Following synthesis of the large sample, a team of chemists conceive and evaluate alternate routes, and then select the preferred route. Once the chemical route is defined, a process development team of closely collaborating chemists and engineers will develop a scaleable commercial route. First, reagents, catalysts, and solvents are chosen. Next, isolation points and unit operation sequences are selected. Recycle strategies and waste treatment methods are evaluated and incorporated into the process concept. Process flow sheets and mass and energy balances are generated. In the

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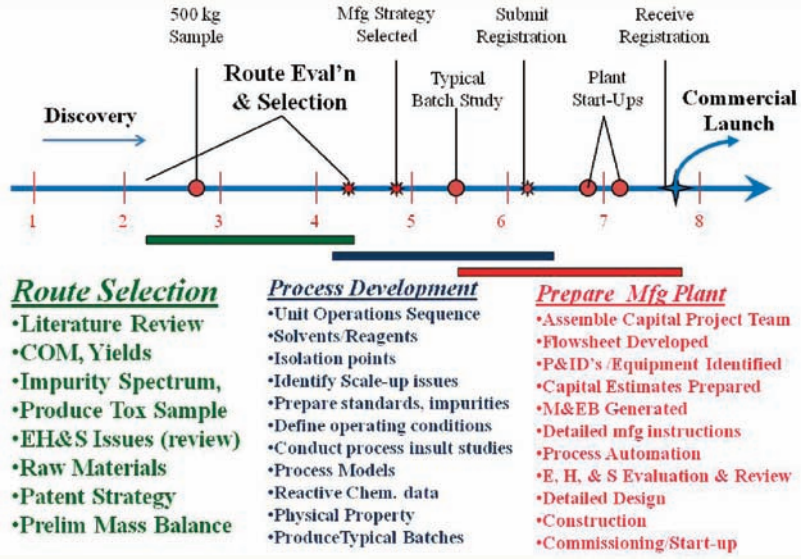

Figure 1. Typical development timeline for an agrochemical.

next stage, variables such as stoichiometry, temperature, pressure, and addition modes are defined and summarized in a detailed operating procedure. These activities often overlap, and there is some iteration of the process as more is learned. The next step is the process demonstration stage where the process may be run at the pilot scale to verify performance and to generate plant design data. Finally, the process is scaled up either to a new or existing production plant to produce commercial quantities. Clearly then, selection of a sound chemical route is the foundation of a good manufacturing process.

Cost of Manufacture Estimate. The cost of manufacture (COM) is often the dominant factor in selecting the commercial route. The total manufacturing cost comprises a variable cost component, which is related to the amount of product produced, and fixed costs, which are largely independent of volume produced by a certain plant. A cost model and disciplined approach should be used to estimate costs for each route.[7]

Early-stage cost estimates should be presented as a range with estimated probability of achieving various levels, as opposed to reporting a single number. A sensitivity analysis should be performed on the key input variables, and the assumptions should be clearly documented for each case. A useful method is the Monte Carlo simulation approach where a predetermined range or distribution of values is selected for each key variable affecting the cost estimate. For instance, the expected yield of a key reaction step may be 85% with a range from 75 to 90%, or the expected price for a raw material may be $12/kg with a range of $9 to $20. A computer program runs through thousands of iterations using the individual parameter distributions in a series of combinations. The output then is a range of manufacturing costs along with the probability that the estimate will fall within a selected percentage of the range. It is also a good idea to perform a discounted cash flow (DCF) analysis over the life of the product. This takes into account the time value of money. Capital must be borrowed at some interest, or "discount" rate at the beginning of the product life. A DCF analysis may illuminate that a route with a higher raw material cost, but lower capital is favored, especially considering that the commercial viability of the product is still unproven. Typically, the unit cost will decrease in time as improvements are implemented and capital is depreciated. Adjustments for inflation of labor and raw material costs can be built into the cost model. In the end, having knowledge of the relative cost contribution of each of the components is useful not only in selecting the route but also for shaping, defining, and optimizing the process as it advances toward commercialization.

Fixed Costs. The capital and conversion costs (fixed costs) are more difficult to estimate than variable costs and can have a large effect on the total cost, particularly at lower production volumes as shown in Figure 2. Fixed costs include a

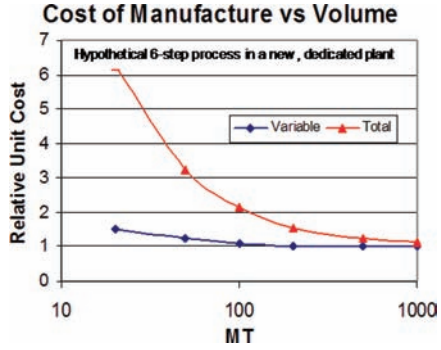

Figure 2. Relative impact of volume on cost of manufacture.

depreciation charge related to the initial capital investment, labor, maintenance and supplies, tax, insurance, and other overhead cost. There are many techniques to estimate capital; however, most require equipment flow sheets, which are usually not developed at the route selection stage.

Within Dow we have developed methods to estimate fixed costs on the basis of historical data from many internally manufactured products. The key inputs are the volume and the number of chemical transformations or, preferably, the number and type of unit operations. Allowances for exotic materials of construction and extreme processing conditions (temperature, pressure, very low concentration, or very slow reactions) are made as they will increase capital and operating costs. Other estimating tools which take into account the types of chemical

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reactions involved are available to predict COM at external manufacturers.[8]

Variable Costs. The variable cost is a function of raw material price, stoichiometry, reaction yields, and recycle rates of solvents or reagents used in excess. The order of the synthesis can have a direct impact on the cost of raw materials. Convergent syntheses are generally more economical than linear routes. If expensive reactants are required, it is best to use these in steps toward the end of the synthesis. In general, the fewer the steps and better atom economy, the lower the overall cost of manufacture.

An Internet search of the Directory of World Chemical Producers (http://www.chemicalinfo.com/) followed by direct phone calls to suppliers is the best method to get accurate pricing. Separate cost estimates may have to be made for unique reagents or intermediates that are not available commercially. Raw material price variability should be included in the cost sensitivity analysis. For each raw material used in the process, the researcher should understand that there will be capital, operational, and other costs incurred in addition to the purchased cost of the raw material. So adding one extra reagent to improve the yield slightly may seem like a good idea, but a total cost of manufacture analysis may prove otherwise.

A significant portion of the total variable cost can be incurred to treat and dispose of byproduct waste streams. A simple method of accounting for this cost is to sum up the total mass input, minus the product output, and then multiply the difference by an assumed unit cost for waste disposal. As the process becomes more refined, specific costs for incineration, aqueous treatment, or landfill can be applied. Certain wastes can be difficult and costly to treat.

Energy costs have long been an important consideration for high-volume, low-cost, commodity-type chemicals. The recent surge in energy costs will begin to have a larger effect even on low-volume, high-cost specialty products, particularly for processes with significant heating and cooling requirements, and so should be considered.

Environmental Health and Safety (EH&S) Factors. When developing and selecting a chemical route it is important that environmental health and safety considerations are addressed early. An approach we use is to conduct an Early Stage Review (ESR) of route options by a panel of subject matter experts from Process Safety, Reactive Chemicals, Industrial Hygiene, Operations, EH&S Delivery, Regulatory, Environmental Operations, and Business Technology Centers. In the ESR the Project team presents an overview of the technology with a focus on EH&S issues. The panel asks probing questions, identifies issues the project team may not have considered, and identifies contacts to help resolve issues necessary to make the route selection decision.

Environmental Factors. In addition to the costs discussed above, there are specific elements which pose problems for incineration such as iodine, bromine, lithium, or heavy metals. Specific regulatory rules make simple aqueous disposal more difficult than in the past. Waste treatment options may drive the selection of the manufacturer and manufacturing site. Typically, if it is not known that a waste can be treated at a local treatment facility, we assume that a volatile stripping operation followed by carbon adsorption will be required at a minimum. These operations should be shown on the flow sheet. Organic vapor streams are usually destroyed in a thermal oxidizer, while acidic vapors can usually be scrubbed. Process odors can have a large impact on manufacturing site selection.

Safety and Health Factors. Decisions made at the time of route selection will have a long-term impact on the safety of operating personnel for many years. The "Inherently Safer Design" (ISD) approach to process development was proposed by Trevor Kletz[9] in the 1980s. The basic premise of ISD is that it is better to reduce or eliminate the hazard rather than to add safety systems to deal with the hazard in the plant. Many of these ISD principles including "elimination", "intensification", "substitution", "attenuation", and "limitation of effects" are very useful guides for the process chemist during the route selection phase.

A viable commercial route must be safe to operate at production scale. A few safety and health related factors which should be considered in selection of the route are given in Table 1.

Table 1. Process safety and health considerations

key issue	route or process design consideration
highly exothermic reaction	limit potential energy in system, consider continuous processing
thermal runaway potential	use thermo chemical evaluation tools determine point of no return vs operating point to establish safe window of operation
flammable solvents and reagents	understanding of flammability envelope, substitution of safer reagent
unstable reagents and intermediates	minimize amount on hand; store under stabilizing conditions, temp, pH, ox/red; store in dilute solution; avoid isolation
highly reactive reagents	may need special precautions to eliminate the hazard (i.e., air or water)
formation of organo-peroxides	vents need to be well purged, stabilizers may need to be added
toxic reagents, intermediates, and side products	obtain tox data, avoid isolation, avoid solid reagents of high toxicity, generate hazardous reagents in situ from safer materials

While some of these issues will not be known or completely addressable at the route selection stage, they will become important in the future, so thinking about this ahead of time is a good idea.

Control of highly exothermic reactions at large scale can be challenging. Calorimeters or thermodynamic calculations should be used to determine the heats of reactions of interest. Limiting the potential energy in the system by such means as metered addition can often be employed. Fast, energetic chemistry may be amenable to continuous processing where the heat removal area/reactor volume is more advantaged. It is good to understand if there is a potential for a thermal runaway and where the "point of no return" is, relative to the operating temperature of the system. Use of accelerating rate calorimetry[10] (ARC) is an effective technique to understand where the exponential rate of heat evolution from the chemistry exceeds the linear rate of heat removal from the system. Reactions that run near the edge of controllability are absolutely to be avoided. It is also necessary to understand the flammability, reactivity, compatibility, and toxicity of envisioned solvents and reagents. Often routes will go through new intermediates with unknown toxicity; thus, a simple battery of acute toxicity tests (oral, dermal, eye, and skin sensitivity) plus an AMES test[11] to assess mutagenic potential can be a wise investment, particularly if the intermediate will be isolated.

Routes using less energetic chemistry and more benign materials are desired. Continuous processing can provide benefits by minimizing the amount of toxic or hazardous

reagent. In situ generation of a toxic reagent from safer precursors is also a good strategy. Additional capital and operating cost may be incurred to handle hazardous materials and to comply with regulatory mandates. Ultimately, researchers need to understand the inherent energy in the system, the potential conditions for release of the energy, and the means of controlling the system safely.

Scaleability of the Chemistry and Process. The simplicity, operability, and robustness of the chemical process are also important considerations for the selection of the synthetic route. Table 2 presents a few of these factors that may serve to further differentiate the routes being evaluated.

Table 2. Process operability and robustness

key issue	route or process design consideration
batch or continuous	batch – traditionally used for small-volume specialty chem., slow kinetics, relatively easy mixing
	continuous – typically used for high-volume commodity, homogeneous, gas phase, fast kinetics
chemistry consistency	inconsistently performing reaction steps increase cost and adversely affect quality
familiarity w/ chemistry	reaction steps which have been scaled previously pose less risk; expertise can be leveraged for more efficient start up
challenging conditions	temperatures outside of −15 °C < T (process) < 150 °C; pressures outside of 10 mbar < P (process) < 10 bar; strongly acidic or basic conditions may require expensive materials of construction
reaction efficiency	dilute reactions <10% of substrate, or long reaction time >24 h will require larger, more expensive equipment
side chemistry	side reactions lead to lower yields and can complicate separation steps adding cost
catalyst	type of catalyst, ease of recycle or recovery, susceptibility to poisons will add cost
solvent volatility	highly volatile solvent may require refrigeration and/or high pressure containment; low volatility solvents may require vacuum, high temperature for solvent recovery
operating window	narrow operating widows will require more precise control and have larger consequences of deviation from control points
type of unit operations	solids isolation steps often involve more expensive equipment and are more unpredictable for scale-up than distillations or extractions; telescoping can have significant benefits
heat and mass transfer issues	heat removal and mass transfer are slower as the volume of the scale increases

One of the first decisions the process development scientist will need to make is whether the process will be run in ***batch*** or ***continuous*** mode. Batch processes are typically favored for low-volume processes with multiple and complex reaction sequences, whereas continuous processes are more often selected for high-volume products with fewer reaction steps. In recent years there is more interest in pursuing continuous processing techniques for low volume specialties even in the pharmaceutical industry.[12] As mentioned above, continuous reactions can have a real advantage for lower capital, more efficient heat removal and for minimizing volumes of hazardous reagents, so routes where reactions are amenable to continuous processing may have benefits.

Chemistry-Related Considerations. Simple, reproducible reactions are desirable because in scaling they pose less risk to the commercial plant. Reactions requiring more extreme temperature and pressure, or more precise control of input variables such as stoichiometry, may incur more scale-up risk. Reactions that fail spectacularly for apparently unknown reasons are to be avoided. Selecting a route with chemistry that has been proven robust at large scale may have an advantage over a route that offers other apparent advantages but is unproven on scale. If an expensive catalyst is required to facilitate the reaction, the feasibility to reuse, recycle, and remove it from the process, as well as its resistance to fouling or poisoning will be important to understand.

Engineering-Related Considerations. In our experience a larger portion of the total capital and operating costs for a new process are required for separation, purification, and waste treatment systems than for the reaction systems and so should be identified as early as possible for each route. Scale-up issues[13] such as mass and heat transfer, solids processing, and the impact of trace chemistry, particularly in recycle loops, are addressed in later stages of process development, but should also be considered during route evaluation. Solid isolations can be quite challenging, particularly if they are hygroscopic, sticky, or pose a dust explosion potential. Separations such as a high vacuum distillation requiring several stages or an extraction that is fraught with emulsions are to be avoided if possible. Routes that can be telescoped offer significant advantages by eliminating difficult or costly separation steps. Reactions which have a wide processing window are generally easier to operate. This can be more important if the process is likely to be run at an external manufacturer who may not have sophisticated process control systems. Again, it is better to select unit operations and processing methods which have been used successfully at production scale over new, unproven techniques which might require significant piloting expense.

Supply Chain Factors. At some point in the future the chemistry being developed will need to run in a manufacturing plant, consequently, supply chain factors should also be included in the route evaluation. A few of these typical factors are included in Table 3.

Table 3. Supply-chain-related considerations

key issue	route or process design consideration
external expertise needed	extremely hazardous or highly toxic chemistry may require specific manufacturing expertise
proprietary technology	risk of losing IP may drive internal manufacturing
stable intermediates	allow for campaigning and reusing equipment for multiple manufacturing segments
similar chemistry	routes that employ the same reaction step tend to be more amenable to fitting into an existing, underutilized asset
common raw material base	avoiding reagents that are only available from a single source is advantageous for cost and supply reliability
regulated reagents	some reagents may not be available in the future or will have extra regulatory hurdles to overcome and thus should be avoided
product integrity	contamination from shared equipment; clean-out protocol needed

Some routes may involve chemistry which requires a particular capability that is outside of the company's expertise. This could include running highly energetic reactions, such as a nitration, or handling extremely toxic reagents such as hydrogen cyanide. The potential list of toll manufacturers may be limited by the unique requirements of the chemistry, so there will likely be a premium conversion charge. If a toll manufacturer is used, there may be a higher risk of the loss of intellectual property, and a greater potential for liability issues related to product contamination from operation in a multiproduct facility. Choosing a route that has stable intermediates and stopping points may offer advantages for running in campaigns which share equipment. Routes that use similar chemistry and reagents as other chemistry which is

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manufactured internally may offer a capital advantage, particularly if the new process can be operated in existing, under-utilized assets instead of in a new, dedicated plant.

The availability of raw materials is a key consideration for the viability of a route. If a raw material is only available from one or two sources the cost will likely be higher, and the supply potentially less secure, than if the raw materials are available from a large number of suppliers. Finally, some reagents and solvents may be regulated either currently or in the future, which may make them difficult to obtain or transport. Examples include compounds that are volatile organic compounds, "ozone depleters", known or suspect carcinogens, or are acutely toxic to aquatic organisms. While commercialization may be a long way off yet, any new chemical will have to be submitted to a regulatory agency prior to large scale manufacturing. It is best to consult with a regulatory expert who is familiar with the ever-changing laws governing specific countries where you expect to be manufacturing and selling product.

Quality and Product Performance Factors. The final product quality and purity must meet the customer's requirements and the regulatory guidelines for it to be a commercial success. Table 4 includes a few considerations in this area.

Table 4. Quality and product performance factors

key issue	route or process design consideration
new impurities	toxic impurities may cause registration issues
ease of purification	may need a final recrystallization to meet purity, may be need to reclaim off-specification batches
product performance	may be route or process sensitive, "product by process"
polymorphs	polymorphism may be route specific, chemical and physical properties may be different which may affect formulation performance

Ultimately registration approval must be obtained from the local governmental agencies which regulate the specific type of product being commercialized. For instance, agricultural chemicals are regulated in the United States by the Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). A confidential statement of formula (CSF), or specification, is established for the impurity levels in the active ingredient based on rigorous analysis of the chronic toxicological test lot and "typical batches" using the manufacturing process. This applies to all impurities at levels >0.1%. If one route is used for the toxicology studies and a different route is selected for the commercial process, new impurities may arise which can cause registration challenges. In the pharmaceutical industry, which is regulated in the United States by the Food and Drug Administration (FDA), similar and even tighter restrictions apply because the chemical will be introduced into humans. An added challenge for the pharmaceutical scientist is that the process for the active ingredient gets "locked in" during the clinical studies reducing some of the flexibility to change the process later. Each country has its own regulating agencies and laws governing the introduction of new chemicals into the marketplace, so a good knowledge of the regulatory hurdles that lay ahead and how they may be affected by the route being selected is important. One approach to reducing impurity levels is to incorporate purification steps along the synthetic pathway. Routes which are more amenable to purification, including reprocessing off-specification batches, offer advantages in this respect.

The active ingredient for both agrochemicals and pharmaceuticals are usually formulated with various additives in order to be effectively delivered to the target pest or patient. Many organic solids can exist in different crystalline lattice forms or polymorphs. While chemically identical these polymorphs can exhibit different chemical and physical properties such as reactivity, melting point or dissolution rate which can affect stability and bioavailability of the active ingredient and thus the efficacy of the product.[14] If polymorphism is exhibited it may be possible that different polymorphs result from different routes.

Intellectual Property Issues. Another important aspect of route selection is having a clear understanding of the patent position of each route. If the company can secure patents on the chemistry or process, this can serve as a competitive advantage. A patent search is a very important step in selecting the commercial route. Typically it is advantageous to gain

Route Selection Criteria Rating Tool

	Weighting	10	8	6	6	4	6	4	4	5	4	2	3		
	Route Selection Criteria (RSC)	Cost of Manufacture	Capital	Process Safety	Industrial Hygiene	Environmental	Process Robustness	Process Simplicity	Supply Chain Factors	Quality Factors	Intellectual Property	Upside Potential	Synergy w/ other Processes	Other	Total
	Route														
	A	3	3	9	3	3	9	9	3	3	3	9	9		312
	B	1	1	9	3	3	3	3	3	9	9	3	3		240
	C	3	1	3	9	3	1	3	9	3	3	3	3		218

1. List the Route Selection Criteria (RSC)
2. Define metrics for each RSC
3. Set the relative Weighting of each RSC
4. Rate each route on a 1-3-9 scale for each RSC
5. Cross-multiply and total

Figure 3. Example of route rating tool.

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"composition of matter" patents on specific molecules as these are broader than process patents and easier to defend. If a route has novel technology which is patentable, the effective patent life of the molecule may be extended. Also, it may be useful to patent competitive routes as a blocking strategy to keep other companies from making the product via these routes. Process patents filed later on significant improvements may be useful to strengthen the current manufacturing position after the composition of matter patents expire.

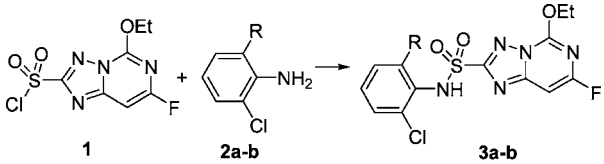
On the other hand, it is equally important to understand if there is freedom to operate the process outside of other company's patents. If a route is blocked by patented technology, it is important to understand the possibility and potential cost of licensing the technology if this is a viable route.

Analysis of the Rating Criteria. Often a clear, winning route is not apparent as there are many benefits as well as drawbacks to each route. There are many approaches to analyzing a set of choices against a set of criteria. One approach is to use a rating tool like a Decision Matrix or Pugh Matrix[15] where each criterion for each option is rated as being better (+), the same (S), or inferior (−) to a base route. A more quantitative decision matrix can be used where relative weighting is assigned to each criterion, and then the "performance" of each route against that criterion is assigned a value, either a "9", "3", or a "1". The sum of each criterion value multiplied by its weighting provides an overall score. This type of exercise can be useful to build consensus on the relative importance of each factor, and serves to document and communicate the rational for the selection to stakeholders in the organization. An example matrix is provided in Figure 3. In the following examples we will illustrate how some of these considerations discussed above contributed to the ultimate selection of the commercial route.

EXAMPLES SECTION

Diclosulam and Cloransulam-Methyl. Diclosulam and Cloransulam-Methyl[16] are two highly selective, low toxicity, soy bean herbicides that were developed and are marketed by Dow AgroSciences. They utilize the same nine-step synthesis to produce the penultimate sulfonyl chloride intermediate **1** as shown in Scheme 1. The two herbicides are then differentiated

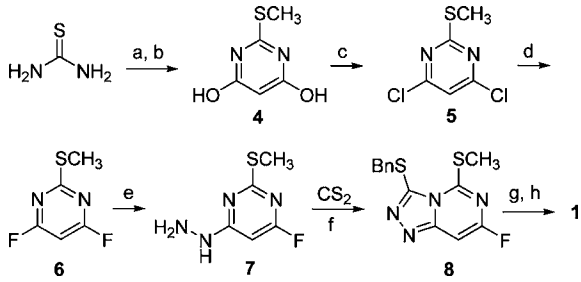
Scheme 1. Final coupling to diclosulam and cloransulam-methyl from common intermediate 1



for North and South American applications by the choice of the aniline in the final coupling step. The route selection process for this common intermediate illustrates the tension and trade-offs between many of the selection criteria previously discussed including (1) flammability concerns, (2) toxicity concerns, (3) atom economy and protecting groups, and (4) avoiding single source reagents. It also illustrates the value of including the engineering perspective in the selection of the route.

One of the key milestones in the early development of an agrochemical is the synthesis of a large sample, (typically 500 kg) that is produced prior to route selection. Since the toxicology work is almost always on the critical path to registration and commercialization, there is little time to do extensive research into more commercially attractive routes prior to making the large sample. Thus the focus of research at this early stage is to come up with a safe, reasonably scaleable route to make the large sample. For these two molecules, hydrazine and carbon disulfide (CS_2) were used to build the triazole ring onto a substituted pyrimidine moiety to form the thio triazolopyrimidine intermediate. This route was dubbed the "Thiomethyl Route" which is given in Scheme 2.

Scheme 2. Thiomethyl Route to intermediate 1[a]



[a](a) Diethyl malonate. (b) Dimethyl sulfate. (c)$POCl_3$. (d) KF. (e) N_2H_4. (f) benzyl chloride. (g) EtONa [Dimroth rearrangement]. (h) Cl_2.

Flammability concerns are often raised whenever manufacturing processes utilize organic solvents or reagents. During an Early Stage Review with manufacturing and safety and loss prevention experts, the use of CS_2 was identified as a cause for significant concern due to its flammability properties. CS_2 has an autoignition temperature of 90 °C and a very broad flammability envelope (1.3−50 vol % in air), such that a fire is likely to result if CS_2 escapes from the process equipment and finds a steam leak or other source of ignition. Flammability issues can often be mitigated through multiple lines of defense; with proper equipment design and selection, use of additional safety systems like nitrogen blanketing, and use of thorough safe operating procedures. These "add-on" systems all add capital and operating cost. Development of an inherently safer, alternate manufacturing process was therefore highly recommended by the review team.

A "Non-CS_2 Route" given in Scheme 3 was investigated to avoid using this hazardous reagent. While the number of steps was roughly the same as the Thiomethyl Route, there were significant differences that made this route cost disadvantaged by an estimated 30%. The Non-CS_2 Route had a lower overall yield (~10% vs ~20%), significantly more distillations and recycle streams, and a much larger byproduct waste volume. Since the heterocycle was built earlier in the synthesis, significantly more complex solid handling and isolations resulted. Additionally, the impurity spectrum from this route would likely be different from the tox lot which could cause issues in getting the molecules registered. For these reasons work on the Non-CS_2 Route was discontinued, and with no other promising route options forthcoming, focus shifted in favor of further exploration of the Thiomethyl Route.

The toxicity of reagents, intermediates, and final products is always a concern for any new process. As parallel work continued on the Thiomethyl Route it was discovered that intermediate **6** exhibited significant dermal toxicity potential.

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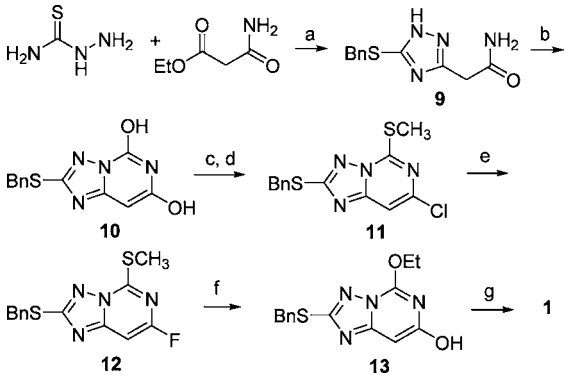
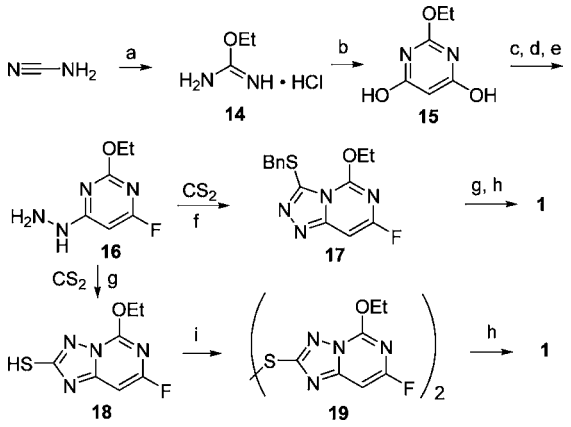
Scheme 3. Non-CS_2 Route to intermediate 1[a]



[a]Reagents and conditions: a) MeONa, BnCl; b) diphenyl carbonate; c) $POCl_3$; d) CH_3SNa; e) KF; f) EtONa; g) Cl_2.

Efforts were then directed on modifications to this route to get around the toxicity issue. The "Ethoxypyrimidine Route" was devised which had the same number of steps, and roughly the same overall yield and cost of manufacture projection. It also used CS_2, but went through lower toxicity intermediates than in the Thiomethyl Route. Without other promising route options, the Ethoxypyrimidine Route given in Scheme 4 was ultimately selected for commercial scale-up. Process research was then directed at developing a safe means of using CS_2.

Scheme 4. Ethoxypyrimidine Route to intermediate 1[a]



[a]Reagents and conditions: a) EtOH, HCl; b) diethyl malonate, EtONa; c) $POCl_3$; d) KF; e) N_2H_4; f) BnCl; g) EtONa; h) Cl_2; i) H_2O_2.

In our work, "route selection" infers that the primary synthetic pathway has been established. In the next phase of process development, the choice of reagents, solvents and unit operations are made. These decisions often have a large impact on equipment design, cost, safety and reliability of the process. One approach we evaluated to mitigate the CS_2 flammability concern was to generate CS_2 *in situ* by acidification of solid potassium ethyl xanthate salt. The concept did have the benefit of eliminating the transportation, storage, and transfer of liquid CS_2 into the reactor, and was shown to provide equivalent yields. However, difficulty in controlling the stoichiometry due to variability of the assay and charge amount of the solid xanthate salt caused us to set the load target high to ensure complete conversion of the expensive intermediate. Thus, a variable amount of excess CS_2 was always present in the post reaction mixture which caused further flammability issues in the subsequent centrifugation operation and associated vent system. Ultimately, a well-engineered CS_2 management system using returnable CS_2 containers, all welded transfer lines, precise liquid metering, nitrogen blanketing, oxygen sensors, fugitive vapor sensors, and an automatic water deluge system were lines of defense that were incorporated into the process design. While these "add on" systems added extra cost, they were deemed necessary. The process has been operated safely for several years at the production scale.

Optimization of atom economy is a key objective of any manufacturing process development effort. In both the Thiomethyl and Ethoxypyrimidine Routes, the labile sulfur on the sulfide intermediate (**18**) needed to be protected prior to the chloroxidation step as shown in Scheme 4. For simplicity, benzyl chloride was initially used as a protecting group directly after the sodium ethoxide-mediated Dimroth rearrangement step. The resulting solid sulfide intermediate was isolated by filtration and was stable to storage. In the subsequent chloroxidation step, benzyl chloride was liberated and needed either to be disposed of at significant raw material cost or to be recycled which would incur a higher capital and operating cost. To solve this issue it was discovered that a disulfide[17] (**19**) could be formed in which the one molecule of intermediate protected another. The disulfide bond was subsequently cleaved in the chloroxidation step affording the sulfonyl chloride in high yield. This eliminated the use of the external protecting group. An added benefit was that the overall yield of the disulfide-based process was slightly higher due to simplification of the chloroxidation step. Since there was no longer a need to remove the benzyl chloride protecting group, it was found that the sulfonyl chloride could be used directly in the final coupling reaction without isolation as shown in Scheme 4.

Finally, it is desirable to build the target molecule from as many readily available reagents as possible, and to avoid using specialty reagents that have limited availability. The selected Ethoxypyrimidine Route started with anhydrous cyanamide which was converted first to the *O*-ethyl isourea (**14**) followed by cyclization with either diethyl or dimethyl malonate in the presence of the companion alkoxide. Water in the isourea preparation was deleterious. Thus, anhydrous cyanamide was required, which was only available in limited quantities at considerable cost from one supplier. It was found that a 50% aqueous solution, available at a much lower cost from multiple sources, could be substituted using a carefully controlled, two-step evaporative drying process.[18] Cyanamide contains a good deal of energy in its triple bond and can dimerize or hydrolyze with the release of significant heat (−25 kcal/mol). This is exacerbated by high concentration, heat, and nonoptimal pH conditions. In this process, the bulk of the water was removed under vacuum while keeping the temperature well below the thermal runaway point. In the second step, the balance of the water was removed by isothermal azeotropic distillation with ethanol which was the solvent for the subsequent isourea formation. Redundant temperature measurement and an automatic water deluge system were employed as additional safeguards in the plant.

Penoxsulam. Penoxsulam[19] (**26**, Scheme 5) is the active ingredient in a highly effective sulfonamide rice herbicide which was commercialized in 2005. Several routes were evaluated during the route selection for this molecule. The key routes utilized a substituted phenyllithium intermediate formed by a

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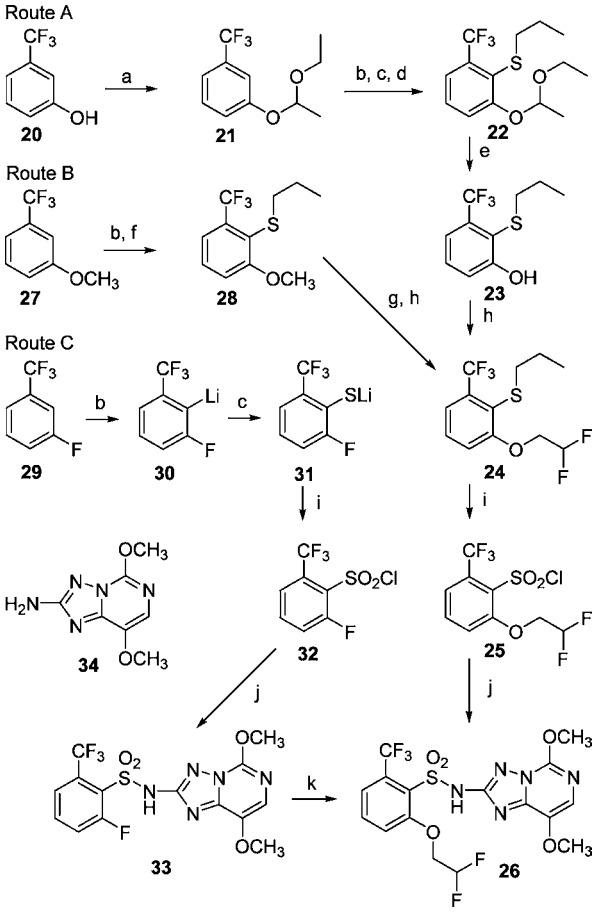
Scheme 5. Three routes to penoxsulam (26)[a]



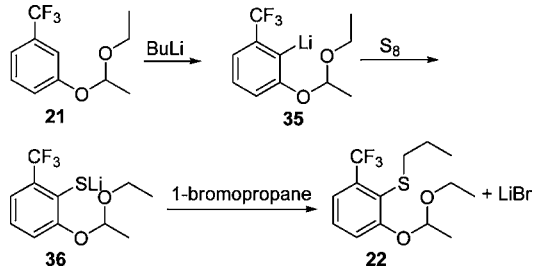
[a]Reagents and conditions: a) ethyl vinyl ether; b) butyllithium, THF; c) sulfur; d) 1-bromopropane; e) H_2SO_4, H_2O; f) dipropyl disulfide; g) NMP, distill; h) 1-bromo-2,2-difluoroethane; i) Cl_2; j) **34**, DMSO catalyst, base; k) 2,2-difluoroethanol, NaH, 1,4-dioxane.

regioselective metalation, which was converted to a thiol and subsequently a sulfonyl chloride (**25** or **32**). The sulfonyl chloride was coupled with a heterocyclic amine to form the sulfonamide. The routes differed in their initial starting material (a phenol for Route A, an anisole for Route B, and a tetrafluorotoluene for Route C), the number of chemical steps in the process, and the way in which the sulfur was incorporated into the molecule. This example is included to illustrate that a simple "reaction step count" is not always a good indicator of the best route.

Intuitively, the order of preference based on step count and atom efficiency would be Route C (five steps), followed by Route B (six steps) and as the last choice, Route A (eight steps) (Scheme 5). Early stage cost estimates were generated which showed that all three routes considered had roughly the same cost of manufacturing, within the error of the estimate. Therefore, other route selection criteria would drive the decision.

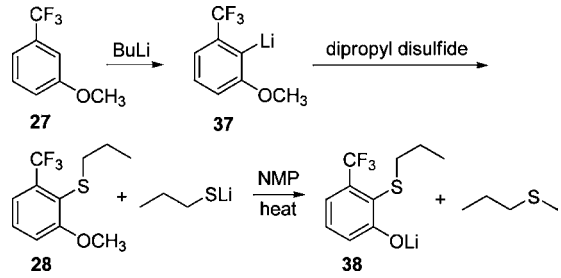
Route C[20] with the fewest reaction steps, was actually the easiest route to eliminate. The lithiated intermediate **30**, because it possesses a fluorine ortho to the lithium, is a highly reactive intermediate that is unstable above about −40 °C due to elimination of lithium fluoride to form a substituted benzyne, leading to a potential thermal runaway. The lithiated intermediates formed in Route A and Route B could be formed and handled at temperatures as high as 25 °C.[21] In addition to the reactive chemicals problem, the penoxsulam produced from Route C had a different impurity profile than that produced by either of the other two routes. Since a variant of Route A was used to produce the sample for toxicological testing in support of the registration, use of Route C would likely have required additional toxicological testing (bridging studies), adding to the cost of development and potentially delaying the registration submission. Route C suffered from having additional solids isolations, and potentially a recrystallization step at the end. Unit operations involving solids are typically expensive and prone to more issues upon scale-up. Finally, the last two steps in Route C required the use and recycle of a fairly toxic solvent (1,4-dioxane or 1,2-dimethoxyethane were the best solvents).[22] Route B offers the advantage over Route A of avoiding the protection and deprotection of the phenol group, thus reducing the step count. A major issue with Route B is that it requires the use of an extremely odorous reagent, dipropyl disulfide, which also has aqueous toxicity issues. In Route A, the lithiation is followed by treatment with elemental sulfur to give the thiolate salt **36**, which is further treated with 1-bromopropane to give intermediate **23** (Scheme 6). None of these intermediates are particularly odorous. In

Scheme 6. Sulfur incorporation in Route A



Route B, the sulfur has to be introduced with dipropyl disulfide, to prevent the methyl group on the anisole from migrating to the sulfur. In addition to the odiferous dipropyl disulfide, the anisole was deprotected by solvent exchange and heating (Scheme 7). The lithium propanethiolate remaining from the

Scheme 7. Sulfur incorporation in Route B



sulfur addition removed the methyl to give methyl propyl sulfide, a volatile and highly odorous byproduct. Control of fugitive odors can be a challenge on the production scale, and so the less odorous route was favored.

While based on a simple "step count" Route A has two more steps than Route B, fitting the laboratory preparation into a plant flowsheet revealed that the two processes were not that different in total number of vessels, which translates to capital and operating cost. Additionally, the phenol protecting group

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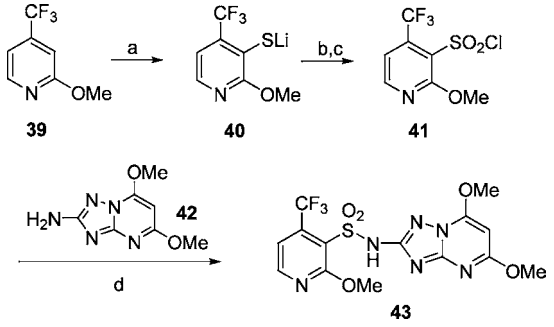
(an ethyl vinyl ether) used in Route A also served to chelate the Li anion increasing the efficiency and yield of the lithiation reaction, whereas TMEDA was used in Route B to accomplish this. In Route A, elemental sulfur afforded a low odor option for the thiolation step. Another advantage of Route A was that it had been successfully demonstrated at the 300-gal pilot scale to produce the large sample and thus posed less commercial scale-up risk than Route B.

An Early Stage Review was conducted to assess the three potential routes. Criteria considered during this effort included the following: overall yield, cost of manufacture, raw material cost, raw material availability, process simplicity, chemistry difficulty, process robustness, type of unit operation, solids handling, block operability, wet-cake isolations, and the impurity profile. The ESR panel provided key input for further work, and supported the recommendation of the route selection team to advance Route A, despite its being the apparently "longer route".

Pyroxsulam. Pyroxsulam,[23] (**43**, Scheme 8), is a highly active sulfonamide herbicide for cereal applications which was launched commercially in 2007.[24] The process development of this molecule has been presented previously.[25,26] The final steps to pyroxsulam (Scheme 8), were determined fairly quickly on the basis of the development and manufacturing experiences with the previous sulfonamides. The primary route selection decision revolved around two very different routes to **39** (Scheme 9). This example provides a good illustration of the contrast of fixed and variable costs on the economics of route selection.

Scheme 8. Final steps to pyroxsulam[a]

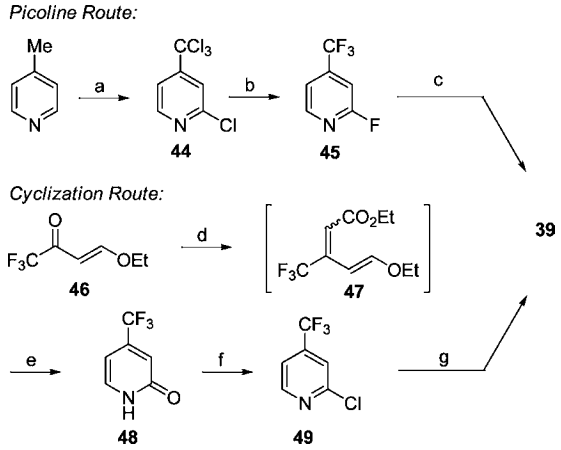


[a]Reagents and conditions: a) LDA; S_8, THF; b) aq HCl; c) chlorine, CH_2Cl_2–H_2O; d) 3,5-lutidine, CH_3CN, cat. DMSO.

The apparent choice was the "Picoline Route", which could employ technology and assets practiced at Dow's specialized chloropyridines facilities. This involved a partial chlorination of γ-picoline, followed by fluorine exchange on the trichloromethyl group. The tetrafluorinated intermediate **45** was then treated with sodium methoxide to afford **39**. Although the chlorination reaction proceeds in a low yield to obtain selectivity, this route offered the fewest number of steps and the lowest raw material costs (γ-picoline, chlorine, and hydrofluoric acid).

The alternate "Cyclization Route", was a batch process that began with a trifluoromethylated building block (ETFBO, **46**) and used a cyclization reaction[27] to form the pyridine ring. Initially, this seemed to be a long shot because it employed significantly more expensive raw materials (ETFBO and TMPA in particular) and had one more step than the picoline route. Also, the yields were only modest as little optimization work had been completed at the time of the route selection decision. However, it had the advantage of using more conventional chemistry which could be run at standard contract facilities without significant capital investment.

Scheme 9. Two Routes to Intermediate 39[a]



[a]Reagents and conditions: a) Cl_2; b) HF; c) NaOMe; d) $(MeO)_2P(O)_2CH_2CO_2Me$ (TMPA), NaOMe; e) NH_4OAc; f) $SOCl_2$, DMF; g) NaOMe.

Further analysis of the picoline route indicated that a significant capital investment would be required due to the high expense of the specialized materials of construction necessary to handle the corrosive conditions. Additionally, there was a potential added cost related to the projected loss of production time of other high-demand products in the chloropyridine facility, which was amplified by the fact that the facility's scale was much larger than desired for the demand of **45**.

The two routes were compared in a 10 year discounted cash flow analysis (Figure 4), revealing that even with modest yield assumptions and expensive starting materials, the Cyclization Route, if manufactured at a contract manufacturer with available equipment, had a statistically significant cost advantage over the Picoline Route. Thus, the Cyclization Route was selected for advancement. This strategy minimizes the up front capital risk when the commercial success of the product is unproven. A decision to invest capital in a more economical, long-term process can always be made later after the product is proven in the market. Since route selection, significant progress was made to improve the yields of the Cyclization Route which resulted in even lower manufacturing cost than originally estimated.

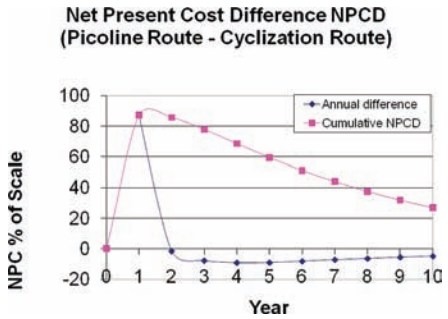


Figure 4. Cash flow analysis comparing picoline and cyclization routes.

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CONCLUSIONS

In summary there are a large number of factors to be considered in the selection of a synthetic route for a new organic molecule. In addition to striving for a low-cost route with good atom efficiency, the route selection team should include safety, health and environmental criteria in the assessment. Process operability, simplicity and supply chain factors will be important as the chemical route is scaled up to the commercial plant. Additionally, product from the selected route will need to achieve the desired efficacy in the commercial application and pass regulatory approval. Finally, there will be a need to have "freedom to practice" the selected route. It has been our experience that one route may have an advantage over other routes in a particular area; however it will have drawbacks in other areas. A clear-cut superior route will not always emerge, so a disciplined strategy that engages many subject matter experts is essential in making a sound *holistic* route selection.

AUTHOR INFORMATION

Corresponding Author

*Telephone: +1-989-636-6158. E-mail: rbleng@dow.com.

Notes

The authors declare no competing financial interest.

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