Industrial Phase-Transfer Catalysis

Achieving Competitive Advantage Using Phase-Transfer Catalysis in

Generic Pharmaceuticals and Agrochemicals

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Summary: The key to gaining competitive advantage in generic pharmaceuticals and agrochemicals is low-cost and high-performance manufacturing. The driving force of low cost has led to a significant shift in production to emerging market countries due to low labor cost. However, the low cost of labor alone may not be sufficient to achieve the lowest cost possible if the process does not approach 100% atomic efficiency using the lowest cost raw materials. Phase-transfer catalysis can be a key contributor to achieving the lowest cost and highest performance process, *even in competition with emerging market facilities* due to significant increases in yield, selectivity, avoiding isolation of intermediates, reducing excess reactants and replacing expensive strong base with inexpensive NaOH. This article will illustrate specific examples of processes which could benefit from using phase-transfer catalysis to achieve lower cost and higher performance for generic pharmaceuticals and agrochemicals.
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Achieving Competitive Advantage Using Phase-Transfer Catalysis in

Generic Pharmaceuticals and Agrochemicals

The key for achieving competitive advantage in the generic pharmaceutical and agrochemical markets is low cost manufacture for the products and intermediates. This article will illustrate examples of reactions likely used for existing generic products and intermediates which either use phase-transfer catalysis or should use phase-transfer catalysis to simultaneously achieve **high performance and low cost**.

This article should be especially interesting to [1] companies which produce pharmaceuticals or agrochemicals, [2] companies which use a strategy of developing low cost processes for compounds with patents expiring within the next few years. Even though phase-transfer catalysis has been well known for over 30 years, many companies still did not incorporate PTC 15 or more years ago when they commercialized their branded pharmaceutical or agrochemical processes. Thus, significant opportunity exists for companies open and willing to incorporate high-performance low-cost PTC processes for the generics and intermediates coming off patent.

A major purpose of this article is to point out that previously developed processes could have been improved had they used PTC so that when you develop future processes for new chemical entities, generic products or their intermediates, you will more appropriately consider PTC. Before discussing specific products and intermediates, we would like to provide some general comments.

General Comments

China and India: The good news/bad news may be that it could be possible to achieve the lowest theoretical cost for many common intermediates and starting materials when combining the low labor cost in emerging market countries with superior PTC performance. One may even speculate that the use of phase-transfer catalysis could eventually be the factor which may differentiate one Chinese producer from another.

Retrofit: It should be noted that even though re-registration of processes can be prohibitive, there are cases in which PTC retrofit of an existing process for pharmaceuticals and agrochemicals does make sense.[1] These include [1] developing advantageous PTC processes for non-regulated key early stage intermediates and starting materials, [2] overcoming selectivity issues magnified during full scale production which threaten meeting specification or [3] the rare case in which a pharmaceutical company announces it is willing to consider changing the process (e.g., Pfizer's announcement for atorvastatin). In addition, generic agrochemicals are usually more amenable to process retrofit.

Workup: One lesson we have learned by participating in several PTC retrofits is that after achieving high reactivity and selectivity, the next most important factor for success is effective and practical separation of catalyst from the product. PTC offers advantage in workup and product isolation relative to using solvents like DMSO, because we can almost always use solvents which easily form two phases with water and separate the valuable product from the catalyst and inorganic waste materials like salts of leaving groups.

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Cognis Aliquat® Phase-Transfer Catalysts

The First Name in Phase-Transfer Catalysts

Did you know that **Aliquat® 336** was cited by name in Starks' first classic paper and patent in which he coined the term "Phase-Transfer Catalysis" in 1971? Yes…Cognis' **Aliquat® Phase-Transfer Catalyst** is truly the first name in phase-transfer catalysts.

Here's a useful guide for the most common phase-transfer catalysts:

Phase-Transfer Catalyst	*When to choose these catalysts for high performance:*
Aliquat® 175	PTC with NaOH at mild to moderate temp with water wash workup; provides low residual catalyst and low aqueous waste
Aliquat® 134	Most PTC applications, usually with non-aqueous workup (distillation, recrystallization, product extraction, other)
Aliquat® 100	Most other standard PTC applications
Aliquat® HTA-1	High-temperature PTC applications
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Following are examples of opportunities and *missed opportunities* relating to using phase-transfer catalysis for generic pharmaceuticals and agrochemicals.

Using Multiple Consecutive PTC Steps to Achieve Advantage

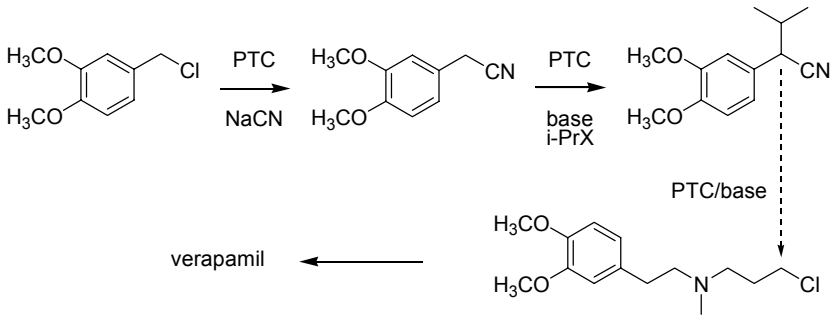
Since PTC excels in > 35 reaction categories (see Table on page 12) which represent many of the most common reactions used in pharmaceuticals and agrochemicals, there can be great advantage in performing multiple consecutive PTC steps to achieve: [1] high yield, selectivity, reduced excess reactants and reduced reaction time in each separate step, [2] less handling losses and reduced processing time by avoiding isolation of intermediates and [3] highly flexible choice of a single solvent for all steps including for an advantageous final workup.

Following are some examples of generic pharmaceuticals and agrochemicals which probably would have achieved advantage had they been originally developed using PTC for multiple consecutive steps.

Verapamil

Verapamil is a generic pharmaceutical which is prepared by a multistep synthesis shown in Figure 1 and lends itself well to the advantages of PTC. We do not know if the process uses PTC for all or even any of the steps, but it should. For the first step, PTC excels for cyanation of benzyl chloride derivatives. For the second step, PTC should provide selective mono-C-alkylation using the sterically hindered isopropyl bromide, especially since it can be manipulated to be performed at a low temperature due to the lower energy of activation which PTC often provides. The C-isopropylation would be followed by another PTC C-alkylation in the third step. The final C-alkylation probably needs to be pushed due to steric hindrance, but one must be careful not to induce dehydrochlorination of the chloropropyl group. The investment of highly specialized PTC expertise to achieve high yield and selectivity in the final step would have been worthwhile since a lot of cost is invested in the two intermediates being condensed in that last step.

Figure 1: Verapamil could have been a good opportunity for multiple consecutive PTC steps



A cross-product opportunity for developing a good PTC cyanation may be 3,4-dimethoxy benzyl cyanide, since it a common intermediate for both verapamil and papaverin.

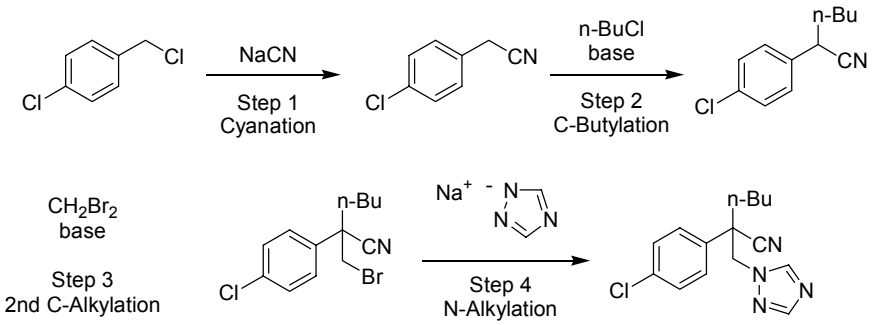
Myclobutanil

When Dow acquired Rohm and Haas' agrochemical product line a few years ago, there were a few products which were amenable to improvement using phase-transfer catalysis. One of the products is myclobutanil (see Figure 2). According to the original patent[2] the inventor already used PTC (tetrabutyl ammonium bromide) for the C-butylation in Step 2. The yield was low and it is expected that the commercial process was optimized with better results. The overall multistep synthesis could greatly benefit from PTC improvements and streamlining. DMSO was used as the solvent for the other three steps. Aqueous workup was used for each of the steps using DMSO and this is usually far from optimal for product isolation and handling losses. PTC can be used to achieve high performance and low cost for each of these cyanation, C-alkylation and N-alkylation reactions separately. Further advantage could be achieved by combining

multiple consecutive PTC steps, especially if a single solvent and single catalyst can be used for all four steps. A single solvent could be chosen for the entire process which would be easily recoverable at the end, in addition to minimizing handling losses and avoiding solvent exchanges. An appropriate phase-transfer catalyst or combination of catalysts could be chosen to enhance reactivity, selectivity, catalyst stability and most importantly, effective catalyst separation from the final product.

The challenges which need to be addressed include [1] minimize dehydrochlorination of butyl chloride while trying to enhance the nucleophilicity of the carbanion derived from p-chlorobenzyl cyanide in Step 2, [2] minimize dehydrobromination is Step 3 and [3] achieve the successful transfer and reaction of the organophobic triazolide anion in Step 4.

Figure 2: Myclobutanil – Opportunity for Multiple Consecutive PTC Steps



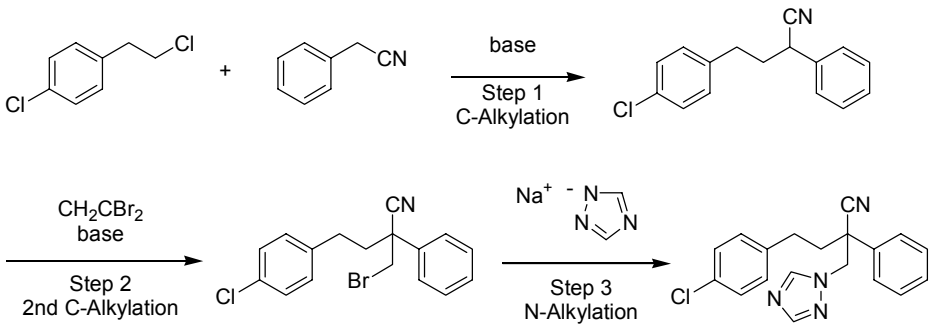
The market is well over 100 metric tons per year and the patent expires within the next few years. PTC Organics would be very interested in partnering with an appropriate company to develop and commercialize an advantageous process for myclobutanil using multiple consecutive PTC steps.

Note regarding p-chlorobenzyl cyanide: The first step for several products is to prepare p-chlorobenzyl cyanide from p-chlorobenzyl chloride. This nitrile is a common starting material for a variety of pharmaceuticals and agricultural chemicals including chlorpheniramine, myclobutanil and fenvalerate. It is available from several sources in China and India. If it is not currently produced PTC, it probably should be.

Fenbuconazole

Similar to myclobutanil, the fenbuconazole process shown in Figure 3 may benefit from multiple consecutive PTC steps. The first C-alkylation step of fenbuconazole may be even more challenging than the first C-alkylation step for myclobutanil due to the driving force to dehydrochlorinate p-chlorophenethyl chloride to a conjugated styrene derivative.

Figure 3: Fenbuconazole process – amenable to multiple consecutive PTC steps

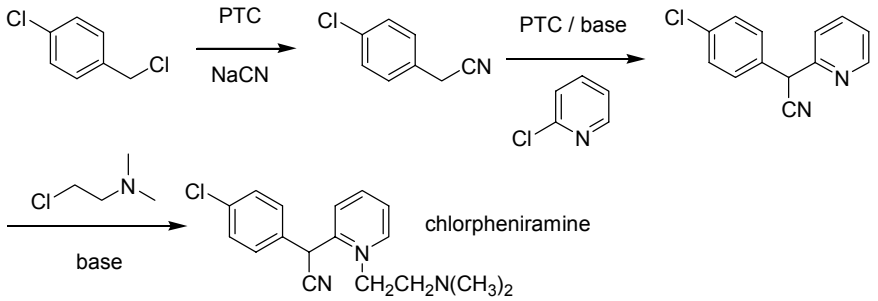


Chlorpheniramine

Chlorpheniramine (Figure 4) is another example of a generic pharmaceutical which could have benefited from multiple consecutive phase-transfer catalysis steps.

It was brought to our attention[3] that the existing process for chlorpheniramine is performed in India and uses PTC. However, to our surprise, excess sodium amide was used as the base for both reactions(!) [1] the reaction of p-chlorobenzyl cyanide with 2-chloropyridine and [2] the N-alkylation. Application of highly specialized expertise in PTC at the right time could have reduced the cost significantly by figuring out how to use a common inexpensive inorganic base (possibly even NaOH) instead of $NaNH_2$ which would also be less hazardous.

Figure 4: Chlorpheniramine



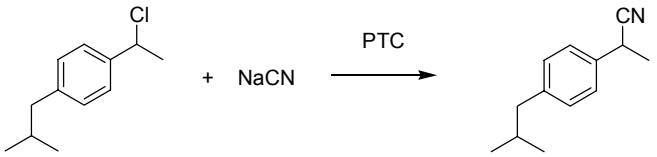
Improving Yield and Selectivity for Nitrile Intermediates

Cyanide/Chloride Exchange for Various Ibuprofen Routes

There are several quite different processes which actually have been implemented for the commercial manufacture of ibuprofen. One of the less desirable processes involves the displacement of chloride by cyanide at a 2^o benzylic position (Figure 5). This process has a major selectivity challenge in that cyanide can act both as a nucleophile (the desired reaction) and as a base to form a stable styrene derivative as an undesired side reaction. It was brought to our attention[3] that this reaction at one time suffered from a yield

of only 65%, due to extensive dehydrochlorination and was already using phase-transfer catalysis. It is possible to make simple adjustments to PTC reaction conditions which meet a variety of process and regulatory constraints, and alter the ratio of nucleophilicity to basicity for cyanide. Yields greater than 90% can be achieved for the substitution product and minimize the dehydrohalogenation product.

Figure 5: Cyanide substitution on secondary benzylic chloride

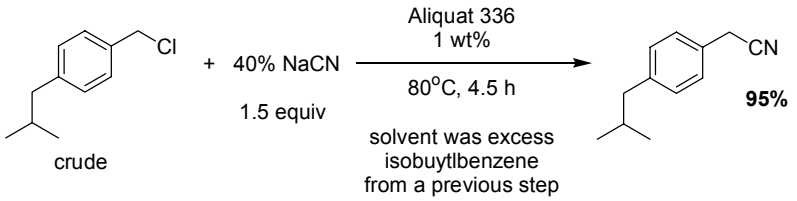


This is an excellent example of how living with a 65% yield when a 90-95% yield could be achieved can result in lost competitive advantage unless/until the best phase-transfer catalysis conditions are pursued and found (although usually requiring highly specialized PTC expertise). This huge yield loss in a highly competitive pricing situation can be the difference between being profitable and going out of business.

One of the routes to ibuprofen cited in a letter to the FDA[4] involves another cyanide/chloride exchange. Figure 6 shows this reaction using reaction conditions reported in a Dow patent.[5]

This reaction uses PTC to achieve high yield cyanation and is quite easy at the primary benzylic carbon. This route avoids the problem of CN^-/Cl^- exchange at a secondary benzylic carbon, but suffers from selectivity problems in a previous chloromethylation step and a subsequent C-alkylation step. As a result, this process was probably not used on a significant commercial basis.

Figure 6: Cyanation

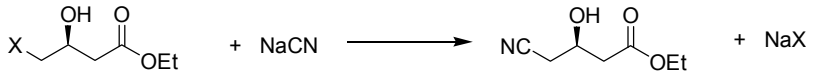


Nevertheless, there are two interesting aspects of this patent which are very instructive and illustrate benefits of PTC for achieving advantageous processes for other low-cost generics. First, one of the great advantages of phase-transfer catalysis is the ability to use almost any organic liquid as a solvent for PTC reactions. In this case, the inventors simply used the excess isobutylbenzene from the previous step as the solvent for the cyanation. This saves an isolation step or a solvent exchange step which in turn greatly minimizes handling losses and processing time. Secondly, the next step is a phase-transfer catalyzed C-alkylation. The catalyst chosen, Aliquat 336®, distributes > 99% into the organic phase and stays with the product of the cyanation reaction into the next PTC step of C-alkylation. Thus, a single solvent and a single catalyst can be used for multiple consecutive steps while avoiding isolation of intermediates.

Cyanation for Atorvastatin Intermediate

A few years ago, Pfizer created a flurry of activity by informing the industry that it may be willing to consider an alternate route to the blockbuster atorvastatin (Lipitor®). Rumor at Informex 2002[3] was that the price of the optically active cyano hydoxy ester shown in Figure 7 was dropping from $700/kg. By Informex 2003, the buzz was that the price was about $140/kg. By Informex 2004, rumor was that the price dropped to under $100/kg.

Figure 7: Cyanation for atorvatstatin intermediate



There are several selectivity challenges for this cyanide substitution. First, it was openly discussed[3] that using the bromo hydroxy ester as the starting material gave high yield of the cyano hydroxy ester, but the chloro hydroxy ester gave a much lower yield. As the price continued to drop, the pressure grew for achieving every possible cost benefit and that included making the chloride work instead of the bromide. However, that would likely mean harsher conditions. Harsher conditions increase the possibility for side reactions such as hydrolysis of the ester from water introduced with the NaCN, dehydrochlorination (remember again the basicity vs nucleophilicity of cyanide), formation and opening of an epoxide and reactions initiated by deprotonation of hydrogen atoms α to the carbonyl of an ester group.

Many companies seemed to be interested in multiple routes and starting materials to form the optically active center and there were published reports that enzymatic processes were delivering outstanding results. However, as of the date of writing this article, to our knowledge no company has yet invested highly specialized expertise in PTC with the goal of achieving the highest yield possible for the cyanation of the optically active chloro hydroxy ester. Sales of atorvastatin have since become the first pharmaceutical to surpass the $10 billion per year sales mark. If you have a lot of patience, it will be curious to see if renewed interest in a PTC cyanation will emerge when atorvastatin goes generic (patent was approved in Dec 1996).

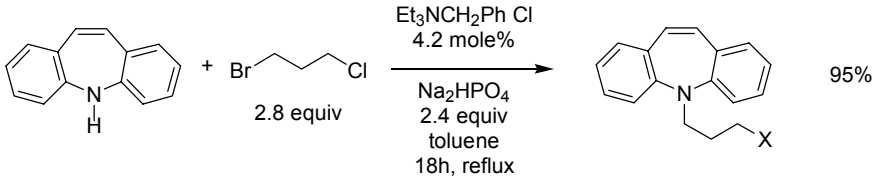
N-Alkylation

Many alkylations which use strong base face the challenge of requiring a base strong enough to deprotonate C-H or N-H groups to form a carbanion or N-anion in preparation for alkylation of the anion,

while not being too strong of a base to cause dehydrohalogenation of the alkylating agent. Companies often use a base such as NaH to avoid this problem. Expert adjustment of PTC conditions using inexpensive inorganic base (often NaOH) can often achieve the desired selectivity.

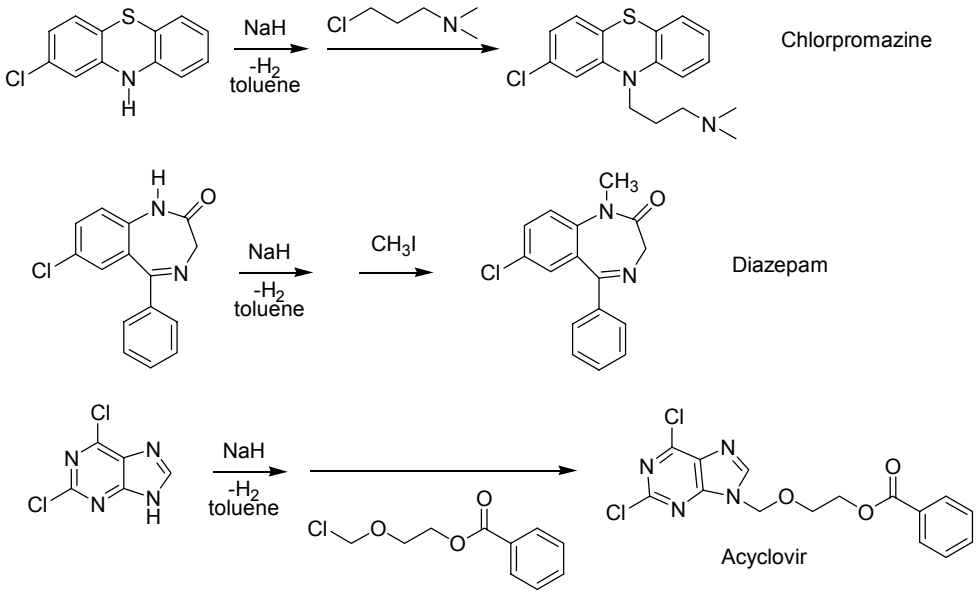
A good example of a related challenge was solved by chemists at Taro[6] in Israel and is shown in Figure 8. The challenge was to perform the N-alkylation without dehydrohalogenating the intermediate shown, which is itself an alkyl halide. The haloethyl group is required for the next step which involves a displacement by an amine to form the API. The inventors achieved this by choosing disodium hydrogen phosphate as the base which under PTC conditions is strong enough to perform the N-alkylation while minimizing the dehydrohalogenation.

Figure 8: Selective N-Alkylation



The classic system to perform these types of N-alkylations without using PTC is to use sodium hydride which is both expensive and hazardous. Other examples of N-alkylation which were speculated to use NaH[7] and which could have used PTC with inexpensive less hazardous base (often simply NaOH) are shown in Figure 9.

Figure 9: Other examples of NaH use[7] – candidates for replacement with PTC-Base



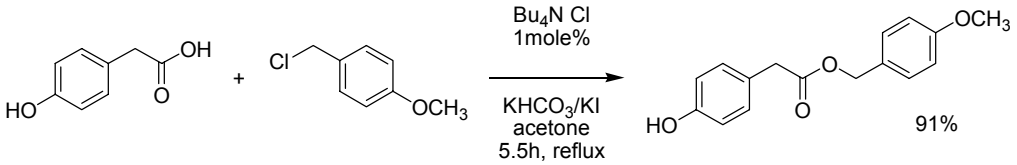
Esterification

PTC usually provides fast, irreversible and high yield esterifications which translate into low cost. In 1980, there was a report[8] that the first commercial PTC application was performed in Europe in the 1970's for an esterification of a penicillin derivative. Before discussing specific applications, it is worthwhile to discuss a sometimes surprising aspect of PTC relevant to many esterifications, namely hydrolysis.

Hydrolysis*:* One of the strengths of PTC is the ability to perform reactions of water-sensitive compounds in the presence of water while avoiding hydrolysis. This can be achieved using phase-transfer catalysis because PTC systems do NOT usually rely on interfacial reactions. PTC uses the *catalyst* to control the reaction and little agitation is usually needed, just enough to achieve ion pair distribution equilibrium between phases. Since hydrolysis is usually an interfacial process, then using PTC with minimal agitation can contribute significantly to reducing undesired hydrolysis side reactions. However, intuition often dictates that multiphase systems such as PTC should be well agitated. It is not uncommon for chemists and engineers to mistakenly conclude that PTC does not work for water-sensitive compounds, due to over-agitation during PTC screening studies. This subject was covered in detail in an earlier issue of this journal.[9]

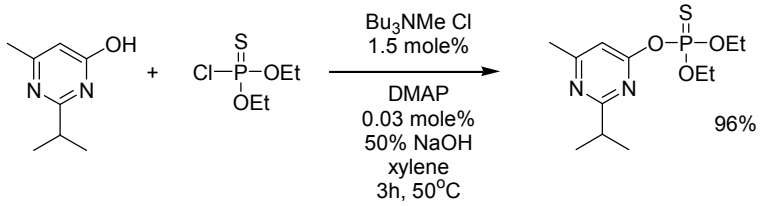
Following is an esterification patented[10] for an intermediate for the antibiotic Ceclor (Cefeclor) originally made by Lilly and now by Ranbaxy. This reaction utilizes the large difference of 4-5 pKa units between the carboxylic acid O-H and the phenol O-H to selectively benzylate the carboxylic acid (Figure 10). Bicarbonate was used as the base because it has an intermediate pKb which is strong enough to deprotonate the carboxylic acid but not the phenol. Iodide was used as co-catalyst which forms the benzyl iodide in situ.

Figure 10: Selective esterification for Cefeclor intermediate



Chlorpyrifos and diazinon are organophosphate insecticides which have been used for many years. A note unrelated to chemistry is that Yahoo posted an article on 1/2/05 which noted that diazinon is an organophosphate, which is of the same family as deadly sarin gas and is being phased out for many applications due to its toxicity (aren't you fed up with media chemo-scare tactics?). Back to PTC…both chlorpyrifos[11] and diazinon[12] were produced using phase-transfer catalysis to achieve yields of 97% and 96% respectively to form phosphate esters using DEPCT (diethyl phosphoro chloridothioate) as a reactant. DEPCT is a quite water-sensitive compound and high yield can be achieved with just a few mole% excess. PTC also helps control the formation of a highly undesirable toxic byproduct in these processes.

Figure 11: Thiophosphate ester formation for diazinon



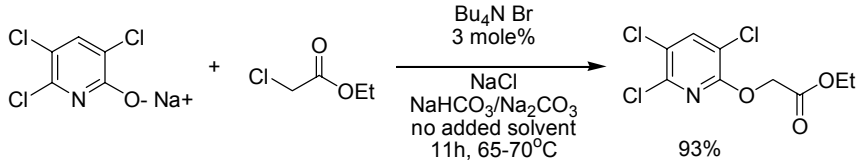
The chlorpyrifos system which also uses DEPCT, not only has high yield and short reaction time, it is also **solvent-free**. At the beginning of the reaction, DEPCT is the organic solvent and at the end of the reaction chlorpryifos itself is the solvent. Again, almost any organic liquid can be an effective solvent for PTC if it is convenient to use.

Etherification

Yet another example of high yield in the presence of a competing hydrolysis while achieving a **solvent-free** system is a PTC patent[13] for the agrochemical shown in Figure 12. The water-sensitive ethyl chloroacetate is reacted with the same trichloropyridinate anion used in chlorpyrifos. The key to minimizing hydrolysis was

to absorb some of the available water in the system by adding inorganic salts at the beginning of the reaction. The solvent-free process replaced an earlier 1976 patent[14] which used toluene as the solvent.

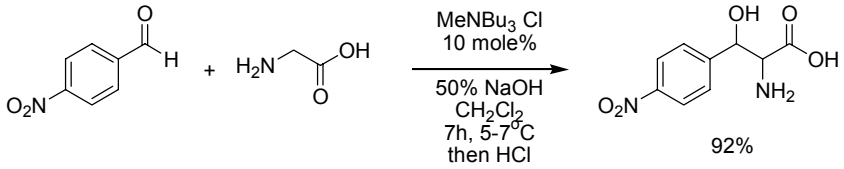
Figure 12: Solvent-Free Etherification



Condensation

PTC was used for the generic pharmaceutical chloramphenicol by Gruppo Lepitit[15] in Italy for a number of years. The reaction is shown in Figure 13.

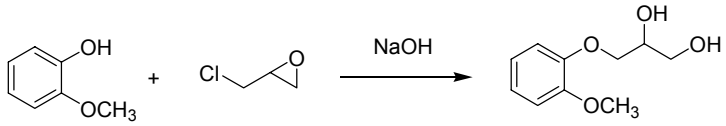
Figure 13: PTC for chloramphenicol



Other Potential Opportunities

PTC excels in reactions using epichlorohydrin. A potential opportunity may be in the synthesis of guaifenesin. PTC can be used either to minimize the hydrolysis of the epoxide and selectively form guaiacol glycidyl ether or if needed, to promote the hydrolysis of the epoxide to form guaifenesin.

Figure 14: Guaifenesin – potential opportunity



As described earlier, PTC excels in performing nucleophilic substitutions using inorganic anions. Figures 15 and 16 show reactions reported to be performed using inorganic anions for intermediates for generics.[7]

Figure 15: Sulfide/chloride exchange for starting material for phenothiazines

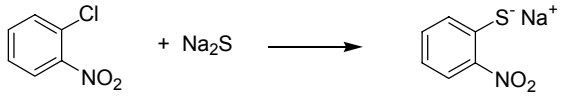
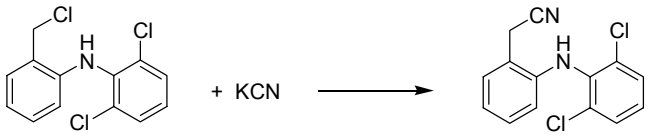


Figure 16: Cyanation for diclofenac intermediate



CONCLUSION

The take away message from this article is that there are many technical and business opportunities to achieve low-cost high-performance processes using phase-transfer catalysis which can be **key to achieving significant business in generics and their intermediates**. Every chemist, business manager and technical manager at companies involved in any stage of generics and their intermediates should be aware of the potential of PTC to enhance their personal performance and careers.

In the past, there have been many missed opportunities to achieve competitive advantage in pharmaceuticals, agricultural chemicals and their intermediates when companies did not use PTC or did not use the best PTC conditions. There will undoubtedly be many more lost opportunities due to lack of highly specialized PTC technical knowledge, resistance to change and even ignorance of PTC's benefits.

Whether or not you take advantage of PTC to gain competitive advantage is 100% your choice. If you think you may have a specific opportunity to use PTC to achieve crucial advantage or even if you are not sure, feel free to call me personally (Marc Halpern at [+1] 856-222-1146 or 800-PTC-7118 in the US) and I'll be glad to discuss your probability of success.

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[2] Fujimoto, T. (Rohm and Haas) US Patent 4,920,139, 24-Apr-1990
[3] Not under secrecy agreement. Note: All the information presented in this article is either public information from patents, peer-reviewed articles or internet-based information of varying reliability or was disclosed without confidentiality restrictions. Some of the concepts presented in this article are speculative ideas based on sources of information described above and are identified as such.
[4] http://www.fda.gov/ohrms/dockets/dailys/01/Oct01/100401/c000239.pdf
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[6] Gutman, D.; Ashkar, M. (Taro) **1996** WO 96/15113
[7] http://www.fs-pharmazie.de/Mat/synth.pdf. This reference is interesting as it shows potential routes for > 60 API's. It is not known if these routes are actually used.
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Table: **Reactions In Which Phase Transfer Catalysis Excels**

- Etherification
- Esterification
- Transesterification
- N-Alkylation
- C-Alkylation
- S-Alkylation
- Other Mercaptan Reactions
- Dehydrohalogenation
- Michael Addition
- Aldol Condensation
- Oxidation
- Epoxidation
- Chloromethylation
- Hydrohalogenation
- Hydrogenation
- Borohydride Reduction
- Chiral Reactions
- Darzens Condensation
- Carbene Reactions
- Condensation Polymerization
- Polymer Modification

Displacements Using:

- cyanide
- fluoride, bromide, iodide
- azide
- thiocyanate, cyanate
- sulfide
- inorganic nucleophiles

Displacements Using:

- benzyl chloride
- allyl chloride
- many alkyl halides
- benzoyl chloride
- other acyl halides
- methanesulfonyl chloride
- other sulfonyl halides
- epichlorohydrin
- PCl_3, $POCl_3$
- other phosphoro halides
- anhydrides

Other reactions involving anions or anionic metal complexes

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Include reactants, molar ratios, solvent, catalyst (if any), time, temperature, yield and key impurities (if important)

Reaction to be improved:

Step 2: **Describe the performance parameter(s) you want to improve**

_____

_____

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add additional pages if necessary

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Issue 18 **2005**

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