When Contract Chemicals was first involved in the manufacture of brominated intermediates after acquiring the bromination plant of Warwick International in 1995, the regulatory framework and technology requirements for these processes were far different from those we face today.

The changes in these and the escalating cost of disposal of halogenated wastes have certainly driven process innovation, but sometimes at the cost of our competitiveness against Far Eastern manufacturers who are not challenged with similar legislation. Despite that, we now use three times more elemental bromine than we did in 1995 and our bromination efficiency has increased by 38% in the past two years, winning the CIA’s manufacturing improvement award for it.

The market for brominated products is also changing, with demand for organobromine compounds falling into two distinct areas. The first utilises the natural fire-resistant properties of bromoorganics. Consequently, brominated flame retardants (BFRs) have become essential and even mandatory in many household items, such as televisions, computers and upholstered furniture.

These products include polybrominated biphenyl and diphenyl oxides and are produced in high volumes from dedicated plant. They have become a target for green groups because of their perceived impact upon the environment and human health. These pressures will probably continue, with a consequent effect on the market.

The second area is the use of organobromine compounds in the synthesis of complex organic molecules used in the pharmaceutical, agrochemical, photographic and fragrance industries. Again, the market is changing as the soil fumigant methyl bromide is phased out on the disputed grounds of ozone depletion and lead anti-knock compounds, which use ethylene dibromide, are withdrawn. However, conventional intermediates that depend on the unique properties of bromine as a leaving group continue to keep the fine chemicals market buoyant.

The chemistry of bromination used to manufacture these intermediates generally falls into one of four areas: the preparation of bromoacids using the Hell-Volhard-Zelinsky (HVZ) Reaction; bromination of alcohols with hydrogen bromide (HBr) gas or solution; the addition of bromine or HBr across a double bond; and, through an activated brominating agent such as N-bromosuccinimide or 5-bromohydantoin. Our major advances have been in the acceleration of the HVZ reaction and subsequent reduction of waste.

**HVZ reaction**

Volhard’s method of preparing halogenated organic acids was first reported in the 1880s¹ and has become known as the Hell-Volhard-Zelinsky (HVZ) Reaction; bromination of alcohols with hydrogen bromide (HBr) gas or solution; the addition of bromine or HBr across a double bond; and, through an activated brominating agent such as N-bromosuccinimide or 5-bromohydantoin. Our major advances have been in the acceleration of the HVZ reaction and subsequent reduction of waste.
The keys to accelerating reaction rates include the ease of enol formation in the precursor, careful temperature control and the catalyst used. Careful combination of these factors has allowed us to achieve an order of magnitude improvement in the speed of the reaction, without the formation of unwanted by-products.

Changes in, and sometimes elimination of, the catalyst have resulted in significant reductions in waste produced from the reaction. The main advances have been:

- Reduction in the amount or elimination of the catalyst
- Reduction in the storage requirements of catalyst, which is significant in the new Seveso II legislation
- Much simpler work-up of reaction mixtures
- A significant increase in reaction rates, leading to much higher throughput of product
- Reduction in the use of bromine towards stoichiometric amounts
- Reduced waste production and a decrease in the disposal costs

We have calculated that to obtain the same increase in ‘notional capacity’ by installation of further reactor capacity would have cost in the region of €3 million.

There is an even larger prize to win, which would involve a significant change in the intermediates we produce. Generally, our bromoacids and esters are racemic mixtures, which go into pharmaceutical and agrochemical synthetic processes that require a costly resolution step to produce a single isomer active product.

It would seem sensible to include the chiral centre as early as possible in the synthetic pathway. Resolution of the racemic mixture or direct synthesis of the single isomer would seem to offer a solution to this problem, especially as brominated intermediates usually appear early in the synthesis of the active material.

Chiral bromination

In partnership with Professor Stan Roberts at the University of Liverpool, Contract Chemicals has commenced a four-year project entitled ‘Novel Stereoselective Approaches to α-Substituted Acids & Esters’. The technology is based around the enzyme-catalysed hydrolysis of α-crotoesters to generate the required enantiomerically pure acid and the enzyme-catalysed esterification of racemic mixtures of α-bromoacids to yield the required ester (Figure 2).

Focused on the production of short chain (typically C3-C6) molecules with ee’s of >95% for use in the pharmaceutical industry, the partnership has just announced the isolation of the first grams of enantiomerically pure 2-bromopropionic and 2-bromobutyric acids. We are now in the process of scale up work to make samples available for commercial evaluation. Figure 3 shows the enzyme catalysed conversion of 2-bromobutyric acid to the corresponding ester with various concentrations of ethyl alcohol.

Plant design & construction.

Whilst it is important to develop efficient, modern chemistry to meet the demands of legislators and customers, all this is to little effect unless the plant achieves the same standards. We believe that our chemistry and our plant represent the best available technology and production facilities for bromination processes.

We have invested €35 million in the new bromination plant at Knowsley, U.K. Without this investment the competitive advantages offered by the new chemistry could not have been fully realised. The features incorporated here represent several advances over conventional bromination facilities to meet the twin challenges of staying ahead of the competition and the legislation. They include:

- Double Pvdf containment pipes with internal automatic leak detection
- Fully computer monitored and controlled bromine storage
- Continuous monitoring of the whole plant area by electrochemical cells for fugitive emissions
- Continuous point emission monitoring for organic materials by photoacoustic sensors
- Silicon carbide condensers for improved mechanical strength and safety over conventional glass condensers
- A full emergency shutdown system

The control of the plant was of equal importance to the safety systems and incorporated: a full SCADA control and monitoring system; mass flow control of bromine addition, fully programmable to match bromine addition to process requirements; and, a purpose-built high containment plant to handle highly irritant and lachrymatory products.

The efficiency of the chemical processes clearly depended on the efficiency of the plant and to achieve the level of performance we needed, to maintain our competitive edge over competition, we built the biggest batch brominator in the world. This 23m3 glass-lined monster features weigh cells on performance we needed, to maintain our competitive edge over competition, we built the biggest batch brominator in the world. This 23m3 glass-lined monster features weigh cells on handling highly irritant and lachrymatory products.

There are other reactors with a range of sizes, versatile enough to adapt to large range of different products and process requirements. Other features include high-efficiency filtration units to ensure product quality; a system to handle and absorb large volumes of effluent gases to improve product throughput; and, a high-vacuum capability to minimise distillation temperatures coupled with high efficiency column packings to improve separation.

References:
1. C. Helf, Ber. 1881, 14, 891; J. Volhard, Ann. 1887, 242, 141; N. Zelinsky, Ber. 1887, 20, 2026

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Figure 3 - Esterification of 2BBA with 1-6 equivalents of EOH