Organic Process Research & Development

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*Editorial*

## What Type of Reactions Do Process Chemists Use on Scale?

A year ago in OPRD,[1] a group of process chemists from Pfizer surveyed the reactions carried out in their pilot plant at Groton, USA over a 17 year period, and this provided valuable insight into the changes over that period. Recently a combined study from the UK process chemistry groups at GlaxoSmithKline, AstraZeneca, and Pfizer, which analysed the chemistry used in the synthesis of 128 drug candidate molecules, was published,[2] and very interesting reading it made too. In this editorial I want to focus on some of the conclusions from this perspective article.

Apart from process chemists, the study should be of interest to academics, because, in the conclusions, it listed the gaps in the process chemists' armoury—the reactions we would like to carry out but presently cannot—that could be filled by appropriate research. The hint is there, but not overtly stated, that funding might be made available to academic groups who would be willing to tackle some of the challenges mentioned in the article.

One particular challenge is for the synthesis of poly-substituted benzene rings in a desired orientation. 1,2,4-Substituted benzene rings occurred in 46 out of 128 molecules, 1,2,3-substitution in 13 cases and 1,2,5 in 5 cases. New—preferably catalytic or environmentally friendly—methods for synthesis of the more difficult substitution patterns would be welcomed.

An interesting point was the consistency of the overall results across the three companies. For example the 128 syntheses analysed contained 1039 chemical transformations, an average of 8.1 steps per API (GSK 7.9, AZ 8.2, Pfizer 8.1) from the purchased raw materials. When the reactions themselves were split into categories (e.g., C−C bond forming, oxidation, reduction, etc.), there was little variation across the three companies.

The article should also be of interest to those in business development in the fine chemicals industry, since it surveys the types of chemistry and the structural characteristics of the 128 drug candidates. For example, those companies making pyridine derivatives would be pleased to see that the pyridine nucleus featured 26 times in 128 molecules and that the ring was synthesised only 3 times and bought in 23 times.

Of the 128 compounds evaluated, 69 (54%) contained at least one stereogenic centre; 67 of these molecules were being developed as single enantiomers and 2 as racemates. 36% of the molecules had only one stereogenic centre, with 19% having two centres and 9% more than two. In 27 of the molecules the "chirality" was bought in, whereas for 30 the chirality was generated in the synthesis, the majority by resolution methods (classical salt formation, dynamic kinetic, enzymatic, or chromatographic). Asymmetric synthesis, surprisingly, in view of the amount of literature on the topic, accounted for only 20% of the stereogenic centres generated, although it could have been used in the synthesis of the chiral molecules purchased as raw materials.

Overall the survey highlights areas where there is a need for new chemistry, such as the alkylation of amines by alcohols, avoiding the need to make and dispose of alkylating agents. Although this chemistry has been used in the bulk chemical industry, using nickel catalysis (e.g., in the synthesis of morpholines), it has not been generally applied in fine chemicals and pharmaceuticals where additional functionality may cause problems. The survey highlights a certain mismatch between what process chemists would like to be able to do and what the academic community, which produces almost all of the process chemists' "toolkit", is currently delivering. The article, and hopefully this editorial too, aims to stimulate discussion and to encourage research into new reactions which can be developed into industrial processes. All process chemists should read it; it is a pity the article was not in OPRD, but one of the authors told me that they wanted it to be read by academics, not just process chemists.

(1) Dugger, R. W.; Regan, J. A.; Brown Ripin, D. H. *Org. Process Res. Dev.* **2005**, *9,* 253−258.
(2) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4,* 2337−2347.

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The July 2006 issue of *Chemical Reviews* (Vol. 106, No. 7) is a Special Issue, devoted to process chemistry and contains, after an introduction by the guest editors Mike Lipton and Tony Barrett, 15 excellent review articles which all process chemists should read. This special issue should be on every process chemists' bookshelf—alongside OPRD of course. Some of these reviews have already been highlighted in our literature reviews, but this issue deserved to be plugged even more. It should do wonders for OPRD's impact factor with most of the reviews highlighting the excellent papers from OPRD over the last 10 years. I hope you enjoy reading this Special Issue.

Trevor Laird
*Editor*

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