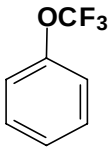
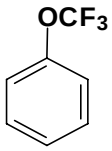
New multi-outlet chemical intermediates and fine chemicals create new business opportunities for companies offering products and services to the lifescience industries. This new monograph from Brychem reports on a compound that is increasingly used in synthesising new agrochemical and pharmaceutical actives.



Trifluoromethoxybenzene

an emerging multi-outlet intermediate



Brychem presents an exhaustive review of the production of TFMB and its derivatives, its application in the synthesis of existing and developing agrochemical and pharmaceutical actives, its main producers and the outlook for growth in the demand for these compounds.

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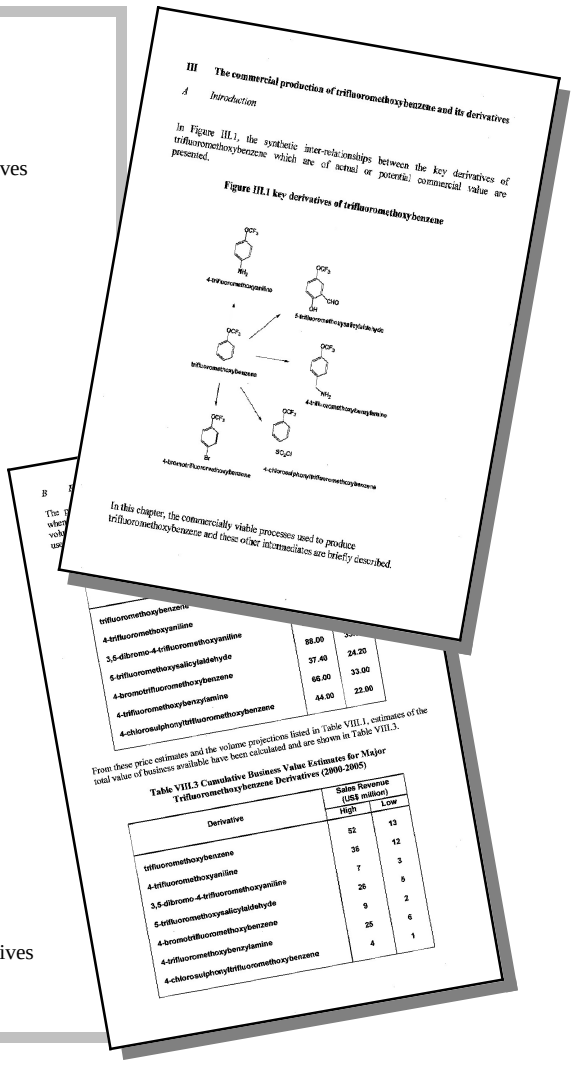

III The commercial production of trifluoromethoxybenzene and its derivatives

A Introduction

In Figure III.1, the synthetic inter-relationships between the key derivatives of trifluoromethoxybenzene which are of actual or potential commercial value are presented.

Figure III.1 key derivatives of trifluoromethoxybenzene

In this chapter, the commercially viable processes used to produce trifluoromethoxybenzene and these other intermediates are briefly described.

From these price estimates and the volume projections listed in Table VIII.1, estimates of the total value of business available have been calculated and are shown in Table VIII.3.

Table VIII.3 Cumulative Business Value Estimates for Major Trifluoromethoxybenzene Derivatives (2000-2005)

Derivative	Sales Revenue (US$ million) High	Low
trifluoromethoxybenzene	52	13
4-trifluoromethoxyaniline	36	12
3,5-dibromo-4-trifluoromethoxyaniline	7	3
5-trifluoromethoxysalicylaldehyde	26	9
4-bromotrifluoromethoxybenzene	9	2
4-trifluoromethoxybenzylamine	25	6
4-chlorosulphonyltrifluoromethoxybenzene	4	1

This report is designed to assist business development professionals working within the international fine chemical industry. The information presented is not widely available and circulation has been restricted to protect the value of the report. Subscribe now in order to keep up with the latest developments in the lifescience application of fine chemical technology.

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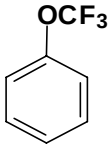
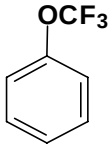


Trifluoromethoxybenzene

an emerging multi-outlet intermediate



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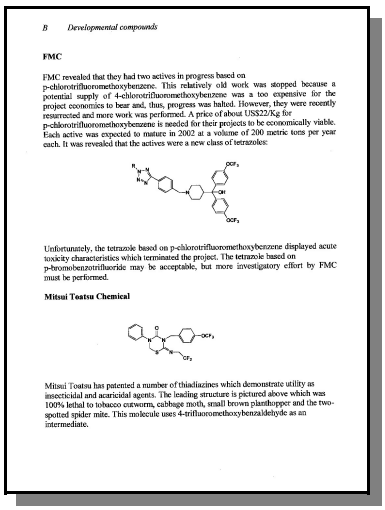


B Developmental compounds

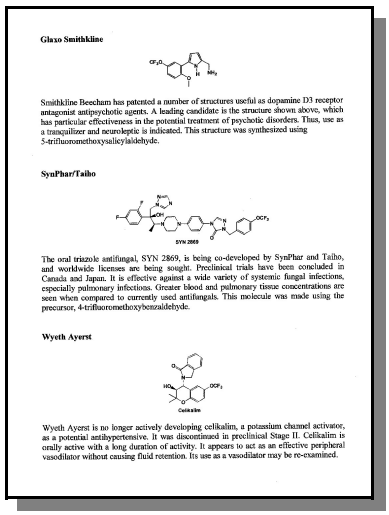
FMC

FMC revealed that they had two actives in progress based on p-chlorotrifluoromethoxybenzene. This relatively old work was stopped because a potential supply of 4-chlorotrifluoromethoxybenzene was a too expensive for the project economics to bear and, thus, progress was halted. However, they were recently resurrected and more work was performed. A price of about US$22/Kg for p-chlorotrifluoromethoxybenzene is needed for their projects to be economically viable. Each active was expected to mature in 2002 at a volume of 200 metric tons per year each. It was revealed that the actives were a new class of tetrazoles:

Unfortunately, the tetrazole based on p-chlorotrifluoromethoxybenzene displayed acute toxicity characteristics which terminated the project. The tetrazole based on p-bromobenzotrifluoride may be acceptable, but more investigatory effort by FMC must be performed.

Mitsui Toatsu Chemical

Mitsui Toatsu has patented a number of thiadiazines which demonstrate utility as insecticidal and acaricidal agents. The leading structure is pictured above which was 100% lethal to tobacco cutworm, cabbage moth, small brown planthopper and the two-spotted spider mite. This molecule uses 4-trifluoromethoxybenzaldehyde as an intermediate.



Glaxo Smithkline

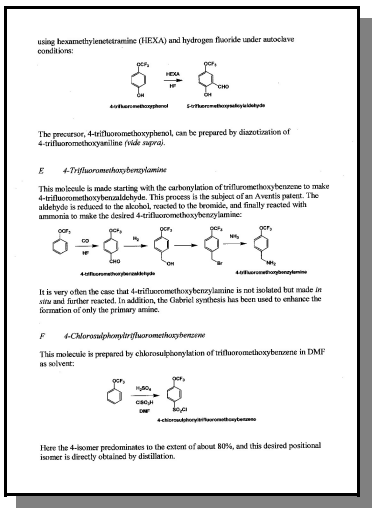
Smithkline Beecham has patented a number of structures useful as dopamine D3 receptor antagonist antipsychotic agents. A leading candidate is the structure shown above, which has particular effectiveness in the potential treatment of psychotic disorders. Thus, use as a tranquillizer and neuroleptic is indicated. This structure was synthesized using 5-trifluoromethoxysalicylaldehyde.

SynPhar/Taiho

The oral triazole antifungal, SYN 2869, is being co-developed by SynPhar and Taiho, and worldwide licenses are being sought. Preclinical trials have been concluded in Canada and Japan. It is effective against a wide variety of systemic fungal infections, especially pulmonary infectious. Greater blood and pulmonary tissue concentrations are seen when compared to currently used antifungals. This molecule was made using the precursor, 4-trifluoromethoxybenzaldehyde.

Wyeth Ayerst

Wyeth Ayerst is no longer actively developing celikalim, a potassium channel activator, as a potential antihypertensive. It was discontinued in preclinical Stage II. Celikalim is orally active with a long duration of activity. It appears to act as an effective peripheral vasodilator without causing fluid retention. Its use as a vasodilator may be re-examined.



using hexamethylenetetramine (HEXA) and hydrogen fluoride under autoclave conditions:

The precursor, 4-trifluoromethoxyphenol, can be prepared by diazotization of 4-trifluoromethoxyaniline *(vide supra)*.

E 4-Trifluoromethoxybenzylamine

This molecule is made starting with the carbonylation of trifluoromethoxybenzene to make 4-trifluoromethoxybenzaldehyde. This process is the subject of an Aventis patent. The aldehyde is reduced to the alcohol, reacted to the bromide, and finally reacted with ammonia to make the desired 4-trifluoromethoxybenzylamine:

It is very often the case that 4-trifluoromethoxybenzylamine is not isolated but made *in situ* and further reacted. In addition, the Gabriel synthesis has been used to enhance the formation of only the primary amine.

F 4-Chlorosulphonyltrifluoromethoxybenzene

This molecule is prepared by chlorosulphonylation of trifluoromethoxybenzene in DMF as solvent:

Here the 4-isomer predominates to the extent of about 80%, and this desired positional isomer is directly obtained by distillation.

✂ ----------

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