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Development of a Continuous Process for the Industrial Generation of Diazomethane[1]

Lee D. Proctor* and Antony J. Warr

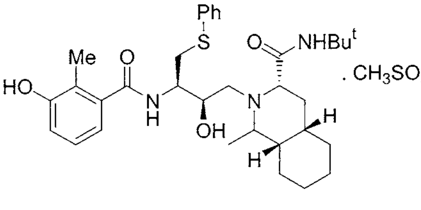
Phoenix Chemicals Ltd., 34 Thursby Road, Bromborough, Merseyside CH62 3PW, United Kingdom

Abstract:

The development of a safe process for the industrial generation of diazomethane is described. Diazomethane is produced and consumed in a continuous process capable of generating between 50 and 60 tonnes per year whilst the maximum inventory is maintained at less than 80 g. The diazomethane production unit is part of an integrated multistage continuous process that produces key intermediates for the latest generation of HIV protease inhibitor drugs. The use of diazomethane in this role has facilitated a direct cost-effective route to compounds such as (2*S*,3*R*)-3-(*N*-benzyloxycarbonyl)-amino-1-chloro-4-phenylthiobutan-2-ol that can be produced in 82% yield from *N*-benzyloxycarbonyl-*S*-phenyl-L-cysteine.

Introduction

Diazomethane is a highly reactive gas (bp = −23 °C) with a wide range of utility in chemical syntheses.[2] It reacts rapidly with carboxylic acids to form the corresponding methyl esters, generally in high yield, with the evolution of gaseous nitrogen. In like manner, diazomethane reacts with phenols and alcohols to form methyl ethers with concomitant release of nitrogen, the rate of reaction depending on the acidity of the substrate. Ordinary alcohols are unreactive unless catalysed by HBF_4 [3] or silica gel.[4] A further example of its use is the formation of carbon−carbon bonds with substrates such as acid chlorides and anhydrides. The so-formed α-diazoketones are themselves useful intermediates.[5] Diazomethane is an efficient reagent for carrying out cyclopropanation reactions with alkenes when catalysed by palladium (II) compounds. Similarly, chain extension or ring expansion of ketones and conversion of ketones to epoxides can be readily achieved with diazomethane. However, it is in the formation of HIV protease inhibitors that diazomethane has found its greatest industrial utility. An example is nelfinivir mesylate **1** (Figure 1), which can be produced on a commercial scale from the key chiral building block (2*S*,3*R*)-3-(*N*-benzyloxycarbonyl)-amino-1-chloro-4-phenylthiobutan-2-ol **2**.[6] There are a number of different industrial syntheses of **1** and **2**[7] that do not use diazomethane; however, the synthetic route incorporating diazomethane is both direct and cost-effective (Scheme 1). For these reasons an effective and safe method for generating diazomethane on an industrial scale was required to provide tonne quantities of key intermediates such as **2**.



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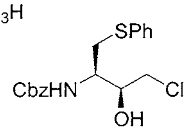

2

Figure 1. **Structures of nelfinavir mesylate 1 and its key intermediate 2.**

Discussion

Diazomethane is a powerful carcinogen and allergen and is highly toxic with a permissible exposure limit of 0.2 ppm averaged over an 8-h period. However, the principle impediment to its industrial use is the explosive nature of the compound.[8] The technical literature for the laboratory synthesis of diazomethane cautions against the use of ground-glass joints, and the use of specially designed fire-polished glassware is recommended. The Aldrich Chemical Co., for example, markets apparatus capable of generating a solution of up to 300 mmol diazomethane in diethyl ether.[9] A method for generating dilute solutions of up to 100 mmol diazomethane in dichloromethane has also been developed by Isis Pharmaceuticals.[10] Aerojet General Corporation is the only company to date to have published procedures capable

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(1) (a) This is a transcript of part of a lecture entitled “Continuous Processing Technology Applications in the Fine Chemical Industry” given at the Third International Conference on Organic Process Research and Development, Montreal, July 10−12, 2000. (b) Warr, A. J.; Proctor, L. D. Generation of Diazomethane. (Phoenix Chemicals Ltd.). GB 2357501A, 2001.

(2) For a review of diazomethane, see: Pizey, J. S. *Synthetic Reagents*; Wiley: New York, 1974; Vol. 2, p 65.

(3) Neeman, M.; Caserio, M. C.; Roberts, J. D.; Johnson, W. S. *Tetrahedron* **1959**, *6*, 36.

(4) (a) Ohno, K.; Nishiyama, H.; Nagase, H. *Tetrahedron Lett*. **1979**, 4405. (b) Ogawa, H.; Hagiwara, H.; Chihara, T.; Teratani, S.; Taya, K. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 627.

(5) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998.

(6) (a) Kaldor, S. W.; Appelt, K.; Fritz, J. E.; Hammond, M.; Crowell, T. A.; Baxter, A. J.; Hatch, S. D.; Wiskerchen, M.; Muesing, M. A. *Bioorg. Med. Chem. Lett*. **1995**, 5, 715. (b) Kaldor, S. W.; Kalish, V. J.; Davies, J. F., II; Shetty, B. W.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979.

(7) (a) Agouron Pharmaceuticals. *Chemical Development of an HIV Protease Inhibitor*. First International Conference on Organic Process Research and Development, San Francisco, November 5−7, 1997. (b) Ikunaka, M.; Matsumoto, J.; Fujima, Y.; Hirayama, Y. *Org. Process Res. Dev.* **2002**, *6*, 49.

(8) Urben, P. G. *Bretherick’s Handbook of Reactive Chenical Hazards*, 5th ed.; Butterworth-Heinemann: Woburn, MA, 1995; Vol. 1, p 164.

(9) Black, T. H. *Aldrichchimica Acta* **1983**, *16*, 3.

(10) Acevedo, O.; Ross, B.; Andrews, R. S.; Springer, R.; Cook, P. D. Apparatus and Processes for the Large Scale Generation and Transfer of Diazomethane. (Isis Pharmaceuticals). U.S. Patent 549243, 1995.

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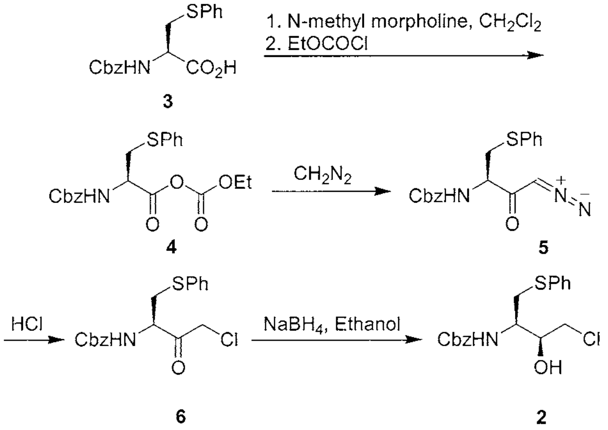
Scheme 1. **Synthesis of 2 using diazomethane**



of producing diazomethane on a truly large scale; the Aerojet batch process[11] is capable of generating solutions of diazomethane in diethyl ether on the 50−25000 g-mol-scale. The process involves treating an *N*-methyl-*N*-nitrosoamine in diethyl ether with an aqueous solution of potassium hydroxide in the presence of a phase-transfer catalyst and continually codistilling an ethereal solution of diazomethane from the reaction mixture. Aerojet[12] has also disclosed a continuous process for the production of ethereal solutions of diazomethane which avoids the need to codistill large amounts of solvent.

The published procedures described have proved to be robust and safe; however, they rely on the use of volatile flammable solvents. Solvents with high vapour pressures are chosen specifically to lower the headspace concentration of diazomethane, which reduces the explosive hazard. This immediately restricts the variety of chemical processes that can be performed if one or more of the substrates are insoluble in the solvent system. The processes described all use conventional lab or plant equipment. Plant batch vessels are inherently complex, comprising many valves, gaskets, and other connections, which increase the risk of material building up in dead-legs and are potential sources of leaks.

The commercial need to design a process capable of generating 200 tonnes/year of the chloromethyl ketone intermediate **6** necessitated developing a process for producing diazomethane at a production rate of >50 tonnes/year. The decision was made very early in the development program to design a process that did not rely on using volatile flammable solvents and to develop a continuous process which would minimise the inventory of diazomethane. The following goals were defined to meet these objectives: (i) develop a chemical system capable of continuously generating diazomethane; (ii) design pilot equipment incorporating a suitable pressure relief safety system to facilitate such development; (iii) develop on-line methods to quantitatively and continuously measure the concentration of diazomethane inside the reactor system and to develop methods for environmental monitoring; (iv) investigate in detail the explosive characteristics of diazomethane, determine its lower explosive limit, and use these data to define the safe operational envelope for diazomethane production; (v) optimise the process using the pilot system; (vi) design, fabricate, and carry out full-scale explosion testing on the plant system; and (vii) commission the full-scale plant system.

Chemical Development

The development of a suitable chemical system for producing diazomethane needs to take into account the subsequent chemistry for which diazomethane will be used. For example, the reaction between mixed anhydride **4** and diazomethane (Scheme 1) is extremely base-sensitive, and any inorganic or organic base will react with **4**. Diazomethane is usually prepared by treating a suitable diazomethane precursor, typically an organic solution of an *N*-methyl-*N*-nitrosoamine with an aqueous solution of an inorganic base. It is therefore essential that the diazomethane produced is purified/isolated. It occurred to us that by using a high-boiling solvent to dissolve the precursor we could isolate/purify diazomethane by using an inert gas such as nitrogen to transport it from solution into the gas phase. De Boer and Backer have published a similar procedure for generating diazomethane in the gas phase;[13] the method involved heating a solution of *N*-methyl-*N*-nitroso-*p*-toluene sulphonamide (Diazald) in anisole with potassium hydroxide in a mixture of di(ethylene glycol) ethyl ether (Carbitol) and water. A gentle stream of nitrogen was passed through the apparatus and the evolved diazomethane immediately quenched into benzoic acid; yields of up to 63% are reported. We believed the choice of solvent was key in terms of safety, operability, and performance; as such we chose the solvent on the basis of the following criteria: (i) nonflammability, (ii) low vapour pressure, (iii) low toxicity, (iv) high water solubility, (v) high solubility of precursor, and (vi) high solubility of reaction byproducts. DMSO fit all these criteria and was chosen as the preferred solvent.

The next key decision was choosing a suitable diazomethane precursor. Several precursors are available including *N*-methyl-*N*-nitrosoamine, 1-methyl-3-nitro-1-nitrosoguanidine (MNNG), *N*-methyl-*N*-nitrosourea (MNU) and *N*-methyl-*N*-nitroso-*p*-toluene sulphonamide (Diazald). The lower-molecular weight precursors were initially considered due to their improved atom efficiency. Investigations into the use of MNU indicated the molecule was unstable at temperatures >20 °C[14] and that one of the decomposition products was methyl isocyanate. Methyl isocyanate is also a reported contaminant in ethereal solutions of diazomethane prepared from MNU.[15] We believed that generating diazomethane from MNU would increase the toxic impact of the process,

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(11) Archibald, T. G.; Huang, D.-S.; Pratton, M. H.; Barnard, J. C. Large Scale batch process for Diazomethane. (Aerojet-General Corporation). U.S. Patent 5,817,778, 1998.

(12) Archibald, T. G.; Barnard, J. C.; Harlan, R. F. Continuous Process for Diazomethane from an *N*-Methyl-*N*-nitrosoamine and from Methylurea through *N*-Methyl-*N*-nitrosourea. (Aerojet-General Corporation). U.S. Pataent 5,854,405, 1998.

(13) De Boer, T. H. J.; Backer, H. J. *Recueil* **1954**, *73*, 229.

(14) Arndt, F. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 461.

(15) (a) Golding, B. T.; Bleasdale, C.; McGinnis, J.; Muller, S.; Rees, H. T.; Rees, N. H.; Farmer, P. B.; Watson, W. P. *Tetrahedron* **1997**, *53*, 4063. (b) Irie, H.; Kishimoto, T.; Uyeo, S. *J. Chem. Soc. C* **1969**, 1645.

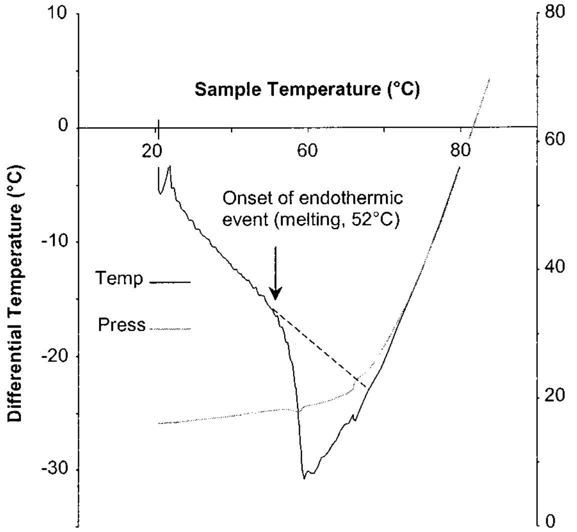

Figure 2. **Ramped Carius tube test for Aldrich Diazald.**

and this prompted the higher-molecular weight precursor, Diazald, to be considered. Diazald also had the advantage of large-scale commercial availability. As part of our routine raw material screening, commercial Diazald from Aldrich was subjected to a ramped Carius tube test to screen for any thermal events (Figure 2). A sample was heated at a rate of 0.5 °C/min to a set-point temperature of 400 °C. Results indicated an endothermic onset temperature of 52 °C (melting) followed by exothermic onset at 59 °C and permanent gas generation at $\sim$60 °C. These results indicated Diazald to be thermally unstable, prompting further investigation. We were particularly concerned with the transport regulations for Diazald and were somewhat surprised to find the compound was unclassified; therefore, a series of experiments was conducted to classify the compound in accordance with the United Nations (UN) transportation of dangerous goods regulations.[16] The tests carried out were: (i) UN gap test to determine the ability of the substance to propagate a detonation under confinement, (ii) Koenen tube test to determine the sensitivity of the substance to intense heating under confinement, and (iii) time/pressure test to determine the effect of ignition under confinement. The results showed Diazald exhibited thermally initiated explosive properties but was insensitive to detonative shock, although the compound was shown to propagate a rapid deflagration under time/pressure conditions. This required Diazald to be classified under the Class 1 (explosives) group. Diazald also exhibited a low self-accelerating decomposition temperature (SADT) ($<$75 °C) which would prohibit the transport of the substance. These findings caused some concern because to generate 50 tonnes of diazomethane, over 250 tonnes of Diazald would be required. Further studies were therefore carried out to determine if the material could be phlegmatised by mixing with an inert material. Water was chosen to desensitise Diazald because commercial Diazald was readily available as a water-damp solid, and the Class 1 tests were repeated with Diazald diluted with 10% water. Under these conditions the material had a medium effect when heated under confinement in the Koenen tube test, and a limiting diameter of 1.5 mm was found. The material did not propagate a rapid deflagration under time/pressure conditions but did propagate a slow deflagration with a minimum time taken from 100 to 300 psia of 36.0 ms (close to the classification limit of 30 ms). These results were encouraging and indicated Diazald may be accepted as a candidate for UN Class 4.1. Three further tests were required to complete classification, and these were a deflagration test,[17] Dutch pressure vessel test,[18] and heat accumulation storage test at 55 °C.[19] Full testing was carried out using Diazald diluted with 10% water, and the Dutch pressure vessel test was repeated using Diazald diluted with both 15 and 20% water. The Dutch pressure vessel tests showed that Diazald diluted with 15% water had a limiting diameter of $<$9 mm corresponding to a test criteria of "medium". This result in conjunction with the previous tests enabled labeling and packaging guidelines for Diazald to be defined.[20]

The chemical reactor system envisaged involved cofeeding a solution of Diazald dissolved in DMSO and an aqueous solution of potassium hydroxide into a reactor where the contents would be continually sparged with nitrogen, aiding removal of the generated diazomethane gas and transfer to a quench medium. This process was believed to have several advantages over the current methods of manufacture. The reaction system is homogeneous, removing the need for phase-transfer catalysis and reducing the risk of a runaway reaction. In addition, purification/isolation of diazomethane is accomplished by transporting the product into the gas phase. To facilitate the development work the design, fabrication, and testing of a pilot-scale reactor system was required.

Pilot Reactor Design

The principal design philosophy was to develop a reactor system capable of dealing with the worst-case scenario, a diazomethane explosion. Published data quantitatively investigating the nature of diazomethane explosions is extremely limited, and an approach based on "over-design" immediately led to glass being ruled out as a construction material in favour of steel. The basic reactor design was constructed of schedule 40 316 S/S pipe of nominal bore of 80 mm, length of 181 mm, and internal volume of 910 cm^3. The reactor was flanged at both ends and the bottom flange equipped with a full-bore graphite bursting disk rated at 30 psi. In the event of a diazomethane explosion it was intended

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(16) (a) *Recommendations on the Transport of Dangerous Goods Model Regulations*, 12th ed.; United Nations: New York NY, 2001. (b) All the Diazald studies were carried out in collaboration with Chilworth Technology, Southampton, UK.

(17) UN Transportation of Dangerous Goods Regulations, Test Series C, Test C.2 (TNO Deflagration test).

(18) UN Transportation of Dangerous Goods Regulations, Test Series E, Test E.2 (DPV test).

(19) UN Transportation of Dangerous Goods Regulations, Test Series H, Test H.4.

(20) Diazald should be classified for packaging and transportation as follows: *N*-methyl-*N*-nitroso-*p*-toluene sulphonamide wetted with not less than 15% water (DIAZALD (85%w/w with water)). Self-Reactive Solid, Type D, Temperature-Controlled, UN Number 3236, UN Class 4.1, temperature control conditions: SADT = 40 °C, control temperature = 30 °C, emergency temperature = 35 °C, packing group II (packing instruction 520), packing method OP7 (limits package size to 50 kg net mass).

for the bursting disk to fail and the contents of the reactor to be ejected into a tank containing a quench medium. It was crucial to test this primary pressure relief system before any active chemistry was attempted. During normal operation it was calculated that the maximum quantity of diazomethane available for a gas-phase detonation was 70 mg. A test study was designed to examine the possible consequences of such a detonation occurring and to assess the likely impact of this on the integrity of the vessel. The test[21] was carried out using 600 mg of pentaerythritoltetranitrate (PETN) electric detonator, representing 8.6 times the theoretical maximum mass of diazomethane. The reactor was half-filled with water to simulate the reaction mixture liquid level, and two tests were carried out. In the first test the detonator was suspended above the liquid level to simulate a gas-phase detonation, and in the second test the detonator was immersed in the water. In both tests, the bursting disks ruptured across their entire cross section. The internal surface of the reactor showed some pitting, but no exterior flaking of the shell had occurred. The reactor had contained the detonation satisfactorily, and this was further confirmed by carrying out nondestructive testing of the reactor welds by X-ray bombardment.

This reactor design was very simple, with agitation being provided solely from the subsurface nitrogen sparge. The design significantly reduced the requirement for valves, gaskets, and other connections associated with standard reaction vessels, thereby adding to the intrinsic safety of the reactor.

The safe operation of the reactor required defining an operational envelope for diazomethane production. This could only be achieved if the explosive limits of diazomethane were known, and to accomplish this, a method for quantitatively measuring the concentration of diazomethane in the gas phase was required.

Diazomethane Monitoring

The success of the reactor detonation studies gave us confidence to operate the reactor in a limited capacity to generate low concentrations of diazomethane in nitrogen. The diazomethane gas stream was reacted with a solution of benzoic acid in DME and the quantity of diazomethane produced back-calculated by quantitative GC analysis of the methyl benzoate produced. This “wet-chemical” method, although extremely accurate, was impractical as a technique for continually monitoring the gas-phase concentration in the reactor. A number of alternative techniques were considered, and of these IR showed most promise. The gas-phase IR spectrum of diazomethane has a strong characteristic CN_2 stretch at 2102 cm^{-1}, and this was used for quantitative analysis using photoacoustic methods, a technique routinely used in industry for environmental monitoring of stack emissions. A gas-handling system was therefore developed which worked in conjunction with a commercial photoacoustic FT-IR instrument, and this system enabled continuous on-line analysis of the reactor headspace. The instrument was calibrated by monitoring the reactor headspace until a steady-state concentration of diazomethane was observed; the diazomethane gas stream was then redirected into a benzoic acid/DME quench solution and wet chemical analysis for methyl benzoate used to retrospectively calibrate the instrument. By providing a means by which monitoring of the diazomethane concentration could be carried out, the photoacoustic system not only was beneficial from a safety perspective but also enabled rapid process development studies to take place.

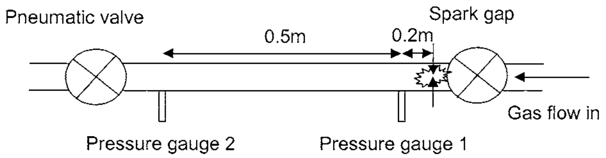

Figure 3. **Schematic of apparatus used for the explosive limit testing.**

The extreme toxicity of diazomethane also required development of environmental monitoring procedures. An analytical method was developed which involved continually pumping air though a prepacked sample tube containing octanoic acid. The tubes were then quantitatively analysed for methyl octanoate by GC and the time-weighted average concentration of diazomethane calculated. These procedures ensured a continual record of any diazomethane contamination within the reactor environment.

Explosion Studies[25]

There are several published reports cautioning against the use of gaseous diazomethane;[22] however, none of these reports provides any quantitative data concerning the nature of such explosions, and surprisingly, even the lower explosive limit of diazomethane has not been reported. This lack of information has prompted compounds whose explosive limits are known to be used as models for diazomethane, for example hydrazoic acid,[23] which has a gas-phase explosive limit of 17%.[24] The importance of obtaining accurate data prompted detailed explosion studies to be carried out. Three experimental objectives were defined: (i) determine the lower explosive limit in air, (ii) determine the explosive limit in nitrogen, and (iii) carry out an explosion test using diazomethane in the pilot reactor. A simple system was developed for carrying out the explosion tests (Figure 3). This comprised a length of PFA tubing equipped with two remotely operated three-way pneumatic valves, two pressure gauges, and a spark gap. Diazomethane was generated using the pilot reactor and the gas concentration continually monitored using the photoacoustic FT-IR monitoring system. When the desired concentration was reached, the remote valves were closed, the spark was ignited, and the pressure

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[21] Testing carried out by Imperial Dynamite Co. Ltd., Neston, UK.

[22] (a) Lombardi, P. *Chem. Ind.* **1990**, 708. (b) Moss, S. *Chem. Ind.* **1994**, 122. (c) Steacie, E. W. R, *J. Phys. Chem.* **1931**, *35*, 1493. (d) Eistert, B. *Newer Methods of Preparative Organic Chemistry*; Interscience: New York, 1948.

[23] Archibald, T. A. *Diazomethane: Commercialization of a Highly Hazardous Material*; First International Conference on Organic Process Research and Development, San Francisco, November 5−7, 1997.

[24] Urben, P. G. *Bretherick's Handbook of Reactive Chenical Hazards*, 5th ed.; Butterworth-Heinemann: Woburn, MA, 1995; Vol. 1, p 1498.

[25] Diazomethane explosion studies were carried out in collaboration with the Centre for Explosion Studies, Aberystwyth, UK.

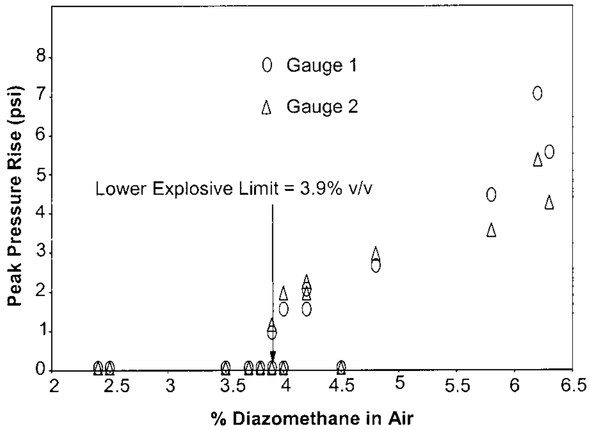

Figure 4. **Diazomethane−air explosion tests (LEL tests).**

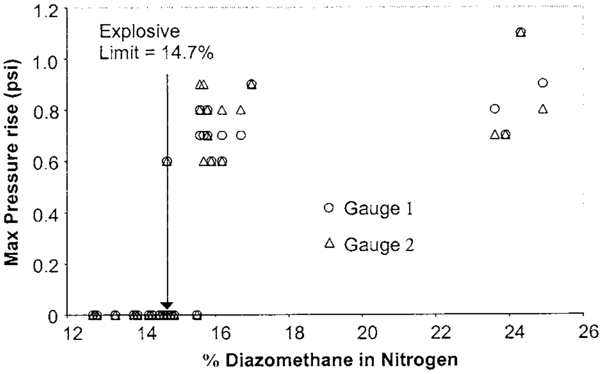

Figure 5. **Diazomethane−oxygen-free nitrogen explosion tests.**

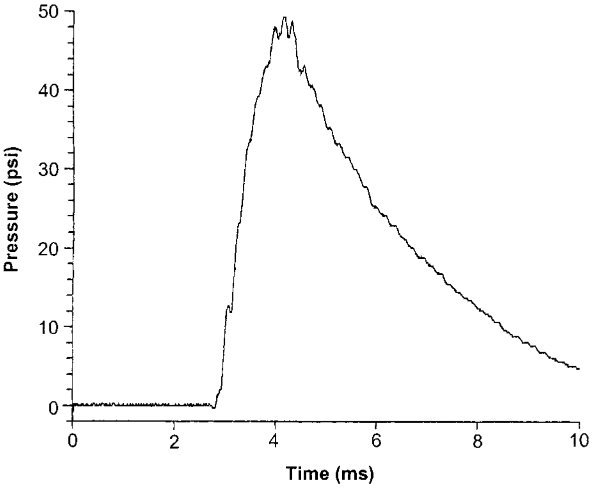

Figure 6. **17% Diazomethane−air explosion pressure response from pilot reactor test.**

responses from the two gauges were logged by a PC. The experimental data enabled the lower explosive limit for diazomethane in air to be defined as 3.9% (v/v) for this particular geometry and initiation energy. The peak pressures in this configuration were found to be of the order of 6 ± 1.5 psi for 6.3% (v/v) diazomethane in air, the maximum concentration tested (Figure 4). Diazomethane was found to explode when diluted with oxygen-free nitrogen, but the pressures generated were low, of the order of 1 psi (Figure 5). The explosive limit for diazomethane in oxygen-free nitrogen was determined to be 14.7% (v/v). Although the overpressures produced by the decomposition of the oxygen free nitrogen system was found to be low, it could be enough to break the seal of a ground-glass joint, thus allowing the mixing of diazomethane and air, facilitating the more violent diazomethane−air explosion to occur. This may explain previous anecdotal or poorly documented accounts of relatively severe explosions of diazomethane under inert conditions.[22] A final test was conducted where the valve leading from the test pipe to the pilot reactor was left open, so that the explosive event was allowed to propagate back into the reactor, which was fitted with a 2-bar-rated graphite bursting disk. The experiment was performed using 17% (v/v) diazomethane in air. The pressure record (Figure 6) clearly shows pressure development in the vessel before the bursting ruptured across its entire cross section, safely ejecting the reaction liquors into a quench tank containing 80% acetic acid. This result provided additional comfort that the fundamental reactor design and pressure-relief system were extremely safe. On the basis of these results an upper safe working limit for operational purposes was set at 10% (v/v) diazomethane in nitrogen.

Pilot Development

The basic pilot reactor was modified to facilitate detailed chemical development and optimisation studies (Figure 7). The modifications included a quench tank attached to the bursting disk flange. The tank contained an acidic medium to quench the reaction liquors in case of bursting disk failure as well as to provide a reservoir to continually neutralise the liquors draining from the reactor. Neutralisation generated potassium acetate and methyl acetate from potassium hydroxide and diazomethane, respectively. The acidity of the tank was maintained at a pH of 5.5 by the controlled continuous addition of 80% acetic acid. The reactor level was controlled by using a differential pressure sensor (LT1, Figure 7) which controlled a drain valve (LCV 1, Figure 7). The evolved diazomethane/nitrogen gas stream was passed through a carousel gas/liquid separator that was directly attached to a packed column. The substrate liquors for the diazomethane reaction (for example, solutions of mixed anhydride or benzoic acid) continually flowed around the packed column.[26] The diazomethane reactor was equipped with a heat-transfer jacket with temperature-feedback control to a heater/chiller unit. Both the headspace and subsurface nitrogen flows (i and iv, Figure 7) were controlled using nitrogen mass flow controllers. Potassium hydroxide solution (ii) was supplied from a pressure-fed tank via a liquid mass flow controller. Diazald solution (iii) was supplied from a storage tank using a pump, the speed and flow of which were controlled using a Coriolis mass flow meter.

The process was initially developed to maximize the yield of diazomethane. The reaction between Diazald and KOH in DMSO/water is quantitative, with no residual Diazald detected in the system, and is also extremely exothermic ($\Delta H = -459$ kJ/mol with respect to Diazald). The most significant

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(26) The details of the subsequent diazomethane chemistry will be covered in a separate publication.

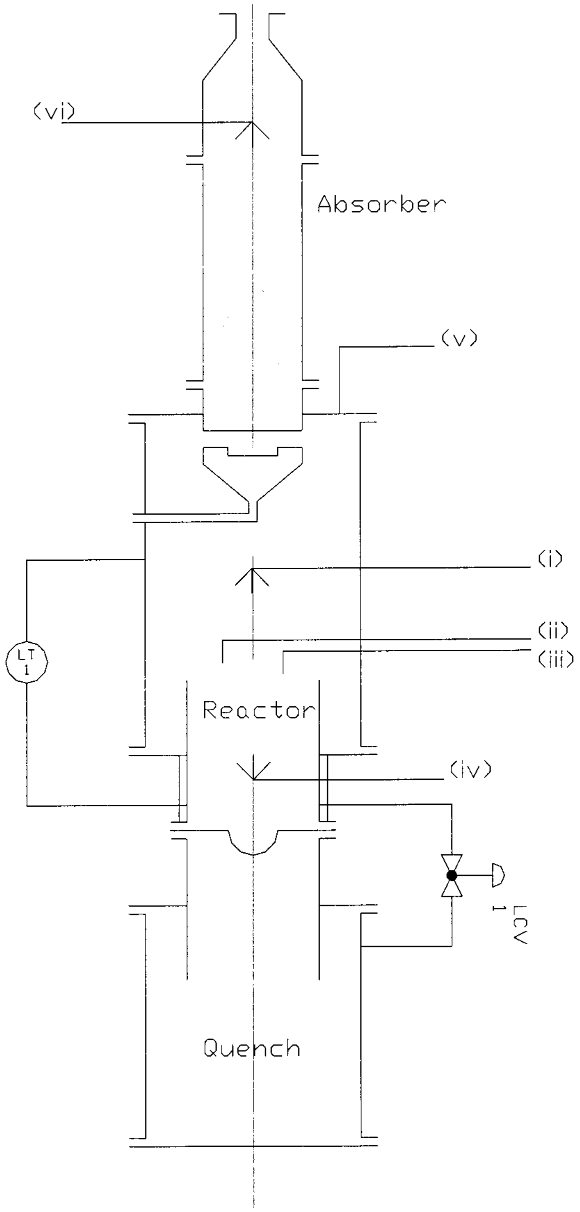

Figure 7. **Schematic of pilot diazomethane reactor. (i) Headspace nitrogen dilution; (ii) Diazald addition port; (iii) potassium hydroxide addition port; (iv) subsurface nitrogen sparge; (v) diazomethane monitoring (photoacoustic FT-IR); (vi) packed column with liquid recycle.**

yield loss was due to diazomethane dissolved in the liquid-waste stream. Studies indicated that increasing the quantity of water in the system greatly reduced the solubility of diazomethane in the reaction mixture; however, this had to be balanced against excess water causing precipitation of Diazald from solution, a potentially hazardous situation. An optimal mix was determined which comprised reacting a 15% (w/w) solution of aqueous potassium hydroxide with a 20% (w/w) solution of Diazald/DMSO in a molar ratio of 1.2:1, respectively. Under these conditions over 50% of the available diazomethane was transported into the gas phase without the need for any subsurface nitrogen (Figure 8). The subsurface nitrogen flow was increased in ratio to the total gas flow and liquid-feed flows to maintain the desired headspace concentration of diazomethane at 10% (v/v).

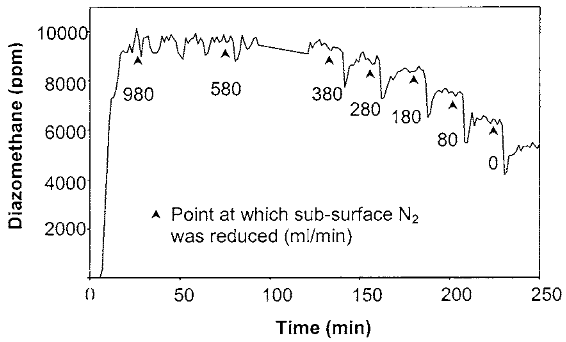

Figure 8. **Variation of the diazomethane concentration with the subsurface nitrogen flow.**

Applying 10% of the total nitrogen flow subsurface afforded a gas-phase yield of diazomethane equal to 96%, the other 4% being lost to the quench system. Optimisation of the subsurface nitrogen flow had the added advantage of reducing the contact time between the diazomethane and water. This was important because diazomethane rapidly reacts with water to generate methanol (half-life = 750 s, at 20 °C and pH = 7.2). The reaction temperature was optimised to ensure rapid conversion to diazomethane and to minimise transport of water vapour through the carousel separator; the optimum temperature was between 40 and 50 °C.

Diazomethane, once in the gas phase, had to be transported as a dilute stream in nitrogen from the headspace of the reactor through the carousel gas−liquid separator and into the packed substrate column. The possibility of nonexplosive gas-phase decomposition induced thermally or by turbulence would potentially reduce the process yield and therefore warranted further investigation. Published data suggested diazomethane was thermally stable in the gas phase;[27] however, no data could be found for the effects of turbulence. A simple experiment was designed whereby the diazomethane gas stream was passed through sections of PFA tube with different internal diameters. The tube length was adjusted to maintain constant residence time, whilst different tube diameters were chosen to investigate the transition from laminar flow ($Re < 2000$) to turbulent flow ($Re > 2000$),[28] and a single experiment was also carried out using standard 316 S/S tube for comparison. Results indicated diazomethane was not significantly affected by turbulent flow between the range $Re = 1200-5500$ (Figure 9). The gas-phase yield was corroborated by reacting the diazomethane/nitrogen stream with a solution of benzoic acid/DME inside the packed column section. Quantitative analysis for methyl benzoate confirmed the yield was 96%.

The development work carried out using the pilot reactor generated a significant array of data which enabled the design and fabrication of the full-size plant system.

Plant Reactor Design and Testing

Scale-up from the pilot system was commercially driven by the need to design a plant reactor capable of generating

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(27) (a) Rabinovich, B. S.; Setser, D. W. *J. Am. Chem. Soc.* **1961**, *83*, 750. (b) Shantarovitch, P. S. *Dokl. Akad. Nauk SSSR* **1957**, *116*, 255.

(28) *Perry's Chemical Engineers' Handbook*, 6th ed.; McGraw-Hill: New York, 1984; pp 5-6, 5-28.

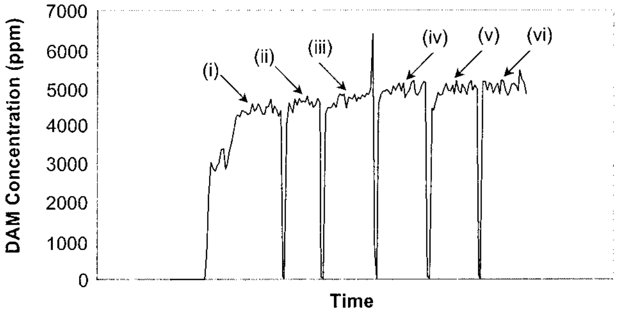

Figure 9. **Variation of diazomethane concentration with Reynolds number. (i) *Re* = 1203, concentration = 4422 ± 60 ppm; (ii) *Re* = 1937, concentration = 4615 ± 52 ppm; (iii) *Re* = 3068, concentration = 4722 ± 57 ppm; (iv) *Re* = 3487, concentration = 4976 ± 66 ppm; (v) *Re* = 5523, concentration = 4984 ± 58 ppm; (vi) 316 stainless steel tube, *Re* = 3452, concentration = 5035 ± 81 ppm.**

Table 1. **Scale comparison between the pilot and plant reactor systems**

	units	pilot	plant	scale factor
	Diazomethane Reactor			
diameter	m	8.00×10^{-2}	5.00×10^{-1}	6.25
cross-sectional area (XA)	m^2	5.03×10^{-3}	1.96×10^{-1}	3.91×10
operational volume	L	6.00×10^{-1}	1.00×10^{2}	1.67×10^{2}
aspect ratio	V/XA	1.19×10^{2}	5.09×10^{2}	4.27
	Reactor Headspace			
head diameter	m	1.50×10^{-1}	1.00	6.67
cross sectional area (XA)	m^2	1.77×10^{-2}	7.85×10^{-1}	4.44×10
head height	m	4.00×10^{-1}	7.00×10^{-1}	1.75
head volume	m^3	7.07×10^{-3}	5.50×10^{-1}	7.78×10
aspect ratio	V/XA	4.00×10^{-1}	7.00×10^{-1}	1.75
subsurface nitrogen flow	L/h	5.88×10	4.80×10^{3}	8.16×10
headspace nitrogen flow	L/h	4.80×10^{2}	2.71×10^{4}	5.64×10
total nitrogen flow	L/h	5.39×10^{2}	3.19×10^{4}	5.91×10
carousel ports	m	1.25×10^{-2}	5.00×10^{-2}	4.00
cross-sectional area (xa)	m^2	1.23×10^{-4}	1.96×10^{-3}	1.60×10
velocity through carousel	m/s	3.05×10^{-1}	1.13	3.70
carousel Reynolds number		2.43×10^{2}	3.78×10^{3}	1.56×10

200+ tonnes/year of the chloromethyl ketone intermediate **6**. However, it was not possible to scale each of the dimensions on the pilot unit to achieve an equivalent plant reactor. For example, if the maximum production rate of the pilot reactor were 1 tonne/year diazomethane, to produce 50 tonnes/year would require a reactor with a 4 m diameter (12.6 m^2 cross section) or else 50 pilot reactors; both options were clearly impractical. Scale-up from the pilot unit was carried out by considering each of the key factors individually and then scaling as appropriate to design a system which was both practical and workable (Table 1). Because of the change in dimensions and its potential impact on safety, we decided to take the unusual step of fabricating two full-scale reactors. One of these reactors was then used to carry out full-scale explosion testing to unequivocally confirm that the reactor and its pressure-relief systems were safe and that in the event of an explosion it would operate according to the engineering design. The dilemma we now faced was how to carry out large-scale explosion tests. Given the difficulty of generating sufficient quantities of diazomethane for a full-scale test, it was necessary to identify another fuel−air gas mixture whose explosion properties were the same as those identified in the worst-case diazomethane−air mixture. To identify a model gas, the tests[25] conducted previously in the small-bore pipe were repeated using a range of ethylene−air compositions. In addition to peak pressures, rates of pressure rise were also compared with the previous test data. In this way, ethylene−air was seen to be an appropriate model gas (Figure 10). Following the selection of ethylene as the model fuel, the pilot diazomethane reactor tests were repeated using ethylene−air mixtures (Figure 11). The conclusion was made that ethylene−air could be used as a reasonable substitute gas in place of diazomethane and that ethylene would generate greater peak pressure, overall duration and impulse than diazomethane. Ethylene−air would thus be a conservative substitute. The full-scale reactor comprised the same key components as those of the pilot reactor (Figure 12), including a quench tank (Figure 12, E), which was fitted with a stainless steel 0.5 m diameter 4.9-bar-rated bursting disk. The main diazomethane reactor (Figure 12, D) was connected to the quench tank via a flange equipped with a full bore stainless steel 0.5 m diameter 3.4-bar-rated bursting disk. The headspace/carousel unit (Figure 12, C) and the packed-column sections (Figure 12, A and B) were connected to the diazomethane reactor as shown. For explosion testing

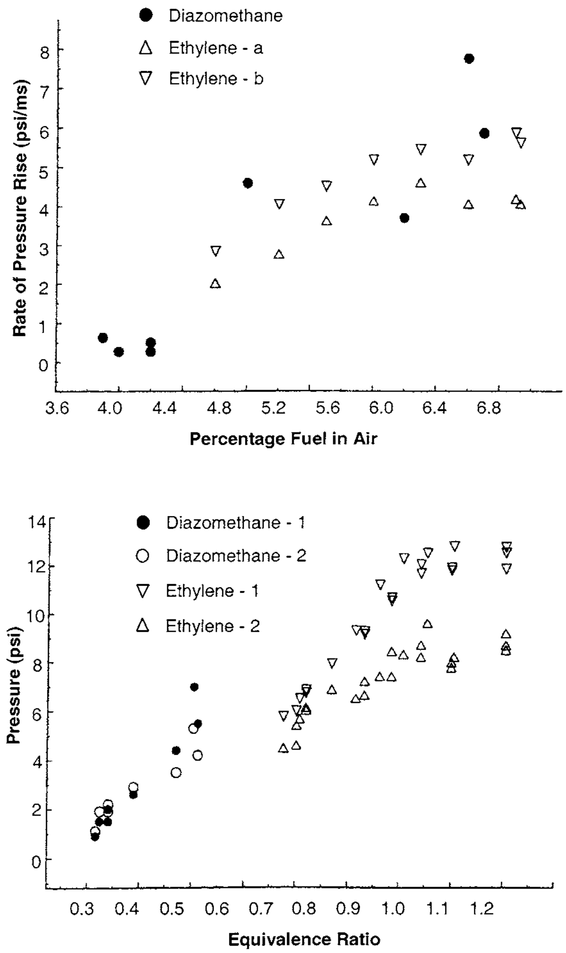

Figure 10. **Comparison between ethylene−air and diazomethane−air explosions in the small-bore tube tests. Variation in rate of pressure rise with fuel composition as a function of percentage fuel (upper chart) and peak overpressure with equivalence ratio (lower chart). Diazomethane/air (circles), and ethylene/air (triangles up - 1st gauge, down - 2nd gauge).**

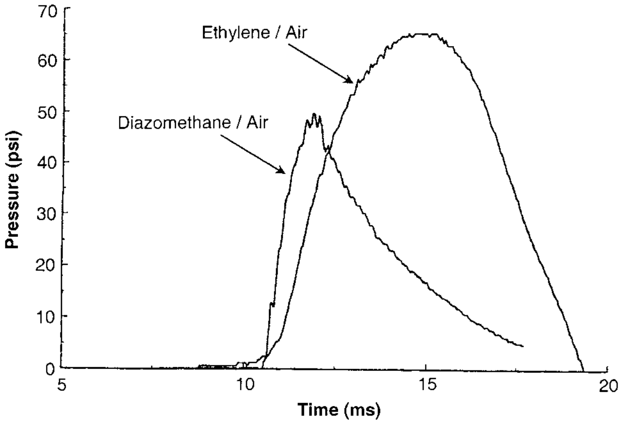

Figure 11. **Comparison between ethylene−air and diazomethane−air explosions in the pilot reactor.**

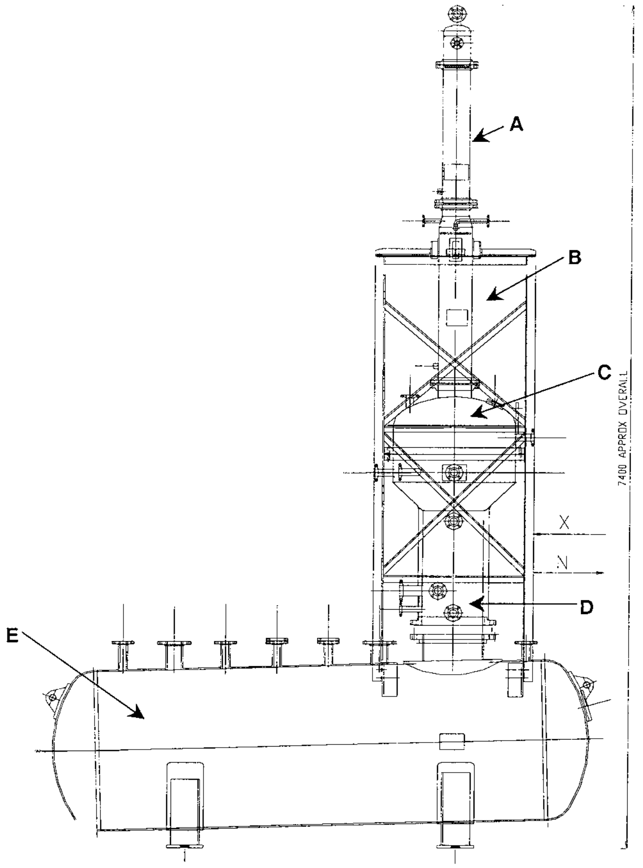

Figure 12. **Schematic of plant reactor.**

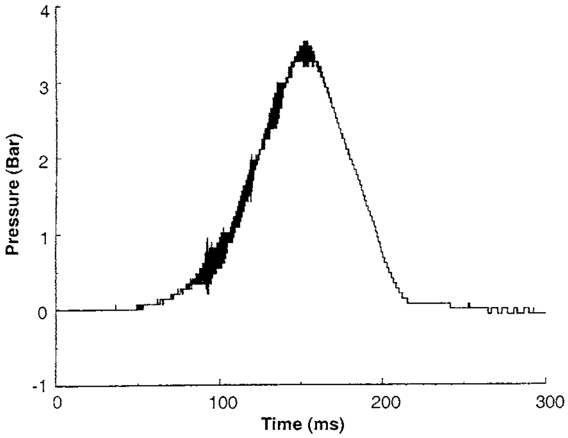

Figure 13. **Pressure response from 7% ethylene−air explosion test in the full-scale reactor.**

the quench tank was half-filled with water to represent the maximum operational fill volume; similarly, the diazomethane reactor section was also half-filled with water. Access flanges to the carousel unit were modified to allow an ethylene−air mixture to be formed by a recirculation procedure. The ethylene composition, 7% in air, was verified against a calibrated IR gas analyser. Ignition was by a nominal 0.6 J spark. Pressure gauges were located at two other flange locations and strain gauges placed in key locations around the welds of the carousel unit. The explosion test resulted in failure of the 3.4-bar-rated bursting disk and ejection of water from the diazomethane reactor into the quench tank. The momentum changes associated with this event led to some slight permanent deformation to the quench tank. The pressure rise observed (Figure 13) was not sufficient to cause the second 4.9-bar-rated bursting disk to fail. The maximum measured strain did not exceed 1500 microstrain on any gauge. This result confirmed the intrinsic safety of the rector design.

Plant Commissioning

The diazomethane reactor was one component of an integrated multistage continuous process designed to produce halomethyl ketone intermediates such as **6**.[1a] The plant was commissioned after all operating and control systems had been through a HAZOP review. Because of the particular hazards associated with the process, a copy of this review was filed with the United Kingdom Health and Safety Executive. The plant incorporates a number of key safety features including the continuous on-line monitoring of diazomethane levels inside the reactor to ensure that the 10% maximum level is not exceeded. Diazomethane monitoring at the exit of the packed substrate reaction column is carried out continuously to ensure zero environmental emissions. The plant is equipped with several secondary fail-safe control loops including oxygen meters, nitrogen mass flow controllers, and Coriolis liquid mass flow meters for monitoring and controlling the Diazald and potassium hydroxide feeds. All these systems are integrally linked in ratio to each other and are operated by computer-based control which includes a back-up system. Failure of any of these key systems will cause automated shutdown of the entire plant in accordance with a preset shutdown procedure. The plant is also environmentally clean; for example, 90% of the total nitrogen flow is recycled, and emissions of volatile solvents are extremely low (<5 mg/m^3 stack emissions to atmosphere).

Experimental Section

Generation of Diazomethane using the Pilot Reactor. Potassium hydroxide solution (15% w/w) was charged to a feed tank. A second feed tank was charged with a solution of Diazald in DMSO (22% w/w). The potassium hydroxide feed was pressure-fed and controlled using a Liqui-flow meter supplied by Krohne. Diazald was fed using a Watson

Marlow 313 peristaltic pump connected to a Krohne Corimass liquid flow meter. Full instrumentation control was provided for feeds, level/pressure, temperature, and on-line analysis. The potassium hydroxide solution flow rate was set at 1.0 kg/h, corresponding to a molar flow of 2.67 mol/h. The Diazald feed was set at 2.15 kg/h corresponding to a molar flow of 2.22 mol/h. Nitrogen was fed subsurface and into the reactor headspace using two nitrogen mass flow meters supplied by Krohne. The subsurface flow was set at a rate of 0.98 L/min and the headspace flow at 6.7 L/min. Commencement of the diazomethane reaction caused the temperature of the mixture to rise, and this was moderated to a control temperature of 40 °C using a Huber CC230 heater/chiller. The diazomethane/nitrogen evolved was continually monitored using an Innova type 1301 Photoacoustic FT-IR gas analyser to ensure that the concentration in the gas phase remained at the control limit of 10% (v/v). The diazomethane generated was continually consumed inside a packed column equipped with a liquid recycle containing the substrate liquors (for example 0.8 M benzoic acid in DME). Typically, at least 96% of the diazomethane produced is removed in the gas phase. The reactor was continually drained to achieve a constant reactant mixture level and maintain steady-state operation. Control was achieved using an Endress Hauser differential pressure sensor that controlled a flow-control valve. The reaction liquors were drained into a stirred quench tank which was maintained at pH 5.5 by the controlled continuous addition of 80% acetic acid. Waste from the reactor typically contains about 4% diazomethane. This procedure allows between 90 to 93 g of diazomethane to be produced per hour, and the maximum inventory of diazomethane at any instant is 0.11 g.

Conclusions

This work demonstrates the development of a safe and efficient process for the industrial-scale production of diazomethane. The process involves the continuous production and consumption of diazomethane, at a maximum production rate of 50−60 tonnes/year, whilst ensuring an overall inventory of less than 80 g at any one time. The diazomethane produced is part of a multistage continuous process designed to produce key intermediates for the latest generation of HIV protease inhibitor drugs. The use of diazomethane for this purpose represents the most cost-effective and direct route to compounds such as (2*S*,3*R*)-3-(*N*-benzyloxycarbonyl)amino-1-chloro-4-phenylthiobutan-2-ol **2**, which can now be produced in high overall yield (82%) from the protected amino acid **3**. The plant has been in operation for 2 years without incident and has successfully produced tonne quantities of these intermediates

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