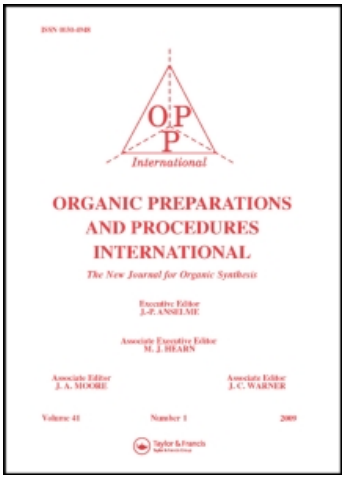

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A NOVEL METHOD FOR HANDLING ORGANIC REACTIONS IN A BOMB TUBE

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OPPI BRIEFS

A NOVEL METHOD FOR HANDLING ORGANIC REACTIONS IN A BOMB TUBE

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Certain organic reactions require temperature control and /or an inert atmosphere. Both could be achieved in a bomb tube, though in practice this method has many disadvantages. Accessories for glass blowing (gas lines for H_2 and O_2, high temperature flame) are needed with a special skill to use them. Reaction pressure exceeding the 5-10 bar region or temperatures higher than 150-200° constitute an important limitation. We now describe an apparatus which overcomes the practical difficulties and makes such reactions simple and convenient.

The apparatus, called High Pressure Asher® and constructed originally for wet decomposition of solid organic samples (making them accessible for atomic spectroscopy methods[1,2]) is based on the well known "Carius Tube". It was designed in a more sophisticated way by combining an old concept with present day techniques. The reaction vessels, covered with a Teflon® film and a quartz lid, are placed in an autoclave. A built in gas regulator system, connected to a commercial nitrogen tank, allows simple pressurizing. In this way the lid is kept pressed against the reaction vessel to ensure a tight seal during the reaction, as long as the internal pressure does not exceed 100 bar. A microprocessor controlled heater unit connected to the autoclave permits the temperature control of a given reaction. The pre-chosen and the actual temperature and pressure values are displayed on a cathode ray tube screen. Some important technical parameters are summarized in Table 1.

TABLE 1. Technical parameters of HPA®

Parameter	Range	Parameter	Range
Temperatur	25-320°	Volume of reaction vessel	2-70 ml
Pressure	0-100 bar	Max. number of vessels/run	8

One of the main advantages is that up to eight reaction vessels can be used in a single run, which makes the determination of the optimum reaction conditions (catalyst, solvent, concentration, etc.) quite easy. To enhance the safe operation and to minimize the damage of an accidental explosion, the lid of the pressure chamber is provided with a rupture disc (Fig. 1). The safety features of the operation and of the system were demonstrated as follows. The

high explosive pentaerythritol tetranitrate (4 g), used as a propellant in mining operations, was put in a reaction vessel and closed in the High Pressure Asher. The high explosive was induced to explode without any damage to the surroundings and after changing the rupture disc, the apparatus was ready for use again. Of course work with higher amounts of dangerous material or the performance of difficultly controllable reactions require some special precautions. It is usually necessary to make preliminary experiments with lesser amounts and /or at reduced temperature in order to prevent the development of extreme temperature and pressure waves. Safer working conditions for the operator can be achieved by using barricades and a remote controller.

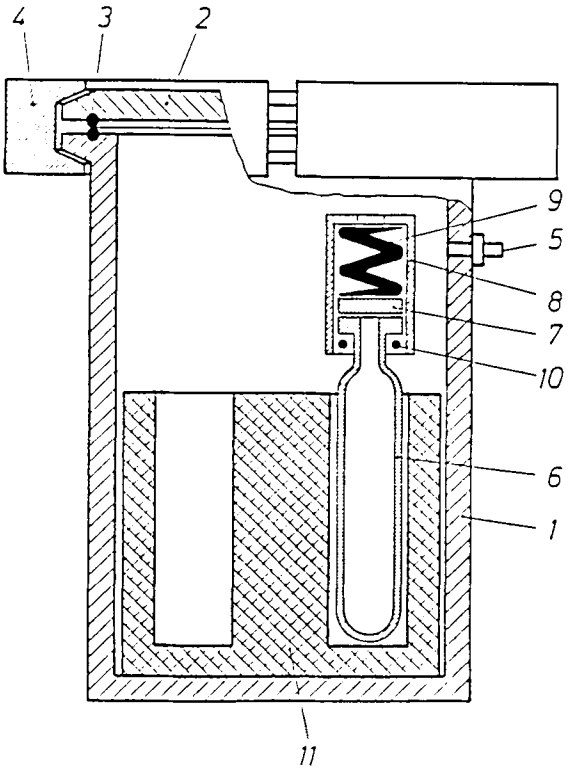

Fig. 1. High Presure Asher Autoclave Schematic Drawing

(1) pressure chamber (2) lid of the pressure chamber (3) O-ring (4) ring retainer
(5) pressure gas inlet (6) quartz vessel (7) quartz lid (8) PTFE cap (9) tungsten spring
(10) cap clasp (11) heating block

To demonstrate the usefulness of this new system and to determine the scope and the limitation, some well described reactions were tested. The first example was an oxidation which demonstrates the usefulness of temperature programming. 2-Picoline was oxidized to 2-pyridinecarboxylic acid with $KMnO_4$.[3] In order to avoid overoxidation we chose a slow

increase in temperature (see **curve a**, Fig. 2). The yield was much higher (81%) than previously reported (51%) due to the applied process control. The next example selected was the conversion of cellulose to chlorodeoxycellulose, using phosphorus oxychloride and dimethylformamide.[4] The absence of stirring was compensated for by a periodic temperature function according to **curve b** (Fig. 2). The degree of substitution of chlorodeoxycellulose is around 1.0 in contrast to the reported literature value of 0.7 (synthesized using the same reagents). The third example was the synthesis of 1,4-diiodobutane,[5] by cleavage of the ether linkage of tetrahydrofuran. The temperature profile was the same as the previous example. The yield (87%) is comparable with the one previously reported (92%).

In order to demonstrate the utility of HPA in the biochemical field, a tetrapeptide and bovine insulin were hydrolyzed at a constant temperature profile (110°) in 6N HCl.[6] Our technique is comparable with the classical method using a sealed glass ampoule, except that in the case of tyrosine and valine, a higher yield was obtained and the mode of operation is much more convenient.

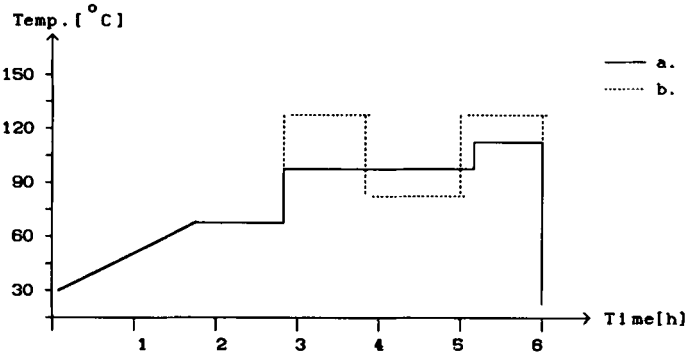

Fig 2. Temperature profile for the reactions

In all these four examples, a higher or a comparable yield was obtained as those previously published. These few examples demonstrate the practical utility and efficiency of this apparatus.

EXPERIMENTAL SECTION

2-Pyridinecarboxylic Acid.- A mixture of 1.74 g (11 mmol) of $KMnO_4$ and 0.55 ml (5.5 mmol) of 2-picoline in 30 ml water was poured in each of four reaction vessels. The controller was programmed with the temperature function according to **curve a** (Fig. 2). The work-up was the same as described in the literature.[3] The yield of product, mp. 229-230°, lit.[3] mp. 228-230°, was 2.2 g (81%). IR(KBr): 3000-2700, 1750, 1400, 1200 cm^{-1}. There was less than 1% of unreacted 2-picoline in the crude reaction mixture as determined by

HPLC (Column 150 x 4.6mm C_{18}, eluent water with 0.1% TFA, detection UV at λ = 285 nm).

Chlorodeoxycellulose.- A solution of 30 ml phosphorus oxychloride with 100 ml abs. dimethylformamide was divided into four reaction vessels (70 ml), each containing 1 g of cellulose. The temperature program was the same as the **curve b** (Fig. 2). After the reaction, the combined suspensions were filtered, washed with 3 x 200 ml water, 3 x 200 ml 0.25 N NaOH, 3 x 200 ml water and 3 x 200 ml 0.25 N HCl. The crude product was boiled in 500 ml of a mixture (1:1) of 10% NaCl and acetic acid. After 20 min., the suspension was filtered and washed with 3 x 200 ml water to yield 4.6 g of a pale yellow powder.

Anal. Calcd for $C_6H_9ClO_4$: C, 39.9; H, 5.0; Cl, 19.6. Found: C, 38.4; H, 4.6; Cl, 18.8

1,4-Diidobutane.- Phosphorous pentoxide (6.5 g) was added to commercial phosphoric acid with cooling. Then 23.2 g of potassium iodide was suspended in the above mixture and 4 ml (49 mmol) of tetrahydrofuran were added. The suspension was transferred to a reaction vessel (70 ml) and the temperature was programmed as in **curve b** (Fig. 2). The work-up was the same as given in the literature[5] and the yield of product, n_D^{20} = 1.6187, lit. n_D^{25} = 1.619 was 13.6 g (87%). The product was 99.9% pure as analyzed on GC (Column OV-1 (10 m), detector FID, T_{Det} = 250°, T_{Inj} = 160°, T_I = 40°, T_E = 200°, Rate = 20° T/min).

Peptide and Protein Hydrolysis.- A 10 mg sample of tetrapeptide (TyrGlyGlyPhe) which was synthesized in solution and 10 mg of insulin from bovine pancreas (obtained from Calbiochem) were each hydrolyzed in 2 ml 6N HCl at 110° for 24 hrs. The amino acid composition was determined by gas chromatography (as tert. butyldimethylsiyl derivative)[7] and with ion exchange chromatography.

Tetrapeptide: Tyr:Gly:Phe = 0.9:1.9:1.0

Insulin: Ala: Arg: (Asp + Asn): Cys: (Glu + Gln): Gly: His: Ile: Leu: Lys: Phe: Pro: Ser: Tyr: Val = 3.02: 1.00: 3.01: 5.83: 7.13: 3.97: 1.96: 0.77: 5.16: 0.99: 3.00: 1.01: 2.72: 3.12: 4.78 (3: 1: 3: 6: 7: 4: 2: 1: 5: 1: 3: 1: 3: 3: 5)

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AN IMPROVED SYNTHESIS OF ALKYL 1-ALKYL-3-METHYL-2-PYRAZOLINE-5-ONE-4-DITHIOCARBOXYLATES

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There are two known preparations of methyl and ethyl esters of 3-methyl-1-phenyl-2-pyrazoline-5-one-4-dithiocarboxylic acid. The reaction of 3-methyl-1-phenyl-2-pyrazoline-5-one with carbon disulfide and ethyl chloroformate (or ethyl bromide) in the presence of anhydrous aluminum chloride,[1] is unsatisfactory, giving at best a 20-30% yield. Our experience with the two-step synthesis involving initial conversion of 3-methyl-2-pyrazoline-5-one to the 4-dithiocarboxylic acid followed by alkylation with dimethyl or diethyl sulfate,[2] shows that the isolation of the dithiocarboxylic acid is less than routine. We have reported the synthesis of alkyl 3-dimethylhydrazonoalkanedithioate by the reaction of N,N-dimethylhydrazones with n-butyllithium, carbon disulfide and alkyl halides,[3] and we decided to apply this synthetic scheme to 1-alkyl-3-methyl-2-pyrazoline-5-ones (1), in order to obtain alkyl esters of 1-alkyl-3-methyl-2-pyrazoline-5-one-4-dithiocarboxylic acids (2).

1 2

i) n-BuLi, THF, 0° ii) CS_2, THF, 0° iii) R_1X, THF, 20°

a) R = C_2H_5, R_1 = n-$C_{12}H_{25}$; b) R = n-$C_{10}H_{21}$, R_1 = C_2H_5; c) R = n-$C_{12}H_{25}$, R_1 = C_2H_5

d) R = n-$C_{12}H_{25}$, R_1 = n-C_6H_{13}; e) R = R_1 = n-$C_{12}H_{25}$