Amino-acids and Peptides. Part II.[1] A New Method for Preparing Diazodiphenylmethane and Related Compounds

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Diazodiphenylmethane has been prepared from benzophenone hydrazone by oxidation with peracetic acid in the presence of a base and a trace of iodine. Two variants of the process are described: (a) benzophenone hydrazone in an organic solvent is oxidised with peracetic acid in the presence of 1,1,3,3-tetramethylguanidine and a trace of iodine; (b) a solution of benzophenone hydrazone, in a two-phase organic solvent–water mixture, is oxidised by adding peracetic acid and sodium hydroxide simultaneously and equivalently at pH ca. 10 in the presence of a phase-transfer catalyst and a trace of iodine. The preparation of a variety of aryldiazoalkanes is reported.

INTEREST in aryldiazoalkanes, particularly diazodiphenylmethane, has increased in recent years owing to recognition of the value of these reagents in peptide synthesis.[2] They are usually prepared in good yield by oxidation of the corresponding hydrazones with metal oxides.[3,4] The most common oxidant is mercury(II) oxide,[5] although silver oxide,[6] manganese dioxide,[7,8] and, less frequently, nickel peroxide [9] have been used. Aryldiazoalkanes can also be prepared in moderate yield by base-induced thermal degradation of tosylhydrazones (Bamford–Stevens reaction).[10]

Although hydrazone oxidations by metal oxides are widely used on a laboratory scale they have disadvantages, e.g. the cost of the metal oxides, the difficulties of preparing suitable active oxides, and waste disposal. We describe here two efficient methods of preparing diazodiphenylmethane and related compounds. The new preparations arose from further study of the hydrazone-peracetic acid esterification previously described by us.[1] In outline, aryldiazoalkanes are prepared in high yield by addition of a peroxy-acid to an arylhydrazone in the presence of a base and with a trace of iodine as catalyst. For best results, non-oxidisable bases are necessary. The base functions by preventing esterification of the reduction product of the peroxy-acid.

Iodine was the most effective catalyst for the reaction. The optimum quantity of iodine required in preparing diazodiphenylmethane is ca. 10^{-4} mol. equiv. Below this, oxidation of the hydrazone was incomplete, and above 10^{-4} mol. equiv., iodine-catalysed decomposition of the diazoalkane to benzophenone azine occurred. Bromine had a weak catalytic effect; chlorine had none. We have made no attempt to elucidate the specific role of iodine in this reaction.

Two variants of the basic process have been developed: (a) the reaction is conducted in a wholly organic medium; (b) it is carried out in an aqueous organic medium in the presence of a phase-transfer catalyst.

Preparation in Wholly Organic Media.—The commercially available peracetic acid (38% solution in acetic acid) was used for most of the work, but m-chloroperbenzoic acid works equally well. Usually, conversion of the hydrazones was best effected by using 0.9—1.50 mol. equiv. of the oxidant.

The structure of the base is important. It should be both compatible with the oxidant, peracetic acid, and sufficiently strong to neutralise the acetic acid in the system. Simple organic bases, e.g. triethylamine, pyri-

[1] Part I, R. Bywood, G. Gallagher, G. K. Sharma, and D. Walker, 1975, 2019.

[2] R. G. Hiskey and J. B. Adams, *J. Amer. Chem. Soc.*, 1965, 87, 3936; A. A. Aboderin, G. R. Delpierre, and J. S. Fruton, *ibid.*, p. 5468; B. Fechtig, H. Peter, H. Bickel, and E. Vischer, *Helv. Chim. Acta*, 1968, 51, 1108; Smith, Kline, and French, West G.P. 2,301,509; Merck, B.P., 1,350,772.

[3] G. W. Cowell and A. Ledwith, *Quart. Rev.*, 1970, 24, 119.

[4] B. Eistert, M. Regitz, G. Heck, and H. Schwall, ' Methoden der Organischen Chemie (Houben Weyl),' 1968, vol. 10 (IV), p. 473.

[5] J. B. Miller, *J. Org. Chem.*, 1959, 24, 560.

[6] W. Schroeder and L. Katz, *J. Org. Chem.*, 1954, 19, 718.

[7] R. W. Murray and A. M. Trozzolo, *J. Org. Chem.*, 1961, 26, 3109.

[8] H. Reimlinger, *Chem. Ber.*, 1964, 97, 3493.

[9] K. Nakagawa, H. Onoue, and K. Minami, *Chem. Comm.*, 1966, 730.

[10] W. R. Bamford and T. S. Stephens, *J. Chem. Soc.*, 1952, 4735.

dine, or dimethylaniline, were themselves preferentially oxidised, so weakening their basic properties. Although some reaction was observed in the presence of these bases, good yields of diazodiphenylmethane were not obtained. An aliphatic base, 2,2,6,6-tetramethylpiperidine, sterically hindered at the basic centre, allowed a 34% yield of diazodiphenylmethane to be obtained.

NN-Dimethylacetamide and *NN*-dimethylformamide are sufficiently basic to enable diazodiphenylmethane to be formed when these amides are used as solvents. However, in the absence of a suitable base in these solvents, the formed diazoalkane slowly reacted with the acetic acid present.

The rate of oxidation of benzophenone hydrazone by peracetic acid was not significantly altered by lowering the reaction temperature, but the rate of esterification by acetic acid is much slower below 0 °C. In one experiment at −20 °C, with *NN*-dimethylacetamide as both solvent and base, partition of the final reaction mixture between dichloromethane and aqueous sodium hydrogen carbonate gave a 64.4% yield of diazodiphenylmethane. The oxidation could also be performed at −30 °C in dichloromethane in the absence of base so long as a base, *e.g.* triethylamine, was added after the oxidation was complete. A 44% yield of diazodiphenylmethane was thus obtained.

In the experiments described above the final reaction mixtures contained some unchanged benzophenone hydrazone and small quantities of benzophenone azine, benzophenone, and diphenylmethyl acetate.

In contrast to the previously described bases, 1,1,3,3-tetramethylguanidine proved to be an ideal strong base. High yields of diazoalkanes were obtained by using this base, with total consumption of hydrazone and little by-product formation.

Other aromatic hydrazones have been converted into the corresponding diazoalkanes by using the peracetic acid–iodine–tetramethylguanidine process. The results are summarised in Table 1. In all these preparations the same molar excesses of peracetic acid and tetramethylguanidine were used as were employed in the preparation of diazodiphenylmethane (see Experimental section). The yields of diazoalkanes reported in Table 1 are all as good as or better than those previously reported.

Other oxidants were examined as replacements for peroxy-acids (Table 2). For most of these iodine was necessary as catalyst. When an acid was released during the reaction a base was incorporated along with the hydrazone. Some *N*-chloro-compounds were useful oxidants. Chloramine T was the most convenient of these because it combined both oxidising and basic properties. The maximum yield (79%) of diazodiphenylmethane was obtained at a 1:1 ratio of oxidant to hydrazone. With greater levels of chloramine T the yield of diazodiphenylmethane was lower, reflecting the known reactivity of the oxidant towards the diazoalkane.[11]

Preparation in Water–Organic Solvent Mixtures.—

[11] A. Schönberg, E. Singer, and W. Knofel, *Tetrahedron Letters,* 1967, 1819.

Aqueous inorganic bases were investigated as alternatives to 1,1,3,3-tetramethylguanidine.

TABLE 1

Diazoalkanes from hydrazones by oxidation with peracetic acid in the presence of iodine and base in 1,2-dichloroethane

Compound	Reaction temp. (°C)	$\nu_{max.}/$ cm^{-1}	$\lambda_{max.}/$ nm	Yield (%)
Diazo-(2-methylphenyl)(phenyl)methane	0	2 050	516	98.6
Diazo(phenyl)-(2-thienyl)methane	0	2 050	526	83.4
Diazodiphenylmethane	0	2 050	525	95.6 [a]
9-Diazofluorene	10—15	2 065	500	86.2
1-Diazo-1-phenylethane	−5	2 040	519	96.0
Diazo(phenyl)methane	0	2 065	492	88.9
Diazo-(4-methoxyphenyl)methane	−20	2 060	509	76.8 [b]
Diazo-(2-furyl)methane	−20	2 070	498	85.4 [b]
Diazo-(2-thienyl)methane	−5	2 067	505	78.7
1,4-Bis-(α-diazobenzyl)benzene	0	2 040	532	69.2 [c]

[a] Reaction carried out in methylene chloride (see Experimental section). [b] Products unstable even at low temperature; gas evolved during work-up. [c] Properties identical with those previously described.[7]

TABLE 2

Oxidants investigated in the preparation of diazodiphenylmethane from benzophenone hydrazone in wholly organic media

Oxidant	Yield (%)	Comments
O$_2$-[(PPh$_3$)$_3$RhCl] [a]	0	
Tetrachlorobenzoquinone	<3	
Manganese dioxide (non-active)	30—40	Similar yields obtained with and without I$_2$ catalyst
Active manganese dioxide (supported on charcoal) [b]	71	I$_2$ catalyst
N-Bromosuccinimide	58	No catalyst
N-Bromosuccinimide	23	I$_2$ detrimental to yield
N-Chlorosuccinimide	76	1 mol. equiv. added together with 1 mol. equiv. tetramethylguanidine. Triethylamine not effective
N-Chlorosaccharin [c]	0	
Chloramine T in aq. 10% dimethylacetamide	79	1.0 mol. equiv. of oxidant
	57	1.1 mol. equiv. of oxidant

[a] J. Blum, H. Roseman, and E. D. Bergmann, *Tetrahedron Letters,* 1967, 3665. [b] L. A. Carpino, *J. Org. Chem.,* 1970, **35,** 3971. [c] H-.S. Dawn, I. H. Pitman, T. Higuchi, and S. Young, *J. Pharm. Sci.,* 1970, **59,** 955.

Initially, a solution of benzophenone hydrazone and iodine in dichloromethane was brought into contact with an aqueous solution of sodium hydrogen carbonate or hydroxide, and peracetic acid was added with stirring. Yields of 20—25% of diazodiphenyl-methane were obtained at 20 °C. Slightly higher yields were obtained at 0 °C but the oxidation of the hydrazone became inconveniently slow. It was concluded that reaction between the two substances in the different phases was inhibited by their inability to come together.

A number of mixtures of water and water-miscible organic solvents were examined for their suitability in promoting the oxidation. Peracetic acid was added to sodium hydrogen carbonate, benzophenone hydrazone, and iodine in the solvent mixture. After the reaction the solution was extracted with dichloromethane. The best

solvent was 50% aqueous dioxan which gave yields of 50—60% of diazodiphenylmethane (temperatures in the range −10 to +15 °C).

This approach was abandoned in favour of using immiscible solvent mixtures and a phase-transfer catalyst.[12] The inclusion of a small quantity of tetra-n-butyl-ammonium hydroxide raised the yield of diazodiphenylmethane from 29.5 to 51.5% in a reaction in which the peracetic acid was added dropwise to a sodium hydrogen carbonate aqueous layer and a dichloromethane layer containing the hydrazone and iodine. With the same amount of peracetic acid, more unchanged hydrazone was always observed in sodium hydroxide mixtures (pH > 12) than in sodium hydrogen carbonate solution (pH 9). The more strongly alkaline solution was thought to be facilitating the decomposition of the peroxy-acid and this led to a study of the oxidation reaction at various pH values. With tetra-n-butylammonium hydroxide as phase-transfer catalyst a maximum yield of 70—78% was obtained at pH 10.

TABLE 3

Preparation of diazodiphenylmethane in water–dichloromethane with added quatenary amonium salt

Phase-transfer catalyst (3 mmol. equiv.)	Yield (%) of			
	Hydra-zone	Benzo-phenone	Diazo-diphenyl methane	Azine
None	45	3	17.5	
Bu₄NOH	5	5	78.6	12
Bu₄NCl	5	7	65.5	
Bu₄NI	9	3	48.0	
(C₈H₁₇)₃ C₃H₇NCl	2	2	84.9	

TABLE 4

Oxidants investigated in the preparation of diazodiphenylmethane from benzophenone hydrazone in water–dichloromethane at 18 °C in the presence of tetra-n-butylammonium hydroxide [a]

Oxidant	Mole ratio (oxidant : hydrazone)	Yield (%)
Hydrogen peroxide [b]	1.1	0
Hydrogen peroxide	1.1	0
Hydrogen peroxide–hexafluoro-acetone complex [c]	1.1	47 [d]
Potassium permanganate	1.0	28
Sodium perborate	1.0	<5
Potassium persulphate	1.0	<5
Potassium persulphate catalysed by silver nitrate [e]	1.0	<5
Sodium hypochlorite	1.0	13
Chloramine T	{1.0	70
	{1.25	51

[a] 0.03 mol. equiv. of tetra-n-butylammonium hydroxide added; pH of aqueous phase maintained at 10. [b] No phase-transfer catalyst added. [c] R. D. Chambers and M. Clark, *Tetrahedron Letters*, 1970, 2741. [d] Reaction performed at pH 8. Hexafluoroacetone could not be used in catalytic quantities to promote oxidation by free H₂O₂. [e] F. P. Greenspan and H. M. Woodburn, *J. Amer. Chem. Soc.*, 1954, **76**, 6345.

Other phase-transfer catalysts were investigated with the two-phase reaction mixture at pH 10 (Table 3). The best yield of diazoalkane was obtained by using trioctylpropylammonium chloride. This is more soluble in

methylene chloride than the tetrabutylammonium salts. Some variation in yield with the anion of the ammonium salt was apparent, the yields falling in the order OH⁻ > Cl⁻ > I⁻.

The lower yields obtained with chlorides and iodides may be due to competition between these anions and peracetate anion for transfer into the organic phase.[13] Also, oxidation of the halide to the halogen may occur, with subsequent loss of the diazodiphenylmethane by oxidation. Both possibilities can account for the greater effect shown by the iodide. The iodide ion is the ' softer ' nucleophile and one would expect it to be transferred to the organic phase more readily. Iodine is a good oxidant for diazodiphenylmethane, causing its immediate decomposition to benzophenone azine as major product.

Other oxidants were examined (Table 4) but again chloramine T was the only one to approach peracetic acid in effectiveness under the conditions used.

EXPERIMENTAL

Peracetic acid was obtained as a 38% w/w solution in acetic acid from Laporte Industries Ltd.

Diazodiphenylmethane was assayed [14] by its absorbance at 525 nm. The other organic products of the reaction were transparent in this region. The Beer–Lambert law was obeyed for solutions in ethanol, ethyl acetate, or dichloromethane over the absorbance range 0—1.5. The extinction coefficients were 94.5, 94.7, and 102.5, respectively. The i.r. spectrum was used to determine, semi-quantitatively the products of the reaction (except azine). By this means benzophenone and diphenylmethyl acetate could be detected.

An alternative method of assay was to measure the volume of nitrogen evolved from a sample of the diazoalkane in 1,2-dichloroethane when treated with glacial acetic acid. Good agreement was obtained with diazodiphenylmethane between the two methods of assay.

Diazoalkanes other than diazodiphenylmethane and 1,4-bis-(α-diazobenzyl)benzene were not isolated but were characterised [15] from their diazo-group i.r. absorption (2 020—2 080 cm⁻¹), their visible maxima, and formation of the appropriate ester with (1S,3S,5R,6R)-2,2-dimethyl-6-phenylacetamidopenam-3-carboxylic acid 1-oxide. The esters were compared with authentic samples [1] by n.m.r. and i.r. spectroscopy and by mixed m.p. The 2-*thienylmethyl ester* had m.p. 161.5—162.5° (from propan-2-ol); τ 8.98 (3H, s, 2-Me), 8.40 (3H, s, 2-Me), 6.49 (2H, s, 7-CH₂·CO), 5.45 (1H, s, 3-H), 5.14 (1H, d, *J* 4.5 Hz, 6-H), 4.55 and 4.83 (2H, ABq, *J* 12.5 Hz, thienyl CH₂), 4.07 (1H, dd, *J* 4.5 and 10 Hz, 7-H), and 2.46—3.2 (9H, m, aromatic and NH); ν_max. (Nujol) 1 810, 1 790, 1 785, and 1 680 cm⁻¹ (Found: C, 56.35; H, 5.0; N, 6.1. C₂₁H₂₂S₂N₂O₅ requires C, 56.45; H, 4.95; N, 6.25%). In the case of 1,4-bis-(α-diazobenzyl)benzene the pure material was isolated by the method of Trozzolo and its properties were those reported.[7]

Preparation with 1,1,3,3-*Tetramethylguanidine as Base.*—Benzophenone hydrazone (19.6 g, 0.1 mol) was dissolved in dichloromethane (100 ml) containing iodine (4 ml; 1% w/v) and 1,1,3,3-tetramethylguanidine (45 ml). To this solution was added peracetic acid solution (1.3 × 0.1 mol) at 0 °C

[12] E. V. Dehmlow, *Angew. Chem. Internat. Edn.*, 1974, **13**, 170.

[13] B. J. Dockx, *Synthesis*, 1973, 441.

[14] J. D. Roberts and W. Watanabe, *J. Amer. Chem. Soc.*, 1950, **72**, 4869.

[15] P. Yates, B. L. Schapiro, N. Yoda, and J. Fogger, *J. Amer. Chem. Soc.*, 1957, **79**, 5756.

over 60 min. The mixture was stirred for an additional 15 min, then washed with water (5 × 250 ml) until the washings were at pH 6. The dichloromethane layer was dried and made up to 500 ml. An assay at 525 nm of a suitably diluted sample corresponded to a 95.6% yield of diazodiphenylmethane. Other solvents may be used, *e.g.* ethanol, butyl acetate, chloroform, or 1,2-dichloroethane.

m-Chloroperbenzoic acid (1.00 mol. equiv.) may equally well be used as oxidant. In this case the quantity of 1,1,3,3-tetramethylguanidine was reduced to a little more than the theoretical amount required to neutralise the formed *m*-chlorobenzoic acid. The yield of diazodiphenylmethane in a typical preparation was 89.9%.

The addition of peracetic acid to hydrazones in the presence of iodine and 1,1,3,3-tetramethylguanidine was also used to prepare other diazoalkanes (Table 1). The more unstable diazoalkanes were prepared at lower temperatures (Table 1) and washed with ice-cold water. Even so, some gas evolution occurred during the reaction and work-up.

Preparation with Chloramine T *as Oxidant.*—Benzophenone hydrazone (19.6 g, 0.1 mol) and iodine (4 ml; 1% w/v) were stirred in *NN*-dimethylacetamide (100 ml) and water (10 ml). A solution of chloramine T (28.2 g, 0.1 mol) was then added slowly over 30 min at 20 °C. The mixture was next stirred for 15 min before partition between dichloromethane

(200 ml) and 5% sodium hydrogen carbonate solution (500 ml). The dichloromethane layer was washed with water (1 × 500 ml; 3 × 250 ml), dried, and made up to 500 ml. An assay at 525 nm of a suitably diluted sample corresponded to a 79% yield of diazodiphenylmethane.

Preparation by the Phase-transfer Catalyst Procedure.—To benzophenone hydrazone (19.6 g, 0.1 mol) in dichloromethane (100 ml) were added trioctylpropylammonium chloride (1.26 g, 2.92 mmol) and iodine (4 ml; 1% w/v). To this stirred system was added peracetic acid solution (17.8 ml; 0.0105 mol) at 0 °C over 15 min, the pH being controlled to *ca.* 10 by simultaneous addition of sodium hydroxide solution. After stirring for 30 min more at 0 °C the organic layer was washed with water (1 × 150 ml; 2 × 250 ml). An assay at 525 nm of a suitably diluted sample corresponded to a yield of 84.9% of the diazoalkane.

The use of other quaternary ammonium compounds (Table 3) followed essentially the same method.