Synthetic Reagents 1

SYNTHETIC REAGENTS

Volume I

Dimethylformamide; Lithium Aluminium Hydride; Mercuric Oxide; Thionyl Chloride

S. S. PIZEY

Department of Chemistry
University of Aston in Birmingham

© 1974 J. S. Pizey

SYNTHETIC REAGENTS
Volume 1

Dimethylformamide; Lithium Aluminium Hydride; Mercuric Oxide: Thionyl Chloride

SYNTHETIC REAGENTS (An Ellis Horwood Series)

This is the first of a new series planned as a coverage of selected reagents in the synthesis of organic compounds. Every volume will contain a small selective group of versatile and often used reagents which will each be treated thoroughly and in depth. It will show how chemical substances can be made, together with the advantages and limitations of the reagent employed.

Thus the series, by bridging the gap between the great encyclopaedic work by Fieser and Fieser ("Reagents for Organic Synthesis") and the review articles which often do not give synthetic details, should provide a world library of valuable reference.

Each volume in general will contain an example of a reductant, an oxidant, a solvent, halogenating material, and some other versatile reagent. The subject matter will be explored in depth, stressing the synthetic side of each reagent with sufficient mechanistic background to convey its mode of action, enabling the chemist to draw parallels with his own system and optimize reaction conditions. Preparation, purification and properties of each reagent are given, with instructions for a preferred and/or typical method of reagent or preparation.

There is a wealth of up-to-date references, The exhaustive index with comprehensive cross references quickens the selection of chemicals or processes. Readership: Chemists in research and industrial production, chemical libraries, senior undergraduates, postgraduates and post-doctoral workers in polytechnics and universities.

In active preparation:
Synthetic Reagents Vol. 2: N-Bromosuccinimide; Diazomethane; Manganese Dioxide; Raney Nickel (J. S. PIZEY)

PREFACE FOR VOLUME 1

The publication of a new series of volumes, each exhaustively discussing the synthetic uses of a number of important reagents, plugs a gap in the chemical literature. Reagents covered in this volume are dimethylformamide, lithium aluminium hydride, mercuric oxide, and thionyl chloride. Volume II will contain N-bromosuccinimide, diazomethane, manganese dioxide, and Raney nickel. The material is planned in such a way that the practising synthetic chemist can readily extract information about his own synthetic needs. Further volumes will preserve a similar balance of significant reagents for organic synthesis.

Each chapter deals with an important reagent in depth, selected both for its use in effecting one of the major types of reactions and for its wide-ranging synthetic utility. Preparation, purification and properties of each reagent have been presented at the beginning of its section. Then, to help the reader find parallels with the system under investigation, follow large numbers of examples of compounds which have been synthesised by using that reagent.

Mechanistic ideas have been introduced when it is felt that they will afford a better understanding of the synthetic possibilities or limitations of the reagent. Important solvents and general reagents have also been discussed. In some instances, where appropriate, the use of other reagents has been suggested.

It is hoped that these books will help chemists to determine both the types of reaction the reagent will effect and its selectivity, and additionally indicate the optimum conditions for the reaction. The books will also enable the reader to find the method of synthesis of a large number of compounds and the original reference will then give him the necessary precise synthetic details.

Rapid retrieval of information is assisted by a very complete index covering all the compounds and types of reaction. There are numerous references to reviews and original literature, and (in most cases) the Chemical Abstracts references for foreign journals.

Thanks are due to my wife for the many hours she spent typing the manuscript and for her constant encouragement, and to my numerous friends and colleagues who, in their varied ways, assisted in the completion of this task.

J. S. Pizey
University of Aston in Birmingham

CONTENTS

vii

CHAPTER 1

DIMETHYLFORMAMIDE (DMF)

A. INTRODUCTION

Dimethylformamide (DMF) is an extremely useful and versatile liquid. It may be employed as a solvent for a wide variety of reactions or it may be used chemically, for example, as a formylating agent or dimethylaminating agent. The physical properties of DMF [1] enable it to be used over a wide variety of laboratory conditions, and its solubility in water often enables reaction products to be readily isolated. In certain cases DMF need only be present in catalytic quantities to accelerate the rate of reaction.

Dimethylformamide has a boiling point of 165·5° and a freezing point of −20°. It has a specific gravity at 15·5° of 0·9448 and a refractive index, $n_D^{25°}$, of 1·4356.

The synthetic uses of DMF have been reviewed by a number of authors [1–6]. Wallace [6] discussed recent advances in the base-catalysed reactions of sulphur compounds.

The purification of DMF generally involves treatment with a drying agent followed by distillation of the amide. Thomas and Rochow [7] evaluated a variety of published purification methods and suggested that the use of calcium hydride, and other basic materials, could produce a considerable amount of dimethylamine. Various methods for the purification of DMF have been given in a large number of papers; the following references should be noted in this connexion [7–13]. Dimethylformamide has been found to give dimethylamine on exposure to strong sunlight [14], a recent report [15] stresses the instability of aqueous DMF systems containing hydroxide ions; the hydroxide ions being consumed fairly rapidly under mild conditions with the release of dimethylamine and formate ions. Methods for the estimation and removal of basic impurities from DMF have been published [16].

Rate constants have been obtained for the abstraction of hydrogen atoms from formamide, N-methylformamide and DMF by methyl radicals [17].

B. DIMETHYLFORMAMIDE AS A SOLVENT OR CATALYST

A very large number of papers have been published on the theory and uses of dipolar aprotic solvents, many of them discussing solvation characteristics and the differences between dipolar aprotic solvents and protic solvents. Dipolar aprotic solvents have been described [18] as those solvents with a dielectric constant >15, which cannot donate suitably labile hydrogen atoms to form strong hydrogen bonds with appropriate species. Dimethylformamide has a dipole moment of 3·82 Debye units and a dielectric constant, at 25°, of 36·71 [1]. The effects of solvation on the properties of anions in dipolar aprotic solvents have been discussed by Parker [18].

Many substances behave as electrolytes when dissolved in DMF and thus produce conducting solutions of ionic substances. The ionizing power of DMF and certain other dipolar aprotic solvents has been studied by Fainberg and his co-workers [13] who found that S_N1-type ionization was not extensive in these

solvents. They ascribed this to the small amount of solvation of both the anion and cation. However, numerous workers have found that DMF solvates cations strongly (see later in this section). A solution of heptyl iodide in DMF showed an increased conductivity indicating that some ionization had taken place [19]. Acyl chlorides and bromides, for example, behave as weakly and strongly dissociated electrolytes respectively when dissolved in DMF, and the latter yield $1:1$ salts, formulated as $[Me_2N^+ = CHOCOR]X^-$, when treated with a limited amount of DMF [20]. Many alkyl and arylchlorosilanes and some organogermanium halides are soluble in DMF with the formation of conducting solutions and hence allow ionic oxidation-reduction and metathetical reactions to be carried out [21]. The conductances of some quaternary ammonium halides in DMF have been determined [22, 23].

A recent review by Parker [4] gives much background information and discusses the use of dipolar aprotic solvents in some detail. Delpuech [24, 25] compares protic and dipolar aprotic solvents and states that the rate of S_N2 reactions is considerably accelerated in dipolar aprotic solvents. He observed an approximate relationship between the rate of reaction of butyl bromide with azide ions with basicity and discussed the difference in activation energy between the two groups of solvents in terms of solvation of the azide ion by solvents capable of hydrogen bonding. The rate constants for S_N2 reactions of anions are greatly decreased in passing from dipolar aprotic to protic solvents [9, 26–30] and this may be ascribed to the lessened solvation of the anion in dipolar aprotic solvents [4, 9, 2(, 28–33]. The effect on the rate of an S_N2 reaction of a change from a protic to a dipolar aprotic system should be general for an anion-dipolar reaction passing through a relatively large negatively charged transition state [29, 30] due, presumably, to the dispersal of charge in the transition state. Thus the rate increase arises from a reduction in the energy level between the reactants and the transition state [26, 34]. The rate of the Menchutkin reaction of certain benzyl chlorides with the uncharged nucleophile pyridine in DMF differs little from that observed in methanol [34].

Rate data have also shown that a polarizable transition state has less molar free energy in DMF than in ethanol and hence is more solvated by DMF than ethanol, although it must be realized that the transition state is a different species in the two solvents [31, cf. 35]. Conversely it has been found that dipolar aprotic solvents solvate cations strongly [18, 22, 36–39] hence leaving the anion free to act as a nucleophile and lessening the influence of ion-pair formation. Many reactions involving the breaking of a carbon-hydrogen bond in the rate-determining step proceed more rapidly in dipolar aprotic solvents than in polar solvents. Thus certain base-catalysed eliminations, condensations, prototropic rearrangements and autoxidations are readily carried out in DMF.

The reactivity of various anions towards methyl iodide in DMF has been shown to decrease in the order $CN^- > F^-$, CI^-, Br^-, $N_3^- > SCN^- >$ picrate$^-$ [30], although over a variety of reactions the relative activities are so varied that a correlation of rates has only a limited application [35]. Two further generalizations may be made; protic solvents differentiate and dipolar aprotic solvents level the nucleophilic tendencies of halides or similar ions whereas protic solvents level and dipolar aprotic solvents differentiate carbon basicity [4, 40]. The rates of

S_N2 reactions in DMF and methanol have been used to estimate hydrogen-bonding activity coefficients which predict closely the effects of anion solvation on acid-base equilibria [41]. A decrease in the enthalpy of activation of S_N2 reactions on transference from methanol to DMF has been reported [27, 34]. The rates of exchange of the strong electrolyte, tetraethylammonium chloride, with simple alkyl bromides in DMF have been determined and the rate constants, activation energies and Arrhenius log B terms compared with those from the reaction with the weak electrolyte, lithium chloride, in acetone [42]. Casapieri and Swart [43, 44] have studied the Finkelstein substitution in DMF and other solvents and discussed 'borderline' nucleophilic substitution under their conditions.

A large number of polar organic molecules, such as alcohols, aldehydes, ketones, esters, aromatics, and heterocyclic molecules are soluble in DMF whereas non-polar species such as alkanes, cycloalkanes, non-polar gases and long-chain fatty acids and alcohols are insoluble [1, 45]. Many synthetic resins and plastics have also been found to be soluble in DMF [1]. The aprotic properties of dipolar aprotic solvents do not appear to be appreciably diminished by the presence of small quantities of water [46].

The interaction between DMF and Lewis acids or protonic acids is discussed in Section C.

1. Addition

A variety of additions has been found to proceed more rapidly in DMF than in protic solvents. Cycloadditions are considered in Section B3.

(a) Preparation of halogeno-compounds

The addition of hydrobromic and hydrochloric acids to $\alpha\beta$-unsaturated acids and esters occurs rapidly in DMF. Diethyl maleate, for example, gave a 76 per cent yield of diethyl chlorosuccinate when gaseous hydrochloric acid was passed into a solution of the ester in DMF at room temperature [47].

Similarly, chlorine has been added to the double bond of acrylic esters, in the presence of a small amount of DMF, to give the dichloro-ester [48–50], e.g. methyl acrylate gave a 97 per cent yield of methyl 2,3-dichloropropionate when treated with chlorine at icebath temperatures in the presence of 2–5 per cent DMF [48], and 2,3-dichloroisobutyrates have been obtained from methacrylates at 20–50° [50].

The addition of iodine azide, generated from iodine monochloride and sodium azide in DMF, in situ, to several alkenes affords a method for stereospecific trans-addition of the azide moiety [51]. Thus, cis- and trans-but-2-ene gave, with iodine azide, the exclusive formation of threo- (67 per cent) and erythro- (64 per cent) 2-azido-3-iodobutane respectively and 5α-cholest-2-ene gave a 20 per cent yield of the trans-diaxial 2β-azido-3α-iodo-5α-cholestane.

The addition of hydrogen halides and thiocyanic acid to dimethyl acetylene-dicarboxylate in DMF has been studied [52] and it was shown that the initial attack was nucleophilic followed by proton addition. The addition of phenol to the reaction mixture increased the rate of addition whereas the addition of aliphatic alcohols had the reverse effect.

(b) Preparation of hydroxyalkyl compounds

Hydroxymethylation of acetylene in DMF, using a polyoxymethylene glycol such as paraformaldehyde, provides a method for the preparation of butyne-1, 4-diol superior to older processes [53].

(c) Preparation of nitriles

The addition of trichlorosilane to acrylonitrile to give a 42 per cent yield of 3-trichlorosilylpropionitrile was found to be catalysed by small quantities of DMF [54, 55].

Sodium cyanodithioformate and other salts have been prepared by treating the appropriate cyanide in DMF with carbon disulphide [56]. The addition was found to be very rapid and the product was stabilized by complexing with three molecules of DMF (cf. Section B1(d)).

The addition of hydrocyanic acid to certain unsaturated materials may be carried out at higher temperatures than usual by complexing the acid with DMF. Thus succinonitrile has been prepared from acrylonitrile under these conditions [57].

(d) Preparation of quaternary compounds

The quaternization of picolinic aldehyde with 9-bromomethyl-2,3,6-trimethoxy-phenanthrene proceeded rapidly at 80° in the presence of small quantities of DMF [58].

p-Xylylene-bistriphenylphosphonium chloride has been prepared analytically pure and in high yield from *p*-xylylene dichloride and triphenylphosphine in DMF [59, 60]. The phosphonium chloride is a useful intermediate for the preparation of distyrylbenzenes [59] and *p*-quinquephenyl [60].

Metal and quaternary ammonium salts of cyanodithioformic acid have been prepared by treating carbon disulphide with the appropriate cyanide in DMF or by treating the sodium cyanodithioformate-DMF complex with the tetra-alkyl-ammonium bromide [61] (cf. Section B1(c)).

(e) Preparation of sulphides

Sulphides may be prepared by treating the appropriate acetylene with the sodium thiolate in DMF and ethanol. The reaction between sodium *p*-toluene-thiolate and phenylacetylene was found to be faster in a mixture of DMF and ethanol than in ethanol alone [62], and gave *cis*-1-phenyl-2-*p*-tolylthioethylene as the major product.

(f) Miscellaneous additions

Triscarbamates have been formed by treating cellulose in DMF with alkyl isocyanates [63]. The reaction does not work using pyridine as a solvent.

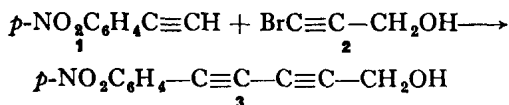Polymerization processes often proceed readily in DMF [4, 64–66].

Azido-iodo-compounds may be prepared by the addition of iodine azide to the alkene [51] (Section B1(a)).

2. Coupling reactions

Dimethylformamide has been used as a solvent in certain coupling reactions. It has, of course, the advantage over some of the more usual solvents in that it may be readily removed from the reaction mixture by tratment with water.

(a) Preparation of acetylenes

The Cadiot-Chodkiewicz procedure for the coupling of acetylenes has occasionally been used with DMF as the solvent [67]. The yields of di-yne are relatively high, approximately 70 per cent, and the temperature is generally kept below 40° when DMF is used. Thus p-nitrophenylacetylene (1) and 3-bromoprop-2-ynol (2) gave an 80 per cent yield of 5-p-nitrophenylpenta-2,4-diyn-1-ol (3) when treated with cuprous chloride, ethylamine, and hydroxylamine hydrochloride in DMF at 40°,

$$p\text{-}NO_2C_6H_4C\equiv CH + BrC\equiv C\text{—}CH_2OH\longrightarrow$$
$$\underset{1}{\qquad\qquad\qquad}\qquad\qquad\underset{2}{\qquad\qquad\qquad}$$

$$p\text{-}NO_2C_6H_4\text{—}C\equiv C\text{—}C\equiv C\text{—}CH_2OH$$
$$\underset{3}{\qquad\qquad\qquad\qquad}$$

and aminocarbonylacetylene and bromophenylacetylene gave a 76 per cent yield of 1-amino-5-phenylpenta-2,4-diyn-1-one using similar reactants in DMF at < 10° [67].

The procedure has been extended to include the coupling of 1-bromo- and 1-iodo-allenes with terminal acetylenes in the presence of cuprous ions, DMF, and a suitable base (tributylamine for 3,3-dialkyl-1-bromo-allenes and ethylamine or t-butylamine for 3-mono-alkyl-1-bromo- or -1-iodo-allenes) [68], e.g. 1-bromohexa-1,2-diene and prop-2-ynol gave a 51 per cent yield of nona-4,5-dien-2-ynol under these conditions.

The oxidative coupling of 3,3,3-trifluoropropyne and the zinc derivative of the propyne in DMF in the presence of cupric chloride gave 1,1,1,6,6,6-hexafluorohexa-2,4-diyne as the major product together with smaller amounts of 1-chloro-3,3,3-trifluoropropyne, cis- and trans-2,3-dichloro-1,1,1,6,6,6-hexafluorohex-2-en-4-yne, and 2-chloro-3(3,3,3-trifluoropropynyl)-1,1,1,6,6,6-hexafluorohex-2-en-4-yne [69].

(b) Preparation of azo-dyes

The alkaline coupling of diazonium salts to produce azo-dyes may be accelerated by the presence of DMF or dimethylacetamide [70].

(c) Preparation of bi-aryls

The use of refluxing DMF in the Ullmann reaction appears to give greater yields than conducting the undiluted reaction at higher temperatures. Kornblum and Kendall [71] stress the ease of removal of DMF and the use of lower temperatures but state that for those halides which are inert under normal Ullmann conditions then this procedure offers no advantages, e.g. α-bromonaphthalene, p-bromonitrobenzene, p-bromophenetole, and m- and p-chloronitrobenzene did not react after refluxing for twenty-four hours in DMF with copper powder.

However, 2-chloro-3-nitroanisole, for example, gave an 84 per cent yield of 6,6'-dimethoxy-2,2'-dinitrobiphenyl when treated with copper powder in DMF and a 70 per cent yield in the absence of DMF [71]. The yield of dinitrobinaphthyls from iodo-nitronaphthalenes was found to be increased by the presence of DMF due to the solvent activity of DMF on the reactants, products, and the copper [72]. In the case of compounds containing two or more halogen atoms the halogen *ortho* to the nitro-group is eliminated, e.g. 4,4'-dibromo-2,2'-dinitrobiphenyl was formed in a 76 per cent yield by heating 1,4-dibromo-2-nitrobenzene with copper bronze in refluxing DMF for six hours [73].

Dimethylformamide appears to be particularly effective for the preparation of bi-aryls containing free aldehyde or ketone groups. Thus, o-iodobenzaldehyde and 2-iodo-4-nitrobenzaldehyde gave biphenyl-2,2'-dicarboxaldehyde (65 per cent) and 5,5'-dinitrobiphenyl-2,2'-dicarboxaldehyde (65 per cent) respectively when treated with copper bronze in refluxing DMF [74] and 2,2'-diacetyl-biphenyl was prepared from o-iodoacetophenone in a 59 per cent yield under similar conditions [75]. The latter paper also gave the preparation of certain other 2,2'-diacylbiphenyls. 2-Bromo-4,5-diethoxybenzophenone (4) gave 2,2'-dibenzoyl-4,4',5,5'-tetraethoxybiphenyl (5) and some 3,4-diethoxybenzophenone (6) when refluxed with copper dust activated with iodine in DMF [76].
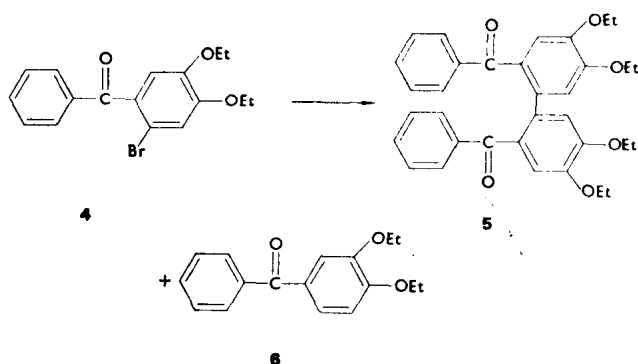
An interesting preparation of 4,4',5,5',6,6'-hexamethoxydiphenic acid in a 40 per cent yield from methyl 2-bromo-O-trimethylgallate using the Ullmann synthesis in DMF followed by saponification of the resulting ester has been given in the literature [77].

In certain cases unsymmetrical bi-aryls have been synthesized using the Ullmann reaction in DMF. The yields, as would be expected, are generally less than 30 per cent, and the three possible products are often difficult to separate [78, 79]. However 1-nitro-2-o-nitrophenylnaphthalene has been prepared by a mixed Ullmann reaction using 2-bromo-1-nitronaphthalene and excess 2-bromo-nitrobenzene [78] and 3-bromo-4-iodo-5-nitrotoluene and 2-bromonitro-benzene were refluxed with copper bronze in DMF for eight hours to give a crude product which was then reduced by sodium sulphide in sodium hydroxide to afford 1-bromo-3-methylbenzo[c]cinnoline-N-oxide (4 per cent), benzo[c]

cinnoline-*N*-oxide and 2-amino-6,6′-dibromo-4,4′-dimethyl-2′-nitrobiphenyl [73].

The use of DMF occasionally gives a dehalogenated product rather than a bi-aryl [72, 76, 77], e.g. the formation of 3,4-diethoxybenzophenone (6) from 2-bromo-4,5-diethoxybenzophenone (4) [76] and methyl tri-*O*-methylgallate from methyl 2-bromo-*O*-trimethylgallate [77].

(d) Preparation of tetra-substituted ethylenes

Isopropylidene dibromomalonate (5,5-dibromo-2,2-dimethyl-1,3-dioxan-4,6-dione) (7) gave a 32 per cent yield of di-isopropylidene-ethylene tetracarboxylate (8) on standing in DMF at room temperature for twenty hours [80].

7   8
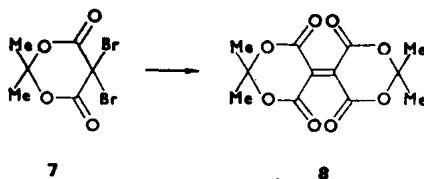
3. Cyclizations

In this section a number of cyclizations is discussed in which the role of DMF is primarily that of a solvent. Cyclizations involving the use of a Vilsmeier-Haack type reagent are discussed in Section C1(b).

Cyclizations appear, in general, to have been used to prepare saturated and unsaturated heterocyclic molecules, but have also been used, to a lesser extent, for the preparation of alicyclic and aromatic molecules. Inclusion in this section does not, of course, imply that these reactions proceed by a common mechanistic pathway, but rather that the syntheses have a common structural cyclic endpoint.

(a) Preparation of alicyclic compounds

The preparation of alicyclic molecules by a cyclization using DMF as a solvent appears to be a relatively unusual procedure. However, 1-but-1-enyl-2-methyl-maleic anhydride has been dimerized to a nine-membered cyclic diene, in a low yield, using sodium hydride in DMF in the presence of triethylamine [81]. Certain allylic dibromides in DMF have been cyclized to large ring 1,5-dienes, in high yields, using a solution of nickel carbonyl in DMF under argon [82], e.g. 1,12-dibromododeca-2,10-diene gave a 59 per cent yield of *trans, trans*-cyclo-dodeca-1,5-diene under these conditions. However, in the case of allylic di-bromides, $BrCH_2CH=CH(CH_2)_n-CH=CHCH_2Br$, in which $n = 2$ or 4, the predominant product arose by 1–6 and 3–8 coupling respectively to give a six-membered ring.

1,3-Dibromo-1-phenylpropane has been cyclized to cyclopropylbenzene in a 75–85 per cent yield using a zinc-copper couple in DMF [83].

(b) Preparation of aromatic carboxylic compounds

The *o*-quinone, 5-cyanomethylene-6-[(dimethylamino)(methylthio)methylene]-