The Reduction of Nitriles to Aldehydes: Applications of Raney Nickel/Sodium Hypophosphite Monohydrate, of Raney Nickel/Formic Acid, or of Raney(Ni/Al)Alloy/Formic Acid, Respectively†

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ABSTRACT

The three title reductant systems have significant advantages in generating aldehydes from nitriles. These include: the utilization of convenient hydrogen sources, namely, sodium hypophosphite monohydrate and formic acid, respectively, and of the relatively inexpensive Raney nickel and Raney (Ni/Al) alloy; the convenience of conducting the reaction(s) in aqueous media at ambient temperatures and pressures, and avoiding the use of trapping agents (except when transforming glycosyl nitriles (*vide infra*)) and of hydrogen cylinders. Numerous examples of the utilization of the title systems are presented (mostly from the more recent literature) that demonstrate the utility of the respective methods in transforming a solo cyano group, or when accompanied by other chemosensitive functions in a structure, to the corresponding aldehyde. Such substrates include benzonitriles, glycosyl nitriles, O-, N- and S-containing heterocyclic nitriles, aliphatic-aromatic situations, and more complex fused heterocyclic and carbocyclic scaffolds. The review reports modifications of the title methods and several notable steric effects.

KEYWORDS

Advantages, modifications, steric effects, benzonitriles, glycosyl nitriles, O-, N- and S-containing heterocyclic nitriles, miscellaneous nitriles.

Table of Contents

1. Introduction

The selective reduction of a nitrile to an aldehyde, especially when the substrate molecule bears one or more other potentially reducible or catalyst-depleting functions, is an important and sometimes essential and/or efficacy-determining reaction, particularly in a (multistep) organic synthesis. A number of methods and a large variety of reagents[1] have been proposed to effect this transformation as is evidenced from an extensive literature.[2]

Among the requisites for a reagent of choice in a nitrile to

†Dedicated to the memory of Professor Otto Guido Backeberg, who initiated the research on the hypophosphite/Raney nickel reduction of nitriles to aldehydes.

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aldehyde reduction are the following: (i) stable, and convenient to handle and measure; (ii) transforms a specific functional group; (iii) results in good yields; (iv) easy to isolate product; (v) relatively inexpensive and safe to handle; (vi) reduction conducted at ambient temperature and pressure; (vii) can be utilized in aqueous media; and (viii) can be utilized with a spectrum of compounds.

Certain of the methodologies[2] most often utilized include:

(a) the classical Stephen aldehyde synthesis[3] (with anhydrous $SnCl_2$ and hydrogen chloride);
(b) partial catalytic hydrogenation of the nitrile with hydrogen and a metal catalyst (usually Pt, Pd or Raney nickel) to provide an intermediate imine which is then hydrolyzed to the aldehyde; over-reduction of the nitrile (to the amine) may be suppressed by use of a trapping agent,[4] followed by hydrolysis of the derivative to liberate the aldehyde product (*cf.* glycosyl nitriles (*vide infra*));
(c) partial reduction by a metal hydride, especially those derived from Al and B, containing only one available hydride and extensively listed by Cha *et al.*[1]

Many of the reagents in (a) and (c) require usage in an anhydrous environment, and in stringent stoichiometric proportions, while those in (b) utilize hydrogen gas from a cylinder. Moreover, some of the hydrides in (c) are able to reduce certain other chemisensitive functions that may accompany a cyano group in a substrate molecule.

Some years ago, several alternate methods for reducing a nitrile to an aldehyde were introduced by Backeberg and the current authors, *viz.* (i) with Raney nickel and sodium hypophosphite in aqueous acetic acid-pyridine[5] (abbreviation: RNP); (ii) with Raney nickel and aqueous formic acid[6] (RNF); and (iii) with Raney (Ni/Al) alloy and aqueous formic acid[7] (RAF). In aqueous formic acid solution, two-electron reduction of the cyano group is accompanied by hydrolysis and always leads to the aldehyde which is not further reduced, as distinct from use in aqueous alkali when four-electron reduction leads to the corresponding primary amine.[2b]

2. RNP General Procedure[5]

In essence, Raney nickel (0.3–0.4 g) is added to the nitrile (1 g) and sodium hypophosphite monohydrate ($NaH_2PO_2.H_2O$) (2 g) in 1:1:2 water-acetic acid-pyridine (20 mL) and the mixture is stirred at 40–45 °C for 1–1.5 h. (Care: the filtered residual nickel is pyrophoric and ignites when allowed to dry in air).

3. RNF General Procedure[6]

In essence, Raney nickel (either a commercial product, or preformed[6] from Raney (nickel/aluminium) alloy (7.5 g) by stirring with aqueous 2 mol L^{-1} NaOH (150 mL) for 30–40 min, the temperature being allowed to rise), and the washed catalyst is added to the nitrile (5 g) in (~90 %) aqueous formic acid (~75 mL) and the mixture stirred at 75–80 °C for 30 min (or until the reduction is complete), after which the aldehyde is isolated. This method succeeds in reducing 'sterically' hindered nitriles[6] (*viz.*, *o*-tolunitrile and α-naphthonitrile).

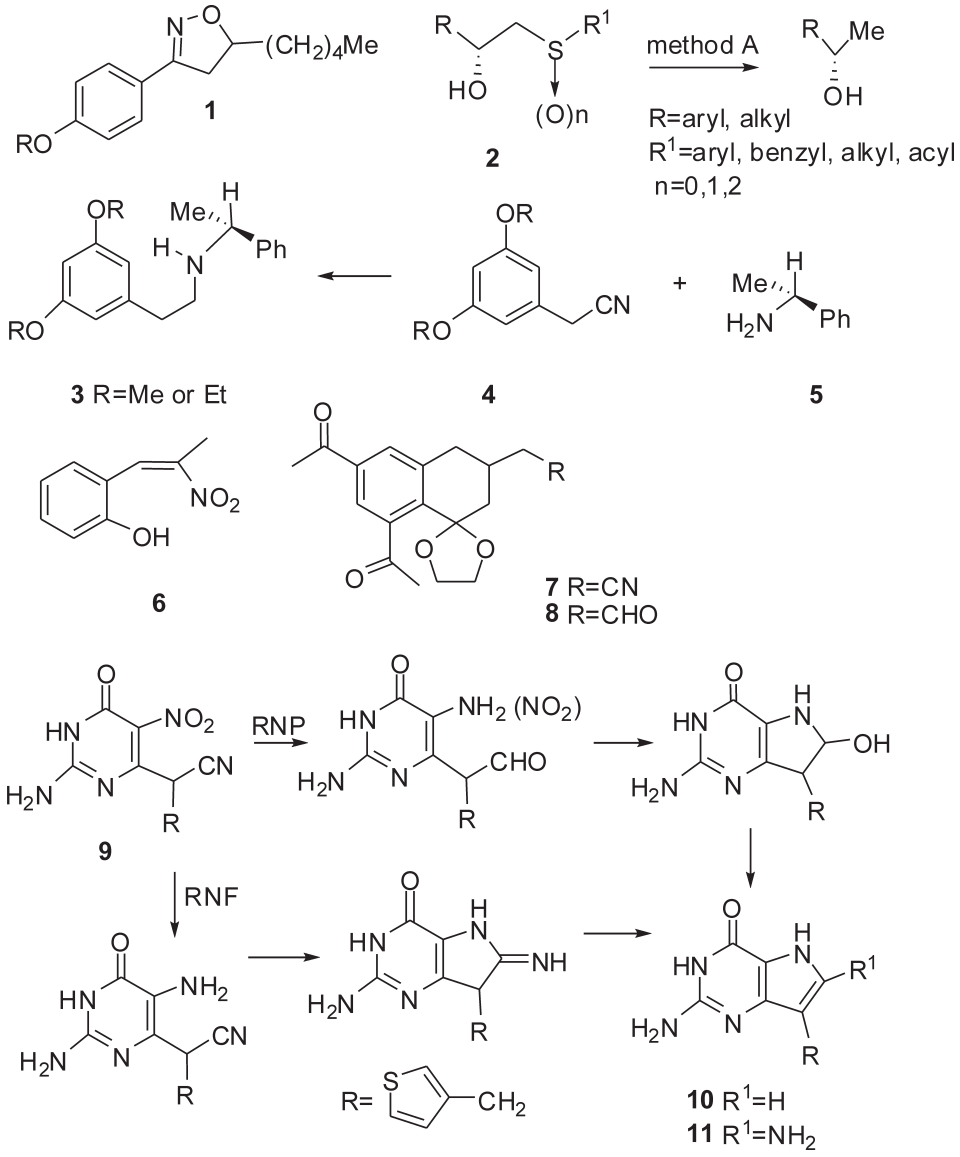
4. RAF General Procedure[7]

In essence, a mixture of Raney alloy (5.0 g), nitrile and 75 % aqueous formic acid (75 mL) is refluxed for l h, after which the aldehyde is isolated. Some studies[7,8] seeking preferred conditions for reaction (4) have been made: optimum yields were obtained by refluxing equal masses of nitrile and Raney nickel alloy in 75 % aqueous formic acid. It was noted that the rate of hydrogen evolution increases with increasing water content. Other acids (e.g. 75 % CH_3COOH, and aqueous HCl) can replace the formic acid, but the yields are lowered. Under the reaction conditions examined with several representative nitriles, it was found that olefins, ketones, esters, aldehydes, amides, halo compounds and acids were generally inert; *m*- and *p*-nitrobenzonitriles were reduced to the respective formamido-benzonitrile derivatives. Generally, the relative proportions of the respective reaction components, and the reaction temperature and time may be varied considerably, as may also the use of either W-2 or W-4 Raney nickel (*vide infra*).

The RNP, RNF and RAF methods each possess one or more of the following features and advantages which could favour its preferred usage for a particular reduction:

(i) The reduction is performed in an aqueous medium, in contrast to the anhydrous environment which is requisite in the Stephen synthesis and with use of a metal hydride. This aspect is of special value when reducing a cyano function in the company of a proton source (i.e. one liable partially or completely to deactivate anhydrous $SnCl_2$ or a metal hydride), such as the hydroxyl (present in many glycosyl cyanides, and in phenols) and the amino function (e.g. in pyrroles, *vide infra*).
(ii) The hydrogen source in RNP is the relatively stable and conveniently handled sodium hypophosphite monohydrate salt, while in the RNF and RAF methods the requisite hydrogen is generated *in situ* from the formic acid acting on the Raney nickel or the Raney alloy, respectively. Consequently, the reductions in all three methods are relatively convenient and safe to perform since high temperatures and pressures and a hazardous hydrogen atmosphere and associated problems as in (b) are avoided.
(iii) The nickel catalyst can be either a commercial product or be conveniently prepared[6,9] when required for the occasion. The Raney alloy (50 % Ni:50 % Al) is less expensive than the equivalent Raney nickel catalyst and is more convenient and considerably safer to use.
(iv) In RNP, the completion of the reduction of the nitrile is usually indicated by a (visible) onset of hydrogen evolution from the reaction.
(v) Little if any over-reduction of the imine intermediate or of the product aldehyde usually occurs or has been noted in either of the three methods, and the aldehyde is liberated as such from *in situ* hydrolysis of the imine.
(vi) Whereas in methodology (c) (*vide supra*), a 1:1 molar stoichiometric proportion of metal hydride:nitrile is generally a requisite, or utilized, or else is to be inversely added in order to avoid over-reduction of the imine intermediate and/or the product aldehyde, such is not required in either of the current methods. Indeed, the reaction temperatures and reaction times and the stoichiometric proportions and concentrations of the constituents in the current reduction methods have been varied considerably with successful outcomes (*vide infra*).
(vii) A useful range of important/ubiquitous functional groups such as NH_2, OH, OMe, CO_2H, COMe, C=C double bond, halogen, and protecting groups such as Boc and THP (*vide infra*), remain unaffected in either method. The application of one or other of the RNP, RNF and RAF methods for the reduction of nitriles to aldehydes generally results in good yields, and is now well established (*vide infra*).

The purpose of this review is to draw attention to the wide variety and types of organic structures bearing a nitrile function, sometimes in the company of one or more other chemosensitive groups, which have been successfully subjected to these



Scheme 1

reductive methods. The selected examples are mostly from the more recent literature, and are intended to highlight an aspect or feature in the reduction and/or in the nitrile substrate that is of more than usual synthetic interest.

5.1 Sodium Hypophosphite Monohydrate

$NaH_2PO_2.H_2O$ is a white crystalline, hygroscopic salt, soluble in water, pH 5.5–8.5, stable under ordinary conditions, but explosive in contact with oxidizers; it is not considered a fire hazard but forms spontaneously flammable phosphine gas when heated. In the absence of a metal catalyst, it has been used under microwave irradiation selectively to reduce the nitro group into an amino group; certain common functional groups including nitrile are not affected.[10]

Generally, the salt is employed in synthesis as a hydrogen source in combination with a metal catalyst, as exemplified with sodium hypophosphite plus Pd/C, which is a mild selective system for the reduction of carbon-carbon double bonds, and for the hydrogenolysis of benzyl ethers and benzyl carbonates.[11]

Boyer *et al.*[12] reported the results of an investigation on the scope and limitations of using sodium hypophosphite as reducing agent in conjunction with a catalytic amount of palladium (5 % on charcoal) on several functional groups. Of the two nitriles examined, *viz.*, benzonitrile and cinnamonitrile, the former was unreactive and the latter was selectively reduced to dihydrocinnamonitrile (87 %). The authors[12] observed little or no reduction of the carbon-nitrogen double bond.

5.2 Nickel/Aluminium (1:1) Alloy

Catalyzed reductions with this alloy, including that of nitriles to aldehydes, have been reviewed.[2b] It should be noted, in the present context, that commercial Ni/Al alloy has varying properties and that refluxing benzaldehyde with Ni/Al alloy in water for 1 h afforded toluene (~95 %), and that benzyl alcohol is intermediate in the reaction.[13]

6. Modifications

Variations in one or other of the RNP, RNF and RAF systems and methodologies have been reported as exemplified by the following:

A combination of Raney nickel and formic acid in methanol at room temperature has been found[14] to cleave azo compounds, both symmetric and unsymmetric, to amines in a very fast, high-yielding reaction, while treatment[15]of some 5-amyl-3-(4-substitutedphenyl)-2-isoxazolines **1** (R=H, benzyl, Ac) (Scheme 1) with Raney nickel in formic acid gave mainly

β-hydroxy ketones and/or β-unsaturated ketones depending on the nature of R and the reaction temperature.

Triethylammonium hypophosphite, $Et_3NH^+H_2PO_2^-.nH_2O$ (a stable liquid at ambient conditions), in THF/MeOH rapidly liberates hydrogen in the presence of Raney nickel at room temperature (as does $NaH_2PO_2.H_2O$) and selectively reduces nitriles to aldehydes in excellent yields.[16] Its activity and selectivity showed some differences from those of $NaH_2PO_2.H_2O$. For example, whereas RNP is not effective with nitrobenzene[5], the new reagent system provides aniline (100 %), and higher product selectivity was found. In the conversion of nitriles to aldehydes it was found[16] that there was competition between hydrogenation (which is predominant in the RNP system), and hydrolysis which predominates in the triethylammonium hypophosphite.nH_2O system. The authors[16] conclude that the $Et_3NH^+H_2PO_2^-.nH_2O$/Raney nickel system in THF/MeOH acts as a modification of the $NaH_2PO_2.H_2O$/Raney nickel in H_2O/AcOH/pyridine system, but by-products such as amines, imines and alcohols are completely avoided, pure aromatic and aliphatic aldehydes are obtained, and that the triethylammonium-hypophosphite system is easy to work with.

Node *et al.*[17] found that a combination of Raney nickel (W-2)-sodium hypophosphite in ethanol and water and acetate buffer (pH 5.2) was an excellent reagent for (i) the desulphurizations of sulphides or sulphoxides bearing an optically active secondary alcohol (**2**) without any loss of the optical activity, and (ii) for the chemoselective reduction of benzylthio or phenylthio ethers bearing benzyl ether. It was noted[17] that the order of addition of the reagents (Raney Ni and $NaH_2PO_2.H_2O$) to the solution of the starting material (**2**) was critical in performing the desulphurization in this combination system.

In the course of synthesizing Michellamines A-C, Hoye *et al.*[18] found the preparation of the unsymmetrical secondary amine **3** to be a challenge, since all attempts to reduce the substrate nitrile **4** to the intermediate aryl-acetaldehyde (e.g. with DIBAlH) as a prelude to reductive amination chemistry was thwarted by a rapid aldol dimerization. The eventual solution was *in situ* reduction of the nitrile **4** with a combination of Raney nickel and sodium hypophosphite in acetic acid/pyridine/water (1:2:1) and hydrogen gas (1 bar), in the presence of *R*-α-methylbenzylamine **5** (at room temperature, 12 h), which provided the desired amine **3** in 72 % yield. Importantly, the Raney nickel, in this system, did not promote benzylic heteroatom bond hydrogenolysis and was compatible with the use of benzyl ether as a protecting group and allowed the direct incorporation of the α-methylbenzylamine chiral auxiliary.

Monti *et al.*[19] converted nitro-olefins (e.g. **6**) into the corresponding saturated ketones or aldehydes in high yield by treatment[19] with Raney nickel and sodium hypophosphite in ethanol-aqueous acetate buffer, pH 5. Under the conditions utilized, (*viz.* a suspension of Raney nickel and an aqueous solution of sodium hypophosphite were added in several portions and under stirring to a solution of the nitro-olefin in the buffer), nitroparaffins are reduced to amines whilst oximes gave the corresponding carbonyl compounds in almost quantitative yield.

A significant finding by Gowda *et al.*[20] was that that aliphatic and aromatic nitro compounds are selectively reduced by Raney nickel in (90 %) formic acid, at room temperature in 10–30 min to their corresponding amino derivatives in good yields and that the system is compatible with the nitrile functionality. Thus, *p*-nitrobenzonitrile gave (92 %) *p*-aminobenzonitrile, and *p*-nitrophenylacetonitrle gave (91 %) *p*-aminophenylacetonitrile. These two outcomes may be compared with (i) the reduction of *m*-and *p*-nitrobenzonitriles with Raney alloy in aqueous (75 %) formic acid under reflux for 1 h to give the corresponding formamidobenzonitrile derivative in (85–90 %) yield, and (ii) that *m*-nitrobenzonitrile is recovered mostly unchanged after stirring with Raney nickel in aqueous (~95 %) formic acid at 75–80 °C for 30 min.[7]

Hydrazinium monoformate[21] is claimed to be a more effective proton donor than formic acid and in the presence of Raney nickel the reduction of nitriles occurs without hydrogenolysis to give the corresponding methylamine derivative. Thus, stirring RCN with Raney nickel and $N_2H_5^+HCO_2^-$ in methanol at room temperature for 10–20 min gave a high yield of RCH_2NH_2. In the case of a nitro nitrile the two moieties are reduced to an amino group and a methylamino group, respectively.[21]

Glatz *et al.*[22] reported that partial reduction of nitrile **7** to the corresponding aldehyde **8** proved to be a troublesome step: reduction with $LiAl(OEt)_3H$ gave **8** in 45 % yield, and reduction with Al(*iso*-Bu)$_2$H led exclusively to eliminative cleavage of the acetal function. Finally, reduction with Raney nickel (W2) in a slightly acid buffer system (*viz.*, pyridine, glacial acetic acid and aqueous trisodium phosphate decahydrate) afforded the aldehyde **8** in 74 % yield. It has been noted[7] that nitrile reductions to aldehyde may also be accomplished by Raney nickel in the absence of sodium hypophosphite, of formic acid, or of hydrogen, in an aqueous acetic acid or aqueous HCl-ethanol system.

In an unusual modification of the RNF method Thompson *et al.*[23] converted 2,4-diaminonicotinonitrile to the corresponding aldehyde in good yield: a solution of the nitrile (5.00 g, 37.3 mmol) and freshly prepared W-7 Raney nickel (120 mg wet catalyst, in absolute EtOH) in 99 % formic acid (150 mL) and water (40 mL) was hydrogenated (60 psi, 20 °C) for 2 days. Fresh catalyst was added (130 mg) and the reaction continued for 5 days, then further catalyst was added (207 mg) and the reaction continued for a final 2 days. Work-up provided the crude solid 2,4-diaminonicotinaldehyde (3.65 g, 71 %). Optimum conditions for this reaction were found to vary greatly with the grade and amount of catalyst used.

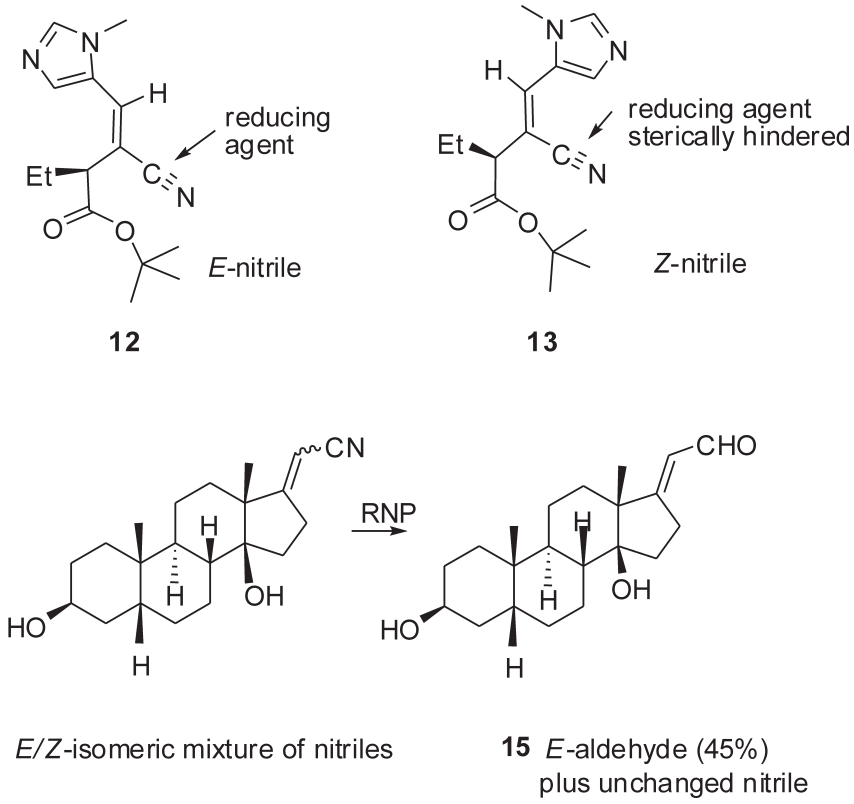
A modification of the RNP method, whereby the reduction is conducted in the presence of a trapping agent was introduced by Moffatt *et al.*[30] (*vide infra*), and has proved of value in accessing aldehydes from glycosyl nitriles.

7. Kinetic and Steric Aspects

The relative failure of *o*-tolunitrile and of α-naphthonitrile to transform to aldehyde by the Stephen and RNP methods has been attributed to steric and to solubility factors.[3,5] Yields are, however, improved in the RNF and RAF procedures.[6,7]

2-Methyl-3-acetylamino-benzonitrile, being configurationally related to the 'sterically' hindered nitriles *o*-tolunitrile and α-naphthonitrile[7]), would be expected to reduce with difficulty[5] in the RNP method, and more successfully with RNF.[6] In a patented[24] (and relatively large-scale) process 60 g of this nitrile in 1 L of 50 % aqueous formic acid was refluxed during which Raney alloy (120 g) was added in portions over a period of 2.5 h to obtain a product mixture (39 g) of the desired aldehyde and the starting nitrile.

In the original RNP[5] and RNF[6] work it was indicated that the nitro group in nitrobenzene remained unaffected under the reaction conditions, whereas with RAF[7] nitrobenzene formed a formamide derivative *via* initial aniline formation. It is therefore noteworthy that Hicks,[25] utilizing the RNP system (at 45–50 °C) coupled with a longer reaction time (18 h), transformed pyrimidine derivative **9** bearing a nitro and a cyano function, into



Scheme 2

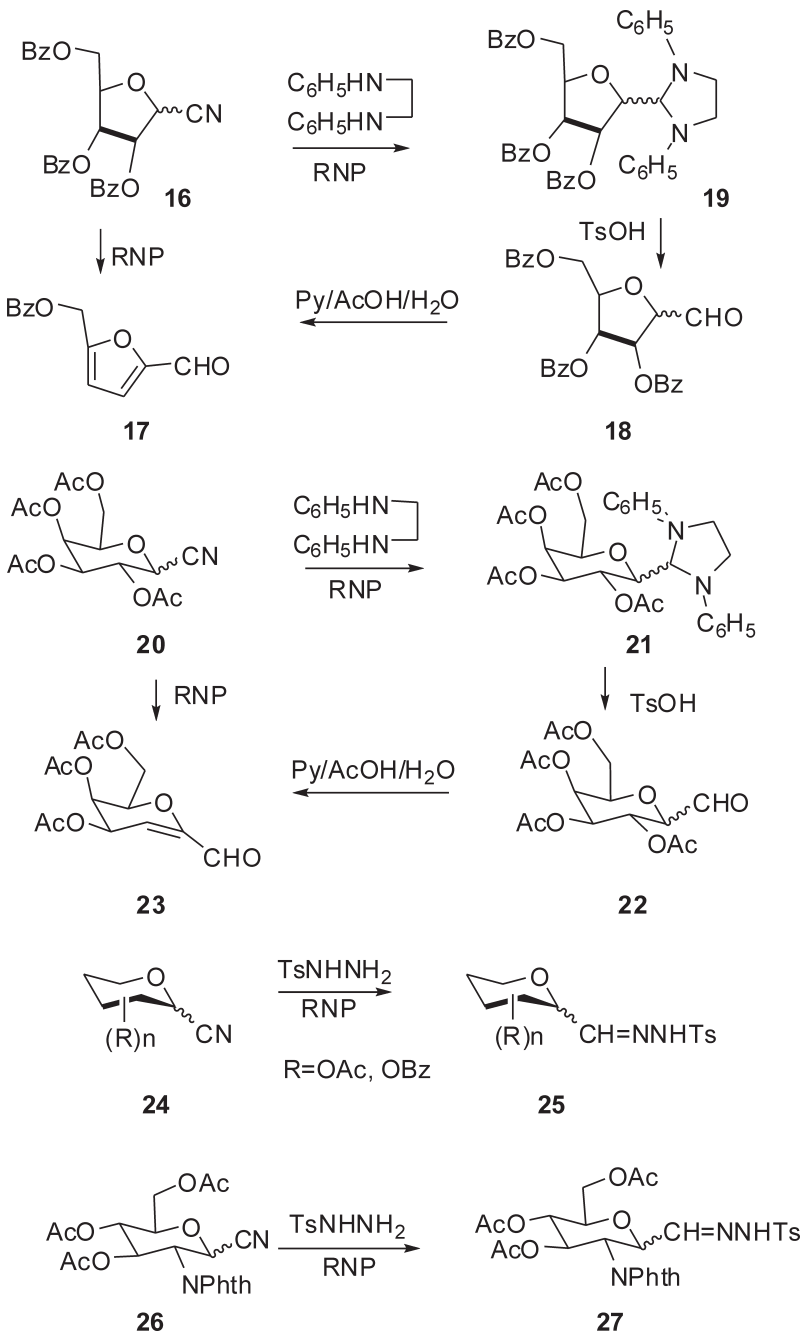
predominantly 2-amino-3,5-dihydro-7-(3-thienylmethyl)-4H-pyrrolo[3,2-d]pyrimidin-4-one **10** with some 2,6-diamino derivative **11**, whereas reduction with the RNF system gave predominantly **11**; the 2-amino-product **10** was present only in trace amount. We consider the above as implying that in RNP the nitrile function transforms to aldehyde more rapidly than does the nitro group to amine, thereby eventuating in predominantly amino product **10**. Further, in the Raney nickel-formic acid reaction it is suggested that the nitro group reduces more rapidly to amine than does the nitrile to aldehyde, eventuating, *via* a spontaneous intramolecular cyclization and subsequent aromatization,[26] to end-product **11**. Gribble[27] has indicated that conventional reduction methods would invariably reduce the nitro group before the cyano group.

Two notable examples of stereoselective outcomes in the RNP method which have been attributed to steric hindrance are the following: (i) dramatically different results were obtained[28] when applying the method to reduce the cyano group of the *E* isomer of olefin **12** (Scheme 2) and the cyano group in the corresponding *Z* isomer **13**. The former olefin yielded the corresponding *E*-aldehyde (64 %) along with recovered nitrile (22 %), whereas the *Z* isomer **13** remained unreactive under the same conditions. The authors[28] suggest that in the *Z* olefin **13** the cyano group is shielded by the *tert*-butyl ester and the imidazole ring thereby severely hindering approach by the reducing reagent from either direction, unlike the situation in **12**. It is of interest to note that to avoid deactivation of the catalyst the Raney nickel was added at 5 h intervals over a period of 24 h at 50 °C with intense stirring, giving an indication of the inertness of this particular aldehyde product in the reducing system; (ii) in the course of synthesizing a series of digitalis-like compounds Cerri *et al.*[29] reported that reduction of the *E*/*Z* isomeric mixture of nitriles **14** with Raney nickel and NaH_2PO_2 (at 60 °C for 24 h) gave the *E*-aldehyde **15** (45 %) whereas the *Z* isomer did not react in the reaction conditions used and was recovered unchanged.

8. Glycosyl Nitriles

One or other of the RNP, RNF and RAF methods has found application in the carbohydrate area as shown by the following: Moffatt *et al.*[30] reported a very facile synthetic route to 3,4,6-substituted derivatives of 2,5-anhydro-D-allose. Normally, the reductive hydrolysis of 2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl cyanide **16** (Scheme 3) with Raney nickel and sodium hypophosphite in aqueous pyridine-acetic acid (RNP) is accompanied by extensive elimination of benzoate to give a furfural aldehyde derivative **17**. It was shown[30] that this elimination took place during the reductive hydrolysis. However, by conducting the reduction in the presence of *N*,*N*′-diphenylethylenediamine, the initially produced aldehyde **18** is trapped as a 1,3-diphenylimidazolidine derivative **19** (74 %). Regeneration of the free 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allose **18** from the imidazolidine derivative was achieved (68 %) by mild *p*-toluenesulphonic acid treatment. The Moffatt modification was later adapted by Dettinger *et al.*[31] to convert 2,3,4,6-tetra-*O*-acetyl-D-galactopyranosyl cyanide **20**, *via* its 1,3-diphenylimidazolidine derivative **21** (72 %), to the corresponding aldehyde **22**; in the absence of the trapping agent, the reaction gave the 3-deoxy-*aldehydo*-D-*lyxo*-hept-2-enose **23** as the ultimate product.

Toth *et al.*[32a] subsequently employed RNP, and tosylhydrazine as the trapping agent, to transform anhydro-aldononitriles (glycosyl cyanides) **24** to the previously unknown 2,5- and 2,6-anhydro-aldose tosylhydrazones (55–90 % yields) **25**, as exemplified with cyanide **26** to give 4,5,7-tri-*O*-acetyl-2,6-anhydro-3-deoxy-3-phthalimido-D-*glycero*-D-*gulo*-heptose **27** (58 %). This was followed[32b] by the reductive transformation of per-*O*-acylated 2,6-anhydro-aldonitriles (glucopyranosyl cyanides of the D-galacto, D-gluco, D-xylo, and D-arabino configuration, with Raney nickel/$NaH_2PO_2.H_2O$ in aqueous pyridine-AcOH solvent mixture, in the presence of benzoylhydrazine, Et carbazate and semicarbazide, respectively, to give the corre-

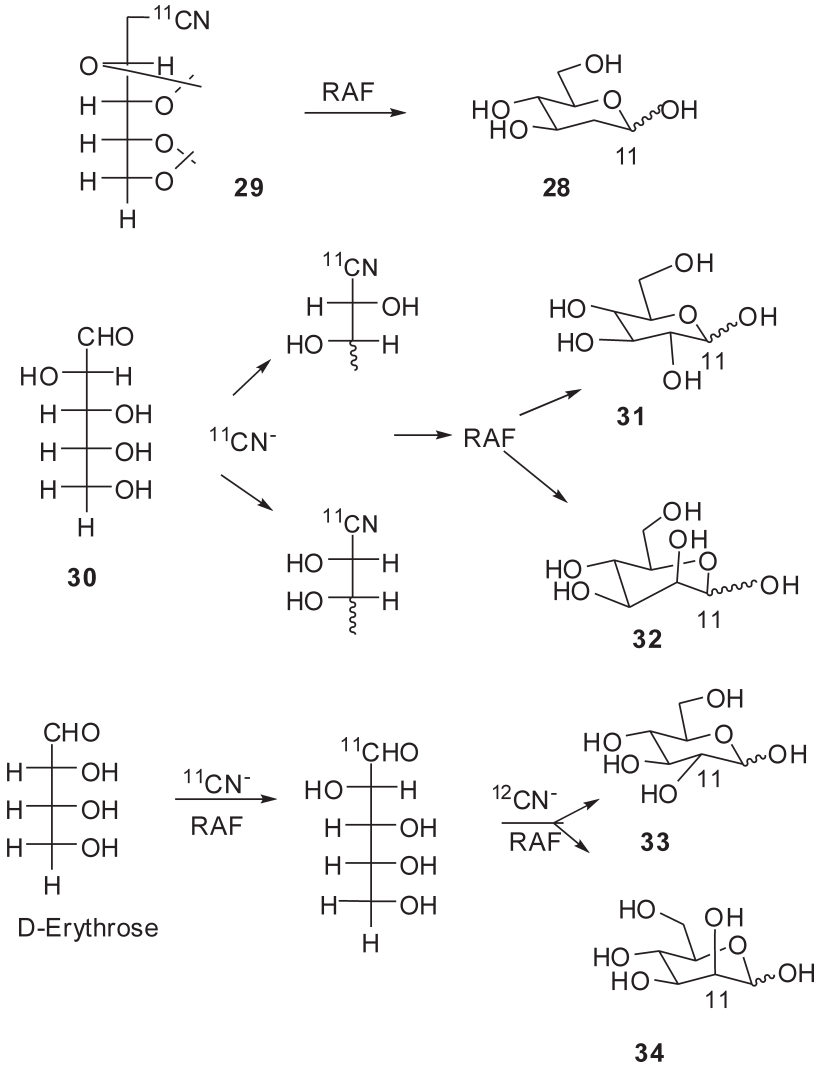


Scheme 3

sponding anhydro-aldose benzoylhydrazones, ethoxycarbonylhydrazones and semicarbazones, respectively. The RNP procedure involving a trapping agent is regarded[32a] as one of the most straightforward ways to obtain *C*-glycosyl aldehydes and/or their derivatives.

An early application of the RAF method was described by MacGregor *et al.*[33] to prepare 2-deoxy-D-[1-^{11}C]glucose **28** (Scheme 4): heating 1-[^{11}C]-cyano-2-deoxy-2,3:4,5-diisopropylidene-D-arabitol **29** in aqueous formic acid in the presence of Raney alloy (Ni/Al) with stirring for ~10 min at 100 °C, led to reduction/hydrolysis of the nitrile to aldehyde and simultaneous cleavage of the protective isopropylidene groups to give the desired product **28** in 60–70 % yield (Scheme 4). Mention is made[33] that for the conversion of the nitrile to the aldehyde, $LiAl(OC_2H_5)_3H$ was unsatisfactory as was diisobutylaluminium hydride, whereas Raney alloy, which could be used in large excess, without the formation of amine as a major product, proved to be a successful catalyst for this conversion, rapidly forming **28** of high specific activity, in a good yield.

Shiue and Wolf[34] modified the classical Kiliani-Fischer cyanohydrin synthesis to prepare D-[1-^{11}C]glucose, D-[1-^{11}C]mannose, D-[1-^{11}C]galactose, D-[2-^{11}C]glucose and D-[2-^{11}C]galactose (for use in nuclear medicine to monitor the metabolism of glucose and galactose) by reaction of the appropriate aldose substrate with an alkali metal ^{11}C-labelled cyanide followed by reduction with Raney alloy in formic acid: for example, D-arabinose **30** was reacted with Na^{11}CN at pH 8 to form a mixture of the appropriate 1-[^{11}C]-aldonitriles in good yield. Reduction of the mixture with Raney alloy and (30 %) aqueous formic acid (RAF), a reductive method being routinely used[33] in the rapid synthesis of 2-deoxy-D-[1-^{11}C]glucose, gave D-[1-^{11}C]glucose **31** and D-[1-^{11}C]mannose **32**. This new synthetic method has the advantage of labelling glucose specifically at the one position and assuring the certainty of the label position. The



Scheme 4

yields of **31** and **32** were pH-dependent.

The same method was applied to synthesize D-[2-^{11}C]glucose **33** and D-[2-^{11}C]mannose **34**, with the [^{11}C]-label at the 2-position, by serial application of the procedure to D-erythrose. A disadvantage of this modified Kiliani-Fischer approach is that a pair of epimers is produced in each instance, (e.g. glucose/mannose ratio obtained of around 0.65), thus necessitating their chromatographic separation and lowering of overall yield. A major improvement was the use of a borate buffer as reaction medium, which afforded a glucose/mannose ratio of between 1.7 and 2.5.[35]

Bender and Gee[35] simplified and automated the synthesis of D-[1-^{11}C]glucose **31** whereby the solid phase-supported reaction of $NH_4{}^{11}CN$ with D-arabinose **30** on Alumina N-Sep-PaKTM instantaneously produced [1-^{11}C] aldonitriles which on reduction with Raney nickel and formic acid at 110 °C for 7 min and semipreparative HPLC afforded [1-^{11}C]glucose with radiochemical purity >95 %. A crucial step for the synthesis based on the Kiliani-Fischer method is the reduction of the aldonitriles to the corresponding aldoses. The Raney nickel/formic acid method gave the best results despite large yield losses of up to 50 %.[35]

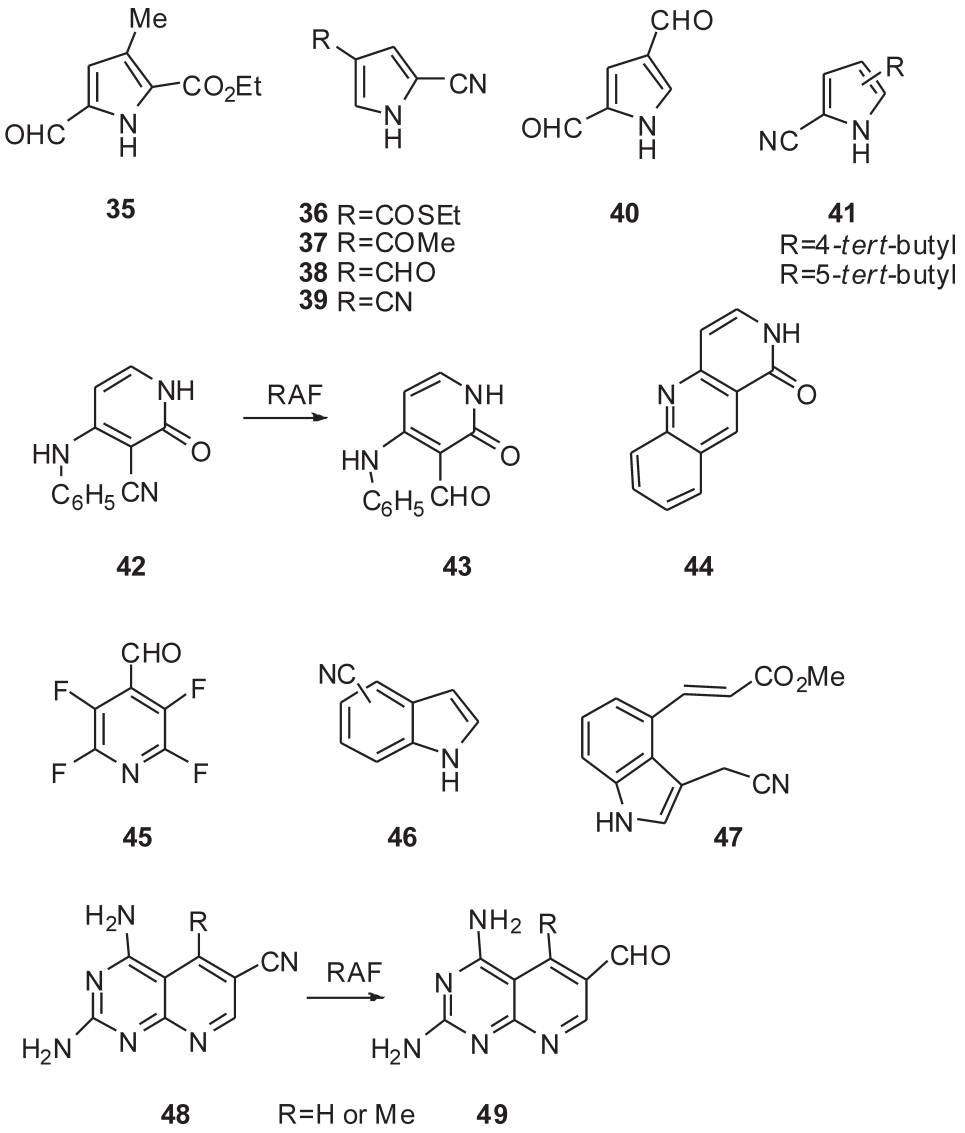
9. Heterocyclic Nitriles

A wide variety[2] of heterocyclic nitriles, on occasion also bearing one or more other chemisensitive functions, have been reduced to the corresponding aldehydes by means of one or other of the RNP, RNF and RAF methods, as exemplified with the following:

9.1. Pyrroles

(i) A final step in the multistep synthesis of an imidazole glycerol phosphate dehydrase inhibitor (IGPDI) possessing a monopyrrole aldehyde moiety, namely, ethyl 5-formyl-3-methyl-1H-pyrrole-2-carboxylate **35** (Scheme 5) involved RNP treatment of the corresponding nitrile at room temperature for 2.5 h to provide the desired aldehyde **35** in 73 % yield.[36]

(ii) Anderson *et al.*[37] reported that Raney alloy in formic acid is a most reliable method for converting 4-substituted 2-pyrrolecarbonitriles to the corresponding 4-substituted-2-pyrrolealdehydes in good yields. In particular, this method cleanly converted (62 %) ethyl 2-cyano-4-pyrrolethiolcarboxylate **36** to ethyl 2-formyl-4-pyrrolethiolcarboxylate without desulphurization of the thiolcarboxylate group. Using the RAF procedure 4-acetyl-2-pyrrolecarbonitrile **37** was converted (82 %) to 4-acetyl-2-pyrrolecarboxaldehyde. Certain of the 4-substituted-2-pyrrolecarboxaldehydes readily tended to decarbonylate when refluxed with W5 Raney nickel in toluene. RAF reduction of 4-formyl-2-pyrrolecarbonitrile[37] **38** and of pyrrole-2,4-dicarbonitrile[38] **39** gave the 2,4-pyrroledicarboxaldehyde **40** in yields of 68 %



Scheme 5

and 56 %,[38] respectively. It was also shown[37] that the 4-*tert*-butyl- and 5-*tert*-butyl-pyrrolecarbonitriles **41**, provided the corresponding aldehydes, 89 % and 70 %, respectively.

9.2. Pyridines

(i) As 3-cyanopyridine is transformed to the aldehyde in 37 % yield, which is substantially lower than that in the reaction with aromatic nitriles (70–97 %),[7] Tugusheva *et al.*[39] decided to study the behaviour of cyano derivatives of 4-aminophenylpyridines under similar reduction conditions, namely, 75 % HCOOH and a large excess of Raney alloy as catalyst. Refluxing the 3-cyano-1,2-dihydro-2-oxo-pyridine derivative **42** with Raney alloy in 50 % formic acid afforded only the pure formyl derivative **43** in 53 % yield. The reaction of **42** in 85 % formic acid and alloy yielded 3-formyl pyridine **43** and also tricyclic product **44**, the latter presumably arising *via in situ* acid-catalyzed cyclization of **43**.

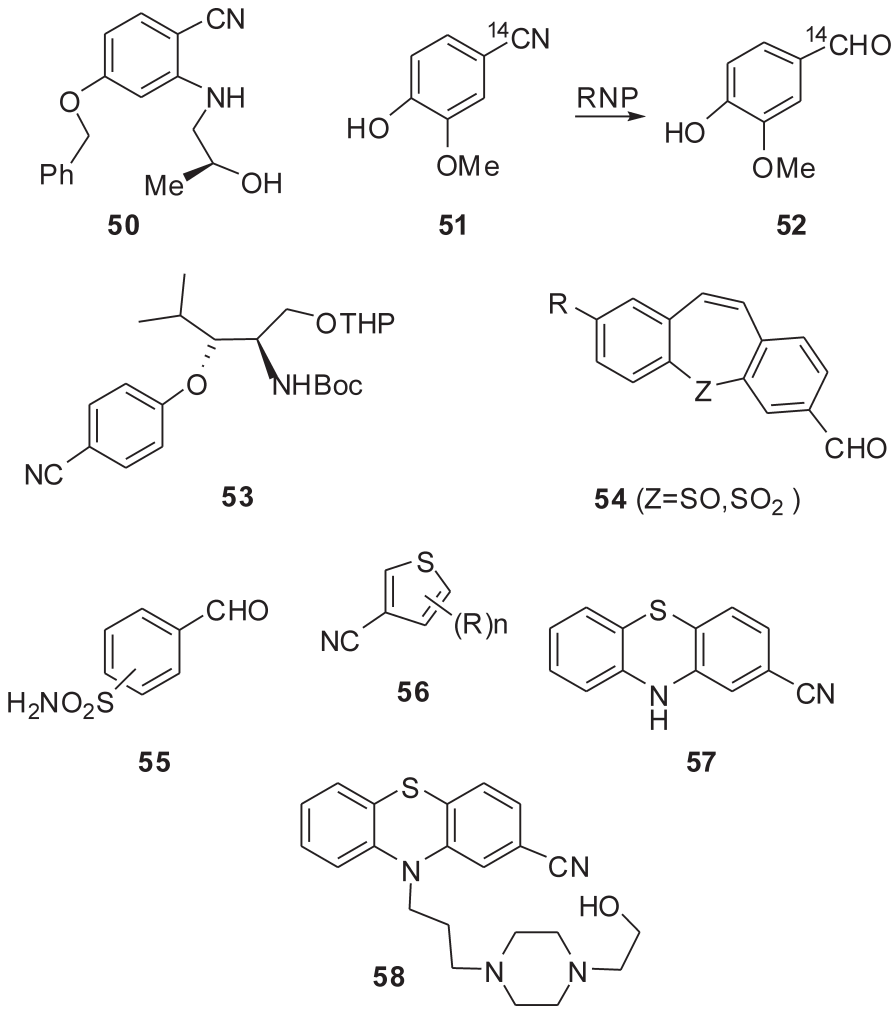
(ii) The highly volatile, sterically hindered, 2,3,5,6-tetrafluoropyridine-4-carbaldehyde **45** that was required in a multistep synthesis of a complex porphyrine, was prepared[40] by several methods that included reduction of the corresponding tetrafluoropyridine-4-carbonitrile with Raney nickel in aqueous formic acid, and by diisobutylaluminium hydride in ether at –20 °C under argon for 14 h. Both reduction methods afforded the desired aldehyde **45** in 45 % yield, with the authors[40] reporting difficulties in controlling the RNF reaction.

(iii) Sanbe[41] set about solving the problem of producing a pyridinecarbaldehyde in good yield within a short time and in which (i) the formation of by-products such as an aminomethylpyridine is inhibited, (ii) the use of hazardous hydrogen and an expensive catalyst such as Pd is not used, and (iii) the reaction is industrially easily controlled. His patented[41] solution included reducing the cyanopyridine by the RNP method (or by a modification thereof) to obtain (92 %) nicotinecarbaldehyde from 3-cyanopyridine.

9.3. Indoles

(i) The 4-, 5-, 6- and 7-cyanoindoles **46** were converted in excellent yields to the corresponding formylindoles by the RNP method.[42]

(ii) Starting from an indol-4-carboxaldehyde, Oppolzer[43] prepared certain not easily accessible ergot alkaloids by a sequence of eleven synthetic operations in overall yield of 14 %. Included in the sequence was the RNP reduction (45 °C, 1.5 h) of a nitrile intermediate **47** to give the corresponding aldehyde in 90 % yield.



Scheme 6

9.4. Pyrimidines

Piper *et al.*[44] obtained the 2,4-diamino-pyrido[2,3-d]pyrimidine-6-carboxaldehydes **49** in good yields by adding a solution of the corresponding nitriles **48** in 95–97 % formic acid in a thin stream with stirring to damp Raney nickel and stirring the mixture at 75–80 °C for 1.5 h. Later, Gaffner-Norberg *et al.*[45] synthesized the aldehydes **49** by refluxing the appropriate nitrile with Raney alloy in 75 % formic acid for 75 min. It is noteworthy that formamide derivatives were not obtained in either instance.

10. Substituted Benzonitriles

(i) In an example[46] of a relatively large-scale (multimolar) RNP reduction, Raney nickel (500 g of a 50 % aqueous suspension) was added to a stirred solution of 4-benzyloxy-2(*R*)-(2-hydroxypropylamino)benzonitrile **50** (Scheme 6) (790 g, 2.8 mol) and sodium hypophosphite monohydrate (986 g, 11.2 mol) in 7 L of a 2:1:1 pyridine-acetic acid-water mixture and stirring was continued at 45 °C for 7 h to give the aldehyde (722 g) in 90 % yield.

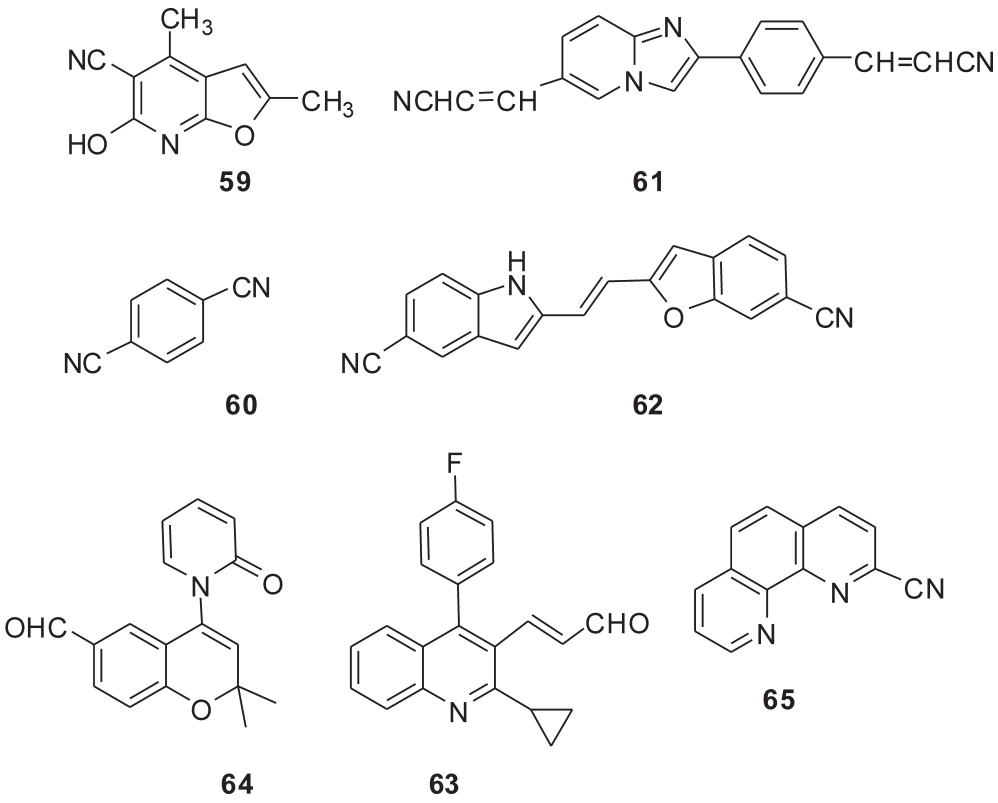
(ii) Hydroxybenzaldehydes labelled in the carbonyl group with ^{14}C were synthesized[47] in a simple 3-step reaction whereby Cu^{14}CN converted a bromophenol to a hydroxyarylnitrile (nitrile ^{14}C) **51** which, when purified, was reduced with RNP (45 °C, 2 h) to the corresponding hydroxybenzaldehyde (carbonyl ^{14}C) **52** in ~90 % yield. The authors[47] confirm that protection of the hydroxyl group(s) in this substrate nitrile is not necessary in this instance.

(iii) Raney nickel (W-2 activity) was added[48] to a mixture of Boc-protected 4-[1*S*, 2*R*]-2-amino-1-isopropyl-3-(tetrahydropyran-2-yloxy)benzonitrile **53** in pyridine:acetic acid:water (2:1:1) containing sodium hypophosphite, at 0 °C under argon. The suspension was stirred for 15 min at 0 °C and then warmed to 40 °C, where it was maintained for 2 h. Work-up provided the corresponding aldehyde as a colourless, sticky foam (93 %). The inertness of these particular protecting groups and of the aldehyde function in this reduction is noteworthy.

11. Sulphur-substituted Nitriles

Thiols and thioethers can be desulphurized by hydrogenolysis with Raney nickel and hydrogen (either adsorbed on the metal surface or applied with the metal catalyst); in general, hydrogenolysis of the carbon-sulphur bond is carried out using excess Raney nickel in refluxing ethanol or dioxin.[2a,17]

Novel dibenzo[b,f]thiepin-3-carboxaldehydes (Z=sulphinyl or sulphonyl), of type **54** and the corresponding 10,11-dihydro compounds, which were required for testing as prostaglandin antagonists useful in treating a variety of conditions such as allergic asthma, were prepared by RAF and RNP reductions of the appropriate nitrile.[49] Thus, in the instance of dibenzo-[b,f]thiepin-3-carboxaldehyde-5,5-dioxide (**54**, Z=SO_2, R=H), the selected nitrile was refluxed with Raney alloy in 80 % formic acid for 4 h, or was stirred with sodium hypophosphite in a pyridine/acetic acid/water mixture at 25 °C for 24 h and then at 45–50 °C for 2 h. RNP reduction yielded the respective aldehyde



Scheme 7

from each of (i) 8-amino-3-cyano-dibenzo[b,f]thiepin-5,5-dioxide, (ii) 3-cyano-8-hydroxy-dibenzo[b,f]thiepin and (iii) 3-cyano-8-hydroxy-dibenzo[b,f]thiepin-5,5-dioxide (in unspecified yields).

The preparation of 4-sulphamoylbenzaldehyde, **55** has been achieved by a number of disparate means:[8] by chromic acid oxidation of 4-toluenesulphonamide, by the Sommelet reaction on 4-chloromethylbenzenesulphonamide, by the Stephen reaction, and by the RAF reduction of 4-sulphamoylbenzonitrile. The latter procedure[8] was subsequently utilized[50] to reduce 3-sulphamoylbenzonitrile to the 3-sulphamoylbenzaldehyde.

Harada *et al.*[51] patented a process for manufacturing thiophenecarboxaldehydes: the title compounds **56** (n=0-3; R=substituent which does nor participate in the reaction) were prepared by reducing the appropriate thiophenecarbonitrile derivative by the RNF method. Thus, a mixture of 3-thiophenecarbonitrile (n=0), aqueous formic acid and Raney nickel was stirred at 60 °C for several hours to give 3-thiophenecarboxaldehyde in 85.6 % yield.

Bossle *et al.*[52] converted phenothiazine-2-carbonitrile **57** to the corresponding phenothiazine-2-carboxaldehyde (44 %) by refluxing in Raney alloy-aqueous formic acid mixture: the *N*-substituted phenothiazine nitrile **58** likewise gave the corresponding aldehyde (35 %).

12. Miscellaneous Nitriles

VanSickle and Rapoport[53] reported that reductions (using RAF and RNP) in acidic or buffered media led to the destruction of the nitrile **59** (Scheme 7) and treatment with DIBAlH gave only the recovered nitrile; presumably the sterically congesting *ortho* substituents of the pyridol inhibit delivery of the hydrogen to the nitrile.

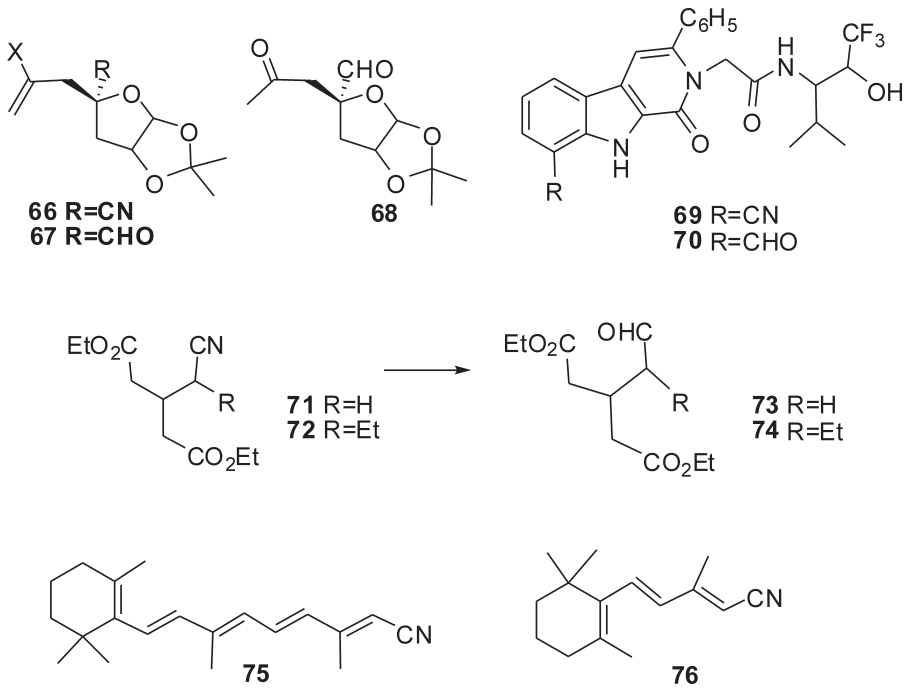
Dinitriles such as terephthalonitrile[7] **60**, pyrrole-2,4-dicarbonitrile[38] **39** (*vide supra)* and nitrile **62** (*vide infra*) have been successfully reduced to the corresponding dialdehydes by the RNP and RAF methods. However, similar attempts[54] to convert the bis-unsaturated nitrile **61** gave the desired dialdehyde in modest yields. In the case of cyanobenzofuran-indolecarbonitrile derivative **62**, RNP reduction led to the corresponding dicarboxaldehyde in >70 % (estimated) yield.[55] 3-[2-Cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]prop-2-enal **63** was prepared (80–90 %) by reducing the corresponding nitrile with (i) Raney nickel in formic acid and (ii) Raney nickel in the presence of an amine salt of formic acid or a lower aliphatic acid having 2 to 5 carbon atoms; the (patented)[56] process is simple and industrially advantageous.

6-Formyl-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2H-1-benzopyran **64**, an analogue of bimakalim, was prepared[57] in 85 % yield by RNP treatment (45 °C, 2 h) of the corresponding nitrile. Sun *et al.*[58] reported that attempts to convert 2-cyano-1,10-phenanthroline **65** into the aldehyde by employing the RNP, RNF and RAF methods, respectively, were not successful, and the aldehyde was eventually obtained *via* another synthetic methodology.

Kuhn *et al.*[59] transformed nitrile **66** (Scheme 8) to the corresponding aldehyde **67** (34 %) by treating with DIBAlH at –78 °C in toluene, and also in 30 % yield (along with starting nitrile and methyl ketone **68**) using the Moffatt[30] modification of the RNP reduction procedure (*vide supra*). Compound **69**, bearing a cyano group, and a variety of other chemosensitive functions also liable to be affected by conventional metallic hydride reductants, when treated by the RNP method (60 °C, 2 h) gave the corresponding aldehyde **70** in ~80 % yield.[60]

Synthetic efforts directed to the preparation of certain 3-acetonyl- and 3-(2-oxoethyl)-glutarates were explored by Amat *et al.*[61] and involved the reduction of nitriles **71** and **72** using the RNP method (50 °C, 5 h). From **71** was obtained aldehyde **73** (64 %) and from **72** was obtained a 4:1 mixture of aldehyde **74** and unchanged nitrile.

Hoffmann-La Roche reported[62] that the RNP method [with



Scheme 8

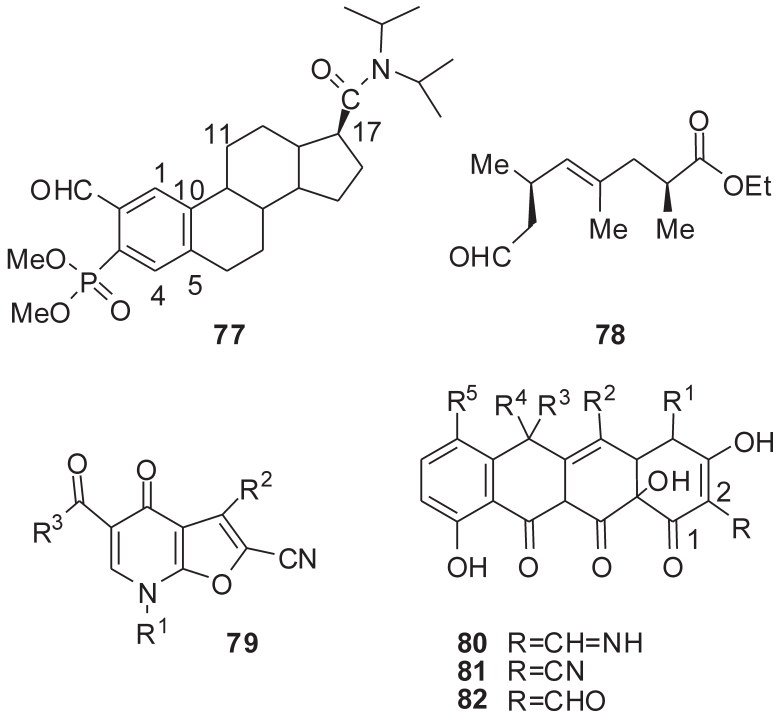
sodium hypophosphite misrepresented in *Chemical Abstracts*[62] as Na_3PO_2 (*cf.* Pizey[2a])], converted vitamin A nitrile **75** to vitamin A aldehyde (~90 %), and β-ionylidine acetonitrile **76** to its aldehyde (~90 %).

A phosphonic acid-substituted aromatic A ring analogue of certain steroidal synthetic compounds, *viz.*, dimethyl-2-formyl-17β-(*N*,*N*-diisopropylcarboxamide)-estr-1,3,5(10)-triene-3-phosphonate **77** (Scheme 9) was prepared[63] by reducing the corresponding 2-cyano derivative with Raney nickel and formic acid.

Aldehyde **78**, a crucial fragment in an enantioselective, divergent total synthesis[64] of the 19-membered depsipeptide (+) jasplakinolide, was obtained (81 %, after chromatographic purification), by RNP (50 °C, 6 h) reduction of the corresponding nitrile.

In the course of synthesizing[65] 4-oxo-4,7-dihydrofuro[2,3-b] pyridine-5-carboxamide derivatives of type **79** (R^3=NHR^4) for testing as antiviral agents, the 2-cyano ester **79** (R^1=Me, R^2=H, R^3=OEt) was treated with Raney nickel and sodium hypophosphite in pyridine/acetic acid/water (1:1:1) at 60 °C for 1 h to provide (~75 %) the corresponding aldehyde.

In all the aforementioned examples, the aldehyde end-product is generally[2] considered to arise from *in situ* acid hydrolysis of an imine intermediate. Korst[66] reported obtaining substituted 2-iminotetracyclines (of type **80**) in good yields from the corresponding 2-cyanotetracyclines **81** using activated (W-2)



Scheme 9

nickel catalyst[9] and aqueous formic acid. This is illustrated by the following: nitrile **81** (R^1=dimethylamino, R^2=R^3=R^4=R^5=H) (2.0 g) was stirred with the nickel catalyst (2.0 g) in 75 % aqueous formic acid (30 mL) at ~50 °C for 45 min under a nitrogen atmosphere to give the corresponding imine (**80**) which was isolated by extraction or by conversion to an acid salt (e.g. ~2.1 g, from use of *p*-toluenesulphonic acid; analyzing correctly for $C_{28}H_{30}N_2O_9S$). Korst[66] proposed that the tetracycline-2-imines surprisingly so obtained resisted acid hydrolysis because the imino group forms an (intramolecular) hydrogen bond with an enolized β-keto group, thereby resisting hydrolysis to the aldehyde function. The 2-formyltetracyclines (**82**) were therefore prepared[66] from the corresponding 2-imines (**80**) by treating the latter compounds with dilute base for several minutes at room temperature followed by acidification of the reaction mixture, which caused the 2-formyltetracycline to separate.

13. Conclusions

The preferred application of one or other of the RNP, RNF and RAF methods to reduce the cyano group to aldehyde in a wide variety of structural types is now well established[2] (*vide supra*). The content should particularly appeal to chemists interested in this functional group transformation and it is hoped that it will stimulate further interest in aspects of the reduction, and suggest alternatives and offer options in their own investigations.

References

1 J.S. Cha, S.H. Jang and S.Y. Kwon, *Bull. Korean Chem. Soc.,* 2002, **23**, 1697–1698.

2 (a) J.S. Pizey, *Synthetic Reagents,* vol. 2, John Wiley & Sons, New York, USA, 1974, pp. 230–232; (b) L.K. Keefer and G. Lunn, *Chem. Rev.,* 1989, **89**, 459–502; (c) R.O. Hutchins and M.G.K. Hutchins, *The Chemistry of Triple-bonded Functional Groups,* part 1, (S. Patai and Z. Rappoport, eds.), John Wiley & Sons, New York, USA, 1983; (d) C. Harcken, *Science of Synthesis,* 2006, **25**, 65–135; (e) *Comprehensive Organic Functional Group Transformations* 2, (A.R. Katritzky and R.J.K. Taylor, eds.), vol. 3, part 1, Elsevier, Amsterdam, 2005, pp. 31–78.

3 H. Stephen, *J. Chem. Soc.*, 1925, **127**, 1874–1877.

4 S. Pietra and C. Trinchera, *Gazz. Chim. Ital.,* 1955, **85**, 1705–1709.

5 O.G. Backeberg and B. Staskun, *J. Chem. Soc.,* 1962, 3961–3963.

6 B. Staskun and O.G. Backeberg, *J. Chem. Soc.,* 1964, 5880–5881.

7 T. van Es and B. Staskun, *J. Chem. Soc.,* 1965, 5775–5777.

8 T. van Es and B. Staskun, *Org. Synth.,* 1971, **51**, 20–23.

9 R. Mozingo, *Org. Synth.,* 1955, collective vol. **3**, p. 181.

10 H.M. Meshram, Y.S.S. Ganesh, K.C. Sekhar and J.S. Yadav, *Synlett,* 2000, **7**, 993–994.

11 R. Sala, G. Doria and C. Passarotti, *Tetrahedron Lett.,* 1984, **25**, 4565–4568.

12 S.K. Boyer, J. Bach, J. McKenna and E. Jagdmann, Jr., *J. Org. Chem.,* 1985, **50**, 3408–3411.

13 K. Ishimoto,Y. Mitoma, S. Nagashima, H. Tashiro, G.K. Surya Prakash, G.A. Olah and M. Tashiro, *Chem. Commun.,* 2003, 514–515.

14 D.C. Gowda, S. Gowda and K. Abiraj, *Ind. J. Chem.,* 2003, **42B**, 1774–1776.

15 V.S. Bezborodov and U.M. Kauhanka, *Chem. Abstr.,* **143**: 172597 (2005).

16 B.T. Khai and A. Arcelli, *J. Org. Chem.,* 1989, **54**, 949–953.

17 M. Node, K. Nishide, Y. Shigeta, K. Obata, H. Shiraki and H. Kunishige, *Tetrahedron,* 1997, **53**, 12883–12894.

18 T.R. Hoye, M. Chen, B. Hoang, L. Mi and O.P. Priest, *J. Org. Chem.,* 1999, **64**, 7184–7201.

19 D. Monti, P. Gramatica, G. Speranza and P. Manitto, *Tetrahedron Lett.,* 1983, **24**, 417–418.

20 D.C. Gowda, A.S.P. Gowda, A.R. Baba and S. Gowda, *Synth. Commun.,* 2000, **30**, 2889–2895.

21 S. Gowda and D.C Gowda, *Tetrahedron,* 2002, **58**, 2211–2213.

22 B. Glatz, G. Helmchen, H. Muxfeldt, H. Porcher, R. Prewo, J. Senn, J.J.Stezowski, R.J. Stojda and D.R. White, *J. Am. Chem. Soc.,* 1979, **101**, 2171–2181.

23 A.M. Thompson, G.W. Rewcastle, S.L. Boushelle, B.G. Hartl, A.J. Kraker, G.H. Lu, B.L. Batley, R.L. Panek, H.D.H. Showalter and W.A. Denny, *J. Med. Chem.,* 2000, **43**, 3134–3147.

24 E. Bisagi, C. Ducrocq, C. Rivalle, P. Tambourin, J.-C. Chermann and L. Montogrier, US Patent 4 444 776, 1984.

25 J.L. Hicks, *J. Labelled Compd. Radiopharm.*, 1995, **36**, 1029–1035.

26 J.C. Sircar, C.R. Kostlan, R.B. Gilbertsen, M.K. Bennett, M.K. Dong and W.J. Cetenko, *J. Med. Chem.*, 1992, **35**, 1605–1609.

27 G.W. Gribble, *Reductions in Organic Synthesis: Recent Advances and Practical Applications,* ACS Symposium Series 641 (A.F. Abdel-Magid, ed.), American Chemical Society, Washington, DC, USA, 1996, p.184.

28 R.S. Compagnone and H. Rapoport, *J. Org. Chem.*, 1986, **51**, 1713–1719.

29 A. Cerri, N. Almirante, P. Barassi, A. Benicchio, G. Fedrizzi, P. Ferrari, R. Micheletti, L. Quadri, E. Ragg, R. Rossi, M. Santagostino, A. Schiavone, F. Serra, M.P. Zappavigna and P. Melloni, *J. Med. Chem.,* 2000, **43**, 2332–2349.

30 H.P. Albrecht, D.B. Repke and J.G. Moffatt, *J. Org. Chem.,* 1973, **38**, 1836–1840.

31 H.-M. Dettinger, G. Kurtz and J. Lehmann, *Carbohydr. Res.,* 1979, **74**, 301–307.

32 (a) M. Toth, K.E. Kover, A. Benyei and L. Somsak, *Org. Biomol. Chem.,* 2003, **1**, 4039–4046; (b) M. Toth and L. Somsak, *Carbohydr. Res.,* 2003, **338**, 1319–1325.

33 R.R. MacGregor, J.S. Fowler, A.P. Wolf, C.-Y. Shiue, R.E. Lade and C.-N. Wan, *J. Nucl. Med.,* 1981, **22**, 800–803.

34 C.-Y. Shiue and A.P. Wolf, *J. Labelled Compd. Radiopharm.*, 1985, **22**, 171–182.

35 D. Bender and A.D. Gee, *J. Labelled. Compd. Radiopharm.,* 1998, **41**, 287–300.

36 M. Shimizu, A. Takahashi and S. Kawai, *Org. Lett.,* 2006, **8**, 3585–3587.

37 H.J. Anderson, C.R. Riche, T.G. Costello, C.E. Loader and G.H. Barnett, *Can. J. Chem.,* 1978, **56**, 654–657.

38 G.H. Barnett, H.J. Anderson and C.E. Loader, *Can. J. Chem.,* 1980, **58**, 409–411.

39 N.Z. Tugusheva, L.M. Alekseeva, A.S. Shashkov, V.V. Chernyshev and V.G. Granik, *Russ. Chem. Bull.,* 2006, **55**, 1475–1486.

40 S.K. Namgoong, J.-S. Lee, J.-H. Shin, S.C. Moon, B.H. Jung, H.S. Kim and B.S. Yu, *Bull. Korean Chem. Soc.,* 2000, **21**, 264–266.

41 O. Sanbe, Japanese Patent 168 743, 2004.

42 F. Troxler, A. Harnisch, G. Bormann, F. Seemann and L. Szabo, *Helv. Chim. Acta,* 1968, **51**, 1616–1628.

43 W. Oppolzer, *Pure Appl. Chem.,* 1981, **53**, 1181–1201.

44 J.R. Piper, G.S. McCaleb, J.A. Montgomery, R.L. Kisliuk, Y. Gaumont and F.M. Sirotnak, *J. Med. Chem.,* 1986, **29**, 1080–1086.

45 M. Graffner-Nordberg, K. Kolmodin, J. Aqvist, S.F. Queener and A. Hallberg, *J. Med. Chem.,* 2001, **44**, 2391–2402.

46 H.-H. Chen, J.A. May, and B.S. Severns, US Patent 6 696 476, 2004.

47 G. Billek, H. Kindl, A. Schimpl and F.P. Schmook, *J. Labelled Compd.,* 1969, **5**, 3–7.

48 S.P. East, F. Shao, L. Williams and M.M. Joullie, *Tetrahedron,* 1998, **54**, 13371–13390.

49 J. Rokach, US Patent 4 535 171, 1985.

50 I. Huc and J.-M. Lehn, *Proc. Nat. Acad. Sci. USA,* 1997, **94**, 2106–2110.

51 K. Harada, S. Nishino, T. Murakami, Y. Fukuda, K. Hirotsu and Y. Yamanaka, Japanese Patent 181 277, 2001.

52 P.C. Bossle, C.P. Ferguson, W.E. Sultan, W.J. Lennox, G.E. Dudley, T.H. Rea and J.I. Miller, *J. Med. Chem.,* 1976, **19**, 370–373.

53 A.P. VanSickle and H. Rapoport, *J. Org. Chem.,* 1990, **55**, 895–901.

54 R.J. Sundberg, S. Biswas, K.K. Murthi, D. Rowe, J.W. McCall and M.T. Dzimianski, *J. Med. Chem.,* 1998, **41**, 4317–4328.

55 J.S. Lazo, R. Nunes, J.J. Skoko, P.E. Queiroz de Oliveira, A. Vogt and P. Wipf, *Bioorg. Med. Chem.,* 2006, **14**, 5643–5650.

56 K. Harada, S. Nishino, H. Shima, T. Harada and N. Okada, US Patent 6 630 591, 2003.

57 R. Mannhold, G. Cruciani, H. Weber, H. Lemoine, A. Derix, C. Weichel and M. Clementi, *J. Med. Chem.,* 1999, **42**, 981–991.

58 W.-H. Sun, S. Jie, S. Zhang, W. Zhang, Y. Song, H. Ma, J. Chen, K. Wedeking and R. Fröhlich, *Organometallics,* 2006, **25**, 666–677.

59 C. Kuhn, L. Skaltsounis, C. Monneret and J.-C. Florent, *Eur. J. Org. Chem.,* 2003, **14**, 2585–2595.

60 C.A. Veale, J.A. Damewood, Jr., G.B. Steelman, C. Bryant, B. Gomes and J. Williams, *J. Med. Chem.,* 1995, **38**, 86–97.

61 M. Amat, O. Bassas, M. Canto, N. Llor, M.M.M. Santos and J. Bosch, *Tetrahedron,* 2005, **61**, 7693–7702.

62 F. Hoffmann-La Roche & Co., A.G., *Chem. Abstr.,* **62**: 9182g (1965).

63 D.A. Holt, M.A. Levy and B.W. Metcalf, US Patent 4 882 319, 1989.

64 A.K. Ghosh and D.K. Moon, *Org. Lett.,* 2007, **9**, 2425–2427.

65 M.M. Cudahy, M.E. Shnute, S.P. Tanis, W.R. Perrault, P.M. Herrinton and S.K. Nair, US Patent 6 878 705, 2005.

66 J.J. Korst, US Patent 3 584 044, 1971.