Tetrahedron Vol. 35, pp. 1675 to 1735
Pergamon Press Ltd., 1979. Printed in Great Britain

TETRAHEDRON REPORT NUMBER 67

THE CHEMISTRY OF FORMAMIDE ACETALS

R. F. ABDULLA* and R. S. BRINKMEYER
Lilly Research Laboratories, Division of Eli Lilly & Company, Greenfield, IN 46140, U.S.A.

(*Received in UK 25 January* 1979)

Abstract—The formamide acetals enter into two main categories of reactions, namely alkylation and formylation. As alkylating agents, they have been used in the synthesis of esters from acids, ethers and thioethers from phenols and aromatic and heterocyclic thiols, and the alkylation of active methines. As formylating agents, formamide acetals are useful in the synthesis of enamines from active methylenes and amidines from amines and amides. Also formamide acetals are efficient reagents for the conversion of α-hydroxycarboxylic acids to alkenes while *trans-vic*-diols yield epoxides. The above conversions as well as othere listed in the review proceed in almost all cases under mild conditions in high yields making these reagents valuable synthetic tools.

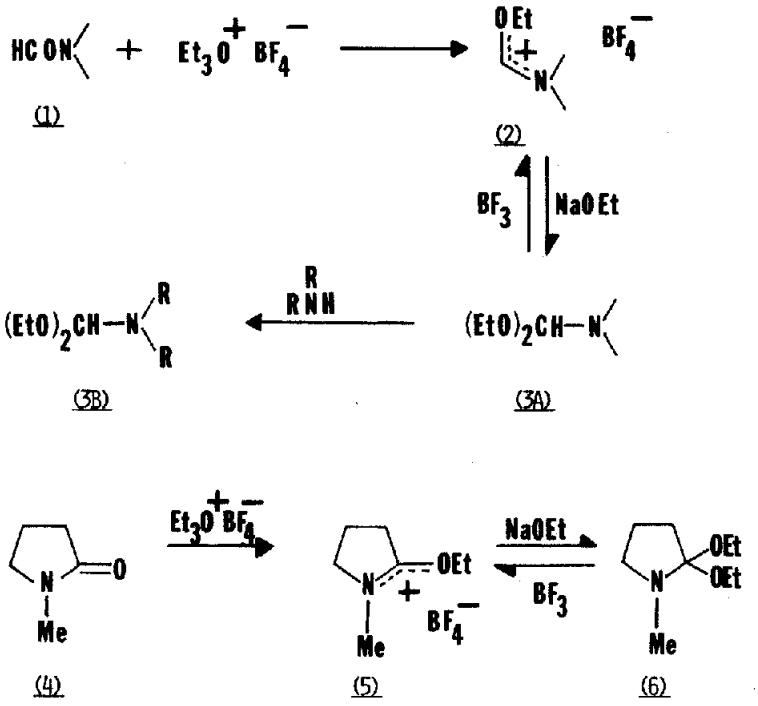
CONTENTS

INTRODUCTION

Since the preparation of N,N-dimethylformamide diethyl acetal, first reported by Meerwin *et al.*,[1] a plethora of transformations have appeared in the literature employing formamide acetals and their derivatives. In addition, a number of useful synthetic procedure are available in the literature for the preparation of formamide and other amide acetals. This review aims at reporting the methods of preparation and the major classes of reactions entered into by the formamide acetals.

THE SYNTHESIS OF FORMAMIDE ACETALS AND THEIR DERIVATIVES

While exploring the chemistry of triethyloxonium fluoroborate, Meerwein *et al.*[1] discovered that this reagent complexed with N,N-dimethylformamide (**1**) to afford a tetrafluoroborate salt (**2**). Treatment of **2** with sodium in ethanol gave N,N-dimethylformamide diethyl acetal (**3a**). A similar sequence of reactions with N-methyl-2-pyrrolidone (**4**) gave the corresponding acetal (**6**) via the cationic intermediate (**5**). The reversibility of these transformations by treatment of either **3a** or **6** with boron trifluoride, thus providing the cationic species (**2** or **5**), respectively, was noted by Meerwein[1] (Scheme 1). They also observed that

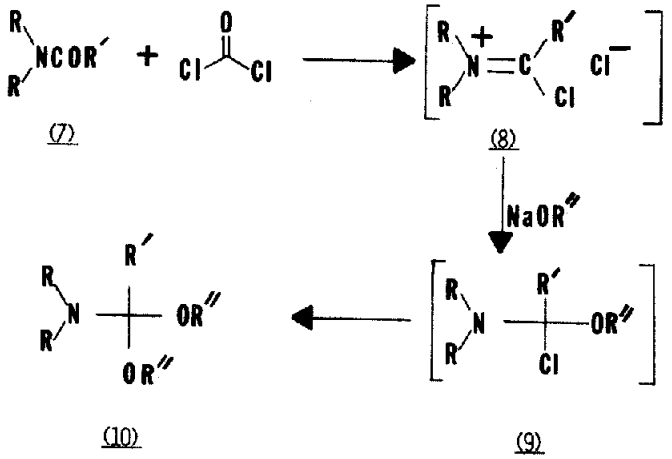


Scheme 1.

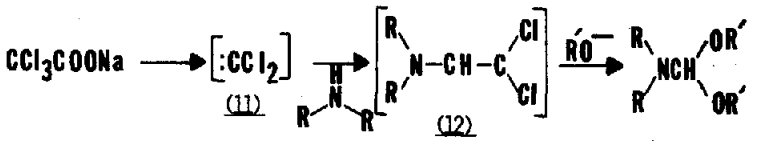
upon refluxing the lower dialkylamide acetals undergo an amine exchange with high boiling secondary amines, such as morpholine, to give the higher dialkylamide acetals (**3b**) in 50–60% yield.

In 1960 Eilingsfeld *et al.*[2] reported the synthesis of eight amide acetals from imidoyl chlorides generated from N,N-dialkylamides (**7**) and phosgene, thionyl chloride or phosphorus pentachloride. The imidoyl chlorides (**8**) were converted with two equivalents of an alkoxide to the desired acetals (**10**) via intermediate amidoester chlorides (**9**). Some additional amide acetals not reported by Eilingsfeld were prepared by Zollinger *et al.*[3] using this method. The respective yields and b.ps of amide acetals prepared by the above methods are shown in Table 1.

Stiltz[4] has synthesized amide acetals from the dichloroamine intermediate (**12**). This intermediate was prepared by the reaction of dichlorocarbene (**11**) with a dialkylamine. The dichloroamine can then be treated with an alkoxide to give the amide acetal. Details of this reaction, however, have not been published.

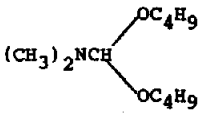
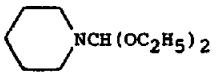
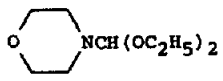
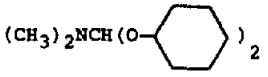


Scheme 2.

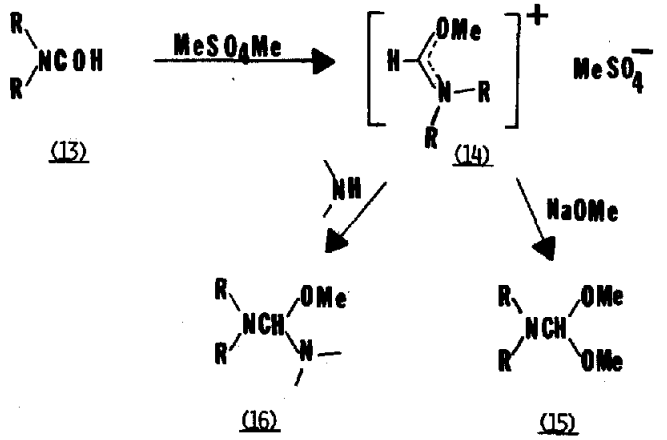


Scheme 3.

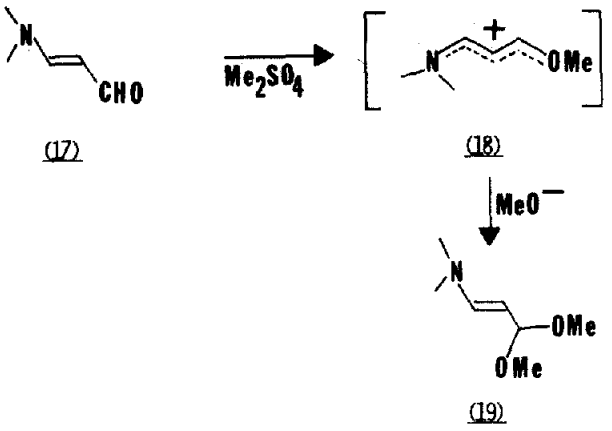
Table 1. Formamide acetals generated from N,N-dialkylformamides

Structure	% Yield	Reference
$(CH_3)_2NCH(OC_2H_5)_2$	60 73	2 1
$(CH_3)_2NCH(OCH_3)_2$	55	2
$(CH_3)_2NCH(OCH_2CH_2CH_3)_2$	27	2
	-	1
$(C_2H_5)_2NCH(OC_2H_5)_2$	35	2
	73	2
	52 64	1 1
	35	3
$(CH_3)_2NCH(OCH_2C_6H_5)_2$	30	3

The alkylation of amides (**13**) with dimethyl sulfate affords a cation (**14**). Alcoholysis of cation **14** afforded amide acetals (**15**) while aminolysis gave the aminal esters (**16**).[5] This process was extended to include the synthesis of the novel vinylogous amide acetals, such as **19**.[6] In this case the exothermal reaction at room temperature between dimethyl sulfate and *trans*-dimethylamino-acrolein (**17**) resulted



Scheme 4.



Scheme 5.

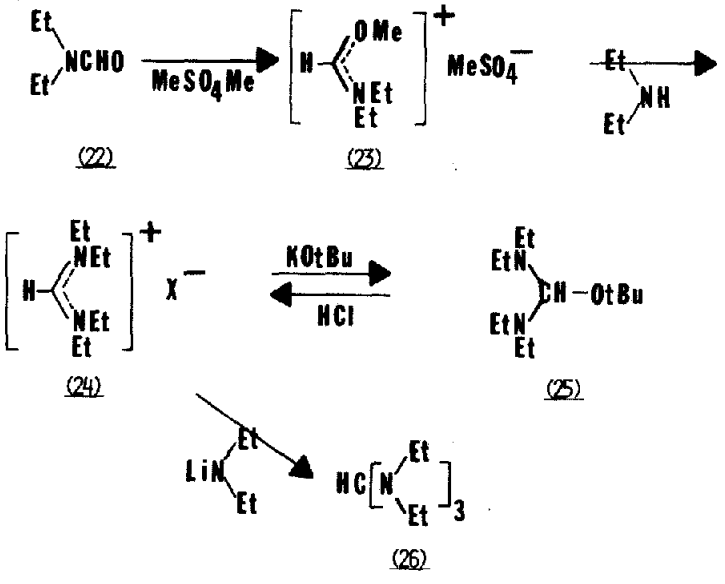
in the delocalized cationic adduct (**18**). Cation **18** reacted readily at ambient temperatures with alkoxides to give the acetal **19**.

The tris(dialkylamino)methanes behave similarly in some respects to the amide acetals and are more effective in analogous conversions. Therefore, their preparation deserves comment. The first synthesis of authentic compounds of the type $(R_2N)_3CR^1$ (**21**) was reported by Weingarten *et al.*[7] from dimethylformamide (**1**) and tetrabis(dimethylamino) titanium (**20**) in ether at 25° in 83% yield.

Subsequently, Bredereck *et al.*[8] published a controlled, stepwise synthesis of tris(dialkylamino)methanes.

In this synthesis, reaction of the formamide **22** with dimethylsulfate afforded the adduct **23**. Upon treatment with one mole of diethylamine, compound **23** gave the resonance stabilized amidinium cation **24** ($X = CH_3SO_4^-$). When **24** ($X = CH_3SO_4^-$) was treated with potassium t-butoxide, the aminal ester **25** was obtained. The amidinium ion **24** ($X = Cl^-$) could be regenerated from the aminal ester **25** by treatment with hydrochloric acid. Similarly, when **24** (X = Cl) was reacted with lithium diethyl amide, the

Scheme 6.



Scheme 7.

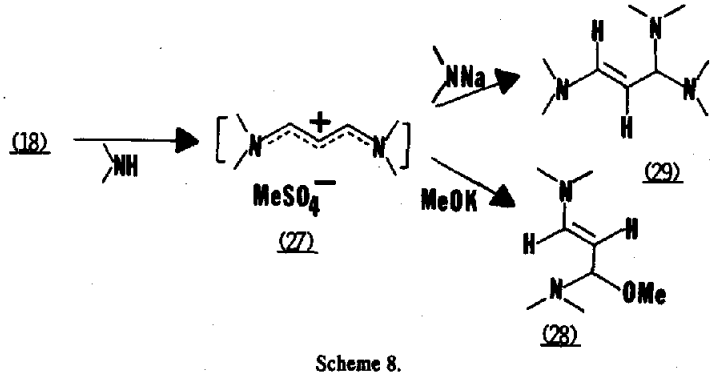
Table 2. Synthesis of tris(dialkylamino)methane and aminal esters

Compound	% Yield	References
$CH[N(CH_3)_2]_3$	67	8
$CH[N(CH_2CH_3)_2]_3$	26	8
$N(CH_2CH_3)_2$ $CH[N(CH_3)_2]_2$	42	8
$N(CH_3)_2$ $CH[N(CH_2CH_3)_2]_2$	37	8
$CH[N(CH_2CH_2CH_3)_2]_3$	11	8
CH_3 $N-C_6H_5$ $CH[N(CH_3)_2]_2$	76	8
CH_3 $N-C_6H_5$ $CH[N(CH_2CH_3)_2]_2$	45	8
OCH_3 $CH[N(CH_3)_2]_2$	62	11
$OC(CH_3)_3$ $CH[N(CH_2CH_3)_2]_2$	47	8
OCH_2CH_3 $CH[N(CH_3)_2]_2$	60	11
$OCH_2CH_2CH_3$ $CH[N(CH_3)_2]_2$	60	11
$OCH(CH_3)_2$ $CH[N(CH_3)_2]_2$		11
$OC(CH_3)_3$ $CH[N(CH_3)_2]_2$		11

tris(diethylamino)methane (**26**) was obtained. Table 2 lists the amide aminals and aminal esters prepared by these methods.

These reactions were successfully extended to the vinylogous aminal esters and amideaminals.[6,9]

Thus, dimethyl-3-dimethylaminoprop-1-enylideneammonium methyl sulfate (**27**), generated from **18** via aminolysis with dimethylamine, reacts with potassium methoxide to give the vinylogous aminal ester **28**. Treatment with sodium dimethylamide provided the vinylogous amide aminal **29**. both **28** and **29** are more reactive than the earlier described vinylogous amide acetal **19** (Scheme 5). Table 3 lists the vinylogous amide acetals, aminal esters and amide aminals made by this method.[6]



Scheme 8.

Table 3. Vinylogous amide acetals, aminal esters and amide aminals[6]

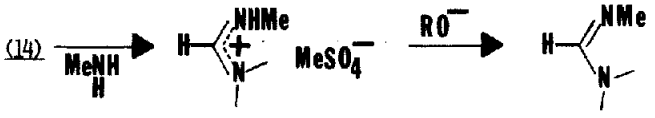
Compound	% Yield
$CH(CH=CH-N(CH_3)_2)(CH(OCH_3)_2)$	65
$CH_3C(CH=C(CH_3)[N(CH_3)_2])(OCH_3)_2$	46
$CH(CH=CH-N(CH_3)_2)(CH(OCH_2CH_3)_2)$	80
$CH(N(CH_3)_2)(OCH_3)(CH=CH-N(CH_3)_2)$	60
$CH(N(CH_2CH_3)_2)(OCH_2CH_3)(CH=CH-N(CH_2CH_3)_2)$	51
$CH(CH=CH-N(CH_3)_2)(CH[N(CH_3)_2]_2)$	61
$CH(CH=CH-N(CH_2CH_3)_2)(CH[N(CH_2CH_3)_2]_2)$	20

Bredereck *et al.* had described the synthesis of N,N,N′-tri-substituted amidinium salts through the condensation of N,N-disubstituted acid amides with $POCl_3$ and primary aromatic and alipathic amines.[10] A similar condensation may be effected with the dimethyl sulfate adducts, such as **23** (Scheme 6) or **14** (Scheme 4), but the intermediate amidinium salts obtained could not be converted to orthoamide derivatives. Instead treatment with alkoxides converts the amidinium salts derived from primary amines to amidines (**30**) via deprotonation.[11]

The tris(dialkylamino)methanes and other trisaminomethanes for numerous carboxylic acids have been prepared by Bredereck,[12] including those derived from formic acid morpholides.

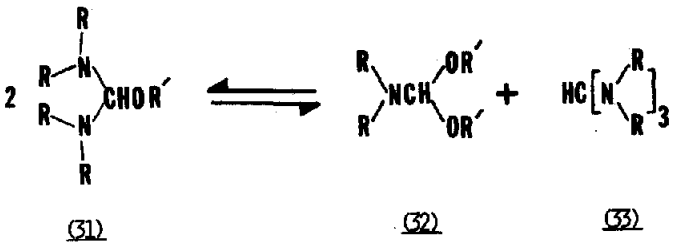
The existence of orthoamide derivatives as ion pairs has some implications regarding the stability of these reagents. Bredereck *et al.*[12,13] have commented on the disproportionation of animal esters such as **31** into acetals (**32**) and tris(dialkylamino)methanes (**33**). This reaction is reversible (Scheme 10).

When pure, the bis(dialkylamino)alkoxymethanes (**31**) are stable at ambient temperatures for periods greater than 7 days. However, at elevated temperatures (e.g. attempted distillation at 50°–80°, 12 mm) up to 25% disproportionation was measured by NMR analysis. Similar results were observed when the aminal esters were incubated in a sealed vessel at 100° for 4 hr. The reverse reaction, viz the recombination of the acetals (**32** with the tris(dialkylamino)methanes **33** to give the aminal esters **31**), was also facile at 100°. Mixtures of **32** and **33**, in equimolar amounts, gave up to 64% of the aminal ester



(30)

Scheme 9.

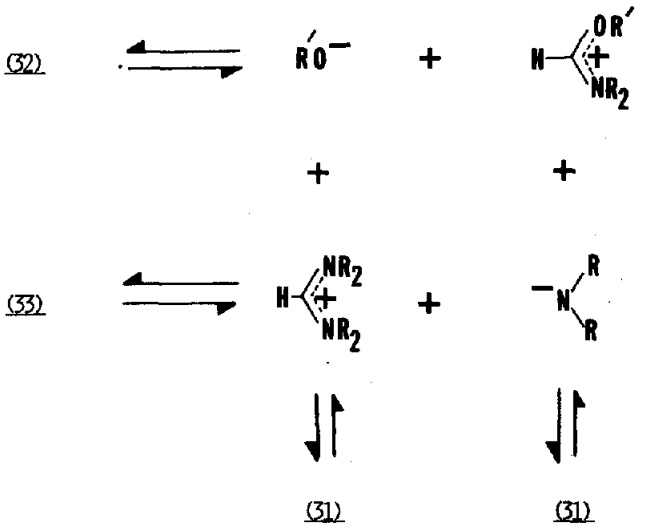


(31) (32) (33)

Scheme 10.

based on the NMR of the mixture. These results are best rationalized by the mechanism outlined in Scheme 11. Table 4 gives some typical experimental results.[13]

The process for the preparaon of the dialkylthioacetals of dimethylformamide parallels that used in obtaining the corresponding oxyacetals.[14] The dimethylsulfate adduct of diethylformamide (**14**) is quenched with ethanthiolate ion to give the thioacetal (**34**). Alternatively, acetal exchange on 3 with an



(32) (33) (31) (31)

Scheme 11.

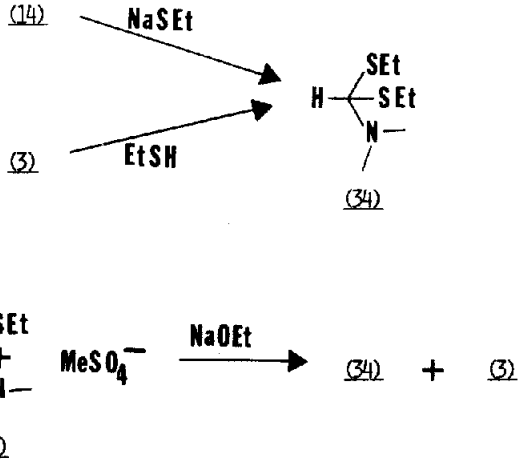
Table 4. Recombination of tris(dialkylamino)methanes and formamide acetals to aminal esters

	% Aminal Ester			
Tris(dimethylamino)methane +	1 hr	2 hr	20 hr	7 days
N,N-dimethylformamide dimethyl acetal	43	44	60	-
N,N-dimethylformamide diethyl acetal	43	43	59	66
N,N-dimethylformamide diisopropyl acetal	25	-	46	50
N,N-dimethylformamide di-t-butyl acetal	6	6.8	20	-

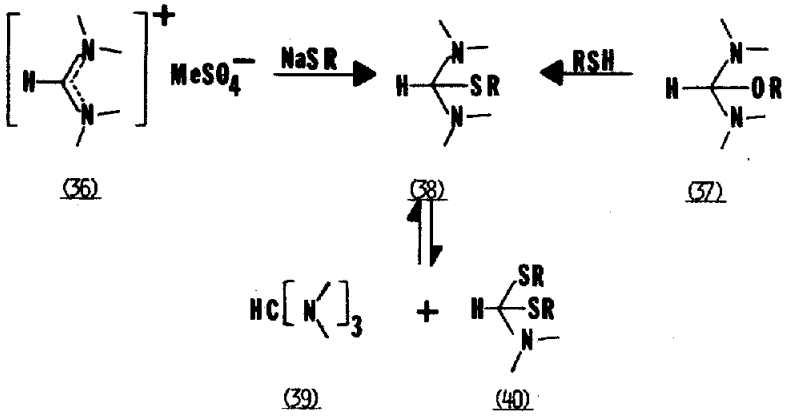
alkyl mercaptan also affords the required thioacetals. Mixed O,S-acetals cannot be prepared by treatment of the dimethyl sulfate adduct of thioformamide (**35**) with sodium ethoxide, since this reaction gives a mixture of the O-acetal (**3**) and the S-acetal (**34a**). these transformations are shown in Scheme 12. Amidinium methylsulfates (**36**) react as expected with sodium alkylthiolates to afford the aminal thioesters (**38**). These compounds may also be obtained by acetal exchange with an alkyl mercaptan and an aminal ester (**37**). The aminal thioesters (**38**) disproportionate in a fashion analogous to their oxygenated counterparts. Table 5 shows the equilibrium proportions of the components from Scheme 13.

In addition to disproportionation, the derivatives of ortho-amides may suffer a second mode of decomposition. Thus, tris-(dimethylamino)methane (**41**) dimerizes on standing with loss of dimethylamine to give tetraaminoethylene (**42**). This compound (**42**) was also obtained in 80% yield upon refluxing **41** for 2 hr.[15]

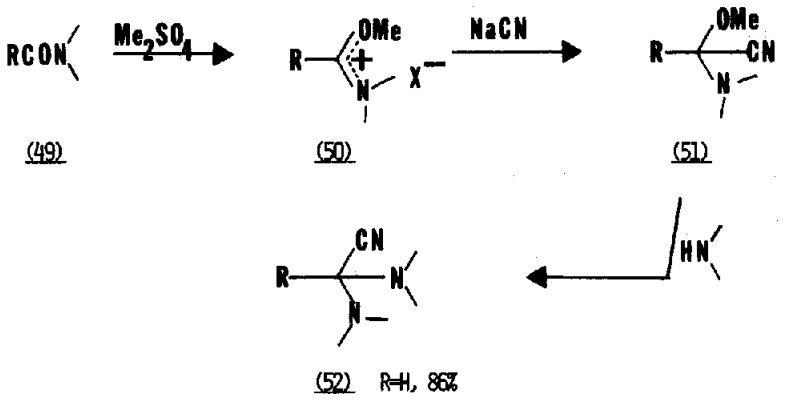
N,O-Acetals of α-ketocarbonitriles are formed by the reaction of dimethylformamide acetals with acyl cyanides (**44**) by the reaction of the adducts of dimethylformamide and dimethyl sulfate with sodium cyanide in water[16] and by reaction of dialkylformamide acetals with hydrogen cyanide.[17] In the first case, the initial adduct (**45**) between the dimethylformamide acetal (**43**) and the acyl cyanide (**44**)



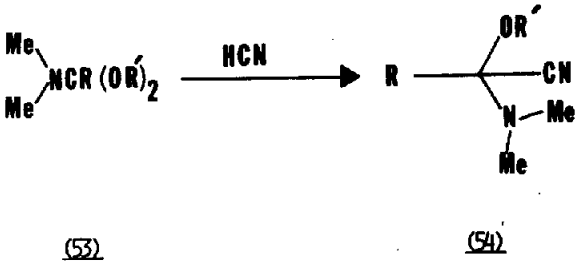
Scheme 12.



Scheme 13.

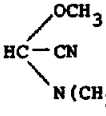
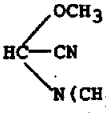
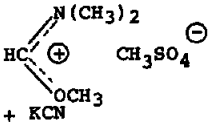
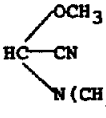
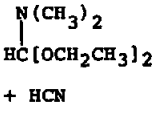
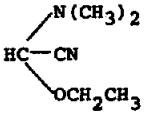


Scheme 16.



Scheme 17.

Table 6. Some N,O-acetals substituted by a cyano group

Reactants	Product	% Yield	Ref.
$(CH_3)_2NCH(OCH_3)_2$ + CH_3COCN		81	16
$(CH_3)_2NCH(OCH_3)_2$ + C_6H_5COCN		78	16
 + KCN		68	16
 + HCN		86	17

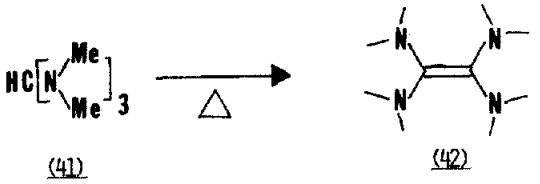
ELECTROPHILIC REACTIONS OF DIMETHYLFORMAMIDE ACETALS

Part (I): *Formamide acetals as alkylating agents*

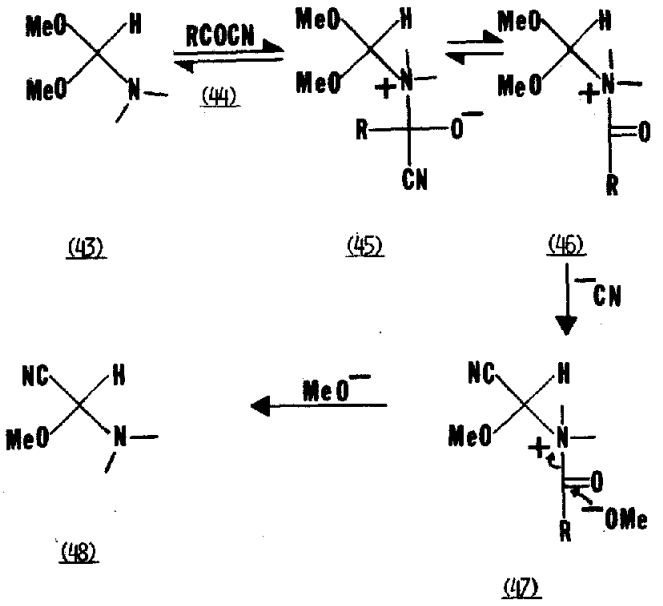
In 1965 Eschenmoser *et al.*[18] described a detailed, conclusive study of the reaction of formamide acetals with carboxylic acids, and recognized that this reaction was a facile process for the preparation of esters. Moreover, they studied the mechanism of this alkylation using optically active (S)-2-butanol (55). Transacetalization of 55 with acetal A gave the corresponding optically active formamide acetal (56). Both 55 and 56 were then converted to the same benzoylated (S)-2-butanol (57) indicating that

Table 5. Disproportionation of aminal thioesters

Starting Material		R	% (38)	(39)	(40)
36		C_2H_5	43	27	28
37	(R^1 = CH_3)	C_2H_5	50	23	31
37	(R^1 = t-Bu)	C_2H_5	60		
36		t-Bu	32		9.8
37		t-Bu	74		18
36		i-Pr	42		19
37		i-Pr	51		14.5



Scheme 14.



Scheme 15.

eliminates cyanide ion which in turn displaces a OMe group in **46** to give **47**. The product **48** is finally obtained upon nucleophilic displacement at the CO group in **47** by methoxid ion. With the dimethyl sulfate adduct of amides, as the starting point to cyano acetals, the reaction sequence follows a simpler course. The O,N-acetals (**51**) react further with dialkylamines to afford ketonitrile aminals (**52**) in good yield (Scheme 16). Hemiaminals of ketonitriles may also be made by the reaction of dialkylformamide dialkyl esters with hydrogen cyanide.[17] This reaction will be described in greater detail under reactions with active methine hydrogen atoms. Table 6 shows some typical O,N-acetals derived from α-ketocarbonitriles,[16] and from hydrogen cyanide[17] (Scheme 17).

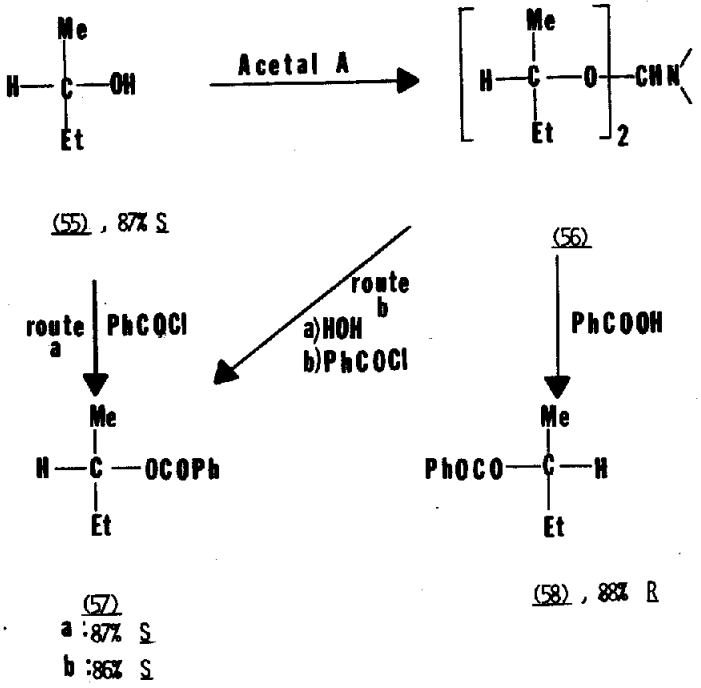
In recent years several amide acetals have become commercially available. These compounds are listed in Table 7.

Table 7. Some commercially available amide acetals

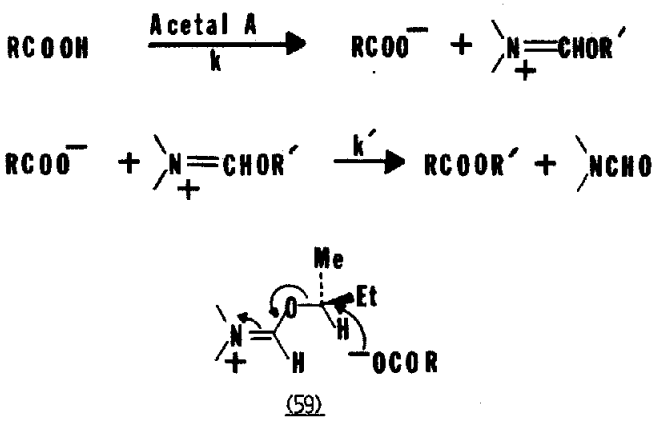
Acetal	Structure
A	$(CH_3)_2NCH(OCH_3)_2$
B	$(CH_3)_2NCH(OCH_2CH_3)_2$
C	$(CH_3)_2NCH(OCH_2-\overset{CH_3}{\underset{CH_3}{C}}-CH_3)_2$
D	$(CH_3)_2NC(CH_3)(OCH_3)_2$
E	$(CH_3)_2NCH\begin{smallmatrix}O-CH_2\\ \\ O-CH_2\end{smallmatrix}$
F	$(CH_3)_2NCH(O-\overset{CH_3}{\underset{CH_3}{C}})_2$
G	$(CH_3)_2NCH(OCH_2CH_2CH_3)_2$
H	$(CH_3)_2NCH(O-C_6H_{10})_2$

enantiomeric purity had been retained during transacetalization in **56**. In contrast treatment of benzoic acid with **56** gave a benzoate (R)-**58** with an optical rotation opposite to that of **57** indicating that inversion had occurred during esterification (Scheme 18).

Eschenmoser *et al.* have thus proposed the following mechanism (Scheme 19) which is consistent

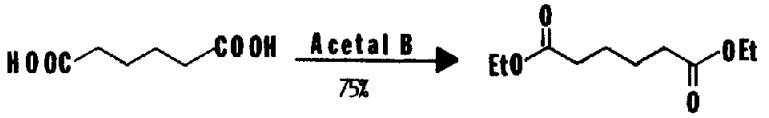


Scheme 18.



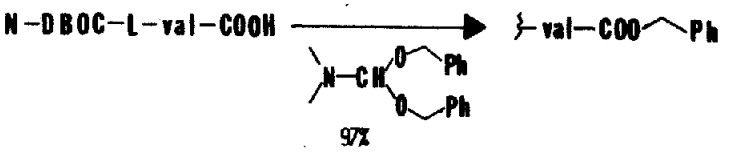
Scheme 19.

with these data. The key step in this mechanism is the S_N2 displacement of dimethylformamide by the carboxylate anion shown as intermediate **59**. This reaction occurs with accompanying Walden inversion thus explaining the formation of (R)-**58** in Scheme 18. This method has since been applied by several groups to the esterification of numerous carboxylic acids. Some uses of this reaction are of note. Vorbrüggen[19] reported the conversion of carboxylic acids to esters with N,N-dimethylformamide diethyl acetal B, and dibenzyl acetal, in high yields (64–75%) under mild conditions (Scheme 20, eqn a).



Scheme 20(a).

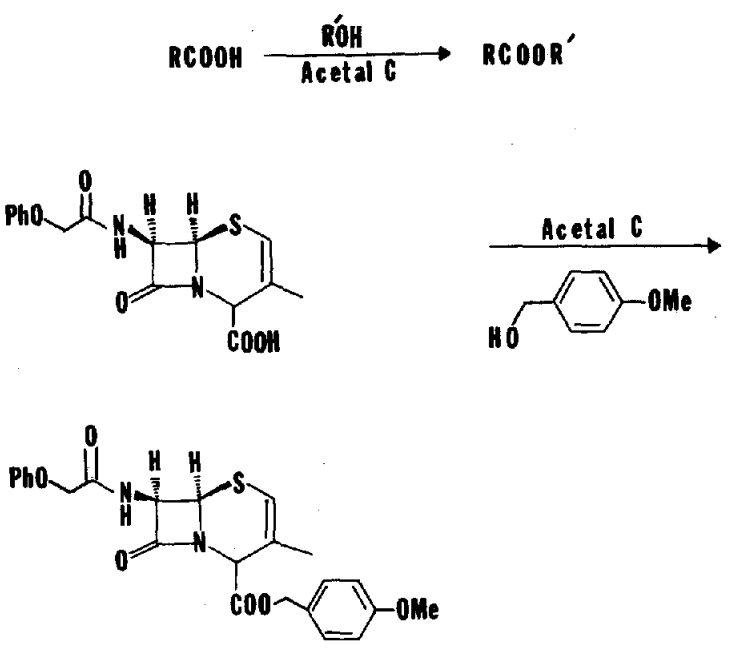
Eschenmoser *et al.*[20,21] in two subsequent papers then described the use of N,N-dimethylformamide dibenzyl acetal to block the carboxylic acid end group in a peptide by conversion to the benzyl ester. This conversion thus allows the protection of the acid with the future possibility of readily cleaving the benzyl group under standard conditions (Scheme 20, eqn b).



Scheme 20(b).

The same authors also reported that while neopentyl acetal C (Table 7) would not esterify acids it would readily enter into acetal exchange reactions with other alcohols. The resulting mixed acetals thus afford a reagent for the esterification of an acid by any alcohol of choice (Scheme 21).

In all of these reactions, the rate-determining step is the alkylation of the carboxylate anion with the alkoxyimmonium ion which is derived from equilibrium with the unionized form of the reagent (Scheme 19).[21] Since neopentyl immonium ion reacts slowly with carboxylate ion, acetal C mediates the esterification with other alcohols that can form more reactive immonium ions.[22] Under more vigorous conditions, phenolic OH groups may be converted to the corresponding ethers using acetal A, B, N,N-dimethylformamide dibenzyl acetal[19a,b] or N,N-dimethylformamide di-t-butyl acetal.[19c] In addition, Webber, Van Heyningen and Vasileff have used acetal C in this same manner for esterifying a cephalosporin with *p*-methoxybenzylalcohol in 90% yield[23a] (Scheme 21). Several additional examples describing tthe use of formamide acetals for esterification are known. Thus, 16-methyl prostaglandin A_2,[23b] polymeric carboxylic acids[23c] and tetrahydro-4-quinoline carboxylic acid[23d] have been successfully esterified by this method. Some esters and ethers made by this method are shown in Table 8.



Scheme 21.

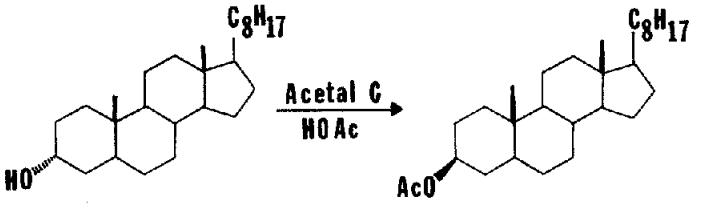
Table 8. Reactions of representative carboxylic acids and phenols with dimethyl formamide dialkyl acetals

Compound	Reagent	% Yield of Ester or Ether	Ref.
N-BDC-gly-L-phe-COOH	a	85	18
N-DOBC-L-ala-COOH	b	83	18
N-DOBC-L-phe-COOH	c	80	18
Fumaric Acid	d	81	19a
Phenol	d	64	19a
1,3,5-trichlorophenol	Acetal B	87	19a
Salicylic Acid	Acetal B	93[e]	19b

[a] Benzyl alcohol/acetal C;
[b] p-Dodecylbenzyl alcohol/acetal C;
[c] p-Methoxybenzyl alcohol/acetal C;
[d] N,N-Dimethylformamide dibenzyl acetal;
[e] Only the acid function was esterified under the mild (22°C/CH_2Cl_2) reaction conditions.

Vorbrüggen[19b] also found that reaction of 5α-cholestan-3α-ol with acetal C in the presence of acetic acid (toluene, 80°) gave 5α-cholestan-3β-yl acetate, (**60**), in 78.5% yield (Scheme 22). As in the case of carboxylic acids (Scheme 19), this reaction proceeds as expected with inversion of the substituent at C-3.

The conversion of amino acids (**61**) to amidino esters (**62**) in one step may be achieved by refluxing a mixture of the amino acid with acetal A or B. The resulting amidino esters are less polar than the precursor amino acids and also more volatile making these derivatives detectable by gas chromatography and mass spectroscopy.[24] Furthermore, the amidino esters may be alkylated at the α-C atom by successive treatment with a lithium dialkylamide and either an alkyl halide or a Michael acceptor to



(60)

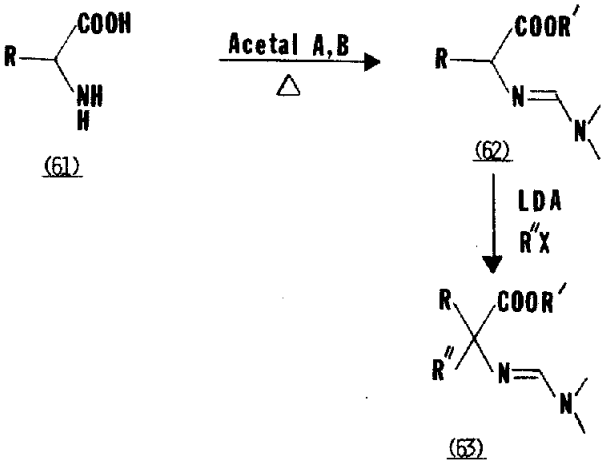
Scheme 22.

Table 9. Formation and alkylation of amidino esters from amino acids (Scheme 23)

Compound (61), R	(62) % Yield	Electrophile	(63), R^2	% Yield
H	80	$C_6H_5CH{=}CH{-}CH_2Br$	$C_6H_5CH{=}CH{-}CH_2-$	65
		p-Cl-C_6H_4-CH=C(CO_2CH_3)(CO_2CH_3)	p-Cl-C_6H_4-CH-CH(MeO_2C)$_2$	63
		$C_6H_5CH{=}CH{-}NO_2$	$C_6H_5-CHCH_2NO_2$	90
$CH_3SCH_2CH_2-$	94	p-Cl-$C_6H_4-CH_2Cl$	p-Cl-$C_6H_4-CH_2-$	84
C_6H_5	86	CH_3I	CH_3-	83
		$CH_2{=}CH{-}COOCH_3$	$-CH_2CH_2COOCH_3$	88
$C_6H_5CH_2$	90	CH_3I	CH_3-	84
		$CH_3CH_2CH_2I$	$CH_3CH_2CH_2-$	80

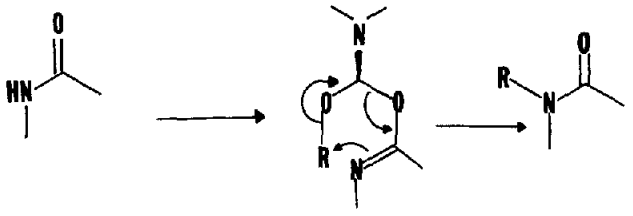
afford amino acid analogs (**63**)[25a] (Scheme 23) (Table 9). This alkylation procedure compares favorably with other amino acid alkylation methods currently available.[25b]

Dimethylformamide acetals have been used in nucleoside chemistry as alkylating agents. Zemlicka *et al.* and others[26] described the N-alkylation of nucleic acid components with acetal A, and proposed the mechanism illustrated in Scheme 24. Alternatively, one may invoke an intermolecular process, consistent with the findings of Eschenmoser *et al.*,[18] in which backside attack would be facilitated (Scheme 19). Some nucleosides that have been alkylated[26] are listed in Table 10.



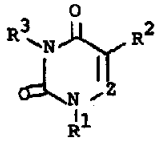
(61) (62) (63)

Scheme 23.



Scheme 24.

Table 10. Alkylation of nucleic acid components with acetal A



R^1	R^2	R^3	Z	% Yield
CH_3	H	CH_3	CH	88[a]
CH_3CH_2	H	CH_3CH_2	N	78[a]
1-(β-D-ribofuranosyl)	H	CH_3	CH	43,[b] 100[c]
"	H	CH_3	N	61[a]
1-(β-D-2-deoxyribo-furanosyl)	CH_3	CH_3	CH	91[a]

[a] Reaction done using DMF acetal as the solvent.

[b] DMF was used as the solvent.

[c] Methanol was used as the solvent.

Holy[27] used acetal A to prepare a number of S-methylated heterocycles from the corresponding thiols in high yields (76–86%). Of particular interest is the alkylation of 2-mercaptopyrimidine with **64**. In this case heating a mixture of **64** with dineopentyl acetal C in the presence of 2-mercaptopyridine gave the sulfide **65**. Subsequent Raney nickel treatment afforded the 5'-deoxy nucleoside derivative **66** (Scheme 25) in 60% overall yield.

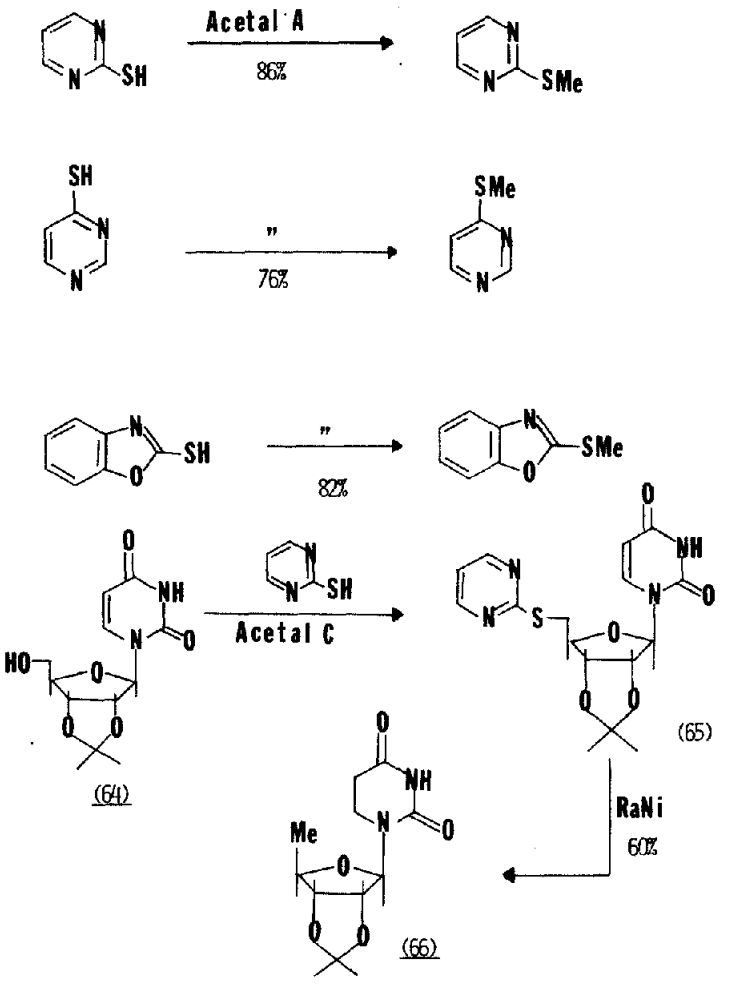
It has also been found that N atoms which are part of a heterocyclic ring system can be intramolecularly alkylated using dineopentyl acetal C. For instance, Zenlicka[28] has reported the formation of a N^3-5'-cyclonucleoside derivative (**68**) in the reaction of xanthosine (**67**) with dineopentyl acetal C via an intramolecular ring closure as shown in Scheme 26.

This unusual ring formation reaction proceeds in 88% yield.

In some cases it is desirable to block the –CONH– function in uridine (**69**) or guanosine (**70**) with a benzyl group. Standard benzylating procedures, such as sodium hydride and benzyl bromide, gave low yields of N-benzylated product.[29] Philips and Horwitz[29] have shown, however, that N,N-dimethylformamide dibenzyl acetal in DMF quantitatively converted uridine (**69**) and guanosine (**70**) to their N-benzylated derivatives (Scheme 27). Although **69** could be readily methylated with N,N-dimethylformamide dimethyl acetal, A, guanosine (**70**) was not.

Yoneda *et al.*[30] have described that heating 3-phenyltoxoflavin (**71**) with dimethylformamide ethylene acetal under gentle reflux followed by concentration and addition of ethanol caused precipitation of 1-(2-hydroxyethyl)-3-methyl-6-phenyl-7-azalumazine (**72**) in 72% yield. It is of interest to note that this transformation proceeds with demethylation (Scheme 28).

The dephosphorylation of ribonucleosides, e.g. **73**, has been reported using either acetal A or C.[31] The mechanism of this reaction is unknown but may be considered to proceed by a process consistent with



Scheme 25.

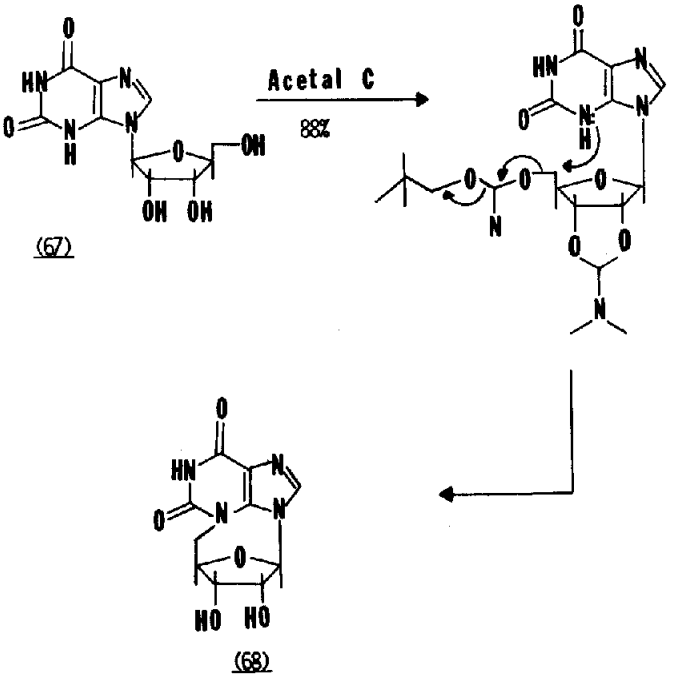
the reported mechanisms of transacetalization (Scheme 29). The overall sequence proceeds in quantitative yield.

Vorbrüggen[32a] has described a selective ketalization of 3-keto steroids, such as **74**, in the presence of C_{17}- or C_{20}-ketonic functions (Scheme 30). A similar ketalization was utilized by Venturella *et al.*[32b] for derivatizing barbiturates for glc analysis. The mechanisms of these ketalization processes are in all likelihood similar to the one for the reaction in Scheme 28.

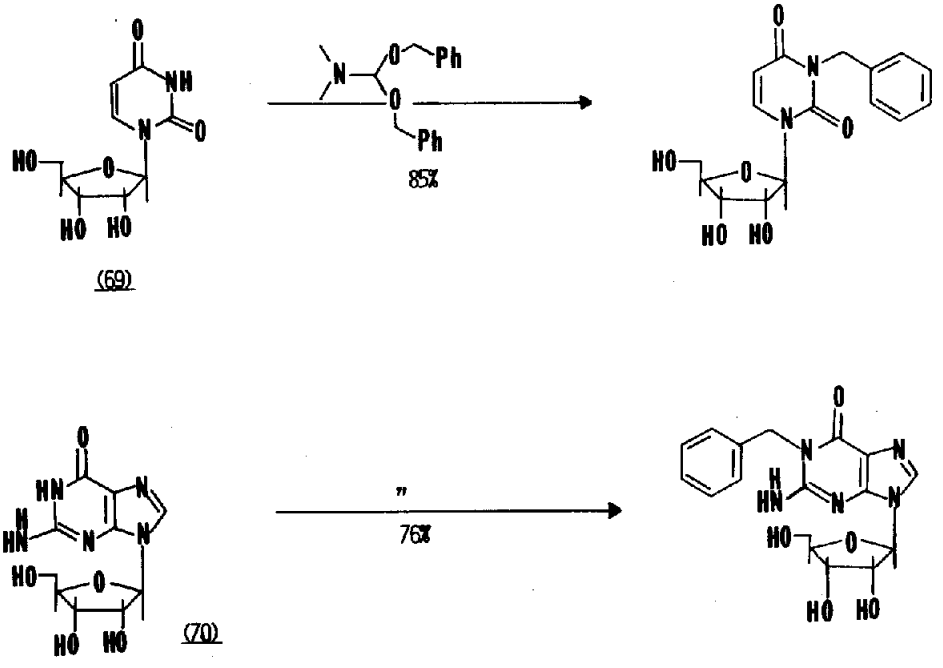
It has been found that a trisubstituted methane derivative with two or three carbanion stabilizing groups, such as phenyl, cyano, or carboxylate, is alkylated by acetal B at temperatures ranging from 90° to 140°.[17] Alkylation did not occur with bis(dimethylamino)-t-butoxymethane or with tris(dimethylamino)methane. Instead, when a trisubstituted methane derivative (**75**) was treated with one of these acetals under mild conditions (20°–60°), the initial product was the formamidinium salt (**76**). Upon further heating (140°) in the presence of t-butanol, the corresponding amide (**77**) was obtained (Scheme 31).

Table 11 lists the active methine compounds and their products upon treatment with tris(dialkylamino)methanes or with acetal B.

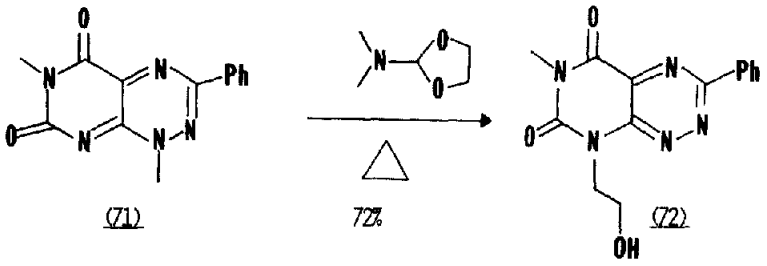
Dimethylformamide acetals have also been found to undergo a variety of reactions with 1,2-diols.[33a,b] For example, the reaction of *trans*-cyclohexan-1,2-diol (**78**) with acetal A led to the formation of cyclohexane epoxide **79** (Scheme 32). On the other hand, *cis*-cyclohexan-1,2-diol gave the transacetalization product **80**. Applying this reaction to *meso*-hydrocarbon (**81**), the *cis*-stilbene epoxide (**82**) was obtained.[33a] This reaction has also been used for the synthesis of K-region oxides.[33c] Eastwood *et al.*[34] have reported on the mechanism of epoxide formation (**82**) by the thermolysis of a cyclic acetal of



Scheme 26.

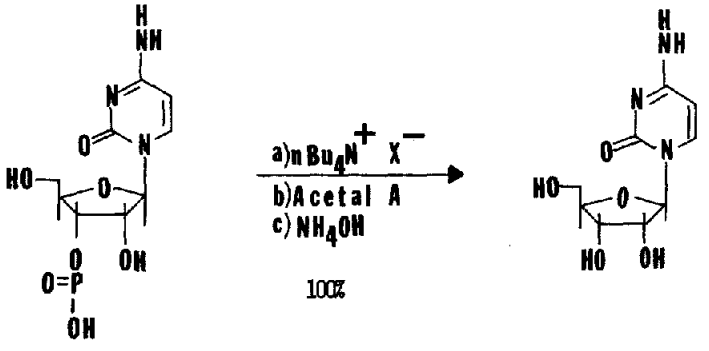


Scheme 27.



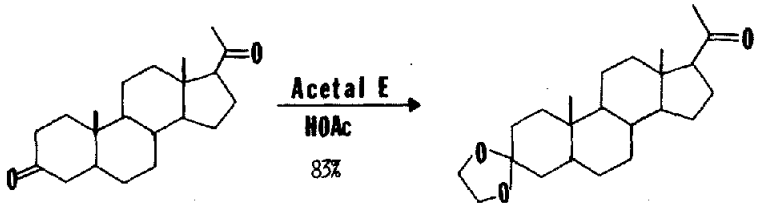
(71) 72% (72)

Scheme 28.



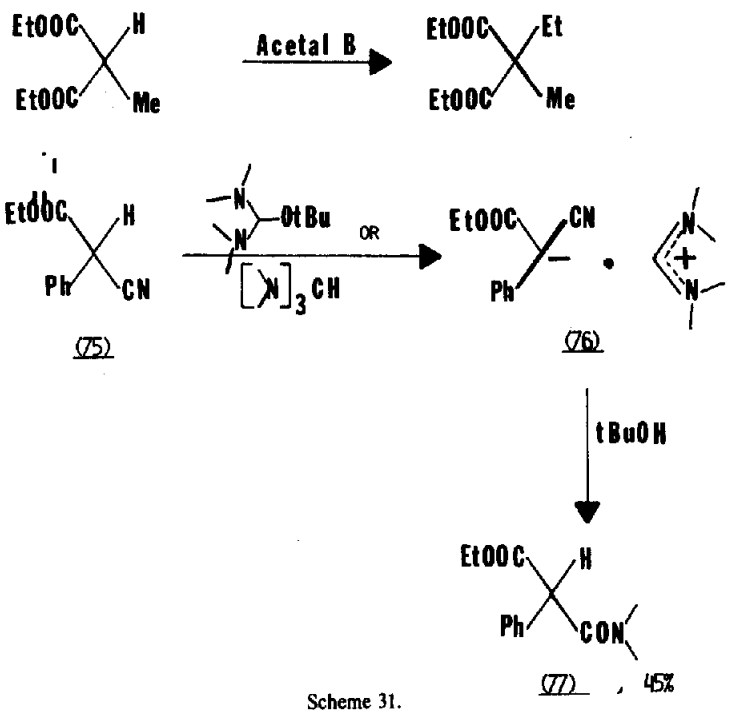
(73)

Scheme 29.



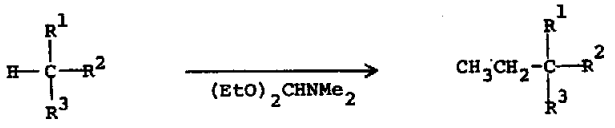
(74)

Scheme 30.



Scheme 31.

Table 11. Condensation of active methine compounds with acetal B

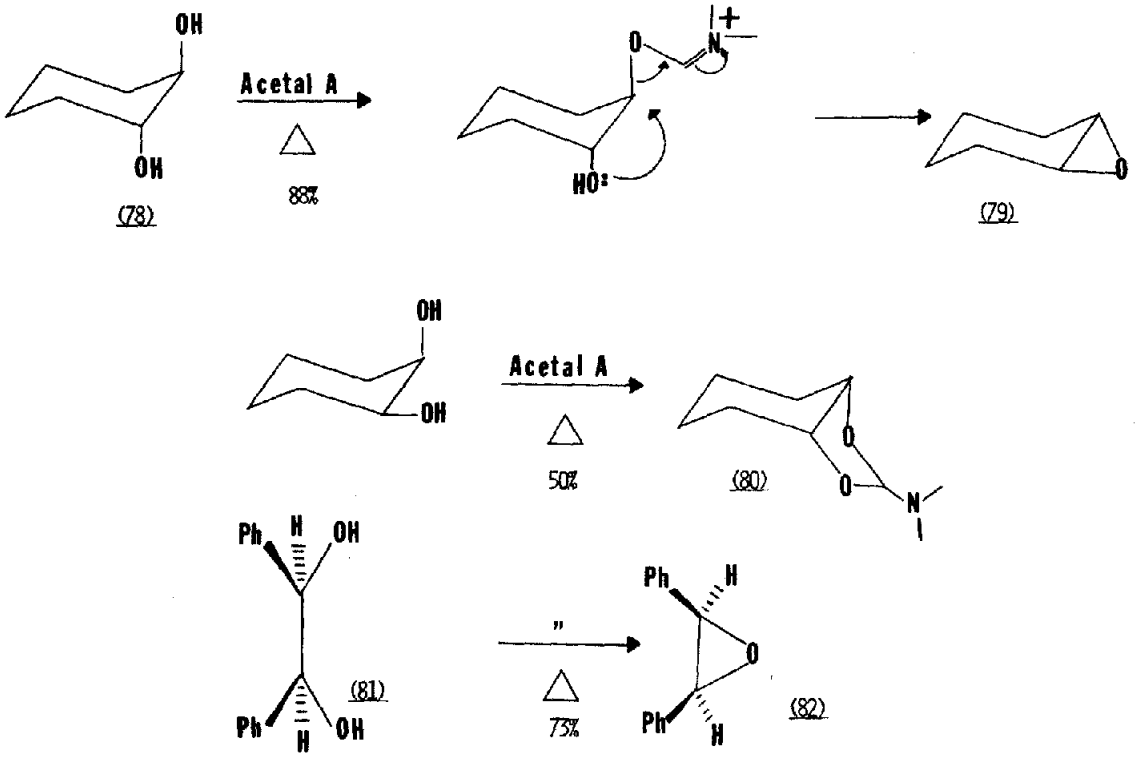


R^1	R^2	R^3	% Yield
CH_3	$COOC_2H_5$	$COOC_2H_5$	a
C_6H_5	$COOC_2H_5$	$COOC_2H_5$	a
CH_3	$COOC_2H_5$	CN	51
C_6H_5	$COOC_2H_5$	CN	70
C_6H_5	CN	CN	47
$COOC_2H_5$	$COOC_2H_5$	$COOC_2H_5$	81

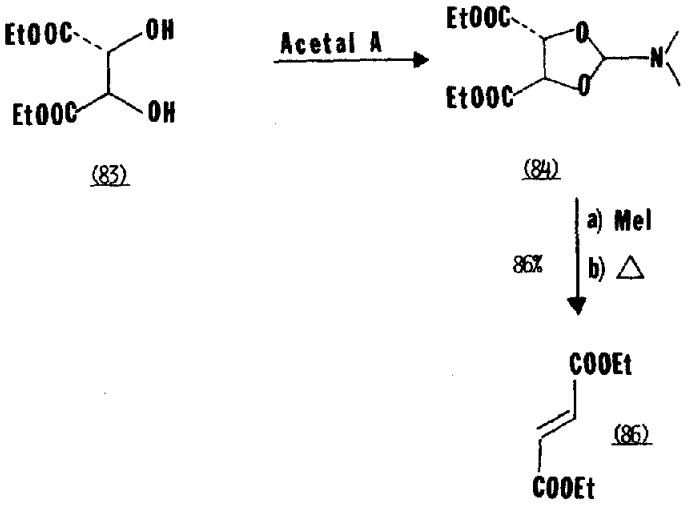
[a] Identified in admixture with starting material by NMR.

81 derived from triethyl orthoformate. It is conceivable that the mechanism of epoxide formation via the dimethylformamide acetals follows a similar course.

Hanessian *et al.*[35] have converted a number of vicinal *cis*-diols, both cyclic and acyclic, into olefins. In a typical example, treatment of diethyl D-tartarate (**83**) with an excess (2–10 equivs) of N,N-dimethylformamide dimethyl acetal, A, in dichloromethane at 25° provided the corresponding 1-dimethylamino(methylene)acetal (**84**). Upon addition of methyl iodide to **84**, the trimethylammonium salt (**85**) precipitates. Thermolysis of **85** in toluene at reflux temperature affords diethylfumarate **86** (Scheme 33). Table 12 indicates other olefins prepared by this useful method.



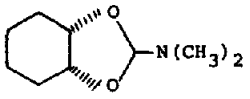
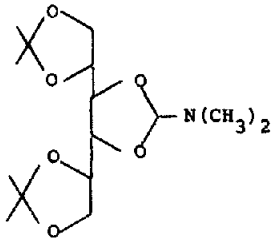
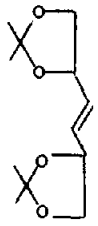
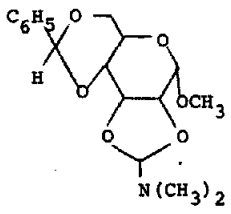
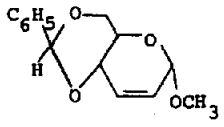
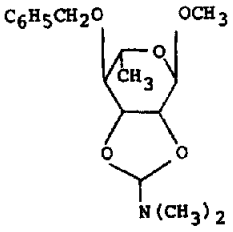
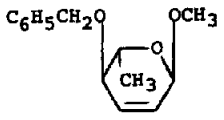
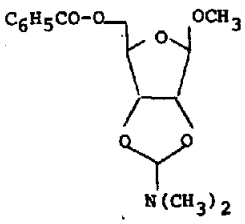
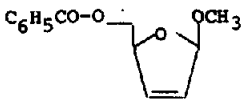
Scheme 32.



Scheme 33.

Dimethylformamide acetals also react with α,ω-hydroxy acids. The products obtained from these reactions depend on the distance between the two functional groups. For example, Vorbrüggen and Krolikiewicz[36] recently described the use of acetal C as a cyclization catalyst for the synthesis of macrocyclic lactones (**88**) from the corresponding hydroxy acids (**87**). In this reaction, a toluene solution of the hydroxy acid and of acetal C was added simultaneously to boiling toluene. Upon workup the required lactones were obtained in 40–50% yields accompanied by ologomers (Scheme 34). In the case where an asymmetric center was present on the carbon adjacent to the alcohol oxygen, cyclization

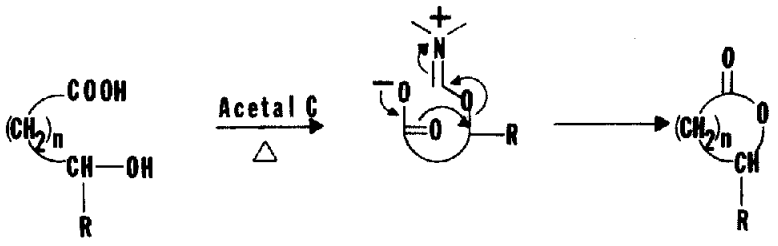
Table 12. Olefins from 1-(dimethylamino)methylene acetals

Acetal	Olefin	% Yield
		90
		95
		85
		95
		89

proceeded with Walden inversion (see Scheme 18). Subsequent saponification and relactonization provided the cyclic ester of the opposite configuration.

β-Hydroxy carboxylic acids, such as **89**, react with acetal A (Scheme 35) under mild conditions to provide substituted alkenes of the type **90** in 55–92% yield (Table 13).[37] Two mechanisms (a and b, Scheme 35) were proposed by Hara *et al.*[37] in support of their results. The first, route a, invokes the formation of the transacetylated intermediate (**91**) which undergoes a thermally allowed 2+2+2 fragmentation to the desired alkene. Their alternate proposal, route b, invokes the imidinium salt (**92**) that decomposes to the lactone (**93**), which in turn loses carbon dioxide to provide the alkene (**90**). These authors concluded after competition experiments that the mechanism invoking the β-lactone intermediate was the less likely process, although their evidence was not conclusive.

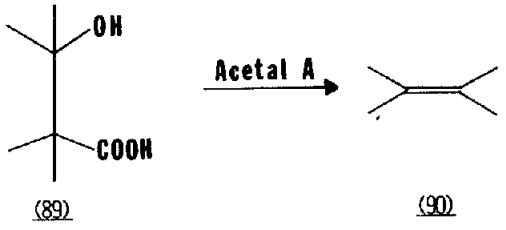
In a mechanistically related process,[37b] Wasserman and Lipshutz described the degradation of α-hydroperoxycarboxylic acids in the presence of acetal A to ketones. The authors invoke a cyclic 6-membered transition state, **91**, preceding the loss of carbon dioxide (Scheme 35).



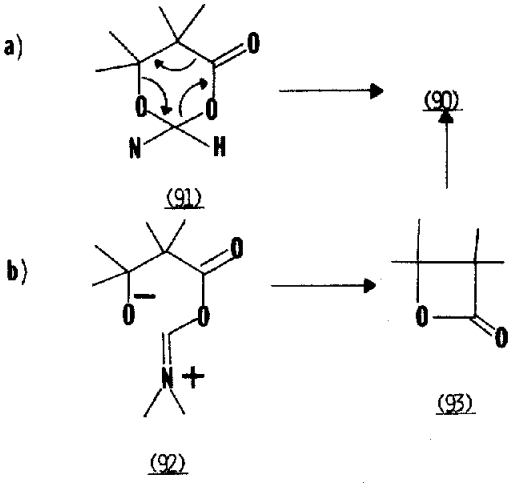
(87) (88)

n= 6, 0% (88)
= 10, 48% (88)
= 14, 40% (88)

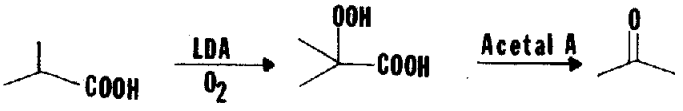
Scheme 34.



(89) (90)

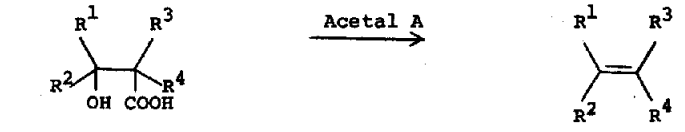


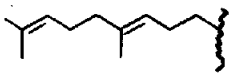
(91) (92) (93)



Scheme 35.

Table 13. Formation of alkenes by treatment of β-hydroxy acids with DMF acetal A



R^1	R^2	R^3	R^4	% Yield
$-(CH_2)_{11}-$		H	H	91
		CH_3	H	92
		CH_3	CH_3	90
$-(CH_2)_9$		C_6H_5	H	84
		H	H	55
$\underline{n}$-C_9H_{19}	H	H	H	55
$\underline{n}$-C_8H_{17}	H	CH_3	CH_3	63
$\underline{n}$-C_9H_{19}	H	CH_3	H	90
C_6H_5	C_6H_5	H	H	88
C_6H_5	H	$\underline{n}$-C_5H_{11}	H	90
	CH_3	CH_3	CH_3	70

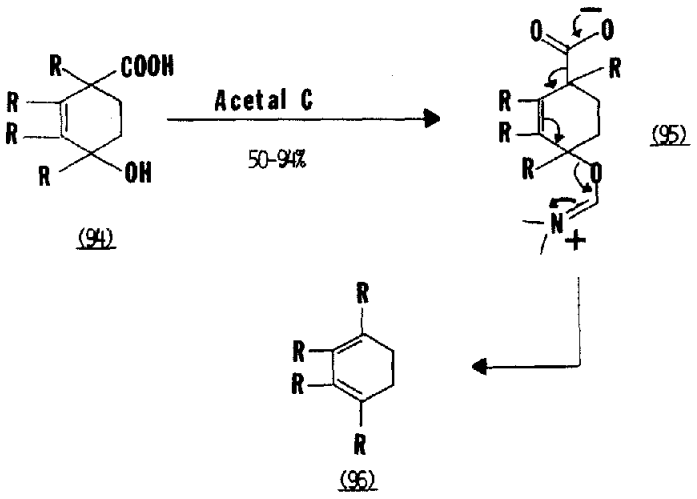
Eschenmoser *et al.*[38] also described the reaction of cyclic, δ-hydroxy carboxylic acids (**94**) with acetal C in the presence of 1-methylnaphthalene (20°–70°) to yield the cyclohexyldienes (**96**) in good overall yields (Scheme 36). The authors proposed that the reaction proceeds via intermediate **95** which undergoes loss of carbon dioxide and dimethylformamide to provide the diene **96**. The conditions of this reaction do not cause double bond isomerization. The overall sequence thus affords dienes which are not readily available by other means.

Part (II): ***Formamide acetals as formylating agents***

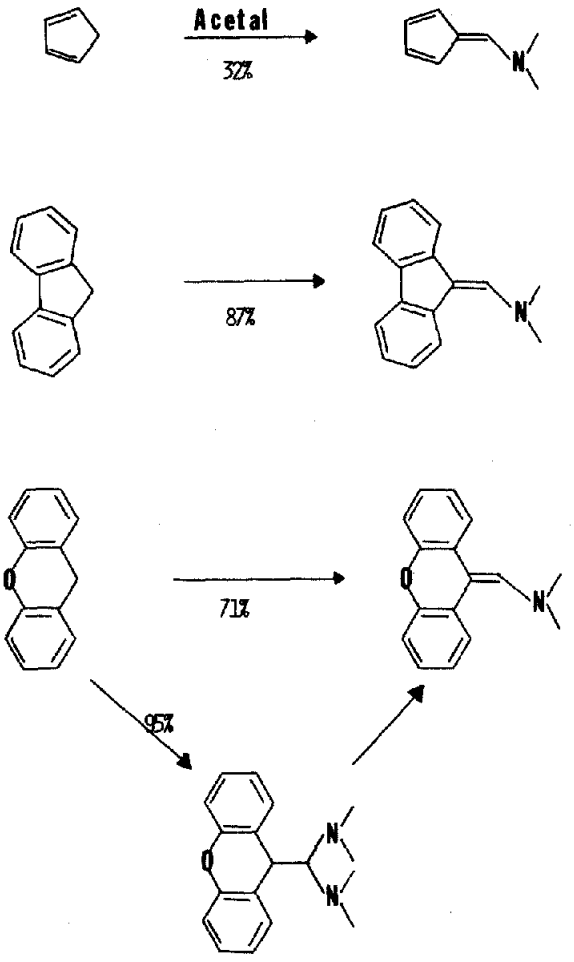
Distinct to their use as alkylating agents, a second major reaction of formamide acetals is formylation of carbon and hetero atoms. In this way they function as modified Vilsmeier–Haack reagents. In the case of C atoms, formamide acetals react smoothly with mono- and diactivated systems (i.e. ketones, malonates) under very mild conditions to provide good-to-excellent yields of the resulting enamines. In several cases, the enamine product from these reactions served as a key intermediate in a synthetic sequence.

Of the hetero atoms described below, nitrogen has received the most attention. Primary amines and primary amides react with formamide acetals to give amidines and acylated amidines, respectively, in good yields under mild conditions. Here again, the amidines from this reaction often supply key intermediates in synthetic schemes.

(A) *Formylation of carbon atoms.* Meerwein[1] described the conversion of cyclopentadiene to 6-aminofulvene by treating cyclopentadiene with N,N-dimethylformamide diethyl acetal, B, (130°) in 32% yield. Later fluorene[39] and xanthene[39,40a] were similarly converted to their enamines with tris(dimethylamino)methane in 87% and 71% yield, respectively (Scheme 37). It is of interest to note that the reactivities of these hydrocarbons towards DMF acetals and aminals is related to their pK_a's. Therefore, xanthene needs more vigorous conditions for conversion to its enamine than does cyclopentadiene[40a,b] or fluorene. Also in the case of xanthene,[39] the intermediate bis(dimethylamino)adduct (**97**) could be isolated in 95% yield by terminating the reaction after 5 hr. The conversion to the enamine normally is complete, in 71% yield, after 48 hr.

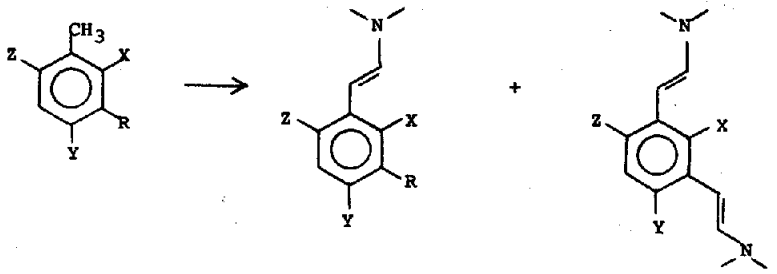


Scheme 36.



Scheme 37.

Table 14. Reaction of formamide acetals with methyl-substituted benzene rings



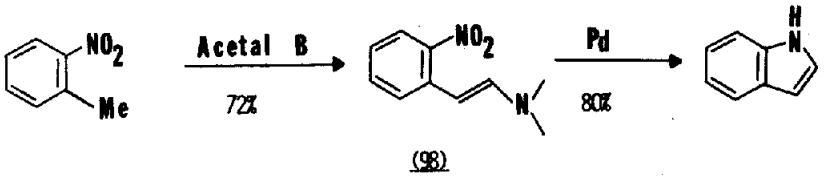
i ii

X	R	Y	Z	Acetal	% Yield i	ii	Ref.
NO_2	H	H	H	$HC(NMe_2)_2O$-t-Bu	47		40a
H	H	NO_2	H	"	73		40a
H	H	NO_2	H	(38) (R=Et)	47		14
CN	H	H	H	$HC(NMe_2)_2O$-t-Bu	55		40a
H	H	CN	H	"	44		40a
H	H	SO_2NMe_2	H	"	60		40a
H	H	CO_2CH_2Ph	H	"	15		40a
H	H	CO_2Me	H	"	10		40a
Cl	H	H	Cl	"	42		40a
NO_2	CH_3	H	H	"	47		40a
H	CH_3	NO_2	H	"	0	48	40a
NO_2	H	NO_2	H	B	50		1
NO_2	H	H		B	-		40c

The reaction of substituted toluenes with formamide acetals and aminals[1,14,40–42] proceeds in generally good yields to the enamines **i** or dienamines **ii** depending on the number of Me groups on the aromatic ring (Table 14). The reaction proceeds in highest yields with strong electron withdrawing substituents (nitro, cyano or sulfonamide) and in lower yields with weaker electron withdrawing substituents.

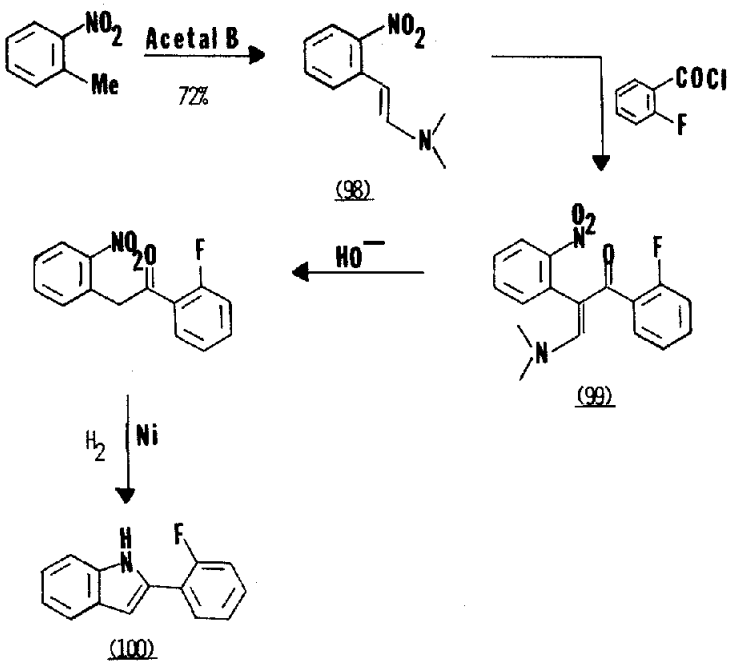
Several groups[41] have used this reaction in the synthesis of a variety of indoles. In a typical example,[41a] *o*-nitrotoluene was treated with dimethylformamide diethyl acetal, B, to give E-β-dimethylamino-2-nitrosytrene, (**98**), in 72% yield. Enamine **98** upon catalytic hydrogenation (Pd on C, H_2) gave indole in 80% yield (Scheme 38).

Enamine **98** was also used by Garcia and Fryer[41b] in the synthesis of substituted indoles. For example, acylation of enamine **98** (Scheme 39) with *o*-fluorobenzoyl chloride gave the enamino ketone



(98)

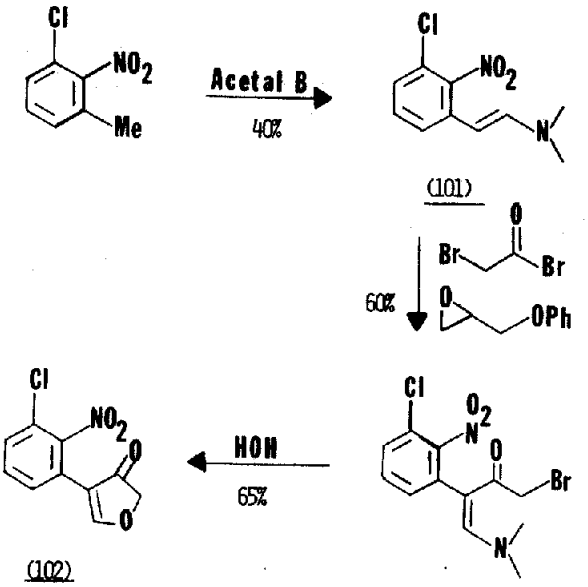
Scheme 38.



Scheme 39.

99. Subsequent hydrolysis of ketone **99** followed by reduction of the nitro group gave 2-(*o*-fluorophenyl) indole (**100**) in good overall yield. These two syntheses thus provide a general method for the preparation of indoles using the formylation reaction of formamide acetals.

Bredereck *et al.*[40a] have described the acid hydrolysis of some of the enamines in Table 14 to the corresponding arylacetaldehydes. Furthermore, enamines of this type have been used in the synthesis of furanone (**102**)[42a] as outlined in Scheme 40. Weigele *et al.*[42b] in a related process have found that derivatives of 1-amino-1-buten-3,4-diones can be converted to 2-methoxy-3-furanones in 52% yield.



Scheme 40.

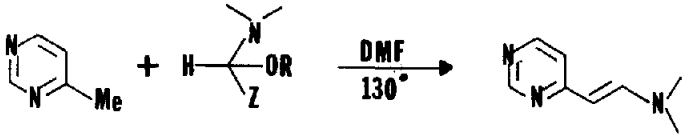
Thus, 3-chloro-2-nitrotoluene when treated with acetal B in refluxing dimethylformamide (24 hr) provided enamine **101** in 40% yield. Acylation of **101** followed by treatment with water gave furanone **102** in 39% overall yield.

Dimethylformamide acetals and aminals have been used in the formylation of activated Me groups on heterocycles.[1,3,4,14,40] In a study by Bredereck *et al.*,[40a] it was found that when 4-methylpyrimidine was treated with three different dimethylformamide acetals, enamine formation proceeded fastest (30 min) and in highest yield (94%) with bis(dimethylamino)-t-butoxymethane (Scheme 41). Table 15 describes the reactions of a variety of methyl heterocycles with formamide acetals.

Meerwein *et al.*[1] first reported the reaction of malononitrile and dimethylformamide diethyl acetal to give enamine **103** (Scheme 42) in 83% yield. Since then, numerous examples of the reaction of formamide acetals and aminals with ketones, esters, and other similar substrates have been published. The following examples serve to illustrate that the DMF acetals function as versatile formylating agents for a wide variety of substrates possessing active methylene groups. The formylation is convenient, usually needing only reflux temperatures for the less active methylene groups while the more active methylene groups are formylated at room temperature. The ease of workup (evaporation of solvent and excess acetal) affords almost pure enamines, making this the process of choice over more conventional methods of formylation. The first group of activated methylenes discussed are those with two activating groups.[1,14,45–47] These compounds (Table 16) react with formamide acetals usually at room temperature to provide the enamine products in high yields. Brannigan *et al.*[44] have published an application of these enamines to the synthesis of pyrazoles **104** (Scheme 43).

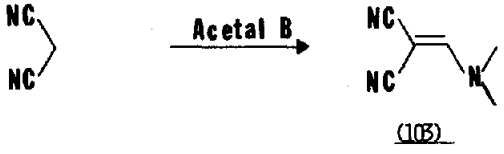
In their example, the enamine from an active methylene is treated with methylhydrazine to give the N-methylpyrazole (**104**).

The number of reactions of monoactivated methylenes, such as esters, nitriles, ketones, amides, etc. with formamide acetals is extensive. This section explores the reactions of monoactivated methylenes

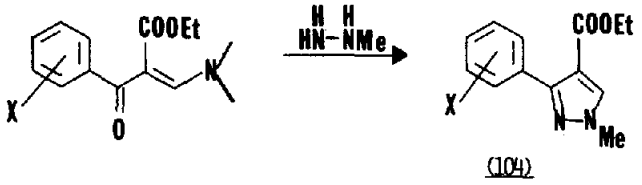


R	Z	Time (min)	% Yield
Et	OEt	360	30
Et	NMe_2	60	62
t-Bu	NMe_2	30	94

Scheme 41.



Scheme 42.



Scheme 43.

Table 15. The reaction of DMF-acetals and aminals with methyl-heterocycles

$$Het\text{-}CH_3 \xrightarrow{\text{DMF-Acetal}} Het\text{-}CH{=}CHNMe_2$$

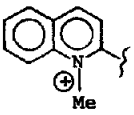
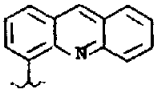
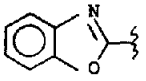
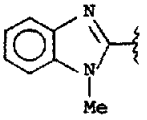
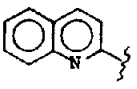
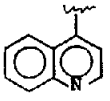
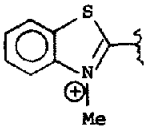
Het-	DMF-Acetal	% Yield	Ref.
	B	60	1
	B	49	3
	$HC(NMe_2)_2O\text{-}\underline{t}\text{-}Bu$	18	40a
	"	42	40a
	"	67	40a
	"	84	40a
	$HC(NMe_2)_2O\text{-}\underline{t}\text{-}Bu$	-	40a
	"	35	40a
	"	70	14,40a, 43
	"	65	40a
	"	32	40a
	"	67	40a
	"	84	40a
	B	78	40a

Table 15 (*Contd*)

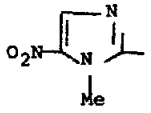
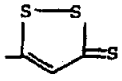
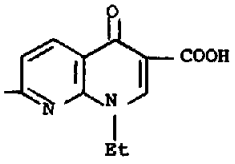
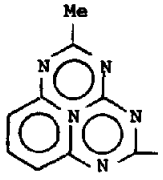
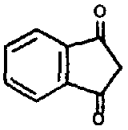
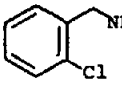
Het-	DMF-Acetal	% Yield	Ref.
	A	-	43a
	B	75-80	43b
	$HC(NMe_2)_2Ot$-Bu	86	43c
	B	88	43d

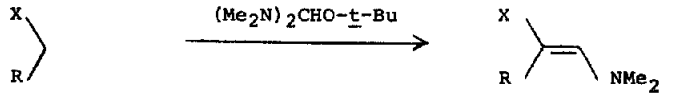
Table 16. Reactions of formamide acetals with active methylene groups

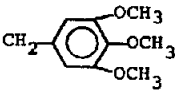
X	Y	Acetal	% Yield	Ref.
CN	CN	B	83	1
CN	CO_2H	$Me_2NCH(OCH_2$-t-$Bu)_2$	96	40a
CN	CO_2Me	$(Me_2N)_3CH$	83	42
		$(Me_2N)_2CHOMe$	89	42
		B	84	1,42
		$Me_2NCH(SEt)_2$	64	14
COMe	CO_2Et	B	77	1
		A	-	57a
	CN	B	-	57b
Ph	CN	B	-	57c

with formamide acetals and aminals. The utility of the resultant enamine product is also presented when it served as an intermediate in the synthesis of more complex systems.

Esters, nitriles, and thioesters react with formamide acetals generally under mild conditions, although at elevated temperatures, to provide the corresponding enamine system in good-to-excellent yields (Tables 17 and 18). As shown in Table 17, thioesters undergo a more facile conversion, under milder conditions in higher yields, to their enamine counterparts than do esters.[48b] Also, the anamines from α-amino esters, generated with, for example, dimethylamino methyl acetate and bis(dimethylamino)-t-butoxymethane (Table 17), can be transformed readily into heterocyclic systems by reaction with reagents having two nucleophilic sites such as hydrazine. Scheme 44 shows an example of the formation of pyrimidine from enamine **105** in 66% yield.[48a] In addition, Bredereck *et al.*[48a] found that the dimethylamino portion of enamine **105** can be exchanged for piperidine in 63% yield (Scheme 44).

Table 17. The reaction of substituted esters, nitriles and equivalent functionalities with bis(dimethylamino)-t-butoxymethane

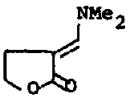
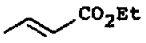
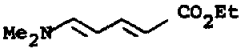
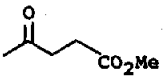
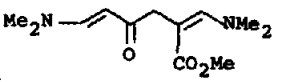
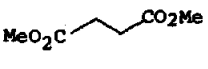
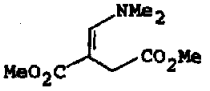
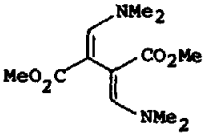
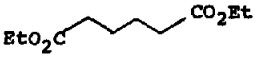
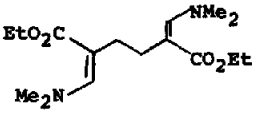
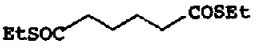
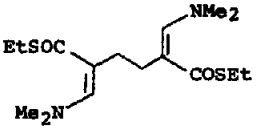


X	R	% Yield	Ref.
NC	NMe_2	75	48a
EtO_2C	NMe_2	55	48a
EtO_2C		54	48a
NC	OMe	61	48a
NC	SEt	60	48a
EtO_2C	OEt	57	48a
EtO_2C	OEt	41	48a
EtO_2C	H	88	48b
EtSCO	H	48	48b
$C_6H_{11}O_2C$	H	66	48b
EtO_2C	Me	48	48b
EtSCO	Me	44	48b
EtS_2C	Me	58	48b
EtOCS	Me	23	48b
NC	H	-	46a
NO_2	H	85[a]	1,50a
NC		-	46b
NO_2		b	50b
PhSO(NCO$_2$Me)-	H	65[a]	50c

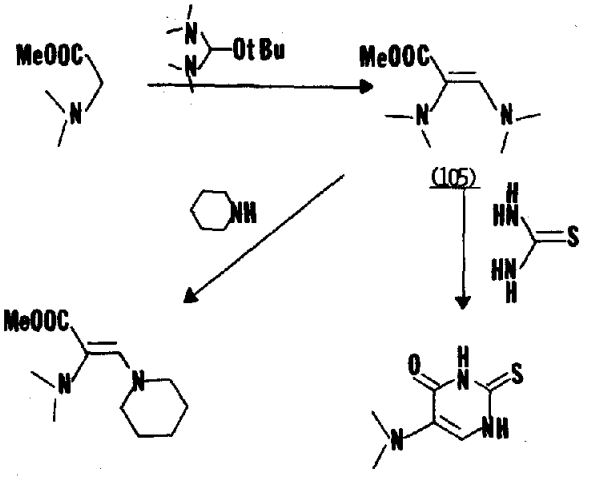
[a] Acetal B was used in this reaction.

[b] Acetal A was used in this reaction.

Table 18. Reaction of miscellaneous esters and lactones with bis(dimethylamino)-t-butoxymethane

Substrate	Product	% Yield	Ref.
		64 96[a]	48b 51
		69	48b 48e
		50	12
		61	12
"		56	12
		16	48b
		48	48b

[a] Using $HC(NMe_2)_3$



Scheme 44.

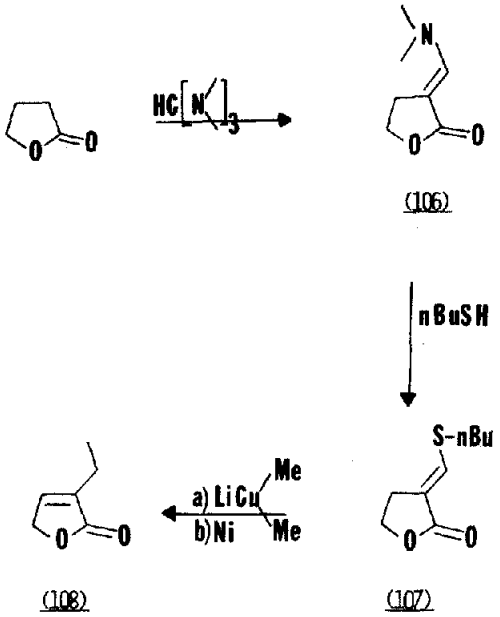
α,ω-Diesters can either be mono- or diformylated (Table 18) depending on the amount of bis(dimethylamine)-t-butoxymethane present and the temperature at which the formylation is done.

Martin and Moore[51] found that when γ-butyrolactone was treated with tris(dimethylamino)methane the enamino lactone (**106**) was obtained in 96% yield. Enamine **106** was allowed to react with n-butyl mercaptan in the presence of *p*-toluene-sulfonic acid to provide the vinyl sulfide **107** (Scheme 45).

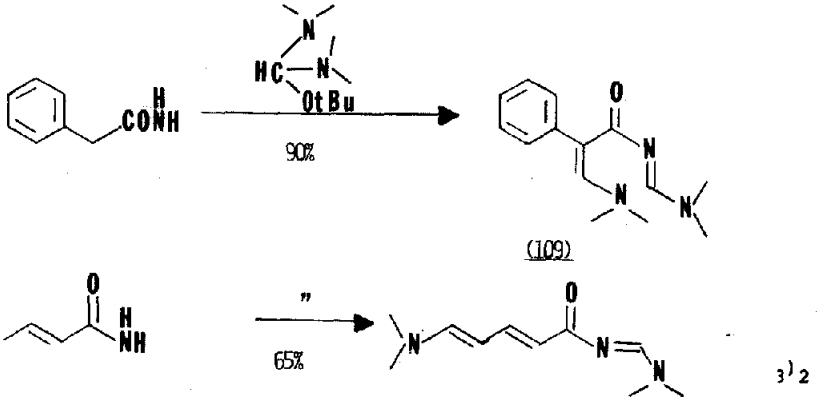
Treatment of **107** with lithium dimethylcuprate and subsequent double-bond migration gave the desired butenolides (**108**) in high overall yields.

Amides,[48b] thioamides,[48b] lactams,[48b] and imides[12] possessing an active methylene group react readily with formamide acetals and animal esters to provide the respective formylated products (Table 19). With primary amides the amino function reacts first to give the corresponding acylamidines. Subsequent reaction with or without isolation then affords carbon formylation to the enamino amidines **109** (Scheme 46). Secondary and tertiary amides, thioamides and imides afford only C-formylated products. Parallel to the case of the thioesters, thioamides react under somewhat milder conditions and afford higher yields of the enamino products. In an unusual reaction, two or more equivalents of formamide acetal react with an imide to provide the *bis* adduct (Table 20) in high yields.

The reaction of formamide acetals and aminals with ketones has provided an efficient method to the synthesis of enamino-ketones or enaminones. This reaction proceeds under mild conditions, under slightly basic pH with heating to provide good-to-excellent yields of the enaminones (Table 21). Enaminones are in themselves of considerable interest,[53] owing to their valuable use as synthetic

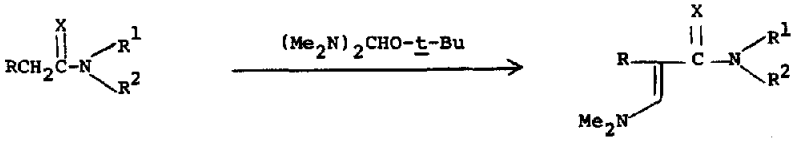


Scheme 45.



Scheme 46.

Table 19. The reaction of amides and thioamides with bis(dimethylamino)-t-butoxymethane[48b]



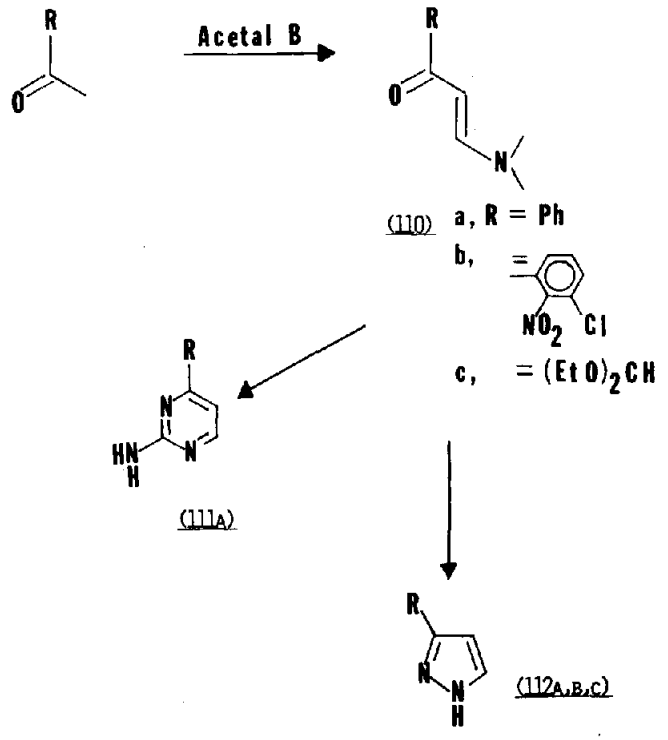
R	R^1	R^2	% Yield X=O[a]	% Yield X=S[b]
H	H	Me	51	72
H	Me	Me	63	74
Me	H	Me	57	81
Me	Me	Me	76	94

a Reactions done at 160°, 4-24 h.

b Reactions proceed at 120°-140°, 15-30 min.

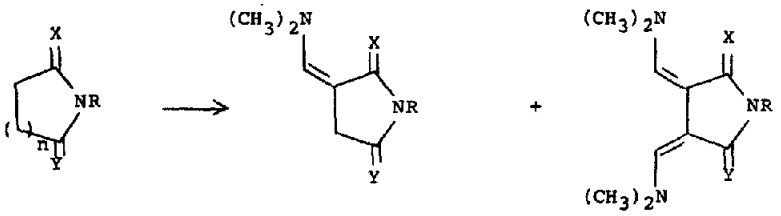
intermediates. This section explores the use of formamide acetals in the synthesis of enaminones and their subsequent application to the synthesis of more complex or difficult-to-obtain compounds.

Bredereck *et al.*[56a] have found that the enaminone from acetophenone **110** ($R = C_6H_5$) (Scheme 47) upon treatment with guanidine carbonate, in the presence of sodium ethoxide and ethanol, yields 2-amino-4-phenylpyrimidine (**111**) in 84% yield. Similarly, the enaminones from cyclohexanone, acetone, and methyl ethyl ketone were converted to the corresponding pyrimidines. When enaminone (**110a**) was treated with hydrazine, 3-phenylpyrazole (**112a**) was isolated in 90% yield. Garcia *et al.*[42] have recently published a similar series of reactions with the enamione from 2-nitro-3-chloroacetophenone (acetal B, benzene, reflux, 90%) and hydrazine and hydroxylamine to give the pyrazole (**112b**) and isoxazole, respectively (Scheme 47).



Scheme 47.

Table 20. The reaction of lactams and imides with formamide acetals and aminals



i ii

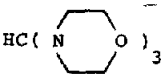
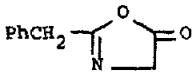
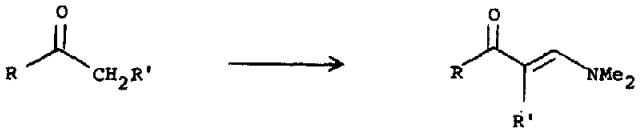
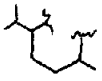
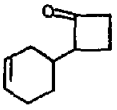
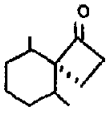
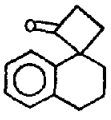
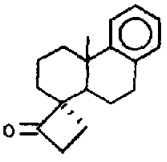
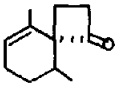
X	Y	R	n	Acetal (equiv)		% Yield i	% Yield ii	Ref.
O	H,H	CH_3	0	$[(CH_3)_2N]_2CHO$ t-Bu	(1)	11	-	48b
O	H,H	CH_3	1	"	(1)	12.5	-	48b
O	H,H	CH_3	2	"	(1)	15	-	48b
S	H,H	CH_3	0	"	(1)	90	-	48b
S	H,H	CH_3	1	"	(1)	76	-	48b
O	O	H	0	"	(1)	50	-	12
O	O	CH_3	0	"	(1)	78	-	12
O	O	H	0	"	(2)	-	64	12
O	O	CH_3	0	"	(2)	-	85	12
O	O	CH_2CH_3	0	"	(2)	-	63	12
O	O	CH_3	0	$CH_3OCH[N(CH_3)_2]_2$	(2)	-	67	12
O	O	CH_3	0	$CH_3OCH(NC_5H_{10})_2$	(1)	-	49	12
O	O	CH_3	0	"	(2)	-	60	12
O	O	CH_3	0		(1)	-	28	12
O	O	CH_3	0	"	(2)	-	38	12
O	O	CH_3	1	$[(CH_3)_2N]_2CHO$ t-Bu	(1)	46	-	12
O	O	CH_3	2	"	(2)	-	78	12
				A	(1)	50	-	49

Table 21. The reaction of ketones with formamide acetals



R	R'	Acetal	% Yield	Ref.
Ph	H	B	72	1,47
Ph	H	$(Me_2N)_2CHOMe$	76	47
PhCH=CH	H	B	90	1
CH_3	H	B	29	47

Table 21 (*Contd*)

R	R'	Acetal	% Yield	Ref.
CH_3	H	$(Me_2N)_2CHOMe$	53	47
$-(CH_2)_4-$	-	B		56
		B		52
$(EtO)_2CH$	H	B	80	57
Ph	CH_3	$(Me_2N)_2CHO$-t-Bu	a	54
Ph	Ph	"	a	54
Pr	Et	"	a	54
$-(CH_2)_{10}-$	-	"	a	54
Cholestan-3-one		"	a,b	54
		"	a	54
		$(Me_2N)_2CHO$-t-Bu	98	55
		"	87	55
		"	95	55
		"	100	55
		"	97	55
		"	91[c]	12
Ph	NMe_2	$(Me_2N)_2CHO$-t-Bu		48
p-Br-C_6H_4	NMe_2	"		48
p-MeO-C_6H_4	NMe_2	"		48

a
No yield given.

b
The product is the 2-enamin-3-one compound.

c
In this case, the bisenamine is formed.

The enaminone from pyruvaldehyde diethyl acetal[56b] was also found to be an efficient precursor to a number of heterocycles by its reaction with 1,2- or 1,3-dinucleophiles. Thus, reaction of enaminone (**110c**) with hydrazine, methylthioguanidine, and formamidine has provided imidazol diethyl acetal (**112c**), 2-methylthio-4-pyrimidal diethyl acetal, and 4-pyrimidal diethyl acetal, respectively, in good overall yields.

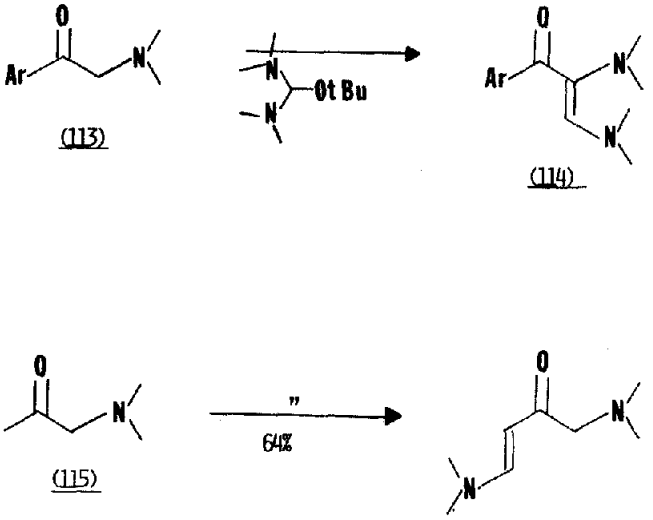
Bredereck *et al.*[48] have also studied the reaction of formamide acetals with α-monosubstituted ketones. In the case of α-dimethylaminomethyl aryl ketones (**113**), reaction with formamide acetals produces 1,2-bis(dimethylamino)ethylene aryl ketones (**114**) in 74–92% yields (Scheme 48). If, however, an unsubstituted methylene is adjacent to the CO, then formylation occurs on the unsubstituted side as is the case with 1-dimethylamino-2-propanone (**115**) (Scheme 48). These 1,2-bis(dimethylamino)enaminones (**114**) also react with 1,2- and 1,3-bisnucleophiles, such as hydrazine and formamidine, to give the respective pyrazole or pyrimidine in good yield (*see* Scheme 47).

Wasserman and Ives[54] have described a facile process for converting ketones to 1,2-diketones via enaminones. In their study treatment of a ketone with bis(dimethylamino)-t-butoxymethane under mild conditions provided the respective enaminone. Without isolation, although they reported the enaminones could be isolated, the enaminone was photo-oxidized ($h\nu$, O_2, $-78°$) to the 1,2-diketone in high overall yields (>68%). Three illustrative examples of this useful, simple transformation are given in Scheme 49.

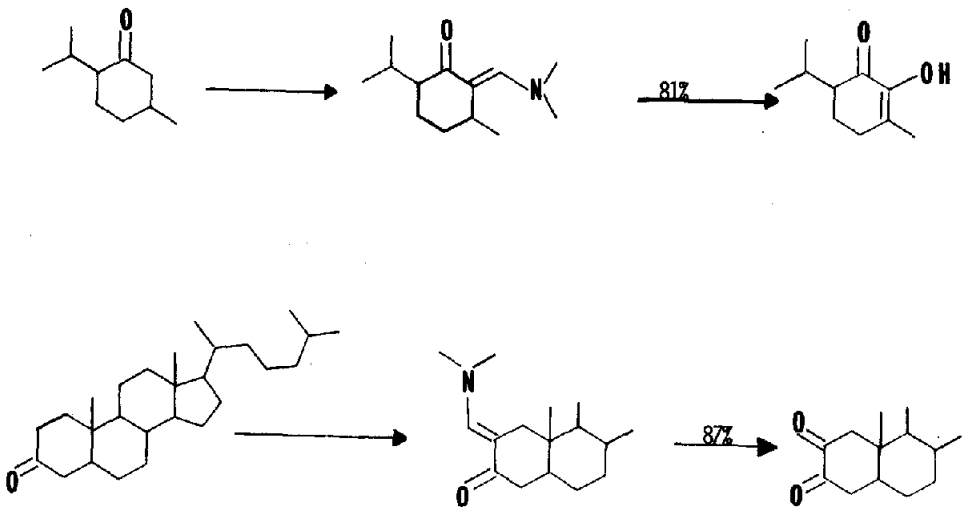
Another application of enaminones as synthetic intermediates was found by Trost *et al.*[55] who described the conversion of ketones to α-keto dithianes (Scheme 50). In this transformation, a cyclobutanone was heated with bis(dimethylamino)-t-botoxymethane at 50°–70° to give the enaminone in excellent yield. Solvolysis of this compound in the presence of trimethylenedithiotosylate, in buffered ethanol, led to replacement of the enamine with a trimethylenedithio group to produce ketone **116** in 62% yield. Cleavage of this α-ketodithiane with sodium methoxide gave ester **117** in 60% yield. Other examples by Trost *et al.* proceed in a similar manner.

A novel use of formamide acetals is found in the synthesis of the adamantane ring system (**119**) from the diketone **118**. Stetter and Dorsch[58] observed that dimethylformamide diethyl acetal acts as a one-carbon lynch pin to close two 6-membered rings. Therefore treatment of diketone **118** with dimethylformamide diethyl acetal, B, in the presence of *p*-toluenesulfonic acid catalyst at 125°–145° gave, via the proposed enamine intermediate, the amino dione **119** in 84% yield (Scheme 51). Other examples of this ring closure with other amide acetals were also reported by these authors.

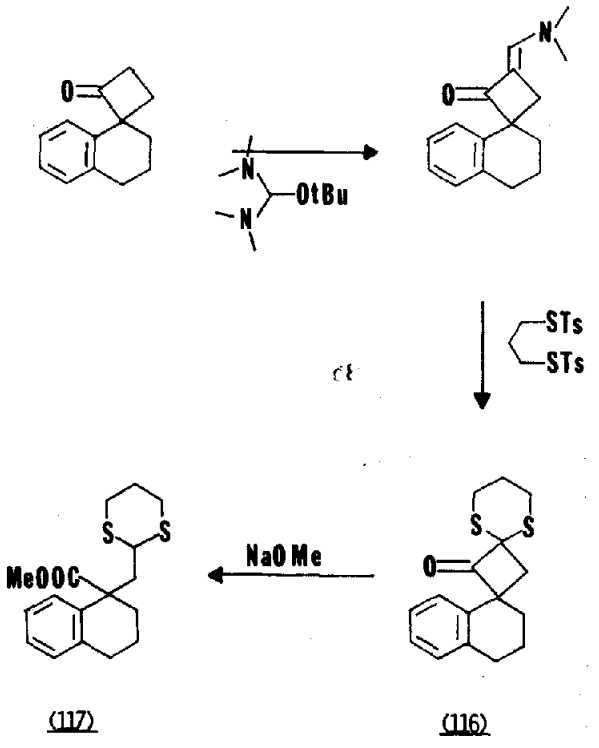
Recently, formamide acetals have found considerable importance in the synthesis of complex heterocyclic systems and natural products. Specifically, formamide acetals have been used in two syntheses of the 4-pyridinone ring system.[59,60] Both routes (Schemes 52 and 53) begin with enaminone **121**. This enaminone is readily available from acylation of enamine **120** with ethyl malonoyl chloride. In Scheme 51 enaminone **121** is treated with either the diethyl or dimethyl acetal of dimethylformamide to



Scheme 48.



Scheme 49.

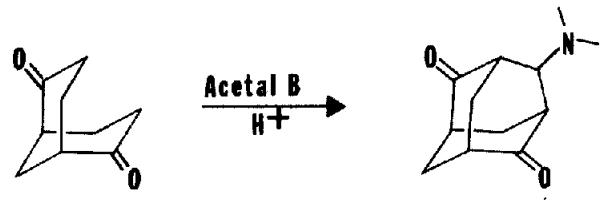


Scheme 50.

provide the bisenaminone **122**. Cyclization of **122** to the 4-pyridinone (**123**) occurs upon treating with methylamine hydrochloride in ethanol under reflux.

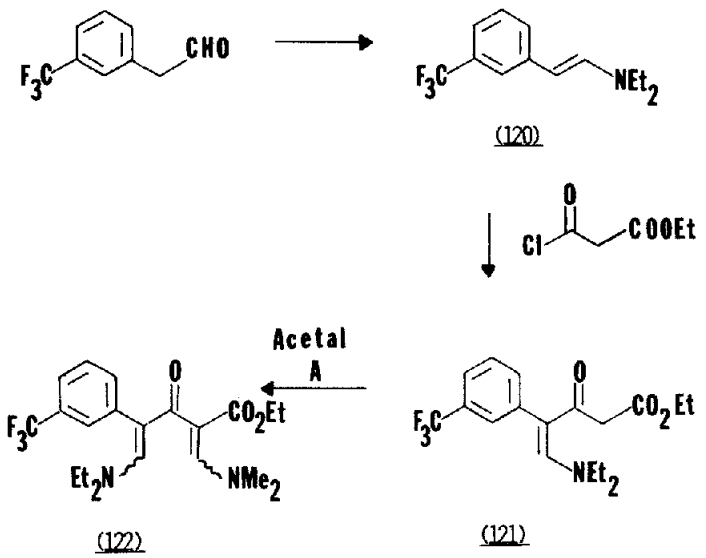
In Scheme 53 enaminone **121** is first treated with aqueous methylamine in methanol or refluxing in ethanol containing methylamine hydrochloride to afford the enaminone **124**. Treatment of **124** with either the diethyl or dimethyl acetal of dimethyl formamide produces the unisolated intermediate **125**, which closes to the pyridinone ring system (**123**). These two routes proceed in comparable yields.

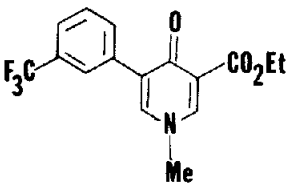
In a similar fashion, Beck and Gajewski[61a] have synthesized pyrimidine (**127**). Formylation of *m*-trifluoromethylphenyl acetamide with dimethylformamide dimethyl acetal (dimethylformamide, 120°)



(118) (119)

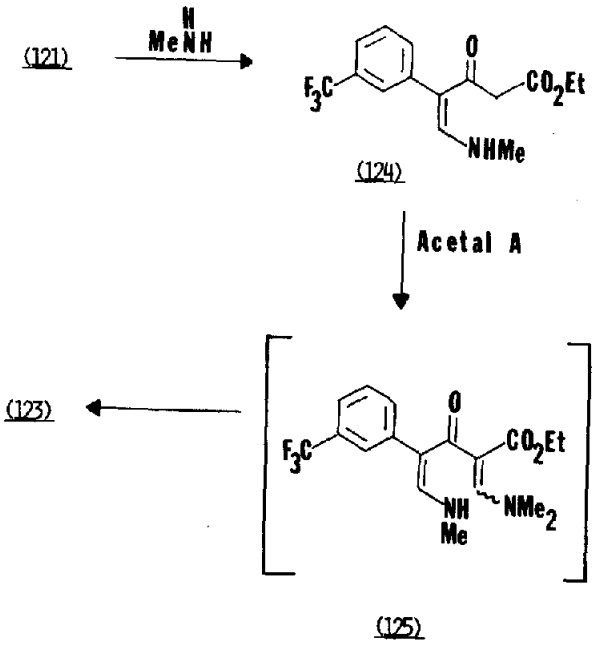
Scheme 51.



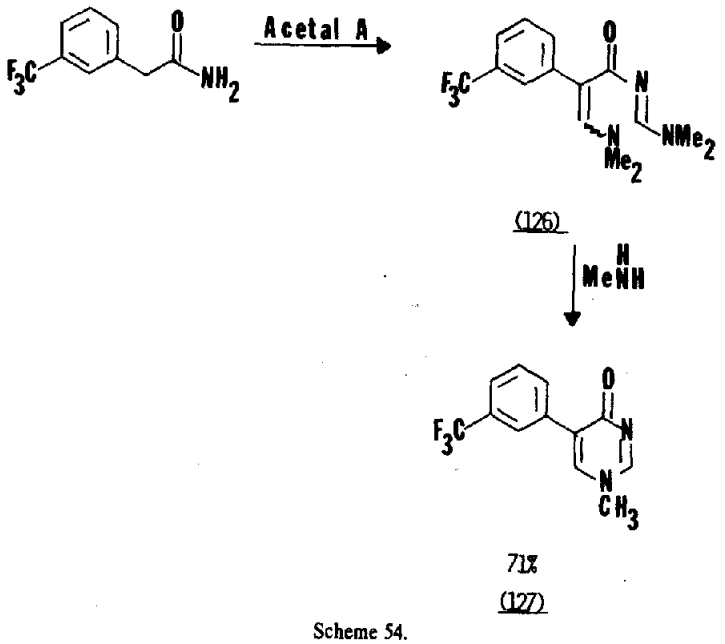


(123)

Scheme 52.



Scheme 53.

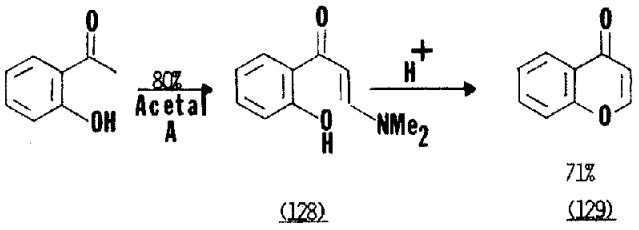


Scheme 54.

provided the enamino amidine (**126**) in 89% yield (Scheme 54). Cyclization of **126** occurs when it is treated with methyl or ethylamine thus providing the pyrimidinone (**127**) in 71% yield.

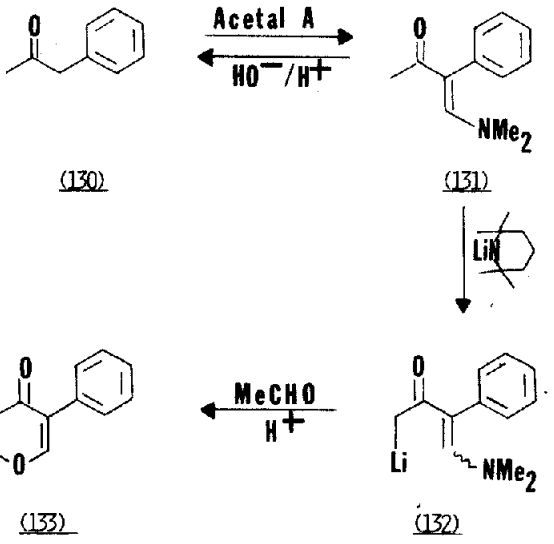
The reaction of the dimethylformamide acetals with the Me group of acetophenones to afford enaminones was used by Föhlisch and others[62] in a convenient synthesis of chromanones. It was found that upon refluxing *o*-hydroxyacetophenone in the presence of acetal A and xylene, with continuous removal of the methanol formed in the reaction, an 80% yield of the intermediate enaminone (**128**) was obtained. Upon treatment of **128** with dilute acid, the desired chromanone (**129**) was produced in 71% yield (Scheme 55).

Vinick and Gschwend[63] have reported that 2,3-dihydro-4-pyrones can be synthesized from enaminones prepared from ketones and formamide acetals. In this route treatment of phenyl acetone (**130**) (Scheme 56) with dimethylformamide dimethyl acetal, A, gave the enaminone (**131**) in 88% yield.



(128) (129)

Scheme 55.



(130) (131) (133) (132)

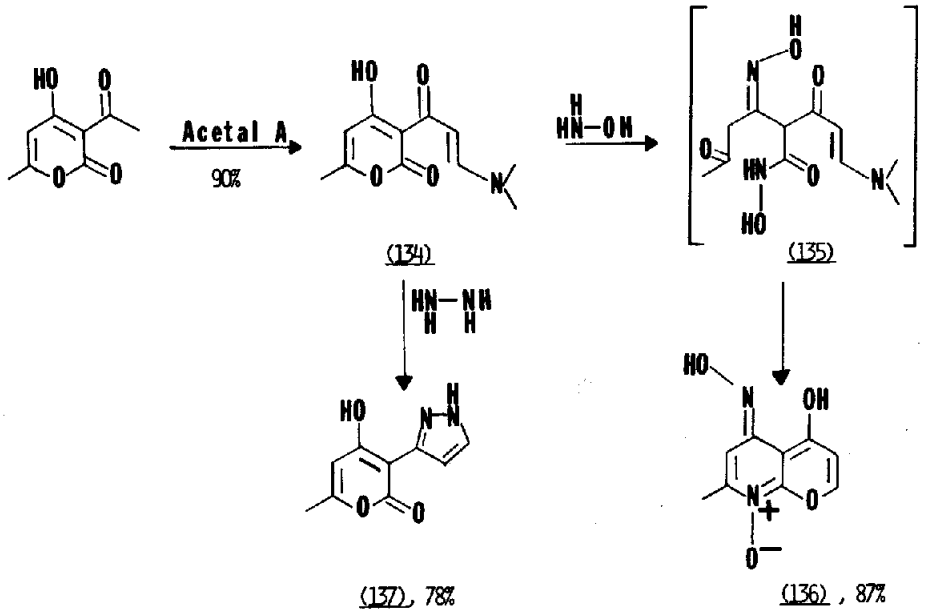
Scheme 56.

The enamine functionality now serves to block the active methylene from reaction with lithium tetramethylpiperidine such that anion (**132**) can be formed. Reaction of the lithio anion (**132**) with acetaldehyde followed by acid hydrolysis gave the α-pyrone (**133**) in 67% yield. Other examples of this reaction were also reported. It is noteworthy that the enamine can be used as an active methylene blocking group, as in **131**, and then can be readily removed by treating with sodium hydroxide followed by aqueous acid to give back ketone **130**[63] (Scheme 56).

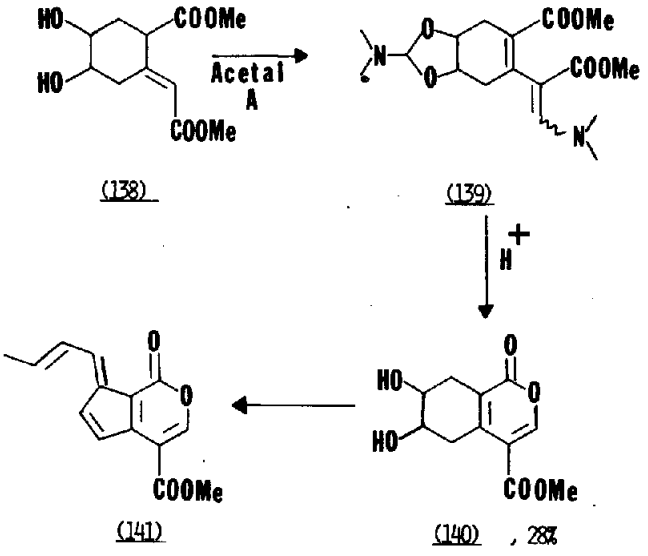
Löwe[64] recently described a two-step synthesis of pyrano(2,3-b)pyridine derivatives. Dehydroacetic acid was condensed with acetal A to give the enaminone **134**. Treatment of this enaminone with hydroxylamine led to lactone ring fission product (**135**), and an alternate cyclization afforded the pyrano(2,3-b)pyridine (**136**) in 87% yield. However, treatment of the intermediate enaminone **134** with hydrazine hydrate produced a different result, giving pyrazole (**137**), via a vinylogous hydrazide, in 78% yield (Scheme 57).

Büchi and Carlson[65] used dimethylformamide dimethyl acetal to effect a key transformation in the total synthesis of fulvoplumierin (**141**) (Scheme 58). Treatment of a mixture of isomeric diols (**138**) with acetal A in dimethylformamide (80°, 5 hr) gave the enaminoester **139**. Treatment of crude **139** with dilute hydrochloric acid effected cyclization of the enaminoester to the α-pyrone with concomitant hydrolysis of the amide acetal to the diol, to provide compound **140** in 28% yield from **138**. This α-pyrone was then converted to fulvoplumierin (**141**).

Chorvat *et al.*[66a] found that dimethylformamide acetals can be utilized to form heterocyclic rings useful in the synthesis of heterosteroids. In particular, the substituted cyclohexanone (**142**) was used as the precursor to the A and B rings of the target azasteroid (**145**), and only a one-carbon lynch pin was needed to close the A ring (Scheme 59). Using a reaction earlier reported by Granile *et al.*,[66b] Chorvat *et al.* demonstrated that upon treating **142** with dimethylformamide diethyl acetal, B, in dimethylformamide



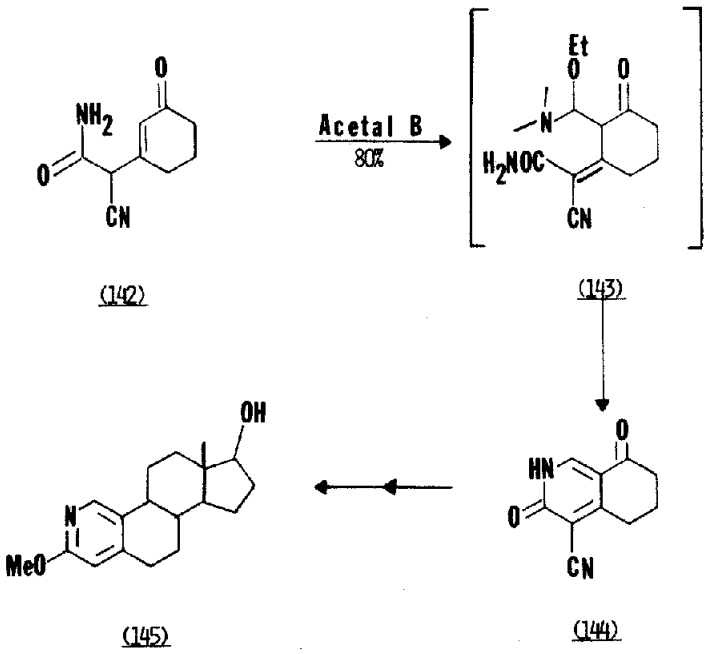
Scheme 57.



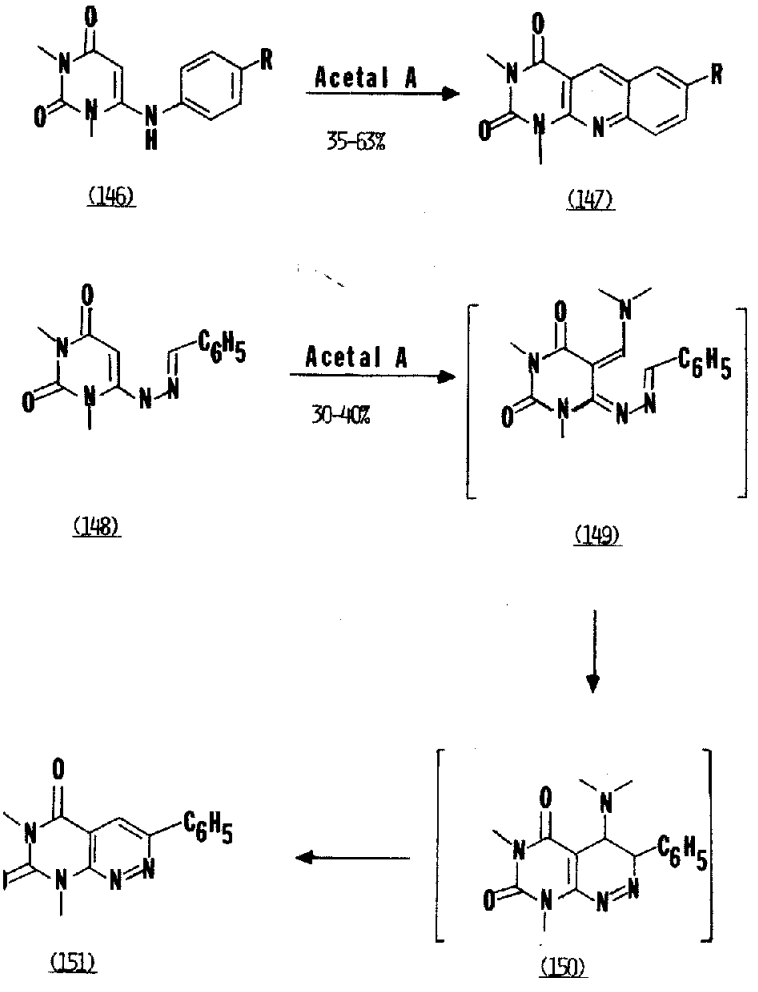
Scheme 58.

at room temperature, the A,B-ring system (**144**) was obtained in 80% yield. The nonisolable intermediate of this reaction appears to be the formylated cyclohexanone (**143**) which after substitution and elimination gives **144**. The A,B-system (**144**) was then carried on to (±)-2-azaestradiol-3-methylether (**145**).

Several groups[67,68] have used dimethylformamide dimethyl acetal, A, as a reagent for the ring closure of substituted pyrimidines (e.g. **146** or **148**) to pyrido pyrimidines[67] (**147**) and pyrimido pyridazines[68] (**151**), respectively (Scheme 60). The key step preceding the electrocyclic ring closure is formation of an enamine at C_5 of the pyrimidine ring (**149**). Annulation to **150** followed by elimination of dimethylamine affords the pyrimidopyridazine (**151**) in 30–40% overall yield. Yoneda *et al.*[68] also observed that the



Scheme 59.



Scheme 60.

Vilsmeier reagent did not effect this cyclization. In a similar reaction sequence, Anderson found this method useful in closing a fused heterocycle on nitrogen.[68]

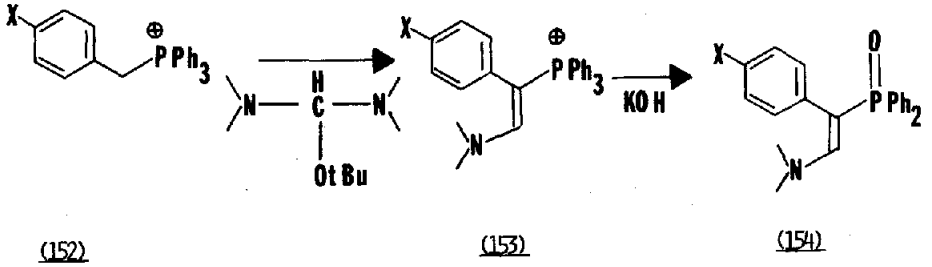
Another type of active methylene which is found to react with formamide acetals is that adjacent to a phosphonium or phosphonate group.[69] Bredereck *et al.*[69a] have reported that phosphonium salts, such as **152**, (Scheme 61) upon treatment with bis(dimethylamino)-t-butoxymethane give the enamine salts (**153**) in 50–96% yield. Subsequent aqueous hydroxide treatment of **153** (X = OMe) gave enamine **154** in 52% yield. In the case where X = H, treatment with sodium ethoxide led to the formation of 1-dimethylaminostyrene (16%) and triphenylphosphine oxide.

Othet types of active C–H compounds have been reported to undergo formylation with formamide acetals. For example, phenylacetylene reacts at 140° with dimethylformamide diethyl acetal, B, and with tris(dimethylamino)methane to give the aminal of an acetyline aldehyde (**155**).[17] Likewise, hydrogen cyanide undergoes formylation in 95% yield bis(dimethylamino)-t-butoxymethane, in 86% yield with acetal B and in 71% yield with tris(dimethylamino)methane (Scheme 62).

The reaction of aromatic aldehydes with bis(dimethylamino)-t-butoxymethane afforded an unexpected product.[11b] If the reactants in a ratio of 1 mole of aldehyde to 3 moles of aminal ester were warmed for 3–4 hr at 110°–140°, the loss of t-butanol was observed. Fractionation of the reaction mixture led to about 30% recovery of the corresponding 1,2-bis(dimethylamino)vinyl aryl ketones (**156**) (Scheme 63). In one instance (X = Me, Scheme 63), the identity of the product was established by alternate synthesis of **156** from dimethylaminomethyl-*p*-tolyl ketone and bis(dimethylamino)-t-butoxymethane. No mechanism has been proposed to explain the formation of **156**.

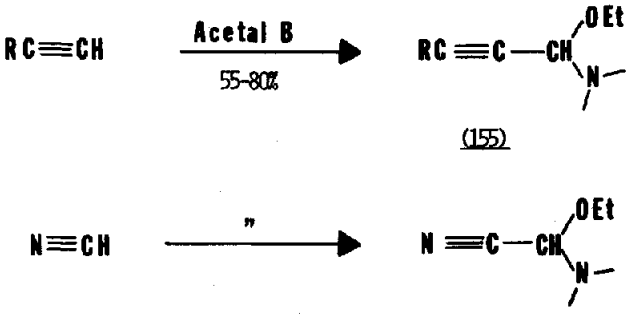
Bredereck *et al.*[73] have also studied the reactions between azomethines and bis(dimethylamino)-t-butoxymethane, which on heating for 6 hr under an inert atmosphere gave 2,2-bis(dimethylamino)-1-anilino-1-phenylethylene. This reaction was very substituent dependent and failed with *p*-methoxybenzylidene aniline and with methyl and cyclohexyl benzylidene amines. With Schiff bases of alipathic aldehydes the aminal ester functioned as a CH formylating agent (Scheme 64).

The reaction of bis(dimethylamino)-t-butoxymethane with azines of aromatic aldehydes affords

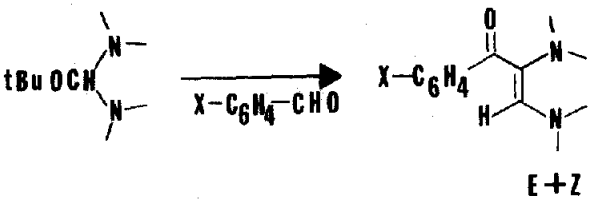


(152) (153) (154)

Scheme 61.

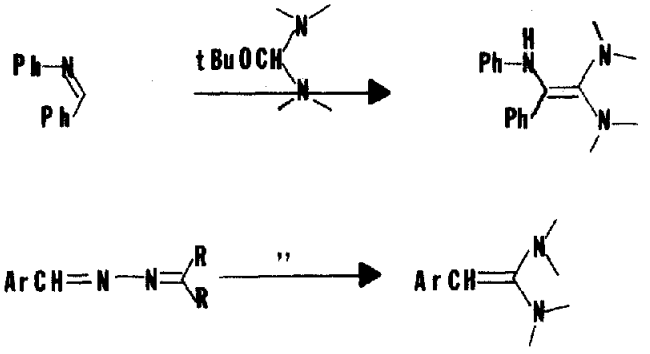


Scheme 62.



(156)

Scheme 63.



Scheme 64.

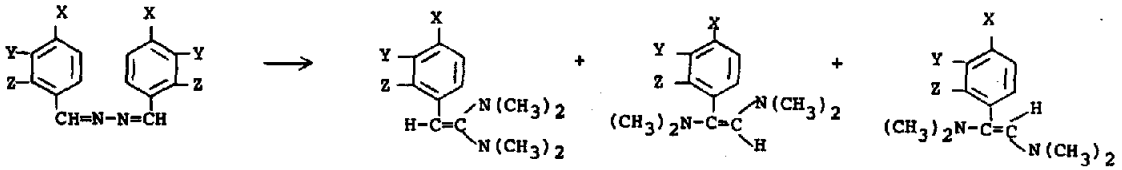
ketene aminals with concomitant formation of diazomethanes according to Scheme 64. Though there is no direct evidence for the formation of the diazomethanes, owing to their unstable nature, the observation of nitrogen evolution and the isolation of dibenzylidene hydrazine provides good circumstantial evidence for invoking a diazoalkane intermediate (Scheme 65).

In addition to ketene aminals, the reaction of aromatic azines with an aminal ester also gives an isomeric mixture of enediamines. The distribution of isomers is shown in Table 22. The reaction of an aminal ester with diphenyl diazomethane alone also afforded mixtures of ketene aminal, and E and Z enediamines. Scheme 66 proposed by Bredereck *et al.* is consistent with the preceding experimental facts.

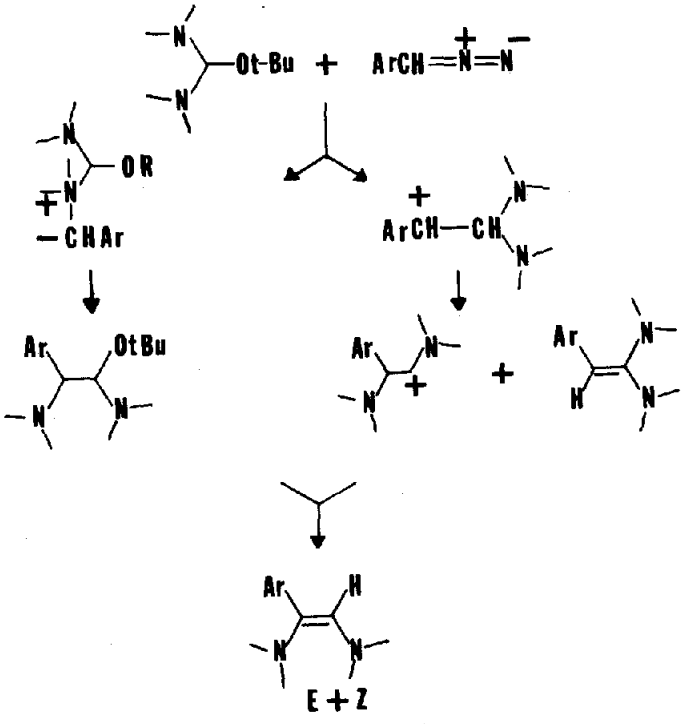
A one-carbon homologation process that converts allylic alcohols (**157**) into β,γ-unsaturated amides (**161**) via a [2,3]sigmatropic was reported by Büchi *et al.*[74a] This reaction occurs when an allylic alcohol is heated with a formamide acetal in a solvent such as collidine or xylene. For example, tertiary allylic

Scheme 65.

Table 22. Condensation of aminal esters with azines of aromatic aldehydes—isomer distribution



X	Y	Z	%	%	%
H	H	H	57	29	14
CH_3	H	H	61	25	14
CH_3O	H	H	56	26	18
Cl	H	H	75	17	8
$(CH_3)_2CH$	H	H	75	17	8
H	CH_3	H	69	23	8
H	OCH_3	H	59	21	20
H	Cl	H	63	29	8
H	H	CH_3	67	33	-
H	H	OCH_3	75	25	-
H	H	Cl	80	20	-

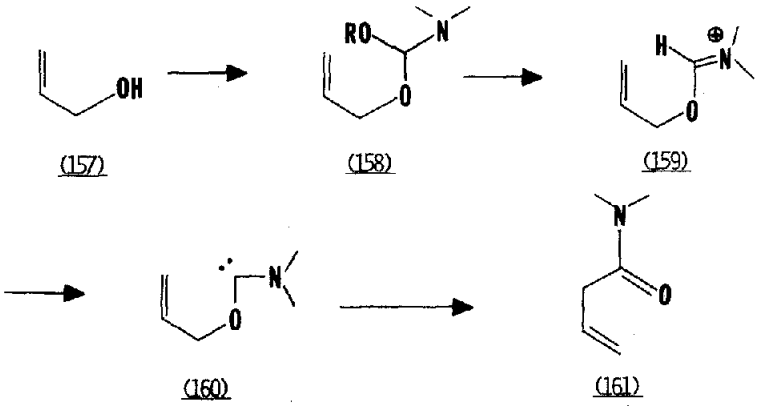


Scheme 66.

alcohols can be converted to mixtures of *E* and *Z* unsaturated amides (**161**) in yields ranging from 66% to 75% using acetal B or C, respectively. Secondary allylic alcohols underwent this transformation at higher temperatures (180°) with comparable yields of the unsaturated amides (56–76%), but with a preponderance of *E* isomer in the product. The mechanism of this transformation according to Büchi begins with the mixed acetal (**158**) which upon heating looses either ethanol or neopentyl alcohol to afford imidate **159**. The imidate (**159**) collapses to a carbenoid species (**160**) which undergoes a [2,3]sigmatropic rearrangement to the amide **161** (Scheme 67).[75,76]

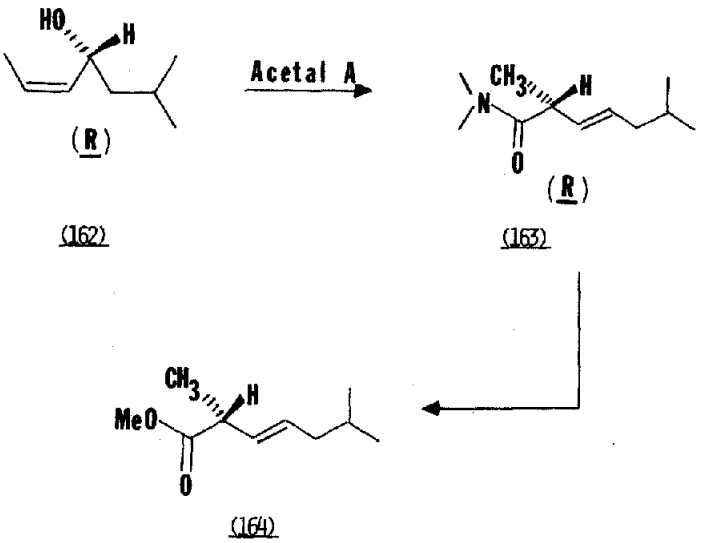
In their study of the mechanism of this reaction, Büchi *et al.* found that (−)-*cis*-carveol undergoes the rearrangement with some enantiomeric bias. More recently, Chan and Saucy[74b] in an expanded investigation of the transfer of chirality via this [2,3]sigmatropic process found that heating optically active (*R,Z*)-allylic alcohols such as **162** with acetal A gave the optically active (*E*)-amides (**163**) and that the process occurred with complete stereoselectivity. By conversion to a compound of known optical purity (**164**), the rearrangement was found to proceed with nearly 100% transfer of chirality (Scheme 68). However, the (*S,E*)-allylic alcohol afforded mixtures of (*R,E*)- and (*S,Z*)-β,γ-unsaturated amides which upon chromatography provided nearly optically pure (*E,E*)-isomer (Table 23). Table 23 delineates some representative examples from the work of Büchi *et al.*[74a] and Chan and Saucey.[74b] In a related investigation, Parker *et al.*[77] have described the conversion of tertiary propargylic alcohols into either dienamines or enamine orthoformates, the ratio of products being substrate dependent (Table 23).

The DMF acetals also react as formylating agents with primary amines and amides providing amidines and cryl amidines, respectively (Scheme 69).[78a,b] This formylation proceeds under generally mild conditions in high yields and as seen in Table 24 is a quite universal procedure. Since these findings, a number of investigators have found these amidines to be useful in the synthesis of more complex



(157) (158) (159) (160) (161)

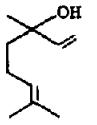
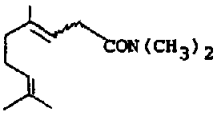
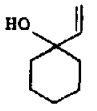
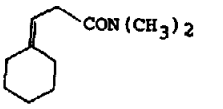
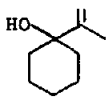
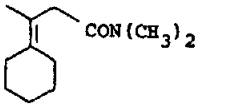
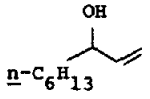
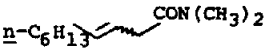
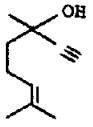
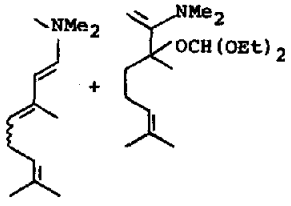
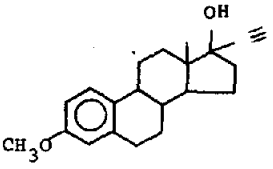
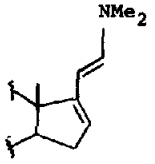
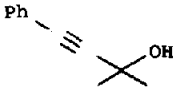
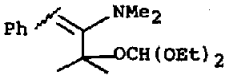
Scheme 67.



(162) (163) (164)

Scheme 68.

Table 23. The reaction of formamide acetals with unsaturated alcohols (Scheme 67)

Alcohol	Product	% Yield (E:Z)	R	S	Ref.
		70[a] (42:58) 75[b]			74a
		76[a] 66[b]			74a
		70[a] 70[b]			74a
		56[a] (89:11) 77[b] (89:11)			74a
Z-(162)	E-(163)	49[c] (100:0)	96	4[d]	74b
E-(162)	E- and Z-(163)	76[c] (87:13)	87	13[c]	74b
	 24% 40%				77
		ca. 90[f]			77
		55			77

[a] Acetal B in xylene.

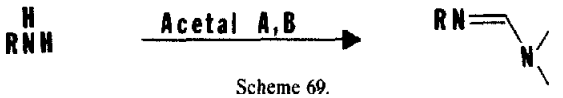
[b] Acetal C in collidine.

[c] Acetal A in xylene.

[d] The enantiomeric composition of (Z)-(162) was 96.5% R, 3.5% S. The resultant chirality transfer is ca. 100%.

[e] The enantiomeric composition of (E)-(162) was 97.8% S, 2.2% R.

[f] Yield based on the yield of the corresponding aldehyde obtained after hydrolysis of the enamine.



Scheme 69.

Table 24. Formation of amidines from amines and dimethylformamide acetals

$R\text{-}NH_2 \longrightarrow R\text{-}N{=}CHN(CH_3)_2$

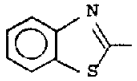
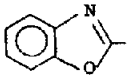
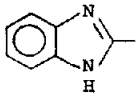
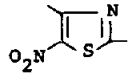
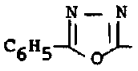
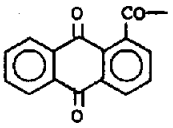
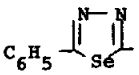
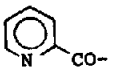
R	Acetal	% Yield	Ref.
CH_3CO	$[(CH_3)_2N]_2CH\text{-}O\text{-}\underline{t}\text{-}Bu$	85	49
CH_3CO	B	-	75
CH_3CH_2CO	$[(CH_3)_2N]_2CH\text{-}O\text{-}\underline{t}\text{-}Bu$	83	49
$CH_3(CH_2)_2CO$	"	84	49
"	A	56	78a
$CH_2{=}CHCO$	B	-	78b
C_6H_5CO	A	75	78a
"	B	-	78b
C_6H_5CS	B	-	78b
$4\text{-}OCH_3\text{-}C_6H_4\text{-}CS$	B	-	78b
-CO-	A	69	78a
"	B	41	80a
$-SO_2-$	B	99	78a
$CH_3CH_2O_2C-$	B	92.5	78a
$H_2NCONH-$	B	69	1
$4\text{-}CH_3\text{-}C_6H_4-$	B	79	1
$4\text{-}NO_2\text{-}C_6H_4NH-$	B	75	1
"	A	97	78a
$4\text{-}NO_2\text{-}C_6H_4$	$HC[N(CH_3)_2]_3$	87	8c
-CS-	B	93	80a
$3,4\text{-}(Cl)_2\text{-}C_6H_3-$	A	68	78a
$2,4\text{-}(NO_2)_2\text{-}C_6H_3-$	A	89	78a
$2,4\text{-}(NO_2)_2\text{-}C_6H_3NH-$	A	97	78a
$(CH_3)_2N-$	A	78	78a,71
$(NC)_2C{=}C<$	A	95	78a
	A	95	78a
$4\text{-}CH_3\text{-}C_6H_4\text{-}SO_2NH-$	A	89	78a
$(C_6H_4O)_2PO-$	A	49	78a
$(CH_3CH_2O)_2PO-$	A	67	78a
	A	85	82
	B	90	85
	B	-	85
	B	-	85

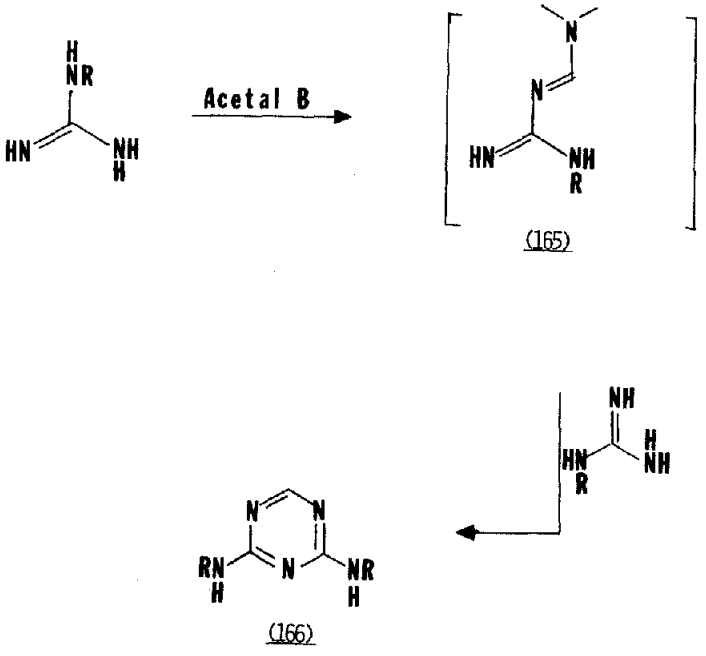
Table 24 (*Contd*)

R	Acetal	% Yield	Ref.
	B	-	81
	B	-	85
	B	-	78b
	B	-	85
	B	90	80a
	B	91	80a
	B	64	80a
	A	85	82
	A	94	82
	B	87	80a
	B	85	80a
$2\text{-}NO_2C_6H_4$-	B	89	80a
$3\text{-}NO_2C_6H_4$-	B	78	80a
$4\text{-}NO_2C_6H_4$-	B	91	80a
	B	80	80a
	B	88	80a
	B	95	80a
C_6H_{11}-	$ROCHCN[N(CH_3)_2]_2$	52	71
$4\text{-}Cl\text{-}C_6H_4$-	"	77	71
CH_3-	"	51	71
$(CH_3)_2CH$-	"	57	71
$CH_3CH_2CH_2$-	"	53	71
$CH_3(CH_2)_3$-	"	61	71

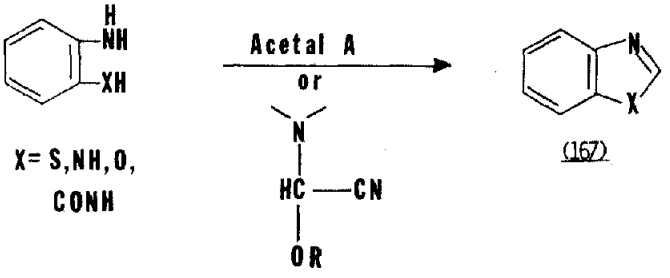
molecules. For instance, Bredereck *et al.* have developed a synthesis of S-triazene (**166**) based on this reaction (Scheme 70). Thus, the reaction of guanidine or its derivatives with acetal B provides the intermediate amidine (**165**). Treatment with a second mole of guanidine followed by ring closure provides triazine (**166**).[80a] For the synthesis of amidines in which the secondary amine is esoteric or difficult to prepare, initial amine exchange may be performed on the formamide acetal and the product then may be used to formylate the readily accessible primary amine.[80b]

When a neighboring heteroatom may undergo intramolecular reaction with the amidine, new syntheses or heterocycles have been developed. Thus, reaction of *ortho*-amino-, mercapto-, or amidoanilines with acetal A[83] at 120° or a cyanoacetal[71] gave the corresponding heterocycles (**167**) in 26–76% yield (Scheme 71). When X is oxygen, the sequence does not afford any benzoxazole with acetal A. Reaction with the cyanoacetal, however, does provide the benzoxazole (**167**, X = 0). Other similar systems have also been synthesized using this reaction sequence.

Amidines are also formed from heterocyclic amino compounds, such as 2-aminobenzothiazole (**168**), and DMF acetals (Table 25) (Scheme 72). Here again, the reaction proceeds under mild conditions and in high yields. The resulting amidines can be viewed as 1,3-diaza-1,3-butadiene systems. These molecules

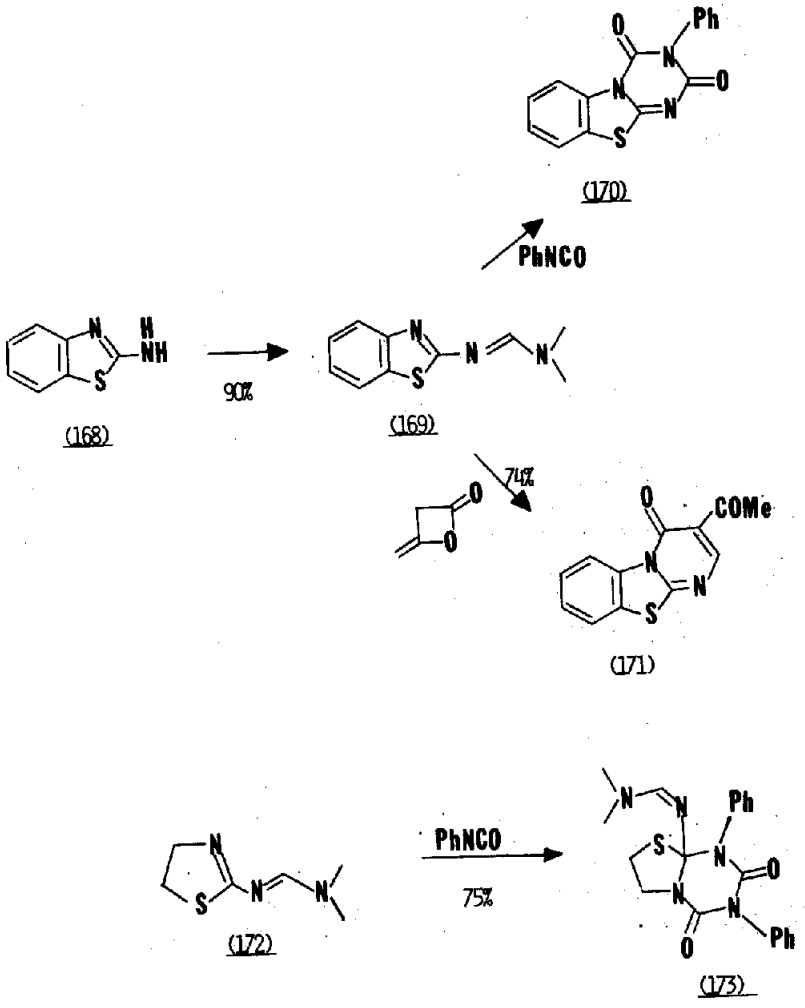


Scheme 70.



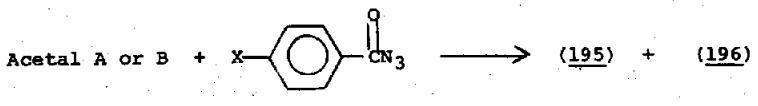
Scheme 71.

are therefore vulnerable to 1,4-dipolar cycloadditions. Richter and Ulrich[82] have found that these heterocyclic amidines will indeed undergo this type of cycloaddition reaction with aryl isocyanates. Thus, when amidine **169** is treated with phenylisocyanate at 240° for 15 min, the fused heterocyclic system **170** is formed. The conditions for these reactions are critical. For example, when amidine **172** is



Scheme 72.

Table 25. Reaction of an acyl azide with acetal A or B



Acetal	X	Conditions (h/°C)	% (195)	% (196)
A	H	7/60°	91	60
B	H	7/60°	88	89
A	OEt	12/63° to 1/80-100°	87	62
A	NO_2	7/65°	-	-

treated with phenylisocyanate for 3 hr at 80° (Scheme 72), the product has incorporated two moles of isocyanate and one mole of **172** to give compound **173** in 75% yield.

In a similar dipolar cycloaddition reaction, Sakamoto *et al.*[84a] have found that these azadienes also react with diketene. In this context, when azadiene **169** was treated with diketene in refluxing benzene for 6 hr, pyrimidone **171** was formed in 74% yield (Scheme 72). This reaction is quite general for cyclic azadiene systems like **169**. In addition, the related thioacylamidines[84b] react in an analogous fashion with ketene to provide 1,3-thiazen-6-ones.

Yoneda *et al.*[85–87] have reported a number of examples of amidines, generated from amines and dimethylformamide acetals, undergoing intramolecular cyclizations to give heterocyclic systems. When 1,3-dimethyl-5-benzalamino-6-aminouracil (**174**) was treated with acetal B, the azahexatriene (**175**) was obtained. Thermolysis of **175** in sulfolane resulted in intramolecular cyclization to the lumazine (**177**). Photolysis, on the other hand, yielded theophylline (**176**) in 70–80% yield via a 1,5-coupling reaction. This sequence was utilized by Yoneda *et al.* to provide a variety of purines and pteridines (Scheme 73).

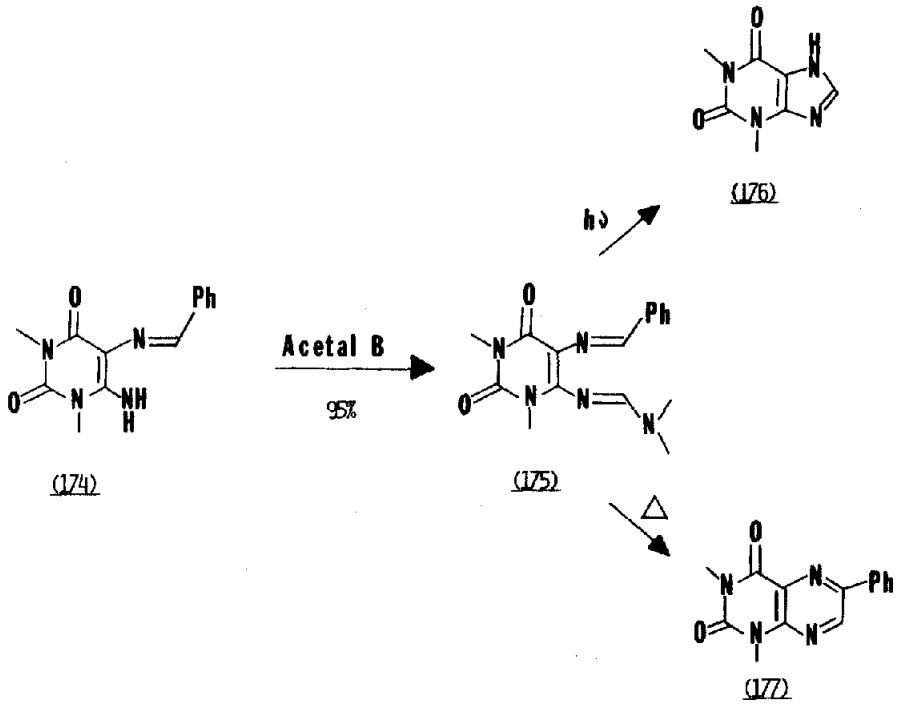
In two previous schemes, amidines have played key roles in: (a) the formation of useful amino acid derivatives (Scheme 23); and (b) the synthesis of 1,5-disubstituted 4(1H)-pyrimidinones (Scheme 54).

Treatment of phosphites or phosphines with a dimethylformamide dialkyl acetals resulted in the replacement of both alkoxy substituents of the formamide for the corresponding phosphorus groups. For example, Gross and Costiaella[88] found that treatment of diethyl phosphite with acetal B at 60°–80° yielded the transphosphorylated formamide (**178**) in 60% yield (Scheme 74). Reaction of this species with sodium hydride followed by an aldehyde gave the enamine phosphonate (**179**) which upon acid hydrolysis gave a carboxylic acid. The overall transformation thus represents a one-carbon oxidative homologation of an aldehyde to an acid. The exchange of only one alkoxy substituent of the formamide acetal was brought about by treating an alkali metal salt of the phosphine with the formamide acetal.

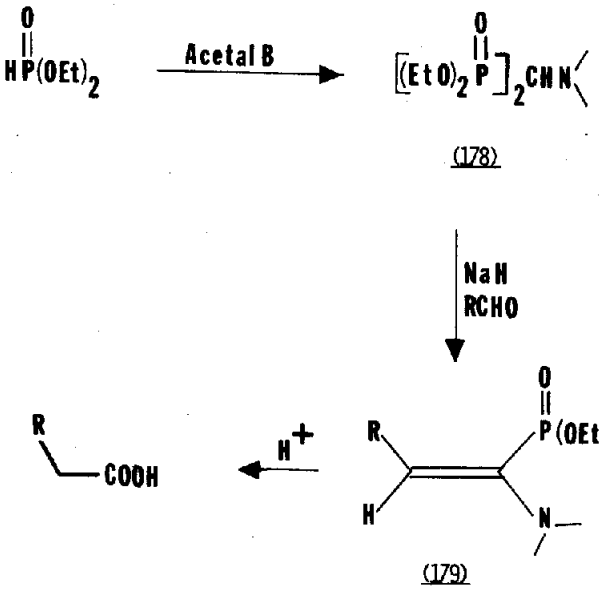
Part (III): *Reaction of formamide acetals as nucleophiles*

Meerwein[1] *et al.* initially described the alkylation of the nitrogen atom of dimethylformamide ethylene acetal with methyl iodide. The ammonium (**180**) lost trimethylamine to give a stabilized carbonium ion which underwent ring fission to give iodoethyl formate (**181**) which upon reaction with the trimethylamine in solution gives the ammonium salt **182** (Scheme 75).

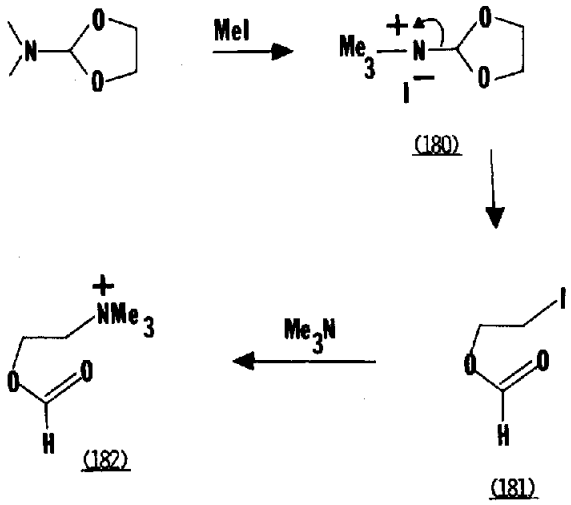
In a similar manner, when dimethylformamide ethylene acetal, E, was treated with hydrochloric acid

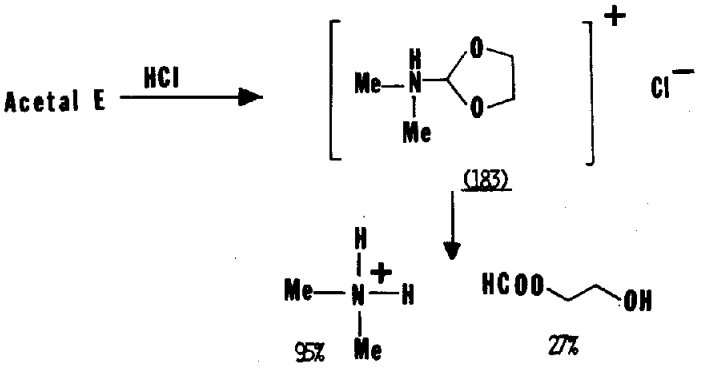


Scheme 73.



Scheme 74.



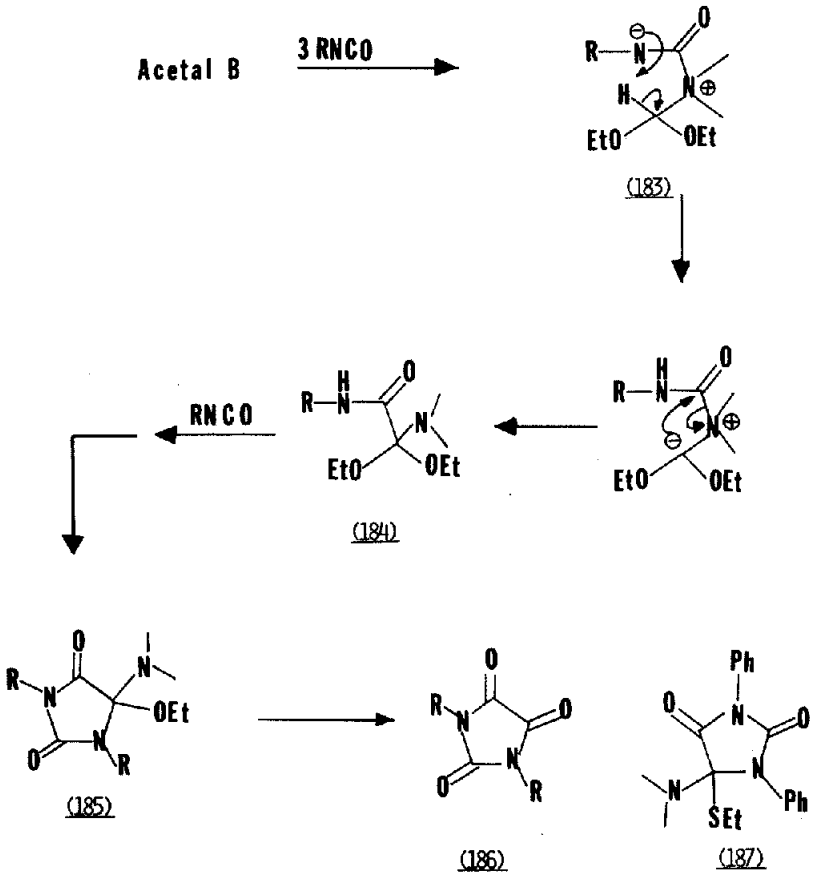


Scheme 75.

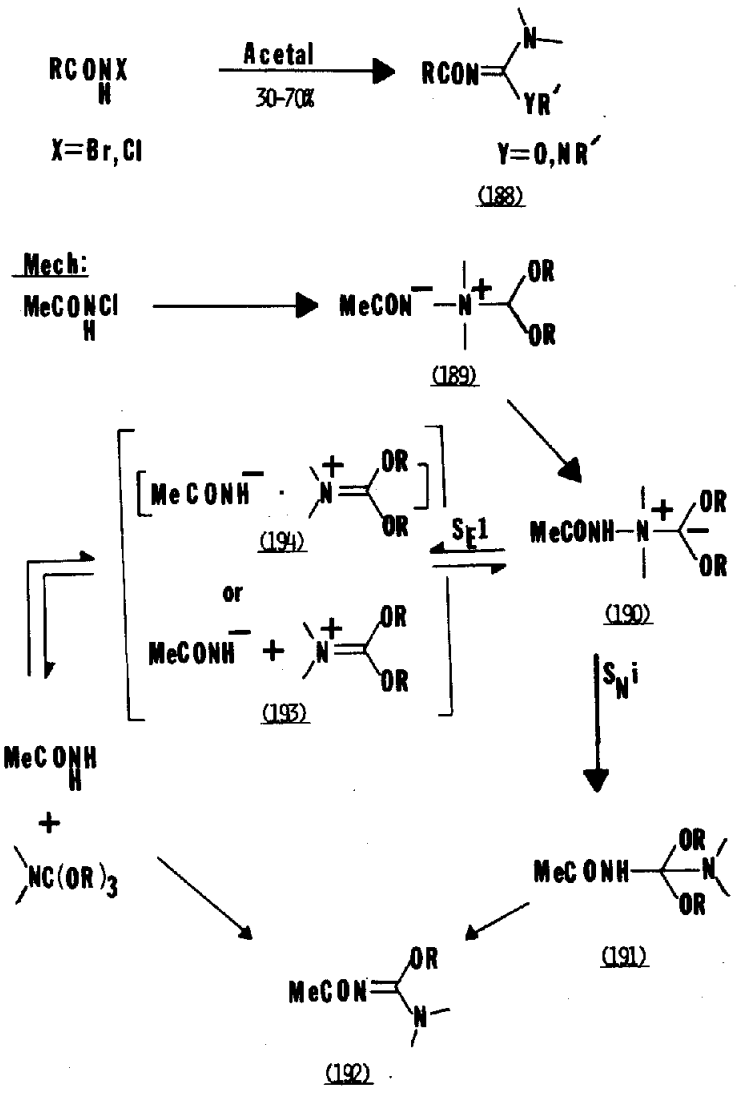
in ether, the intermediate cation (**183**) was formed. Hydrolysis then gave dimethyl amine hydrochloride in 95% yield and 2-hydroxyethyl formate in 27% yield. Similar reactions are also seen with other formamide acetals.

The reaction of DMF acetals with aliphatic or aromatic isocyanates and isothiocyanates proceeds in high yield (>90%) to give the corresponding parabanic acid N,O-acetals (**185**) (1,3-disubstituted 5-dimethylamino-5-alkoxy-2,4-dioxoimidazolidines.[89] The mechanism (Scheme 76) proposed by Bredereck *et al.* proceeds by attack of the nucleophilic N atom in the DMF acetal on the isocyanate to give the ylid **183**. This ylid can rearrange to the acylated formamide acetal **184** and then react with a second equivalent of isocyanate to afford the imidazolidine (**185**). The formamide dithioacetal (**34a**)[14] also reacts with phenylisocyanate to give the imidazolidine (**187**). Further evidence for the mechanism proposed by Bredereck *et al.*[89a] was provided by Reiffen and Hoffmann[89b] wherein the carbenoid species obtained from the formamide acetal and sodium hydride reacted analogously with isocyanates and isothiocyanates.

Bredereck *et al.*[90] reported an analogous reaction between dimethylformamide acetals or bis(dimethylamino)-t-butoxymethane and either N-halocarboxamides, N-haloureas, or N-chlorourethanes to give acylisocyanate-O,N- or -N,N-acetals (**188**) (Scheme 77). The mechanism proposed for this transformation[91] involves initial formation of the ylid **189** which upon proton abstraction gives ylid **190**. Ylid **190** can subsequently decompose by two pathways, either an S_E1 or an S_Ni. Both possibilities are shown in Scheme 77. The S_Ni mechanism gives a rearrangement of ylid **190** to the acetalurea **191** which upon elimination of ROH yields the product **192**. The S_E1 mechanism proceeds via decomposition of **190** to either a dissociated ion pair (**193**) or a tight ion pair (**194**). In either case the ion pair must recombine via the amide and acetal to the urreaacetal **191**, as in the S_Ni mechanism and thence afford product **192**.



Scheme 76.



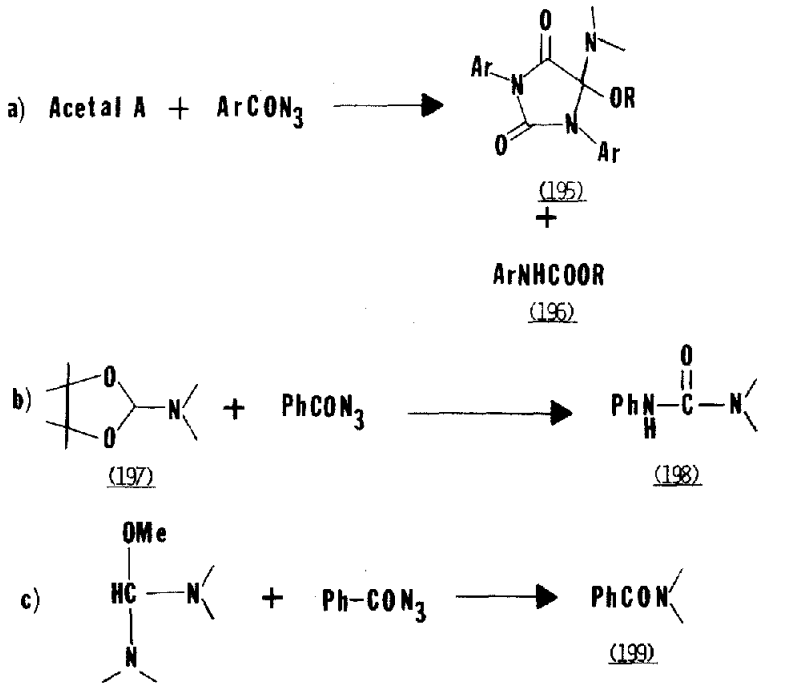
Scheme 77.

In a similar example, Bredereck *et al.*[92] treated formamide acetals with acyl azides. However, the products from this reaction varied, depending on the acetal, azide, and reaction conditions, either thermal or photochemical. For instance, the diethyl and dimethyl acetals of dimethylformamide react with acyl azides under thermal conditions to give the N,O-acetal of an imidazolidine (**195**) as shown in Scheme 78 (see also Scheme 77) with carbamate **196** as the side prroduct. Imidazolidine **195** results from the reaction of two moles of azides with one molar equivalent of acetal. The side product, carbamate **196**, results from transformation of acyl azide to isocyanate (Table 25). In the case of the *p*-nitro acyl azide, neither of these products was formed.

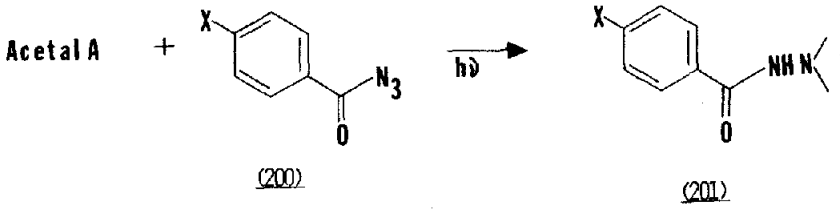
Other acetals likewise gave different results. For example, acetal **197** (Scheme 78) gave the urea **198** in 45% yield while bis(dimethylamino)-t-methoxymethane with benzoylazide gave dimethyl benzamide (**199**).

Photolysis of benzoylazide (**200**) in the presence of acetal A gave benzoylhydrazide (**201**) in moderate yield (Scheme 79). Isolation of this product suggests the intervention of the nitrene pathway indicated earlier.

To explain these results Bredereck proposed the following mechanism (Scheme 80). The aroylazide (**200**) can first decompose either to a nitrene or an isocyanate. Reaction of these intermediates with the



Scheme 78.



Scheme 79.

formamide acetals gave either ylid **202** or **203**. Ylid **202**, in the *nitrene* path, rearranges to ylid **204** which can then decompose to the dimethylhydrazide **205** thus explaining the products from the photochemical reaction in Scheme 79. Ylid **204** may also rearrange to acetal **206** (see Scheme 77) which leads to N,O-acetal **207** which in turn leads to the carbamate **208** (Scheme 80, route a).

In the case where the acyl azide rearranges to the isocyanate, reaction with a formamide acetal would give ylid **203**, as was the case in Scheme 77.[90,91] This ylid, as described in Scheme 77, leads to the N,O-acetal of an imidazolidine explaining the products in Scheme 78.

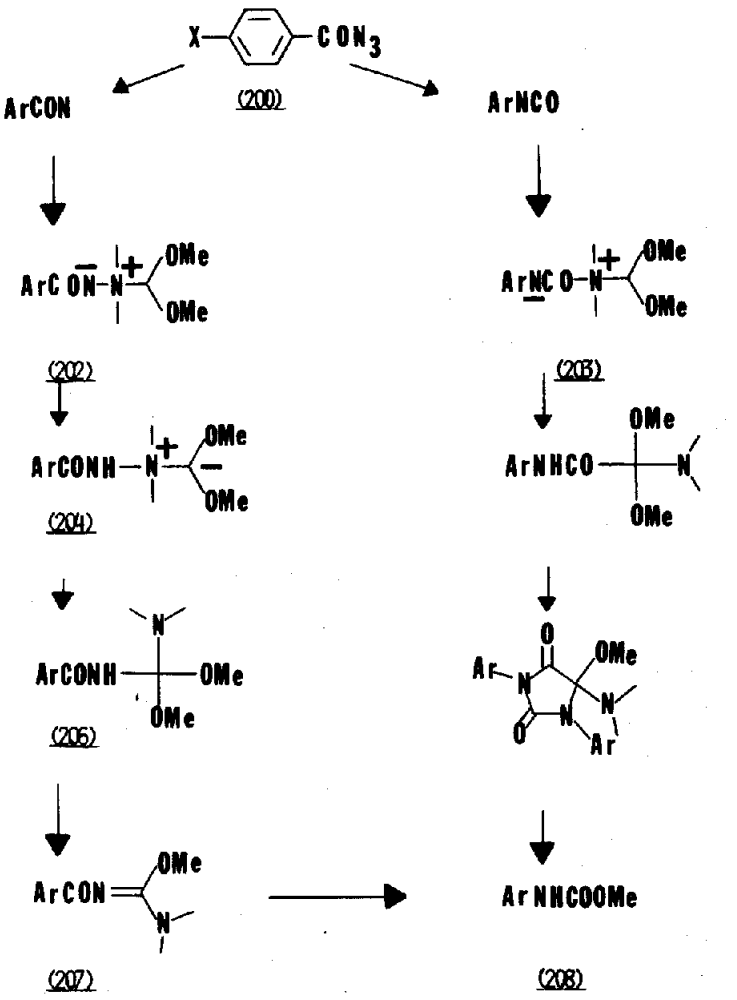
Dimethylformamide acetals have also been found to undergo reaction with α-chloroisocyanates.[93] In this case reaction of 1,2,2,2-tetrachlorethyl isocyanate with acetal A or B yields a mixture of the 1-alkoxy-2,2,2-trichloroethyl isocyanate (**209**) in 47–50% yield and the imino ester **210** in 22–28% yield (Scheme 81).

Part (IV): *Miscellaneous reactions of formamide acetals*

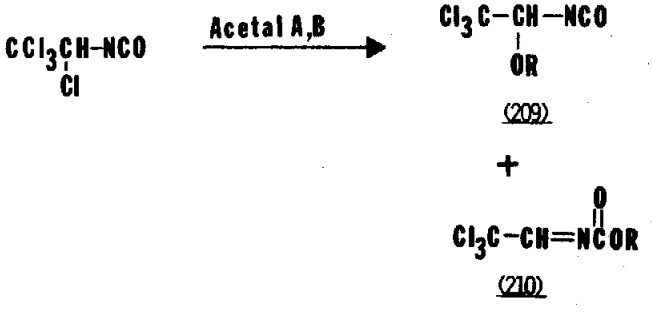
Some reactions of formamide acetals are reported which are not readily categorized under the preceding sections. Therefore, they have been grouped together as miscellaneous reactions.

Leimgruber and Ulick[94] have reported the methylenation of catechols using either formamide acetals, aminal esters, or tris(dialkylamino)methanes in the presence of dichloromethane (Scheme 82). Thus, the function of the orthoamide was that of a strong organic base.

Hanessian and Banoub[95a] have reported a mild, stereocontrolled process for the preparation of 1,2-*trans*-alkyl glycosides from peracyl derivatives. The reaction required activation of the sugar derivatives with a Lewis acid such as stannic chloride in dichloromethane followed by treatment with an N,N-dialkylformamide acetal. These authors also used the glycosidation reaction to synthesize disac-

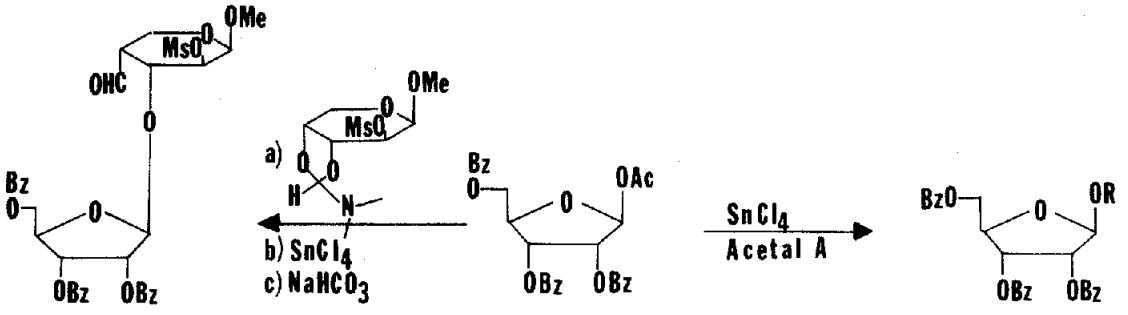


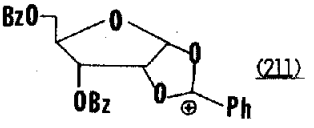
Scheme 80.



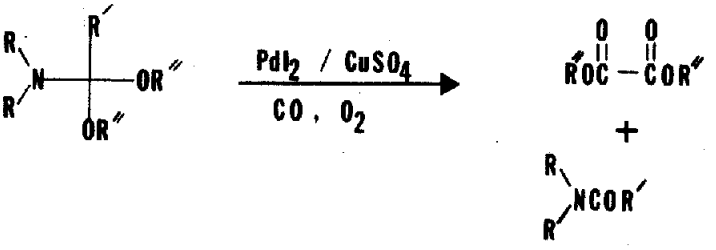
Scheme 81.

Scheme 82.





Scheme 83.



Scheme 84.

charides.[95b] The reaction occurs with retention of stereochemistry (Scheme 83). The authors invoked the intervention of an anomerically activated transition state (**209**) explaining the retention of stereochemistry.

The synthesis of oxalate esters by the oxidative carbonylation of amide acetals was reported by Zehner and Zajacek[96] (Scheme 84). In this reaction catalytic oxidation of the amide acetal in the presence of a metal salt catalyst, an amine base, and a catalytic amount of an alcohol gave the oxalate derivatives in near quantitative yields.

Acknowledgements—The authors are pleased to acknowledge the support of Mrs. Judy Clark for preparing the manuscript and of Dr. James Beck for his helpful discussions.

REFERENCES

[1a]H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt and J. Spille, *Chem. Ber.* **89**, 2060 (1956); [b]H. Meerwein, W. Florian, N. Schön and G. Stopp, *Liebigs Ann.* **641**, 1 (1961).
[2]H. Eilingsfeld, M. Seefelder and H. Weidinger, *Angew. Chem.* **72**, 836 (1960).
[3]H. H. Bosshard, E. Jenney and H. Zollinger, *Helv. Chim. Acta* **44**, 1203 (1961).
[4]W. Stiltz, unpublished work, quoted in Ref. 2.
[5]H. Bredereck, F. Effenberger and G. Simchen, *Angew. Chem.* **73**, 493 (1961); H. Bredereck, G. Simchen, S. Rebsdat, W. Kantlehner, P. Horn, R. Wahl, H. Hoffmann and P. Grieshaber, *Chem. Ber.* **101**, 41 (1968).

[6]H. Bredereck, F. Effenberger and D. Zeyfang, *Angew. Chem.* **77**, 219 (1965); H. Bredereck, F. Effenberger, D. Zeyfang and K. A. Hirsch, *Chem. Ber.* **101**, 4036 (1968).
[7]W. Weingarten and W. A. White, *J. Am. Chem. Soc.* **88**, 850 (1966).
[8a]H. Bredereck, F. Effenberger, T. Brendle and H. Muffler, *Chem. Ber.* **101**, 1885 (1968); [b]H. Bredereck, G. Simchen and H. U. Schenk, *Ibid.* **101**, 3058 (1968); [c]H. Bredereck, F. Effenberger and T. Brendle, *Angew. Chem.* **78**, 147 (1966).
[9]H. Bredereck, F. Effenberger, R. Gleiter and K. A. Hirsch, *Angew. Chem.* Internat. Ed. **4**, 955 (1965).
[10]H. Bredereck, R. Gompper, K. Klemm and H. Rempfer, *Chem. Ber.* **92**, 837 (1959).
[11a]H. Bredereck, F. Effenberger and G. Simchen, *Ibid.*, **98**, 1078 (1965); [b]H. Bredereck, G. simchen, H. Hoffmann, P. Horn and R. Wahl, *Angew. Chem.* Internat. Ed. **6**, 356 (1967); [c]H. Bredereck, F. Effenberger and G. Simchen, *Ibid.* Internat. Ed. **1**, 331 (1962).
[12]H. Bredereck, G. Simchen and G. Beck, *Liebigs Ann.* **762**, 62 (1972); See also W. Leimgruber and A. E. Häck, *Ger. Offen.* **2**, 214, 497.
[13]G. Simchen, H. Hoffmann and H. Bredereck, *Chem. Ber.* **101**, 51 (1968).
[14]H. Bredereck, G. Simchen and H. Hoffmann, *Ibid.* **106**, 3725 (1973).
[15]H. Bredereck, F. Effenberger and H. J. Bredereck, *Angew. Chem.* Internat. Ed. **5**, 971 (1966).
[16]H. Bredereck, G. Simchen and W. Kantlehner, *Chem. Ber.* **104**, 924 (1971).
[17]H. Bredereck, G. Simchen and P. Horn, *Ibid.* **103**, 210 (1970).
[18]H. Brechbühler, H. Büchi, E. Hatz, J. Schreiber and A. Eschenomoser, *Helv. Chim. Acta* **48**, 1746 (1965).
[19a]H. Vorbrüggen, *Angew. Chem.* Internat. Ed. **2**, 211 (1963); [b]H. Vorbrüggen, *Liebigs Ann.* **821** (1974); [c]W. Leimgruber and E. Mohacsi, *U.S. Pat.* 3,920,746.
[20]H. Brechbühler, H. Büchi, E. Hatz, J. Schreiber and A. Eschenmoser, *Angew. Chem.* Internat. Ed. **2**, 212 (1963).
[21]H. Büchi, K. Steen and A. Eschenmoser, *Ibid.* Internat. Ed. **3**, 62 (1964).
[22]F. Cramer and H. J. Baldauf, *Chem. Ber.* **92**, 370 (1959).
[23a]J. A. Webber, E. M. Van Heyningen and R. T. Vasileff, *J. Am. Chem. Soc.* **91**, 5674 (1969); [b]R. Aries, *Fr. Pat.* 2,235,925; [c]H. L. Cohen, *J. Polym. Science, Polym. Chem. Ed.* **14**, 7 (1976); [d]J. A. Hirsch and G. Schwartzkopf, *Synth. Commun.* **4**, 215 (1974).
[24]J. P. Thenot and E. C. Horning, *Anal. Lett.* **5**, 519 (1972); I. Horman and F. J. Hesford, *Biomed. Mass Spectrom.* **1**, 115 (1974).
[25a]J. J. Fitt and H. W. Gschwend, *J. Org. Chem.* **42**, 2639 (1977); [b]L. F. Fieser and M. Fieser, *Advanced Organic Chemistry*, p. 1028, 1029, Reinhold (1961).
[26]J. Žemlička, *Coll. Czech. Chem. Commun.* **28**, 1060 (1963); *Ibid.* **35**, 3572 (1970). See also A. Holý, R. W. Bald and Ng. D. Hong, *Ibid.* **36**, 2658 (1971); A. Holý, S. Chladek and J. Zemlicka, *Ibid.* **34**, 253 (1969); K. Hirota, K. Watanabe and J. J. Fox, *J. Heterocyclic Chem.* **14**, 537 (1977); K. Noda, A. Nakagawa, T. Motomura and H. Ide, *Jap. Pat.* 75,100,088; K. Noda, A. Nakagawa and T. Hachiya, *Jap. Pat.* 75,148,369; K. Noda, A. Nakagawa, S. Miyata and H. Ide, *Jap. Pat.* 76,122,093; K. Noda, A. Nakagawa, S. Yamasaki, K. Noguchi and H. Ide, *Jap. Pat.* 76,143,697.
[27]A. Holý, *Tetrahedron Letters* 585 (1972).
[28]J. Žemlička, *Coll. Czech. Chem. Commun.* **33**, 3796 (1968); *J. Am. Chem. Soc.* **97**, 5896 (1975).
[29]K. D. Philips and J. P. Horwitz, *J. Org. Chem.* **40**, 1856 (1975).
[30]F. Yoneda and T. Nagamatsu, *J. Heterocyclic Chem.* **11**, 271 (1974).
[31]J. Žemlička and S. Chladek, *Tetrahedron Letters* 715 (1969).
[32a]H. Vorbruggen, *Steroids* **1**, 45 (1963); [b]V. S. Venturella, V. M. Gualario and R. E. Lang, *J. Pharm. Sci.* **62**, 662 (1973).
[33a]H. Neumann, *Chimia* **23**, 267 (1969); [b]C-D. Li and J. Žemlička, *J. Org. Chem.* **42**, 7061 (1977); [c]R. G. Harvey, S. H. Goh and C. Cortez, *J. Am. Chem. Soc.* **97**, 3468 (1975).
[34]G. Crank and F. W. Eastwood, *Aust. J. Chem.* **17**, 1392 (1964); J. S. Josan and F. W. Eastwood, *Ibid.* **21**, 2013 (1968); G. Crank and F. W. Eastwood, *Ibid.* **17**, 1385 (1964).
[35]S. Hanessian, A. Bargiotti and M. La Rue, *Tetrahedron Letters* 737 (1978).
[36]H. Vorbrüggen and K. Krolikiewicz, *Angew. Chem.* Internat. Ed. **16**, 876 (1977).
[37a]S. Hara, H. Taguchi, H. Yamamoto and H. Nozaki, *Tetrahedron Letters* 1545 (1975); [b]H. H. Wasserman and B. H. Lipshutz, *Ibid.* 4611 (1975).
[38]A. Rüttimann, A. Wick and A. Eschenmoser, *Helv. Chim. Acta* **58**, 1450 (1975).
[39]H. Weingarten and N. K. Edelmann, *J. Org. Chem.* **32**, 3293 (1967).
[40a]H. Bredereck and G. Simchen, *Angew. Chem.* Internat. Ed. **2**, 738 (1963); H. Bredereck, G. Simchen and R. Wahl, *Chem. Ber.* **101**, 4048 (1968); [b]F. G. Fick and K. Hartke, *Ibid.* **109**, 3939 (1976); [c]E. E. Garcia, *Org. Prep. Proceed. Int.* **6**, 11 (1974).
[41a]A. Batcho and W. L. Leimgruber, *U.S. Pat.* 3,732,245 (1973); [b]E. E. Garcia and R. I. Fryer, *J. Heterocyclic Chem.* **11**, 219 (1974); for further uses of this reaction in the synthesis of indoles, see: A. D. Batcho and W. Leimgruber, *U.S. Pat.* 3,976,639; R. I. Fryer and E. E. Garcia, *U.S. Pat.* 3,979,410 (1976); M. E. Flaugh and J. A. Clemens, *Ger. Offen.* 2,645,865; F. Bennington, R. D. Morin and R. J. Bradley, *J. Heterocyclic Chem.* **13**, 749 (1976); A. A. Prokopov and L. N. Yakhontov, *Khim. Geterotsikl. Soedin* 1135 (1977); C. F. Huebner, *Ger. Offen.* 2,609,289; P. G. Gassman and W. N. Schenk, *J. Org. Chem.* **42**, 3240 (1977).
[42a]E. Garcia, L. E. Benjamin and R. I. Fryer, *J. Heterocyclic Chem.* **11**, 275 (1974); [b]M. Weigele, R. Czajkowski, J. Blount, S. Bernardo, J. P. Tengi and W. Leimgruber, *J. Org. Chem.* **41**, 388, 390 (1976); R. Cleeland, E. Grunberg, W. Leimgruber and M. Weigele, *Ger. Offen.* 2,407,899.
[43a]C. Rufer and E. Schroeder, *Ger. Offen.* 2,164,412; [b]C. Metayer, G. Duguoy and H. Quiniou, *Bull. Soc. Chim. Fr.* 163 (1974); [c]C. Rufer, H. J. Kessler and K. Schwartz, *Eur. J. Med. Chim-Chim Ther.* **12**, 27 (1977); [d]J. T. Shaw, C. M. Balik, J. C. Holoduak and S. Prem, *J. Heterocycle Chem.* **13**, 127 (1976).
[44]L. H. Brannigan, J. E. Franz and R. K. Howe, *South Africa Pat.* 766,342.
[45]K. Stern, footnote from Ref. 12.
[46a]W. Leimgrubber and M. Weigele, *U.S. Pat.* 3,542,848; 3,655,716; 3,966,791; 3,965,141; 3,792,076; [b]T. Suzuki, S. Himoto and K. Nakagawa, *Ger. Offen.* 2,303,919.
[47]H. Bredereck, F. Effenberger and H. Botsch, *Chem. Ber.* **97**, 3397 (1964).
[48a]H. Bredereck, G. Simchen and W. Griebenow, *Ibid.* **107**, 1545 (1974); [b]H. Bredereck, G. Simchen and B. Funke, *Ibid.* **104**, 2709 (1971); [c]V. G. Granik, N. B. Marchenko, E. O. Sóchneva, T. F. Vlasova, A. B. Grigor'ev, M. K. Polievktov and R. G. Glushkov, *Khim. Geterotsikl Soedin* 1505 (1976); [d]H. O. Bayer and P. J. Nulte, *U.S. Pat.* 3,711,488; [e]T. A. Bryson, D. M. Donelson, R. B. Dunlap, R. R. Fisher and P. D. Ellis, *J. Org. Chem.* **41**, 2066 (1976).
[49]D. Hoffe, *Liebigs Ann.* 2185 (1976). For related examples, see also H. W. Gschwend, *U.S. Pat.* 3,947,585; *Ger. Offen.* 2,524,048; 2,543,383. H. Pieper, G. Krüger, J. Keck, K. R. Noll and J. Kaehling, *Ger. Offen.* 2,324,962; 2,234,150; J. B. Taylor and D. R. Harrison, *Ger. Offen.* 2,605,652; H. Pieper, G. Krüger, J. Keck and K. R. Noll, *Ger. Offen.* 2,326,657; I. R. Ager, G. W. Danswan, D. R. Harrison, D. P. Kay, P. D. Kennewell and J. B. Taylor, *J. Med. Chem.* **20**, 1035 (1977).
[50a]G. Simchen, *Angew. Chem.* **76**, 860 (1964); [b]J. E. Powell, *U.S. Pat.* 4,015,001; 3,981,871; [c]K. Schaffner-Sabba, H. Tomaselli, B. Henrici and H. B. Renfroi, *J. Org. Chem.* **42**, 952 (1977).

[51]S. F. Martin and D. R. Moore, *Tetrahedron Letters* 4459 (1976).
[52]Z. Arnold and M. Korniloff, *Coll. Czech. Chem. Commun.* **29**, 645 (1964).
[53]For a review on enaminones, see J. V. Greenhill, *Chem. Soc. Revs.* **6**, 277 (1977).
[54]H. H. Wasserman and J. L. Ives, *J. Am. Chem. Soc.* **98**, 7868 (1976).
[55]B. M. Trost and M. Preckel, *Ibid.* **95**, 7862 (1973); B. M. Trost, M. Preckel and L. M. Leichter, *Ibid.* **97**, 2224 (1975).
[56a]H. Bredereck, F. Effenberger, H. Botsch and H. Rehn, *Chem. Ber.* **98**, 1081 (1965); *Cf. Ref.* 61*b*; [b]H. Bredereck, R. Sell and F. Effenberger, *Chem. Ber.* **97**, 3407 (1964).
[57a]L. Vilhelma and A. Arens, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* 315 (1972); [b]P. J. McNulty and H. L. Warner, *U.S. Pat.* 4,028,084; [c]J. R. Beck, *U.S. Pat.* 4,012,224; For other examples of the reaction of active methylene groups with formamide acetals giving enaminones, see A. V. Prakosh, *Swiss Pat.* 561,203; [d]P. D. Hammen and G. N. Milne, *Ger. Offen.* 2,360,096; [e]F. Eiden and A. Schawmberg, *Ger. Offen.* 2,250,377; [f]C. Rufer, K. Schwarz and E. Winterfeld, *Liebigs Ann.* 1465 (1975); [g]R. W. Hoffmann, F. Frickel and K. Blatt, *Chem. Ber.* **108**, 831 (1975); [h]F. Eiden, *Arch. Pharm.* **309**, 529 (1976); [i]F. Eiden, *Ger. Offen.* 2,506,980; [j]B. Chantegrel, *J. Chem. Res.* S, 127 (1977).
[58]H. Stetter and U. P. Dorsch, *Liebigs Ann.* 1406 (1976).
[59]R. F. Abdulla, T. L. Emmick and H. M. Taylor, *Synth. Commun.* **7**, 305 (1977).
[60]R. F. Abdulla, K. H. Fuhr and H. M. Taylor, *Ibid.* **7**, 313 (1977).
[61]J. R. Beck and R. P. Gajewski, *J. Heterocyclic Chem.* **13**, 605 (1976); For additional examples of the synthesis of heterocycles from enaminones, see: H. W. Gschwend, *U.S. Pat.* 3,939,271; C. Rufer, K. Schwarz and H. J. Kessler, *Ger. Offen.* 2,412,656; C. Rufer, K. Schwarz and E. Winterfeld, *Liebigs Ann.* 1465 (1975); R. G. Glushkov, O. Y. Belyaeva, V. G. Granik, M. K. Polievktov, A. B. Girgor'ev, V. E. Serokhvostova and T. V. Vlasova, *Khim. Geterosikl. Soedin.* 1640 (1976); F. Eiden and R. B. van Rautenfeld, *Ger. Offen.* 2,530,458; *Arch. Pharm.* **309**, 309 (1976); H. W. Gschwend, *U.S. Pat.* 4,022,800; 4,022,801; 4,028,381; J. R. Beck and R. P. Gajewski, *U.S. Pat*, 4,000,155; *Ger. Offen.* 2,651,008; H. M. Taylor, *Ger. Offen.* 2,628,992; G. B. Bennett, R. B. Mason, L. J. Alden and J. R. Roach, *J. Med. Chem.* **21**, 623 (1978).
[62]B. Föhlisch, *Chem. Ber.* **104**, 348 (1971); W. Czuba and M. Woznick, *Rocz. Chem.* **47**, 2361 (1973); F. Eiden and G. Heja, *Synthesis* 148 (1973); W. Ried and E. Nyiondi-Bonguen, *Liebigs Ann.* 1 (1973); A. Pelter and S. Foot, *Synthesis* 326 (1976); F. Eiden and L. Prielipp, *Acta Pharm.* **310**, 109 (1977); W. Loewe, *Ibid.* **310**, 506 (1977).
[63]F. J. Vinick and H. W. Gschwend, *Tetrahedron Letters* 315 (1978).
[64]W. Löwe, *J. Heterocyclic Chem.* **14**, 931 (1977).
[65]G. Büchi and J. A. Carlson, *J. Am. Chem. Soc.* **90**, 5336 (1968).
[66a]R. J. Chorvat, J. R. Palmer and R. Pappo, *J. Org. Chem.* **43**, 966 (1978); [b]V. G. Granik, N. B. Marchenko, T. F. Vlasova and R. G. Glushkov, *Khim. Geterotsikl. Soedin* 1509 (1976).
[67]K. Senga, K. Shimizu, S. Nishigaki and F. Yoneda, *Heterocycles* **6**, 1361 (1977).
[68]S. Nishigaki, M. Ichiba, J. Sato, K. Senga, M. Noguichi and F. Yoneda, *Ibid.* **9**, 11 (1978); R. S. Klein, M. I. Lin, S. Y-K. Tam and J. J. Fox, *J. Org. Chem.* **43**, 2536 (1978); K. Senga, Y. Kanamori, H. Kanazawa, S. Nishigaki and F. Yoneda, *Synthesis* 176 (1977); P. L. Anderson, *U.S. Pat.* 4,004,009.
[69a]H. Bredereck, G. Simchen and W. Griebenow, *Chem. Ber.* **106**, 3732 (1973); [b]M. Grossberger, *Leibigs Ann.* 1872 (1975).
[70]H. Bredereck, G. Simchen and P. Horn, *Angew. Chem.* Internat. Ed. **4**, 523 (1965).
[71]H. Bredereck, G. Simchen and W. Kantlehrner, *Chem. Ber.* **104**, 932 (1971).
[72]The C–C bond forming process in this transformation may be considered somewhat analogous to the benzoin and related condensations; *see* H. Stetter and M. Schreckenberg, *Chem. Ber.* **107**, 240, 2453 (1974).
[73]H. Bredereck, G. Simchen and G. Kapaun, *Ibid.* **104**, 792 (1971).
[74a]G. Büchi, M. Cushman and H. Wüest, *J. Am. Chem. Soc.* **96**, 5563 (1974); [b]K. K. Chan and G. Saucy, *J. Org. Chem.* **42**, 3828 (1977).
[75]G. Simchen, S. Rebsdat and W. Kantlehrner, *Angew. Chem.* Internat. Ed. **6**, 875 (1967); G. Simchen and W. Kantlehrner, *Tetrahedron* **28**, 3535 (1972).
[76]J. E. Baldwin and J. A. Walker, *J. Chem. Soc.* Chem. Commun. 354 (1972).
[77]K. A. Parker, R. W. Kosley, S. L. Buchwald and J. J. Petraitis, *J. Am. Chem. Soc.* **98**, 7104 (1976).
[78a]H. E. Windberg, *U.S. Pat.* 3,121,084 (1964); *Chem. Abst.* **60**, 13197d (1964); [b]H. Weidinger and H. Eilingsfeld, *Belg. Pat.* 629972.
[79]Amidines from aliphatic amines: R. N. Knowles, *U. S. Pat.* 3,689,675, 3,678,109; E. Enders and I. Hammann, *Ger. Offen.* 2,405,546; F. J. Lund, *Ger. Offen.* 2,430,375; 2,404,587; N. B. Marchenko, V. G. Granik, R. G. Glushkov, L. I. Budanova, V. A. Kuzovkin, V. A. Parshin and R. A. Al'tshuler, *Khim-Farm Zh.* **10**, 46 (1976); D. H. Robinson and G. Shaw, *J. Chem. Soc.* Perkin I, 774 (1974); From carboxamides: G. Pissiotas and E. Nikles, *Ger. Offen.* 2,410,239; C. L. McIntosh, *Brit. Pat.* 1,494,018; R. J. Perchalski and B. J. Wilder, *Clin. Chem.* **20**, 492 (1974); From sulfonamides: W. Schroth, G. Dill, T. K. D. Nguyen, N. T. M. Khoi, P. T. Binh, H. J. Waskiewicz and A. Hildebrandt, *Z. Chem.* **14**, 52 (1974); J. R. DeBaun, F. M. Pallos and E. G. Teach, *U.S. Pat.* 4,012,527; 3,959,368; J. Dusemund, *Arch. Pharm.* **307**, 881 (1974); W. J. A. Vandenheuvel and V. F. Gruber, *J. Chromatogr.* **112**, 513 (1975); From aminophosphonates: W. Sirrenberg, I. Hammann and B. Homeyer, *Ger. Offen.* 2,420,069; J. Bader, *Swiss Pat.* 590,612; H-L. Lam and E. G. Teach, *Ger. Offen.* 2,704,894; E. Beriger, O. Kristiansen, K. Ruefenacht and J. Bader, *Ger. Offen.* 2,312,738; L. J. Stach, *Ger. Offen.* 2,706,794; From heterocyclic or aromatic amines: G. Westphal and R. Schmidt, *J. Prakt. Chem.* **315**, 791 (1973); R. Bosshard and H. U. Brichbühler, *U.S. Pat.* 4,020,066; J. Hahndl, E. Schroeder and H. W. Kelm, *Eur. J. Med. Chem.-Chim. Ther.* **10**, 121 (1975); S. Hanessian, *J. Med. Chem.* **16**, (1973); B. Koren, F. Kovac, A. Petric, B. Stanovnik and M. Tisler, *Tetrahedron* **32**, 493 (1976); K. Babic, S. Molan, S. Polanc, B. Stanovnik, J. Stres-Brotos, M. Tisler and B. Verček, *J. Het. Chem.* **13**, 487 (1976); C. D. Chang and J. K. Coward, *J. Med. Chem.* **19**, 684 (1976); H. Berger, R. Gall, K. Stach, R. Hoffmann, W. Schaumann and W. Voemel, *Ger. Offen.* 2517411; H. Berger, R. Gall and K. Stach, *Ger. Offen.* 2261735; E. Winkelmann, W. Raelter, H. Hartung and W. H. Wagner, *Arzneim-Forsch.* **27**, 82 (1977); P. F. Fabio, Y-I Lin, S. A. Lang and A. S. Tomcufcik, *U.S. Pat.* 4,029,788; S. A. Lang, P. F. Fabio, Y-I Lin, K. C. Murdock and F. L. Fields, *Ger. Offen.* 2,637,544; E. C. Taylor and J. LaMattina, *J. Org. Chem.* **42**, 1523 (1977); R. Jaunin, *Helv. Chim. Acta* **57**, 1934 (1974); J. Faganeli, S. Polanc, B. Stanovnik and M. Tisler, *Croat. Chem. Acta* **48**, 161 (1976); B. Jenko, B. Stanovnik and M. Tisler, *Synthesis* 833 (1976); R. I. Fryer and L. H. Sternbach, *U.S. Pat.* 3,795,702.
[80a]H. Bredereck, F. Effenberger, A. Hoffmann and M. Hajek, *Angew. Chem.* Internat. Ed. **2**, 655 (1963); H. Bredereck, F. Epenberger and A. Hoffmann, *Chem. Ber.* **97**, 61 (1964); [b]A. Ilvespaa, *Swiss Pat.* 557,372.
[81]*Belg. Pat.* 636,256 (1964); *Chem. Abstr.* **61**, 13314d (1964).
[82]R. Richter and H. Ulrich, *Chem. Ber.* **103**, 3525 (1970). See also K. Seckinger, *Swiss Pat.* 590,214.
[83]B. Stanovnik and M. Tisler, *Synthesis* 120 (1974). See also F. Yoneda, M. Higuchi and A. Hayakawa, *Ibid.* 264 (1975); *Japan Kokai* 7688994. J. A. Claisse, M. W. Toxton, G. I. Gregory, A. H. Sheppard, E. P. Tiley, W. K. Warburton and M. J. Wilson, *J. Chem. Soc.* Perkin I, 2241 (1973); G. MacKenzie and G. Shaw, *Ibid.* Chem. Commun. 47 (1975); J. A. Maddison, P. W. Seale, E. P. Tiley and W. K. Warburton, *Ibid.* Perkin I, 81 (1974); S. Goya, A. Takadate and T. Tanaka, *Yakugaku Zasslin* **96**, 700 (1976); W. F. Keir, H. A. MacLennan and H. C. S. Wood, *J. Chem. Soc.* Perkin I, 1321 (1977).

[84a]M. Sákamoto, K. Miyazawa and Y. Tomimatsa, *Chem. Pharm. Bull.* **15**, 3360 (1977); [b]J. P. Pradene, *C. R. Hebd Seances Acad. Sci. Sec.* C, 119 (1975); J. C. Meslin and H. Quiniou, *Tetrahedron* **31**, 3055 (1975).
[85]F. Yoneda, M. Higuchi and T. Nagamatsu, *J. Am. Chem. Soc.* **96**, 5607 (1974).
[86]F. Yoneda, M. Higuchi and M. Kawamura, *Heterocycles* 4, 1659 (1976).
[87]F. Yoneda and M. Higuchi, *J. Chem. Soc.* Perkin Trans. I, 1336 (1977).
[88]H. Gross and B. Costiaella, *Agnew. Chem.* Internat. Ed. **7**, 391 (1968); K. Issleib and M. Lischewski, *J. Organometal Chem.* **46**, 297 (1972); M. Lischewski, K. Issleib and H. Tille, *Ibid.* **54**, 195 (1973).
[89a]H. Bredereck, G. Simchen and E. Göknel, *Chem. Ber.* **103**, 236 (1970); H. Bredereck, G. Simchen and S. Rebsdat, *Angew. Chem.* Internat. Ed. **4**, 523 (1965); H. Bredereck, G. Simchen and E. Göknel, *Ibid.* **76**, 861 (1964); [b]M. Reiffen and R. W. Hoffmann, *Chem. Ber.* **110**, 37 (1977).
[90]H. Bredereck, G. Simchen and H. Porkert, *Ibid.* **103**, 245 (1970); *Angew. Chem.* Internat. Ed. **5**, 841 (1966).
[91]H. Bredereck, G. Simchen and H. Porkert, *Chem. Ber.* **103**, 256 (1970).
[92]H. Bredereck, G. Simchen and G. Beck, *Ibid.* **104**, 394 (1971).
[93]A. D. Sinista, S. V. Bonadyk and L. N. Markovskii, *Zh. Org. Khim.* **13**, 721 (1977).
[94]W. Leimgruber and A. E. Wick, *Ger. Offen.* 2,214,498; *U.S. Pat.* 3,922,285.
[95a]S. Hanessian and J. Banoub, *Tetrahedron Letters* 657 (1976); [b]*Ibid.* 661 (1976).
[96]L. R. Zehrner and J. G. Zajacek, *U.S. Pat.* 4,041,067.