RECENT ADVANCES IN THE CHEMISTRY OF *as*-TRIAZINIUM SALTS

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Abstract - Recent studies on protonation and alkylation of *as*-triazines and the synthesis of *N*-alkyl-*as*-triazinium salts are summarized. The reactions of *as*-triazinium cations and the features of their chemical behaviours in comparison with those of neutral species are discussed.

Contents

1. Introduction.....
2. Preparation of *as*-Triazinium Salts.....
2.1 Monocyclic *as*-Triazinium Salts.....
2.1.1. Protonation of *as*-Triazines.....
2.1.2. *N*-Alkylation of *as*-Triazines.....
2.1.3. *O*- and *S*-Alkylation of Triazin-5-ones, Triazine-3,5-diones.... and Triazine-5-thiones.....
2.2. Condensed *as*-Triazinium Salts.....
2.2.1. Protonation of Condensed *as*-Triazines.....
2.2.2. Alkylation of Condensed Triazines.....
2.2.3. Annelation of Heterocyclic Systems to the *as*-Triazine Ring.....
2.2.4. Annelation of the Triazinium Fragment to Heterocyclic Systems..
2.2.5. Other Synthetic Ways to Fused as-Triazinium Systems.....

3. Reactions of *as*-Triazinium Salts.....
3.1. Action of Bases.....
3.2. Reactions with Nucleophilic Reagents.....
3.2.1. The Formation of σ-Adducts.....
3.2.2. Nucleophilic Substitution Reactions.....
3.2.3. Cyclizations with Bifunctional Nucleophiles.....
3.2.4. Ring Opening and Ring Transformation Reactions.....
3.3. Cycloaddition Reactions.....
4. Conclusion.....
5. References.....

1. Introduction

The chemistry of *as*-triazines has been studied for many decades because many derivatives of this heterocyclic system are important for practice and have found their application in medicine, agriculture and other fields.[1-9] Far less attention has been paid to the synthesis and chemical behaviour of charged triazines. Information concerning *as*-triazinium cations is almost imperceptible in comparison with enormous body of data on neutral triazines accumulated in the literature.[1-9] At the same time, it is well known that the transfer from azines to azinium cations enhances their reactivity towards nucleophilic reagents and enables azinium cations to undergo new types of reactions. Indeed, recent studies[10-26] on *as*-triazinium salts revealed a great deal of new reactions which would be considered as rather unusual in the chemistry of uncharged azines but proved to occur with *as*-triazinium substrates. This is why we would like to concentrate in this review on the chemistry of *as*-triazinium salts.

2. Preparation of *as*-Triazinium Salts

2.1. Monocyclic as-Tiazinium Salts

2.1.1. Protonation of as-Tiazines

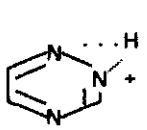
Nitrogen atoms in the majority of *as*-triazines are basic enough[1] to react with mineral acids yielding NH-*as*-triazinium salts as rather stable solids which can be stored under normal conditions.[1] The structure of *N*-protonated triazines has long been under discussion.[5] Probably it is accounted for by the fact that three nitrogen atoms [$N_{(1)}$, $N_{(2)}$ and $N_{(4)}$] are potential sites for the proton attack and, therefore, finding the real centre of protonation doesn't seem to be an easy problem. A certain theoretical interest[11,27-32] has prompted us and other researchers to use physical and quantum chemistry methods to solve this problem. Calculations of the parent *as*-triazine and some of its 3-substituted derivatives revealed that the ($\sigma+\pi$) negative charge on nitrogen atoms is decreasing in the following order: $N_{(4)}>N_{(2)}>N_{(1)}$ (Table 1).[11,27,28] This sequence is in full agreement with chemical shifts[27-30] of the nitrogen atoms in the ^{15}N nmr spectra of 3-substituted *as*-triazines (Table 1). According to the ($\sigma+\pi$) charge distribution over the ring nitrogens the formation of the $N_{(4)}$-H triazinium cations can be expected to occur first.

On the other hand, σ-charges on the ring atoms in aromatic systems have usually a smaller influence on the proton attack than the π-charge distributions.[33] The π-charge densities in monocyclic *as*-triazines are somewhat different: $N_{(2)}>N_{(4)}>N_{(1)}$ (Table 1), thus indicating the $N_{(2)}$ atom to be the most likely protonation centre.

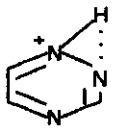
The thermodynamic stability of *as*-triazinium salts is another important feature.[1,33] The data of *ab initio* calculations performed for the parent triazine show that protonation energies for $N_{(1)}$ and $N_{(2)}$ atoms are less than that for $N_{(4)}$ (Table 2).[31,32] Unfortunately, the *ab initio* methods used did not take into account interaction of the $N_{(1)}$ and $N_{(2)}$ electron

pairs, which results in the deviation of the $N_{(1)}$ and $N_{(2)}$ *p*-orbitals from the plane perpendicular to the molecular framework and thus lowers the effectivity of π-electron conjugation in the ring. In this connection it is clear that the formation of $N_{(1)}$-H and $N_{(2)}$-H triazinium cations is even more favoured thermodinamycally because protonation of one of two neighbouring nitrogen atoms eliminates the repulsion of electron pairs.[33] Also, it has been suggested that $N_{(2)}$-H *as*-triazinium cations (1) can be stabilized by the intramolecular $N_{(2)}$-H···$N_{(1)}$ hydrogen bond formation.[31] The same advantage is easy to imagine for $N_{(1)}$-protonated triazines (2) as well (Scheme 1).

Scheme 1.



1

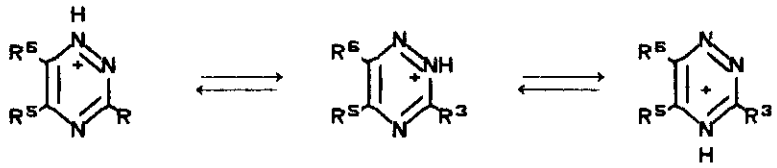


2

The protonation process has also been studied experimentally.[27,34] Hypsochromic shifts of the main absorption band in the uv spectra of some *as*-triazines were attributed to the formation of cationic species, $N_{(2)}$-H or $N_{(4)}$-H.[34] However this method did not allow to differentiate between these protonation sites.[34]

The most convincing and reliable data concerning protonation of *as*-triazines have been obtained by means of nmr spectroscopy.[27] The ^{1}H, ^{13}C and ^{14}N nmr studies performed on some 3-substituted *as*-triazines have revealed that a mixture of interconverting prototropic forms (3-5) is present in solution with preferential contribution of the $N_{(1)}$-H isomeric salt (3) (Scheme 2).[27]

Scheme 2.



3 4 5

R^3= Me, SMe, OMe, NH_2, morpholino; R^5, R^6= H, Me, OMe

Table 1. (σ + π) and π-Charge distribution over the ring nitrogen atoms in molecules of 3-substituted *as*-triazines (CNDO/2) and ^{14}N and ^{15}N-chemical shifts[27-30]

R^a	(σ+π)-charge densities (π-charge values are given in parenthesis)			^{14}N (in $CDCl_3$) and ^{15}N (in DMSO-d_6) (in parenthesis) chemical shifts		
	$N_{(1)}$	$N_{(2)}$	$N_{(4)}$	$N_{(1)}$	$N_{(2)}$	$N_{(4)}$
H	-0,043 (0,009) -0.062[b] (-0,002)[b]	-0,101 (-0,072) -0,126[b] (-0,069)[b]	-0,134 (-0,047) -0,185[b] (-0,049)[b]	422[a] (420)	378[a] (382)	299[a] (318)
OMe	-0,024 (0,033)	-0,140 (-0,140)	-0,184 (-0,100)	435 (416)	335 (322)	261 (254)
SMe	-0.034 (0.024)	-0.119 (-0.112)	-0.159 (-0.079)	430 (412)	366 (351)	288 (282)
NH_2	-0,029	-0,147	-0,181	(416)	(319)	(250)
NMe_2	-0,018 (0,042)	-0,167 (-0,157)	-0,207 (-0,110)			
morpho-lino	-[c]	-[c]	-[c]	432	338	265
Ph	-0,048 (-0,021)	-0,116 (-0,094)	-0,163 (-0,062)			
CO_2Me	-0.057	-0,085	-0,105			

[a]In Et_2O. [b]The data of INDO calculations. [c]For the calculation data see the previous compound.

Table 2. Protonation energies, E (kcal/mol), for the parent *as*-triazine calculated by the *ab initio* method

as-Triazine	$N^{+}_{(1)}$-H	$N^{+}_{(2)}$-H	$N^{+}_{(4)}$-H	References
	218.7	229.9	212.2	31
	218.6	222.8	211.9	32

This conclusion is based on the following arguments. In the ^{1}H nmr spectra of protonated azaaromatic compounds the signal of H-β (relative to the charged nitrogen atom) undergoes a greater shift to a lower field than that of H-α.[35] Analyzing chemical shifts of H-5 and H-6 protons in the ^{1}H nmr spectra of 3-methylthio- and 3-methoxy-*as*-triazines in $CDCl_3$ and CF_3COOH one reaches the conclusion that the $N_{(1)}$-H isomeric salts contribute mainly to the overall picture of prototropic equilibria in these molecules.[27] In the case of 3-amino substituted *as*-triazines protonation of the exocyclic nitrogen may contribute significantly (Table 3).

In the ^{13}C nmr spectra of 3-methylthio-*as*-triazine in $CDCl_3$ the C-6 resonance signal is mostly affected by addition of CF_3COOH. With an increase in acidity of the solution it is shifted gradually upfield ($\Delta\delta$ reaches 3.4 ppm) while the resonance signals of C-3 and C-6 undergo only slight downfield shifts.[27] Taking into account the literary data[35] these shifts are in agreement with the predominant protonation of $N_{(1)}$.

In the ^{14}N nmr spectra of 3-substituted *as*-triazines (3-methoxy, 3-methylthio and 3-morpholino) in $CDCl_3$ the resonance signals of all nitrogen atoms are shifted and broadened on protonation by CF_3COOH. However strong upfield shifts of the $N_{(1)}$ resonance signals (14-26 ppm) are diagnostic enough to reach the same conclusion of preferential contribution of the $N_{(1)}$-H isomeric salts.[27]

Table 3. The ^1H nmr spectral data for mono- and disubstituted *as*-triazines in $CDCl_3$ and CF_3COOD and protonation effects Δ[10,27,35-37]

Triazine	Solvent	Chemical shifts	
		$H_{(5)}$	$H_{(6)}$
3-OMe	$CDCl_3$	8.53	9.06
	CF_3CO_2D	9.30	9.01
	Δ	(0.77)	(-0.05)
3-SMe	$CDCl_3$	8.41	8.96
	CF_3CO_2D	9.25	9.08
	Δ	(0.84)	(0.12)
3-morpholino	$CDCl_3$	8.14	8.54
	CF_3CO_2D	8.45	8.91
	Δ	(0.31)	(0.37)
3-pyrrolidino	$CDCl_3$	8.14	8.52
	CF_3CO_2D	8.45	8.91
	Δ	(0.31)	(0.39)
$3-NH_2$	DMSO-d_6	8.53	8.88
	CF_3CO_2D	8.62	9.07
	Δ	(0.09)	(0.19)
3-SMe, 5-Ph	$CDCl_3$	-	8.77
	CF_3CO_2D	-	8.87
	Δ	-	(0.10)
3-SMe, 6-Me	$CDCl_3$	8.22	-
	CF_3CO_2D	9.17	-
	Δ	(0.95)	-

2.1.2. N-Alkylation of as-Triazines

N-Alkylazinium salts are more attractive cationic species than their N-H analogues since they are usually more stable,[1,5] they cannot loose easily the *N*-alkyl group (for the dequaternization reaction of *N*-alkyl-*as*-triazinium salts see Section 3.1.3) and, therefore, no equilibria between

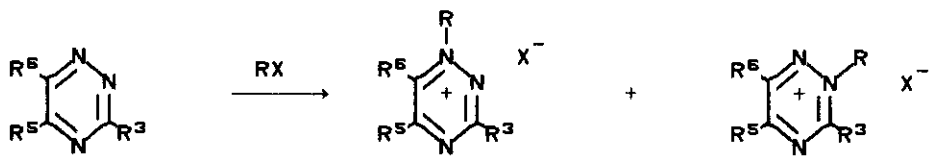
isomeric *N*-alkylazinium cations can exist in solutions. In spite of that, only a few reports on the synthesis of monocyclic *N*-alkyltriazinium salts have so far been published.[10-15,38-44]

Three types of isomeric *N*-alkyl-*as*-triazinium salts can possibly be obtained from alkylation of *as*-triazines depending on electronic and steric effects of the ring substituents and thermodynamic stabilities of the forming quaternary salts.[10-15,38-44] As already mentioned, the basic character of nitrogen atoms in the majority the *as*-triazines is changed as follows: $N_{(4)} > N_{(2)} > N_{(1)}$ (Table 1).[11,27,28] However, according to the CNDO/2 molecular orbital calculations the $N_{(1)}$- and $N_{(2)}$-methyl-*as*- triazinium salts are more favoured thermodynamically.[11,27] Experimental data show that alkylation of *as*-triazines is governed predominantly by steric effects of the ring substituents.[10-15,38,39]

Alkylation of 3-substituted and 3,5-disubstituted *as*-triazines (6) containing a bulky substituent at C-3 (3-phenyl, 3-morpholino, 3-piperidino, 3-dimethylamino etc.) with alkyl iodides or triethyloxonium tetrafluoroborate occurs exclusively at N-1 (Table 4), even for triazines bearing the methyl group at C-6.[10-15,38,39] In other cases a mixture of $N_{(1)}$- and $N_{(2)}$-alkyl-*as*-triazinium salts (7,8) is formed (Scheme 3, Table 4).

Introduction of a more bulky *i*-propyl group or aryl substituents at C-6 hinders quaternization of N_1 and, depending on the nature of substituents at C-3, both $N_{(1)}$-methyl and $N_{(2)}$-methyl-*as*-triazinium salts are derived from the methylation reaction with methyl iodide (Scheme 3).[38,39]

Scheme 3.

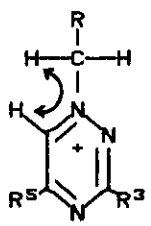


6 7 8

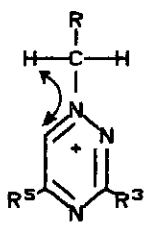
Quaternization of 3-amino and 3-alkylamino substituted *as*-triazines also yields the mixture of $N_{(1)}$-alkyl- and $N_{(2)}$-alkyl-*as*-triazinium salts (Scheme 3).[15,38] In this reaction the ratio of isomers is affected by the nature of the alkylating agent. Previously reported data[40] to the effect that quaternization of 3-amino-5,6-dimethyl-*as*-triazine by ethyl iodide results in the mixture of $N_{(1)}$and $N_{(4)}$-ethyl-*as*-triazinium salts appear to be incorrect. Reinvestigation of this reaction has revealed that $N_{(1)}$ and $N_{(2)}$ nitrogens, but not $N_{(4)}$, are quaternized with methyl iodide in methanol.[38]

Combined application of ^{1}H and ^{13}C nmr spectroscopy usually enables one to differentiate between isomeric structures. In particular, the formation of $N_{(1)}$-alkyl-*as*-triazinium cations is characterized by the following spectral features: in the ^{13}C nmr spectra the C-6 (C-α relative to the charged nitrogen) resonance signals undergo strong upfield shifts of 6-10 ppm; in the coupled ^{13}C nmr spectra the vicinal coupling constants between C-6 (C-α) carbons and protons of the $N_{(1)}$-alkyl group are usually observed; in the ^{1}H nmr spectra the H-6 (H-α) resonances are either broadened or splitted due to long range coupling constants ^{4}J between H-6 (H-α) and N-CH_2- (N-CH_3) protons; the vicinal coupling constants ^{3}J between C-α and H-β are usually decreased of 4-5 Hz (Scheme 4).[10-12,14,15] Unequivocal evidence for the structure of $N_{(1)}$-ethyl-3-butynylthio-5-phenyl-*as*-triazinium tetrafluoroborate has also been obtained by its X-ray analysis.[12]

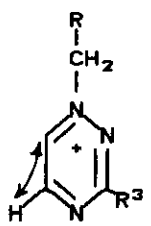
Scheme 4.



^{4}J= 0.6-1 Hz



^{3}J(C-α, NCH_2R)



Δ ^{3}J(C-α, H-β)= 4-5 Hz

Table 4. Alkylation of *as*-triazines

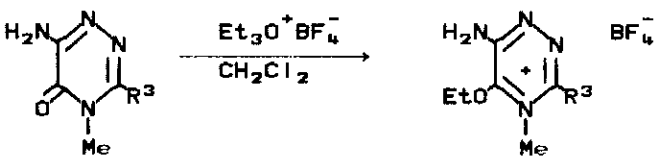
No	Starting triazine			Alkylation agent	Procedure*	Ratio of isomers		References
	R^3	R^5	R^6			$N_{(1)}$	$N_{(2)}$	
1	Ph	H	H	$Et_3O^+BF_4^-$	B	100	0	11
2	morpholino	H	H	$Et_3O^+BF_4^-$	B	100	0	10
3	NH_2	Ph	H	MeI	A	50	50	38
4	NH_2	Ph	H	EtI	A	60	40	15
5	NH_2	Ph	H	PrI	A	70	30	15
6	NH_2	Ph	H	BuI	A	66	34	15
7	NH_2	Ph	H	$Et_3O^+BF_4^-$	B	80	20	27
8	NH_2	Me	Me	MeI	A	30	70	38
9	NH_2	Et	Et	MeI	A	14	86	38
10	NH_2	i-Pr	i-Pr	MeI	A	0	100	38
11	NH_2	t-Bu	H	MeI	A	50	50	38
12	NH_2	Ph	Me	MeI	A	0	100	38
13	NH_2	Ph	Ph	MeI	A	0	100	38
14	NHMe	Me	Me	MeI	A	70	30	38
15	NHMe	Ph	Ph	MeI	A	62	38	38
16	NMe_2	H	H	MeI	A	100	0	38
17	NMe_2	Me	H	MeI	A	100	0	38
18	NMe_2	Me	Me	MeI	A	100	0	38
19	NMe_2	t-Bu	H	MeI	A	100	0	38
20	NMe_2	Ph	H	MeI	A	100	0	15
21	morpholino	Ph	H	MeI	A	100	0	27
22	morpholino	Ph	H	$Et_3O^+BF_4^-$	B	100	0	15
23	morpholino	Ph	H	PrI	A	100	0	15
24	morpholino	Ph	H	BuI	A	100	0	15
25	morpholino	Ph	H	$CF_3CH_2CH_2I$	A	84	16	15
26	morpholino	Ph	H	$PhCH_2I$	A	100	0	15
27	MeS	Ph	H	MeI	A	100	0	15
28	MeS	Ph	H	$Et_3O^+BF_4^-$	B	92	8	27
29	MeS	Ph	H	BuI	A	100	0	15
30	MeO	Ph	H	MeI	A	100	0	15
31	MeO	Ph	H	$Et_3O^+BF_4^-$	B	100	0	15
32	3-butynylthio	Ph	H	$Et_3O^+BF_4^-$	B	100	0	23

*A) reflux with an excess of alkylating agent in alcohol; B) on treatment with $Et_3O^+BF_4^-$ in CH_2Cl_2 at room temperature.

2.1.3 O- and S-Alkylation of N-Substituted Triazine-5-ones, Triazine-3,5-diones and Triazin-5-thiones

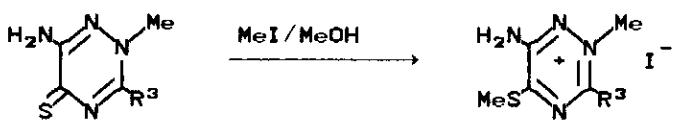
Another approach to the synthesis of *N*-alkyl-*as*-triazinium salts is based on using *N*-substituted triazin-5-ones (9) and triazine-5-thiones (10).[41,42] In these alkylation reactions, which usually take place at the exocyclic oxygen or sulphur atoms, triazinium salts (11,12) of definite structure without any isomers are formed (Scheme 5).[41,42]

Scheme 5.



9 11

R^3= Me, SMe

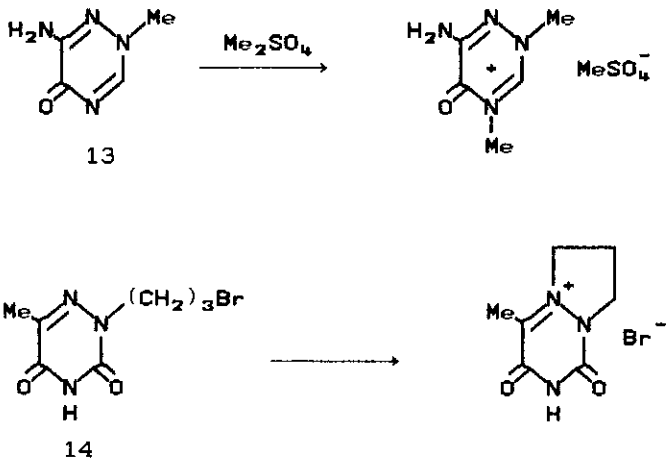


10 12

R^3= SMe, Ph, 4-Cl-C_6H_4

However, in some cases alkylation of triazin-5-ones and triazine-3,5-diones takes place at the ring nitrogens.[43,44] An example is the reaction of 6-amino-2-methyl-*as*-triazin-5-one (13) with dimethyl sulphate where the ring nitrogen $N_{(4)}$ is the site of methylation.[43] Intramolecular alkylation of 6-methyl-*as*-triazine-3,5-dione (14) has also been found to occur at the ring nitrogen $N_{(1)}$ (Scheme 6).[44]

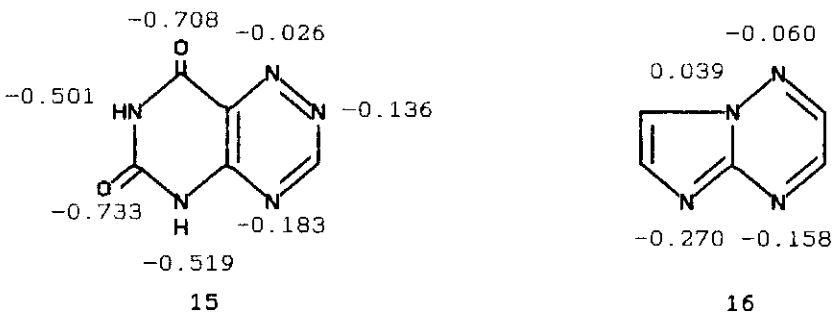
Scheme 6.



2.2. Condensed as-Triazinium Salts

Annelation of carbo- and heterocycles to the *as*-triazinium ring may cause considerable changes in charge distributions in both rings, as illustrated by the MO calculation data for pyrimido[4,5-*e*]*as*-triazine[45] and imidazo-[1,2-*b*]-*as*-triazine (**16**) (Scheme 7).[46,47]

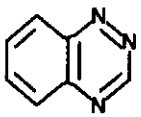
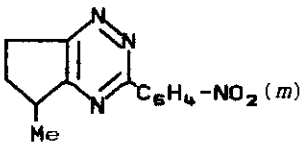
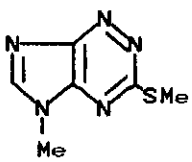
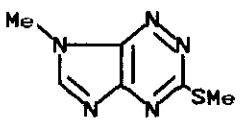
Scheme 7. π-Charge distributions for pyrimido[4,5-*e*]*as*-triazine (**15**) and imidazo[1,2-*b*]*as*-triazine (**16**)



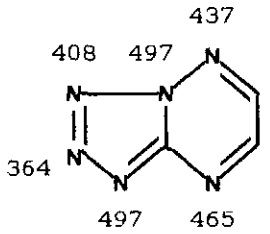
The ^{15}N nmr spectral data for some [*e*]-annelated *as*-triazines (Table 5)[28,48-50] show that this type of annelation does not change the sequence of chemical shifts for the triazine ring nitrogens $N_{(1)} > N_{(2)} > N_{(4)}$

relative to that of monocyclic triazines.[27-30] Therefore, one can expect the same features in protonation of such triazines. Another sequence of ^{15}N-chemical shifts for the triazine ring resonances is observed in the ^{15}N nmr spectrum of the [*b*]annelated tetrazolotriazine (**17**) and, therefore, in this fused system the tetrazole ring nitrogens are the most likely protonation sites (Scheme 8).[51]

Table 5. ^{15}N Nmr Spectral data for selected [*e*] annelated *as*-triazines[28, 48-50]

Triazine	Solvent	^{15}N Chemical shifts		
		$N_{(1)}$	$N_{(2)}$	$N_{(4)}$
	DMSO-d_6	448	403	282
	$CDCl_3$	393	353	280
	DMSO-d_6	392	319	240
	DMSO-d_6	393	319	362

Scheme 8. ^{15}N-Chemical shifts for tetrazolo[5,1-*b*]*as*-triazine (**17**) in DMSO-d_6



17

2.2.1. Protonation of Condensed Triazines

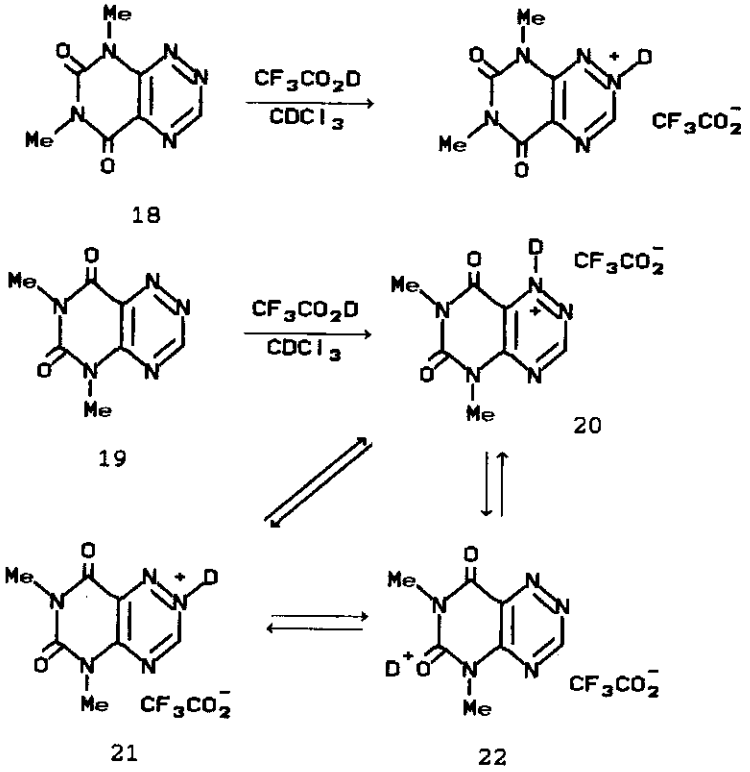
Protonation of condensed triazines has been studied by means of both uv[52,53] and nmr spectroscopy.[54-57] As shown by ^{1}H and ^{13}C nmr, in fervenulin (**18**) the nitrogen $N_{(2)}$ is protonated predominantly, while protonation of isofervenulin (**19**) results in a mixture of three prototropic forms (**20-22**) (Scheme 9).[54]

The type of annelation is very important in protonation reactions of fused triazines. Indeed, according to ^{13}C nmr studies, 7*H*-*imidazo*[4,5-*e*]-*as*-triazines are protonated at $N_{(1)}$,[56] but in the case of imidazo[1,2-*b*]-annelated *as*-triazines the imidazole ring nitrogen $N_{(5)}$ is the most likely protonation site[57] which is in full agreement with π-charge distribution in this heterocyclic system (see Scheme 7).

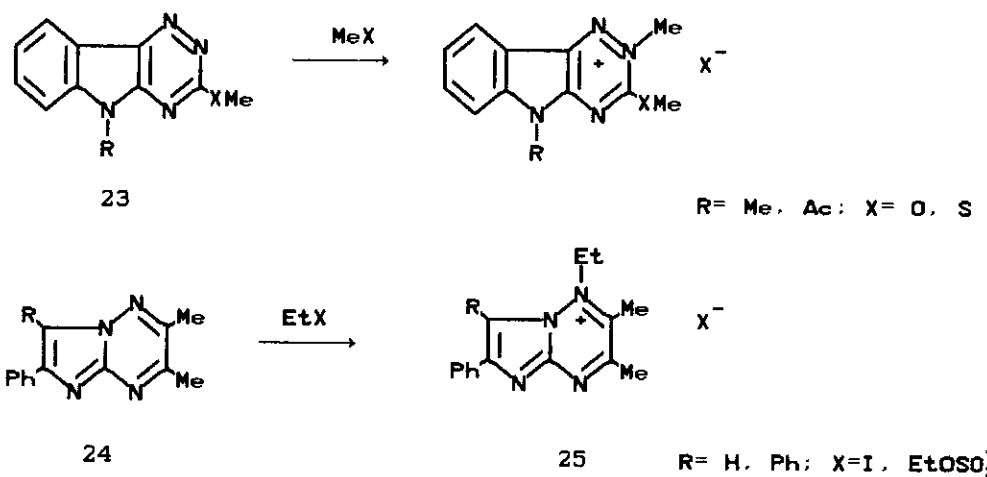
2.2.2. Alkylation of Condensed as-Triazines

The type of annelation and the nature of substituents are probably main factors determining the site selectivity in the alkylation reaction of fused triazines. For instance, indolo[*e*]annelated *as*-triazines (**23**) are quaternized by methyl iodide exclusively at $N_{(2)}$,[58-60] while alkylation of [b]annelated triazines (**24**) yields $N_{(1)}$-alkylimidazo[4,5-*b*]triazinium salts (**25**) (Scheme 10).[61,62]

Scheme 9.

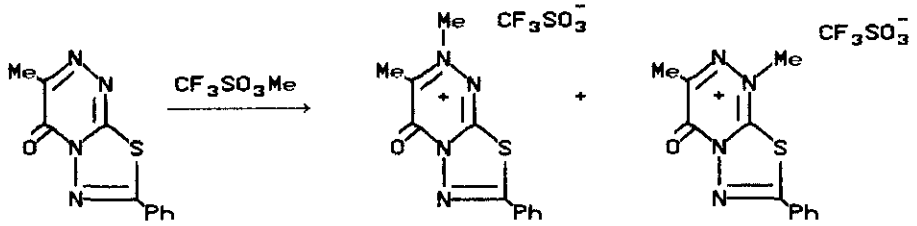


Scheme 10.



Alkylation of [*c*]-annelated *as*-triazines proceeds less selectively. Thus, methyl trifluoromethanesulfonate reacts with 1,3,4-thiadiazolo[2,3-*c*]-*as*-triazine (**26**) in dichloroethane to give rise a mixture of $N_{(1)}$- and $N_{(2)}$-*methyltriazinium salts* (**27**) *and* (**28**) *in the ratio* 3:1 (Scheme 11).[63]

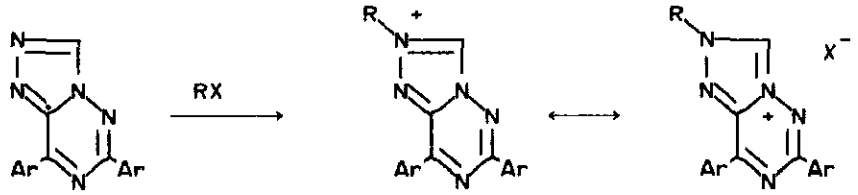
Scheme 11.



26 **27** **28**

In the case of *as*-triazolo[3,4-*f*]*as*-triazines (**29**) containing bulky aryl substituents in the triazine ring quaternization takes place at the triazole ring (Scheme 12).[64]

Scheme 12.



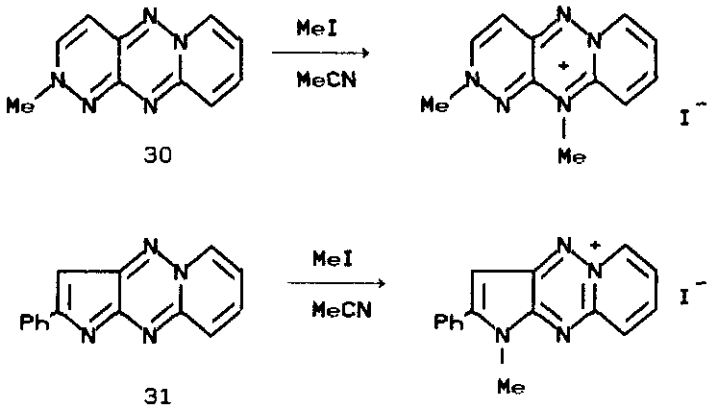
29

Ar= Ph, *m*-Cl-C_6H_4; R= Me, $PhCH_2$, $PhCOCH_2$; X= $MeSO_4$, Cl, Br

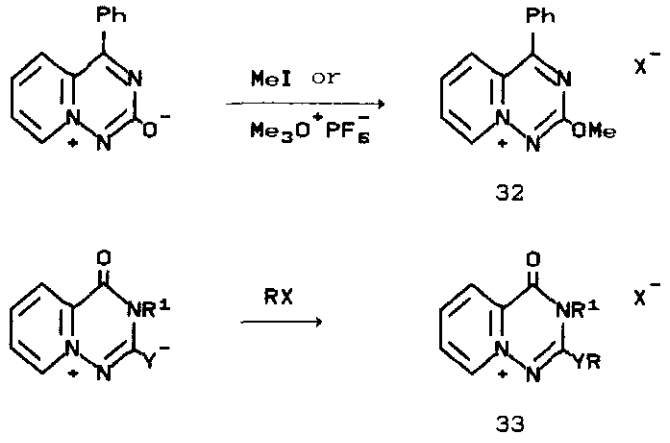
Methylation of tricyclic systems (**30**) and (**31**) has been found to occur at both the triazine ring and the annelated pyrrole fragment (Scheme 13), as shown by nmr using DNOE and INEPT long-range techniques.[65]

Alkylation of fused triazinium betaines containing O^- or S^- groups at $C_{(3)}$ of the *as*-triazine ring usually proceeds smoothly on these exocyclic groups yielding quaternary *as*-triazinium salts (**33**) (Scheme 14).[16,17,66]

Scheme 13.



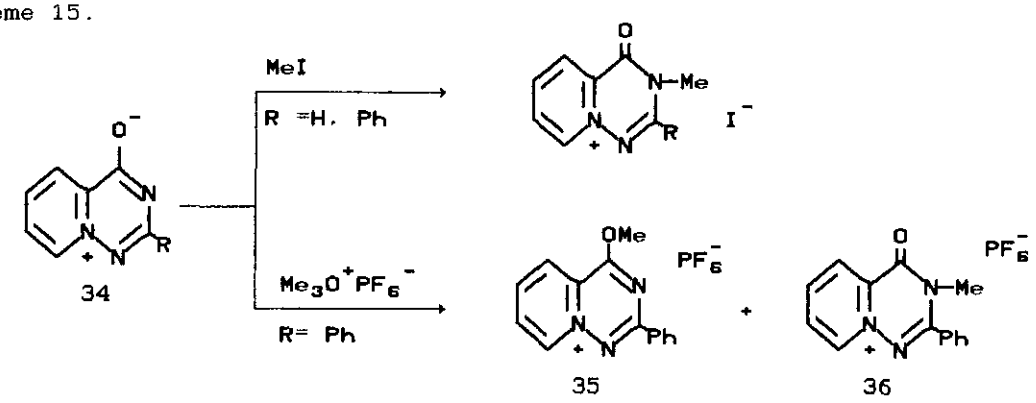
Scheme 14.



Y= O, S; R= Me, $ArCOCH_2$ (Ar= Ph, *p*-MeO-C_6H_4, *p*-Cl-C_6H_4 e.a.); R^1= H, NH_2; X= F_3CSO_3, Br, BF_4

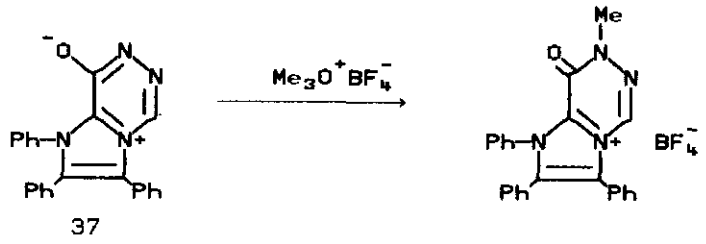
Triazinium-5-olates (34) are more sensible to steric effects of substituents at $C_{(3)}$ and to the nature of alkylating agents as well. With $C_{(3)}$ bearing hydrogen or an alkylthio group the methylation reaction takes place exclusively at $N_{(4)}$.[16,17] When the phenyl group is present at $C_{(3)}$ a difference between methylation reactions with soft methyl iodide and hard trimethyloxonium hexafluorophosphate is observed (Scheme 15). In the latter case the mixture of *O*- and *N*-alkylation products (35) and (36) is formed in the ratio 1:1.[16]

Scheme 15.



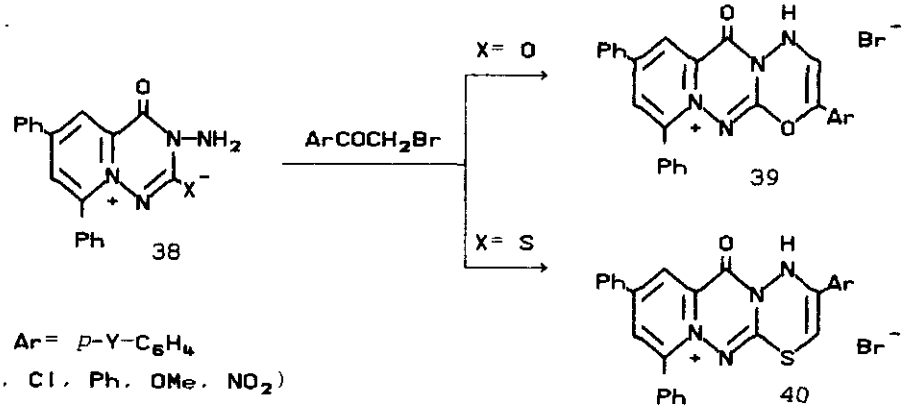
Triazinium-6-olates (37) are methylated with trimethyloxonium tetrafluoroborate exclusively at the $N_{(1)}$ atom.[18] An example is given in Scheme 16.

Scheme 16.



Combining alkylation reactions of triazinium betaines (38) with their further intramolecular cyclizations enables derivatives of polycyclic *as*-triazinium salts (39) and (40) to be obtained (Scheme 17).[17,66,67]

Scheme 17.

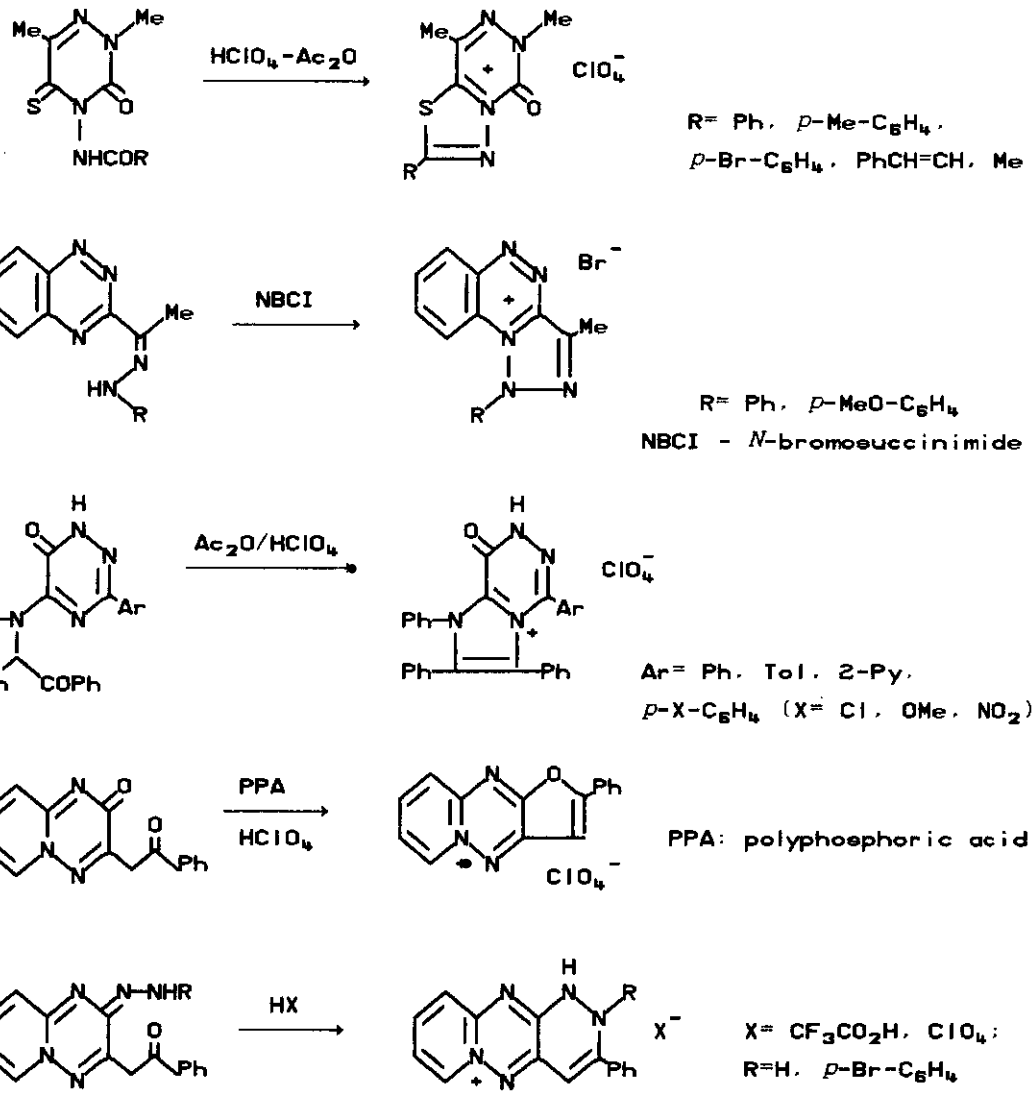


X= O, S; Ar= *p*-Y-C_6H_4
(Y= H, Br, Cl, Ph, OMe, NO_2)

2.2.3. Annelation of Heterocyclic Systems to the as-Triazine Ring

A common synthetic route to fused triazinium salts is based on using triazines containing appropriate substituents in the ring which, being protonated, are able to undergo intramolecular cyclizations into *as*-triazinium salts annelated with thiadiazole,[63,68] triazole,[69] imidazole,[18] furan[70] and pyridazine[70] rings. Some examples are given in Scheme 18.

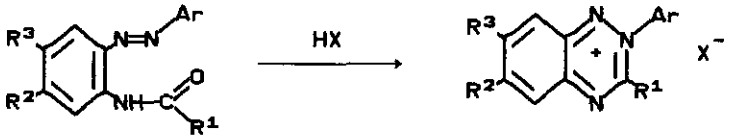
Scheme 18.



2.2.4. Annelation of the Triazinium Fragment to Heterocyclic Systems

There are two approaches to annelation of the *as*-triazinium fragment. The first one is based on using appropriately substituted arenes and hetarenes which can be transformed into fused triazinium salts via intramolecular cyclizations. For instance, when treated with mineral acids *ortho*-acylamino substituted azobenzenes (**41**) are cyclized into $N_{(2)}$-arylbenzo[*f*]*as*-triazinium salts (**42**) (Scheme 19).[71]

Scheme 19.

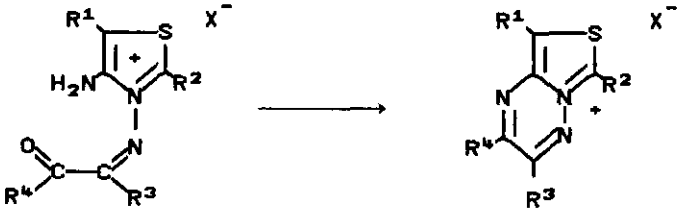


41 42

R^1= H, NH_2, Me, OEt, Ph; R^2= OMe, NEt_2, NMePh, NMe_2
R^3= H, Me, OMe, COOEt; Ar= *p*-Y-C_6H_4, (Y =MeO, EtO, Et_2N, NO_2)
X= BF_4, Cl, BF_4

Also, it has been found that generated *in situ ortho*-aminotriazolium cations (**43**) are easily transformed into triazolo[3,4-*b*]*as*-triazinium salts (**44**) (Scheme 20).[72-77]

Scheme 20.



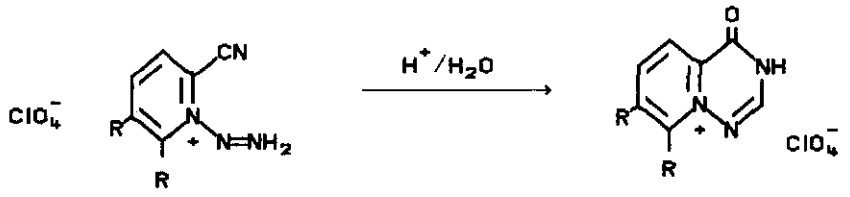
43 44

R^1=H, Ph; R^2= SMe, Me; X= $PhSO_3$, ClO_4; R^3, R^4= H, Me, Ph

Acidic hydrolysis of *N*-substituted 2-cyanopyridinium salts (**45**) followed by the intramolecular condensation is another example of using this metho-

dology for the synthesis of fused benzo[*f*]*as*-triazinium salts (46) (Scheme 21).[78]

Scheme 21.

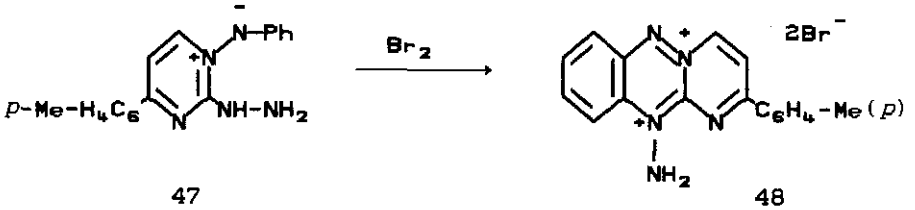


45 46

R= H, benzo

Unexpected intramolecular cyclization into the tricyclic dicationic triazinium salt (48) has been found to occur on treatment of 2-hydrazinopyrimidinium *N*-ylide (47) with bromine (Scheme 22).[79]

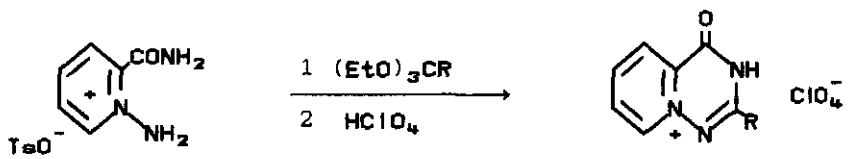
Scheme 22.



47 48

Another way to fused *as*-triazinium salts is based on using *ortho-substituted N-aminoazinium cations* and, depending on the nature of substituents in these *N*-aminoheterocycles, from one to several atoms of the reagents used can be incorporated into the forming *as*-triazine ring. For instance, when condensing *N*-aminopiridinium tosylate (49) with *ortho*-ethers, pyrido[2,1-*f*]*as*-triazinium salts (50) are formed, in which the $C_{(2)}$-R fragment originates from the starting ether (Scheme 23).[80]

Scheme 23.



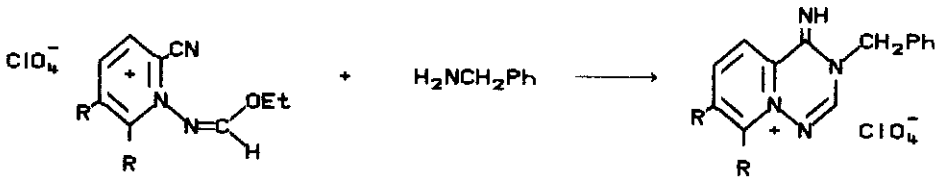
49 50

R= H, Me, Ph

Similarly a number of *as*-triazinium salts, in which the *as*-triazine ring is fused with quinoline, isoquinoline and benzoquinoline systems have been obtained.[81]

2-Cyanopyridinium cations (51) can be converted into pyrido[2,1-*f*]triazinium salts (52) by action of amines through incorporation of the nitrogen atom (Scheme 24).[78]

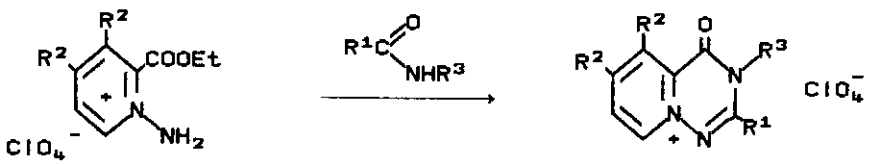
Scheme 24.



51 R= H, benzo 52

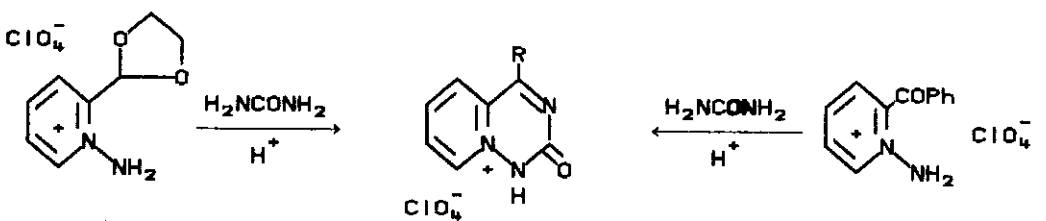
If 1 aminopyridinium cations (53-55) bear at $C_{(2)}$ a modified carbonyl group (2-formyl in the form of cyclic acetals, 2-phenylcarbonyl, 2-ethoxycarbonyl etc.), then two atoms, C and N, are needed to form the triazine ring. Amides and ureas appear to be appropriate reagents for such condensations, as shown below (Scheme 25.)[16,82,83]

Scheme 25.



53

R^1= H, Me, Ph, *p*-Cl-C_6H_4; R^2= H, benzo, R^3= H, Me.

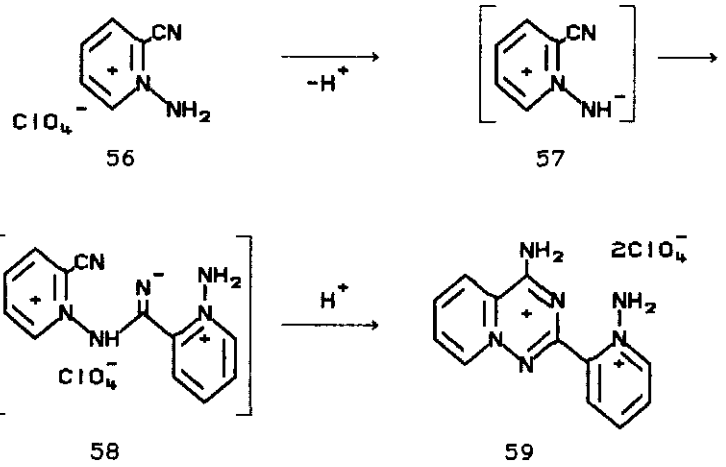


54 55

R= H, Ph

In extraordinary dimerization of 1-amino-2-cyanopyridinium salt (56) the C-N fragment needed for the formation of the triazine ring is provided by the starting material (Scheme 26).[84]

Scheme 26.

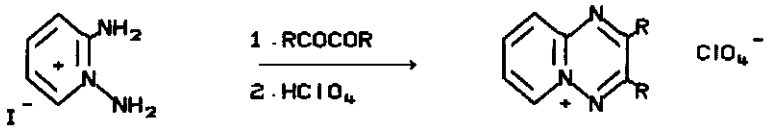


56 57 58 59

The reaction is supposed to involve the formation of the *N*-ylide (57) which then couples with the starting cation (56) to give the intermediate (58). Cyclization of the latter followed by deprotonation results in the formation of dicationic species (59).[84]

Condensation of 1,2-diaminopiridinium salts (60) with 1,2-dicarbonyl compounds leads to pyrido[2,1-*f*]*as*-triazinium salts (61) in which the $C_{(2)}$-$C_{(3)}$ fragment is donated by 1,2-dicarbonyl reagents (Scheme 27).[85-87]

Scheme 27



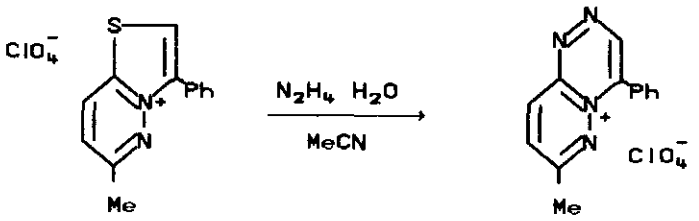
60 61

R= H, Me

2.2.5. Other Synthetic Ways to Fused as-Triazinium Salts

Other syntheses of fused *as*-triazinium salts involve using of ring transformation reactions or oxidation of condensed dihydrotriazine systems. For instance, treatment of thiazolo[3,2-*b*]pyridazinium perchlorate (**62**) with hydrazine hydrate results in pyridazo[6,1-*e*]as-triazinium salt (**63**) through the ring transformation reaction according to the ANRORC (Addition of the Nucleophile, Ring Opening, and Ring Closure) mechanism (Scheme 28).[88]

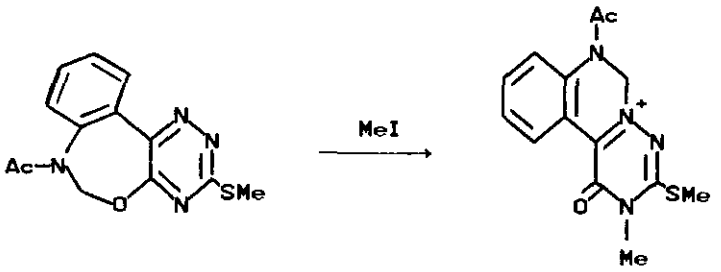
Scheme 28.



62 **63**

Alkylation of the triazine (**64**) with an excess of methyl iodide causes opening of the 1,3-oxazepine ring followed by the recyclization reaction yielding tricyclic *as*-triazinium salt (**65**) (Scheme 29).[59]

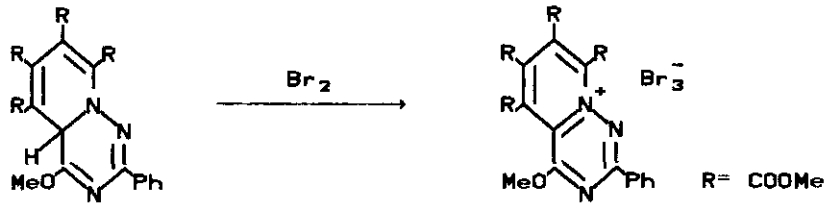
Scheme 29.



64 **65**

The pyrido[2,1-*f*]*as*-triazinium salt (**67**) has been obtained by oxidation of dihydropyrido[2,1-*f*]*as*-triazine (**66**) with bromine (Scheme 30).[89]

Scheme 30.



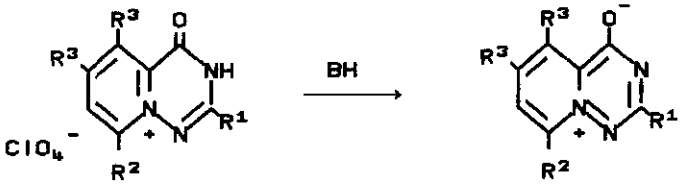
66 67

3. Reactions of *as*-Triazinium Salts

3.1 Action of Bases

Several processes may compete in the reactions of *as*-triazinium salts with bases depending on the basic character and electron-donating ability of the base used and the nature of *as*-triazinium salts.[14-19,25,82,90] In particular, *as*-triazinium salts (**68**) with the bridgehead nitrogen atom containing rather acidic NH or OH groups are easily deprotonated by action of such bases as triethylamine or potassium hydroxide to yield betaines (**69**) (Scheme 31).[16-18,82]

Scheme 31.



68 69

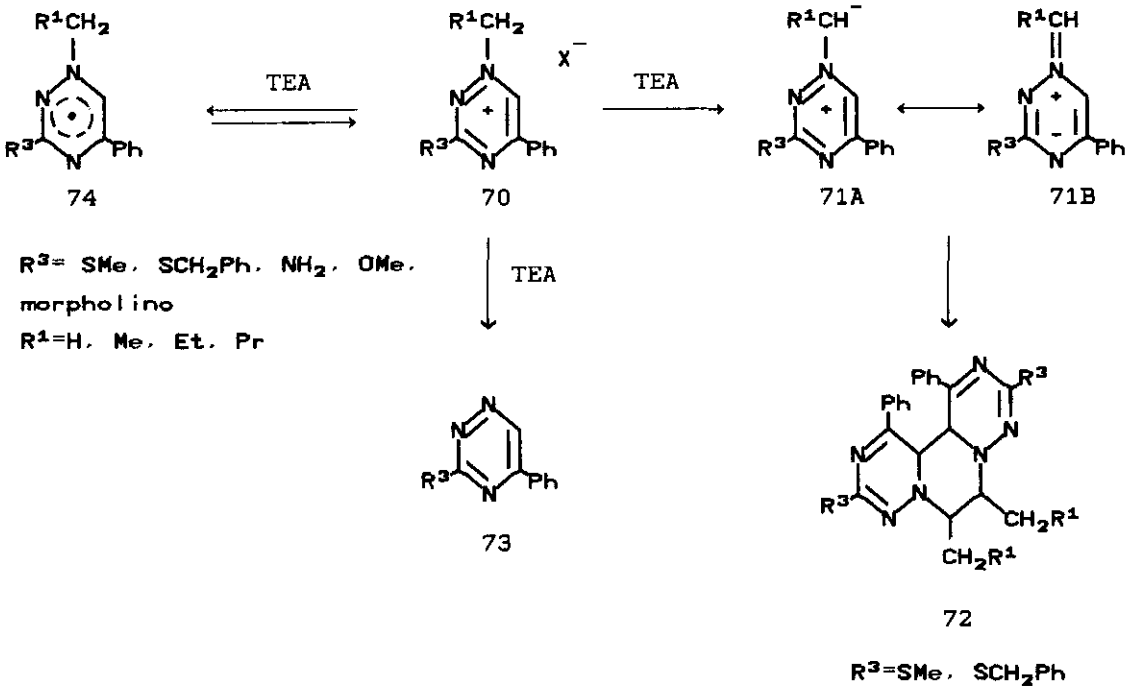
BH= KOH, Et_3N; R^1= H, Me, Ph, SCH_2COPh; R^2= H, Ph; R^3= H, benzo

Interaction of *N*-alkyl-*as*-triazinium salts with bases is more complicated. The charged triazinium ring causes a large increase in the CH- acidity of the neighbouring *N*-alkyl group, thus facilitating its deprotonation into ylides.[15] It is worth mentioning that the formation of azomethine ylides from *N*-alkylpyridinium, pyrimidinium and other *N*-alkylazinium cations is a common phenomenon provided those ylides bear an electron withdrawing group

(cyano, carbonil, etc.) next to the carbanionic centre.[91-94]

Only a few papers describe the formation of nonstabilized pyridinium methylides.[95-97] Deprotonation of 1-alkyl-5-phenyl-*as*-triazinium salts (70) by triethylamine (TEA) has recently been found to result in ylides (71) which are comparatively stable due to large inductive effect of the triazinium group coupled with its ability to delocalize the negative charge (71A) ⟷ (71B) (Scheme 32).[15-19] Evidence for the formation of ylides (71) is provided by their participation in the cycloaddition reaction with acetylenedicarboxylate (see Section 3.3). Ylides (71) are probably responsible for dimerization of 1-alkyl-3-alkylthio-5-phenyl-*as*-triazinium salts (70) into 4a,4b,9,10-tetrahydro-1,3,6,8,8a,10a-hexaazaphenantrenes (72) (Scheme 32).[25]

Scheme 32.



Another possibility is reduction of 1-alkyl-*as*-triazinium salts by TEA due to one electron transfer. The fine structure of radical species registered by ESR has been found to be in full agreement with the formation of radi-

cals (74) (Scheme 32).[14]

The chracteristic feature of 1-alkyl-*as*-triazinium salts (70) is the dequaternization reaction which proceeds very easily even at room temperature. Kinetic studies on dequaternization of 1-alkyl-5-phenyl-*as*-triazinium salts (70) have revealed that the observed pseudo-first rate constants k_{obs} are approximately 10^{-3} sec^{-1} at 25°,[15] while *N*-alkylpyridinium salts are dequaternized much slower (k_{obs}~10^{-5} sec^{-1} at 100°).[98]

3.2 Reactions with Nucleophilic Reagents

Molecular orbital (MO) calculations using the CNDO/2 method revealed that for three *N*-methyl isomeric *as*-triazinium cations, regardless of the position of the quaternary nitrogen, the charge distribution is as follows: $C_{(3)} > C_{(5)} > C_{(6)}$.[11,27] Nearly the same picture is observed in the case of NH-*as*-triazinium salts (Table 6). One can see that this sequence of charge densities for quaternary triazinium salts coinsides with that of the parent triazine. However, alkylation or protonation of $N_{(1)}$ activates the $C_{(6)}$ position more than $C_{(5)}$, thus making these salts capable of reacting with nucleophiles both at $C_{(5)}$ and $C_{(6)}$.[11,27]

Table 6. ($\sigma+\pi$) Charge distributions in molecules of isomeric NH- and *N*-methyl-*as*-triazinium salts[11,27]

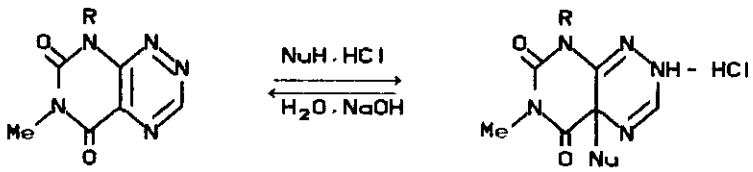
Quaternary nitrogen atom	($\sigma+\pi$) Charges on carbon atoms		
	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$
N_1^+-H	0.187	0.116	0.129
N_2^+-H	0.249	0.184	0.072
N_4^+-H	0.209	0.182	0.050
N_1^+-Me	0.193	0.125	0.094
N_2^+-Me	0.204	0.165	0.068
N_4^+-Me	0.185	0.130	0.057
as-triazine	0.163	0.108	0.034

Indeed, uncharged *as*-triazines usually add nucleophiles at C-5 yielding monoadducts with a variety of *N*-, *O*- and *C*-nucleophilic reagents.[5,99-105] *as*-Triazinium salts proved to be more reactive toward nucleophilic reagents and, depending on positions and the nature of substituents, they are able to give both mono- and diadducts.

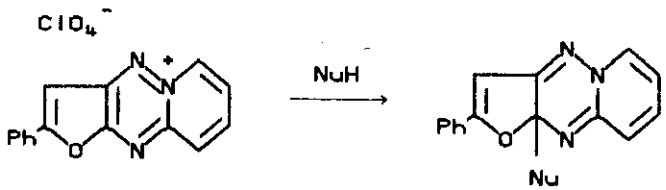
3.2.1. The Formation of σ-Adducts

A great majority of *as*-triazinium salts add nucleophiles at C-5 giving rise to comparatively stable monoadducts.[5,11,27,99-104] The $C_{(5)}$-adducts are formed even in those cases when the triazine ring is annelated across the $C_{(5)}$-$C_{(6)}$ bond with five (six)- membered heterocycles (Scheme 33).[20,55,58,70,105-108]

Scheme 33.



NuH= indole, H_2O, $PhNHNH_2$; R= H, Me



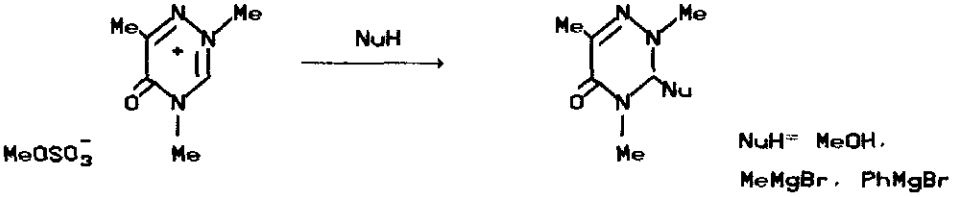
NuH= MeOH, pirrolidine

The formation of C-3 adducts has been observed on treatment of the 2-methyl-*as*-triazinium salt (74) with sodium methoxide or Grignard reagents (Scheme 34),[43] and in the reaction of 5,6-disubstituted NH-*as*-triazinium salts with alcohols as well.[109]

as-Triazinium salts bearing no substituents at C-5 and C-6 exhibit a marked tendency to add two molecules of nucleophilic reagents. For instance, 3-substituted 1-alkyl-*as*-triazinium salts (75) add two molecules

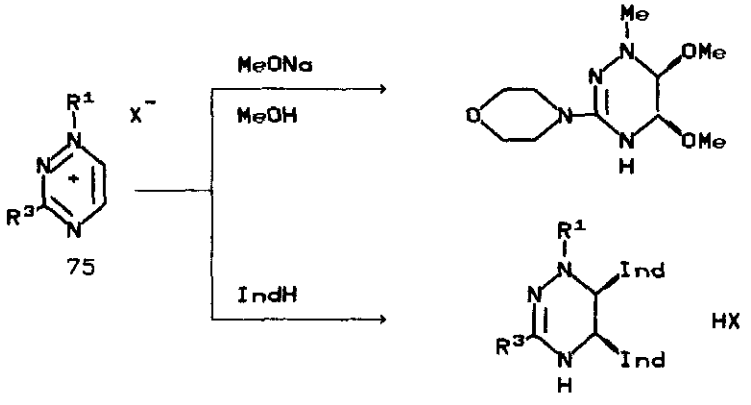
of indole and the methoxide anion (Scheme 35).[10,11] The adducts formed have a *cis*-orientation of the 1,4,5,6-tetrahydro-*as*-triazine ring, as follows from the vicinal coupling constants ^{3}J between $H_{(5)}$ and $H_{(6)}$ protons (2-4 Hz)[11] and the literary data on diadducts of a similar structure derived from 1-alkylpyrazinium salts.[35]

Scheme 34.



74

Scheme 35.

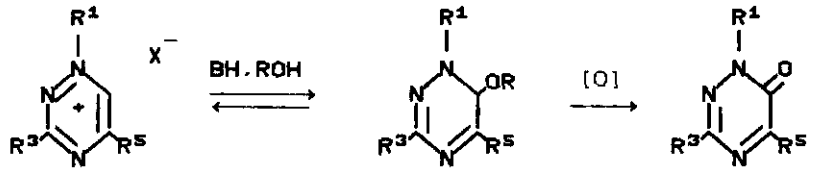


75

R1= Me, Et; R3= OMe, morpholino, pyrrolidino;
Ind= Indolyl, 2-Me-Indolyl; X= I, BF_4

If a nucleophilic attack at C-5 is hindered or blocked by a bulky substituent, then the addition reaction takes place at C-6, as illustrated by the reaction of 1-alkyl-3,5-disubstituted *as*-triazinium salts (76) (Scheme 36). The nmr evidence for the formation of σ-adducts (77) with alcohols have been obtained;[14,15] they have also been oxidized into triazin-6-ones (78).[13,21]

Scheme 36.



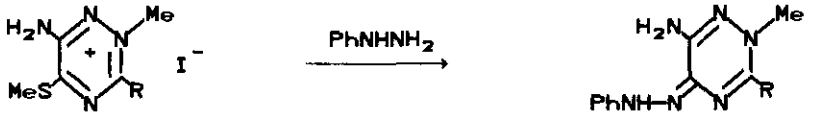
76 77 78

R= H, Me, Et; R^1= Me, Et; R^3= H, SMe, OMe, NMe_2, morpholino; R^5= H, Me, Ph; BH: NEt_3, NaOH

3.2.2. Nucleophilic Substitution Reactions

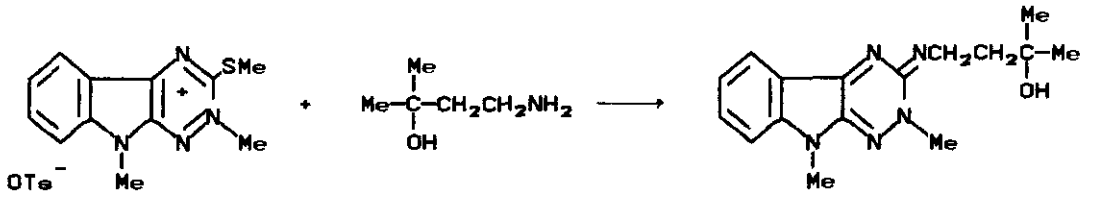
Only a few examples of the displacement of nucleofugic groups in $N_{(2)}$-methyl substituted *as*-triazinium salts (79) and (80) have so far been published (Scheme 37).[44,58]

Scheme 37.



79

R= Ph, Tol, *p*-Cl-C_6H_4



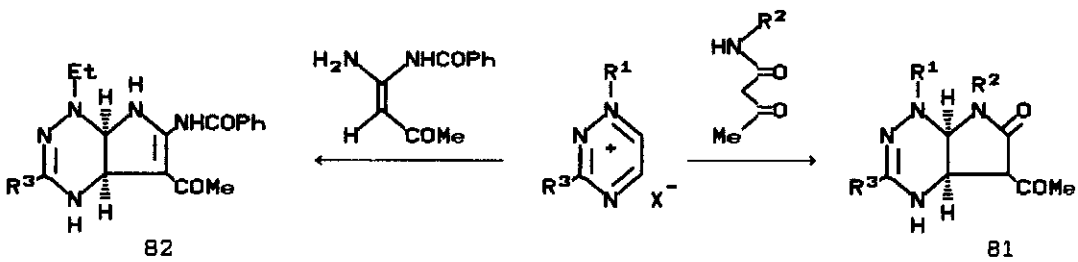
80

3.2.3. Cyclizations with Bifunctional Nucleophiles

The tendency of NH- and 1-alkyl-*as*-triazinium salts to give diadducts with nucleophilic reagents can be applied successfully to the synthesis of

condensed triazines. Amides of acetoacetic acid, *N,N*- and *N,S*-ketene acetals proved to be effective reagents for the synthesis of fused pyrrolo[3,2-*e*]triazines (81) and (82) by means of cyclizations with both *N*-alkyl and NH-*as*-triazinium salts (Scheme 38).[5,11,22-24]

Scheme 38.



82 81

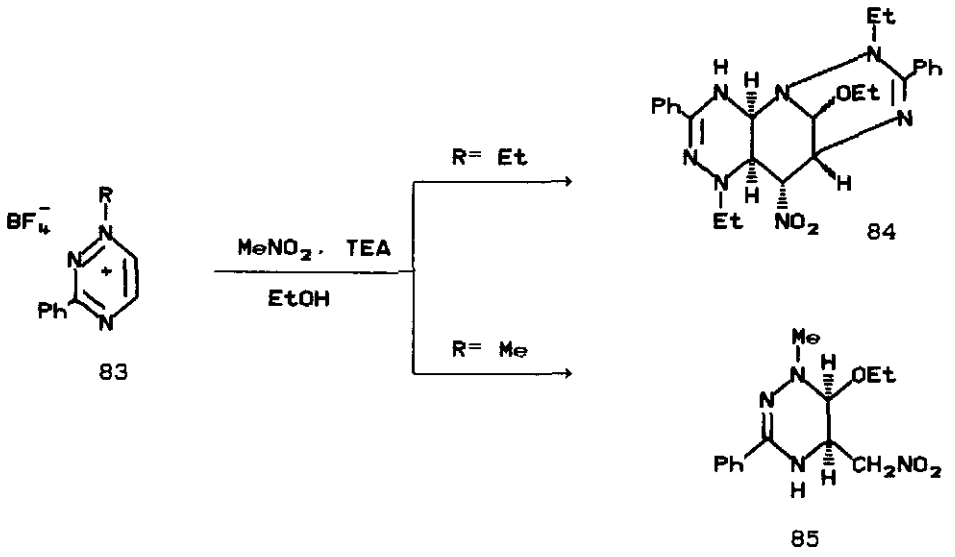
R^3= Ph, morpholino

R^1= H, Me, Et; R^2= Ph, *p*-Tol, CH_2Ph; R^3= SMe, Ph, morpholino; X= BF_4, I

In the ^1H nmr spectra of pyrrolo[3,2-*e*]triazines (81) and (82) values of the vicinal coupling constants between the ring junction protons proved to be in the range 6-8 Hz.[22,23] These values correspond to a *cis*-orientation of these hydrogen atoms, as shown by x-ray diffraction study performed on the $N_{(4)}$-nitrozo derivative of (81) with R^1= NO, R^2= C_6H_4-Me(*p*) and R^3= morpholino.[22,23]

The diaddition process is also realized in the reaction of 1-alkyl-3-phenyl-*as*-triazinium salts (83) with nitromethane in methanol in the presence of triethylamine. Depending on the nature of the *N*-alkyl group one or two molecules of the *as*-triazinium salt participate in the reaction giving rise to either diadducts (85) or cyclization products (84) (Scheme 39).[15] In the latter case nitromethane behaves itself like 1,1- dinucleophile. The stereochemical features of this cyclization reaction and a plausible mechanism for the formation of compounds (84) advanced on the basis of nmr studies are presented in Scheme 39.

Scheme 39.



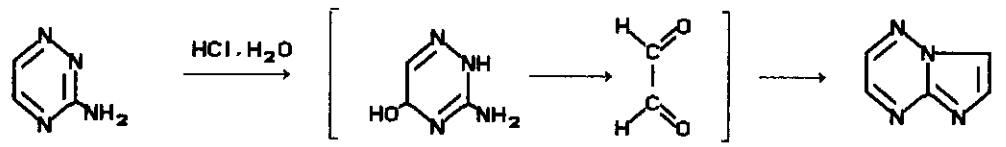
3.2.4. Ring Opening and Ring Transformation Reactions

The formation of σ-adducts in reactions of *as*-triazinium salts with nucleophiles is usually observed in solutions at room or lower temperatures. Heating the solutions may provoke opening of the triazine ring followed by intramolecular rearrangements resulting in the ring transformation products. For instance, when treated with water at 100 °C in the presence of hydrochloric acid, 3-amino-*as*-triazine (86) is transformed into imidazo[1,2-*b*]-*as*-triazine (89) (Scheme 40).[110,111] The reaction is presumed to be initiated by covalent hydration of the NH-*as*-triazinium salt (σ-adduct (87) which facilitates the ring opening and the formation of glyoxal (88). The latter participates in condensation with the starting 3-amino-*as*-triazine (86) to give the final product (89) (Scheme 40).

Decomposition of the *as*-triazine ring into glyoxal has also been caused by the diaddition of phenylhydrazine to 1-ethyl-3-morpholino-*as*-triazinium tetrafluoroborate (90) (Scheme 41).[11]

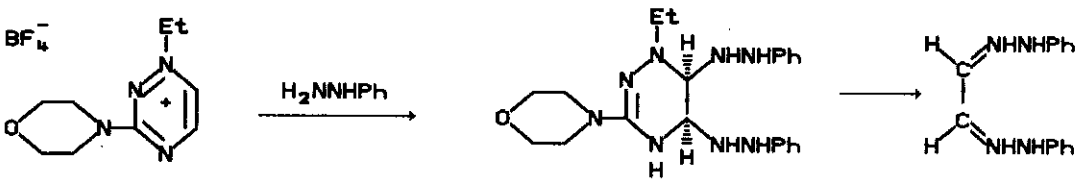
Opening of the *as*-triazine ring has also been observed on heating of fervenulin in 6N hydrochloric acid.[105]

Scheme 40.



86 87 88 89

Scheme 41.

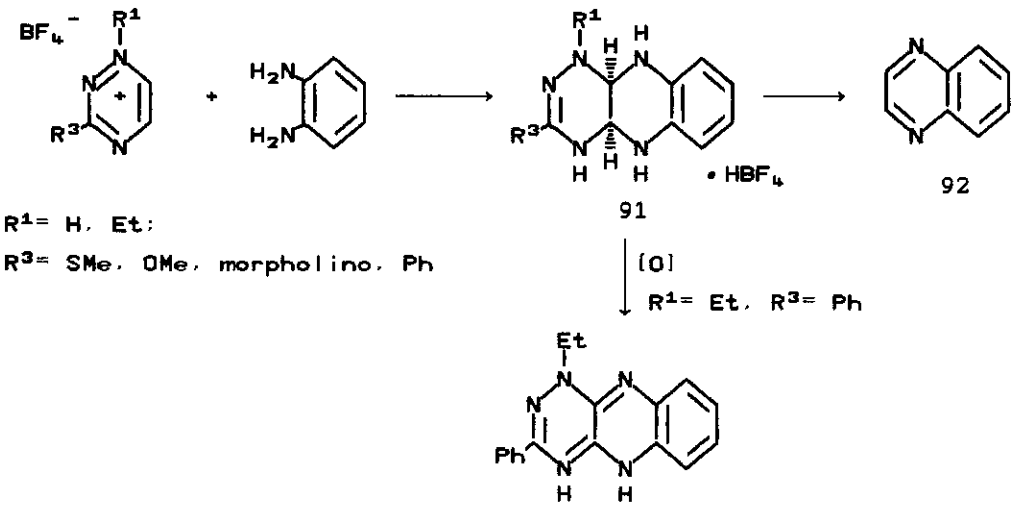


90

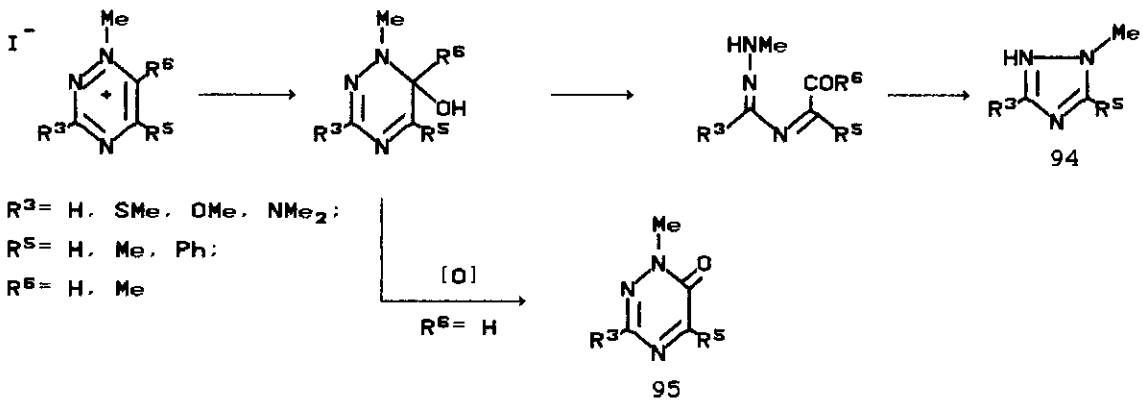
N-Alkyl- and NH-*as*-triazinium salts have recently been found to under-go the ring transformation into condensed pyrazines by action of aromatic 1,2-diamines (92). In this reaction the *as*-triazinium salt donates its C-C fragment to the forming pyrazine ring. Intermediate cycloadducts (91) have been isolated or registered by ^{1}H nmr spectroscopy (Scheme 42).[5,11,26] They can also be oxidized by potassium permanganate into tricyclic systems with retention of the triazine ring, as shown in Scheme 42.[5,11]

Addition of the hydroxide ion at C-6 of 1-methyl-*as*-triazinium salts (93) provokes their transformation into 1,2,4-triazole derivatives (94). The formation of triazin-6-ones (95) as by-products under oxidative conditions provides some support for the suggested ANRORC mechanism (Scheme 43).[13,21] The triazine to pyridine ring transformations of 1-alkyl-*as*-triazinium salts proceeding as the intramolecular Diels-Alder cycloaddition reactions are discussed below (Section 3.3).

Scheme 42.



Scheme 43.

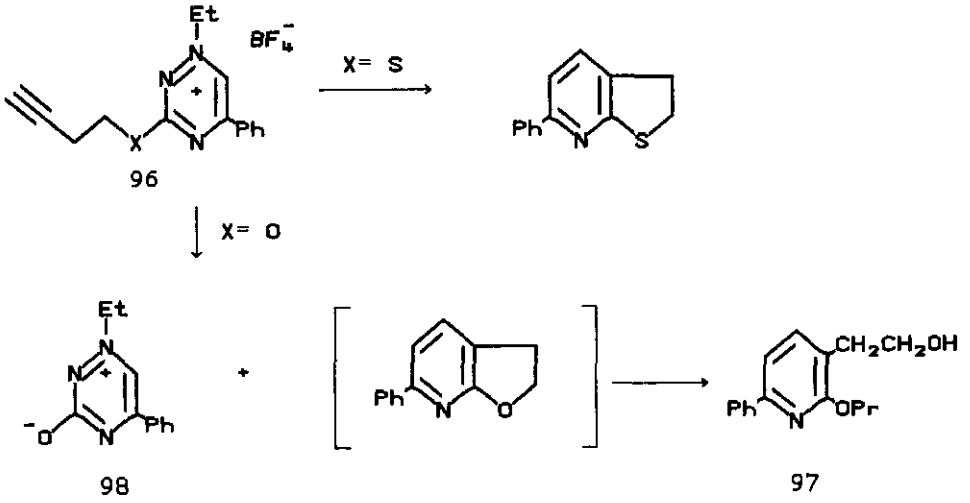


3.3 Cycloaddition Reactions

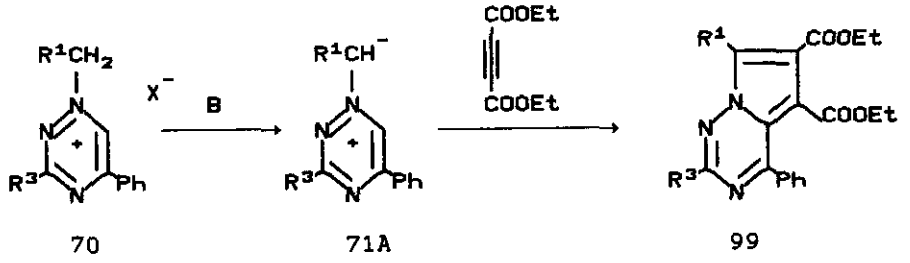
Uncharged 1,2,4-triazines are known to be appropriate substrates for the Diels-Alder cycloaddition reactions.[9] Since introduction of electron-withdrawing substituents in the triazine substrate enhances its reactivity towards electron-rich dienophiles, it was a good idea to use quaternary 3-alkynyl substituted 1-alkyl-1,2,4-triazinium salts as the starting materials in intramolecular Diels-Alder reactions. Indeed, 3-alkynylthio-

1-ethyl-5-phenyl-*as*-triazinium salts (96) (X=S) proved to undergo the cycloaddition reaction under considerably milder conditions (even at room temperature) than their neutral analogues (Scheme 44).[12] The intramolecular cyclization of the 3-butynyloxy-5-phenyl-*as*-triazinium salt (96) (X= O) requires more rigid conditions (reflux in propanol) and is accompanied by opening the furan ring to give pyridine (97) and the formation of the by-product (98) (Scheme 44).[15]

Scheme 44.



Scheme 45.



R1= H, Me, Et, *n*-Pr; R3= NH_2, SMe, OMe

As already mentioned above (see Section 3.1) deprotonation of 1- alkyl-5-phenyl-1,2,4-triazinium salts (70) with triethylamine yields the ylides

(71A) which are capable of reacting with diethyl acetylenedicarboxylate to form pyrrolo[2,1-*f*]*as*-triazines (99). The reaction has been effectively applied to 1-methyl, 1-ethyl, 1-*n*-propyl- and 1-*n*-butyl-5-phenyl-*as*-triazinium salts bearing amino, morpholino, piperidino, methylthio or methoxy substituents at C-3 of the triazine ring (Scheme 45).[19]

4. Conclusion

The data discussed above show that *as*-triazinium salts can easily be obtained through *N*-protonation, *N*-alkylation and also by means of a great deal of condensation reactions. Being more reactive towards nucleophilic reagents than neutral triazines they are able to undergo a variety of reactions, which sometimes are rather unusual. Recent studies on *as*-triazinium cations show that it might be a very promising area for the development of new syntheses of heterocyclic compounds.

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