Chemistry of Heterocyclic Compounds, Vol. 30, Nos. 11-12, 1994

THIRTY YEARS OF PYRIMIDINE CHEMISTRY IN THE LABORATORY OF ORGANIC CHEMISTRY AT THE WAGENINGEN AGRICULTURAL UNIVERSITY, THE NETHERLANDS (REVIEW)

Henk C. van der Plas

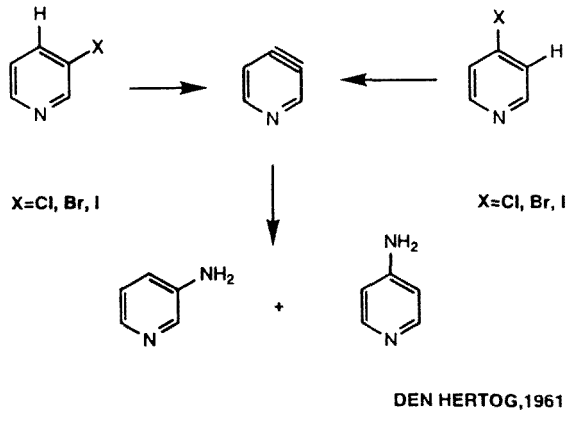
In this review attention is paid to two topics, which were of great interest to us during 30 years of studies in pyrimidine chemistry in our laboratory: first, the development of our concepts of the ANRORC processes, which occur in ring transformation reactions; second, the intra- and intermolecular inverse Diels-Alder reactions in which the pyrimidine ring acts as the electron-poor diazadiene system. Their use in synthetic chemistry is illustrated and evidence is presented, based on experiments and molecular mechanics calculations, that in intramolecular Diels-Alder reactions the geometry of the side-chain plays a vital role.

INTRODUCTION

On the occasion of the celebration of the 30th anniversary of the journal *Chemistry of Heterocyclic Compounds*, I was asked to write a "short review on your investigations." I took this opportunity to highlight some important work in the field of pyrimidine chemistry, which we carried out in our Laboratory of Organic Chemistry of the Agricultural University at Wageningen during about the same period of existence of the Journal. It is evident that this short review cannot cover all the important features of our work. It is a matter of personal choice and therefore limited. It is my aim to bring into perspective the different venues and outcomes of our research activities and to indicate which considerations have directed us in our research programs during these last 30 years.

After the discovery that in reactions of 3-X- and 4-X-pyridines (X = Cl, Br, I) with potassium amide in liquid ammonia at —33°C a mixture of 3-aminopyridine and 4-aminopyridine was obtained (ratio 1 : 2), which ratio was found to be independent of the position and nature of the halogen atom; the transient existence of 3,4-pyridyne was postulated as intermediate (Scheme 1) [1].

Scheme 1

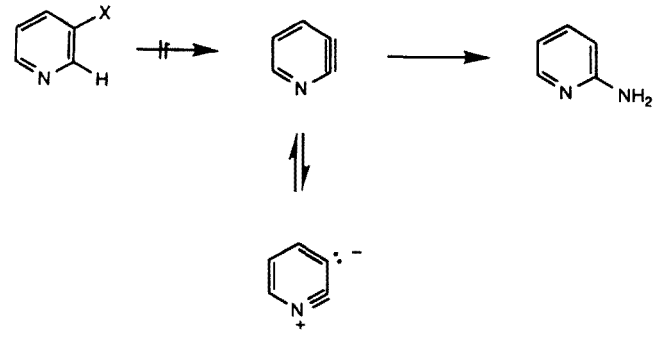


Laboratory of Organic Chemistry, Wageningen Agricultural University, Dreijenplein 8, 6703 NB Wageningen, The Netherlands. Published in Khimiya Geterotsiklicheskikh Soedinenii, Nos. 11-12, pp. 1649-1668, November-December, 1994. Original article submitted August 31, 1994.

0009-3122/94/1112-1427 ©1995 Plenum Publishing Corporation

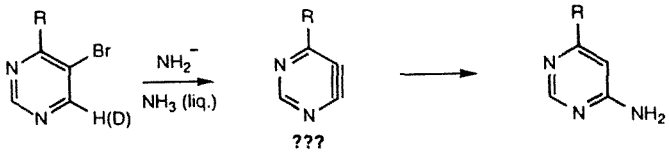
The same results, leading to the same conclusion, were obtained when lithium piperidide/piperidine was used as base system [2]. In all these reactions no indication for the intermediacy of 2,3-pyridyne was found, since it can be expected, based on mesomeric considerations as well as molecular orbital calculations [3], that addition of the amide ion or lithium piperidide to the "triple" bond in 2,3-pyridyne would lead to 2-aminopyridine or 2-piperidinopyridine respectively. However, the formation of the compounds was not observed (Scheme 2).

Scheme 2



In order to establish whether a "2,3-pyridyne-type" intermediate could be generated in reactions of 4-bromopyrimidines, we studied the amination of 4-R-5-bromopyrimidines with potassium amide in liquid ammonia at —33°C. In all these reactions the corresponding 4-R-6-aminopyrimidines were obtained. No indication for the formation of 4-R-5-aminopyrimidines was found [4]. Would, in these reactions, a 5,6-pyrimidyne be formed as transient intermediate, which then undergoes a one-sided addition at C-6? There are several experimental results suggesting the intermediacy of a 5,6-pyrimidyne. Amination of 5-bromo-6-deuteropyrimidines with potassium amide in liquid ammonia revealed that i) in the 6-amino compound obtained no deuterium is present and ii) under the conditions of the reaction no deuterium-hydrogen exchange takes place in the starting material. Also control experiments with 6-amino-5-deuteropyrimidines showed that in these 6-amino compounds no D/H-exchange at C-5 occurs [4]. These results are not contradictory to the existence of the intermediacy of 5,6-pyrimidyne. For the time being the hetaryne mechanism was accepted as a useful working hypothesis (Scheme 3). Based on spectroscopic work, years later, this hypothesis proved to be wrong (see later in the text).

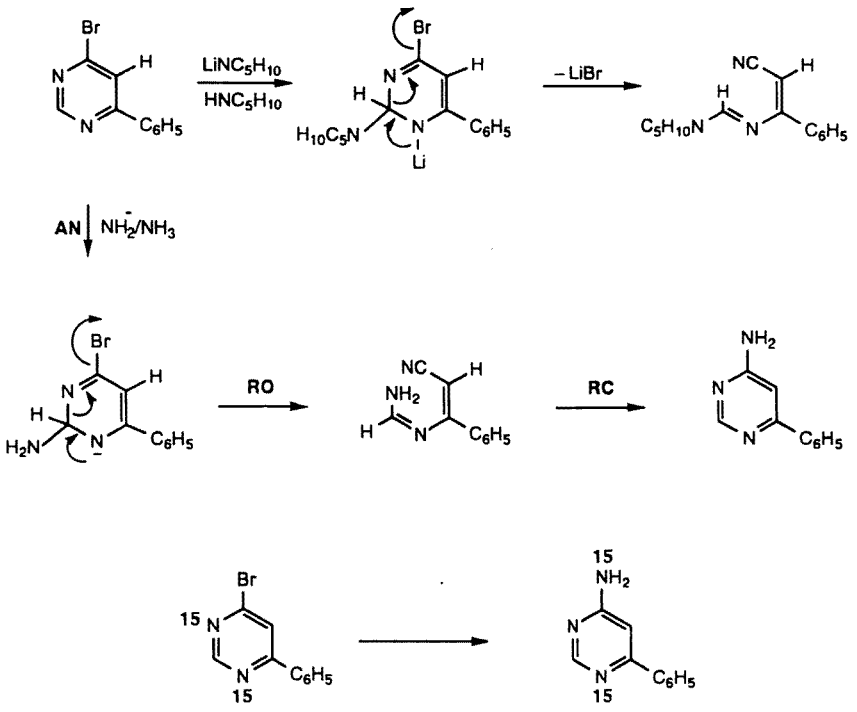
Scheme 3



R=OCH_3, C_6H_5, t-C_4H_9,$CH_3NC_6H_5$

A logical extension of our studies was directed to an investigation on the amination of 4-bromopyrimidines with the strong basic systems potassium amide/liquid ammonia and with lithium piperidide/piperidine. Could, in these reactions, a 4,5-pyrimidyne as intermediate be involved? Using 4-bromo-6-phenylpyrimidine as substrate we found, to our surprise, that with these two reagents completely different products were obtained: with lithium piperidide/piperidine a Z/E mixture of 2-aza-4-cyano-3-phenyl-1-piperidino-1,3-butadiene was formed [5], and with potassium amide/liquid ammonia, 4-amino-6-phenylpyrimidine [6]. It is evident that the formation of the azabutadiene can only be explained by opening of the pyrimidine ring. From the structure of the open-chain product it is justified to conclude that this ring opening has to occur between N-1 and C-2. It is suggested that this ring opening takes place in the adduct formed by addition of lithium piperidide across the bond between N-1 and C-2 (Scheme 4).

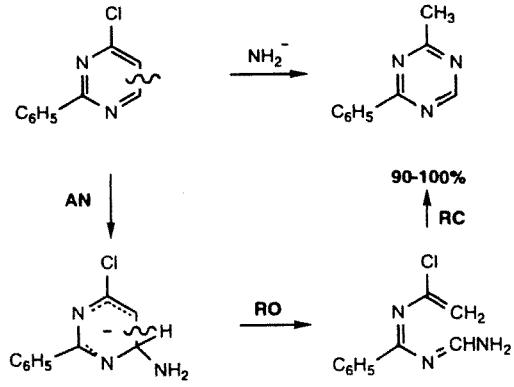
Scheme 4



Is it possible that not only lithium piperidide but also the amide ion is able to add to C-2? An interesting question arises. If addition indeed occurs, followed by ring opening into the 1-amino-2-aza-1,3-butadiene, then this aminoazadiene can, in contrast to the 1-piperidino-2-aza-1,3-butadiene, undergo a subsequent ring closure into 4-amino-6-phenylpyrimidine. So instead of forming the 4-amino compound by the classical S_N (AE) substitution at C-4 or maybe via a 5,6-pyrimidyne, its formation can be described as a sequence of reactions involving an addition-nucleophile-ring opening-ring closure process (ANRORC mechanism). Unequivocal evidence for the occurrence of this ANRORC process was obtained when carrying out the amination with 1(3)-^{15}N-labelled 4-bromo-6-phenylpyrimidine [6]. It was found that in the 4-amino compound obtained 50% of the ^{15}N-label is present on the ring nitrogen and 50% on the exocyclic amino nitrogen. A new mechanism for nucleophilic substitution was born! We refer to this nucleophilic substitution mechanism as S_N (ANRORC) (Scheme 4) [7]. To denote that the amino group is introduced in the same (ipso) position as where the leaving group was present, we prefer to add the superscript ipso, thus [S_N (ANRORC)^{ipso} mechanism]. This addition is useful in order to differentiate it from nucleophilic substitutions according to S_N (ANRORC)^{cine} and S_N (ANRORC)^{tele} mechanisms (see later).

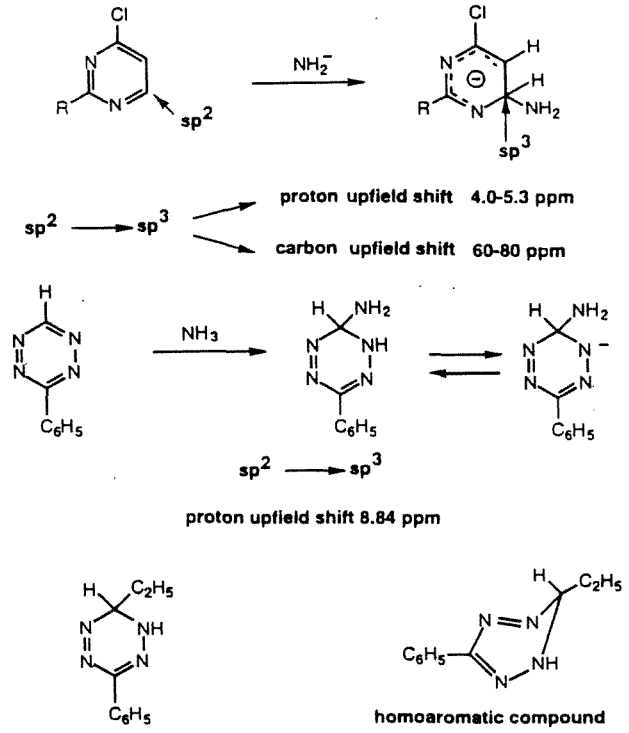
In a further elaboration of the limitation and scope of the S_N (ANRORC) mechanism, we extended our studies subsequently to an investigation on the amination of 4-chloro-2-phenylpyrimidine with potassium amide in liquid ammonia. In this compound position 2 is now blocked due to the presence of the phenyl group. An addition at C-2 cannot take place and therefore it is interesting to observe what will occur if the reaction is forced to take another pathway. Again, to our surprise, we found that besides the 4-amino compound the main product of the reaction was a ring transformation product, i.e., 4-methyl-2-phenyl-1,3,5-triazine! Apparently under the reaction conditions applied a carbon—carbon ring-opening process of the pyrimidine ring takes place (Scheme 5) [8]. Since *a priori* it is not evident whether the carbon—carbon bond fission occurs between C-4 and C-5 or between C-5 and C-6, we synthesized radioactive ^{14}C-labelled 4-chloro-2-phenylpyrimidine-4-^{14}C, performed a reaction with potassium amide in liquid ammonia, and established on which position(s) in the 1,3,5-triazine the ^{14}C-label is present. Acid degradation of the radioactive methylphenyl-1,3,5-triazine into benzoic acid, acetic acid, and carbon dioxide showed that the ring carbon of the triazine ring to which the methyl group is attached is the radioactive one [9]. This result unequivocally proved that the ring opening process has to occur between C-5 and C-6 of the pyrimidine ring. The ring transformation reaction occurs according to an ANRORC mechanism, involving addition of the amide ion to C-6, a subsequent ring opening, and recyclization into the 2-methyl-4-phenyl-1,3,5-triazine (Scheme 5).

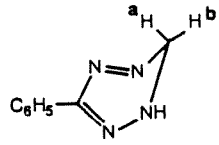
Scheme 5

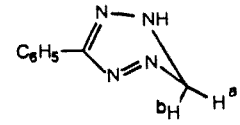


The development of PMR- and C-NMR spectroscopy in the seventies provided us with new excellent diagnostic tools for (re)studying the reactions discussed above [10]. By PMR as well as C-NMR spectroscopy of solutions of appropriate pyrimidines in liquid ammonia containing potassium amide, it was generally observed that position 2 and position 4 of the pyrimidine ring are extremely vulnerable to addition of amide ions [11]. It leads to an anionic 1:1 adduct, i.e., an aminodihydropyrimidinide which can readily be recognized by a characteristic upfield shift of carbon-13 of about 60-80 ppm, due to the change of hybridization from sp^2 to sp^3 on addition. In the PMR spectrum a corresponding upfield hydrogen shift of about 4 to 5 ppm is observed, as exemplified for 2-substituted 4-chloropyrimidines in Scheme 6 [11]. Several years later a very unusual upfield shift was observed on adduct formation with 1,2,4,5-tetrazine [12]. This heterocycle has a high tendency to give adducts with liquid ammonia and does not need a strong nucleophile such as the amide ion for adduct formation. There is conclusive evidence that in the liquid ammonia not the neutral dihydro compound but its anion is present [12]. The sp^2 to sp^3 change, occurring when addition takes place, causes an upfield shift of hydrogen of 8.84 ppm (!), a value never observed in adduct formation with diazines and triazines. Extensive PMR investigations with model compounds, i.e., 1,6-dihydrotetrazines, have shown that they feature a homoaromatic structure, in which the sp^3 carbon is tilted from the plane of the homoaromatic ring, bringing the sp^3-hydrogen in a position above the ring current of the plane. A similar structure is very likely also present in the aminodihydrotetrazinide (Scheme 6).

Scheme 6

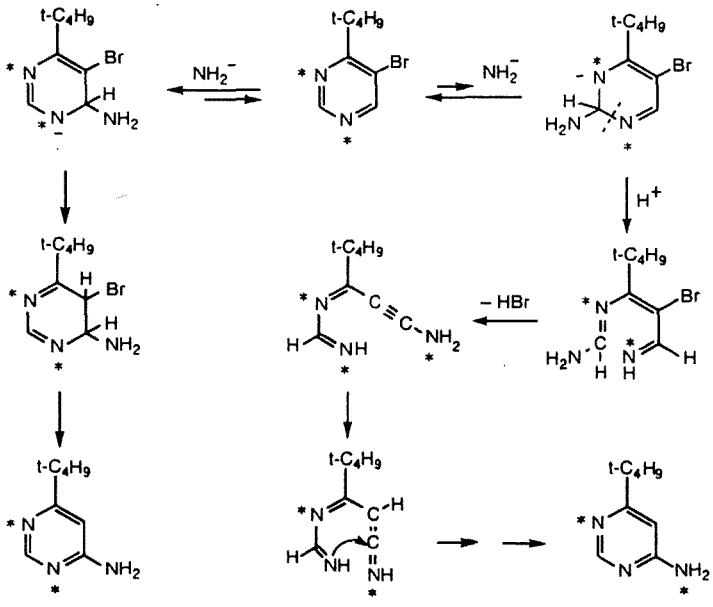






On reinvestigating the amide-induced amination of 5-bromopyrimidines using PMR spectroscopy, we found that a solution of 5-bromo-4-t-butylpyrimidine in liquid ammonia, containing potassium amide, clearly showed the presence of the anionic σ-adduct at C-6, as shown by the upfield shift of the H-6 (about 4 ppm) and moreover by the triplet formation of H-6 signal due to coupling of the attached amino group (J_{HCNH} = 7.5 Hz) [13]. It became clear that the existence of such an anionic 1:1 σ-adduct does not give any support to the intermediacy of 4-t-butyl-5,6-pyrimidyne in the amination, as previously suggested [4]. Further insight into the mechanism of this amination was obtained when using the ^{15}N-labelled 5-bromo-4-t-butyl-1(3)-^{15}N-pyrimidine as substrate [14]. Surprisingly we found that the 6-amino compound obtained showed two different labelling patterns: 50% of the amino compound is labelled on both ring nitrogen and the exocyclic amino nitrogen, the other 50% is only labelled on a ring nitrogen (Scheme 7). The formation of the exocyclic ^{15}N-labelled 6-amino compound is remarkable since one cannot deny the conclusion that ring opening is involved in its formation. However, the difficulty is how to explain the formation of the exocyclic labelled amino function from the 6-amino anionic σ-adduct. This real complication can only be solved if one assumes that the formation takes place via the C-2 amino adduct (Scheme 7), which, however, can only be present in a very low concentration since by NMR spectroscopy its presence cannot be detected. The very slow rate of the amination reaction is in agreement with the at best low concentration of the 2-amino σ-adduct. Once the addition has taken place the ring opening must occur rapidly since the PMR data show no indication at all of the existence of any species besides the 6-amino adduct. After ring opening, loss of hydrogen bromide, and protonation, the ketenimine is formed, which subsequently cyclizes into the 6-amino-4-t-butylpyrimidine with the exocyclic amino function ^{15}N-labelled (Scheme 7).

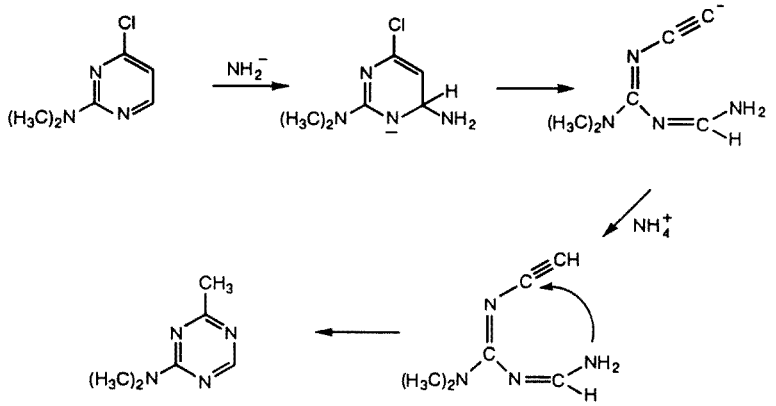
Scheme 7



It is of interest to mention that the 5-bromo-4-t-butylpyrimidine which converts into the 6-amino-4-t-butylpyrimidine with exocyclic ^{15}N-labelling occurs via an ANRORC process in which the nucleophile is introduced into a position cine to the one vacated by the bromo atom. We refer to that process as the S_N (ANRORC)^{cine} mechanism. That part of the substrate which is converted into the 6-amino compound with retention of the ^{15}N-label only on the ring nitrogen is suggested to react via the intermediacy of a 5,6-dihydro compound, which undergoes a base-induced removal of hydrogen bromide [15].

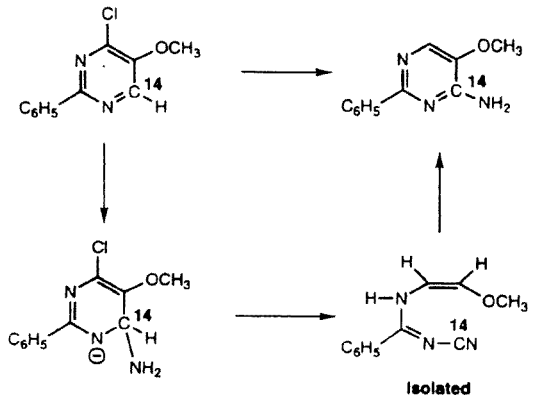
NMR spectroscopy was also successfully used in elucidating the mechanism of the amide-induced ring transformation of the 4-chloro 2-substituted pyrimidines into 2-substituted-4-methyl-1,3,5-triazines [16]. A careful PMR and ^{13}C-NMR study of the intermediates formed during the ring transformation of 4-chloro-2-dimethylaminopyrimidine into 2-dimethylamino-4-methyl-1,3,5-triazine in liquid ammonia containing 2 equivalents of potassium amide revealed the exclusive formation of the anionic 1:1 C-6 amino adduct. In the presence of 4 equivalents of potassium amide this σ-adduct reacts further with an open-chain derivative, i.e., the aminoethynyldiazabutadiene anion, whose ion is rather stable and therefore easily detectable. It converts further into the 1,3,5-triazine derivative when the reaction is quenched with ammonium chloride. It is the conjugate acid, which easily undergoes cyclization (Scheme 8).

Scheme 8



The new concepts in aromatic nucleophilic substitutions [S_N (ANRORC)^{ipso}, S_N (ANRORC)^{cine}, and ANRORC-type ring transformations] induced us to extend our investigations to the reactivity of 2-phenyl-4-halogenopyrimidines containing a substituent R at position 5. With R a carbethoxy, carboxamide, carboxyl, cyano, or phenyl group, ring transformation into 2-phenyl-4-CH_2R-1,3,5-triazines was observed, although the yields are moderate [17]. However, new interesting phenomena were observed when R is a methoxy, methyl, or amino group. When 4-chloro-5-methoxy-2-phenylpyrimidine was treated with potassium amide/liquid ammonia, the reaction does not lead to the expected ring transformation product, i.e., 2-phenyl-4-methoxymethyl-1,3,5-triazine, but surprisingly to an open-chain compound, i.e., N-cyano-N'-(β-methoxyvinyl)benzamidine in good yield (Scheme 9) [18]. From the structure of the product it is evident that ring opening has taken place: is it between C-5 and C-6 or alternatively between C-4 and C-5? By ^{14}C-labelling we could get an answer to that question. When reacting 4-chloro-5-methoxy-2-phenylpyrimidine-6-^{14}C with potassium amide/liquid ammonia, it was established that in the benzamidine derivative the ^{14}C-label is only located on the cyano group, providing sound evidence that the ring fission occurred between C-5 and C-6 and not between C-4 and C-5. This ring fission takes place in the initially formed anionic adduct, i.e., 6-amino-1,2-dihydro-4-chloro-5-methoxy-2-phenylpyrimidinide (Scheme 9).

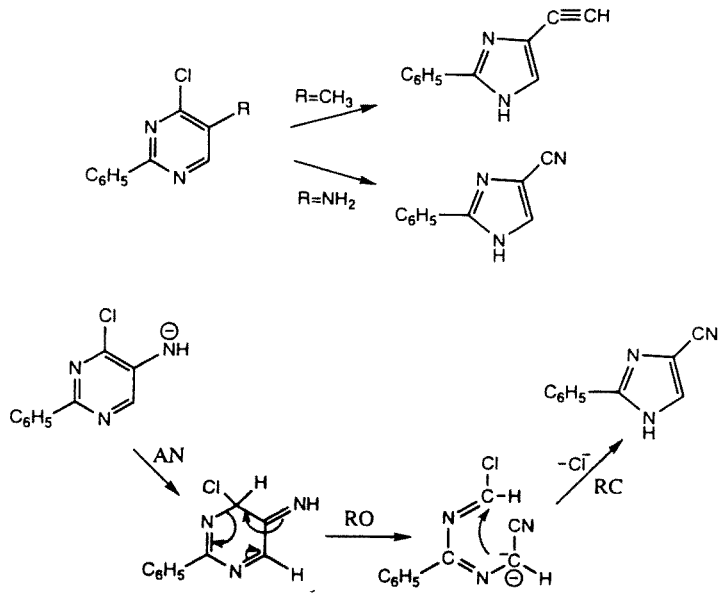
Scheme 9



The cyanobenzamidine appeared to isomerize on heating; it leads to 6-amino-5-methoxy-2-phenylpyrimidine-6-^{14}C. The formation of a 6-amino compound from a 4-chloro derivative is an example of a tele substitution. Usually in tele substitutions no ring opening is involved. Since in our case an open-chain compound is intermediate, obtained by addition and ring opening, the above-mentioned reaction is categorized as an S_N (ANRORC)^{tele} mechanism. So, in conclusion we were very successful in establishing that the nucleophilic aromatic substitutions which occur according to an S_N (ANRORC) process can be found in ipso, cine, as well as tele substitutions.

A completely different set of reactions occurred when R at position 5 of 4-chloro-2-phenylpyrimidine is a methyl or amino group. When reacting these compounds with potassium amide/liquid ammonia, in both reactions a ring contraction reaction was observed, 4-(cyano, ethynyl)-2-phenylimidazole being obtained (Scheme 10) [19].

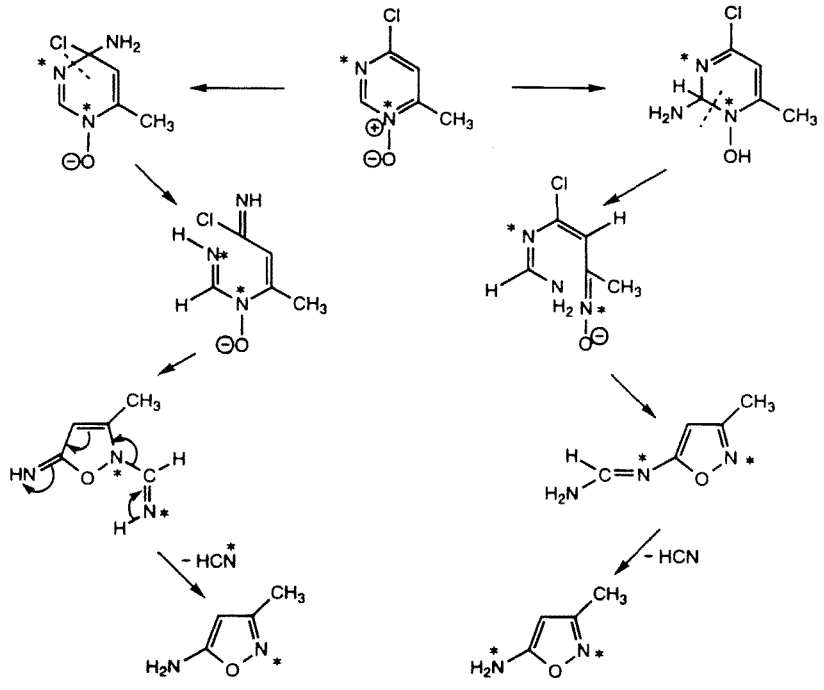
Scheme 10



That no trace of a 1,3,5-triazine derivative is formed is probably due to the fact that in this strong basic medium both amino and methyl groups are deprotonated and that the strongly resonance-stabilized anion formed is deactivated for addition of the amide ion. The reaction course is proposed to take place according to the pathway, as exemplified in Scheme 10 for the formation of the cyano compound, involving a ring opening between C-4 and C-5.

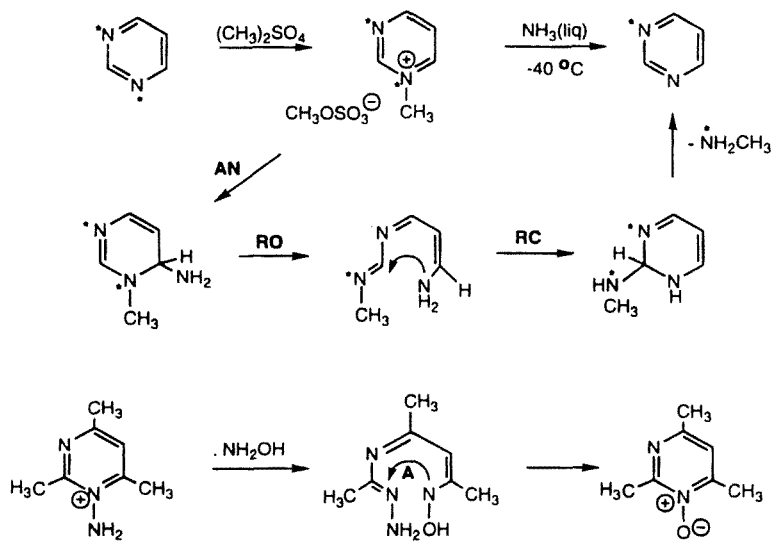
It can be expected that nucleophilic addition reactions are promoted when the electrophilic character of the pyrimidine ring is enhanced by quaternization of the ring nitrogen. Indeed, when one of the ring nitrogen atoms is quaternized, for example by oxidation, greater reactivity towards amines is observed: amination of 4-chloro-6-methylpyrimidine 1-oxide can already be achieved in liquid ammonia at —33°C (thus without the presence of potassium amide). To our surprise, however, besides the corresponding 4-aminopyrimidine N-oxide a ring-contracted product, i.e., 5-amino-3-methylisoxazole, was obtained [20]. Investigations of the reaction with the ^{15}N-labelled pyrimidine N-oxide revealed that in the formation of the 4-amino product the ^{15}N content was nearly the same as in the starting material excluding the occurrence of an S_N (ANRORC) process. Additional studies with 5-D labelled substrates prove that an S_N(EA) mechanism is not operative in the amination and that most likely the amination occurs according to an S_N(AE) process. Furthermore it was established that in the 5-amino-3-methylisoxazole the nitrogen-15 is present on the exocyclic nitrogen as well as in the ring (^{15}N content ratio of ring nitrogen to amino nitrogen is 3 to 1). By degradation studies it has been shown that a mixture of differently labelled isoxazoles is present [21]. These results can only be explained if one assumes that addition at C-4 (with consecutive ring opening and ring closure) as well as addition at C-2 occurs (see Scheme 11).

Scheme 11



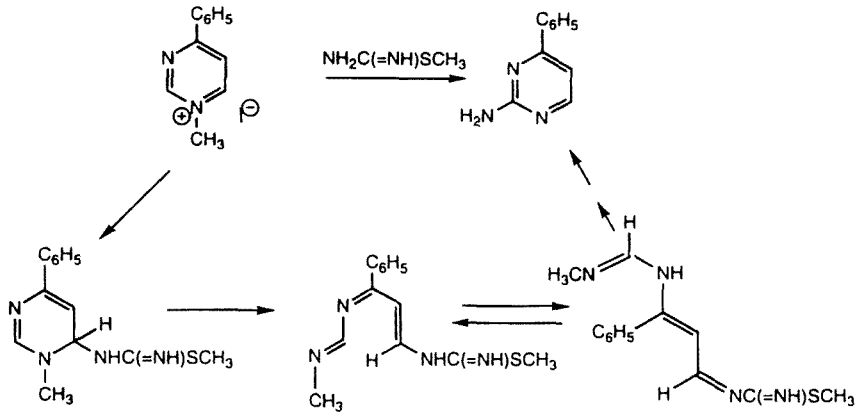
A similar enhancement of the reactivity of the pyrimidine ring towards nucleophiles has been observed with N-methylpyrimidinium salts. For example, treatment of 1-methylpyrimidinium methylsulfate with liquid ammonia at —33 °C leads to demethylation into the parent pyrimidine system [22]. It was observed that demethylation of the double ^{15}N-labelled 1-methyl-[1,3-^{15}N]pyrimidinium salt yields mono ^{15}N-labelled pyrimidine. Apparently the demethylation reaction involves an ANRORC process, initiated by addition of the ammonia at C-6, forming the 6-amino-1,6-dihydro-1-methylpyrimidine. By PMR spectroscopy the formation of this C-6 addition product was unequivocally proven [22]. A somewhat similar deethylation reaction was found with 6-ethoxy-1-ethyl-4-phenylpyrimidinium tetrafluoroborate and liquid ammonia [23]. An interesting N-amino-N-oxygen replacement has been observed on treatment of the 1-amino-2,4,6-trimethylpyrimidinium salt with hydroxylamine, 2,4,6-trimethylpyrimidine N-oxide being obtained (Scheme 12) [24].

Scheme 12



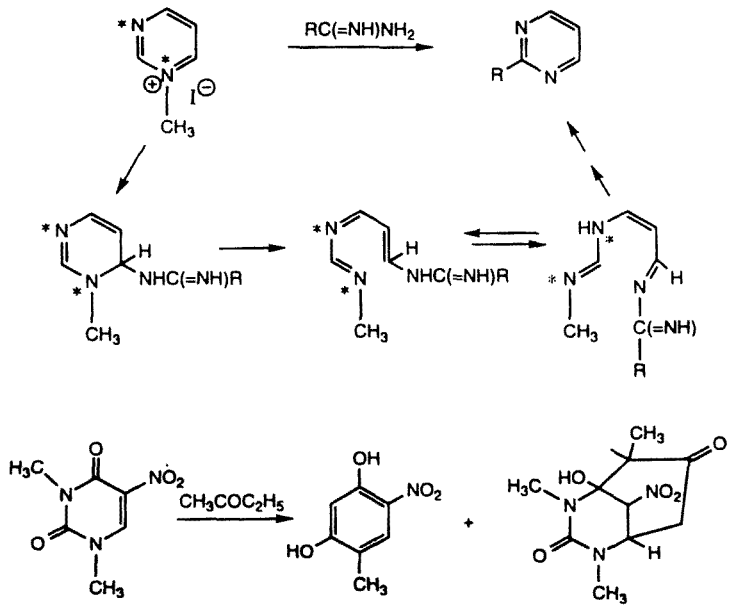
In nearly all previous examples dealing with amination, ring transformation, and demethylation, the reagents (ammonia, amino ion) replaces one of the nitrogens of the pyrimidine ring. We became interested in reactions in which not only the N-atom but a two-atom fragment of the pyrimidine ring could be replaced. Indeed, we observed that, when an ethanolic solution of 1-methyl-4-phenylpyrimidinium iodide and sodium ethoxide was heated with bis-[S-methylisothiouronium]sulfate, 2-amino-4-phenylpyrimidine was obtained in 70% yield [25]. It is evident that the amino compound is formed by a displacement of the two-atom (C-2 and N-1) fragment of the pyrimidinium salt by the N—C fragment of the nucleophile, involving as open chain intermediate the 4-amidino-1-methyliminomethyl-1-azabuta-1,3-diene (Scheme 13). Recyclization occurs by loss of the methylthio group. The same ring transformation also occurs with O-methylisourea and cyanamide reagents. These reactions present an interesting method of introducing an amino group at position 2 of the pyrimidine ring using a ring opening, ring closure sequence (Scheme 13).

Scheme 13



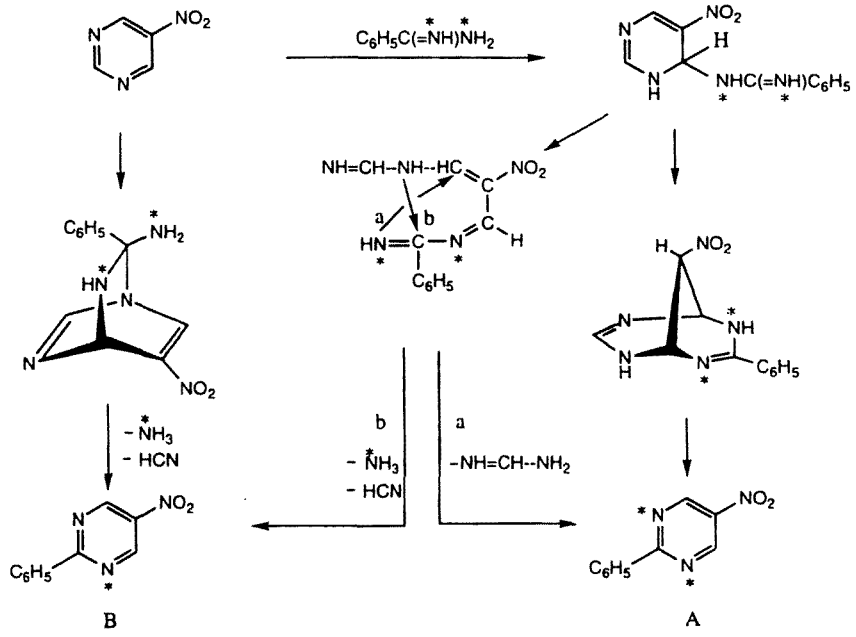
Other interesting examples of ring transformations involving a three-atom replacement are observed when reacting N-methylpyrimidinium iodide with t-butyl- or benzamidine, 2-t-butyl or 2-phenylpyrimidine respectively being obtained [25]. Carrying out the reaction with the ^{15}N-labelled N-methyl[1,3-^{15}N]pyrimidinium iodide and benzamidine, unlabelled 2-phenylpyrimidine is obtained. It is evident that in this reaction the pyrimidine NC_2N fragment is replaced by the NCN fragment of the amidine. This replacement can be described as an ANRORC process, involving the C-6 adduct as the initial addition product. Reaction of 1,3-dimethyl-5-nitrouracil with methyl ethyl ketone gives – in low yield – methylnitroresorcinol, a clear example of an NC_2N—CCC replacement. As side product a meta-bridged bicyclic product was isolated, being formed by addition of the ketone to the 4,6-position of the uracil ring (Scheme 14) [26].

Scheme 14



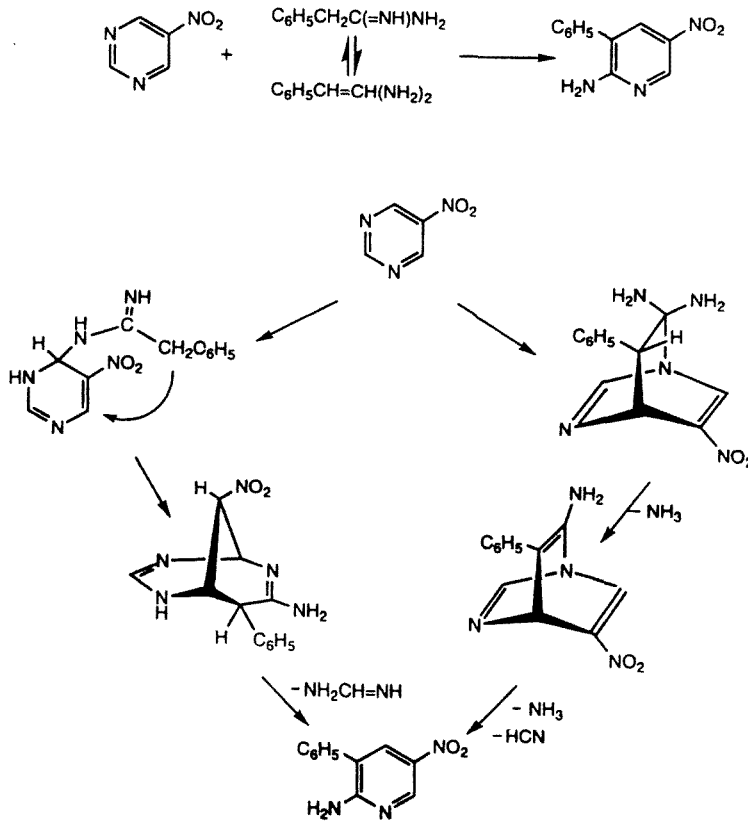
Besides activation of the pyrimidine ring for nucleophilic attack by quaternization, introduction of a strong electron-withdrawing group also enhances the electrophilicity of the ring. Therefore it was not too surprising that reflux of an ethanolic solution of 5-nitropyrimidine with benzamidine afforded 5-nitro-2-phenylpyrimidine in 84% yield [27]. Experiments with ^{15}N-labelled amidines have shown that in fact two differently labelled 5-nitro-2-phenylpyrimidines are formed, i.e., a mono ^{15}N-labelled compound (B) and a compound (A) containing two labelled nitrogen atoms in the pyrimidine ring; the ratio A/B = 44 : 56 (Scheme 15). This result justifies the conclusion that the reaction proceeds according to two pathways and that apparently the amidine is able to act as donor of both the N—C—N as well as C—N fragments. The reaction involves initial addition at C-6, in which the amidine nitrogen covalently binds to the pyrimidine ring. After ring opening the open chain product is obtained in which ring closure takes place according to route a, which leads after aromatization to the double ^{15}N-labelled product (A), and according to route b, which leads after loss of hydrogen cyanide and ammonia to the mono ^{15}N-labelled pyrimidine derivative (B). The bicyclic adduct in the formation of the double ^{15}N-labelled product can be advanced as alternative intermediate in the formation of compound A (Scheme 15) [27-29].

Scheme 15



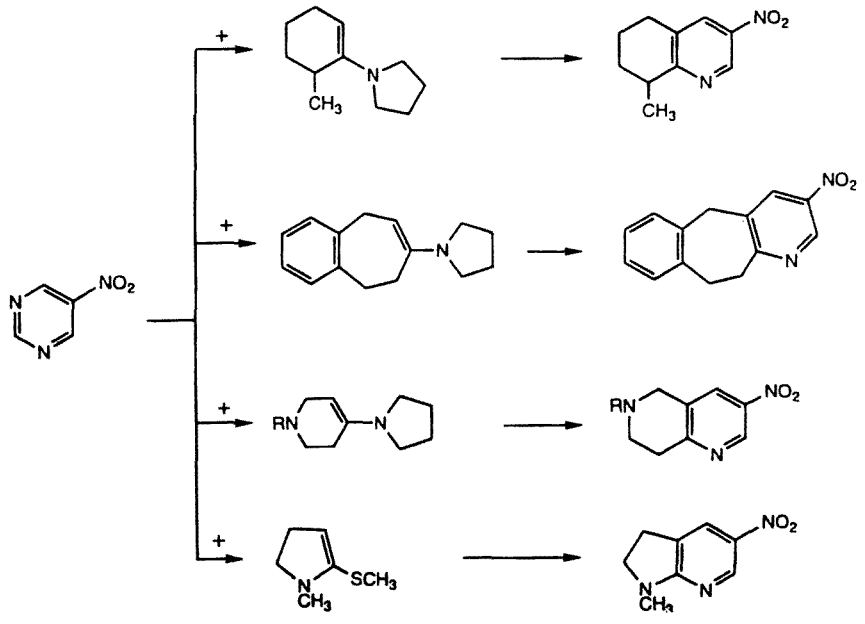
In later studies it was unequivocally established that 5-nitropyrimidine can easily undergo ($4\pi + 2\pi$) Diels-Alder cycloaddition reactions with an inverse electron demand when reacting with electron-rich olefins [30]. It seems very tempting to explain the formation of the mono labelled compound by a regiospecific addition of the electron-rich carbon-nitrogen double bond in the amidine across the N-1 and C-4 position of the pyrimidine ring (Scheme 15) followed by loss of ^{15}N-labelled ammonia and hydrogen cyanide from the cycloadduct. It is evident that by the cycloaddition pathway the formation of the double labelled 5-nitropyrimidine derivative cannot be explained. In studies using C—H active amidines ($R—CH_2—C(=NH)NH_2$, R = hydrogen, methyl, phenyl), it was found that, besides the formation of 2-substituted 5-nitropyrimidines, ring transformation into 2-amino-5-nitro-3-R-pyridines occurs [28]. With phenylacetamidine, 2-amino-3-phenyl-5-nitropyridine ($R = C_6H_5$) is even obtained as the sole product. The formation of this pyridine derivative follows the same addition pattern as described before in Scheme 13 for benzamidine, but with the important difference that the initial addition to C-6 of the pyrimidine ring does not involve the nitrogen of the amidine group but the "acidic" carbon neighboring the amidine carbon. As suggested in Scheme 15, the formation of the aminopyridine can also be described as the result of a cycloaddition reaction with inverse electron demand, if one assumes that benzamidine can react as an diaminostyrene (Scheme 16). Although there is no real evidence for such an equilibrium, as a working hypothesis it appeared to be very useful and formed the basis for our extensive studies on inter and intra Diels-Alder cycloaddition with inverse electron demand, using pyrimidines as diazadienes and electron-rich enes and ynes as dienophiles (Scheme 16).

Scheme 16



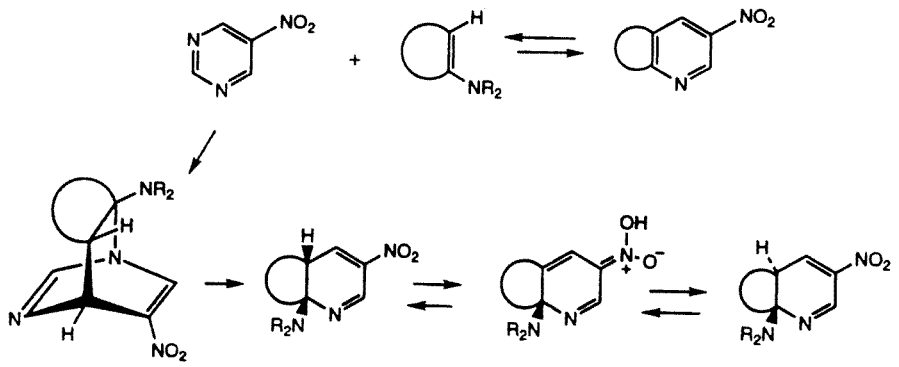
Initially the intermolecular cycloadditions were studied between 5-nitropyrimidines and enamines, N,N- or O,O-ketene acetals as dienophiles [30]. These reactions occur quite easily and give an appropiate entry to the preparation of differently substituted 3-nitropyridine derivatives [31]. The reaction with a great variety of cyclic enamines gives an easy access to b-fused pyridines. The cycloaddition reaction is regioselective and occurs by addition across N-1 and C-4. This observed regioselectivity is supported by calculations using the FMO-perturbation theory (Scheme 17) [32]. Quite recently the conversion of 5-nitropyrimidine into 3-nitrocyclododeca[b]pyridine by the enamine of cyclododecanone has been reported [33].

Scheme 17



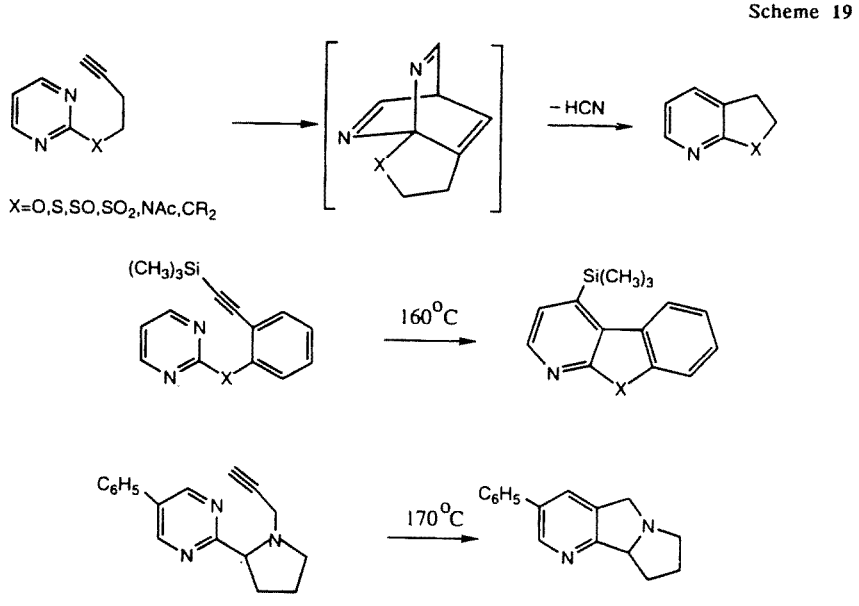
It is noteworthy to mention that when a cyclic enamine is used as dienophile, in the bicyclic adduct obtained after loss of hydrogen cyanide the amino function and the hydrogen present on the bridgehead positions are in cis-orientation. In order to make elimination of the amine possible, cis-trans isomerization has to take place. This isomerization process is certainly stimulated by the presence of the nitro group, forming the aci-form (Scheme 18).

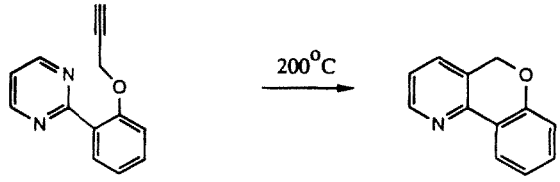
Scheme 18



The cycloadduct is in general not stable enough to be isolated or even to be detected at low-temperature by NMR spectroscopy. Therefore the assumption is justified that the initial addition reaction is rate determining; due to the easy removal of hydrogen cyanide, the retro Diels-Alder reaction is fast. Increase of the reactivity of a Diels-Alder reaction can be achieved by introduction of a molecular chain of appropriate length between the diaza diene and the dienophile, thus creating a molecule suitable for performing an intramolecular Diels-Alder reaction. The increased reactivity of an intramolecular Diels-Alder reaction versus an intermolecular one is due to the entropic assistance of the molecular chain connecting the reactants. Because the Diels-Alder reaction has a highly ordered transition state, the effect of a "tether" on the reduction of the entropy of activation can be very dramatic. It can be expected that the reactivity of an intramolecular Diels-Alder reaction decreases strongly when increasing the length of the connecting chain. In general the effect of a "tether" on the reactivity of a Diels-Alder reaction is found to be largest when the length of the side-chain is five atoms. With a length of seven atoms the effect of the tether is negligible. Examples of the generality of these cycloadditions are shown in Scheme 19. They are chosen from the many reactions which have been found in our work. They illustrate the potentiality of the methodology for preparative organic chemistry [34-36].

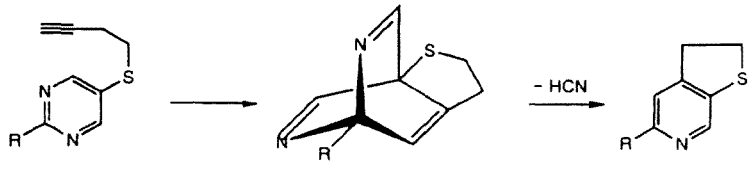
Scheme 19





The generality of these Diels-Alder reactions can also be demonstrated by the occurrence of reactions in which the double or triple bond containing side-chain is present at position 5 of the pyrimidine ring, instead of position 2. This can be exemplified by the high yield conversion of the 5-butynylthiopyrimidine into 2,3-dihydrothieno[2,3-c]pyridine in high yield (Scheme 20) [35]. So the Diels-Alder methodology is also effective in the preparation of heterocyclic systems c-fused to the pyridine ring.

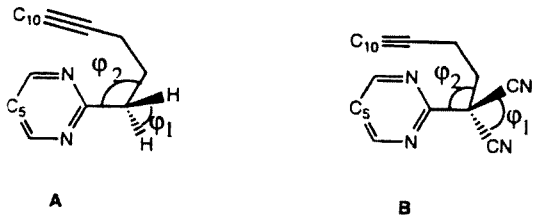
Scheme 20



R=C_6H_5,$NHCOCH_3$,$N(COCH_3)_2$

Although from our studies it can be concluded that the length of the dienophilic side chain is very important for a successful intramolecular cycloaddition, it appeared to be not the only factor influencing the reactivity. Recent studies [37] have demonstrated that introduction of large groups on the dienophilic side chain, especially on the atom connected to the ring carbon, leads to an increased reactivity, probably due to the so-called Thorpe-Ingold effect [38] or "gem-dialkyl" effect [39]. To illustrate this effect, the intramolecular Diels-Alder reaction of 2-pent-4-yn-1-ylpyrimidine (A) reacts at a much higher temperature than its α,α-dicyano derivative (B) [210°C versus 130°C]. This difference in reaction rate can be explained by the scissoring effect [38], which means that in the dicyano compound the repulsion between the cyano groups forces the bond angle ϕ_1 to increase and as a consequence decreases the corresponding bond angle ϕ_2. In the α,α-cyano compound the reactive sites (C-5 and C-10) are brought into closer proximity, resulting in added entropic assistance and rate increase (Scheme 21).

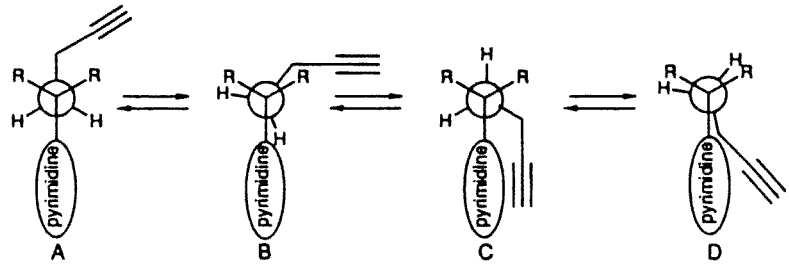
Scheme 21



A B

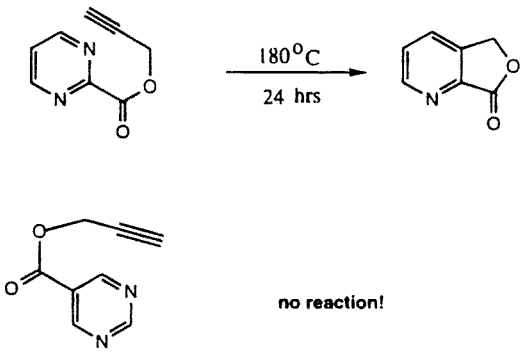
Another argument which possibly plays a role in explaining the difference in reactivity of both compounds (Scheme 21) is the change of conformational equilibria of the electron-rich side-chain connected with the electron-poor pyrimidine [39, 40]. In 2-pent-4-yn-1-ylpyrimidines steric interactions between large cyano groups (R) and the ϕ-pentynyl group destabilize the unreactive antiperiplanar conformation A and the anticlinal conformation B as compared to a dihydro compound (R = H). This results in a higher population of the reactive syn-clinal conformation C and syn-periplanar D and therefore to a higher reactivity for the compound bearing large substituents R (Scheme 22). It is also possible that the strong electron-attracting character of both cyano groups on the α-positions enhances the electrophilicity of the pyrimidine ring and consequently its reactivity towards the electron-rich triple bond.

Scheme 22



Summarizing the results obtained thus far, it can be concluded that the reactivity in intermolecular inverse Diels-Alder reactions is determined by the electron deficiency of the diazadiene system as well as the conformational properties of the side-chain. To substantiate these results more firmly and to gain greater insight into the relation between the reactivity of a compound and its conformational properties, the 2-(propynyloxycarbonyl)pyrimidine and its isomeric 5-(propynyl-oxycarbonyl)pyrimidine were synthesized and subjected to Diels-Alder reaction conditions and the results were compared with semiempirical (MNDO-PM3) and molecular mechanics (MMX) calculations. Based on our previous experience we expected that the 2-(propynyloxycarbonyl)pyrimidine and its 5-isomer do not differ considerably in reactivity. However, it was quite surprising to observe that heating of the 2-isomer at 180°C for 24 hours gave furo[3,4-b]pyridin-7 (5H)-one in more than 90% yield, while the 5-isomer under the same reaction conditions was completely unreactive! [41] (Scheme 23).

Scheme 23



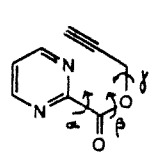
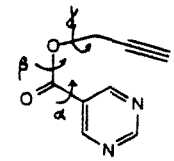
A computational study was carried out in which the energies of the HOMO and LUMO were determined with the MNDO-PM3 Hamiltonian in the semiempirical VAMP program. From the results, as seen in Table 1, several conclusions can be drawn. First, the intramolecular cycloaddition in the 2-isomer can be characterized as an inverse Diels-Alder reaction; second, if the 5-isomer should have reacted, the reaction could also be characterized as an inverse Diels-Alder reaction; third, the calculations predict that the 2-isomer would be more reactive than the 5-isomer, which is in good agreement with the observed order of reactivity. However, it is also evident that the relatively small difference in ΔE ($HOMO_{dp}$-$LUMO_{de}$) between both compounds, i.e., $\Delta E = 0.284$ eV (about 7 kcal) cannot be responsible for the great difference of reactivity between the 2-isomer and of the 5-isomer. This needs clarification. Since we have seen that the conformation of the side-chain strongly influences the rate of the reactions, the conclusion seems justified that apparently the side-chain in the 5-isomer has a much less unfavorable conformation to react than the side-chain in the 2-isomer. This concept of an unfavorable geometry preventing the intramolecular Diels-Alder reactions is supported by calculation of the geometries of the lowest energy conformation, as determined with the MMX program [41]. From these calculations (see Table 2) it is quite evident that in the lowest energy conformation of the nonreactive 5-isomer the plane of the pyrimidine ring and that of the carbonyl group are more or less planar ($a = -1.36°$), whereas in the lowest energy conformation of the 2-isomer both planes have a twisted geometry of about 90°. Whereas the geometry of the side-chain and plane of the pyrimidine ring in the 5-isomer prevents the approach of the triple bond to the diazadiene system, rotation of γ in the 2-isomer of about 180° brings the triple bond near the reaction centers C-2 and C-5 in the pyrimidine ring, an orientation suitable for the cycloaddition.

TABLE 1. Observed Reactivities (extrapolated to 170°C) and Energy Differences between the HOMO and LUMO of the Diene (de) and the Dienophile (dp) Moieties of the 2- and 5-(Propynyloxycarbonyl)pyrimidines

Compounds	$t_{1/2}$[a]	$\Delta_{(HOMO_{de}-LUMO_{dp})}$[b]	$E_{(HOMO_{dp}-LUMO_{de})}$[b]
2-isomer	10,0	11,857	9,826
5-isomer	[c]	11,536	10,110

[a]in hours.
[b]ΔE in eV.
[c]no reaction observed.

TABLE 2. Most Important Geometric Parameters, Optimized within the MMX Force Fields of 2-(Propynyloxycarbonyl)pyrimidine and Its 5-Isomer

Compounds	α	β	γ
2-isomer	96,85	0,79	-179,03
5-isomer	-1,36	0,02	-179,33

I want to finish this review by thanking my students, PhD graduates, postdoctoral fellows, and staff members, who worked during those thirty years for a longer or shorter period in our laboratory. Several of them are mentioned in the reference list, but many of them are not, due to the impossibility of highlighting all their work in this short review. But to all of them, I am very grateful for their dedication and for their efforts to bring into light new concepts in heterocyclic chemistry. Without them, this review could not have been written.

They are Adickes H. W., Alexeev S. G., Ammers M. van, Angelino S. A. G. F., Baloniak S., Baranski A., Barczynski P., Berg I. E., Bie D. A. de, Biedrzycki M., Blees W. J. F., Bode J. W. A. de, Boer E. de, Bonger J. F., Boom J. H. van, Bosma E., Bouw J. P., Boven H. G. van, Breedveld M. W., Breuker K., Brons H. J., Brouwer A. C., Brouwer M. S., Brown H. C., Buurman D. J., Castegnaro M., Charushin V. N., Chupakhin O. N., Counotte-Potman A. D., Crawford T. H., Czuba W., Darwinkel-Risseeuw P. S., Davelaar E., Declercq J. P., Deeleman R. A. F., Dekkers J. J., Dlugosz A., Dijk M. van, Eldred C. D., Ellen G., El Sayed El Ashry, Engbersen J. F. J., Evans R. F., Folstar P., Fontaine M. la, Franssen M. C. R., Frissen A. E., Garderen G. van, Geerts J. P., Geurtsen G., Gönczi C., Grotenhuis P., Grzegozek M., Haak H. J. W. van den, Haase B., Haider N., Ham D. W. M. van, Häming L., Hara H., Harkema S., Hartog J. A. J. den, Hassoun A., Hennink W. E., Henrie R. N., Heus J. G. de, Heijdenrijk D., Hoeve L., Hofstra U., Holterman H. A. J., Hijwegen T., Jansen F., Jansma J. D., Johnson D. G., Jongejan H., Joosten M. H. A., Kaaden A. van der, Kleibeuker J. F., Klinge D. E., Koehorst R. B. M., Koetsier A., Koning G. P., Kos N. J., Koudijs A., Kraus W., Kroon A. P., Kuilen A. van der, Laane C., Landheer C. A., Liebscher J., Link P. A. J., Lont P. J., Marcelis A. T. M., Marel G. A. van der, Martens R. J., Meerssche M. van, Meester J. W. G. de, Meeteren H. W. van, Melger P., Melger W. C., Meijer E. M., Middelhoven W. J., Mohr W. B., Morita Y., Müller F., Naeff H. S. D., Nagel A., Nieman N., Nijdam K., Oostveen E. A., Ostrowicz A., Peereboom R., Persoons C. J., Petrovic S., Pieterse M. J., Pilnik W., Plat H., Pollmann C. A. M., Posthumus M. A., Rasmussen C. A. H., Reinecke M. G., Ribot S. A., Roeterdink F., Rykowski A., Sakamoto T., Sanders G. M., Sansone E. B., Schaafsma T. J., Schoemaker H. E., Schols A., Shadid B. R., Simig G., Sladowska H., Smit P., Stam C. H., Stoel R. E. van der, Stolle W. A. W., Streef J. W., Stork G. A., Streef J. W., Suy I. M. L., Swistun Z., Tomula M., Tondys H., Tramper J., Tromp M. G. M., Tucker S. P., Valk J. de, Valkengoed B. H., Veldhuizen A. van, Verbeek A. J., Verhoeven J. W., Veurink J. M., Vincken J. P., Vollering M. C., Vonk C. R., Vos C. M., Vroom E. de, Vrijhof P., Vuyk D. H., Wang

Y., Wasielewski M. R., Wayne H., Wei Y. Y., Weis A. L., Wever R., Weijnen J. G. J., Wiersum U. E., Wiley, Wozniak M., Yamaguchi T., Yeldez El Kilany, Zuurdeeg B., and Zwinselman J. J.

REFERENCES

1. M. J. Pieterse and H. J. den Hertog, Rec. Trav. Chim. Pays Bas., 1961, Vol. 80, P. 1376 and 1962, Vol. 81, P. 855; H. J. den Hertog and H. C. van der Plas, in: Advances in Heterocyclic Chemistry, 1965, Chapter 4, P. 21, A. R. Katritzky (ed.), Academic Press, New York; H. J. den Hertog and N. C. van der Plas, in: Chemistry of Acetylenes, 1969, Chapter 17, P. 1149, H. C. Viehe (ed.), Marcel Dekker, New York.
2. Th. Kaufmann and F. P. Boettcher, Chem. Ber., 1962, Vol. 95, P. 1528.
3. W. Adam, A. Grimison and R. Hoffman, J. Amer. Chem. Soc., 1969, Vol. 90, P. 2590.
4. H. C. van der Plas and G. Geurtsen, Tetrah. Lett., 1964, P. 2093; H. C. van der Plas, Tetrah. Lett., 1965, P. 559; H. C. van der Plas, P. Smit and A. Koudijs, Tetrah. Lett., 1968, P. 9.
5. H. C. van der Plas and A. Koudijs, Rec. Trav. Chim. Pays Bas., 1970, Vol. 89, P. 129.
6. J. de Valk and H. C. van der Plas, Rec. Trav. Chim. Pays Bas., 1971, Vol. 90, P. 1239; J. de Valk and H. C. van der Plas, Rec. Trav. Chim. Pays Bas., 1972, Vol. 91, P. 1414.
7. The S_N (ANRORC) mechanism has been found to be a general mechanism in nucleophilic amination of many azaheterocycles, e.g., pyridines, isoquinolines, pyrazines, triazines, pteridines, quinazolines, purines, naphthyridines, etc. For a general review, see H. C. van der Plas, "The S_N (ANRORC) mechanism: a new mechanism for nucleophilic substitution," Acc. of Chem. Res., 1978, Vol. 11, P. 462.
8. H. C. van der Plas, B. Haase, B. Zuurdeeg, M. Vollering, Rec. Trav. Chim. Pays Bas., 1966, Vol. 85, P. 1101.
9. H. W. van Meeteren and H. C. van der Plas, Rec. Trav. Chim. Pays Bas., 1967, Vol. 86, P. 567.
10. J. A. Zoltewicz and L. S. Helmick, J. Amer. Chem. Soc., 1972, Vol. 94, P. 682; J. A. Zoltewicz, L. S. Helmick et al., J. Org. Chem., 1973, Vol. 38, P. 1947.
11. J. P. Geerts, H. C. van der Plas and A. van Veldhuizen, Rec. Trav. Chim., 1973, Vol. 92, P. 1232; J. P. Geerts, H. C. van der Plas and A. van Veldhuizen, Org. Magn. Res., 1975, Vol. 7, P. 86.
12. A. Counotte-Polman, H. C. van der Plas and A. van Veldhuizen, J. Org. Chem., 1981, Vol. 46, P. 2138 and J. Org. Chem., 1981, Vol. 46, P. 3805.
13. J. P. Geerts, C. A. H. Rasmussen, H. C. van der Plas and A. van Veldhuizen, Rec. Trav. Chim. Pays Bas., 1974, Vol. 93, P. 231.
14. C. A. H. Rasmussen and H. C. van der Plas, Rec. Trav. Chim. Pays Bas., 1977, Vol. 96, P. 101.
15. C. A. H. Rasmussen and H. C. van der Plas, P. Grotenhuis and A. Koudijs, J. Heterocyclic Chem., 1978, Vol. 15, P. 1121.
16. J. P. Geerts and H. C. van der Plas, J. Org. Chem., 1978, Vol. 43, P. 2682.
17. H. W. van Meeteren and H. C. van der Plas, Tetrah. Lett., 1966, P. 4517.
18. H. W. van Meeteren and H. C. van der Plas, Rec. Trav. Chim. Pays Bas., 1971, Vol. 90, P. 105; see also H. C. van der Plas, Lectures in Heterocyclic Chemistry, Vol. II, P. 83 (1974).
19. H. W. van Meeteren and H. C. van der Plas, Rec. Trav. Chim. Pays Bas., 1968, Vol. 87, P. 1089; H. W. van Meeteren, H. C. van der Plas and D. A. de Bie, Rec. Trav. Chim. Pays Bas., 1969, Vol. 88, P. 728.
20. R. Peereboom, H. C. van der Plas and A. Koudijs, Rec. Trav. Chim. Pays Bas., 1974, Vol. 93, P. 58.
21. R. Peereboom and H. C. van der Plas, Rec. Trav. Chim. Pays Bas., 1974, Vol. 93, P. 277.
22. E. A. Oostveen, H. C. van der Plas and H. Jongejan, Rec. Trav. Chim. Pays Bas., 1974, Vol. 93, P. 114.
23. E. A. Oostveen and H. C. van der Plas, Rec. Trav. Chim. Pays Bas., 1977, Vol. 96, P. 68.
24. F. Roeterdink and H. C. van der Plas, Tetrah. Lett., 1976, P. 3337.
25. E. A. Oostveen, H. C. van der Plas and H. Jongejan, Rec. Trav. Chim. Pays Bas., 1976, Vol. 95, P. 209; see also H. C. van der Plas, "Ring-modifying reactions of pyrimidines containing a quaternary nitrogen. Review," Heterocycles, 1978, Vol. 9, P. 33 and H. C. van der Plas "Wiadomosci chemiczne," 1980, Vol. 34, P. 491.
26. T. L. Su, K. A. Watanabe and J. J. Fox, Tetrahedron, 1982, Vol. 38, P. 1405; J. Org. Chem, 1982, Vol. 47, P. 1081.
27. P. Barczynski and H. C. van der Plas, J. Org. Chem., 1982, Vol. 47, P. 1077.

28. V. N. Charushin and H. C. van der Plas, J. Org. Chem., 1983, Vol. 48, P. 2667.
29. H. C. van der Plas, J. Org. Chem., 1986, Vol. 51, P. 71.
30. V. N. Charushin and H. C. van der Plas, Tetrah. Lett., 1982, P. 3965.
31. A. T. M. Marcelis and H. C. van der Plas, Tetrahedron, 1989, Vol. 45, P. 2693.
32. A. T. M. Marcelis, H. C. van der Plas, D. W. M van den Ham and J. W. Verhoeven, J. Org. Chem., 1986, Vol. 59, P. 4040.
33. G. P. Shkil and R. Sagitullin, Tetrah. Lett., 1994, Vol. 35, P. 2075.
34. A. E. Frissen, A. T. M. Marcelis et al., Rec. Trav. Chim. Pays Bas., 1987, Vol. 106, P. 547.
35. A. E. Frissen, A. J. M. Marcelis and H. C. van der Plas, Tetrah. Lett., 1987, P. 1589 and Tetrahedron, 1989, Vol. 45, P. 803.
36. For a review article on this subject see A. T. M. Marcelis and H. C. van der Plas, Trends in Heterocyclic Chemistry, 1988, Vol. 1, P. 111.
37. A. E. Frissen, A. T. M. Marcelis, G. Geurlsen, D. A. de Bie and H. C. van der Plas, Tetrahedron, 1989, Vol. 45, P. 5151.
38. R. M. Beesley, C. K. Ingold and J. F. Thorpe, J. Chem. Soc., 1915, P. 1080; C. K. Ingold, J. Chem. Soc., 1921, P. 305.
39. D. D. Sternbach, D. M. Rossana and K. D. Onan, Tetrah. Lett., 1985, P. 591; N. L. Allinger and V. Zalkow, J. Org. Chem., 1960, Vol. 25, P. 70.
40. M. E. Jung and J. Gervay, Tetrah. Lett., 1988, P. 2429; R. K. Boeckmann Jv and S. S. Koo, J. Amer. Chem. Soc., 1982, Vol. 104, P. 1033.
41. W. A. W. Stolle, A. E. Frissen, A. T. M. Marcelis and H. C. van der Plas, J. Org. Chem., 1992, Vol. 57, P. 3000.