Molecules **1996**, *1*, 242 – 250

© Springer-Verlag 1996

Thermal Rearrangement of 4-Alkyl-1,2,4-triazoles. Rearrangements in the Crystalline State

Per Carlsen*, Odd R. Gautun and Kåre B. Jørgensen

Department of Chemistry, Norwegian University of Science and Technology, N-7034 Trondheim, Norway; Tel.: +47-73-59-3968; Fax: +47-73-59-4256 (carlsen@kjemi.unit.no)

Received: 19 October 1996 / Accepted: 30 January 1997 / Published: 27 February 1997

Abstract

Studies of the thermolyses of 4-alkyl substituted 1,2,4-triazoles was reviewed. They were observed to rearrange at 200–350 °C to the corresponding 1-alkylated triazoles. When substituted in the 4-position with aryl- or vinylic substituents the triazoles were inert to thermolysis, contrary to what was observed for the 4-alkyl- and 4-allyl substituted systems. The mechanisms for the reactions were elucidated, e.g., by studies of substituents effects and by kinetic measurements in solution as well as for the neat samples. Reactions in solutions were slow. The rearrangements in melts of the neat triazoles readily proceeded to the products, and were proposed to take place via a series of nucleophilic displacement steps. X-ray crystallographic measurements of selected structures, showed that the interatomic distances and angles between the relevant atoms in these structures, to a large degree resembled the geometry expected for the S_N2-type transition states proposed for the rearrangement mechanism. Thus, thermolyses of a series of triazole structures at temperatures below their melting points, confirmed that rearrangements actually did take place. The "kinetics" of the reactions in the crystalline state were investigated and rate constants and thermodynamic data were correlated with the structural characteristics of the crystals.

Keywords: 1,2,4-Triazoles, rearrangement, thermolysis, solid state, mechanism, review

Introduction

Conjugate heterocyclic polymeric materials often exhibit interesting electro-optical properties, such as non-linear optical, (NLO) properties and electric conductivity. Representative examples are polypyrrole [1], polyphenylene [2] and polythiophene [3]. These materials are semi-conductors and when doped with an appropriate doping agents they may exhibit conductivities comparable to those of the common metallic conductors. However, characteristic for these materials are their normally low chemical, photochemical and thermal stabilities, limiting their uses for practical applications. In the search for new, stable materials we turned our attention to the 1,2,4-triazole system, as these compounds are in general stable. Some polymeric materials containing the 1,2,4-triazole system are known [4], al-

* *To whom correspondence should be addressed*

† *Presented at the Joint 12th Symposium on the Chemistry of Heterocyclic Compounds (SCHHC) and the 6th Blue Danube Symposium on Heterocyclic Chemistry (BDSHC), Brno, Czech Republic, September 1–4, 1996.*

though they have not been reported to have conducting properties.

Discussion

Substituted 1,2,4-triazoles were interesting candidates for our purposes. As model systems we have studied 4-substituted 3,5-diphenyl-4*H*-1,2,4-triazole. They were in general stable under chemical and photochemical conditions. Their behavior under thermolytic conditions were investigated. The 4-phenyl substituted triazole was unchanged when the neat compound was heated to 400–450 °C. The 4-methyl substituted triazole on the other hand under the same conditions was found to undergo ready conversion to the corresponding 1-methyl substituted triazole as the exclusive product [5], (Fig. 1).

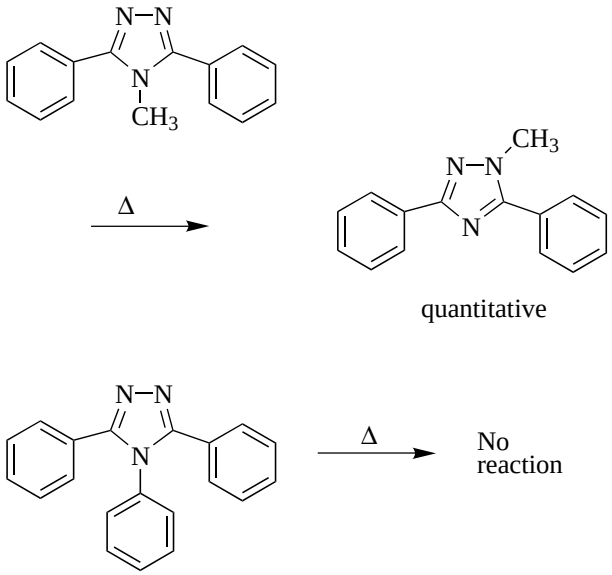


Fig. 1. *Thermolysis of 4-aryl and 4-alkyl substituted 1,2,4-triazoles.*

Similar types of rearrangements have been observed before in the azole chemistry [6]. Examples are shown in Fig. 2. The first reaction was proposed to proceed via a concerted alkyl shift mechanism, while the last reaction was shown to follow a dissociative pathways.

The mechanism for the rearrangement of the 4-methyl substituted triazole may thus proceed by one of the reaction pathways shown in Fig. 3, i.e., a) a concerted 1,3-methyl shift mechanism, b) a ring cleavage-recombination reaction involving the formation of a 1,3-dipolar type intermediate (an imine nitrene), c) a dissociative mechanism, in which the alkyl-triazole bond was cleaved, in either a radical or an ionic mechanism.

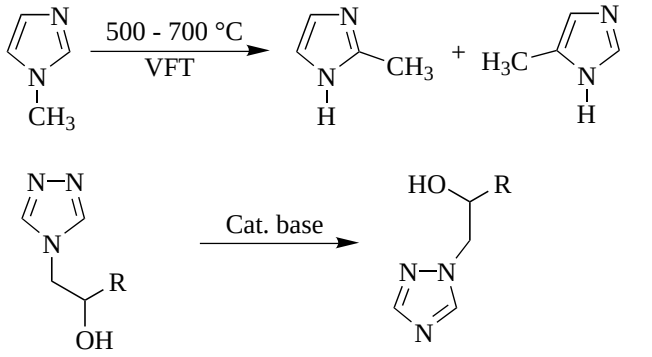


Fig. 2. *Alkyl shift reactions of azoles.*

Under vacuum flash thermolysis (VFT) conditions at 500–900 °C and 0.01 mm Hg, 4-alkyl substituted triazoles did not produce the rearranged products, but complex mixtures of products, mostly unidentified. Benzonitrile formation was not observed. Gilchrist and Rees have studied the VFT chemistry of 4-aryl substituted triazoles and shown that ring cleavage reactions take place under these reaction conditions [7]. Our results appeared to rule out a concerted 1,3-alkyl shift mechanism as well as a ring cleavage mechanism.

Further support for this view was obtained upon thermolysis of 4-ethyl-3,5-diphenyl-4*H*-1,2,4-triazole which was selectively labeled with N-15 in the 4-ring position [8]. On thermolysis at 320 °C of the neat compound, two products were formed, the 1-ethyl-substituted triazole together with small amounts of the elimination product, 3,5-diphenyl-1,2,4-triazole, (Fig. 4). It was demonstrated by the characteristic mass spectroscopic properties of both of these products, that the N-15 atom remained in the 4-ring position.

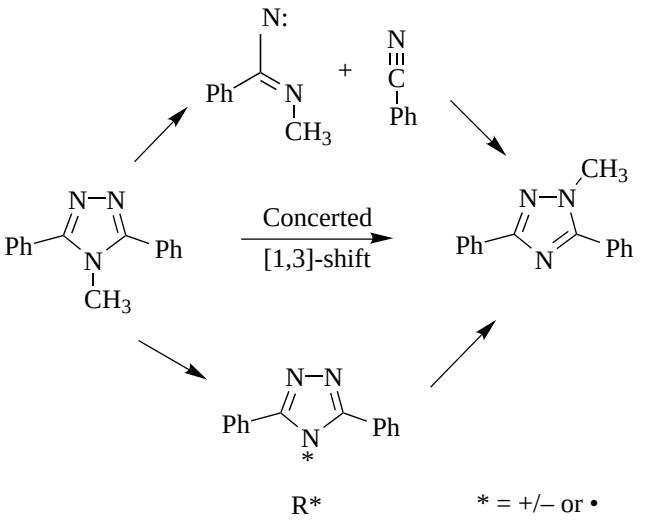


Fig. 3. *Possible mechanistic routes for the rearrangements of 4-alkyl substituted 1,2,4-triazoles.*

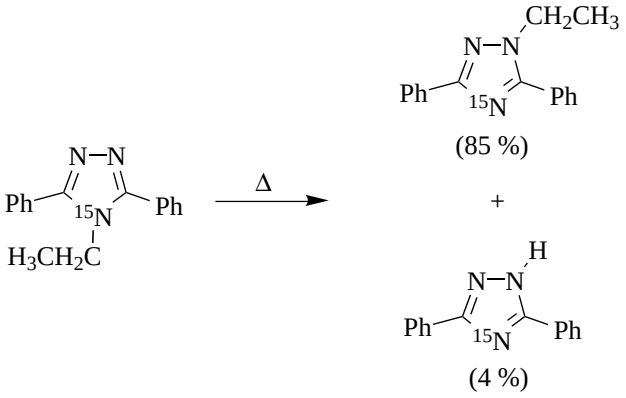


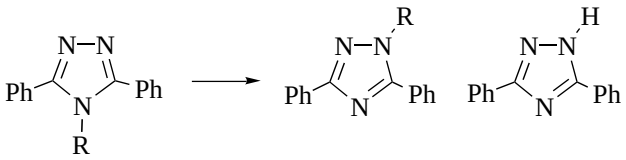
Fig. 4. *Thermal rearrangement of N-15 labelled 4-ethyl-3,5-diphenyl-4*H*-1,2,4-triazole.*

These results confirmed that ring cleavage did not take place during the reaction. The mechanism may therefore involve a cleavage of the alkyl group - triazole bond either in a concerted alkyl group migration or a stepwise dissociative mechanism. The possibility of the last pathway was also strengthened by the formation of the elimination product. It is, however, difficult to distinguish between unimolecular concerted and stepwise reactions.

To gain further insight into the nature of the rearrangement mechanism, was studied a series of 4-alkyl substituted triazoles [9]. The compounds were all thermolyzed in the neat at temperatures in the range 320 to 380 °C. In general, only two types of products were formed, the 1-alkyl triazole, **2,** together with the elimination product, 3,5-diphenyl-1,2,4-triazole, **3**. Selected examples are shown in Table 1. In most cases a satisfactory mass balance was obtained. For some substrates some carbonation was observed.

The results from these experiments showed formation of increasing amounts of elimination product **3** for increasing size and branching of the 4-alkyl substituent. This behavior actually resembled the known competition between the S_N2 and E2-pathways for alkyl halides or sulfonates upon treatment with bases. Thus, during the rearrangement reactions, eventually in an activated form, the triazole moiety may function as a leaving group, allowing for competing substitution/elimination reactions. The 4-vinyl- and cyclopropyl substituted triazoles did not form

Table 1. *Thermolysis of neat 4-substituted 1,2,4-triazoles.*



1 **2** **3**

R	Temp. (°C)	min.	Products, %		
			1	**2**	**3**
Methyl	320	30		92	
Ethyl	316–335	30		85	4
1-Octyl	380	10		57	8
2-Propyl	365	20	12	53	21
2-Butyl	330	36		37	43
2-Octyl	320	30		14	83
Cyclohexyl	380	10		12	33
Benzyl	320	33	43	33	7
Cyclopropyl	355	120	82		
Vinyl	330	120	91		

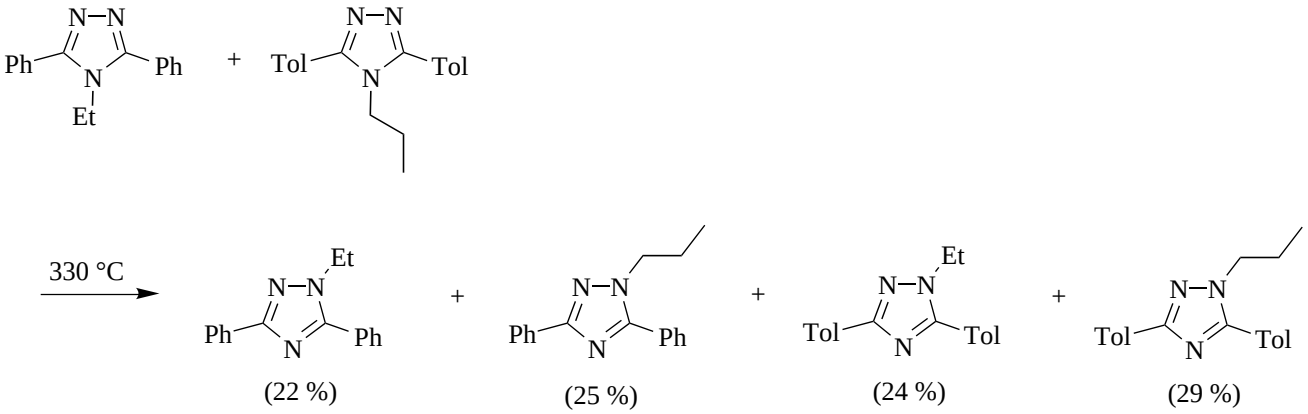


Fig. 5. *Thermolysis of 4-ethyl-3,5-diphenyl- and 4-propyl-3,5-ditolyl substituted triazoles under "Cross-over" conditions.*

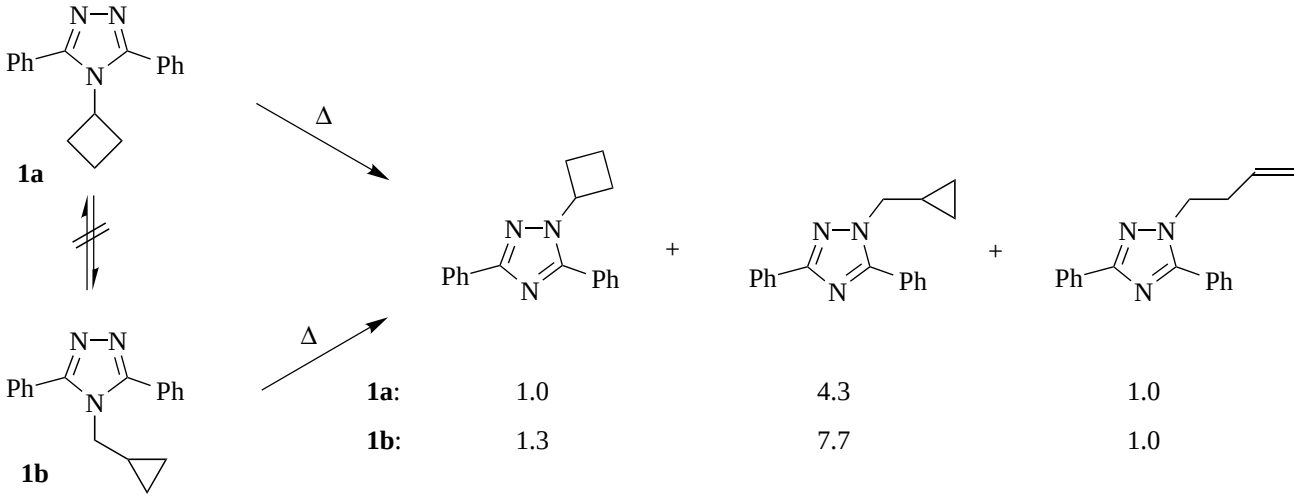


Fig. 6. *Thermolysis of 4-cyclobutyl- and 4-cyclopropylmethyl substituted triazoles.*

rearrangement products, even after prolonged periods of time. Some carbonation was observed. Vinyl halides do not easily participate in nucleophilic substitutions. Cyclopropyl halides are known to resist S_N2 type substitution reactions, and nucleophilic attack would lead to ring opening products.

The data presented in the above agreed with a bimolecular type mechanism. To further distinguish between possible unimolecular and bimolecular mechanisms, a series of cross-over experiments were performed [10]. A typical example is shown in Fig. 5.

These results were clearly in agreement with a bi-molecular group transfer mechanism, as thermolysis resulted in essentially a statistical mixture of all the possible products. Electronic effects were of little importance in the system shown in Fig. 5.

The feasibility of a bi-molecular mechanism was further strengthened by a kinetic study, where the rearrangement was carried out in solution in 15-Crown-5 at 330 °C in an inert atmosphere. The kinetic data were in good agreement with second order kinetics. The concentration dependent reaction order was determined to 1.96. Kinetic measurements were also carried out in octadecane at 330 °C. The rate of reaction in this non-polar solvent was too slow to yield reasonable kinetic data. However, it was estimated that the rate of reaction in the poorly solvating solvent (octadecane) was approximately 2 orders of magnitudes less than in the crown ether solvent. This observation agreed with a polar reaction mechanism.

The results in the above did not totally rule out a possible homolytic cleavage of the alkyl-group - triazole bond. To establish a possible radical pathway, was studied the thermolysis of triazoles substituted with cyclopropylmethyl groups [11]. Homolytic cleavage pathways was expected to result in formation of the cyclopropylmethyl radical, which is known to undergo fast transformations to the corresponding homoallylic radical. The application in this radical clock reaction has been widely used as a probe to establish radical mechanisms. Upon thermolysis the 4-cyclopropylmethyl substituted triazole was converted to a mixture of cyclobutyl, cyclopropylmethyl and homoallyl 1-substituted triazoles as shown in Fig. 6.

This was the product composition expected for an ionic mechanism. The corresponding 4-cyclobutyl substituted starting materials were expected to give a similar product composition. This was confirmed as is indicated in Fig. 6. These result were in agreement with the results reported on the diazotization reaction of cyclopropylmethyl amine and of cyclobutyl amine, which in ionic mechanisms were converted to mixtures of cyclopropylmethanol, cyclobutanol and 3-buten-1-ol of comparable compositions.

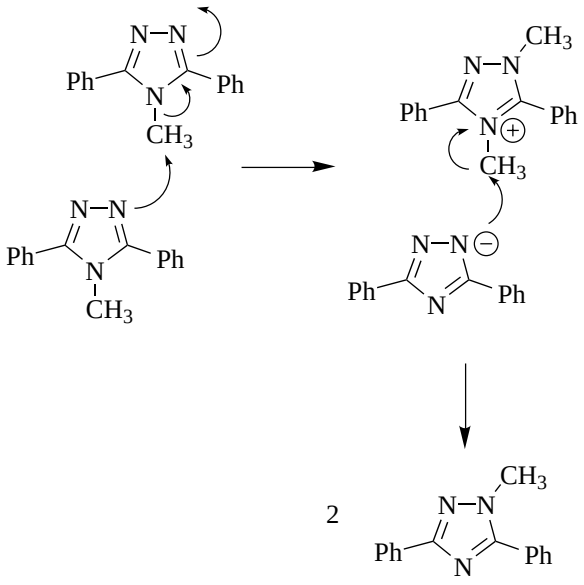


Fig. 7. *Proposed bi-molecular mechanism for the rearrangement of 4-alkyl substituted triazoles.*

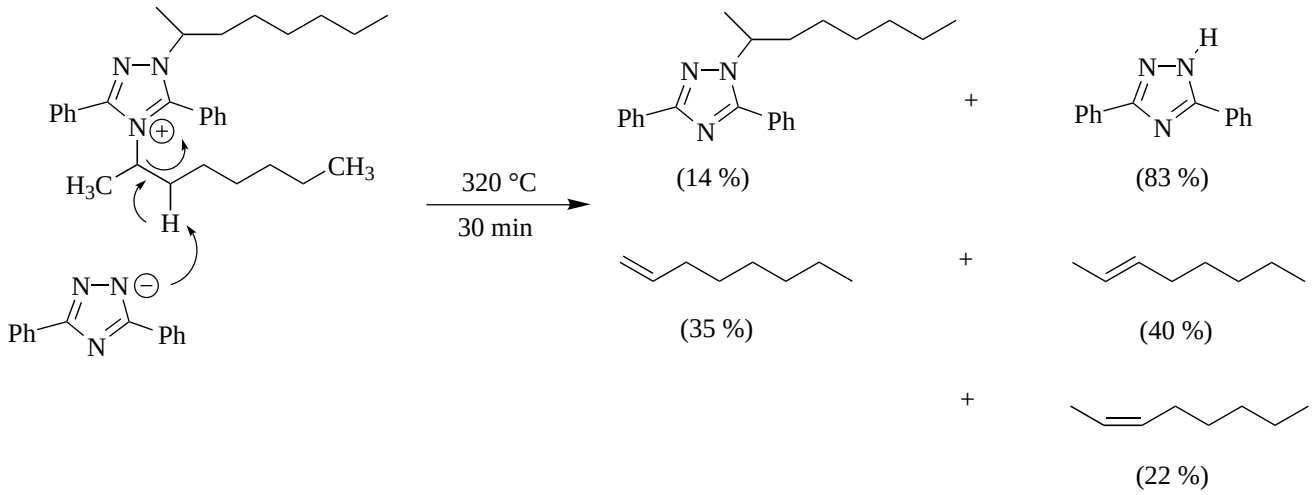


Fig. 8. *Mechanism for the formation of the elimination- and rearrangement products on thermolysis of the 4-(2-octyl) substituted triazole.*

The combined evidence from the above indicated a bimolecular mechanism, consisting of two consecutive S_N2 type reactions. Initially, in a rate determining step, the *N*1 ring atom of one molecule attack the a-atom of the 4-alkyl group of another triazole, resulting in the formation of what can be described as a triazolium triazolate salt. This salt subsequently in a new S_N2 type reaction created two molecules of product, Fig. 7. Alternatively product formation may take place via reactions where one or both of the salt components reacted with neutral triazole molecules, in what may then appear as a chain mechanism.

In this context, the competing elimination and the substitution reactions may now be described by the mechanistic scheme shown for the 4-(2-octyl)-substituted triazole in Fig. 8.

The triazolium triazolate next participated in competing S_N2 and E2 mechanistic pathways with the triazole moiety as the leaving group yielding the rearrangement and the elimination products. The composition of the olefinic products resembled that for a corresponding Hoffmann elimination of a quaternary ammonium salt.

The possibility of concerted or ion-pair mechanisms, resulting in unimolecular rearrangements was investigated by the study of the thermal rearrangement of the optically active *(S)*-4-(2-butyl) substituted triazole [12]. Information about the proposed double displacement mechanism as well as the properties of the triazolium triazolate salt would also be gained. It was shown that inversion of the configuration of the 2-butyl group took place during the rearrangement although accompanied with approx. 30% racemization. Partial thermolysis of the optically active 4-

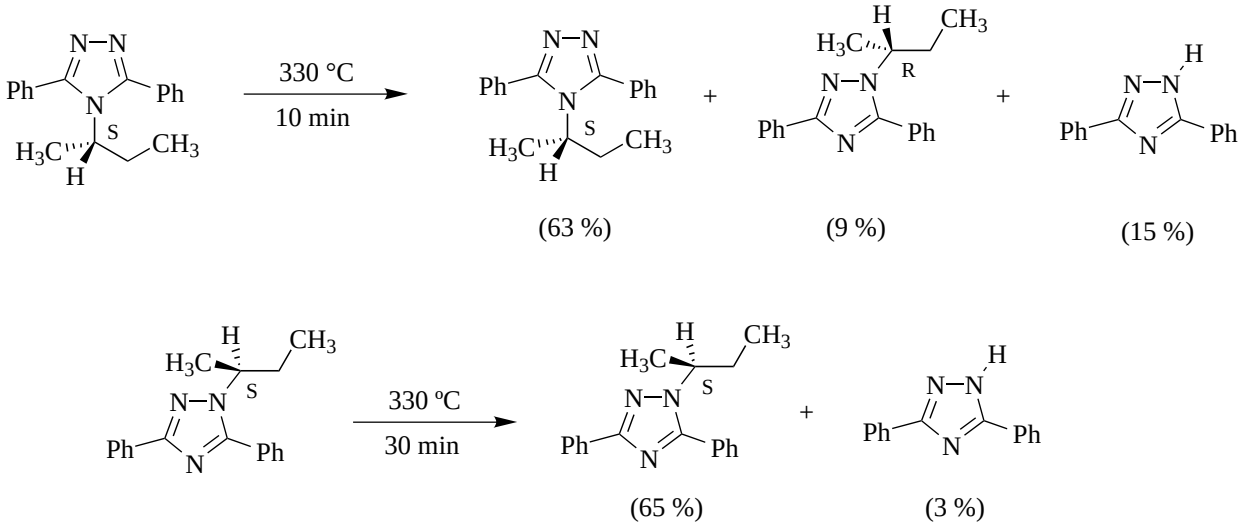


Fig. 9. *Thermolysis of 4-(*S*-2-butyl)-3,5-diphenyl-4*H*-1,2,4-triazole.*

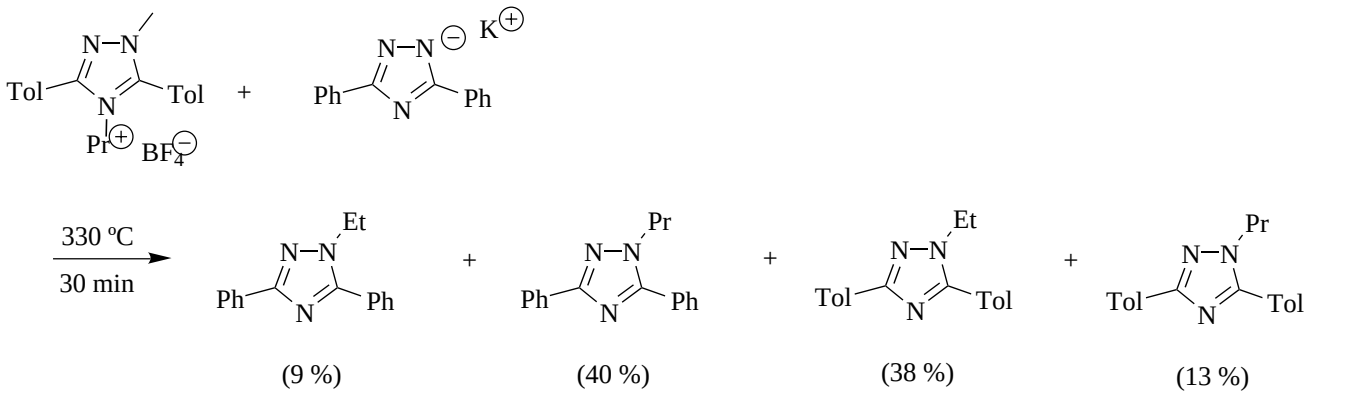


Fig. 10. *Thermolysis of a dialkyl triazolium tetrafluoroborate salt with a potassium triazolate.*

alkyl substituted triazole showed that the recovered 4-alkyl triazole exhibited CD-spectra and specific optical rotation identical to that of the starting material, (Fig. 9).

Similarly, after thermolysis of the pure (*S)*-1-(2-butyl) substituted triazole measurements of optical rotation and CD-spectra indicated that no racemization had taken place [13]. From these results was concluded, that for this particular type of substituent the observed partial razemization did not take place from neither the starting material nor the product, but apparently took place from intermediates formed during the thermal reaction. Thus, ion-pair formation and accompanying racemization did not take place. Further evidence for this point of view was obtained on partial thermolysis of the triazoles shown in Fig. 6. In no cases were the 4-cyclopropylmethyl and the 4-cyclobutyl substituted triazole found to exist in an equilibrium. These results further excluded the possibility of a unimolecular stepwise reaction and thereby strengthening the possibility of a two-step bi-molecular mechanism.

As indicated in Fig. 7 the product formation may take place via a nucleophilic attack of a triazolyl anion on the 4-alkyl substituent of the triazolium cation. The feasibility of such a mechanism taking place was confirmed by carrying out cross-over experiments with a dialkyltriazolium tetrafluoroborate and a potassium triazolate, Fig. 10.

Indeed, all the possible products were observed, indicating that the nucleophilic attack took place at substituents at the 4- as well as the 1-positions of the dialkyltriazolium ion [14]. The partial racemization of the optically active triazole can not be rationalized by a unimolecular cleavage of the alkyl-triazole bond nor by ion-pair formation, but rather by a nucleophilic attack at both alkyl positions as shown in Fig. 11.

In the melts, two triazole molecules from a triazolium triazolate salt which undergo a subsequent nucleophilic reaction, as the triazolyl anion preferentially attack the 4-alkyl substituent of the dialkyl triazolium ion, resulting in formation of the product molecules. The partial racemization was caused by the triazolate attack the 1-alkyl substituent. Thus, route *a* gives the product with inversion of the alkyl group configuration. Route *b* yields rearranged product with over-all retention of alkyl group configuration.

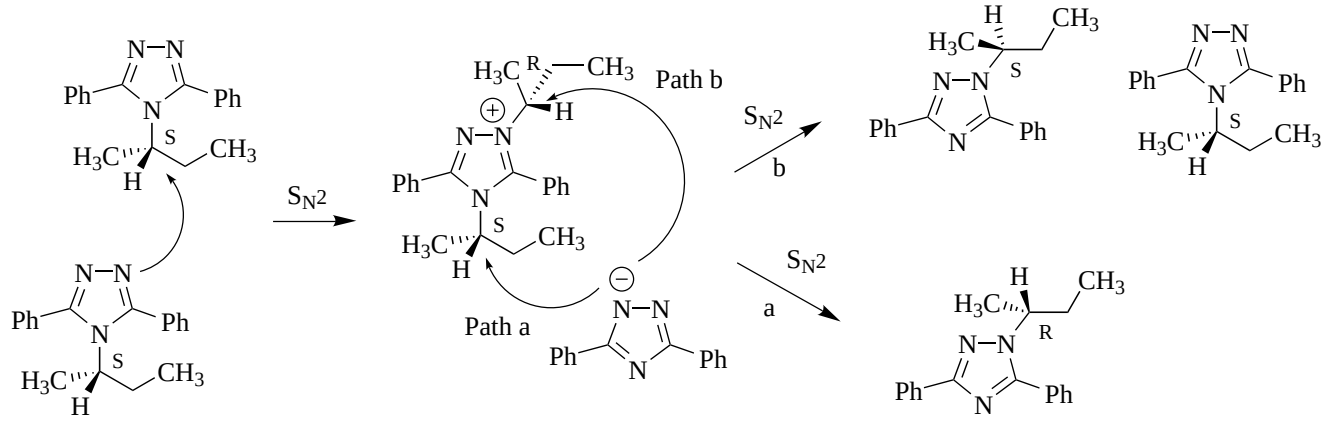


Fig. 11. *Proposed mechanism for the rearrangement of 4-(*S*-2-butyl)-3,5-diphenyl-4*H*-1,2,4-triazole.*

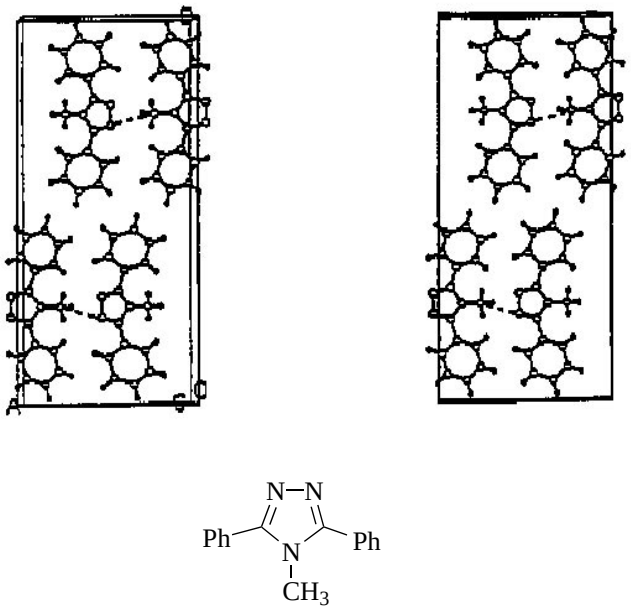


Fig. 12. *Stereographic representation of the crystal structure of 4-methyl-3,5-diphenyl-4*H*-1,2,4-triazole.*

Transition States in the Crystalline Phase?

A number of the 3-alkyl substituted triazoles presented in this study, exhibited NLO-properties. For the purpose of gaining insight into the role of the electrostatic interactions in determining the crystal structures and the NLO properties, the crystal structures of selected triazoles were investigated by X-ray diffraction measurements. Thus, the structure of 4-methyl-3,5-diphenyl-4*H*-1,2,4-triazole was investigated [15]. A stereographic representation is shown in Fig. 12.

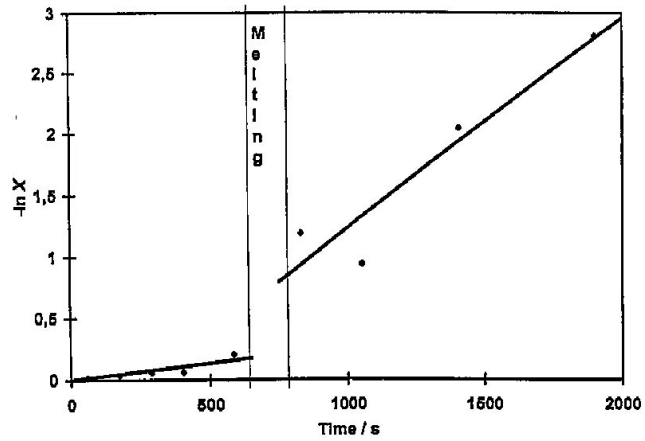


Fig. 13. *Thermolysis 4-methyl-3,5-diphenyl-4*H*-1,2,4-triazole (mp. 246–247 °C) at 215 °C.*

Having in mind the proposed mechanism for the thermal rearrangements of 4-alkyl substituted triazoles, it was interesting to note, that the *N*1 atom of one triazole molecule in the crystal was situated in close proximity to the α-carbon of a neighboring molecule, to some extend resembling the transition state of the proposed initial S_N2 type reaction. In the crystals of the corresponding ethyl substituted triazole was found a similar feature [16]. The appropriate distances and angles for the two crystal structures are summarized in Table 2.

In both cases the distances and angles resembled those for a proposed transition state of the initial S_N2-type reac-

Table 2. *Interatomic distances and angles in the crystals of the 4-methyl- and 4-ethyl substituted 1,2,4-triazoles.*

Molecule B

Molecule A

Compound	Distance, Å $C(\alpha)_B$-$N1_A$	Angle $N1_A$-$C(\alpha)_B$-$N4_B$
Methyl	3.242(5)	167.1(8)°
Ethyl	4.609(9)	161.1(4)°

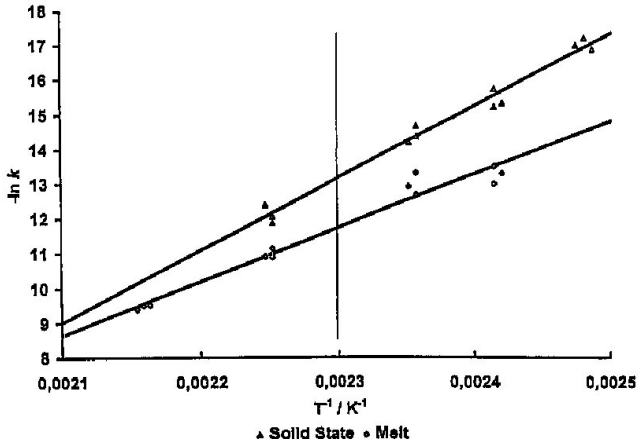


Fig. 14. *Arrhenius plot for the thermolysis of 4-methyl-3,5-diphenyl-4*H*-1,2,4-triazole. The upper line represent the rearrangement in the crystalline state while the lower one is for the reaction in the melt.*

tion that was proposed on the thermal rearrangement mechanism. The distance was shorter for the methyl compound (3.24 Å), actually shorter than the sum of the standard Van der Waal radii of CH_3 and N. Thus, the rearrangement reaction may therefore be possible in the crystalline state. Indeed, upon thermolysis of the 4-methyl substituted triazole at 205 °C which was well below the melting point (239 °C), rearrangement was found to take place. Unfortunately, but as expected, at conversions higher than ca. 15%, the crystals melted, due to contamination of the 4-methyl substituted triazole with the rearrangement product.

In order to correlate the crystal structures with the reactivities of the rearrangement of the triazoles in the crystalline state, activation parameters were determined. Thus, kinetic measurements were carried out. Taking into account the proposed bi-molecular mechanism, a second order rate law may be expected. However, methods used in traditional kinetics has little meaning in the concentrated, condensed phase of the reactants. Never the less, thermolysis was in all cases best correlated with (pseudo) first order kinetics.

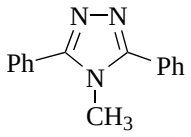
At temperatures lower than the melting points, the plot of *ln*X vs. time could be devided up in two regions, one corresponding to the reaction in the crystalline state and another for reaction in the melt. As a typical example, the results from the thermolysis of the crystalline 4-methyltriazole at 214 °C is shown in Fig. 13. The slopes of these sections yielded the first order rate constants in the crystalline and the melted state respectively. The rate of reactions was faster in the melts than in the crystalline state.

Activation parameters were obtained by a standard Arrhenius treatment. Thus, as illustrated for the thermolysis of the 4-methyl substituted triazole in Fig. 14, the plot of ln*k* vs. 1/T defined two lines, one for the reaction in the melts, and another for the reaction in the solid, crystalline state.

Interestingly, at temperatures slightly higher than the melting point, the compounds behaved as in the crystalline state. This can be rationalized in terms of a structurally ordered melt, e.g., a liquid crystal phase. Similar data were obtained for the ethyl substituted triazole. The activation parameters determined by the Arrhenius analysis are shown in Table 3.

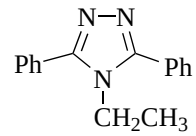
The activation may be correlated with the crystal structures. Thus, the C(α)–*N1* distance is shorter for the CH_3-substituted triazole than for the corresponding Ethyl-substituted compound. This can be the rationale for the lower E_a- value of the Methyl compound. However, the differences in interatomic distances may not be the only reason for the trends in the activation energies, as steric hindrance may start to play a role for the Ethyl compound. The $\Delta S^{\#}$-values were all large and negative, reflecting the ordered nature of the transition states. The kinetic data also agreed with the assumption that the initial salt formation constituted the rate determining step. However, the data presented here, did not elucidate any of the mechanistic details of the final steps towards the product formation in the crystalline state.

Table 3. *Thermodynamic parameters for the rearrangements of the 4-methyl- and 4-ethyl substituted 1,2,4-triazoles.*



d 3.242(5) Å < 167.1(8)°

	Solid State		**Melt**
(*A*)	17.2 (3.3)	n(*A*)	16.1 (2.8)
E_a	104 (13) kJ/mol	E_a	89 (12) kJ/mol
$\Delta H^{\#}$	100 (13) kJ/mol	$\Delta H^{\#}$	85 (12) kJ/mol
$\Delta S^{\#}$	-115 (27) J/mol.K	$\Delta S^{\#}$	-124 (23) J/mol.K



d 4.609(9) Å < 161.1(4)°

	Solid State		**Melt**
ln(*A*)	34.7 (4.2)	ln(*A*)	23.8 (2.1)
E_a	173 (14) kJ/mol	E_a	128 (7.7) kJ/mol
$\Delta H^{\#}$	170 (14) kJ/mol	$\Delta H^{\#}$	124 (7.7) kJ/mol
$\Delta S^{\#}$	-32 (35) J/mol.K	$\Delta S^{\#}$	- 58 (18) J/mol.K

Acknowledgment: The authors wish to thank The Norwegian Research Council for financial support.

References.

1. Hatano, M.; Kambara, S. and Okamoto, S. *J. Polym. Sci.* **1961**, *51*, S26.
2. Ivory, D.M.; Miller, G.G.; Sowa, J.M.; Shacklette, L.W.; Chance, R.R. and Baughman, R.H. *J. Chem. Phys.* **1979**, *71*, 1506.
3. Tourillon, G. and Garnier, F. *J. Electroanal. Chem.* **1981**, *135*, 173.
4. Gebben, B.; Mulder, M.H.V. and Smolders, C.A. *J. Membrane Sci.* **1989**, *46*, 29.
5. Carlsen, P.H.J. *Acta Chem. Scand*. **1987**, *B41*, 302.
6. Begg, C.G.; Grimmett, M.R. and Wethey, P.D. *Aust. J. Chem*. **1973**, *26*, 2435; Bentley, T.W.; Howle, L.M. Wareham, P.J. and Jones, R.V.H. *Tetrahedron* **1992**, *48*, 7969.
7. Gilchrist, T.L.; Rees, C.W. and Thomas, C.J. *J. Chem. Soc. Perkin 1* **1975**, 12.

8. Gautun, O.R. and Carlsen, P.H.J. *Acta Chem. Scand.* **1992**, *46*, 469.
9. Carlsen, P.H.J. and Gautun, O.R. *Acta Chem. Scand.* **1994**, *48*, 411.
10. Carlsen, P.H.J. and Gautun, O.R. *Submitted for publ.*
11. Carlsen, P.H.J. and Gautun, O.R. *Submitted for publ.*
12. Carlsen, P.H.J. and Gautun, O.R. *Acta Chem. Scand.* **1990**, *44*, 485.
13. Carlsen, P.H.J. and Gautun, O.R. *Submitted for publ.*
14. Carlsen, P.H.J. and Gautun, O.R. *Submitted for publ*
15. Carlsen, P.H.J.; Jørgensen, K.B.; Gautun, O.R. Jagner, S. and Håkonsson, M. *Acta Chem. Scand.* **1995**, *49*, 676.
16. Carlsen, P.H.J.; Gautun, O.R.; Samuelson, E.J.; Helgesson, G. and Jagner, S. *Synthetic Metals* **1990**, *38*, 263.