On the Mechanism of the Thermal Rearrangement of 4-Alkyl-4*H*-1,2,4-Triazoles. Synthesis and Reaction of Optically Active Triazoles

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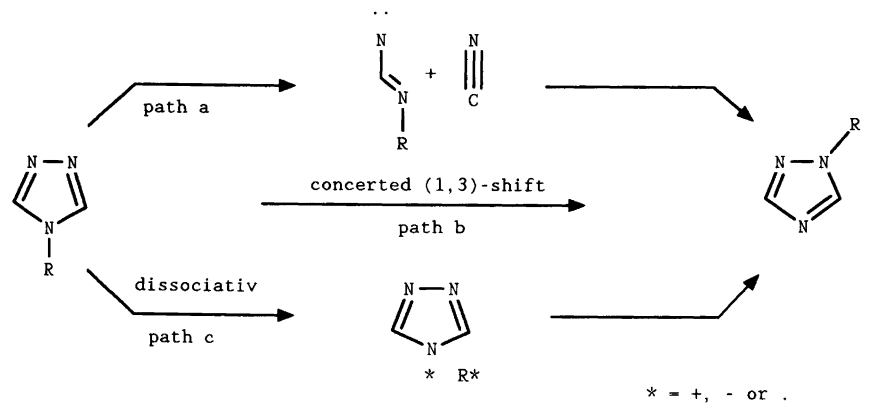
In order to elucidate the mechanism of the thermal rearrangement of 4-alkyl-substituted 4*H*-1,2,4-triazoles to the corresponding 1-alkyl-1*H*-1,2,4-triazoles, the behaviour of 4-[(*S*)-2-butyl]-3,5-diphenyl-4*H*-1,2,4-triazole has been studied. The thermal rearrangement proceeded with inversion and some racemization to yield 1-[(*R*)-2-butyl]-3,5-diphenyl-1*H*-1,2,4-triazole as the major product together with 3,5-diphenyl-1,2,4-triazole. An authentic sample of the optically active 1-substituted triazole was prepared by the Mitsunobu procedure from (*R*)-(−)-2-butanol and 3,5-diphenyl-1,2,4-triazole. An ion pair mechanism is proposed.

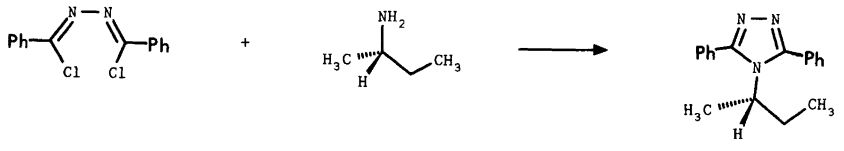


Scheme 1.

In a recent publication we reported the thermal rearrangement of neat 4-alkyl-4*H*-1,2,4-triazoles to the corresponding 1-alkyl-1*H*-1,2,4-triazoles.[1] However, the mechanism of this reaction has not as yet been satisfactorily established. According to our working hypothesis we considered the three possible mechanistic pathways depicted in Scheme 1, i.e. a ring cleavage 1,3-dipolar mechanism (path a), a concerted (path b) or a dissociative, inter- or intra-molecular ionic or radical mechanism (path c). In order to explore the mechanistic details, we have studied the rearrangement process for 1,2,4-triazoles substituted with a chiral alkyl group in the 4-position. Such compounds should give information about the stereochemical course of the reaction.

Results and discussion

The optically active triazole (**1**) was prepared in 47 % yield analogously to known procedures.[2] Thermolysis of neat 4-[(*S*)-2-butyl]-3,5-diphenyl-4*H*-1,2,4-triazole, (*S*)-(+)-**1**, ($[\alpha]_D^{28}$ = +49.5°) at 330 °C for 36 min and subsequent TLC purification, yielded 37 % of chemically pure rearranged product, consisting mainly of the 1-[(*R*)-2-butyl]-3,5-diphenyl-1*H*-1,2,4-triazole enantiomer, (*R*)-(−)-**2**, ($[\alpha]_D^{28}$ =



Scheme 2.

(*S*)-(+)-**1**

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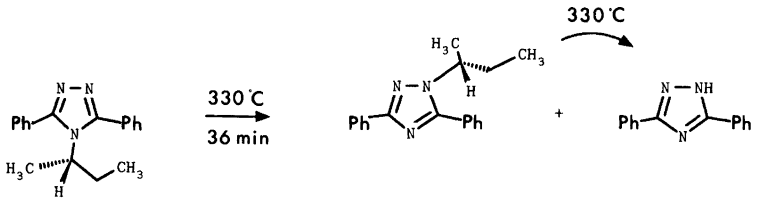
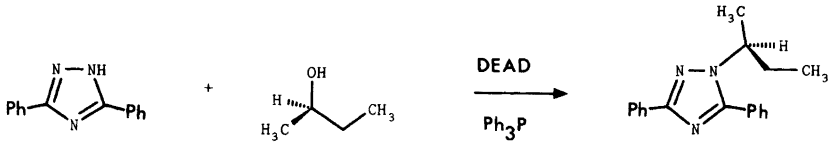


Scheme 3.

14.3°) (*c* 9.4×10^{-3} M, MeOH), together with 43 % of 3,5-diphenyl-1*H*-1,2,4-triazole (**3**). The complete picture of the origin of **3** is complicated by the observation that under the reaction conditions this compound can be formed from (*R*)-(−)-**2**.

To confirm the assignment of the configuration of the product **2**, an authentic sample with known configuration



Scheme 4.

was needed. To the best of our knowledge, optically active 1-alkyl-4*H*-1,2,4-triazoles have not been described previously. However, we found that an authentic sample of (*S*)-(+)-**2** was easily obtained by alkylation of triazole **3** with (*R*)-(−)-2-butanol under Mitsunobu reaction conditions,[3] according to Scheme 4.

It is generally accepted that this reaction proceeds with virtually complete inversion of configuration of the alcohol. Thus, without any further independent proof, we assume that the product so obtained can be assigned as (*S*)-(+)-**2**. The pure product was obtained in 34 % yield, and exhibited $[\alpha]_D^{22}$ = +16.9° (*c* 5×10^{-4} M, MeOH). Because of the low concentrations of the substrates in the measurements of optical rotations, the numbers obtained are subject to considerable uncertainty. Thus, in order to determine the degree of inversion in the thermal rearrangement of (*S*)-(+)-**1**, we performed a CD analysis of the rearrangement product and the authentic sample. The results are illustrated in Fig. 1. The optical purity of the product from the arrangement reaction was determined to be 70(5) %.

Rearrangement of the triazoles via ring cleavage to form an iminonitrene and a nitrile, path a, has so far been excluded, as cross-over experiments with different aromatic nitriles gave no indication of mixed products.[4] This was also supported by our observation that rearrangement of the optically active triazole proceeded with a high degree of inversion, 70 %, around the *N*-bearing carbon atom in the 4-alkyl group.

The stereochemical course of the rearrangement was in agreement with a concerted 1,3-shift. However, the reaction was also associated with some racemization, ca. 30 %. This, together with the formation of the elimination product **3**, is indicative of a non-concerted process. This view is also supported by molecular orbital symmetry considerations on 4-aryl substituted triazoles, that would be expected to undergo facile concerted shift reactions. However, these systems have never been observed to undergo migration reactions, even under very forcing reaction conditions.

The formation of the elimination product **3** indicates that a dissociative mechanism is probably operative. The increased ability of secondary over primary alkyl groups to form the elimination product indicates an ionic rather than

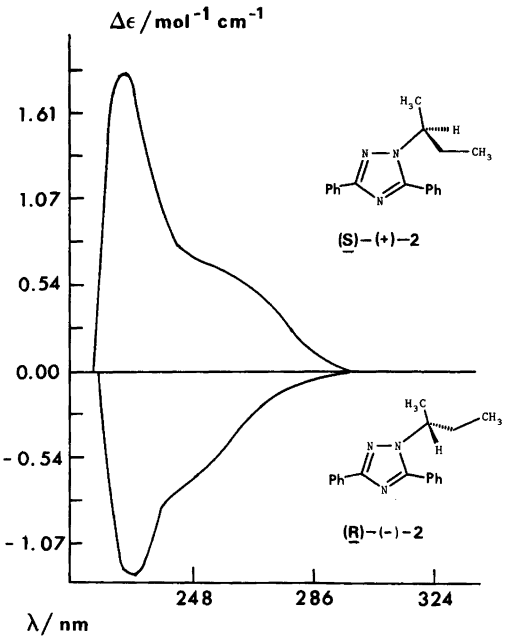


Fig. 1. CD spectra of product (*R*)-(−)-**2** and authentic (*S*)-(+)-**2**.

a radical pathway. Bearing in mind the rule stated by Ingold that 'mechanism S_N1 involves inversion of configuration mixed with racemization in any proportion to both limits'[5] we propose a possible mechanism involving a mono- or bi-molecular ion pair type of mechanism. A possible supplement or alternative to this mechanism was recently proposed by Bentley *et al.*[6] However, the work described in the present paper is inconclusive with regard to distinguishing between the various mechanisms.

Conclusion

Based solely on the work described here, it is not possible to decide conclusively which mechanism is operative in the reaction described. However, it supports the view that ring cleavage of the triazole does not take place. Though a concerted mechanism was not been fully excluded, the rearrangement presumably proceeds via an ion-pair mechanism or a bimolecular nucleophilic displacement reaction.

Experimental

General. ^{1}H NMR spectra were recorded on a JEOL FX-100 NMR spectrometer. IR spectra were obtained on a Nicolet 20SXC FT-IR spectrometer, and mass spectra on an AEI MS-902 spectrometer at 70 eV. CD spectra were recorded at room temperature on a Jobin Yvon Auto Dictograf, and optical rotation were measured on a Perkin-Elmer 241 polarometer. GLC measurements were performed on a Varian 3700 gass chromatograph equipped with a BP-5 capillary column (25 m). Preparative TLC was performed on 20×20 cm^2 glass plates covered by Merck silica gel $HF_{254+366}$ using chloroform as the eluent.

Chiral chemicals. (*S*)-(+)-2-Butylamine, 99 % (JPS Chimie Jeanneret) and (*R*)-(−)-2-butanol, 98 % (Janssen). [α] = −12° (neat).

4-[(S)-2-Butyl]-3,5-diphenyl-4H-1,2,4-triazole, (*S*)-(+)-**1**, was synthesized similarly to a general procedure reported for 4-alkyl-3,5-diphenyl-4*H*-1,2,4-triazole.[2] Bis(α-chlorobenzylidene)hydrazine (0.47 g, 1.7×10^{-3} mol) and (*S*)-(+)-2-butylamine (0.51 g, 6.97×10^{-3} mol) were dissolved in 2.13 g of dry benzene, and then heated in a sealed pressure glass tube, for 15 h at 141–149 °C in an oil bath. The reaction mixture was cooled to room temperature and the resulting white crystals were filtered and washed repeatedly with water. The filtrate was extracted with dichloromethane (5×5 ml) and the combined organic phases were evaporated to dryness. The residue, together with the white crystals, was dissolved in ethanol (2.5 ml), and reprecipitated by the addition of water (ca. 5 ml). After being dried under reduced pressure, 0.22 g (47 %) of the product were isolated as white crystals, m.p. 182–183.5 °C, $[\alpha]_D^{28}$ = +49.5° (*c* 0.012, MeOH). The product exhibited the following spectroscopic properties: CD nm (Δε) (MeOH): 215 (0.00), 229 (0.62), 236 (0.98), 248 (0.72), 260 (0.24), 286 (0.09), 324 (0.05), 400 (0.00). IR, MS and ^{1}H NMR spectra were identical in all details with those described in the literature.[1] ^{13}C NMR [25.1 MHz, $CDCl_3$]: δ 11.2, 22.0, 29.3, 55.7, 128.6, 129.0, 130.3, 130.5, 155.7.

1-[(S)-2-butyl]-3,5-diphenyl-1H-1,2,4-triazole, (*S*)-(+)-**2**. This was prepared according to a procedure described for the synthesis of *N*-[(2*R*)-octyl]phthalmide.[3] A reaction mixture containing 3,5-diphenyl-1*H*-1,2,4-triazole (0.14 g, 6.33×10^{-4} mol), *R*-(−)-2-butanol (0.06 g, 8.09×10^{-4} mol) and triphenylphosphine (0.18 g, 6.86×10^{-4} mol) in dry THF (1.05 g), was stirred for 15 min in a nitrogen atmosphere at room temperature. A solution of diethyl azodicarboxylate (DEAD) (0.12 g, 6.89×10^{-4} mol) in dry THF (0.5 g) was added over a period of 5 min, and then stirred at room temperature for another 4 h. The solution was then evaporated to dryness under reduced pressure. The residue was refluxed in ether (4 ml) for 1 min, then cooled and the resulting crystals, which consisted of triphenylphosphine oxide and diethyl azodicarboxylate were filtered off. The filtrate was evaporated to dryness and dichloromethane (2 ml) added. The mixture was filtered and the crystals were washed with another portion of dichloromethane (ca. 1 ml). The filtrate was again evaporated to dryness and the dichloromethane treatment was repeated twice more. The resulting filtrate residue was purified by preparative TLC, to yield 0.0603 g (34.4 %) of white crystals of 99.5 % purity (GC), with m.p. 98–99.5 °C, $[\alpha]_D^{22}$ = +16.9° (*c* 5.04×10^{-3}, MeOH) and it exhibited the following spectroscopic properties: CD nm (Δε) (MeOH): 217 (0.00), 221 (1.27), 227 (1.84), 242 (0.82), 258 (0.64), 286 (0.11), 324 (0.00). ^{1}H NMR and MS spectra were identical in all details with those described in the literature.[1] ^{13}C NMR [25.0 MHz, $CDCl_3$]: δ 10.7, 21.1, 29.7, 56.5, 126.3, 128.4, 128.8, 129.0, 129.8, 131.3, 131.8, 155.6, 161.2.

Thermolysis of 4-[(S)-2-butyl]-3,5-diphenyl-4H-1,2,4-triazole, (*S*)-(+)-**1**. 4-[(*S*)-2-butyl]-3,5-diphenyl-4*H*-1,2,4-triazole (0.0411 g, 1.48×10^{-4} mol) was placed in a sealed glass tube (inner diameter 0.5 cm, length 3.1 cm), under reduced pressure (oil vacuum), and heated in a oven at 330 °C for 36 min. After being cooled to room temperature, the reaction products were separated by preparative TLC using chloroform as the eluent. Two fractions were isolated. Fraction 1 (R_f = 0.76) contained 0.0152 g (37 %) of pure (100 % by GLC), 1-[(*R*)-2-butyl]-3,5-diphenyl-1*H*-1,2,4-triazole with m.p. 99–100.5 °C and $[\alpha]_D^{24}$ = −14.3° (*c* 9.4×10^{-3}, MeOH). The product exhibited the following spectroscopic properties: CD nm (Δε) (MeOH): 218 (0.00), 221 (−0.69), 229 (−1.29), 242 (−0.75), 258 (−0.46), 286 (−0.06), 324 (0.00). The ^{1}H NMR and MS spectra were identical in all respects with those described in the literature.[1]

Fraction 2, (R_f = 0.13) contained 0.0140 g (43 %) of pure

3,5-diphenyl-1*H*-1,2,4-triazole (100 % by GLC), and all ^{1}H NMR and MS spectra were identical with those described in the literature.[7]

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