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AN UNUSUAL REACTION OF N-ALKYL IMINES WITH tert-BUTYLCYANOKETENE

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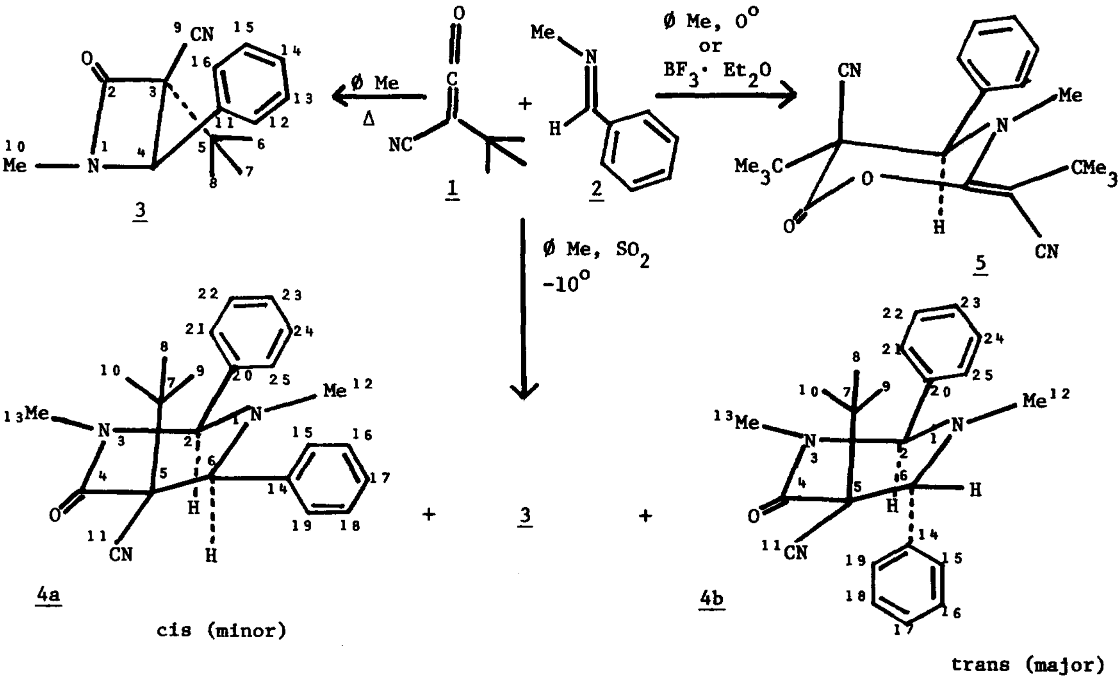
The facile generation of cyanoketenes from appropriately substituted 2,5-diazidoquinones has aroused considerable interest in this class of heterocumulenes.[1a-c] Although the cycloaddition reactions of tert-butylcyanoketene (1) with allenes,[2a-c] alkynes,[3] olefins,[1c,4a-e] dicyclohexylcarbodiimide,[1c] ylids,[1c] enamines,[1c] tert-amines,[5] and imino ethers[6] have been reported, no one has yet investigated the cycloaddition reactions of this compound with Schiff's bases. As a result of our interest in the reactions of ketene and Schiff's bases in liquid sulfur dioxide, we decided to examine the reactions of (1) with N-alkyl imines.



cis (minor)

trans (major)

tert-Butylcyanoketene (1) was generated in situ from 5 g (0.0165 mol) of 2,5-diazido-3,6-di-tert-butyl-1,4-benzoquinone in boiling toluene.[1a] The cycloaddition of 1 and benzylidenemethylamine (2) was then carried out by adding 2 (3.9 g, 0.033 mol) to a toluene solution (75 ml) of 1 at room temperature and refluxing the reaction mixture for 30 min. Removal of solvent gave an oil which upon crystallization from a 1:1 hexane-ether mixture afforded 6 g (75% yield) of product (mp 125-127°) identified as N-methyl-3-tert-butyl-3-cyano-4-phenyl-2-azetidinone (3). The IR spectrum (KBr) of 3 showed absorptions at 2210 (CN) and 1770 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.23 (s, 9H, CMe_3), 2.81 (s, 3H, NMe), 4.58 (s, 1H, NCH), and 7.39 (m, 5H, =CH); ^{13}C NMR ppm 161.42 (C-2), 133.26 (C-11), 129.40 (C-14), 129.03 (C-12, C-16), 127.00 (C-13, C-15), 115.28 (C-9), 69.08 (C-3), 61.31 (C-4), 34.81 (C-5), 27.12 (C-10), and 25.80 (C-6, C-7, C-8). Coupling between C-4 and H-4 (J=152 Hz) supports the ring size (four atoms). Irradiation of the tert-butyl group caused a 20% increase in the integrated intensity of the methine proton (H-4) indicating that the tert-butyl and phenyl groups are trans to each other (Nuclear Overhauser Effect, NOE). Therefore, the most stable β-lactam is formed preferentially. No other product could be detected under these conditions.

A solution of 2,5-diazido-3,6-di-tert-butyl-1,4-benzoquinone (4 g, 0.0132 mol) in 75 ml of toluene was converted to 1 as described above and then added dropwise to a stirred solution of 2 (3.14 g, 0.0264 mol) in liquid sulfur dioxide (100 ml) at -78°. The reaction mixture was stirred 2 h longer at -78° and then was allowed to warm gradually to room temperature with continued stirring for another 12 h. Removal of toluene yielded an oil which was treated with 30 ml of ethanol. After 24 h, the crystals that formed were collected and purified by recrystallization from hexane (0.100 g, 13% yield based on 2) to afford 4a, mp 180-183°. The IR spectrum (KBr) of 4a showed absorptions at 2220 (CN) and 1670 (CO) cm^{-1}. ^1H NMR δ 1.26 (s, 9H, CMe_3), 2.30 (s, 3H, NMe), 2.66 (s, 3H, CONMe), 5.66 (s, 1H, CH), and 7.32 (m, 5H, =CH); ^{13}C NMR ppm 163.65 (C-4), 141.03 (C-20), 140.92 (C-14), 129.4 (C-15, C-19, C-21, C-25), 128.8 (C-16, C-18, C-22, C-23, C-24), 128.2 (C-17), 118.52 (C-11), 79.43 (C-2), 69.83 (C-6), 54.24 (C-5), 41.40 (C-12), 37.14 (C-7), 32.55 (C-13), 27.73 (C-8, C-9, C-10). The remaining ethanolic solution was concentrated and adsorbed on 2.5 g of silica gel and chromatographed on a silica gel (200 g) dry column using a 3:1 hexane-ether solution. The first fraction contained 4b (2 g, 22.5% yield), mp 175-178°, which was purified by recrystallization from hexane. The IR spectrum (KBr) of 4b showed absorptions at 2330 (CN) and 1635 (CO) cm^{-1}. ^1H NMR δ 1.50 (s, 9H, CMe_3), 1.88 (s, 3H, NMe), 2.70 (s, 3H, CONMe), 4.30 (s, 1H, CH), 4.44 (s, 1H, CH), and 7.08-7.30 (m, 5H, =CH); ^{13}C NMR 164.11 (C-4), 137.3 (C-20), 131.5 (C-14), 129.3 (C-17), 128.7 (C-15, C-19, C-21, C-23, C-25), 128.6 (C-16, C-18, C-22, C-24), 118.4 (C-11), 79.00 (C-2), 67.02 (C-6), 57.08 (C-5), 39.50 (C-7), 39.04 (C-12), 32.42 (C-13), and 29.02 (C-8, C-9, C-10). Evaporation of the second fraction and recrystallization of the residue from a 1:1 hexane-ether solvent mixture afforded 0.98 g (15.7% yield) of 3.

It is clear from the analytical and spectral data that 4a and 4b are isomeric hexahydropyrimidones. Similar 1,2 adducts have only been observed in the reactions of unhindered imines[7] and/or in the presence of Lewis acid catalysts.[8] Although rare, this mode of addition could be of interest since it represents a convenient route to functionalized hexahydropyrimidones of potential theoretical and biological interest. A Dreiding model of the molecular framework for 4a,b resembles a flattened chair with one quasi axial position

(C-5) and two axial positions (C-2 and C-6) below the plane of the ring. The most favorable conformation for the trans structure (as defined by the relationship of the 5-tert-butyl and 6-phenyl groups) is that in which the 5-tert-butyl and 6-phenyl groups are axial and the 2-phenyl group is equatorial. The conformer with equatorial 5-tert-butyl, equatorial 6-phenyl, and axial 2-phenyl groups is energetically less favorable as it affords the 5-tert-butyl group less rotational mobility.[9] We have assigned the cis structure to 4a and the trans to 4b.[10] The relative positions of the substituents were established by irradiation (NOE) and low temperature nmr studies. The proton nmr spectrum of 4a contains a narrow multiplet at approximately 7.32 δ for the aromatic protons. The two methine protons at C-2 and C-6 absorb at δ 5.66 and δ 4.26 which is reasonable for protons adjacent to two nitrogen atoms and one nitrogen atom respectively. Irradiation of the 5-tert-butyl group did not show any significant enhancement of the absorption of the 6-methine proton, thereby suggesting a trans relationship between the 5-tert-butyl group and the 6-methine proton and, consequently, a cis relationship between the 5-tert-butyl and 6-phenyl groups. The proton nmr of 4a changed drastically with decreasing temperature (+35° to -70°C). The changes involved a broadening of the resonances of the 1-N-methyl group, the 6-methine proton, and the 5-tert-butyl group. Further lowering of the temperature caused the sharpening of the signals of the 1-N-methyl group and the 6-methine proton at chemical shifts only very slightly removed from the original resonances. The resonance of the 5-tert-butyl group is concurrently split into signals both downfield and upfield from the original resonance. This phenomenon may be attributed to the restricted rotation of the 5-tert-butyl group as a result of interactions with the adjacent 6-phenyl substituent.[11a,b] This effect is confirmed by the low temperature ^{13}C NMR which shows three different carbon resonances for the three methyl groups of the 5-tert-butyl substituent. In contrast with these results, the ^{1}H NMR spectrum of 4b showed no major temperature dependence. The ^{1}H NMR spectrum of 4b exhibited a more complex and spread out aromatic region (δ 7.05-7.30), presumably as a result of phenyl rings in both an axial and equatorial environment. Irradiation studies of the 5-tert-group and the 1- and 3-N-methyl groups showed significant resonance enhancements involving the 5-tert-butyl group and the 6-methine proton (20%), and the 1-N-methyl group and the 6-methine proton (18%), thereby supporting the relatively close approach of these groups to the 6-methine proton. The experiment thus confirms a cis relationship between the 5-tert-butyl group and the 6-methine proton. In addiiton, irradiation of the ortho protons (δ 7.05, doublet of doublets, C-15, C-19) of the 6-phenyl group produced a significant enhancement of the 2-methine resonance (19%), and a somewhat lesser enhancement of the 6-methine resonance (13%), thereby supporting the axial position of the 6-phenyl group and, at the same time, accounting for the shielding (δ 4.30) of the 2-methine proton. The shielding influence of the 6-phenyl group is also manifest in the relative chemical shifts of the tert-butyl groups in 4a (δ 1.26, cis 6-phenyl group) and 4b (δ 1.50, trans 6-phenyl group). Irradiation of the bulk of the aromatic region (∿ δ 7.30) in 4b (presumably including the ortho protons, C-21 and C-25, of the equatorial 2-phenyl group) produced a large enhancement of the 2-methine proton resonance but no NOE for the 6-methine proton, thereby confirming the overall assignment of the system.

Since it was conceivable that 4a and 4b could have been formed via the reaction of 3 with 2 in liquid sulfur dioxide, we decided to test this possibility. Compound 2 (0.24 g, 0.002 mol) dissolved in 10 ml of anhydrous toluene was added dropwise to 3 (0.5 g, 0.002 mol) in 25 ml of liquid sulfur dioxide, with stirring, at -10°. The reaction mixture was allowed to warm gradually to ambient temperature overnight. Excess toluene and sulfur dioxide were removed *in vacuo* and the residual oil was then treated with cyclohexane to afford a solid which was identical to 3. The cyclohexane solution contained only 2, confirming that no reaction had taken place. It also appeared possible that the formation of 4a and 4b was attributable to the low temperature employed with liquid sulfur dioxide as solvent. Therefore, we examined the reaction of 1 and 2, in toluene, at 0°. Compound 1, generated from the corresponding 2,5-diazidoquinone (3.4 g, 0.01 mol) in 50 ml of anhydrous toluene, was cooled to 0° and treated with a solution of benzylidenemethylamine (1.2 g, 0.01 mol) in 10 ml of toluene. The reaction mixture was stirred at 0° for 1 h and then was allowed to warm gradually to ambient temperature. The toluene was evaporated and the remaining residue was chromatographed on a dry silica gel column using 1:1 (v/v) ether:petroleum ether (bp 30-60°) as the eluent. The first fraction afforded the 2:1 adduct of 1 and 2, mp 150-151° (1.86 g, 51.5% yield based on 2), 2-(1-cyano-2,2-dimethylpropylidene)-5-(1,1-dimethylethyl)tetrahydro-3-methyl-6-oxo-4-phenyl-2*H*-1,3-oxazine-5-carbonitrile (5). The IR spectrum (KBr) of 5 showed absorptions at 2195 (CN), 1775 (CO), and 1610 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.32 (s, 18H, CMe_3), 3.19 (s, 3H, NMe), 4.51 (s, 1H, C-H), and 7.40 (m, 5H, =CH). The remaining chromatography fractions contained 3 (0.968 g, 40% yield based on 2).

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