CARBENOID REARRANGEMENTS OF A CYCLOADDUCT FROM PHENYL AZIDE

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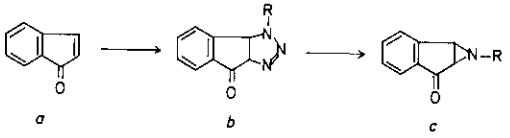
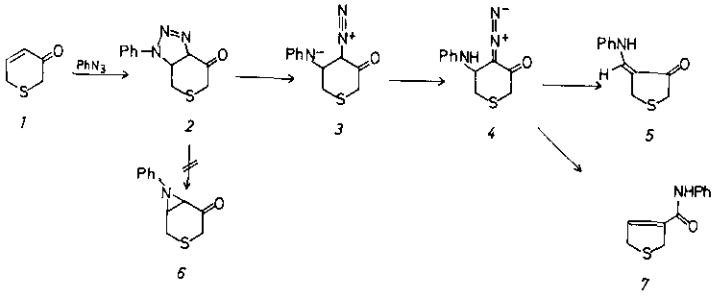
Abstract - Cycloaddition between phenyl azide and 2H-thiopyran-3(6H)-one is followed by isomerisation of the adduct to 5-anilino-4-diazo-4,5-dihydro-2H-thiopyran-3(6H)-one 4. On heating, 4-(anilinomethylene)-4,5-dihydrothiophen-3(2H)-one 5 and N-phenyl-2,5-dihydrothiophene-3-carboxamide 7 are formed by carbenoid rearrangements.

Azides and olefins form triazoline adducts which can be transformed into aziridines by thermal or photolytic extrusion of a nitrogen molecule.[1] Regioselective adduct formation with an electron deficient olefin yields the Δ^2-1,2,3-triazoline with the electron withdrawing substituent in the 4-position.[2,3] We have used this reaction sequence to synthesise aziridines from inden-1-one (a → c).[4] Cyclopent-2-enone, which lacks the fused benzo ring of inden-1-one, failed to form an adduct with phenyl azide, possibly because it is less polarisable than inden-1-one.[5] The higher homologue, cyclohex-2-enone, reacts slowly with phenyl azide.[5] Herein we report studies of a heterosubstituted cyclohex-2-enone, viz. 2H-thiopyran-3(6H)-one 1. The 1,3-dipolar cycloaddition of azides may be a slow reaction; thermal instability of the triazoline products and of the azides themselves frequently preclude heating the reaction mixture.[1,2] The reaction between the α,β-unsaturated ketone 1 and phenyl azide, which was run at room temperature in the dark, had not gone to completion when the mixture was worked up after two months. The major product (30% yield), after chromatographic separation, has been identified as the 2-diazo ketone 4. Absorption bands in the IR spectrum at 3420 and 2120 cm^{-1} are ascribed to the amino and diazo groups, and a band at 1620 cm^{-1} is due to carbonyl absorption. These values are comparable with the vibrations at 2082 and 1619 cm^{-1} which have been reported for the analogous 4-anilino-3-diazopentan-2-one.[2] The highest mass number in the mass spectrum corresponds to a



Scheme 1



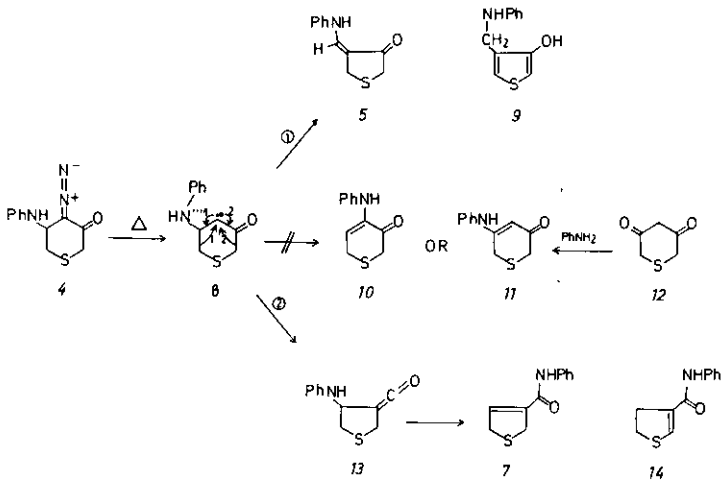
species arising from 4 by expulsion of nitrogen, as expected for diazo ketones.[6] The ^{1}H NMR spectrum shows one methine proton on sp^3-hybridised carbon as it should for structure 4. The formation of 4 presumably is caused by instability of the triazoline 2. Triazolines with an electron withdrawing 4-substituent are prone to base catalysed or autocatalysed ring opening and equilibria are set up between the cyclic and the open forms.[2,7] In this case only the open form was seen, whereas only the cyclic form of the corresponding indenone derivative b was obtained.[4]

Addition of azides to electron deficient olefins at elevated temperatures may lead to aziridines even when the addition at room temperature yields the diazo derivatives.[8] When a solution of 1 and phenyl azide in chloroform was heated under reflux for 10 days two isomeric products were isolated. The products were identified as 1:1 adducts which had lost a molecule of nitrogen, but neither isomer showed the spectroscopic properties expected for the aziridine 6. Both isomers gave strong molecular ions at m/e 205. A 1,2-hydrogen shift to the carbenoid centre yielding the α,β-unsaturated ketone is frequently a major reaction path in the thermal decomposition of diazo ketones.[9,10] The corresponding formation of the enamine 11, however, was excluded by comparison with authentic 5-anilino-2H-pyran-3(6H)-one 11, which was synthesised from thiopyran-3,5-dione 12 and aniline. Instead the product with carbonyl absorption in IR at 1685 cm^{-1} has been identified as the lower ring homologue 5, and the assigned structure has been verified by an X-ray analysis.[11]

The IR spectrum of the second product shows NH stretch at 3320 cm^{-1} and α,β-unsaturated amide absorptions at 1650 and 1530 cm^{-1}, and the UV spectrum has absorption maxima at 310 and 265 nm. The ^1H NMR spectrum shows a vinyl proton singlet at δ 6.82 and two sets of methylene protons which resonate as a singlet at δ 3.90. The product is assigned the 2,5-dihydrothiophene-3-carboxamide structure 7, which has been verified by an X-ray analysis.[11]

The isomers 5 and 7 were also isolated in low yields, 4 and 2%, respectively, from the reaction in the cold when the diazo ketone 4 was the major product.

Scheme 2



Compound 5 is tautomeric with 3-hydroxy-4-anilinomethylthiophene 9. 3-Hydroxythiophenes without ortho-substituents are chemically unstable; 2,5-disubstituted 3-hydroxythiophenes exist in tautomeric equilibria with thiophen-3(2H)-ones.[12] In contrast 5 was a stable compound, and the aromatic thiophene tautomer was not seen in the ^1H NMR.

Thermolysis of α-diazo cycloalkanones yields oxo-carbenoid intermediates which undergo a 1,2-hydrogen shift to the α,β-unsaturated ketone or undergo the Wolff rearrangement with ring contraction to a keten.[9,13] Similarly the formation of 5 can be rationalised by a carbenoid intermediate 8. The cleavage of the C5-C6 bond in the 1,2-shift which results in the new bond between C4 and C6, presumably is facilitated by participation of the lone pair of electrons on the nitrogen atom in overcoming transient electron deficiency on C5. The formation of 7 is rationalised by a Wolff rearrangement from the same carbenoid intermediate 8. In the

following reaction the keten 13 presumably adds a molecule of aniline, with concurrent or successive elimination of aniline from the 4-position. The net result is a transfer of an anilino group from the 4-position to the keten carbon atom in the 3-position. An intramolecular path involving a ß-lactam intermediate can also be written for this reaction. Either path yields the isomer with the double bond in the 3,4-position and the isomeric vinyl sulfide 14 was not seen (^{1}H NMR). In the Wolff rearrangement the intermediacy of oxirines has been demonstrated.[12] A corresponding interchange of the carbenoid and carbonyl functions in 8 would yield the same product 7. Migration of the anilino group with formation of 4-anilino-2H-thiopyran-3(6H)-one 10 was not seen in accordance with observations that the amino nitrogen atom shows less tendency than the carbon atom for a 1,2-shift to a carbenoid centre.[14] The amino group, however, presumably participates in stabilisation of the carbenoid centre at C4, and the tendency for Wolff rearrangement is thus decreased.[14]

The X-ray structure analyses of 5 and 7 show normal bond lengths and bond angles. Compound 5 has the (E)-configuration and the five-membered ring has an envelope conformation with the sulfur atom 0.384 and 0.401 Å out of the plane through the carbon atoms. In 7 the five-membered ring is planar.[11]

EXPERIMENTAL

5-Anilino-4-diazo-4,5-dihydro-2H-thiopyran-3(6H)-one 4. A mixture of 2H-thiopyran-3(6H)-one[15] (0.46 g, 0.004 mmol) and phenyl azide[16] (0.48 g, 0.004 mol) was left in the dark at room temperature. The progress of the reaction was monitored by TLC. When the reaction mixture was worked up after 2 months there was still some unreacted 2H-thiopyran-3(6H)-one present. The mixture was chromatographed on a silica gel column using dichloromethane. The components were eluted in the order phenyl azide, the thiopyranone 1, N-phenyl-2,5-dihydrothiophene-3-carboxamide 7 (2%), 4-(anilinomethylene)-4,5-dihydro-2H-thiophen-3(6H)-one 5 (4%), and the title compound 4 in 30% yield (0.28 g); the product was a yellow, oily material. ^{1}H NMR ($CDCl_3$): δ 2.8 (2H-6 , m), 3.17 (2H-2, s), 4.9 (H-5, t), and 6.6--7.3 (Ph). IR (film) 3420 (NH), 2120 (N_2) and 1620 cm^{-1} (CO, Ph). MS [70 eV; m/e (% rel.int.)]: m/e 205 (23, [M-N_2]), 130(25), 113(9), 93(100), 92(11) and 77(13).

4-(Anilinomethylene)-4,5-dihydro-2H-thiophen-3(6H)-one 5 and N-phenyl-2,5-dihydrothiophene-3-carboxamide 7. A solution of 2H-thiopyran-3(6H)-one (2.28 g, 0.02 mol) and phenyl azide (2.38 g, 0.02 mol) in chloroform (100 ml) was heated under reflux for 10 days. The solvent was then evaporated off and the residue triturated repeatedly with ether. The solid which remained (1.4 g, 35%) was a mixture of 5 and 7 in the ratio 3:2 (NMR). The components can be separated on a silica gel column using dichloromethane; 7 is eluted before 5. Alternatively 7 is extracted into chloroform by repeated extractions with small volumes (TLC can be used for monitoring). Recrystallisation of the residue from acetonitrile yields 5 chromatographically pure. Addition of hexane to the chloroform solution precipitates 7, which becomes chromatographically pure after recrystallisation from THF.

4-(Anilinomethylene)-4,5-dihydro-2H-thiophen-3(6H)-one 5; m.p. 198-200 °C (MeCN). ^{1}H NMR (DMSO-d_6): δ 3.33 (2H-2, s), 3.72 (2H-5, br.s), 7.3 (6H, m) and 9.35 (NH, d). IR (KBr): 3250 and 1560 (NH), 1685 (CO), and 1600 and 1500 cm^{-1} (Ph). UV [96% EtOH (log ε)]: 352(4.42), 295(3.70), 285(3.64) and 232(3.97) nm. MS [70 eV, m/e (% rel.int.)]: 205(97, M), 204(21), 131(23), 130(100), 113(31), 104(10), 93(16) and 77(37).

N-Phenyl-2,5-dihydrothiophene-3-carboxamide 7; m.p. 145-147 °C (THF). ^{1}H NMR (DMSO-d_6): δ 3.90 (2H-2 and 2H-5, s), 6.82 (H-4, s), 7.0--7.8 (Ph, m) and 9.78 (NH, s). IR (KBr): 3320 (NH), 1650 (CO, amide I), 1630 (C=C) and 1530 cm^{-1} (NH, amide II). UV [96% EtOH (log ε)]: 310(3.31) and 265(3.91) nm. MS [70 eV, m/e (% rel.int.)]: 205(95, M) and 93(100).

5-Anilino-2H-thiopyran-3(6H)-one 11. A solution of thiopyran-3,5-dione[17] (3.4 g, 0.026 mol) and aniline (2.9 g, 0.031 mol) in benzene (100 ml) was heated under reflux for 5 h using a Dean & Stark trap to remove the water liberated. The precipitate was filtered from the cold reaction mixture and dissolved in THF, the decolorised solution (active charcoal) was evaporated, and the residual material was recrystallised from benzene; yield 2.4 g (45%), m.p. 178-179 °C. Anal. $C_{11}H_{11}NOS$: C, H. ^{1}H NMR (DMSO-d_6): δ 3.25 (2H-2, s), 3.65 (2H-6, s), 5.37 (H-4, s), 7.1--7.7 (Ph, m) and 9.10 (NH, s). IR (KBr): 3215 and 1540 (NH), 1600 and 1580

(β-amino-α,β-unsat. CO, Ph) and 1500 cm^{-1} (Ph). UV [96% EtOH (log ε)]: 310 (4.19) and 230 (3.83) nm. MS [70 eV; m/e (% rel.int.)]: 205(40, M), 160(11), 159(100), 158(38), 131(12), 130(48), 117(26), 93(15), 92(19) and 77(33).

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