The Fragmentation of 2,3-Dihydroisothiazol-3-one 1,1-Dioxide Derivatives: A Novel Cheletropic Process

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Abstract. Adducts obtained by 1,3-dipolar cycloadditions to 2,3-dihydroisothiazol-3-one 1,1-dioxides are inclined to undergo a cheletropic process, by which the newly formed heterocyclic part undergoes aromatization, while SO₂ is extruded and an isocyanate is generated. The isocyanates are stable under the conditions of their formation, and are subject to standard isocyanate reactions. The process might be employed to synthesize isocyanates and derivatives of urethanes, ureas etc., whenever the use of mild and neutral reaction conditions is dictated by the sensitivity of the intermediates and products involved.

Previous Studies

The anti inflammatory agent tenoxicam 2b (Tilcotil®), invented [1] and developed [2] at our research laboratories in the late 70's and the early 80's, has been the target of considerable supportive and peripheral synthetic work [3][4]. In the course of these studies, access to structural types 2a and 2b (Scheme 1) and other related oxi cam analogs was investigated. Specifical ly, various 1,3-dipolar cycloaddition reactions were carried out, inter alia establishing building blocks of the type 1 as useful dipolarophiles in several cases (for the synthesis of I, see [3][5]). Especially with less reactive 1,3-dipoles, however, this procedure failed to yield the desired products; e.g., copious amounts of the triazole 5 (see [6] for an alternative preparation) were obtained, when the dipolarophile 1d was brought to reaction with the azide 3 (see [7] for the preparation and use of 3).

A Novel, Concerted Process

To explain the formation of 5, we speculated that the reaction of 1 with the relatively inert 3 had initially taken its due course, forming the adduct 4, but that the conditions required for the formation of 4 had sufficed for the initiation of a novel, concerted, cheletropic extrusion reaction, yielding three fragments: the triazole 5, benzyl isocyanate, and sulfur dioxide. An attempt was, therefore, made to gather evidence for this hypothesis, using the adduct 7a [3] (Scheme 2) because of its relative availability and stability.

Firstly, a base-induced mechanism had to be excluded, since the simultaneous formation of 5 and 6 might be considered to originate in a base-catalyzed SO₂ elimination, followed by some sort of solvoly sis and decarboxylation. In fact, when a solution of 7a in CH₂Cl₂ was treated with Et₃N, elimination of SO₂ proceeded at ambient temperature, yielding the carboxamide 8 as the sole product; no trace of a decarboxylated component was found. The structure of 8 was further confirmed by an acid-induced hydrolysis to the known [8] carboxylate 9. It was tentatively concluded, that whatever trace of 6 had been formed in the azide reaction, this would most probably be the result of a similar base-induced elimination, presumably due to the presence of a basic impurity in the azide 3.

The adduct 7a was then subjected to the conditions used in the attempted azide addition, i.e. refluxing toluene. The known [9] 1,3-diphenylpyrazole 11 (Scheme 3) was indeed formed as the only detectable product. This finding considerably supported our notion concerning the origin of
5; still, to propose the unfolding of a concerted fragmentation, we needed to prove the intermediate occurrence of an isocyanate species such as 10b or 10d of Scheme 3.

The problem was addressed using two further substrates, namely 7b and 7d, both readily available by alkylation of 1a (see Exper. Part), followed by a reaction with diphenyl nitrite imine. The following experiments were carried out: solutions of the adducts 7b or 7d, were maintained at reflux temperature in toluene for 1–5 h in the presence of 1–3 equiv. of either MeOH or PhCH₂OH. The pyrazole 11 was generated quantitatively, along with the postulated methyl (12) or benzyl (13) carbamates, both isolated in 70–74% yield after chromatography. The isocyanates proved to be stable under the conditions of their formation; thus, when 7d was kept at reflux temperature for 1 h in the absence of proton donors, and the solution was then allowed to cool to ambient temperature, it contained the isocyanate 10d and the pyrazole 11 as the only components: the addicition of 1 equiv. of PhCH₂NH₂ initiated the instantaneous precipitation of the derived 1,3-dibenzylurea 14, which was isolated in 83% yield. These combined findings appear to secure the intermediacy of isocyanates and herewith the likelihood of a concerted mechanism, as is depicted in Schemes 1 and 3.

It may be argued, that the force driving the fragmentation is mainly the aromatization energy inadvertently gained during the reaction. Indeed, 15 (itself readily obtained by reducing 1c, see Exper. Part) turns out to be thermally stable, by no means undergoing a fragmentation process as outlined in Scheme 4.

Applications

Alkyl halides can be easily converted into the respective tetrahydroisothiazol-1,1-dioxide derivatives by simply alkyllating the Na salt of 1a, as is standard procedure with, e.g., the Na salt of saccharin or the K salt of phthalimide. With motives quite similar to the latter two cases, an amine function – in the case at hand an isocyanate group or one of its derivatives – can be liberated by exposing the isothiazoles first to a 1,3-dipole, then to heat. The process might be useful, particularly when isocyanate groups are to be generated from halides, while the sensitivity of the starting materials and/or the products dictate the observance of mild, neutral, and aprotic conditions.

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Experimental Part

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General. M.p.: uncorrected. IR spectra (cm⁻¹); in KBr. ¹H-NMR spectra: chemical shifts (ppm) reI. to TMS, coupling constants in Hz. Correct elemental analyses were obtained for all compounds.

1. [2+2] Addition of 2,3-Dihydro-2-phenyl-isothiazol-3-one-1,1-Dioxide (1d) and 1-(Azidomethyl)-4-methoxybenzene (3). A soln. of 1d (223 mg, 1 mmol) and 3 (7) (245 mg, 220 µl, 1.5 mmol) in dry toluene (2.5 ml) was maintained at 100° for 18 h with stirring. Upon slowly cooling, the initially clear soln., white crystals of anal. pure N-benzyl-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxamide (6) (32 mg, 10%) were deposited, and were collected by filtration. M.p. 201°. IR: 3310s, 3080s, 2940w, 1655s, 1618w, 1581s, 1519s. ¹H-NMR (80 MHz, CDCl₃): 7.94 (s, 1 H); 7.45 (br., 1 H); 7.34 (m, 5 H); 6.18 (s, 2 H); 4.18 (t, J = 6 Hz).
Scheme 4

systems: 7.23 (m, 2 H) and 6.90 (m, 2 H). 4.63 (d, J = 6, 2 H); 3.80 (s, 3 H). MS: 322 (M'). 201 ([M - CH₃CO₂H]⁺), 121 (CH₃CO₂H). The filtrate, after evaporation, consisted mainly of 1-(4-methoxybenzyl)-1H-1,2,3-triazole (5). Colorless crystals of anal. pure 5 (101 mg, 53%) could be obtained by fractional crystallization from hexane/Et₂O. M.p. 90-91.5°: IR: 3102s, 2842w, 1611s, 1516s, 1484m. [13-NMR (80 MHz, CDCl₃): 7.75 (d, J = 1, 1 H); 7.53 (d, J = 1, 1 H); AA'BB' systems: 7.31 (2 H) and 6.97 (2 H); 5.45 (2 H); 2.83 (3, 3 H). MS: 189 (M'), 161 (M - N₃), 121 (CH₃CO₂H). 2. Base-Induced SO₂ Elimination of the Nitrite Imine Adduct. 7a: pale yellow crystals from CH₃Cl/Hexane in 50% yield from 1e [5]. M.p. 132-132.5°. 13-NMR (80 MHz, CDCl₃): 7.25-7.15 (m, 5 H); 3.80 (s, 3 H). MS: 223 (M'). 159 ([M-SO₂]).

4. 1,3-Dipolar Adducts of 1 with Diphenyl Nitrite Imine. The adducts were prepared as described previously [3]: 7a: pale yellow crystals from CH₃Cl/Hexane in 50% yield from 1e [5]. M.p. 132-132.5°. 13-NMR (80 MHz, CDCl₃): 7.25-7.15 (m, 5 H); 3.80 (s, 3 H). MS: 223 (M'). 159 ([M-SO₂]).

5. Thermally Induced Fragmentation of the Diphenyl Nitrite Imine Adducts. 7a. A soln. of 7d (417 mg, 1.8 mmol) and PhCH₂OH (162 mg, 1.5 mmol) in dry toluene (2.5 ml) was stirred at reflux temp. for 1.5 h under Ar. The solvent was evaporated, and the remaining brown oil was chromatographed on silica gel (200 g, benzene). The first fraction, a white solid, consisted of 1,3-diphenylpyrazole (11) (220 mg, 100%). Recrystallization from pentane gave 132 mg of white crystals. M.p. 84-85° (91:86-87°). MS: 220 (M'). The second fraction, a colorless oil, proved to be benzyl N-benzylcarbamate (13) (170 mg, 70%). Recrystallization from E₂O/pentane gave 92 mg of white crystals. M.p. 64° (reported: 64° [12]). In full analogy, thermolysis of 1 mmol of 7b and 4 mmol of MeOH in dry toluene (2.5 ml), after 5 h under Ar at reflux temp., afforded chromatography on silica gel (50 g, CH₂Cl₂, followed by CH₂Cl₂/EtOAc 1:1) white crystals of 11 (190 mg, 86%). M.p. 82-84°, and N-methoxycarbonyl-3-benzylamine ethyl ester (12) as a colorless oil (130 mg, 74%). [13-NMR (60 MHz, CDCl₃): 5.65-5.95 (br., 1 H); 4.15 (dd, 2 H); 3.66 (s, 3 H); 3.44 (dd, 2 H); 2.51 (s, 2 H); 1.24 (s, 3 H). Furthermore, thermolysis of 1 mmol of 7d was carried out in dry toluene (2.5 ml) in the absence of any alcohol. After 1 h at reflux temp., the soln. was allowed to cool to 20°, and benzylamine (107 mg, 1.0 mmol) was injected, whereby the precipitation of white product was started. After 30 min, the solid was collected by filtration and dried. White crystals of anal. pure 1,3-dibenzylurea (14) (200 mg, 83%). M.p. 168-169° (130:173°). The filtrate, on evaporation, consisted of spectroscopically (1H-NMR) pure 11 (white solid, as above).

6. 2,3-Dihydro-2-(4-methoxybenzyl)sulfoxiazole-3-one 1,1-Dioxide (15). A soln. of 1c (3.0 g, 11.8 mmol) in glacial AcOH (72 ml) and H₂O (8 ml) was cooled with an ice-bath, and Zn dust (6 g) was added in one portion. After vigorously stirring for 15 min at 5°, Zn was removed by filtration, and the filtrate was poured into 5% aq. NaOAc soln. (1.6 l). The product was extracted with three 200 ml portions of CH₃Cl, the combined org. phases were dried (Na₂SO₄) and evaporated. The white residue (2.91 g, 96%), after one recrystallization from CH₂Cl₂/hexane, afforded white crystals of anal. pure 15 (2.3 g, 83%). M.p. 125-126°. IR: 2842m, 1722s. [13-NMR (60 MHz, CDCl₃): AB'BB' systems: 7.35 (m, 2 H) and 6.83 (m, 2 H); 4.64 (s, 2 H); 3.79 (s, 3 H); AB'BB' systems: 3.55 (m, 2 H) and 3.04 (m, 2 H). MS: 255 (M'), 191 ([M-SO₂]).

7. Attempted Fragmentation of 15. A soln. of 15 (128 mg, 0.55 mmol) and (optionally) PhCH₂OH (81 mg, 79 µl, 0.75 mmol) in dry toluene (1.5 ml) was heated to reflux temp. for several days. TLC and 'H-NMR monitoring reveals the presence of starting components only, with no indication of decomposition.

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