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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 SO_2 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 antiinflammatory 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 oxicam analogs was investigated. Specifically, 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 **1**, 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 SO_2 elimination, followed by some sort of solvolysis and decarboxylation. In fact, when a solution of **7a** in CH_2Cl_2 was treated with Et_3N, elimination of SO_2 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 trace 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

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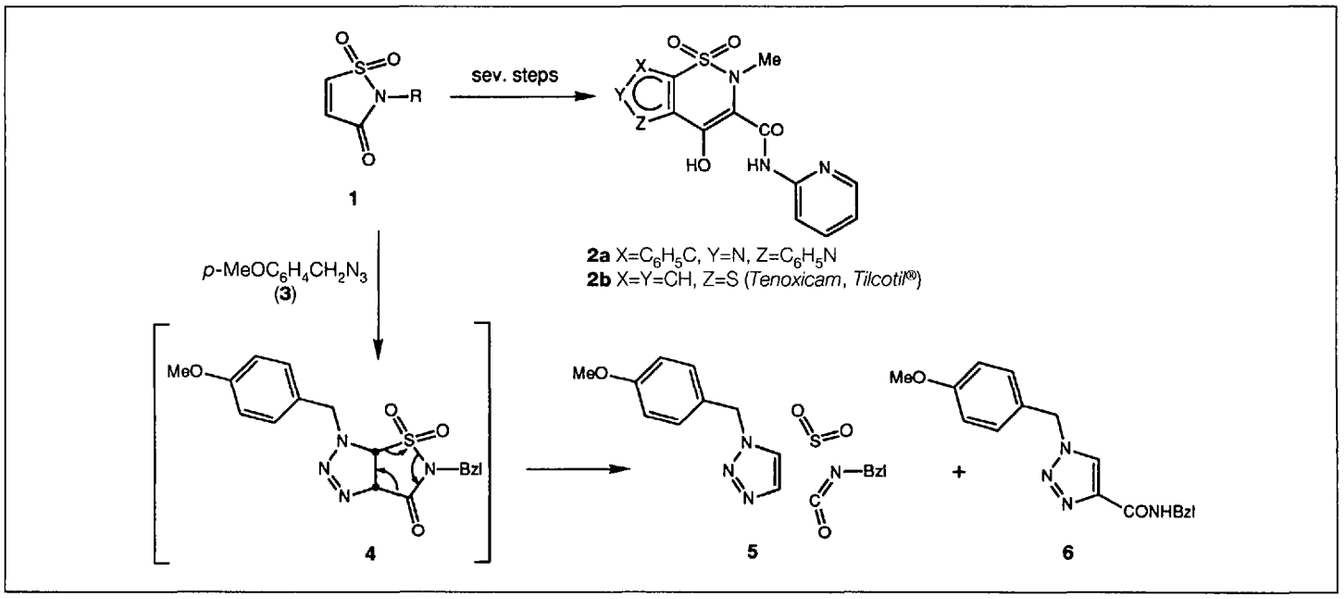
Scheme 1



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 nitrile 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 $PhCH_2OH$. 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 addition of 1 equiv. of $PhCH_2NH_2$ 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 tetrahydroisothiazolone 1,1-dioxide derivatives by simply alkylating 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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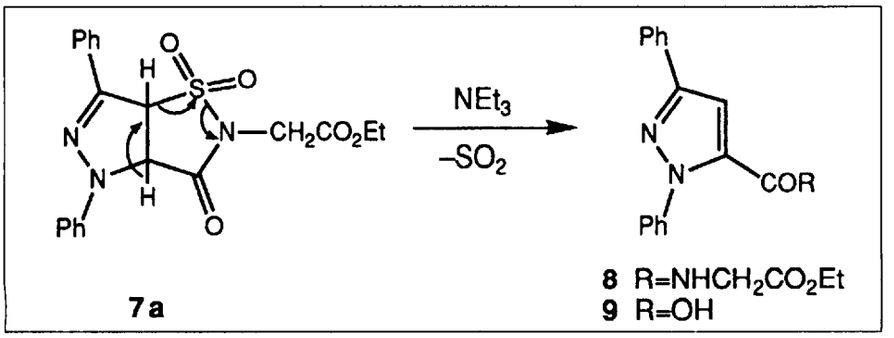
Experimental Part

(The author wishes to thank Mr. *Rolf Dittmar* and Mrs. *Heidy Schär-Morath* for their experimental work)

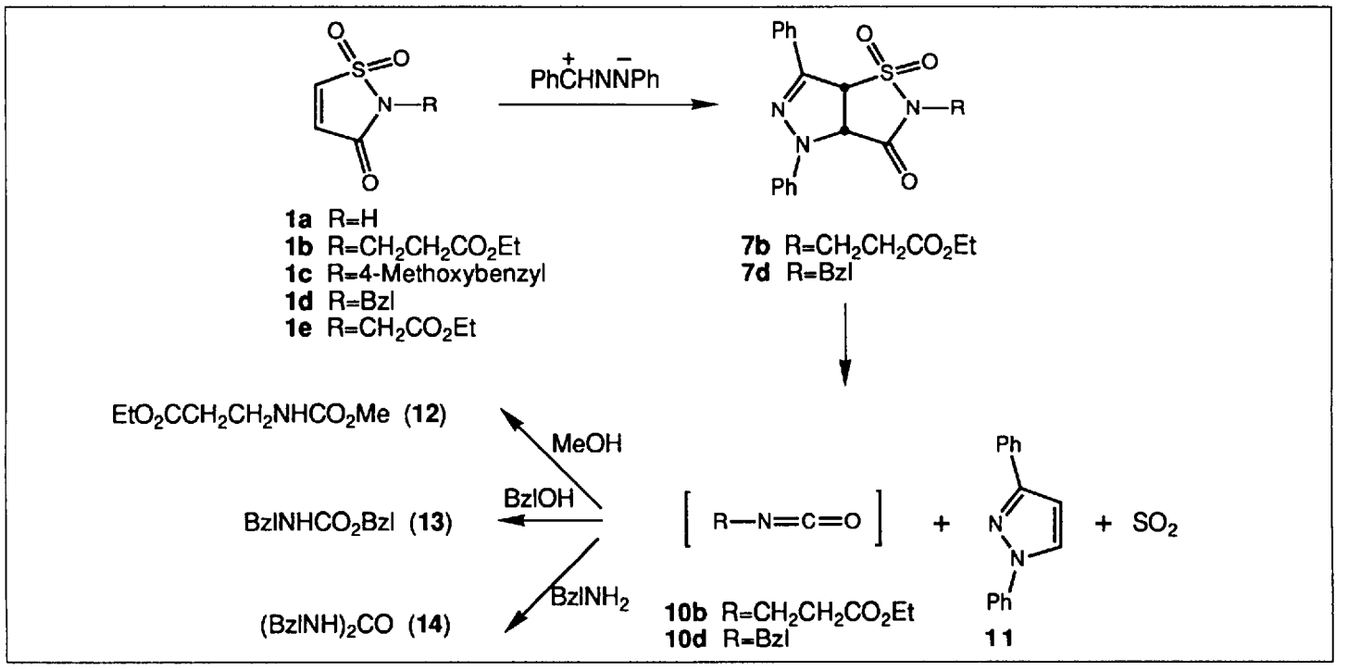
General. M.p.: uncorrected. IR spectra (cm^{-1}): in KBr. ^{1}H-NMR spectra: chemical shifts in ppm rel. to TMS, coupling constants *J* in Hz. Correct elemental analyses were obtained for all compounds.

1. *[3+2] Addition of 2,3-Dihydro-2-benzyl-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: 3310*s*, 3080*m*, 2840*w*, 1655*s*, 1618*w*, 1581*s*, 1519*s*. ^{1}H-NMR (80 MHz, $CDCl_3$): 7.94 (*s*, 1H); 7.45 (br., 1 H); 7.31 (*m*, 5 H); *AA'BB'*

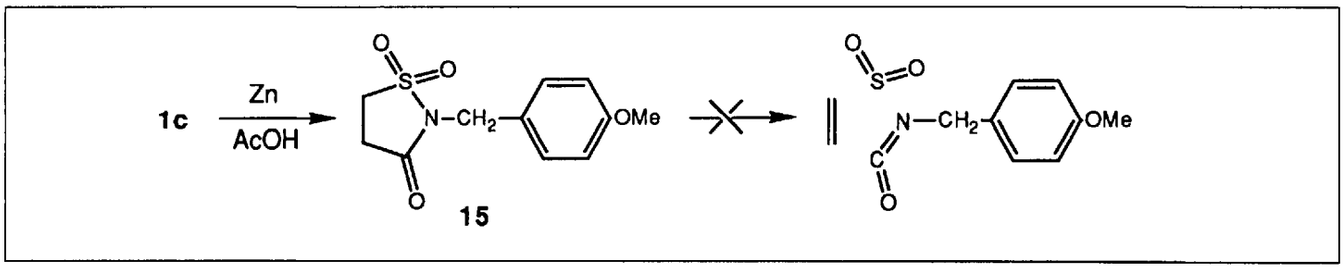
Scheme 2



Scheme 3



Scheme 4



systems: 7.23 (*m*, 2 H) and 6.90 (*m*, 2 H); 5.47 (*s*, 2 H); 4.63 (*d*, *J* = 6, 2 H); 3.80 (*s*, 3 H). MS: 322 (M^+), 201 ($[M-CH_3OC_6H_4CH_2]^+$), 121 ($CH_3OC_6H_4CH_2^+$). 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/Et_2O. M.p. 90–91.5° ([6]: 89–91°). IR: 3102*s*, 2842*w*, 1611*s*, 1581*m*, 1516*s*, 1484*m*. ^{1}H-NMR (80 MHz, $CDCl_3$): 7.75 (*d*, *J* = 1, 1 H); 7.53 (*d*, *J* = 1, 1 H); *AA'BB'* systems: 7.31 (*m*, 2 H) and 6.97 (*m*, 2 H); 5.54 (*s*, 2 H); 3.83 (*s*, 3 H). MS: 189 (M^+), 161 ($[M-N_2]^+$), 121 ($[CH_3OC_6H_4CH_2]^+$).

2. *Base-Induced SO_2 Elimination of the Nitrile Imine Adduct* **7a**; *N-(1,3-Diphenylpyrazole-5-carboxamido)glycine Ethyl Ester* (**8**). A soln. of *ethyl* (cis-*3,3a,4,6a-tetrahydro-4,6-diphenyl-2H-pyrazolo[3,4-d]isothiazol-2-yl)acetate 1,1-dioxide* (**7a**) [3] (1.00 g, 2.42 mmol) and Et_3N (0.73 g, 1.01 ml, 7.26 mmol) in CH_2Cl_2 (20 ml) was stored at ambient temp. for 14 h. The solvent was removed under vacuum, and the residue was partitioned between H_2O (100 ml) and AcOEt (twice 70 ml). The org. phases were washed with NaCl soln., combined, dried (Na_2SO_4), and evaporated, leaving 840 mg of a yellowish solid. After recrystallizing from CH_2Cl_2/hexane, yellowish crystals of anal. pure **8** (640 mg, 76%) were collected. M.p. 151–152°. IR: 3300*s*, 3120*w*, 1754*s*, 1653*s*. ^{1}H-NMR (90 MHz, (D_6)DMSO): 9.21 (*d*, *J* = 7, 1 H); 7.87 (*m*, 2 H); 7.44 (*m*, 9 H); 4.05 (*q*, 2 H); 3.97 (*d*, *J* = 7, 2 H); 1.21 (*t*, 3 H). MS: 349 (M^+), 247 ($[M-NHCH_2CO_2Et]^+$), 219 ([247–CO]$^+$). For further identification, **8** was hydrolyzed to *1,3-diphenylpyrazole-5-carboxylic acid* (**9**) [8] by refluxing in 6N HCl for 14 h. M.p. 228°.

3. *2,3-Dihydroisothiazol-3-one 1,1-Dioxide* (**1a**) was prepared according to the literature method [10] from the corresponding *N-tert*-butyl compound.

2,3-Dihydro-2-(4-methoxybenzyl)isothiazol-3-one 1,1-Dioxide (**1c**) was synthesized as described previously [3].

Ethyl (2,3-Dihydro-3-oxo-isothiazol-2-yl)propionate 1,1-Dioxide (**1b**). To a soln. of **1a** (2.0 g, 15.0 mmol) in dry DMF (30 ml; from 4 Å sieves) was added NaH (0.72 g of a 55% dispersion in oil, 30.0 mmol), and the suspension was stirred at r.t. for 1 h. Under Ar, freshly distilled ethyl 3-bromopropionate (8.1 g, 5.7 ml, 45 mmol) was added, and the mixture was stirred for 5 h at 80°. It was poured into ice-cold H_2O (300 ml), and neutralized with 1N aq. HCl. The aq. phase was extracted with CH_2Cl_2 (4 × 100 ml), the org. phase was dried (Na_2SO_4), and the volatile components were removed under high vacuum. The remaining yellow oil was chromatographed on silica gel (100 g; CH_2Cl_2/MeOH 49:1), affording a yellowish liquid of anal. pure **1b** (1.95 g, 55%). ^{1}H-NMR (60 MHz, $CDCl_3$): 7.50, 6.83 (*AB*, *J* = 7.5); 4.13 (*dd*, 2 H); 3.95 (*t*, 2 H); 2.77 (*t*, 2 H); 1.23 (*t*, 3 H).

2-Benzyl-2,3-dihydroisothiazol-3-one 1,1-Dioxide (**1d**) was prepared in 87% yield from 2-benzyl-2,3-dihydroisothiazol-3-one [11] by *m*-chloroperbenzoic acid oxidation [5]: white crystals from CH_2Cl_2/hexane. M.p. 90–91°. MS: 223 (M^+), 159 ($[M-SO_2]^+$).

4. *1,3-Dipolar Adducts of* **1** *with Diphenyl Nitrile Imine*. The adducts were prepared as described previously [3]: **7a**: pale yellow crystals from CH_2Cl_2/hexane in 50% yield from **1e** [5]. M.p. 132–132.5°; *ethyl* (cis-*3,3a,4,6a-tetrahydro-4,6-diphenyl-2H-pyrazolo[3,4-d]isothiazol-2-yl)propionate 1,1-dioxide* (**7b**): yellow crystals from CH_2Cl_2/hexane in 68% yield from **1b**. M.p. 128–129°. IR: 1738*s*, 1600*s*, 1560*w*, 1500*s*. MS: 363 ($[M-SO_2]^+$), 220 ($[M-SO_2-OCNCH_2CH_2CO_2Et]^+$); and *2-benzyl-4,6a-dihydro-4,6-diphenyl-2H-pyrazolo[3,4-d]isothiazol-3(3aH)-one 1,1-dioxide* (**7d**): yellowish crystals from $CHCl_3$ in 65% yield from **1d**. M.p. 152–153°. IR: 1741*s*, 1602*s*, 1501*s*. MS: 353 ($[M-SO_2]^+$), 220 ($[M-SO_2-BzlNCO]^+$), 133 ($BzlNCO^+$).

5. *Thermally Induced Fragmentation of the Diphenyl Nitrile Imine Adducts* **7**. A soln. of **7d** (417 mg, 1.0 mmol) and $PhCH_2OH$ (162 mg, 155 µl, 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 (20 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° ([9]: 86–87°). MS: 220 (M^+). The second fraction, a colorless oil, proved to be *benzyl N-benzylcarbamate* (**13**) (170 mg, 70%). Recrystallization from Et_2O/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 after chromatography on silica gel (50 g, CH_2Cl_2, followed by CH_2Cl_2/EtOAc 1:1) white crystals of **11** (190 mg, 86%). M.p. 82–84°, and *N-(methoxycarbonyl)-β-alanine ethyl ester* (**12**) as a colorless oil (130 mg, 74%). ^{1}H-NMR (60 MHz, $CDCl_3$): 5.6-5.1 (br., 1 H); 4.13 (*dd*, 2 H); 3.66 (*s*, 3 H); 3.44 (*dd*, 2 H); 2.51 (*t*, 2 H); 1.24 (*t*, 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, 109 µl, 1 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° ([13]: 171°). The filtrate, on evaporation, consisted of spectroscopically (^{1}H-NMR) pure **11** (white solid, as above).

6. *2,3-Dihydro-2-(4-methoxybenzyl)isothiazol-3-one 1,1-Dioxide* (**15**). A soln. of **1c** (3.0 g, 11.8 mmol) in glacial AcOH (72 ml) and H_2O (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 0–5°, 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 CH_2Cl_2, the combined org. phases were dried (Na_2SO_4) and evaporated. The white residue (2.91 g, 96%), after one recrystallization from CH_2Cl_2/hexane, afforded white crystals of anal. pure 15 (2.51 g, 83%). M.p. 125–126°. IR: 2842*m*, 1722*s*. ^{1}H-NMR (60 MHz, $CDCl_3$): *AA'BB'* systems: 7.35 (*m*, 2 H) and 6.83 (*m*, 2 H); 4.64 (*s*, 2 H); 3.79 (*s*, 3 H); *AA'BB'* systems: 3.55 (*m*, 2 H) and 3.04 (*m*, 2H). MS: 255 (M^+), 191 ($[M-SO_2]^+$).

7. *Attempted Fragmentation of* **15**. A soln. of **15** (128 mg, 0.5 mmol) and (optionally) $PhCH_2OH$ (81 mg, 78 µl, 0.75 mmol) in dry toluene (1.5 ml) was heated to reflux temp. for several days. TLC and ^{1}H-NMR monitoring reveals the presence of starting components only, with no indication of decomposition.

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[1] U.S. Patent 4,180,662; Eur. Pat. 1113, both to *F. Hoffmann-La Roche Ltd.*
[2] D. Binder, O. Hromatka, F. Geissler, K. Schmied, Ch. R. Noe, K. Burri, R. Pfister, K. Strub, P. Zeller, *J. Med. Chem.* **1987**, *30*, 678.
[3] K. F. Burri, *Helv. Chim. Acta* **1989**, *72*, 1416.
[4] K. F. Burri, *Helv. Chim. Acta* **1990**, *73*, 69.
[5] S. N. Lewis, G. A. Miller, M. Hausmann, E. C. Szamborski, *J. Heterocycl. Chem.* **1971**, *8*, 591.
[6] R. A. Wildonger, U.S. 4,227,004; 07 Oct 1980 to *ICI Americas, Inc.*, CA 94, P 84138c. N. Bruvele, E. Gudriniece, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* **1970**, 198 (*CA:* 73, 56037s).
[7] F. Moulin, *Helv. Chim. Acta* **1952**, *35*, 167.
[8] R. Huisgen, M. Seidel, G. Wallbillich, H. Knupfer, *Tetrahedron* **1962**, *17*, 3.
[9] H. L. Davies, *J. Am. Chem. Soc.* **1941**, *63*, 1677.
[10] M. Abou-Gharbia, J. A. Moyer, U. Patel, M. Webb, G. Schiehser, T. Andree, J. T. Haskins, *J. Med. Chem.* **1989**, *32*, 1024.
[11] S. N. Lewis, G. A. Miller, M. Hausmann, E. C. Szamborski, *J. Heterocycl. Chem.* **1971**, *8*, 571.
[12] D. Ben-Ishai, A. Berger, *J. Org. Chem.* **1952**, *17*, 1564.
[13] J. Chapman, F. J. Wilson, *J. Chem Soc.* **1931**, 507.