The Synthesis of *N*-Substituted Isothiazol-3(2*H*)-ones from *N*-Substituted 3-Benzoylpropionamides

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N-Substituted isothiazol-3(2*H*)-ones can be easily prepared from *N*-substituted 3-benzoylpropionamides in two experimentally simple steps, in satisfactory overall yields. Reaction of the amides with excess thionyl chloride results in the formation of *N*-substituted 5-benzoylisothiazol-3(2*H*)-ones, which are readily debenzoylated with alkali to the corresponding *N*-substituted isothiazol-3(2*H*)-ones. This method has now been successfully applied to the synthesis of isothiazolones *N*-substituted with a bulky alkyl group, such as the *tert*-butyl group, and with a phenyl group bearing either a strong electron-withdrawing substituent, such as the 3-nitrophenyl and 4-nitrophenyl group, or an electron-releasing substituent, such as the 4-methylphenyl and 4-methoxyphenyl group.

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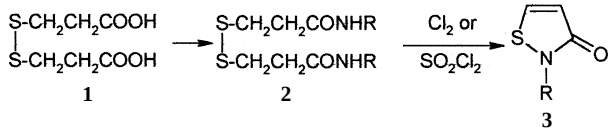
Introduction.

The synthesis of a series of *N*-substituted isothiazol-3(2*H*)-ones **3** was first reported in 1971 by Lewis *et al*. [1] starting with 3,3'-dithiodipropionic acid (**1**) (Scheme 1). This was achieved by the one-step chlorination-cyclization of the readily available 3,3'-dithiodipropionamides **2**.

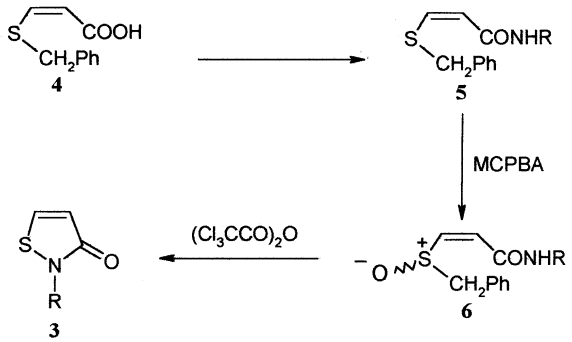
Scheme 1



However, Beeley *et al*. [2] have recently experienced difficulties in the cyclization of secondary amides **2** with sulfuryl chloride; the corresponding isothiazolones **3** were obtained only in low yields, contaminated by appreciable quantities of 5-chloroisothiazol-3(2*H*)-ones.

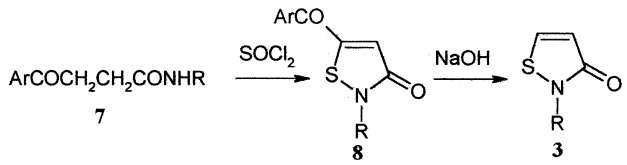
A novel general route to the synthesis of *N*-substituted isothiazolones **3** was then developed by Beeley *et al*. [2], *via* a ring closure reaction of *N*-substituted (*Z*)-3-(benzylsulfinyl) propenamides **6** (Scheme 2). The readily available acid **4** was activated with diphenylphosphinic chloride and reacted with a range of aliphatic and aromatic amines to yield the amides **5**, which were then oxidized to the corresponding sulfoxides **6** on reaction with 3-chloroperbenzoic acid in good overall yields. Cyclization of the sulfoxides **6** was accomplished using trichloroacetic anhydride in dichloromethane and the corresponding isothiazolones **3** were isolated in good yields, after chromatographic separation from benzyl trichloroacetate formed during the reaction. The method was successfully used for a wide range of *N*-substitution, including the bulky *N*-*tert*-butyl group (R=-CMe_3). However, the cyclization step, **6** → **3,** failed in the case of an aromatic amide **6** bearing a strong electron-withdrawing substituent, R=-$C_6H_4NO_2$-4.

Scheme 2



We have already described [3] the preparation of isothiazolones **3** (R=-CH_3, -CH_2Ph, -C_6H_5 and -C_6H_4Cl-4) from the appropriate 3-aroylpropionamides **7**, by the sequence of reactions shown in Scheme 3. A simple cyclization reaction of amides **7** with excess thionyl chloride has been shown to give the corresponding 5-aroylisothiazolones **8**, which are readily dearoylated with alkali to the corresponding *N*-substituted isothiazolones **3**. We now report an extension of this approach to the synthesis of isothiazolones **3** *N*-substituted with either a bulky alkyl group or a phenyl group bearing

Scheme 3



7a/8a Ar= -C_6H_5, R= -CMe_3
7b/8b Ar= -C_6H_5, R= -$C_6H_4NO_2$-3
7c/8c Ar= -C_6H_5, R= -$C_6H_4NO_2$-4
7d/8d Ar= -C_6H_5, R= -$C_6H_4CH_3$-4
7e/8e Ar= -C_6H_5, R= -$C_6H_4OCH_3$-4

3a R= -CMe_3
3b R= -$C_6H_4NO_2$-3
3c R= -$C_6H_4NO_2$-4
3d R= -$C_6H_4CH_3$-4
3e R= -$C_6H_4OCH_3$-4

both electron-withdrawing and electron-releasing substituents.

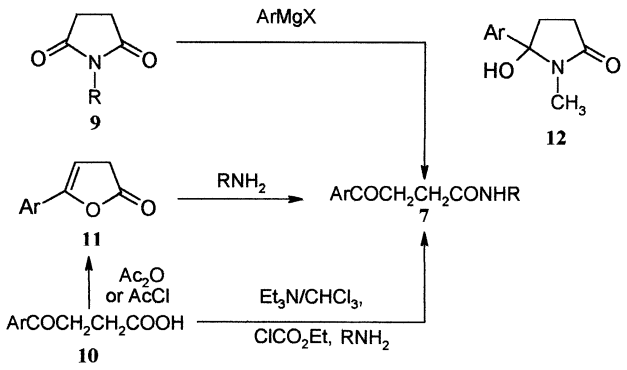
Results and Discussion.

The synthesis of isothiazolones **3**, as shown in Scheme 3, will finally depend on (a) the availability of the appropriate open chain amides **7**, (b) their transformation to the aroylisothiazolones **8**, and (c) the dearoylation of the latter to the isothiazolones **3**. The preparation of amides **7** and their transformations to isothiazolones **8** and **3** are discussed in the following sections, with respect to the synthesis of the *N*-*tert*-butyl, *N*-3-nitrophenyl, *N*-4-nitrophenyl, *N*-4-methylphenyl and *N*-4-methoxyphenyl isothiazolones **3** (compounds **3a**-**3e**, in Scheme 3).

A. *N*-Substituted 3-Aroylpropionamides **7**.

N-Substituted 3-aroylpropionamides **7**, mostly 3-benzoylpropionamides (**7**, Ar=-C_6H_5), have been prepared using the Grignard reaction of ArMgX with *N*-substituted succinimides **9** [4] (Scheme 4). On the other hand, a large number of *N*-substituted 3-aroylpropionamides **7** have been prepared starting with the corresponding 3-aroylpropionic acids **10**, where Ar is a phenyl group bearing both electron-withdrawing and electron-releasing substituents.

Scheme 4



Acids **10** are easily lactonized to the corresponding 5-arylfuran-2(3*H*)-ones **11** by heating with acetic anhydride or with acetyl chloride [5]. Primary amines RNH_2, where R is an alkyl, an aralkyl or a substituted aryl group, readily react with lactones **11** to yield *N*-substituted 3-aroylpropionamides **7** [4,7]. The only exception to this general method was noted for the reaction with *tert*-butylamine; in this case, the lactones **11** (Ar= -C_6H_5 and -$C_6H_4OCH_3$-4) were reported to isomerize to the corresponding 5-arylfuran-2(5*H*)-ones [4]. However, the isolation of the *N*-*tert*-butyl amide **7a** (Scheme 3), from the reaction of the lactone **11** (Ar=-C_6H_5) and *tert*-butylamine in refluxing acetonitrile, has been described [8].

An equally effective method for the preparation of *N*-substituted amides of the general formula **7** from 3-aroylpropionic acids **10**, using the mixed anhydride conditions (Scheme 4), has also been described [9]. Actually, under these conditions, we have prepared the *N*-*tert*-butyl amide **7a** in excellent yield, and the *N*-4-methylphenyl and *N*-4-methoxyphenyl amides (compounds **7d** and **7e**, respectively) in satisfactory yields as well (see Experimental).

The *N*-3-nitrophenyl and *N*-4-nitrophenyl 3-benzoylpropionamides (compounds **7b** and **7c**, respectively) were obtained in satisfactory yields from the reaction of the lactone **11** (Ar=-C_6H_5) with the corresponding nitroanilines (see Experimental). These two amides were, however, isolated as pale pink-colored solids, the color probably resulting from the formation of "Pechmann dyes" in alcoholic solutions of the lactones **11** [6].

γ-Keto amides of the general formula **7** are known to exhibit ring-chain tautomerism [10]. 3-Benzoylpropionamide and its *N*-substituted derivatives have been shown to exist as the open chain amides **7** (Ar=-C_6H_5; R=-H, -C_6H_5, -CH_2Ph and -C_6H_{11}), while the *N*-methyl derivative was assigned the cyclic hydroxy-pyrrolidinone structure **12** (Ar=-C_6H_5) shown in Scheme 4 [7]. The tautomeric structure of a series of *N*-substituted 3-aroylpropionamides has been studied by Chiron and Graff [4] and these compounds were also assigned the open chain amide structure **7**, with the exception of the *N*-methyl derivatives. The cyclic hydroxy-pyrrolidinone structure **12** was actually observed for Ar=-$C_6H_4NO_2$-3, -C_6H_4Br-4, -C_6H_5 and -$C_6H_4CH_3$-4. However, the open chain amide structure was observed when the aroyl group of the *N*-methyl derivative was substituted with an electron-releasing substituent (compound **7**, Ar=-$C_6H_4OCH_3$-4, R=-CH_3).

Pmr spectroscopy has been used in order to establish the open chain or ring structure of 3-aroylpropionamides [4,11]. The open chain amides **7** are characterized by the -CH_2CH_2- methylene proton signals, which appear as two distinct triplets, J= 6 Hz, at approximately δ 2.65 and 3.35 ppm. Moreover, the characteristic aromatic protons' signals of the benzoyl group, at δ 7.20-8.00 ppm, appear in the spectra of the open chain 3-benzoylpropionamides (**7**, Ar=-C_6H_5).

The tautomeric structure of the γ-keto amides is directly related to the present study, since aroylisothiazolones **8** are readily obtained from the corresponding open chain amides **7** (Scheme 3), as described in the following section.

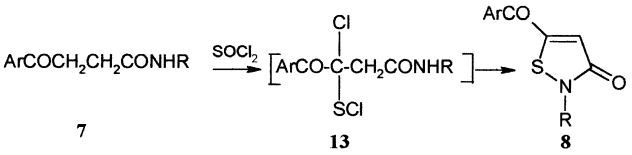
B. *N*-Substituted 5-Aroylisothiazol-3(2*H*)-ones **8**.

A simple cyclization reaction of 3-benzoylpropionamides **7** (Ar=-C_6H_5) has been shown to give the corresponding 5-benzoylisothiazolones **8** (Scheme 3). Thus, a mixture of the amide **7** (Ar=-C_6H_5, R=-CH_2Ph) and an excess of thionyl chloride was stirred at room temperature for 1 hour, when a dark solution was obtained, the excess thionyl chloride was then removed under vacuum and the

solid residue was crystallized from ethanol to give the corresponding isothiazolone **8** as a yellow product, in 70% yield [12]. Following this simple procedure, *N*-aryl 5-benzoylisothiazolones **8** (Ar=-C_6H_5 and R=-C_6H_4X, where X is either an electron-withdrawing or an electron-releasing substituent) could also be easily isolated in better than 50% yields. On the other hand, Beer and Wright [13] reported the synthesis of *N*-substituted 5-benzoylisothiazolones **8** (Ar=-C_6H_5; R=-C_6H_5, -CH_2Ph, -C_6H_4Cl-4 and -$C_6H_4NO_2$-4) using similar reaction conditions; the corresponding amides **7** were refluxed with thionyl chloride and compounds **8** were finally isolated, after chromatography, in about 40% yield.

The cyclization reaction of amides **7** with thionyl chloride has been suggested [12,13] to proceed through intermediate sulfenyl chlorides **13** (Scheme 5), resulting from

Scheme 5



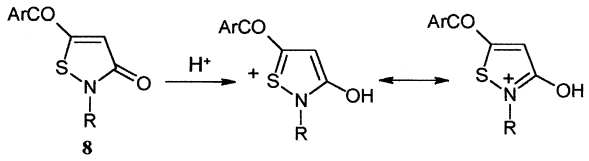
7 **13** **8**

the oxidation of the methylene group adjacent to the aroyl carbonyl. Formation of such an intermediate would only be possible for the open chain amides **7** and the *N*-methyl aroylisothiazolone **8** was actually obtained from the open chain (4-methoxybenzoyl)propionamide **7** (Ar=-$C_6H_4OCH_3$-4, R=-CH_3) [12]. Other 3-aroylpropionamides **7** have been found to be equally reactive; thus, the *N*-benzyl isothiazolones **8** (R=-CH_2Ph) with variously substituted aroyl groups, such as the 4-chlorobenzoyl [14], the mesitoyl [15] and the 3-nitrobenzoyl [3] derivatives, have been prepared in good yields. Moreover, the cyclization reaction with thionyl chloride has been used in the preparation of a series of compounds **8**, with a wide range of aroyl groups and *N*-substituents, which were investigated as active fungicides [9].

We have experienced some difficulty in preparing the *N*-*tert*-butyl 5-benzoylisothiazolone **8a** (Scheme 3). This compound could not be easily isolated from the reaction of the corresponding 3-benzoylpropionamide **7a** with an excess of thionyl chloride either at room temperature or at reflux. However, the *hydrochloride* of compound **8a** was isolated in very good yield when the amide **7a** was treated with an excess of thionyl chloride in ether at room temperature (see Experimental). Lewis *et al*. [1] have already noted the weak basic character of isothiazolones **3**; these compounds could be isolated from the reaction of amides **2** with chlorine or sulfuryl chloride (Scheme 1) as the corresponding hydrochlorides, which were completely dissociated in water. In agreement with this observation, the isothiazolone **8a** (as the base) was readily isolated when a chloroform solution of its hydrochloride was just washed with water (see Experimental).

The basic character of the isothiazolone **8a** could be observed in its pmr spectra. The signal of the vinyl proton of **8a** (as the base) appears as a singlet at δ 6.60 ppm in deuteriochloroform [16] and at δ 7.38 ppm in trifluoroacetic acid. The significant downfield shift of this signal in acid solution is consistent with the formation of the conjugate acid of **8a** (Scheme 6). Furthermore, the structure

Scheme 6



8

of the *hydrochloride* of **8a** is confirmed from its spectrum in deuteriochloroform; the vinyl proton appears again at a significantly low field, δ 7.63 ppm, while a strongly deshielded one-proton singlet at δ 15.13 ppm can be assigned to the protonated enol form. In agreement with the weak basic character of the isothiazolone **8a** and the ready hydrolysis of its hydrochloride, the spectrum of the latter in deuteriochloroform after addition of pyridine-d_5 or deuterium oxide is identical to the spectrum of the base **8a** in deuteriochloroform.

The preparation of the *N*-substituted 5-benzoylisothiazolones **8b-8e** has already been reported [12,13]. A reexamination of the cyclization reaction of the amides **7b** and **7c** revealed, however, that appropriate experimental conditions should be used in this case (see Experimental). The 3-nitrophenyl isothiazolone **8b** could be isolated in 67% yield from the reaction of the amide **7b** with an excess of thionyl chloride at room temperature. On the other hand, the cyclization reaction of the 4-nitrophenyl amide **7c** was only possible on refluxing with thionyl chloride and the corresponding isothiazolone **8c** was then isolated in 55% yield.

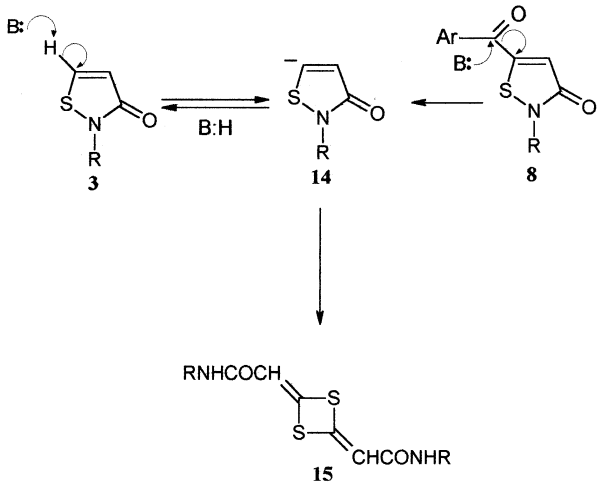
5-Aroylisothiazolones **8** are thus readily accessible from the corresponding 3-aroylpropionamides **7**. The cyclization reaction (Scheme 5) is effectively accomplished with a variety of open chain γ-keto amides **7**, for a wide range of β-aroyl groups and *N*-substituents. Compounds **8** are suitable intermediates in a general synthesis of the corresponding *N*-substituted isothiazolones **3**, as described in the following section.

C. *N*-Substituted Isothiazol-3(2*H*)-ones **3**.

N-Substituted isothiazolones **3** have been found [17] to dimerize readily by bases to 2,4-bismethylene-1,3-dithietanes **15** (Scheme 7). The dimerization was shown to

proceed through attack of the initially formed 5-anion **14** on the S-N bond of a second isothiazolone molecule. Dithietanes of the general formula **15** were also obtained

Scheme 7



[12,15] from *N*-substituted 5-aroylisothiazolones **8**; in this case, the 5-anion **14** would result from a nucleophilic displacement on the 5-aroyl group of compound **8**. When, however, a solution of an aroylisothiazolone **8** in benzene was stirred at room temperature, usually for 24 to 48 hours, with a 10% aqueous sodium hydroxide solution, the corresponding isothiazolone **3** was actually isolated almost quantitatively from the benzene layer [3]. In the two-phase aqueous-organic system, the anion **14** resulting from the displacement reaction is protonated and the isothiazolone **3** is finally transferred into the organic phase prior to its transformation to the dithietane derivative **15**. The overall transformation of aroylisothiazolones **8** to the corresponding isothiazolones **3** was also found to proceed easily and almost quantitatively when a solution of compound **8** in benzene was stirred for just five minutes at room temperature in the presence of solid sodium hydroxide.

The dearoylation reaction, **8** → **3**, would be expected to depend only on the reactivity of the aroyl group. Actually, the isothiazolones **3** (R=-CH_2Ph, -C_6H_5 and -C_6H_4Cl-4) were obtained [3] from the corresponding 5-benzoylisothiazolones (**8**, Ar=-C_6H_5). The *N*-methyl isothiazolone (**3**, R=-CH_3) was prepared from the corresponding (4-methoxybenzoyl)isothiazolone (**8**, Ar=-$C_6H_4OCH_3$-4), while the reaction of a (3-nitrobenzoyl)isothiazolone (**8**, Ar=-$C_6H_4NO_2$-3, R=-CH_2Ph) was found to proceed faster. On the other hand, a mesitoylisothiazolone (**8**, Ar=-$C_6H_2Me_3$-2,4,6, R=-CH_2Ph) was recovered unchanged from a similar treatment, since the sterically hindered carbonyl of the mesitoyl group is not accessible to nucleophilic attack.

Isothiazolones **3a**-**3e** were also readily obtained from the corresponding benzoylisothiazolones, **8a**-**8e** (Scheme 3). Compounds **8a**-**8c** are hardly soluble in benzene, but it was found that the debenzoylation reaction could be successfully accomplished when a solution of the benzoylisothiazolone in dichloromethane was treated either with a 10% aqueous sodium hydroxide solution or with solid sodium hydroxide (see Experimental). Thus, the *hydrochloride* of **8a** in dichloromethane was stirred at room temperature for 40 minutes with solid sodium hydroxide and the *N-tert*-butyl isothiazolone **3a** was isolated in 80% yield. The synthesis of the isothiazolone **3a** has thus been accomplished by two experimentally simple reactions (Scheme 3), in 62% overall yield from the readily available benzoylpropionamide **7a**. Likewise, compounds **8b**-**8e** in dichloromethane were stirred at room temperature for 5 days with a 10% aqueous sodium hydroxide solution and the corresponding *N*-substituted isothiazolones **3b**-**3e** were isolated in excellent yields, about 80%.

Conclusion.

N-Substituted isothiazol-3(2*H*)-ones **3** can be prepared from *N*-substituted 3-aroylpropionamides **7**, *via* the corresponding 5-aroylisothiazol-3(2*H*)-ones **8** (Scheme 3), in satisfactory overall yields. In particular, *N*-substituted 3-benzoylpropionamides, readily available from 3-benzoylpropionic acid, are suitable starting materials in a general synthesis of isothiazolones **3** *N*-substituted with various alkyl, aralkyl and aryl groups.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ir spectra were obtained with a Perkin Elmer 267 spectrometer (as nujol mulls) or with a Nicolet Magna 560 spectrometer (in potassium bromide pellets) and were calibrated against the polystyrene 1601 cm^{-1} band; absorption bands, in reciprocal centimeters, are characterized as of strong (s), medium (m) or weak (w) intensity and as broad (br) or sharp (sh). The pmr spectra were recorded on a Varian EM-360 60 MHz spectrometer; chemical shifts are given in ppm (δ) downfield from TMS (internal standard) and are accurate to ±0.02 ppm. Elemental analyses were obtained from the microanalytical laboratory of CNRS (France) and from the Liverpool University Chemistry Department (England).

N-tert-Butyl-3-benzoylpropionamide (**7a**).

To a solution of 3-benzoylpropionic acid (5 g, 28 mmoles) and triethylamine (4 ml) in dry chloroform (50 ml), cooled at 0°, ethyl chloroformate (2.7 ml, 28.3 mmoles) was added dropwise. After stirring for 20 minutes, a solution of *tert*-butylamine (2.5 g, 34.2 mmoles) in chloroform (25 ml) was added and the mixture was stirred at room temperature for 20 hours. The mixture was then washed successively with 10% hydrochloric acid and 5% aqueous sodium hydrogen carbonate, and the organic layer was separated, dried (magnesium sulfate) and concentrated under

vacuum. The white solid residue (5.5 g, 84%), mp 110-113°, proved to be almost pure amide **7a** (pmr spectrum). Recrystallization from ethyl acetate-petroleum ether yielded a crystalline solid (72% yield), mp 116-117°, lit [8] mp 115-116° (after recrystallization from benzene-hexane); ir (nujol): 3425 (br, m), 1678 (sh, s), 1642 (sh, s) and 1555 (sh, s); pmr (deuteriochloroform): 1.33 (s, 9H, -CMe_3), 2.50 and 3.28 (two t, J=6 Hz, 4H, -CH_2CH_2-), 5.61 (br s, 1H, -NH-) and 7.26-8.00 (m, 5H, aromatic protons). The ir and pmr data agree with those already reported [8].

N-3-Nitrophenyl-3-benzoylpropionamide (**7b**).

A mixture of 8.99 g (56.2 mmoles) of 5-phenylfuran-2(3*H*)-one, obtained from the reaction of 3-benzoylpropionic acid with acetyl chloride [6], and 7.9 g (57.2 mmoles) of 3-nitroaniline in 50 ml of ethanol was refluxed for 15 hours. The insoluble material was then filtered and washed successively with ethanol and ether. Compound **7b** was thus obtained as a slightly pink-colored solid (12.1 g, 72%), mp 154-156° dec., lit [18] mp 157° (after recrystalization from methanol). A recrystallization from dimethyl sulfoxide gave an analytically pure sample, mp 156-157°dec.; ir (nujol): sharp bands at 3345 (m), 1703 (m), 1666 (s), 1592 (m) and 1526 (s); pmr (trifluoroacetic acid): 3.15 and 3.75 (two t, J= 6 Hz, 4H, -CH_2CH_2-), 7.28-8.62 (m, 9H, aromatic protons) and 9.30 (br s, 1H, -NH-).

Anal. Calcd. For $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.57; H, 4.51; N, 9.53.

N-4-Nitrophenyl-3-benzoylpropionamide (**7c**).

A mixture of 16.02 g (0.1 mole) of 5-phenylfuran-2(3*H*)-one, obtained from the reaction of 3-benzoylpropionic acid with acetyl chloride [6], and 13.81 g (0.1 mole) of 4-nitroaniline was heated at a steam bath for 6 hours. The solid mixture was then crystallized from dimethyl sulfoxide-ethanol to give compound **7c** as a slightly pink-colored solid (15 g, 50%), mp 216-219° dec., lit [18] mp 198° (after recrystalization from benzene-petroleum ether). A recrystallization from dimethyl sulfoxide gave an analytically pure sample, mp 219-220° dec.; ir (nujol): sharp bands at 3314 (m), 1709 (s), 1667 (s), 1611 (m), 1593 (m), 1559 (s) and 1505 (s); pmr (DMSO-d_6): 2.80 and 3.38 (two t, J=6 Hz, 4H, -CH_2CH_2-), 7.33-8.30 (m, 9H, aromatic protons) and 10.6 (br s, 1H, -NH-).

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.32; H, 4.75; N, 9.42.

N-4-Methylphenyl-3-benzoylpropionamide (**7d**).

Following the procedure described for the preparation of compound **7a**, 3-benzoylpropionic acid (10 g, 56 mmoles) was treated with 4-aminotoluene. The solid residue obtained after the workup and concentration of the organic layer was recrystallized from ethanol to give compound **7d** as a crystalline solid (11.1 g, 74%), mp 134-136°, lit [18] mp 136° (after recrystallization from methanol); ir (nujol): sharp bands at 3268 (s), 1678 (s), 1656 (s), 1603 (s) and 1538 (s); pmr (deuteriochloroform): 2.25 (s, 3H, -CH_3), 3.06 and 3.33 (two t, J=6 Hz, 4H, -CH_2CH_2-), 6.73-8.00 (m, 9H, aromatic protons) and 8.13 (br s, 1H, -NH-).

N-4-Methoxylphenyl-3-benzoylpropionamide (**7e**).

Following the procedure described for the preparation of compound **7a**, 3-benzoylpropionic acid (10 g, 56 mmoles) was treated with 4-methoxyaniline. The solid residue obtained after the workup and concentration of the organic layer was recrystallized from ethanol to give compound **7e** as a crystalline solid (11 g, 69%), mp 121-123°, lit [19] mp 124°; ir (nujol): sharp bands at 3268 (s), 1681 (s), 1658 (s), 1597 (w) and 1534 (s); pmr (deuteriochloroform): 2.82 and 3.44 (two t, J=6 Hz, 4H, -CH_2CH_2-), 3.81 (s, 3H, -OCH_3), 7.66-8.25 (m, 9H, aromatic protons) and 8.40 (br s, 1H, -NH-).

5-Benzoyl-2-*tert*-butylisothiazol-3(2*H*)-one (**8a**).

Thionyl chloride (10 ml) was added to a suspension of the keto amide **7a** (3 g) in ether (30 ml) and the mixture was stirred at room temperature. The initially insoluble material gradually dissolved, while a new precipitate appeared after some time. After 20 hours, the reaction mixture was concentrated under vacuum and the solid residue was triturated with ether, filtered and washed again with ether to give the *hydrochloride* of isothiazolone **8a** as an almost colorless solid (3 g, 78%), mp 129-131°; pmr (deuteriochloroform): 1.80 (s, 9H, -CMe_3), 7.43-8.00 (m, 6H, aromatic protons and vinylic proton –the vinylic proton appears as a singlet at δ 7.63 ppm) and 15.13 (s, 1H, acidic proton); after addition of pyridine-d_5 or deuterium oxide: 1.70 (s, 9H, -CMe_3), 6.60 (s, 1H, vinylic proton) and 7.40-8.00 (m, 5H, aromatic protons).

Anal. Calcd. for $C_{14}H_{16}ClNO_2S$: C, 56.46; H, 5.41; N, 4.70. Found: C, 56.74; H, 5.42; N, 4.66.

The hydrochloride of **8a** (0.1 g) was dissolved in chloroform (5 ml) and the solution was washed twice with 10 ml of water; the organic layer was dried (magnesium sulfate) and concentrated under vacuum to give the isothiazolone **8a** (0.08 g, 91%) as a yellowish solid, mp 83-85°; this compound has been reported to be an oil [9]. A recrystallization from ether-petroleum ether gave an analytical sample as a yellow crystalline solid, mp 85-86°; ir (nujol): sharp bands at 1661 (s), 1634 (s), 1595 (w) and 1548 (w); pmr (deuteriochloroform): 1.71 (s, 9H, -CMe_3), 6.60 (s, 1H, vinylic proton) and 7.36-8.03 (m, 5H, aromatic protons); (trifluoroacetic acid): 1.92 (s, 9H, -CMe_3), 7.38 (s, 1H, vinylic proton) and 7.48-8.06 (m, 5H, aromatic protons).

Anal. Calcd. for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.78; N, 5.36. Found: C, 64.37; H, 5.78; N, 5.33.

5-Benzoyl-2-(3-nitrophenyl) isothiazol-3(2*H*)-one (**8b**).

A mixture of the keto amide **7b** (2.7 g) and thionyl chloride (40 ml) was stirred at room temperature for 24 hours. The excess thionyl chloride was then removed under vacuum and the residue was triturated with ethanol, filtered and washed with ethanol and ether to give compound **8b** (2 g, 67%) as a yellow solid. A recrystallization from dimethyl sulfoxide gave an analytical sample, mp 220-222° dec., lit [12] mp 220-222°; ir (nujol): sharp bands at 1670 (s), 1637 (m) and 1527 (s); pmr (deuteriochloroform/trifluoroacetic acid): 7.29 (s, 1H, vinylic proton) and 7.65-8.77 (m, 9H, aromatic protons).

Anal. Calcd. for $C_{16}H_{10}N_2O_4S$: C, 58.89; H, 3.09; N, 8.58; S, 9.83. Found: C, 58.92; H, 3.13; N, 8.55; S, 9.78.

5-Benzoyl-2-(4-nitrophenyl) isothiazol-3(2*H*)-one (**8c**).

A mixture of the keto amide **7c** (1 g) and thionyl chloride (20 ml) was refluxed for 4 hours. The excess thionyl chloride was then removed under vacuum and the yellow-greenish residue was briefly heated with 20 ml of ethanol. The insoluble material was filtered and washed with ether to give compound **8c** (0.6 g, 55%) as a yellow solid. A recrystallization from dimethyl sulfoxide gave an analytical sample, mp 224° dec, lit [13] mp 240-242°; ir

(nujol): sharp bands at 1667 (s), 1629 (m), 1595 (m) and 1510 (m); pmr (trifluoroacetic acid): 7.26 (s, 1H, vinylic proton) and 7.56-8.63 (m, 9H, aromatic protons).

Anal. Calcd. for $C_{16}H_{10}N_2O_4S$: C, 58.89; H, 3.09; N, 8.58. Found: C, 58.70; H, 3.08; N, 8.48.

5-Benzoyl-2-(4-methylphenyl) isothiazol-3(2*H*)-one (**8d**).

A solution of the keto amide **7d** (7 g) in thionyl chloride (45 ml) was stirred at room temperature for 45 minutes. The excess thionyl chloride was then removed under vacuum and the residue was recrystallized from ethanol to give compound **8d** (4.15 g, 53%) as a yellow crystalline solid, mp 153-156°, lit [12] mp 154-156°; ir (nujol): sharp bands at 1650 (s) and 1631 (w); pmr (deuteriochloroform): 2.47 (s, 3H, -CH_3), 6.96 (s, 1H, vinylic proton) and 7.25-8.25 (m, 9H, aromatic protons).

5-Benzoyl-2-(4-methoxylphenyl) isothiazol-3(2*H*)-one (**8e**).

Following the procedure described for the preparation of compound **8d**, compound **8e** was obtained from the keto amide **7e** (6g) as a yellow crystalline solid (3.56 g, 54%, after recrystallization from ethanol), mp 143-145°, lit [12] mp 145-146°; ir (nujol): sharp bands at 1664 (s) and 1645 (m); pmr (deuteriochloroform): 3.92 (s, 3H, -OCH_3), 6.95 (s, 1H, vinylic proton) and 6.98-8.28 (m, 9H, aromatic protons).

2-*tert*-Butylisothiazol-3(2*H*)-one (**3a**).

To a solution of the hydrochloride of compound **8a** (2 g, 6.7 mmoles) in dichloromethane (40 ml), powdered solid sodium hydroxide (0.8 g) was added. The mixture was stirred vigorously at room temperature for 40 minutes, when a fading of the initially yellow color of the organic solution was observed. The dichloromethane layer was then filtered and concentrated under vacuum to give a colorless solid residue. This material, 0.84 g (80%), proved to be pure compound **3a**, as evidenced from its pmr spectrum in deuteriochloroform [1,2]. Recrystallization from ether-petroleum ether yielded 0.7 g (66%) of compound **3a**, mp 84-85°, lit mp 85-86° [1] and 83.5° [2]; pmr (deuteriochloroform): 1.62 (s, 9H, -CMe_3), 6.08 and 7.88 (two d, J=6.5 Hz, 2H, vinylic protons); (trifluoroacetic acid): 1.87 (s, 9H, -CMe_3), 6.93 and 8.80 (two d, J=6.5 Hz, 2H, vinylic protons).

2-(3-Nitrophenyl)isothiazol-3(2*H*)-one (**3b**).

To a solution of the benzoylisothiazolone **8b** (0.5 g, 1.53 mmoles) in dichloromethane (170 ml) a 10% aqueous sodium hydroxide solution (70 ml) was added and the mixture was stirred vigorously at room temperature for five days. The organic layer was then separated, washed successively with 10% sulfuric acid and water, dried (magnesium sulfate) and concentrated under vacuum to give compound **3b** as a yellow solid (0.29 g, 85%), mp 156-157° dec. A recrystallization from toluene gave an analytical sample, mp 156-157° dec; ir (nujol): sharp bands at 1653 (s), 1603 (m), 1570 (w) and 1508 (s); pmr (deuteriochloroform/DMSO-d_6): 6.26 (d, J=6.5 Hz, 1H, vinylic proton), 7.75-8.65 (m, 5H, aromatic protons and vinylic proton –the vinylic proton appears as a doublet, J=6.5 Hz, at δ 8.55ppm).

Anal. Calcd. for $C_9H_6N_2O_3S$: C, 48.64; H, 2.72; N, 12.60. Found: C, 48.83; H, 2.72; N, 12.63.

2-(4-Nitrophenyl)isothiazol-3(2*H*)-one (**3c**).

Following the procedure described for the preparation of compound **3b**, the benzoylisothiazolone **8c** (1.2 g, 3.68 mmoles) in dichloromethane was vigorously stirred at room temperature for two days with aqueous sodium hydroxide solution and compound **3c** was obtained as a yellow solid (0.72 g, 88%), mp 208-210°. A recrystallization from ethanol gave an analytical sample, mp 208-210°, lit [1] mp 188-190°; ir (nujol): 1624 (br, s), 1583 (sh, m) and 1506 (sh, m); pmr (deuteriochloroform/DMSO-d_6): 6.23 (d, J=6 Hz, 1H, vinylic proton), 7.88 and 8.25 (two d, J=9 Hz, 4H, aromatic protons), and 8.43 (d, J=6 Hz, 1H, vinylic proton).

Anal. Calcd. for $C_9H_6N_2O_3S$: C, 48.64; H, 2.72; N, 12.60. Found: C, 48.73; H, 2.68; N, 12.65.

2-(4-Methylphenyl)isothiazol-3(2*H*)-one (**3d**).

To a solution of the benzoylisothiazolone **8d** (3 g, 10.17 mmoles) in dichloromethane (60 ml) a 10% aqueous sodium hydroxide solution (30 ml) was added and the mixture was stirred vigorously at room temperature for five days. The organic layer was then separated, washed successively with 10% sulfuric acid (15 ml) and water (10 ml), dried (magnesium sulfate) and concentrated under vacuum. The solid residue was recrystallized from ethanol to give compound **3d** as a yellowish crystalline solid (1.35 g, 69%), mp 89-91°, lit. [20] mp 91-93°. A second recrystallization from ethanol gave an analytical sample, mp 92.5-93°; ir (potassium bromide): sharp bands at 3115 (s), 3086 (s), 1609 (s) and 1512 (s); pmr (deuteriochloroform): 2.35 (s, 3H, -CH_3), 6.20 (d, J=7 Hz, 1H, vinylic proton), 7.11 and 7.40 (two d, J=9 Hz, 4H, aromatic protons), and 8.03 (d, J=7 Hz, 1H, vinylic proton).

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32; S, 16.77. Found: C, 62.83; H, 4.58; N, 7.34; S 17.03.

2-(4-Methoxyphenyl) isothiazol-3(2*H*)-one (**3e**).

Following the procedure described for the preparation of compound **3d**, compound **3e** was obtained from the benzoylisothiazolone **8e** (3 g, 9.64 mmoles) as a yellowish crystalline solid (1.6 g, 80%, after recrystallization from ethanol), mp 115-116.5°, lit [2] mp 92-93° [21]. This material proved to be almost pure compound **3e**, as evidenced from its pmr spectrum. A second recrystallization from ethanol gave an analytical sample, mp 124.5-127°; ir (potassium bromide): sharp bands at 3151 (s), 3104 (m), 1646 (s), 1604 (m) and 1508 (s); pmr (deuteriochloroform): 3.78 (s, 3H, -OCH_3), 6.16 (d, J=7 Hz, 1H, vinylic proton), 6.86 and 7.30 (two d, J=9 Hz, 4H, aromatic protons), and 8.05 (d, J=7 Hz, 1H, vinylic proton).

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 57.95; H, 4.38; N, 6.76; S, 15.47. Found: C, 57.86; H, 4.28; N, 6.36; S, 15.09.

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