Novel 2-Amino-4-Aryl-Substituted and 2-Amino-4,5-Disubstituted-Thiazoles

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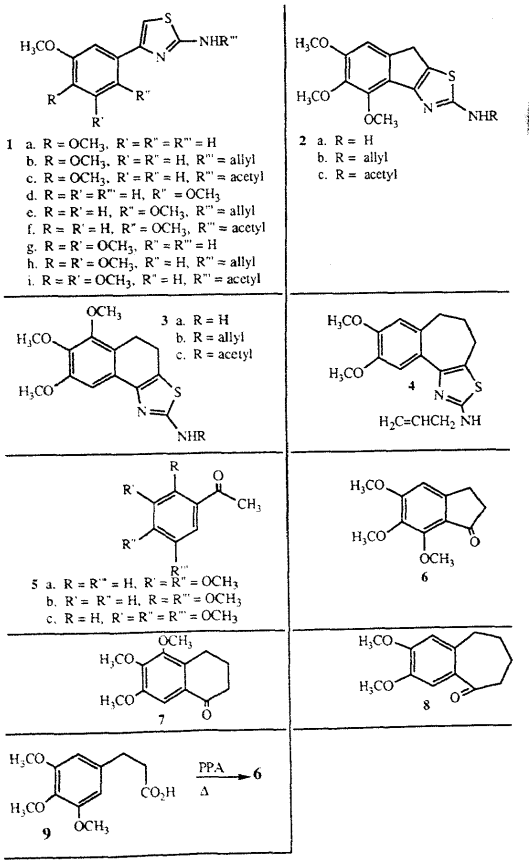
A series of new 2-amino- or 2-allylamino-4-aryl-substituted thiazoles have been prepared from the corresponding α-brominated acetophenones via reaction of the latter with thiourea or allylthiourea in $HCCl_3$:C_2H_5OH(abs) in a one-pot sequence. The brominated ketones were, in turn, obtained by direct bromination of the parent ketones. Purification of the thiazoles was most easily achieved by sublimation. A few *N*-acetyl derivatives of the 2-aminothiazoles were prepared by reaction with acetic anhydride in glacial acetic acid. One suberone derivative, namely 2-allylamino-8,9-dimethoxysubero[1,2-*dl*]thiazole, was synthesized, but the starting material 7,8-dimethoxysuberone was not known. Preparation of the latter ketone was initiated by conversion of 3,4-dimethoxyacetophenone with sodium hydride in diethyl carbonate to the corresponding *β*-keto ester. The respective enolate was generated from this keto ester, and upon treatment with ethyl 3-bromopropionate, led to, after neutralization, 5-(3',4'-dimethoxyphenyl)-5-oxopentanoic acid. Reduction of the carbonyl group in this keto acid with hydrogen over Pd/C followed to give 5-(3,4-dimethoxyphenyl)pentanoic acid which was cyclized with 115% polyphosphoric acid near 75 °C to give 7,8-dimethoxysuberone.

INTRODUCTION

The chemistry of 2-aminothiazoles has been reviewed (1), and the importance of such heterocycles and derivatives in medicinal chemistry is recognized (2). In view of the wide range of biological activity present in substituted aminothiazoles (1,2), it was surprising to discover from a literature search that highly substituted 2-amino-4-arylthiazoles and related fused systems, such as indenothiazoles and naphthenothiazoles were rare.

GENERAL APPROACH

In connection with specific studies focused on the influence of methoxy groups, strategically located with respect to nitrogen atoms, on certain biological activity when situated within a system (3), we have synthesized a series of thiazoles **1-4**. Key precursor ketones **5** are all currently available and **7** is known (4), but **6** and **8** had to be prepared.



RESULTS AND DISCUSSION

3-(3',4',5'-Trimethoxyphenyl)propanoic acid (**9**), from a commercial source, was cyclized with 115% polyphosphoric acid (PPA) to obtain ketone **6**. Similarly, **10** was converted to **8**. However, **10** was unknown; it was made from **5a**. Standard techniques were used in this series of transformations for **5a-->11-->12-->10-->8 as** illustrated on page 31.

The ketones **5-8** were dissolved in $HCCl_3$/EtOH (1:1, v:v), with a trace of HOAc added, and brominated with Br_2 at

TABLE 1. Physical properties of the thiazoles.

Cmpd	Yield[a] %	Formula	mp °C	Elemental Analysis (or M^+ Matching) Calculated	Found
1a	42	$C_{11}H_{12}N_2O_2S$	193–94	55.93[c];5.08[b]	55.66[c]; 5.06[b]
1b	87	$C_{14}H_{16}N_2O_2S$	98–99	60.87[c]; 5.79[b]	60.72[c]; 5.87[b]
1c	56	$C_{13}H_{14}N_2O_3S$	97–98	278.0725	278.0723
1d	40	$C_{11}H_{12}N_2O_2S$	123–24	236.0621	236.0630
1e	47	$C_{14}H_{14}N_2O_2SCl$[d]	138–39	309.0458	309.0461
1f	70	$C_{13}H_{14}N_2O_3S$	196–97	278.0724	278.0700
1g	34	$C_{12}H_{14}N_2O_3S$	169–71	266.0724	266.0720
1h	24	$C_{15}H_{19}N_2O_3S$	70–71	306.1037	306.1031
1i	70	$C_{14}H_{16}N_2O_4S$	187–88	308.0826	308.0817
2a	47	$C_{13}H_{14}N_2O_3S$	279–80	278.0724	278.0728
2b	40	$C_{14}H_{16}N_2O_2S$	103–06	318.1033	318.1025
2c	68	$C_{15}H_{16}N_2O_4S$	275–76	320.0831	320.0840
3a	33	$C_{14}H_{16}N_2O_3S$	166–68	292.0881	292.0875
3b	17	$C_{17}H_{20}N_2O_3S$	136–37	332.1194	332.1187
3c	57	$C_{16}H_{18}N_2O_4S$	221–22	334.0987	334.0993
4	20	$C_{17}H_{20}N_2O_2S$	169–70	316.1245	316.1248

[a] Based upon starting ketone. [b] Hydrogen. [c] Carbon. [d] Isolated as the hydrochloride.

TABLE 2. Proton spectral data for the thiazoles (δ values from TMS)[a]

Cmpd	H_3C	C=CH	CH_2–CH=CH_2[e]	C(O)CH_3	Ar–H
1a	3.90/3.94	6.58			6.85
1b	3.91	6.54	3.91 5.94 5.18		6.94
1c	3.91	7.03		1.86	6.90/7.36
1d	3.80/3.86	6.81			7.21/7.64
1e	3.80/3.85		4.14 5.94 5.20/5.48		7.06/7.34
1f	3.74/3.88	6.86		1.89	7.58
1g	3.83/3.86	6.64			7.01
1h	3.86		3.86 5.72 5.06/5.25		
1i	3.80/3.92	7.25		1.74	6.98
2a[b]	3.88/3.92/4.04				6.86
2b[b]	3.82/3.86/4.02		3.96 5.84 5.13/5.36		6.80
2c[b]	3.90/3.94			2.16	6.91
3a[c]	3.77/3.86				6.80
3b[c]	3.80/3.86/3.92		3.96 5.94 5.14		7.25
3c[c]	3.90/3.96			2.01	7.28
4[d]	3.88/4.06		3.92 5.82 5.38/5.50		7.38

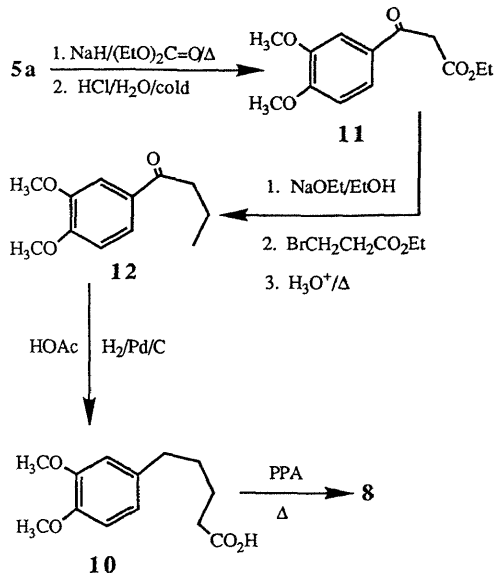
[a] All spectra taken in $DCCl_3$ unless otherwise specified.
[b] The CH_2 in the ring occurs at δ 3.62 (**2a**), 3.66 (**2b**), and 3.78 (**2c**). In **2c**, one methyl signal overlapped.
[c] The proton signals for the (CH_2-CH_2) group of the ring occur at δ 2.79 (**3a**), 2.82 (**3b**), and 2.98 (**3c**) in $(D_3C)_2SO$, $DCCl_3$, and $(D_3C)_2SO$, respectively. In **3a** and **3c**, two methyl signals overlapped.
[d] Proton signals for the ($CH_2CH_2CH_2$) group of the ring occur at δ 2.10 (2 H) and 2.80 (4 H).
[e] Chemical shifts are in order, left to right.

room temperature overnight. The crude bromoketones in $HCCl_3$/EtOH(abs) (1:1, v:v) were treated directly with two equivalents (in regard to the starting ketone) of thiourea or allylthiourea and the resulting solution was boiled for 24 h. Reaction mixtures were very complex and defied separation by crystallization or chromatographic technology. The thiazoles and *N*-allyl-substituted thiazoles could be purified only by careful sublimation of the solid residue obtained after evaporation of solvent. Formation of the corresponding *N*-acetylated thiazoles **1c, 1f, 1i, 2c,** and **3c** was achieved by treating **1a, 1d, 1g, 2a**, and **3a** in HOAc (room temp) with acetic anhydride. All such derivatives were also sublimed. Physical properties of the triazoles are given in Table 1 and proton NMR spectral data in Table 2. The IR data are not especially definitive but are available upon request.

The yields of thiazoles and aminothiazoles in this study are reminiscent of those found in the literature (1). The method reported herein is the most facile available. Unfortunately, yields vary considerably,

probably because of similarity of solubility characteristics of products as well as byproducts, making purification difficult. Proton NMR analysis is the most distinguishing technique for identifying such compounds and all spectra are relatively simple, as can be seen from Table 2. The proton NMR signal for the vinylic proton on the thiazole ring in members of **1** ranges from δ 6.54 to 7.25 in our series and is diagnostic. The remaining signals are unremarkable and are clearly defined in Table 2 and footnotes thereto.

In summary, we have prepared a series of new and novel thiazoles starting from readily available ketones. Direct bromination of these ketones with bromine/acetic acid yielded the corresponding bromides (detectable by IR and ^{1}H NMR analyses of the mixtures), but such compounds proved extremely difficult to purify by conventional methods. Immediate treatment of the bromide with thiourea or allylthiourea gave the appropriate thiazole. Some aminothiazoles were converted to *N*-acetyl derivatives with acetic anhydride. The overall procedure proved successful in terms of using one pot to obtain the thiazoles or allylthiazoles.



EXPERIMENTAL PROCEDURES

General Information. The IR spectra were recorded on a Beckman IR-5A instrument. The proton NMR spectra were recorded on a Varian XL-100 (15) with the frequency at 100.00 MHz. Mass spectral data were collected for peak matching on an LKB-9000 unit. Elemental analyses were obtained from Galbraith Labs, Knoxville, TN.

General Method for the Preparation of the Thiazoles. The following procedure for **1b** is illustrative of the general methodology employed to obtain the amino- and allylaminothiazoles. Ketone **5a** (1.5 g, 8.3 mmol) was dissolved in $HCCl_3$:EtOH(abs) (25 ml:25 ml), and 2 drops of glacial acetic acid were added. Bromine (1.53 g, 10 mmol) in 10 ml of $HCC1_3$ was added dropwise over a period of 2 h after which time the solution was light red-brown. This solution was stirred under N_2 for 15 h, and then the solution was washed (25 ml, sat. NaCl). Separation and evaporation of the dried organic layer gave a pale yellow-brown solid. This crude bromide was dissolved in $HCCl_3$:EtOH(abs) (25 ml:25 ml) along with allylthiourea (2 g, 0.017 mol). The resulting solution was boiled under N_2 for 24 h and then cooled and evaporated to a solid. Dissolution of the solid was effected (5 ml, 95% EtOH:H_2O, 1:20). Adjustment of the pH of this solution to 10 was done with conc. NH_4OH, and then the solution was cooled (5 °C) overnight. The yellow solid obtained was filtered out, dried, and purified by sublimation (150 °C/0.13 mbar) to give **1b** (2.0 g, 87%), mp 98-99 °C. All other thiazoles were prepared in a similar manner.

General Procedure for the Preparation of the N-Acetyl Derivatives. The procedure for obtaining *N*-acetyl derivative **1c** is illustrative of the general approach. Aminothiazole **1a** (1g, 3.6 mmol) was added to glacial acetic acid (10 ml) and warmed to effect dissolution. After this solution was slowly cooled to near room temperature, acetic anhydride (5 ml, 50 mmol) was added, and the final solution as stirred at room temperature (24 h under N_2). Dilution was effected with H_20 (10 ml), and the new solution was first neutralized (sat. Na_2CO_3) and then allowed to stand overnight (5 °C). The solid precipitate was filtered out, washed (cold H_20), and sublimed (100 °C/0.13 mbar) to give **1c** (0.56 g, 56%).

Preparation of **11**. To sodium hydride (50% oil disp., 13.5 g by wt) in diethyl carbonate (100 ml) was added dropwise 50(0.278 mol) of ketone **5a** in 100 ml of diethyl carbonate (N_2, stirring). Evolution of gas was immediately observed and the mixture turned tan in color. After the addition was completed, the mixture was boiled overnight and poured into an ice-water:HCl (200 ml:20 ml)

slurry. Extracts ($HCCl_3$, 6x50 ml) of the aqueous mixture were combined, dried ($CaCl_2$), and evaporated to a yellow oil (19.8 g) which was used directly. This slightly impure **11** gave the following spectral data: IR (neat) 1740 (C=O), 1675 (OC=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.24 (t, 3 H, J = 6 Hz, CH_3), 3.74 (s, 2 H, CH_2), 3.94 (s, 6 H, two OCH_3), 3.20 (q, 3 H, J = 6 Hz, CH_2), 6.88 (d, 1 H, J = 8 Hz, Ar-H).

5- (3, 4'-Dimethoxyphenyl)-5-oxopentanoic Acid (**12**). Sodium (3.5 g, 0.15 mol) was dissolved in abs. ethanol (250 ml) with stiffing. While the solution was warmed (@ 40 °C), keto ester **11** (28.2 g, 100 mmol) was added all at once. After stirring for 15 min, the new solution was cooled ice/H_2O), and then ethyl 3-bromopropionate (Aldrich, 6.0 g, 38 mmol) was added slowly. After this solution was stirred (1 h), additional ethyl 3-bromopropionate (12.0 g, 75.5 mmol) was added, and this solution was stirred overnight. The resulting mixture was cooled to room temperature, diluted with water (1:1), acidified (50% HCl) and then extracted thoroughly with ether. The extracts were washed (water, 2x100 ml) and dried ($MgSO_4$), and then the aqueous layer was evaporated to a pale yellow oil. This oil was boiled in 250 ml of aqueous H_2SO_4 (20%) for 45 h. After cooling the mixture to room temperature, it was extracted extensively with ether, and then the aqueous layer was evaporated to a residue. The residue was boiled with sodium hydroxide (5%, 200 ml) for one h. Acidification (HCl), followed by filtration, gave acid **12** (15 g, 55%), mp 145-147 °C. This acid **12** was used without further purification but did produce the following spectral data which support the structure: IR (KBr) 3400 (O-H), 1760 (broad, C=O) cm^{-1}. ^1H NMR ($DCCl_3$) δ 2.06 (q, 2 H, J= 6 Hz, CH_2), 2.48 (t, 2 H, J= 6 Hz, CH_2), 3.02 (t, 2 H, J= 6 Hz, CH_2), 3.92 (s, 6 H, two OCH_3), 6.88 (d, 1 H, J = 8 Hz, Ar-H), 7.52 (m, 2 H, Ar-H).

5-(3',4'-Dimethoxyphenyl)pentanoic Acid (**10**). Acid **12** (10 g, 39 mmol) was dissolved in glacial acetic acid (100 ml), and the solution was placed in a Paar hydrogenation bottle. Catalyst (10% Pd/C, 1 g) was added, and the resulting mixture was shaken at 60 °C under 35 psi of hydrogen pressure for one h. The reaction was terminated and the catalyst was filtered out (Celite). Evaporation of the solvent, followed by dilution with cold (5 °C) water (100 ml), gave new acid **10** (8.9 g, 95%), mp 165-167 °C. This acid **10** was used directly in the next step but did give the following spectral data: IR (KBr) 3100 (O-H), 1700 (C=O) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.65 (m, 4 H, two CH_2), 2.38 (t, 2 H, J=5 Hz, CH_2), 2.58 (t, 2 H, J=5 Hz, CH_2), 3.84 (s, 3 H, OCH_3),, 3.86 (s, 3 H, OCH_3), 6.72 (m, 3 H, Ar-H).

7,8-*Dimethoxysuberone* ***(8).*** *Acid* **10** (5 g, 21 mmol) was dissolved in 50 g of 115% polyphosphoric acid. The viscous mixture was heated to near 75 °C and then stirred for 2 h. The resulting dark red syrup was poured into an ice water slurry (200 ml), and the mixture was allowed to stand (5 °C) overnight. A precipitate formed which was filtered out and sublimed to give **8** (3.9 g, 84%), mp 61-63 °C. The ketone appeared to be pure and gave the following spectral data: IR (KBr) 1760 (C=O) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.82 (m, 4 H, two CH_2), 2.78 (t, 2 H, J=5 Hz, CH_2), 2.90 (t, 2 H, J=5 Hz, CH_2), 3.90 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 6.66 (s, 1 H, Ar-H), 7.38 (s, 1 H, Ar-H). Ketone **8** was converted to the allylthiazole **4** which was submitted for peak matching via mass spectrometry.

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