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A general synthesis of 3-amino-3-alkylpropenenitriles is described. These intermediates are further transformed to 5-amino-3-alkylisothiazoles. Also described is the synthesis of the novel isomer, 3-amino-5-*t*-butylisothiazole.

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5-Amino-3-methylisothiazole is commercially available as the hydrochloride salt [1], and has been extensively used as an intermediate [2a-d]. 5-Amino-3-arylisothiazoles are also known and have been exploited as intermediates [3a,b]. The absence of references to the higher alkyl analogs is a reflection of the difficulty of synthesis by established methods.

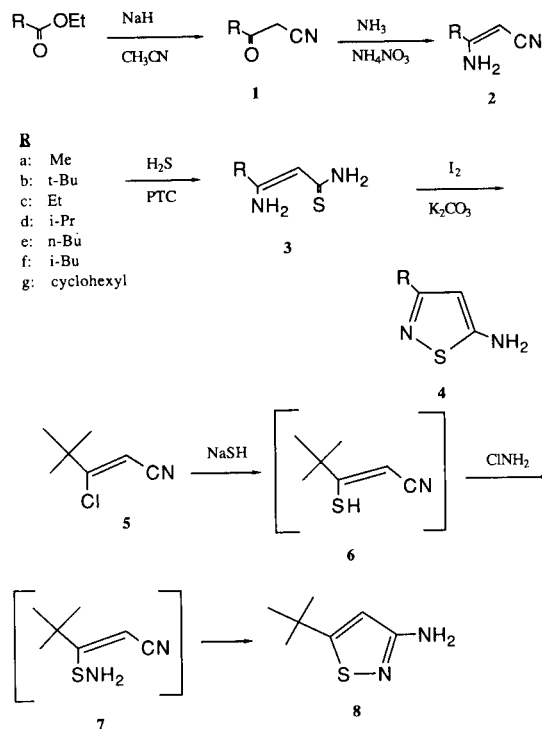
We wish to report a method of circumventing the difficulties in making the higher alkyl analogs. These isothiazole amines are useful intermediates to compounds which are highly active as algicides and herbicides [4], and the higher alkyl analogs are typically more active than the corresponding methyl derivatives. In addition, we describe the synthesis and properties of 3-amino-5-*t*-butylisothiazole.

Established pathways [3a,5] to isothiazolamines involve the intermediacy of enamines **2**. When R is methyl, the enamine is made by the self-condensation of acetonitrile under basic conditions [6]. When R is aryl, the enamine is made by condensing an aromatic nitrile with the acetonitrile anion [7], and this reaction is kinetically preferred to the acetonitrile self-condensation.

When R is alkyl with an  $\alpha$ -hydrogen, competing condensations occur, which can result in four possible products. The self-condensation product **2a** usually predominates for steric reasons. When R is *t*-butyl, only two products are possible, **2a** and **2b**, but the pivalonitrile is too hindered for ready attack by the acetonitrile anion, and **2a** is the major product.

One such enamine **2** has been made by the addition of ammonia to an allene [8], but this is not a general method, and cannot be used to make the *t*-butyl derivative **2b**. Brown [9] has shown that addition of an alkanenitrile to the acetonitrile anion (made using lithium diethylamide) at low temperature gives some enamines **2** in good yield.

We have demonstrated that the *t*-butyl enamine **2b** was conveniently made by reaction of the ketonitrile **1b** with ammonia in the presence of an ammonium salt. Compound **2b** was obtained in almost quantitative yield after a 16 hour reaction in refluxing ethanol. Less conveniently,



the conversion was effected with ammonia under pressure at elevated temperature.

When R is equal to small alkyl, the ketonitriles **1** are unstable because of self-condensation and dehydration, and this tendency has been mentioned in the literature [10]. We have studied this self-condensation, and the isolation of dimers and trimers will be the subject of a future publication. The result of this instability is much lower yields in each step of the sequence to the isothiazoles **4**, with the most difficulty encountered when R is equal to ethyl. Table I list some of the aminonitriles which we have made. Isomers are observed in every case except **2b** and **2g**, but they were carried on as mixtures of isomers to the next step.

Many different procedures exist for converting nitriles to thioamides, but in our hands the thioamides **3** were

Table I

## 3-Amino-3-alkylpropenenitriles 2

No.	mp (°C) or bp/mm Hg	Molecular Formula	Elemental Analysis %			<sup>1</sup> H NMR Spectrum Deuteriochloroform (ppm)
			Calcd./ C	Found H	Found N	
2b	49-50	C <sub>7</sub> H <sub>12</sub> N <sub>2</sub>	67.70	9.74	22.56	4.9 (broad, 2H), 3.95 (s, 1H), 1.2 (s, 9H)
			67.49	9.57	22.83	
2c	80-85/1	C <sub>5</sub> H <sub>8</sub> N <sub>2</sub>	62.47	8.39	29.14	5.2 (NH <sub>2</sub> ), 4.05 and 3.80 (s, 1H, isomers) 2.4 and 2.1 (q, 2H), 1.15 and 1.1 (t, 3H)
			62.25	8.22	28.87	
2d	94-97/0.5	C <sub>6</sub> H <sub>10</sub> N <sub>2</sub>	65.42	9.15	25.43	5.0 (NH <sub>2</sub> ), 4.0 and 3.75 (s, 1H), 3.2-2.0 (m, 1H), 1.15 (d, 6H)
			65.22	8.92	25.50	
2e	oil	C <sub>7</sub> H <sub>12</sub> N <sub>2</sub>	67.70	9.74	22.56	5.2 (NH <sub>2</sub> ), 4.0 and 3.68 (s, 1H), 2.29 and 2.06 (q, 2H), 1.5-1.2 (m, 4H), 0.86 and 0.83 (t, 3H)
			67.73	9.50	22.28	
2f	oil	C <sub>7</sub> H <sub>12</sub> N <sub>2</sub>	67.70	9.74	22.56	5.2 (NH <sub>2</sub> ), 4.1 and 3.6 (s, 1H), 2.8-1.7 (m, 3H), 1.0 (m, 6H)
			67.68	9.48	22.47	
2g	60-63	C <sub>9</sub> H <sub>14</sub> N <sub>2</sub>	71.96	9.39	18.65	4.7 (NH <sub>2</sub> ), 3.7 (s, 1H), 2.0-1.0 (m, 11H)
			72.17	9.54	18.90	

Table II

## 3-Amino-3-alkylpropenethioamides 3

No.	mp (°C) or bp/mm Hg	Molecular Formula	Elemental Analysis %			<sup>1</sup> H NMR Spectrum Deuteriochloroform (ppm)
			Calcd./ C	Found H	Found N	
3b	119-120	C <sub>7</sub> H <sub>14</sub> N <sub>2</sub>	53.12	8.92	17.70	8.3 (NH <sub>2</sub> ), 6.2 (NH <sub>2</sub> ), 5.3 (s, 1H), 1.2 (s, 9H)
			53.10	8.76	17.50	
3c	22-25	C <sub>5</sub> H <sub>10</sub> N <sub>2</sub> S	46.12	7.74	21.51	7.8 (NH <sub>2</sub> ), 6.1 (NH <sub>2</sub> ), 5.14 (s, 1H), 2.19 (q, 2H), 1.18 (t, 3H)
			45.85	7.97	21.46	
3d	oil	C <sub>6</sub> H <sub>12</sub> N <sub>2</sub> S	49.96	8.39	19.42	8.2 (NH <sub>2</sub> ), 6.65 (NH <sub>2</sub> ), 5.3 (s, 1H), 2.3 (m, 1H), 1.2 (d, 6H)
			50.02	8.16	19.14	
3e	43-45	C <sub>7</sub> H <sub>14</sub> N <sub>2</sub> S	53.12	8.92	17.70	8.1 (NH <sub>2</sub> ), 6.5 (NH <sub>2</sub> ), 5.12 (s, 1H), 2.17 (t, 2H), 1.56 (q, 2H), 1.37 (q, 2H), 0.92 (t, 3H)
			53.22	8.91	17.65	
3f	oil	C <sub>7</sub> H <sub>14</sub> N <sub>2</sub> S	53.12	8.92	17.70	8.1 (NH <sub>2</sub> ), 6.6 (NH <sub>2</sub> ), 5.2 (s, 1H), 2.7-1.8 (m, 3H), 1.0 (m, 6H)
			53.01	8.80	17.48	
3g	141-143	C <sub>9</sub> H <sub>16</sub> N <sub>2</sub> S	58.65	8.75	15.20	8.0 (NH <sub>2</sub> ), 6.2 (NH <sub>2</sub> ), 5.15 (s, 1H), 2.3-0.6 (m, 11H)
			58.75	9.00	15.17	

most conveniently made using a phase-transfer catalyst [11]. Preparation of the thioamides was frequently accompanied by dark, aliphatic impurities, and these impurities were a larger percentage as the alkyl group became smaller. The thioamides could be purified by reversed-phase chromatography, but were often used without purification because it was much easier to remove the impurities from the isothiazolamines by acid/base treatments. Conventional chromatography of the thioamides on silica gel results in some hydrolysis of the enamine.

The thioamides **3** may be cyclized to the isothiazole **4** using established procedures [3a,5], but we found iodine to be the most convenient reagent on a laboratory scale. Isothiazoles made using this sequence are listed in Table III.

For comparison purposes, we desired the isomeric isothiazolamine **8**, and we found it was not in the literature. There is a report of 3-amino-5-phenylisothiazole [12], but we were unable either to repeat this work or to adapt it to the *t*-butyl analog.

Z-3-Chloro-4,4-dimethyl-2-pentenitrile **5** [13] was

Table III  
5-Amino-3-alkylisothiazoles 4

No.	mp (°C)	Molecular Formula	Elemental Analysis %			<sup>1</sup> H NMR Spectrum Deuteriochloroform (ppm)
			Calcd./C	Found/H	Found/N	
4b	91-93	C <sub>7</sub> H <sub>12</sub> N <sub>2</sub> S	53.81	7.74	17.93	6.3 (s, 1H), 4.5 (NH <sub>2</sub> ), 1.33 (s, 9H)
			53.60	7.45	17.63	
4c	oil	C <sub>5</sub> H <sub>8</sub> N <sub>2</sub> S	46.85	6.29	21.85	6.14 (s, 1H), 4.7 (NH <sub>2</sub> ), 2.63 (q, 2H), 1.23 (t, 3H)
			47.03	6.35	21.75	
4d	49-51	C <sub>6</sub> H <sub>10</sub> N <sub>2</sub> S	50.64	7.09	19.70	6.1 (s, 1H), 5.0 (NH <sub>2</sub> ), 2.9 (m, 1H), 1.25 (d, 6H)
			50.44	6.88	19.50	
4e	oil	C <sub>7</sub> H <sub>12</sub> N <sub>2</sub> S	53.81	7.74	17.93	6.1 (s, 1H), 5.0 (NH <sub>2</sub> ) 2.6 (t, 2H), 1.6 (m, 2H), 1.4 (m, 2H), 0.9 (t, 3H)
			53.52	8.01	17.90	
4f	oil	C <sub>7</sub> H <sub>12</sub> N <sub>2</sub> S	53.81	7.74	17.93	6.1 (s, 1H), 5.0 (NH <sub>2</sub> ) 2.5 (d, 2H), 2.0 (m, 1H), 0.9 (d, 6H)
			53.82	7.60	17.69	
4g	132-136	C <sub>9</sub> H <sub>14</sub> N <sub>2</sub> S	59.30	7.74	15.34	6.1 (s, 1H), 4.5 (NH <sub>2</sub> ) 2.6 (m, 1H), 2.2-1.2 (m, 10H)
			59.28	7.91	15.26	

made from pinacolone in a one-pot procedure adapted from that published for acetophenones [14]. Treatment of **5** with sodium hydrosulfide is presumed to give **6**, which was treated *in situ* with chloramine. Ring closure of the presumed intermediate **7** resulted in formation of the 3-aminoisothiazole **8**.

### EXPERIMENTAL

Melting points were determined on a Mel-Temp open capillary melting point apparatus and are uncorrected. The <sup>1</sup>H nmr spectra were recorded on Varian T-60 and Bruker WM250 spectrometers and are reported as ppm downfield from TMS. Mass spectra were taken on a Hewlett-Packard 5985.

#### Preparation of 3-Oxoalkanenitriles **1**.

These intermediates were made by treatment of the esters with acetonitrile and sodium hydride in tetrahydrofuran according to a published procedure [15]. The compounds are known [4c,10,16]. Compound **1c** should be used as soon as possible because of its tendency to self-condense. Compounds **1d-g** are also unstable upon standing for longer periods of time or when heated, but compound **1b** is very stable.

#### Preparation of 3-Aminopropenenitriles **2**.

Preparation of the *t*-butyl derivative **2b** is described by two routes. The preferred route uses ammonia with ammonium nitrate analogous to a published route for an aminoester [17]. Several examples are listed in Table I. With the exception of **2b** and **2g**, 2 isomers were seen in the nmr. The tendency of some ketonitriles **1** to self-condense often results in impure **2**, but these impure samples could be passed over a short silica gel (Davisson Grade 62) column in methylene chloride to obtain pure samples. Because of the marked instability of **1c**, it is preferable not to heat the mixture when treating with ammonia.

#### Method A.

Pivaloylacetone nitrile **1b** (12.5 g, 0.1 mole) and ammonium

nitrate (4.0 g, 0.05 mole) in ethanol (100 ml) were stirred under reflux for 16 hours as ammonia gas was bubbled through the solution. Water (50 ml) was added and most of the ethanol was removed under vacuum. Aqueous sodium hydroxide (70 ml, 0.3*N*) was added and the mixture was extracted with ethyl ether (200 ml). The ether extract was washed with water (25 ml) and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to leave an oil. Hexane (50 ml) was added and a resulting white solid was collected by filtration. The yield was 11.7 g (94%), and the product is described in Table I.

#### Method B.

Pivaloylacetone nitrile **1b** (250 g), liquid ammonia (150 ml) and ethanol (100 ml) were heated in a sealed vessel at 130° for 16 hours. The solvent was removed under vacuum and hexane (600 ml) was added. Beige crystals (222 g, 90%) were collected by filtration, mp 48-50°, and were shown to be identical to that obtained by Method A.

#### Preparation of 3-Aminopropenenitriles **3**.

Preparation of the *t*-butyl derivative **3b** is described, and Table II lists the additional derivatives. The thioamides were often accompanied by dark aliphatic impurities. They could be chromatographed, but were usually used without further purification because it was much easier to remove the impurities from the isothiazolamines by acid/base treatment. Product **3c** was typically only about 10% of the dark oil, but as the chain lengthened, the percentage of product in the dark product oil increased, and **3e** was obtained in 50% yield. Chromatography on silica gel results in some hydrolysis of the enamine to the ketone, but pure samples were obtained by reversed-phase chromatography on a C<sub>18</sub> column, eluting the thioamide as the fastest-running material in 1:1 methanol-water.

The nitrile **2b** (121.5 g, 0.98 mole), sodium sulfide nonahydrate (8.4 g, 0.035 mole), tetrabutylammonium chloride (4.6 g, 0.016 mole), benzene (350 ml), and water (140 ml) were stirred at 70° under an atmosphere of hydrogen sulfide gas for two days. Ethyl acetate (350 ml) was added and the layers were separated. The

organic layer was washed with water (100 ml) and dried over anhydrous magnesium sulfate before removing the solvents under vacuum. The resulting oil solidified upon standing and the solid was recrystallized from methylene chloride/hexane to give yellow crystals (121.5 g, 78%) of **3b**, described in Table II.

#### Preparation of 5-Amino-3-alkylisothiazoles **4**.

The preparation of **4b** is an example of starting with a pure thioamide, and the preparation of **4e** demonstrates the use of a crude thioamide with appropriate workup to yield pure product.

The thioamide **3b** (121 g, 0.68 mole) and potassium carbonate (187.6 g, 1.36 moles) in ether (2 l) were stirred under reflux as iodine (172 g, 0.68 g-atom) in ether (1 l) was added in a steady stream. The mixture was allowed to stir under reflux for two hours after the addition was complete. Water (500 ml) was added and the layers were separated. The ether solution was evaporated to dryness and the ether removed under vacuum to leave an oil which solidified upon standing. Recrystallization from acetone-pentane gave 99 g (93%) of **4b** in two crops.

A very dark oil (95 g) containing about 50% of **3e** (<sup>1</sup>H nmr assay) and potassium carbonate (84 g) in ether (1,500 ml) were stirred under reflux as iodine (77 g) in ether (600 ml) was added in a steady stream. The mixture was allowed to stir under reflux for one hour after the addition was complete. Water (500 ml) was added and the layers were separated. The organic layer was washed with 500 ml of water before extracting product into two portions of 1*N* hydrochloric acid of 175 ml each. The combined aqueous extracts were washed with four portions of methylene chloride (300 ml each), which removed almost all of the color. The aqueous acid was made basic with 50% sodium hydroxide and the product extracted into 2-150 ml portions of methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate and the solvent removed under vacuum to leave 16.6 g of a straw-colored oil which was identified as pure **4e**. The other product oils were also obtained pure in this way, except for **4c**. This ethyl derivative could be obtained pure by starting with pure thioamide.

#### Preparation of Z-3-Chloro-4,4-dimethyl-2-pentenitrile **5**.

Phosphorous oxychloride (89.5 ml, 0.96 mole) was added slowly to dimethylformamide (80.4 ml, 1.04 moles) with sufficient cooling to keep the temperature below 25°. A solution of pinacolone (50 ml, 0.4 mole) in 64 ml of 1,2-dichloroethane was added. The reaction solution was heated at 50-55° for 2 hours, and then at 70-75° for 2 hours. Hydroxylamine sulfate (77.6 g, 0.96 mole) was added in small portions, and the temperature was raised gradually to 85°, and held at this temperature for one hour before cooling to room temperature. Water and hexane (400 ml each) were added. The hexane layer was dried over anhydrous magnesium sulfate and the hexane removed under vacuum to leave 51.4 g (89%) of an oil, identified as **5**: <sup>1</sup>H nmr (deuteriochloroform): 5.5 (s, 1H) and 1.2 (s, 9H).

*Anal.* Calcd. for C<sub>7</sub>H<sub>10</sub>ClN: C, 58.55; H, 6.97. Found: C, 58.27; H, 6.99.

#### Preparation of 3-Amino-5-*t*-butylisothiazole **8**.

The nitrile **5** (14.3 g, 0.1 mole) was stirred under nitrogen in 75 ml of ethanol as sodium sulfide nonahydrate (24 g, 0.1 mole) and 100 ml of 1*N* hydrochloric acid was added. The mixture was stirred for 2 hours before cooling to 10°. A chloramine solution was prepared separately by adding dropwise 5.25% aqueous sodium hypochlorite (142 ml, 0.1 mole) to ice-cold concentrated ammonium hydroxide (60 ml). The contents of the original flask were poured into the chloramine solution, still with ice-cooling. The mixture was allowed to warm to room temperature, and then to stir for 16 hours before removing most of the ethanol under vacuum. The mixture was made acidic with 6*N* hydrochloric acid and extracted with 2-200 ml portions of ether. The remaining aqueous layer was filtered and made basic with 50% aqueous sodium hydroxide. The product was extracted into 2-100 ml portions of methylene chloride and the combined extracts dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to leave a semi-solid which was recrystallized from hexane to give 2.1 g (13%) of product **8**, mp 60-61°; <sup>1</sup>H nmr (deuteriochloroform): 6.2 (s, 1H), 4.4 (broad, 2H), and 1.3 (s, 9H); ms: m/z 156, 141, 113, 101; ir (chloroform): 3480, 3395, 3200, 2960, 1605, 1547, 1425, 1362, 827, 810 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>7</sub>H<sub>12</sub>N<sub>2</sub>S: C, 53.81; H, 7.74; N, 17.93. Found: C, 53.79; H, 7.59; N, 17.72.

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