

PRACTICAL SYNTHESIS OF 3-AMINO-5-*tert*-BUTYLISOXAZOLE FROM
4,4-DIMETHYL-3-OXOPENTANENITRILE WITH HYDROXYLAMINE

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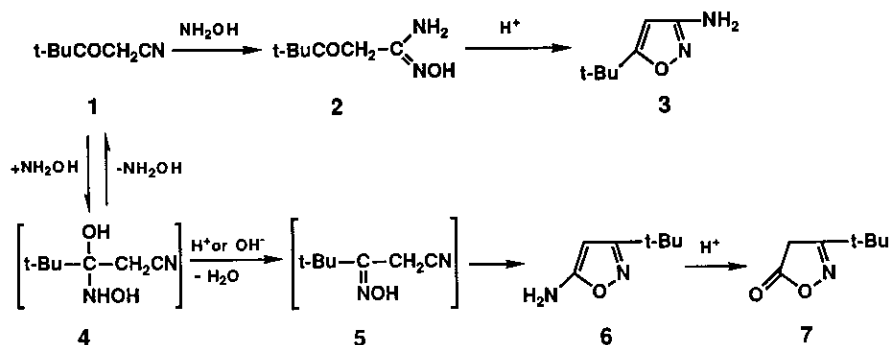
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Abstract—A good yield of 3-amino-5-*tert*-butylisoxazole (**3**) was obtained regioselectively from a reaction of 4,4-dimethyl-3-oxopentanenitrile (**1**) with hydroxylamine in the aqueous solution of which was adjusted to weak basic, followed by treatment of the resulting 4,4-dimethyl-3-oxopentaneamidoxime (**2**) with hydrochloric acid.

3-Amino-5-*tert*-butylisoxazole (**3**) is a key intermediate for 3-(5-*tert*-butylisoxazolyl)-1,1-dimethylurea (common name: isouron) which is useful as a herbicide for sugar cane and several other crops as well as for non-croplands.¹ Synthesis of 3-aminoisoxazole was first reported by Quilico in 1931.² Since then, 3-aminoisoxazoles have been prepared by many different procedures.³⁻¹⁰ However, these methods have not been very satisfactory or economical. We developed a practical synthesis for obtaining **3** regioselectively from 4,4-dimethyl-3-oxopentanenitrile (pivaloylacetone nitrile, **1**) with hydroxylamine sulfate.

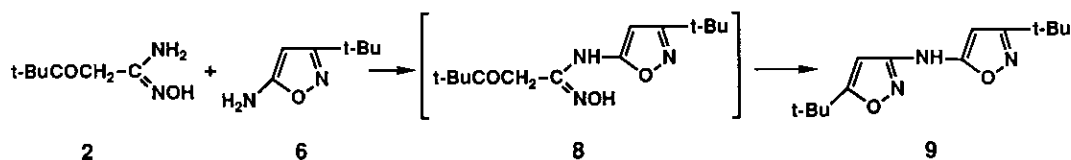
The reaction of 3-oxoalkanenitriles (β -ketonitriles) with hydroxylamine usually gives 5-aminoisoxazoles.¹¹⁻¹⁴ Wahlberg¹² reported that 5-amino-3-*tert*-butylisoxazole (**6**) was also formed by the reaction of **1** with hydroxylamine hydrochloride. One exception was reported by Elnagdi and his associates¹⁵ that the reaction of α -arylhydrazono- β -ketonitriles with hydroxylamine gave 5-substituted 3-amino-4-aryloisoxazoles in good yields. We synthesized **3** by a modification of the method of Elnagdi et al. as shown in Scheme 1. The reaction of **1** with hydroxylamine was carried out in the aqueous solution of which was adjusted to weak basic at 60°C to 100°C and the reaction mixture was heated subsequently with hydrochloric acid. The addition-elimination equilibrium between **1** and **4** exists under weak basic condition, and attack of NH₂OH at the CN group in **1** proceeds preferentially while the equilibrium exists. 4,4-Dimethyl-3-oxopentaneamidoxime (**2**) is consequently formed because of irreversible addition of NH₂OH to **1**, and the desired **3** is obtained in a good yield on treatment with hydrochloric acid. 3-*tert*-Butyl-5-isoxazolone (**7**) can be obtained as an acidic by-product by the



Scheme 1

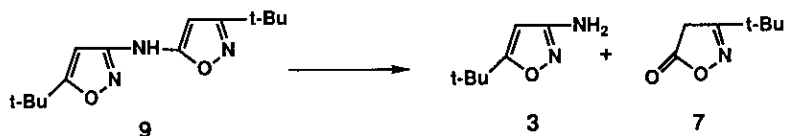
hydrolysis of **6**.¹¹ Therefore, the desired **3** was isolated by extraction with CHCl₃ from basic solution. The reaction under acidic or basic conditions is accelerated the dehydration from **4** to ketoxime (**5**), and **6** is produced by rapid ring closure of **5**.

Table 1 summarizes the effects of various conditions on the synthesis of **3**. The structure of the main by-product contained as an impurity in crude **3** of Runs 1-8 was proposed to be *N*-(3-*tert*-butylisoxazol-5-yl)-5-*tert*-butyl-3-aminoisoxazole (**9**) by ir, ¹H-nmr spectra and elemental analysis. In practice, the reaction of **2** with **6** gave **9** as shown in Scheme 2, and ir and ¹H-nmr spectra of the product were identical with those of the by-product (**9**).



Scheme 2

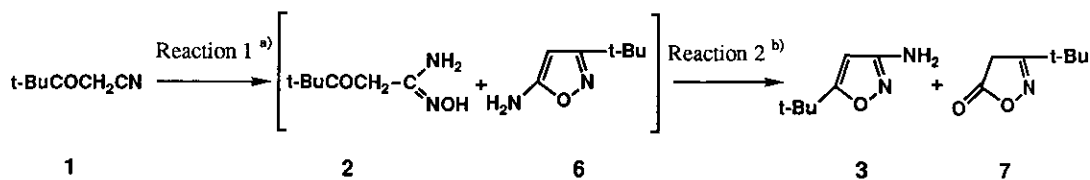
In addition, hydrolysis of **9** with hydrochloric acid gave **3** and **7** as shown in Scheme 3.



Scheme 3

The formation of **9** decreased on treatment with hydrochloric acid under stronger conditions. These findings led to improvements in the qualities and yields of **3** (Runs 10 and 12-14).

Sodium hydroxide used as a neutral agent was excellent base in comparison with other bases, LiOH, KOH, K₂CO₃, Na₂CO₃, NaHCO₃ and Et₃N, in view of the yield and cost.

Table 1. Synthesis of 3-Amino-5-*tert*-butylisoxazole (3) in Various Conditions

| Run | H ₂ O (l/mol) | pH ^{c)} initial | reaction 1 °C ^{d)} | reaction 1 h | 36% aq. HCl eq. mol | reaction 2 °C | reaction 2 h | Crude yield (%) | Content (%) ^{e)} 3 | Content (%) ^{e)} 9 | 7 yield (%) |
|------------------|--------------------------|--------------------------|-----------------------------|--------------|---------------------|---------------|--------------|-----------------|-----------------------------|-----------------------------|-------------|
| 1 | 2.0 | 8.10 | 60 | 18 | 1.29 | 70 | 0.5 | 87.6 | 94.4 | 3.1 | 10.1 |
| 2 | 2.0 | 8.10 | 70 | 4 | 1.29 | 70 | 0.5 | 86.6 | 94.4 | 2.4 | 11.0 |
| 3 | 2.0 | 8.10 | 100 | 0.25 | 1.30 | 70 | 0.5 | 82.0 | 92.2 | 2.1 | 14.9 |
| 4 | 2.0 | 8.10 | 100 | 1 | 0.90 | 100 | 0.25 | 85.1 | 95.0 | 2.3 | 11.3 |
| 5 | 1.5 | 7.90 | 100 | 1 | 0.90 | 100 | 0.25 | 83.5 | 91.9 | 4.2 | 12.8 |
| 6 | 1.5 | 8.20 | 100 | 1 | 0.90 | 100 | 0.25 | 86.8 | 93.9 | 3.3 | 10.3 |
| 7 | 1.5 | 8.50 | 100 | 1 | 0.90 | 100 | 0.25 | 84.0 | 91.8 | 4.5 | 13.2 |
| 8 | 1.0 | 8.50 | 100 | 1 | 0.90 | 100 | 0.25 | 87.9 | 90.9 | 5.3 | 9.8 |
| 9 | 1.5 | 8.30 | 100 | 1 | 2.20 | 100 | 1 | 85.7 | 94.3 | 1.3 | 7.9 |
| 10 | 1.5 | 8.20 | 100 | 1 | 2.50 | 100 | 1 | 85.7 | 95.8 | 0.2 | 7.4 |
| 11 | 1.5 | 8.20 | 100 | 1 | 2.50 | 100 | 0.5 | 84.8 | 95.2 | 1.1 | 9.5 |
| 12 ^{f)} | 1.5 | 8.20 | 100 | 1 | 2.55 | 100 | 1 | 85.8 | 97.1 | 0.2 | 7.6 |
| 13 ^{g)} | 1.5 | 8.20 | 100 | 1 | 2.60 | 100 | 1 | 86.0 | 98.3 | 0.2 | 7.5 |
| 14 | 1.0 | 8.50 | 100 | 1 | 2.50 | 100 | 1 | 85.6 | 95.5 | 0.3 | 7.4 |

a) 1) NaOH (1.10 aq.) / H₂O, 2) NH₂OH·1/2 H₂SO₄ (1.10 aq.). b) 36% aq. HCl. c) Adjusted with 5% aq. NaOH or 10% aq. H₂SO₄ (before heating, 25°C). d) Rate of heating: 60°C, 11 min; 70°C, 18 min; 100°C, 23-34 min.

e) Determined by hplc of the crude product. f) NH₂OH·1/2 H₂SO₄ (1.15 eq.). g) NH₂OH·1/2 H₂SO₄ (1.20 eq.).

In the course of the studies described above, we developed that 6 was obtained in quantitative yield from the reaction of 1 with hydroxylamine sulfate in the presence of two equivalent sodium hydroxide in aqueous solution at 100°C.

On the other hand, the reaction of 3-oxobutanenitrile, 4-methyl-3-oxopentanenitrile and benzoylacetonitrile instead of 1 with hydroxylamine gave 3-aminoisoxazoles in poor yields (trace, 27% and 38%, respectively) and 5-isoxazolones were obtained mainly *via* 5-aminoisoxazoles in each case. These results indicate that attack of NH₂OH at the CO group in 1 is affected by the steric hindrance of the bulky *tert*-butyl group. Therefore, attack of NH₂OH at the CN group is favored. Another reason for the low yield of 3-amino-5-phenylisoxazole is the increase of the by-product owing to the high acidity of the active methylene in benzoylacetonitrile.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on a Hitachi 260-10 spectrophotometer. ¹H-Nmr spectra were recorded on a JEOL GSX-270 or Varian T-60 spectrometer with tetramethylsilane as an internal

standard. Hplc was performed on a Waters Model 6000-A, Nucleosil 10 C₁₈ 4.6 mm × 250 mm, at 245 nm (MeOH-H₂O 45:55) for **3** and **6** and at 260 nm (MeCN-H₂O 60:40) for **9**. For column chromatography, Kiesel gel 60 (70-230 mesh), Merck, was used. Compound (**1**) was prepared by the method of Sugasawa et al.¹⁶ Benzoylacetonitrile was purchased commercially. 3-Oxobutanenitrile and 4-methyl-3-oxopentanenitrile were prepared by a modification of the method of Nishiwaki and Saito.¹⁴ Typical procedures are shown in the following examples.

4,4-Dimethyl-3-oxopentaneamidoxime(**2**).

Hydroxylamine sulfate (3.61 g, 0.044 mol) was added to a solution of **1** (5.00 g, 0.06 mol) and NaHCO₃ (5.04 g, 0.06 mol) in H₂O (65 ml) at room temperature. The mixture was stirred at 60°C for 8 h. The reaction mixture was extracted 4 times with CHCl₃. The extract was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to yield an oily product (5.20 g). After this oily product had been crystallized from benzene, it was filtered and washed with Et₂O-hexane to yield **2** (2.30 g, 36.3%). mp 104-105°C. ¹H-Nmr (CDCl₃) δ: 1.20(9H, s), 3.33(2H, s), 5.08(2H, br), 7.80(1H, br). Ir (CHCl₃): 3590, 3490, 3370, 1708, 1663 cm⁻¹.

3-Amino-5-*tert*-butylisoxazole(**3**).

Method A : By Cyclization of 2 — A solution of 36% aq. HCl (0.048 g, 0.47 mmol) was added to a solution of **2** (300 mg, 1.90 mmol) in MeOH (1 ml) and the mixture was stirred at 50°C for 3 h. The reaction mixture was mixed with water and extracted 3 times with CHCl₃. The extract was dried over Na₂SO₄ and concentrated under reduced pressure to yield **3** (262 mg, 98.5%) as a nearly pure solid. mp 112-112.5°C (C₆H₆). ¹H-Nmr (270 MHz)(CDCl₃) δ: 5.50(1H, s), 3.86(2H, br), 1.30(9H, s). Ir (CHCl₃): 3495, 3405, 2975, 1625, 1475 cm⁻¹.

Method B: From 4,4-Dimethyl-3-oxopentanenitrile(1**) with Hydroxylamine (Run 6).**

A solution of hydroxylamine sulfate (9.03 g, 0.110 mol) in water (36 ml) was added to a stirred solution of **1** (12.52 g, 0.100 mol) and 96% NaOH (4.58 g, 0.110 mol) in water (114 ml) at 25°C. After the mixture had been adjusted to pH 8.20 with 5% aq. NaOH, it was heated to 100°C over 30 min and kept at this temperature for 1 h. Next, 36% aq. HCl (9.12 g, 0.090 mol) was added to the reaction mixture, which was then heated at 100°C for 15 min. After cooling, the reaction mixture was adjusted to pH 11 with 30% aq. NaOH and extracted 3 times with CHCl₃. The extract was washed with water, dried over Na₂SO₄ and concentrated under reduced pressure to give **3** as a light yellow solid (12.17 g, 86.8%). After **3** had been extracted, the aqueous layer was acidified to pH 1 with 36% aq. HCl and extracted with CHCl₃. The extract was dried (Na₂SO₄) and concentrated under reduced pressure to give **7** as a light yellow-brown solid (1.45 g, 10.3%).

Method C: From 1 with Hydroxylamine (Run 10). — After the reaction of **1** with hydroxylamine sulfate had been carried out as in Method B, 36% aq. HCl (25.32 g, 0.250 mol) was added to the reaction mixture, which was then heated at 100°C for 1 h. The reaction mixture was worked up as described in Method B

and gave **3** as a light yellow solid (12.01 g, 85.7%) and **7** as a light yellow-brown solid (1.04 g, 7.4%).

5-Amino-3-tert-butylisoxazole(6).

Hydroxylamine sulfate (86.17 g, 1.05 mol) was added to a stirred solution of **1** (125.17 g, 1.00 mol) and NaOH (82.00 g, 2.05 mol) in H₂O (1.0 l). The mixture was stirred at 100°C for 2.5 h. The reaction mixture was extracted 2 times with CHCl₃. The extract was washed with water, dried over Na₂SO₄ and concentrated under reduced pressure to give **6** (136.89 g, 97.6%) as a nearly pure solid. mp 90.0-91.0°C (cyclohexane). ¹H-Nmr (270 MHz)(CDCl₃) δ: 5.03(1H, s), 4.32(2H, br), 1.28(9H, s), Ir(CHCl₃): 3485, 3390, 2950, 1635, 1470 cm⁻¹.

3-tert-Butyl-5-isoxazolone(7).

A mixture of **6** (9.81 g, 0.070 mol) and 36% aq. HCl (8.51 g, 0.084 mol) in water (140 ml) was stirred at 50°C for 4 h. The reaction mixture was extracted with CHCl₃, washed with water, dried (Na₂SO₄) and concentrated under reduced pressure to give **7** (9.84 g, 99.6%) as a nearly pure solid. mp 106-107°C (C₆H₆). ¹H-Nmr(270 MHz)(CDCl₃) δ: 3.41(2H, s), 1.26(9H, s). Ir(CHCl₃): 2975, 1805, 880 cm⁻¹.

N-(3-tert-Butylisoxazol-5-yl)-5-tert-butyl-3-aminoisoxazole(9).

A mixture of **2** (633 mg, 4.0 mmol) and **6** (561 mg, 4.0 mmol) in 50% aq. EtOH (8 ml) was heated at 85-90°C for 23 h. Next, 36% aq. HCl (1.15 g, 11.4 mmol) was added and the mixture was stirred at 60°C for 2 h. The reaction mixture was worked up as described above for the preparation (Method B) of **3** and gave a crude solid (594 mg) which was separated by silica gel column chromatography (C₆H₆-Et₂O 1:1) into **9** (37 mg, 3.5%) and **3** (528 mg, 94.1%). The aqueous layer contained **7** (532 mg, 94.2%) as an acidic compound. Physical properties of **9** : mp 167-168°C (C₆H₆). ¹H-Nmr (270 MHz)(CDCl₃) δ: 6.98(1H, br), 5.86(1H, s), 5.82(1H, s), 1.34(9H, s), 1.33(9H, s). Ir (CHCl₃): 3440, 3260, 2980, 1635, 1610, 1590, 1570, 1475, 1373 cm⁻¹. Anal. Calcd for C₁₄H₂₁N₃O₂: C, 63.85; H, 8.04; N, 15.96. Found: C, 63.93; H, 8.10; N, 15.97.

Hydrolysis of 9.

A mixture of **9** (263 mg, 1.0 mmol) and 5% HCl-EtOH (10 ml) was refluxed for 16 h. The reaction mixture was concentrated under reduced pressure to remove EtOH and worked up as described in the preparation (Method B) of **3** to give crude **3** (140 mg, 100%) and crude **7** (70 mg, 50%).

3-Amino-5-isopropylisoxazole.

Hydroxylamine sulfate (1.81 g, 0.022 mol) was added to a stirred solution of 4-methyl-3-oxopentanenitrile (2.22 g, 0.020 mol) and 96% NaOH (1.04 g, 0.025 mol) in H₂O (40 ml). The mixture was stirred at room temperature (25°C, pH 7.97), then at 40°C for 70 h. Next, 36% aq. HCl (3.24 g, 0.032 mol) was added to the mixture, which was stirred at 50°C for 2.5 h. The reaction mixture was worked up as described above for the preparation (Method B) of **3** and gave a crude product (1.01 g). Purification of the product by silica gel column chromatography (C₆H₆-Et₂O 1:1) gave 3-amino-5-isopropylisoxazole (0.67 g, 26.6%). mp 74-75°C (C₆H₆). ¹H-Nmr (270 MHz)(CDCl₃) δ: 5.52(1H, s), 3.88(2H, br), 2.94(1H, sept, J=6.8 Hz), 1.27(6H, d, J=6.8 Hz). Ir (CHCl₃): 3490, 3400, 2975, 1620, 1470 cm⁻¹.

3-Amino-5-phenylisoxazole.

Hydroxylamine sulfate (0.90 g, 0.011 mol) was added to a stirred solution of benzoylacetonitrile (1.45 g, 0.010 mol) and 96% NaOH (0.48 g, 0.0115 mol) in 50% aq. EtOH (20 ml). The mixture was stirred at room temperature (25 °C, pH 7.65), then heated at 80 °C for 22 h. 36% aq. HCl (1.52 g, 0.015 mol) was added to the mixture, which was stirred at 80 °C for 2 h. The reaction mixture was worked up as described above for the preparation (Method B) of **3** and gave a crude product (0.90 g). Purification of the product by silica gel column chromatography (C₆H₆-Et₂O 1:1) gave 3-amino-5-phenylisoxazole (0.61 g, 38.1%). mp 137.5-138 °C (C₆H₆). ¹H-Nmr (270 MHz)(CDCl₃) δ: 7.37-7.74(5H, m), 6.09(1H, s), 4.00(2H, br). Ir(CHCl₃): 3490, 3410, 3000, 1635, 1470 cm⁻¹.

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