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

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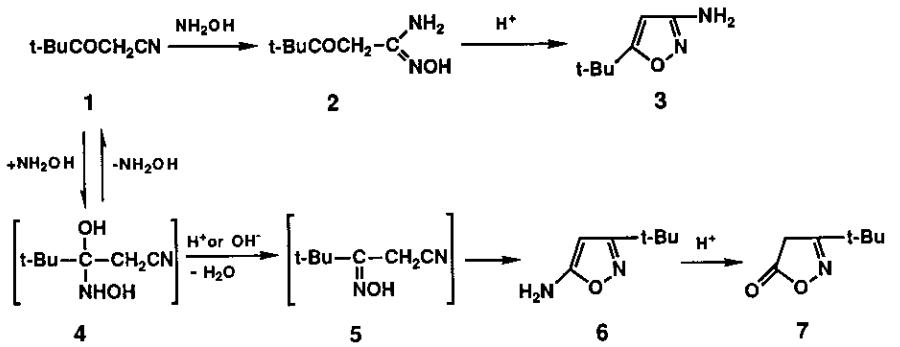
Abstract——A good yield of 3-amino-5-*tert*-butylisoxazole (**3**) was obtained regioselectively from a reaction of 4,4-dimethyl-3-oxopentanenitrile (**1**) with hydroxylamine in the aqueous solution of which was adjusted to weak basic, followed by treatment of the resulting 4,4-dimethyl-3-oxopentaneamidoxime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

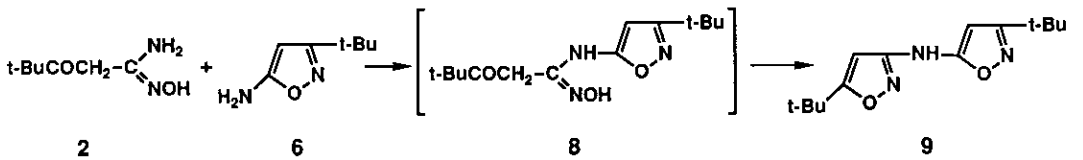
The reaction of 3-oxoalkanenitriles (β-ketonitriles) with hydroxylamine usually gives 5-aminoisoxazoles.[11-14] Wahlberg [12] reported that 5-amino-3-*tert*-butylisoxazole (**6**) was also formed by the reaction of **1** with hydroxylamine hydrochloride. One exception was reported by Elnagdi and his associates [15] that the reaction of α-arylhydrazono-β-ketonitriles with hydroxylamine gave 5-substituted 3-amino-4-arylazoisoxazoles 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℃ to 100℃ 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 NH_2OH 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 NH_2OH 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

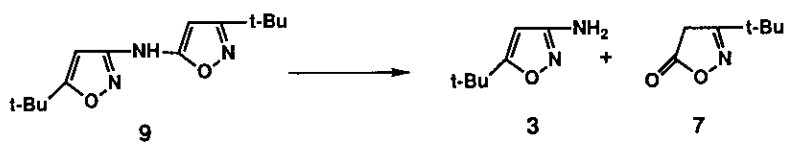
hydrolysis of **6**.[11] Therefore, the desired **3** was isolated by extraction with $CHCl_3$ from basic solution. The reaction under acidic or basic conditions is accelerated the dehydration from **4** to ketoxime (**5**), and **6** is produced by rapid ring closure of **5**.

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, ^{1}H-nmr spectra and elemental analysis. In practice, the reaction of **2** with **6** gave **9** as shown in Scheme 2, and ir and ^{1}H-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.

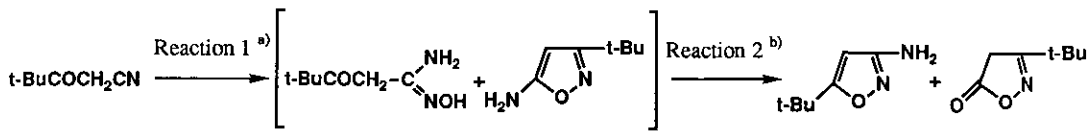


Scheme 3

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 an neutral agent was excellent base in comparison with another bases, LiOH, KOH, K_2CO_3, Na_2CO_3, $NaHCO_3$ and Et_3N, in view of the yield and cost.

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



1 **2** **6** **3** **7**

Run	H_2O (l/mol)	pH c) initial	reaction 1 °C d)	h	36% aq. HCl eq. mol	reaction 2 °C	h	Crude yield (%)	Content (%) e) **3**	**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.) / H_2O, 2) $NH_2OH \cdot 1/2\ H_2SO_4$ (1.10 aq.). b) 36% aq. HCl. c) Adjusted with 5% aq. NaOH or 10% aq. H_2SO_4 (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) $NH_2OH \cdot 1/2\ H_2SO_4$ (1.15 eq.). g) $NH_2OH \cdot 1/2\ H_2SO_4$ (1.20 eq.).

In the cource 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 NH_2OH at the CO group in **1** is affected by the steric hindrance of the bulky *tert*-butyl group. Therefore, attack of NH_2OH 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. ^{1}H-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 C_{18} 4.6 mm × 250 mm, at 245 nm (MeOH-H_2O 45:55) for **3** and **6** and at 260 nm (MeCN-H_2O 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 $NaHCO_3$ (5.04 g, 0.06 mol) in H_2O (65 ml) at room temperature. The mixture was stirred at 60℃ for 8 h. The reaction mixture was extracted 4 times with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 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 Et_2O-hexane to yield **2** (2.30 g, 36.3%). mp 104-105℃. ^{1}H-Nmr ($CDCl_3$) δ: 1.20(9H, s), 3.33(2H, s), 5.08(2H, br), 7.80(1H, br). Ir ($CHCl_3$): 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℃ for 3 h. The reaction mixture was mixed with water and extracted 3 times with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated under reduced pressure to yield **3** (262 mg, 98.5%) as a nearly pure solid. mp 112-112.5℃ (C_6H_6). ^{1}H-Nmr (270 MHz)($CDCl_3$) δ: 5.50(1H, s), 3.86(2H, br), 1.30(9H, s). Ir ($CHCl_3$): 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℃. After the mixture had been adjusted to pH 8.20 with 5% aq. NaOH, it was heated to 100℃ 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℃ for 15 min. After cooling, the reaction mixture was adjusted to pH 11 with 30% aq. NaOH and extracted 3 times with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 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 $CHCl_3$. The extract was dried (Na_2SO_4) 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℃ 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 H_2O (1.0 l). The mixuture was stirred at 100℃ for 2.5 h. The reaction mixuture was extracted 2 times with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to give **6** (136.89 g, 97.6%) as a nearly pure solid. mp 90.0-91.0℃ (cyclohexane). ^{1}H-Nmr (270 MHz)($CDCl_3$) δ: 5.03(1H, s), 4.32(2H, br), 1.28(9H, s), Ir($CHCl_3$): 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℃ for 4 h. The reaction mixture was extracted with $CHCl_3$, washed with water, dried (Na_2SO_4) and concentrated under reduced pressure to give **7** (9.84 g, 99.6%) as a nearly pure solid. mp 106-107℃ (C_6H_6). ^{1}H-Nmr(270 MHz)($CDCl_3$) δ: 3.41(2H, s), 1.26(9H, s). Ir($CHCl_3$): 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℃ for 23 h. Next, 36% aq. HCl (1.15 g, 11.4 mmol) was added and the mixture was stirred at 60℃ 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 (C_6H_6-Et_2O 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_6H_6). ^{1}H-Nmr (270 MHz)($CDCl_3$) δ: 6.98(1H, br), 5.86(1H, s), 5.82(1H, s), 1.34(9H, s), 1.33(9H, s). Ir ($CHCl_3$): 3440, 3260, 2980, 1635, 1610, 1590, 1570, 1475, 1373 cm^{-1}. Anal. Calcd for $C_{14}H_{21}N_3O_2$: 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 H_20 (40 ml). The mixture was stirred at room temperature (25℃, pH 7.97), then at 40℃ for 70 h. Next, 36% aq. HCl (3.24 g, 0.032 mol) was added to the mixture, which was stirred at 50℃ 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 (C_6H_6-Et_2O 1:1) gave 3-amino-5-isopropylisoxazole (0.67 g, 26.6%). mp74-75℃ (C_6H_6). ^{1}H-Nmr (270 MHz)($CDCl_3$) 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 ($CHCl_3$): 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℃, pH 7.65), then heated at 80℃ for 22 h. 36% aq. HCl (1.52 g, 0.015 mol) was added to the mixture, which was stirred at 80℃ 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 (C_6H_6-Et_2O 1:1) gave 3-amino-5-phenylisoxazole (0.61 g, 38.1%). mp 137.5-138℃ (C_6H_6). ^{1}H-Nmr (270 MHz)($CDCl_3$) δ: 7.37-7.74(5H, m), 6.09(1H, s), 4.00(2H, br). Ir($CHCl_3$): 3490, 3410, 3000, 1635, 1470 cm^{-1}.

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