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A New Synthetic Route to 5-Isoxazolamines

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Abstract: 5-Isoxazolamines were synthesized from α-cyano-β-nitro compounds by treatment with titanium trichloride.

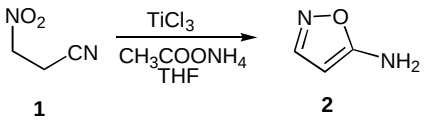
Keywords: Synthesis, 5-isoxazolamines, titanium trichloride.

5-Isoxazolamines have been used as intermediates for the synthesis of derivatives of antihistaminic, analgetic, antibacterial, insecticidal, herbicidal and fungicidal activity[1]. Usually they are synthesized by the intramolecular condensation of hydroxyl amine and β-nitrile group[2]. Other approaches, such as reductive cyclization of Z-α-cyano-β-nitro ethylenes and lithium aluminum hydride reduction of 3-cyano oxazoles have also been reported[3-6]. Here we report a new synthetic route of these compounds.

Ohno and Naruse [7] have reported that the reaction of 2-chlorocyclohexanone oxime with potassium or sodium cyanide in DMSO or ethanol afforded 3-amino-4,5,6,7-tetrahydrocyclohexa[C]-isoxazole in 48 % yield. They explained the reaction mechanism in terms of the displacement of the chlorine atom with a cyanide anion, followed by an instantaneous ring closure of the oxime and the cyano group. Interestingly, this reaction was appplied only to α-chloro-oximes of cycloalkanones, the application of this reaction to acyclic α-chloro-oximes failed to give 5-isoxazolamines, but gave the corresponding α-cyano oximes. Though, Bellec *et al*. reported that electroreduction of Z α-cyano-β-nitrostyrenes gave 5-isoxazolamines through intermediates of acyclic α-cyano oximes[4].

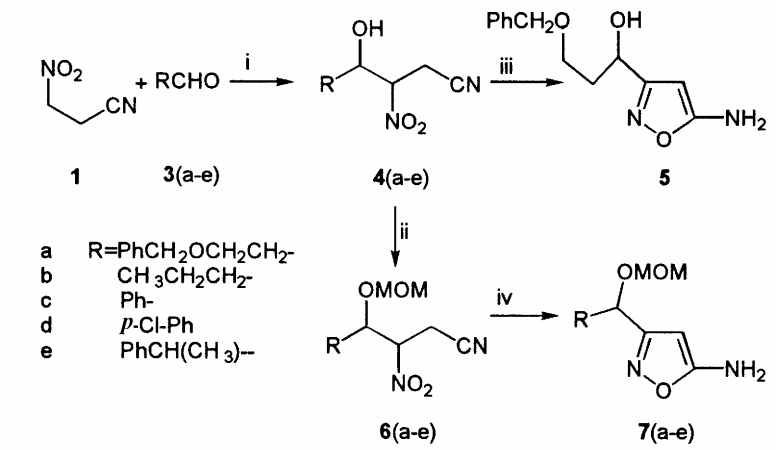
It has long been known that nitro compounds could be converted to aldehydes or ketones by aqueous titanium trichloride and oximes were supposed to be the intermediate of these reactions[8]. Should the oximes be the intermediate, treatment of α-cyano β-nitro compounds with aqueous titanium trichloride would result in 5-isoxazolamines instead of carbonyl compounds. Based on this consideration, a reaction of 3-nitro-propionitrile **1** with aq. titanium trichloride was carried out in tetrahydrofuran solution and 5-isoxazolamine **2** (75-77°C) was obtained in a yield of 64 %. (**Scheme 1**) Compound **2**, which is a useful starting material of some medicines and pesticides, has been reported to be prepared from α-alkoxy-β-cyano ethylenes by treatment of hydroxyamine in aq. sodium hydroxide (yield 63 %)[9].

Scheme 1



Because it is quite easy to introduce a substituent at the carbon atom which bears the nitro group. This method could be a very efficient way of synthesizing 3-substituted-5-isoxazolamines. Treatment of an isopropyl alcohol solution of 3-nitro-propionitrile **1** and aldehyde **3** (a-e) with potassium fluoride gave compound **4** (a-e), which without purificaion was treated with dimethoxymethane to protect the hydroxyl group, giving compound **6** (a-e) in fairly good yields (59-78 %). Treated with titanium trichloride **4**a and **6** (a-e) gave 3-substituted-5-isoxazolamines **5** and **7** (a-e) respectively. (**Scheme 2**) (**Table 1**)

Scheme 2



Conditions: i) KF, $(CH_3)_2CHOH$, 18-Crown-6, r.t., 6 hr.
ii) P_2O_5, $CH_3OCH_2OCH_3$, CH_2Cl_2,
iii) $TiCl_3$, CH_3COONH_4, THF, r.t
iv) $TiCl_3$, aq. NH_4OH, THF, r.t..

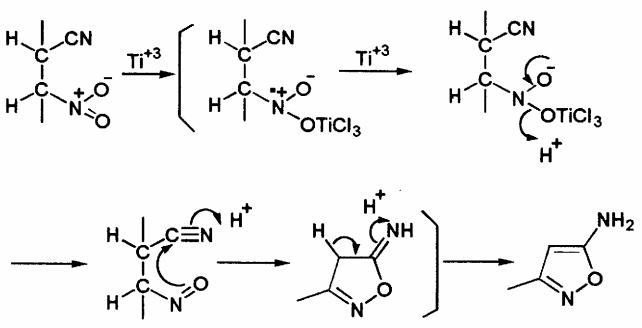
Table 1 Preparation of some 3-substituted 5-isoxazolamines

substrate	method	product	yield%
6a	A	**7a**	56.4
6b	B	**7b**	54.0
6c	B	**7c**	71.2
6d	B	**7d**	67.8
6e	B	**7e**	70.7
1	A	**2**	64.0

4b	B	**5**	42.5

The formation of isoxazole ring can be explained by the reduction of nitro group with titanium trichloride followed by nucleophilic attack on to the cyano group under very weak basic condition. (**Scheme 3**) Since the reaction was carried out under nearly neutral pH, functional groups labile to acid are intact.

Scheme 3



The Typical Procedure for the Reactions

(A). To a stirred solution (5 ml) of compound **1** (100 mg, 1 mmol) in tetra-hydrofurane was added aq. ammonium acetate (4 g in 4 ml water). Stirring was continued for 10 minutes. Aq. titanium trichloride solution (3 ml, 15 %) was added drop-wise to the vigorously stirred solution at room temperature under nitrogen atmosphere. The reaction mixture was stirred until compound **1** disappeared and then poured into ether (100 ml). The ether layer was washed with 5 % aq. sodium bicarbonate, brine, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by chromatography on silica gel giving a white solid **2**, m.p. 75-77°C (yield 64 %).

(B). To a stirred solution (5 ml) of compound **6**a (292 mg, 1 mmol) in tetra-hydrofurane was added 3 ml conc. aq. ammonium hydroxide solution. Stirring was continued for 30 minutes. Aq. titanium trichloride solution (3 ml, 15 %) was added dropwise to the vigorously stirred solution at room temperature under nitrogen atmosphere. Reaction mixture was treated as described in method A, giving a white solid **7**a, m.p. 68-70°C (yield 56.4 %).

References and Notes

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10. All new compounds have been satisfactorily characterized.

7a: m.p.68-70°C, δ_H ($CDCl_3$, 300 MHz) 7.31 (m, 5H), 5.08 (s, 1H), 4.78 (dd, J=6 Hz, 1H), 4.64 (d, J=6.7 Hz, 1H), 4.58 (d, J=6.7 Hz 1H), 4.55 (br., 2H), 4.49 (s, 2H), 3.66 (m, 2H), 3.36 (s, 3H), 2.08 (m, 2H). δ_C ($CDCl_3$, 75MHz) 168.8, 166.3, 138.4, 128.4 (2), 127.7 (3), 94.9, 76.7, 73.1, 68.3, 66.4, 55.8, 35.5. ν (film) 3331, 2891, 1640, 1597, 1497, 1100, 1033. m/z: 293 (M^++1, 1.9), 261 (4.8), 247 (2.0), 186 (9.7), 141 (13.4), 113 (12.8), 111 (13.3), 91 (100), 45 (72.1). Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H,6.90; N 9.59. Found C, 61.62; H, 7.01; N, 9.39.

7b: m.p.74-76°C, δ_H ($CDCl_3$, 300 MHz) 5.07 (s, 1H), 4.62 (d, J=6.7 Hz, 1H), 4.55 (dd, J=6.2 Hz, 7.7 Hz, 1H), 4.53 (d, J=6.7 Hz, 1H), 4.50 (br., 2H, NH_2), 3.36 (s, 3H), 1.8 (m, 1H), 1.67 (m, 1H), 1.44 (m, 2H), 0.94 (t, J=7.4 Hz, 3H). ν (film) 3393, 3327, 3206, 2945, 1658, 1595, 1497, 1038. m/z 201 (M^++1, 12.5), 169 (15.7), 140 (19.5), 139 (19.9), 111 (36.8), 45 (100). Anal. Calcd for $C_9H_{16}N_2O_3$: C, 53.98 ; H, 8.05; N, 13.99; Found C,53.97; H,8.11; N 13.74.

7c: m.p. 116-118°C, δ_H 7.36 (m, 5H), 5.71 (S, 1H), 5.06 (s, 1H), 4.75 (d, J=7 Hz, 1H), 4.69 (d, J=7 Hz, 1H), 4.39 (br., 2H), 3.39 (s, 3H). δ_C ($CDCl_3$, 75MHz) 168.6, 166.4, 139.2, 128.6 (2), 128.2, 126.8 (2), 94.3, 76.7, 72.1, 55.9. ν (film) 3381, 3316, 3199, 1650, 1593, 1491, 1453. m/z 235 (M^++1, 2.48), 174 (17.5), 173 (34.6), 157 (45.7) 130 (22.1), 45 (100). HRMS $C_{12}H_{14}N_2O_3$ Requires 234.1005,
Found 234.1000.

7d: m.p. 111-113°C, δ_H ($CDCl_3$, D_2O, 300MHz) 7.38 (m, 4H), 5.68 (s, 1H), 5.04 (s, 1H), 4.74 (d, J=6.6 Hz, 1H), 4.67 (d, J=6.6Hz,1H), 3.39 (s, 3H). ν (film) 3335, 3205, 1639, 1598, 1492. m/z 269 (M^++1, 5.6), 209 (15.1), 207 (43.7), 173 (8.9), 164 (8.4), 139 (7.5), 45 (100). HRMS $C_{12}H_{13}N_2O_3Cl$ Requires 268.0615, Found 268.0629.

7e: (diastereoisomer) m.p. 98-100°C, δ_H ($CDCl_3$, 300MHz) 7.27 (m, 5H), 5.07 & 4.97 (s, CH-O), 4.69 (d, J=7Hz, 1H), 4.61 (d, J=7Hz, 1H), 4.49 (d. J=5.3, 1H), 4.35 (br., 2H, NH_2), 3.18 (s, 3H), 2.81 (s, 1H), 1.42 & 1.18 (d, J=7Hz, CH_3).ν (film) 3377, 3185, 1658, 1597, 1502. m/z 263 (M^++1, 26.9), 262 (M^+, 4.9), 231 (20.6), 201 (46.7), 184 (21.9). HRMS $C_{14}H_{18}N_2O_3$ Requires 262.1317, Found 262.1327.

5: liquid, δ_H ($CDCl_3$, 300MHz) 7.30 (m, 5H), 5.11 (s, 1H), 4.88 (t, J=6. Hz, 1H), 4.59 (br, 2H), 4.51 (s, 2H), 3.71 (m, 2H), 2.05 (m, 2H). δ_C ($CDCl_3$, 75MHz,) 168.4, 168.0, 137.5, 128.1 (2), 127.4 (3), 76.3, 73.0, 67.7, 66.1, 35.6. ν (film) 3328, 3200, 1635, 1587, 1496. m/z: 249 (M^++1, 11.0), 232 (1.6), 157 (3.1), 141(4.6), 114(14.0), 91(100). HRMS: $C_{13}H_{16}N_2O_3$ Requires 248.1161, Found, 248.1169.

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