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Communications

Regioselective Synthesis of 3-Amino-4-arylisoxazol-5(4*H*)-ones

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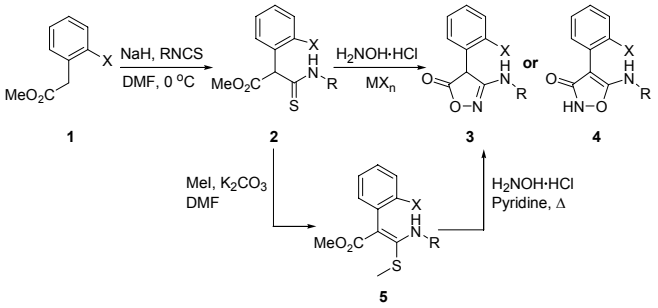
3-Aminoisoxazol-5(4*H*)-one is an important building block of many biologically active compounds including antimicrobial and antioxidant,[1] K channel opener,[2] and kinase inhibitors.[3] Besides, it could be transformed to fused heterocyclic compounds such as indoles, imidazopyridines,[4] and isoxazolopyrimidines.[5] Condensation reaction of α-cyanoacetate with hydroxylamine was a well known method to access either 3-aminoisoxazol-5(4*H*)-one or isomeric 5-aminoisoxazol-3(4*H*)-one depending upon condition.[6] For instance, reaction under the neutral condition provided 3-aminoisoxazolone isomer *via* acetamidoxime intermediate, whereas 5-aminoisoxazolone isomer was obtained under the alkaline condition. There were only few methods reported in the literature for the preparation of 3-alkyl/arylaminoisoxazoles-5(4*H*)-ones **3**, such as cyclization of 3-chloroacryloyl chloride,[7] α-amidoximino etser,[8] and thiocarbamoyl malonate with hydroxylamine.[4a] Alkylation of readily available 3-aminoisoxazolone occurred predominantly at isoxazolone ring nitrogen.[6a] Therefore, we were interested in development of new synthetic method to 3-alkyl/arylaminoisoxazol-5(4*H*)-ones **3**. We expected the condensation of thiocarbamoyl ester **2** with hydroxylamine in the presence of Hg(II) or Ag(I) complex would provide 3-aminoisoxazolones **3** selectively (Scheme 1). Hg(II) or Ag(I) complex have been used for the preparation of amidines and amidoxime *via* activation of thiocarbonyl.[9]

The starting thiocarbamoyl ester **2** was prepared from methyl arylacetate **1** by modified known procedure.[10,11] Cyclization of thiocarbamoyl ester **2** with hydroxylamine was investigated under the various conditions (Table 1). Treatment of **2a** with hydroxylamine hydrochloride and triethylamine (3.0 equiv) in refluxing ethanol for 17 h resulted in recovery of **2a** (entry 1). However, 3-aminoisoxazolone **3a** was produced in good yield in the presence of mercury oxide (entry 2). Cyclization with mercury (II) chloride afforded an improved yield of **3a** (entry 3). We then attempted regioselective cyclization of **2a** to 5-aminoisoxazol-3-one **4a**, based upon the literature example of the use



Scheme 1

Table 1. Preparation of thiocarbamoyl esters **2** and cyclization to 3-aminoisoxazol-5(4*H*)-ones **3** in various conditions

entry	X	R	Yield of **2** (%)	condition	Yield of **3** (%)
1				$NH_2OH.HCl$/TEA, EtOH, 80 °C	**3a** (0)
2				$NH_2OH.HCl$/TEA, HgO, CH_2Cl_2, rt	**3a** (60)
3				$NH_2OH.HCl$/TEA, $HgCl_2$, CH_2Cl_2, rt	**3a** (72)
4	Br	Me	**2a** (61)	$NH_2OH.HCl/AlCl_3$, toluene, 110 °C	**3a** (trace)
5				$NH_2OH.HCl/ZrCl_4$, toluene, 110 °C	**3a** (trace)
7				$NH_2OH.HCl/Zr(OBu\text{-}t)_4$, toluene, 110 °C	**3a** (32)
8				i. MeI, K2CO3, ii. $NH_2OH.HCl$/pyridine, 110 °C	**3a** (45)
9	Br	Ph	**2b** (58)	NH_2OH·HCl/TEA, $HgCl_2$, CH_2Cl_2, rt	**3b** (52)
10	H	Me	**2c** (61)	NH_2OH·HCl/TEA, $HgCl_2$, CH_2Cl_2, rt	**3c** (78)
11	H	Ph	**2d** (59)	NH_2OH·HCl/TEA, $HgCl_2$, CH_2Cl_2, rt	**3d** (88)
12	Me	Me	**2e** (74)	NH_2OH·HCl/TEA, $HgCl_2$, CH_2Cl_2, rt	**3e** (69)
13	OBn	Me	**2f** (56)	NH_2OH·HCl/TEA, $HgCl_2$, CH_2Cl_2, rt	**3f** (40)
14	OBn	Ph	**2g** (53)	NH_2OH·HCl/TEA, $HgCl_2$, CH_2Cl_2, rt	**3g** (45)

of aluminum and zirconium complex in transformation of ester to amde.[12] However, use of $AlCl_3$ or $ZrCl_4$ did not give **4a**, but afforded a trace amount of **3a** instead (entry 4-6), which was presumably produced by uncatalyzed thermal cyclization reaction at elevated temperature. To examine the scope of this method in preparation of other substituted 3-aminoisoxazol-5-ones, we attempted the cyclization of various thiomalonamic esters (**2a-g**) to the corresponding aminoisoxazoles (**3a-g**) as listed in Table 1. As shown in Table 1, most of the thiocarbamoyl esters were converted to the corresponding 3-aminoisoxazol-5-one under mercuric chloride mediated condition in moderate to high yield.

The structure of **3a** was elucidated by the comparison of its spectroscopic data with those of the compound prepared *via* the conversion of thiocarbamoyl ester **2a** to ketene N, S acetal **5a** followed by cyclization with hydroxylamine hydrochloride in refluxing pyridine (Entry 8).[13]

In summary, we have demonstrated a new and efficient method for the synthesis of 3-substituted aminoisoxazoles from readily available thiocarbamoyl esters. Mercury (II) chloride appeared to be a Lewis acid of choice among the metals tested in this cyclodesulfurization reaction. Application of this method for the synthesis of substituted aminopyrazoles is now under investigation in our laboratory.

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13. a) A typical experimental procedure for mercuric chloride mediated cyclization reactions: To a solution of thiocarbamoyl ester **2a** (0.53 g, 1.75mmol), hydroxylamine hydrochloride (0.13 g, 1.92 mmol), and mercuric chloride (0.62 g, 2.28 mmol) in dichloromethane (18 mL) was added triethylamine (0.49 mL, 3.50 mmol) at rt. The reaction mixture was stirred for 24 h, filtered, and washed with dichloromethane (2 × 10 mL). The combined organic layer was washed with 1 N hydrochloric acid (20 mL), water (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The remaining material was purified by flash column chromatography (hexane:ethyl acetate = 2:1) to give **3a** (0.34 g, 72%). b) The ^{1}H- and ^{13}C NMR spectroscopic data for compound **3a** prepared from entry 3 and 8 are identical. ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.72 (d, J = 5.2 Hz, 3H), 5.00 (m, 1H), 7.09-7.32 (m, 3H), 7.56-7.60 (m, 1H), 10.73 (bs, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 28.3, 79.4, 125.8, 127.6, 129.1, 131.6, 132.6, 133.7, 164.6, 169.9; IR (KBr) 3382, 2995, 1707, 1616 cm^{-1}; MS (70 eV, *m/z*) 268 [M^+], 270 [M^+ + 2], 209, 195, 183, 131, 89.