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Synthesis of 2-aminooxazolines from isonitriles and iodine

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Abstract

A novel one-pot protocol for the synthesis of substituted 2-aminooxazoline from isonitriles and 2-aminoethanol was developed and the reactions involved imidoyl diiodide intermediates, which were generated by mixing isonitriles and iodine in CH_2Cl_2 at room temperature.

Keywords: 2-Aminooxazoline; Isonitrile; Imidoyl diiodide

Imidoyl dichloride, acting as an electrophilic reagent, is a versatile intermediate to the synthesis of various heterocyclic compounds [1]. However, the preparation of imidoyl dichloride usually required toxic reagents and harsh conditions, which limited its application in organic synthesis [2]. Recently, imidoyl dibromide and diiodide, as efficient substitution for imidoyl dichloride, attracted more and more interests for their easy generation by mixing isonitriles and bromine or iodine [3], and these compounds could undergo subsequent conversion *in vivo* without further purification, which makes the reactions more convenient [4].

In our previous work, we reported the synthesis of substituted guanidines by guanylation of amines with isonitriles in the presence of iodine and sodium bicarbonate and the reaction involved imidoyl diiodides intermediate [5]. We envisaged that such an intermediate could also be trapped by a molecular containing two nucleophlic groups, and then a heterocyclic compound would be obtained by dehydroiodination.

Initially, we investigated the reaction of 4-nitrophenylisonitrile (**1a**) and ethylenediamine in the presence of iodine and sodium bicarbonate in CH_2Cl_2 at room temperature, but no product was found. When glycol was used instead of ethylenediamine, a new compound could be detected as monitored by TLC, but underwent decomposition during workup. In case of 2-aminoethanol **2a**, a stable product was isolated in the yield of 82% and was identified as *N*-(4-nitrophenyl)-2-aminooxizole **3a**. Encouraged by such a result, we examined the scope of the reaction and the results are summarized in Table 1. Different aryl isonitriles gave the desired products in moderate yields regardless of electron-donating or electron-withdrawing groups linked on the benzene ring (Table 1, entries 1−8). Regrettably, alkyl isonitriles such as p-methoxy benzyl isonitrile **1e** and *t*-butyl isonitrile **1f** failed to the reaction (Table 1, entries 9−10). In most cases, 1-amino-2-propanol **2b** gave similar yields as **2a**.

The reaction of 4-nitrophenylisonitrile **1a** and 3-amino-1-propanol **4** was also tested. Interestingly, guanidine **5** was obtained as the only product and no cyclic product was detected (Scheme 1).

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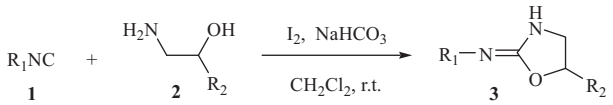
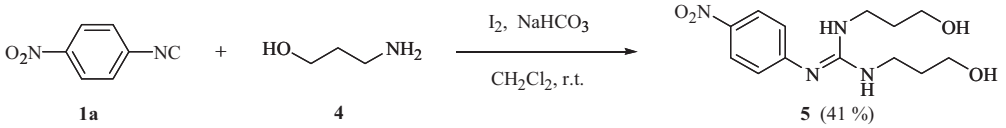
Table 1
Synthesis of substituted 2-aminooxazoline from isonitriles and 2-aminoethanol.



Entry	R^1	R^2	Product	Yield (%)[a]
1	4-$NO_2C_6H_4$ **1a**	H **2a**	**3a**	82
2	4-$NO_2C_6H_4$ **1a**	CH_3 **2b**	**3b**	74
3	4-$MeOC_6H_4$ **1b**	H **2a**	**3c**	52
4	4-$MeOC_6H_4$ **1b**	CH_3 **2b**	**3d**	61
5	4-*t*-BuC_6H_4 **1c**	H **2a**	**3e**	76
6	4-*t*-BuC_6H_4 **1c**	CH_3 **2b**	**3f**	72
7	4-ClC_6H_4 **1d**	H **2a**	**3g**	41
8	4-ClC_6H_4 **1d**	CH_3 **2b**	**3h**	36
9	4-$MeOC_6H_4CH_2$ **1e**	H **2a**	**3i**	Trace
10	*t*-Bu **1f**	H **2a**	**3j**	Trace

[a] Isolated yields.



Scheme 1. Reaction of 4-nitrophenylisonitrile **1a** and 2-amino-1-propanol **4** in the presence of iodine and sodium bicarbonate.

1. Experimental

A mixture of isonitrile (1.0 mmol), 2-aminoethanol (1.0 mmol) and $NaHCO_3$ (168 mg, 2.0 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C, then a solution of iodine (254 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise within 15 min. After stirring at room temperature for 4 h, the reaction was quenched with water. The organic layer was dried with anhydrous Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by aluminum oxide chromatography (Hexane/EtOAc = 2:1) to give the product. **3a** [6] yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, 2H, J = 8.4 Hz), 6.68 (d, 2H, J = 8.4 Hz), 4.04 (s, 1H), 3.73 − 3.68 (m, 2H), 3.60 − 3.56 (m, 2H). **3b** [7] white solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, 2H, J = 8.4 Hz), 6.66 (d, 2H, J = 8.4 Hz), 4.07 (s, 1H), 3.88 − 3.81 (m, 2H), 3.68 − 3.60 (m, 1H), 1.18 (d, 2H, J = 7.5 Hz). **3c** [6] yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, 2H, J = 6.0 Hz), 6.95 (d, 2H, J = 6.0 Hz), 4.16 (s, 1H), 3.79 (s, 3H), 3.69 − 3.62 (m, 2H), 3.89 − 3.85 (m, 2H). **3d** [7] yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, 2H, J = 6.0 Hz), 7.15 (d, 2H, J = 6.0 Hz), 4.30 (s, 3H), 4.12 (s, 1H), 3.88 − 3.81 (m, 2H), 3.68 − 3.60 (m, 1H), 1.23 (d, 2H, J = 7.5 Hz).

In summary, we developed a convenient method to the synthesis of 2-amino oxizoles from isonitriles and 2-aminoethanol in the presence of iodine and sodium bicarbonate in CH_2Cl_2 at room temperature. The reaction is easy to handle and the yields are moderate to good.

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