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A New and Efficient Synthesis of 2H-3, 1-Benzoxazine Compounds

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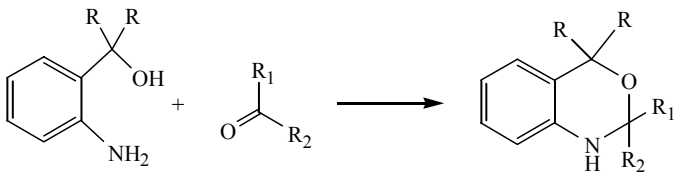
Abstract: 2H-3, 1-Benzoxazine derivatives were synthesized by cyclocondensation of 5-nitro-2-cyanoaniline with relative ketone or aldehyde with $ZnCl_2$ as a catalyst. This is a new efficient synthetic route of 2H-3, 1-benzoxazine cyclic compounds.

Keywords: 2H-3, 1-Benzoxazine, cyclocondensation, synthesis.

2H-3, 1-Benzoxazine heterocyclic compounds are a series of potent nonsteroidal progesterone receptor agonists[1-3] and have many other applications such as carbonaceous electrode, plant growth regulating and anti-stress activities[4-6], *etc.*. Comparing to other benzoxazine series, such as 1, 4-benzoxazine, 2H-1, 3-benzoxazine, *etc.*, little attentions have been paid for this series of compounds. There is only one method for the preparation of 2H-3, 1-benzoxazine, *e.g.* cyclocondensation of *o*-aminophenyl alcohol with ketone or aldehyde (**Scheme 1**). Here, we will describe a new efficient synthetic route for 2H-3, 1-benzoxazine.

As tacrine (9-amino-1, 2, 3, 4-tetrahydroacridine, THA), one of AchEIs (acetylcholinesterase inhibitors), possesses serious toxicity, for reducing the toxicity of tacrine, a large number of THA's derivatives and analogs have been synthesized. Among those compounds, 6-substituted tacrines, such as 6-methoxy-, 6-bromo- or 6-chloro-derivatives, perform a good pharmoactivity. So, we designed a derivative **2**, bearing nitro substitute

Scheme 1 General synthetic method of 2H-3,1-benzoxazine derivatives



R=H, Me, *etc.*; R_1=H, Me, *etc.*; R_2 =H, *etc.*

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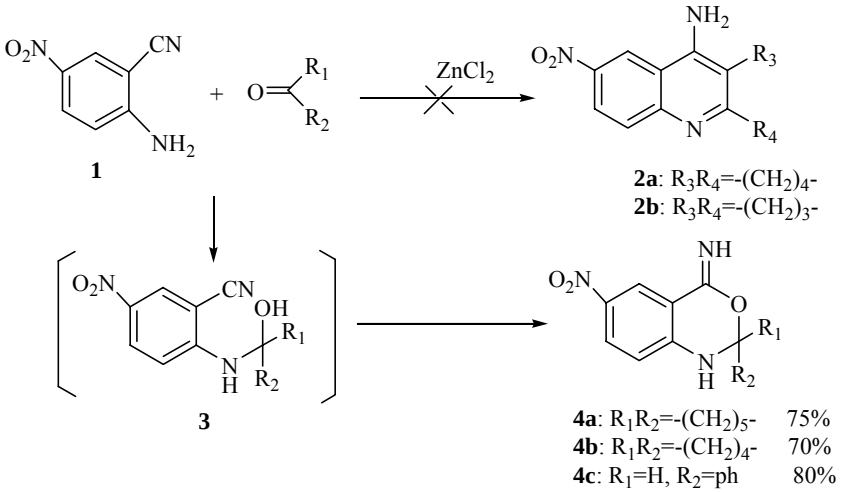
Scheme 2 The synthetic route of 2H-3, 1-benzoxazine derivatives



at aromatic ring of tacrine. Unfortunately, the target 7-nitrotacrine could not be obtained by the reaction of 5-nitro-2-cyanoaniline with cyclohexanone under $ZnCl_2$ as a catalyst, but an unknown yellow solid was afforded. The new compound was 2H-3, 1-benzoxazine derivative (spiro [2H-6-nitro-3, 1-benzoxazine-2, 1′-cyclohexan]-4 (1H)-imine **4**, seen **Scheme 2**). This is the new approach for the synthesis of 2H-3, 1-benzoxazine derivative.

When cyclopentanone replaced cyclohexanone, the relative compound **4b** was obtained. Compound **4c** was unique product when phenyl aldehyde replaced cyclohexanone. The synthetic route was outlined in the **Scheme 2**.

5-Nitro-2-cyanoaniline (1.0 g, 6 mmol) was refluxed in cyclohexanone (10.0 mL) under the catalysis of zinc chloride (1.0 g, 7 mmol) for 1 hour. Then, the reaction mixture was filtrated. The filtration residue was dispersed into water and alkalized by sodium hydrate to pH=13. After filtration, the rude product was recrystallized from ethanol to give the target compound of spiro[2H-6-nitro-3, 1-benzoxazine-2, 1′-cyclohexan]-4 (1H)-imine.

In summary, this paper described a new synthetic route for the preparation of 2H-3, 1-benzoxazine. The new compound of spiro[2H-6-nitro-3, 1-benzoxazine-2, 1′-cyclohexan]-4 (1H)-imine and its derivatives were synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. The spectral data of the target compound **4a** were shown in the note[7]. This work will be continued.

Acknowledgments

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References and Note

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7. Spectral data of **4a**:
   IR (KBr): v 3359, 3188, 3061, 2935, 1672, 1618, 1529, 1505, 1313 cm^{-1}. ^1H NMR (400 MHz, DMSO, δ ppm): 8.44 (s, 1H, =NH), 8.39 (d, 1H, *J*=2.8 Hz, ArH), 8.10 (dd, 1H, *J*=2.8, 7.7 Hz, ArH), 8.08 (s, 1H, R_1R_2NH), 6.94 (d, 1H, *J*=7.7 Hz, ArH), 1.80-1.05 (m, 10H, C_5H_{10}). ^{13}C NMR (DMSO, δ ppm): 21.13, 24.74, 38.36, 69.19, 112.88, 114.99, 124.57, 129.26, 137.27, 151.85, 161.66. ESIMS (*m/z*): 262.2 ($M+H^+$), 284.2 ($M+Na^+$), 300.2 ($M+K^+$). Elemental analysis: Calcd. for $C_{13}H_{15}N_3O_3$ C 59.76, H 5.78, N 16.08; Found C 59.73, H 5.79, N 16.09.

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