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Design and Synthesis of 3, 4-Dihydropyrrolo[2, 1-c][1, 4]oxazin-1-one and its 7-Acyl Derivatives

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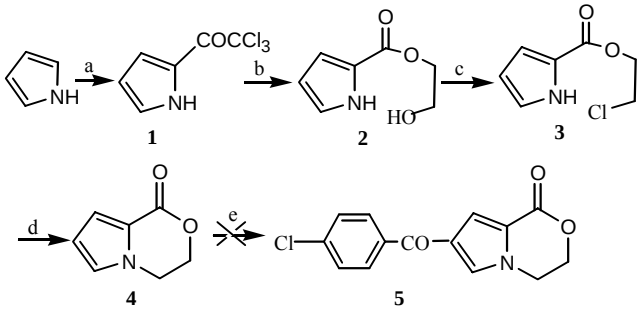
Abstract: Starting from 1*H*-pyrrole, unreported 3, 4-dihydropyrrolo[2, 1-c][1, 4]oxazin-1-one **4**, 7-(4-chlorobenzoyl)-3, 4-dihydropyrrolo[2, 1-c][1, 4]oxazin-1-one **5** and 7-benzoyl-3, 4-dihydro-pyrrolo [2, 1-c][1, 4]oxazin-1-one **9** were designed and synthesized. They may have antipyretic and analgesic activities.

Keywords: 3, 4-Dihydro-pyrrolo[2,1-c][1,4]oxazin-1-one, 7-acyl derivatives, synthesis, antipyretic, analgesic.

Some analogs of 3*H*-1, 2-dihydro-1-pyrrolizinone, such as 5-(4-chlorobenzoyl)-3*H*-1, 2-dihydro-1-pyrrolizinone, have strong antipyretic and analgesic activities, and less side effects[1]. To develop more efficient antipyretic and analgesic drugs of new structures with low toxicity to livers and digestive systems, 3, 4-dihydro-pyrrolo[2,1-c] [1,4] oxazin-1-one, and its 7-acyl derivatives(with chemical structure similar to 3*H*-1, 2-dihydro-1-pyrrolizinone), were designed according to the bioisosterism principle of medicinal chemistry[2], and synthesized by three routes respectively, as shown in **Scheme 1, 2** and **3.**

Scheme 1



Reagents and conditions: a) Cl_3CCOCl, 2-methyl pyridine/$CHCl_3$, reflux 3 h, 50%; b) $NaO(CH_2)_2OH$/THF, r. t, 5 h, 61%; c) $PBr_3/CHCl_3$, r. t. 6 h, 59%; d) NaH/DMF, r. t. 0.5 h, reflux 7 h, 80%;

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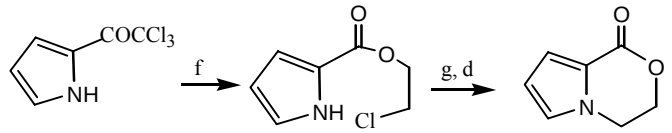
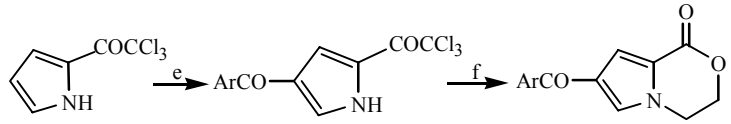
Scheme 2



1 **6** **4**

Scheme 3



1 **7 or 8** **5 or 9**

f) $Cl(CH_2)_2OH$, Na_2CO_3/DMF, reflux 6.5 h, compd. **6**, 73%; g) NaI/Me_2CO, reflux 6 h, g and d overall yield 68%; e) ArCOCl, $AlCl_3$/$Cl(CH_2)_2Cl$, r. t, 0.5 h, reflux 4h, compd. **7**, 70%, compd. **8**, 73%; f) compd. **5**, 65%; compd. **9**, 62%.

So far there is no report about the synthesis of compounds **4**, **5** and **9**. Esterification of 2-trichloroacetyl 1*H*-pyrrole **1**(prepared from 1*H*-pyrrole[3]) with the monosodium salt of ethylene glycol afforded 2-hydroxyethyl-2-(1*H*-pyrrolyl) formate **2**, which was then brominated by phosphorous bromide[4]. Thus prepared 2-bromoethyl-2-(1*H*-pyrrolyl) formate **3** was successfully cyclized to 3, 4-dihydropyrrolo[2, 1-c][1, 4]oxazin-1-one **4** by sodium hydride[5], but surprisingly compound **4** could not react with 4-chlorobenzoyl chloride under usual Friedel-Crafts acylation condition to get compound **5** (**Scheme 1**). Compound **4** could also be prepared more conveniently by treatment of compound **1** with 2-chloroethanol under basic condition **(Scheme 2)**.

Compound **1** reacted with acyl chloride under the catalysis of alumium chloride to produce 4-aroyl-2-trichloroacetyl-1*H*-pyrrole **7** and **8** separatedly[6], which reacted with 2-chloroethanol under basic condition to get 7-acyl-3, 4-dihydropyrrolo[2, 1-c][1, 4] oxazin-1-one **5** or **9** in one step reaction **(Scheme 3**), better than our original plan to get them in successive esterification and cyclization reactions.

This is the first report about the preparation of 3, 4-dihydropyrrolo[2, 1-c][1, 4] oxazin-1-one compounds by this method. The successful preparation of **4**, **5** and **9** played a very important role in our structure-activity study of 3*H*-1, 2-dihydro-1-pyrrolizinone analogs and structure-alike compounds, and provided a new synthetic route of these compounds.

In summary, three derivatives of 3, 4-dihydropyrrolo[2, 1-c][1, 4]oxazin-1-one were synthesized. Eight unreported compounds **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9** as shown in **Scheme 1**, **2**, and **3**, were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, HRMS or elemental analysis. The spectral data of target compounds **4**, **5** and **9** were shown in reference[7].

Acknowledgment

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References and Notes

1. S. F. Zhang, et al. Acta Pharmaceutica Sinica, **1988**, 23, 28.
2. Z. M. Qiu, Drug Design, Higher Education Press, Beijing, **1999**, 7.
3. J. W. Harbuck, et al. J. Org. Chem., **1972**, 32, 3618.
4. H Pines, *et al*. *J. Am. Chem. Soc*., **1952**, *24*, 4063.
5. E. P. Papadopoulos, *et al*. *J. Org. Chem*., **1968**, *33*, 1299.
6. H. J. Anderson. *Can. J. Chem*., **1957**, *35*, 21.
7. Spectra data of new compounds
   Compound **4** IR (KBr): ν 1717, 1534, 1404, 1348, 1318, 1185, 1071, 1046, 745cm^{-1}. ^{1}H NMR (200MHz, $CDCl_3$): δ 7.11-6.28(m, 3H, ArH), 4.60-4.41(t, 2H, J=5.0Hz), 4.20(t, 2H, J=5.0Hz, CH_2N); ^{13}C NMR(50MHz, $CDCl_3$): 42.13, 65.56, 109.69, 116.15, 118.24, 124.63, 158.26 EIMS(*m/z*): 137(M^+), 107(M-CH_2O), 79(M-CO_2CH_2); HRMS calcd. for $C_7H_7NO_2$ 137.0477 found 137.0470. Compound **5** IR(KBr): ν 1715, 1642, 1539, 1379, 1251, 1074, 856, 758, 698 cm^{-1}; ^{1}H NMR(200MHz, $CDCl_3$): δ 7.27-7.82(m, 6H, ArH), 4.67(t, 2H, J=8.2Hz, CH_2O), 4.31(t, 2H, J=13.2Hz, CH_2N); ^{13}C NMR(50MHz, $CDCl_3$): 188.33, 179.58, 157.97, 138.63, 136.73, 132.01, 128,51, 125.25, 119.00, 110.45, 65.90, 43.66; Elemental analysis::calcd. C 64.75 H 3.88 N 5.39 found C 64.52 H 3.69 N 5.54. Compound **9** IR(KBr): ν 1715, 1642, 1585, 1539, 1379, 1251, 1019, 856, 758, 698, 508cm^{-1}; ^{1}H NMR(200MHz, $CDCl_3$): δ 7.86-7.28 (m, 7H, ArH), 4.68(t, 2H, J=1.2Hz, NCH_2), 4.31(t, 2H, J=1.3Hz, OCH_2); ^{13}C NMR (50MHz, $CDCl_3$): 179.65, 132.31, 130.84, 128.92, 129.00, 125.96, 118.42, 117.15, 110.52, 65.89, 45.01; Elemental analysis: calcd. C 74.65 H 4.92 N 6.22 found C 74.38 H 4.75 N 6.43.

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