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Synthesis of 5-Aryl-1, 2-dihydro-1-pyrrolizinones

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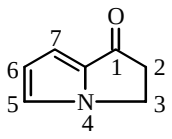
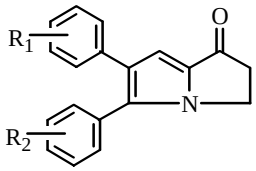
Abstract: In order to search for new potent anti-inflammatory and analgesic agents in pyrrolizinones, the title compounds were designed and synthesized. A series of the compounds were prepared with two different synthetic schemes. Some of the compounds showed remarkable anti-inflammatory and/or analgesic activities on mice.

Keywords: 5-Aryl-1, 2-dihydro-1-pyrrolizinone, anti-inflammation, analgesic, synthesis.

It has been reported that some *1H*-1, 2-dihydro-1-pyrrolizinone (**1)** derivatives showed potent anti-inflammatory and analgesic activities[1]. Based on the theory of structure-activity relationship (SAR) of COX-2 inhibitor, Li Qin ZHAO *et al*. designed and synthesized a series of 5, 6-diaryl derivatives of *1H*-1, 2-dihydro-1-pyrrolizinone **(2)**, and studied their SAR with computer-aid three dimensional quantitative structure-activity relationship (3D-QSAR)[2]. The results suggested that the 6-aryl substituent seemed to make little contribution to their activities. Therefore, we designed a series of 5-aryl-1, 2-dihydro-1-pyrrolizinones (**3**), and wished to find new anti-inflammatory and analgesic agents with potent activities and lower toxicity.



1



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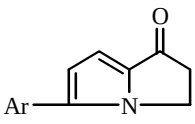

3

As far as we know, the only successful synthesis of 1, 2-dihydro-1-pyrrolizinone in literatures is the cyclization of 3-(1-pyrrolyl)propanenitrile by Heosch reaction, and the nitrile was prepared from pyrrole and acrylonitrile. Therefore, the preparation of 2-arylpyrrole is the key step for the synthesis of compounds **3**. Severin and Poehlmann have reported the synthesis of 2, 3-diarylpyrroles from 1, 2-diarylethanones and glyoxal dimethylhydrazone[3]. Based on this synthetic scheme, 2-arylpyrroles could be synthesized from acetophenones instead of diarylethanones. Thus, acetophenone reacted

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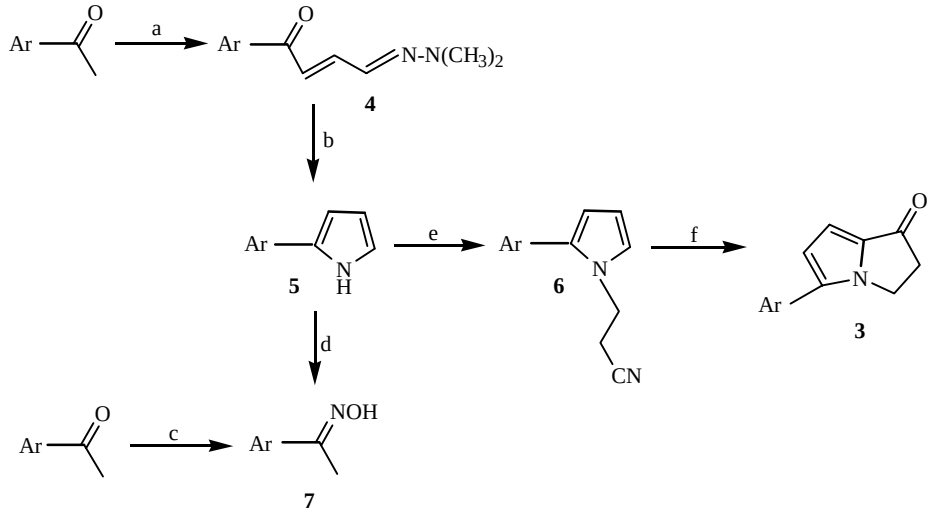
with glyoxal dimethylhydrazone to produce 4-aryl-4-oxo-2-butenal dimethylhydrazone (**4**). Reduction-cyclization of compound **4** with $Na_2S_2O_4$ afforded 2-arylpyrrole (**5**). 2-Arylpyrroles were proved to undergo N-alkylation with acrylonitrile readly to give 3-(2-arylpyrrol-1-yl) propanenitrile (**6**), which were converted to compounds **3** by Heosch reaction (**Scheme 1**).

Generally, with this synthetic route, the yields of converting compound **4** to **5** were low, and could not apply to the preparations when the aryl contains some sensitive groups to the reducing agent $Na_2S_2O_4$, such as halogen, nitro and pyridine ring system. Therefore, some new synthetic schemes were tried for the synthesis of compounds **3**.

Scheme 1



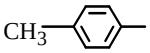
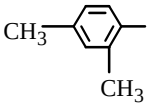
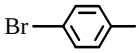
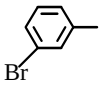
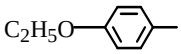
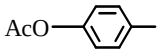
a.$HOCCHNN(CH_3)_2/C_2H_5ONa/C_2H_5OH$, reflux; b.$Na_2S_2O_4/C_2H_5OH/H_2O$, reflux; c.$NH_2OH.HCl$ /NaOAc/C_2H_5OH/H_2O, reflux; d. $C_2H_4Cl_2$/KOH/DMSO, 120°C; e. CH_2=CHCN/TEBA/THF, rt; f. HCl/THF/$C_2H_5OC_2H_5$; NaOH/H_2O;30-40°C, 85-90°C

Trofimov B.A. reported that acetophenone oximes reacted with 1, 2-dichloroethane to produce 2-phenylpyrroles with moderate yield[4]. With similar procedure, a variety of compounds **5,** and then **3** were prepared (**Scheme 1**). This synthetic route was specially suitable to the preparation of the compounds containing sensitive groups to reducing agents $Na_2S_2O_4$, such as nitro, pyridine ring system, and halogen.

The N-alkylation of compounds **5** with acrylonitrile was carried out in THF catalyzed by TEBA to give compounds **6**. The reactions were completed within 30 min at room temperature, yields over 90%. Compounds **6** were cyclized by Hoesch reaction to give compounds **3**. The reaction could be carried out in ether or THF depending on the reactant, and the yields were also satisfactory.

With two schemes, compounds **3** were prepared. Their structures and some physical data were listed in the **Table 1.**

Table 1 Structure , mp and ^{1}HMR of compounds

Compd.	Ar	Mp (°C)	^{1}H-NMR (δ,ppm,$CDCl_3$)
3a		92-94	3.13(t, 2H), 4.47(t, 2H), 6.71(d, 1H), 6.84(d,1H), 7.36-7.58(m, 5H).
3b		113-114	2.40(s, 3H), 3.13(t, 2H), 4.45(t, 2H), 6.68(d, 1H), 6.84(d, 1H), 7.27(d, 2H), 7.45(d, 2H).
3c		101-103	2.27(s, 3H), 2.38(s, 3H), 3.08(t, 2H), 4.12(t, 2H), 6.46(d, 1H), 6.83(d, 1H), 7.07(d, 1H), 7.15(s, 1H), 7.17(d,1H).
3d		145-147	3.14(t, 2H), 4.44(t, 2H), 6.69(d, 1H), 6.82(d, 1H), 7.41(d,2H), 7.57(d, 2H).
3e		121-123	3.14(t, 2H), 4.47(t, 2H), 6.71(d, 1H), 6.83(d, 1H), 7.33-7.36(m, 1H), 7.48-7.51(m, 2H), 7.71(t, 1H).
3f		114-116	1.44(t, 3H), 3.11(t,2H), 4.04(q, 2H), 4.42(t, 2H), 6.62(d, 1H), 6.82(d, 1H), 6.95(d, 2H), 7.46(d, 2H).
3g		131-132	2.34(s, 3H), 3.14(t, 2H), 4.45(t, 2H), 6.68(d, 1H), 6.83(d, 1H), 7.17-7.22(m, 2H), 7.55-7.60(m, 2H).
3h		141-142	3.09(t, 2H), 4.10(t, 2H), 6.68(d, 1H), 6.93(d, 1H), 7.51-7.58(m, 4H), 7.82-7.84(m, 1H), 7.92-7.95 (m, 2H).
3i		126-127	3.14(t, 2H), 4.45(t,2H), 6.71(d, 1H), 6.79(d, 1H) 7.10(m, 1H), 7.27(m, 1H), 7.33(m, 1H).
3j		145-147	3.17(t, 2H), 4.49(m, 2H), 6.77(d, 1H), 6.85(d, 1H), 7.39-7.43(m, 1H), 7.86-7.89(m, 1H), 8.59-8.61(m, 1H), 8.87(m,1H).

Experimental

Melting points were determined with capillary tube method, and are uncorrected. ^{1}H-NMR spectrum was recorded on a Bruker ARX-300 spectrometer. MS was measured with GCMSQP-1000 instrument.

*1-aryl-1-oxo-2-butenal dimethylhydrazone (**4**)*

General procedure: To a mixture of 30 mmol of acetophenone and 36 mmol of glyoxal monodimethyl- hydrazone in 50 mL of ethanol was added dropwise a solution of sodium ethoxide prepared by dissolving 35 mmol of sodium metal in 20 mL ethanol. The reaction mixture was stirred at room temperature for 2 h. The resulting precipitate was filtered and washed with cold ethanol.

*2-Arylpyrrole (**5**)*

General procedure 1: A mixture of 12 mmol of 1-aryl-1-oxo-2-butenal dimethylhydrazone (**4**) and 72 mmol of sodium hydrosulfite in 120 mL of ethanol/water (2:1) was refluxed for 2 h, and then poured into 300 mL of ice water, and then extracted with

methylene chloride, the organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the corresponding product. General procedure 2: A mixture of 16 mmol of ketoxime (7) and 128 mmol of potassium hydroxide in 22 mL DMSO was vigorously stirred at 120°C. To the mixture was added a solution of 48 mmol of 1, 2-dichloroethane in 5 mL DMSO was added batchwise at 120°C within 5 h, and then stirred for another 0.5 h. After cooled to room temperature, the reaction mixture was poured into 200 mL ice-water. The formed precipitate was filtered and washed with cold water. The crude product was purified by recrystallization from cyclohexane.

*3-(2-arylpyrrolyl)propanenitrile (**6**)*

General procedure: To a mixture of 11 mmol of 2-arylpyrrole (**5**) and 110 mmol of vinyl cyanide in 30 mL of tetrahydrofuran, was added 0.3 mL of 40% benzyltriethyl ammonium hydroxide at room temperature with stirring. The resulting mixture was stirred at room temperature for another 0.5 h, and then evaporated under reduced pressure. The residue was dissolved in 50 mL of ethyl acetate, and the insoluble material was removed by filtration. The filtrate was washed with water, dried over Na_2SO_4. After removing the solvent, crude product was obtained. Most of the crude products were purified by silica-gel column chromatography.

*5-Aryl-2,3-dihydro-1-pyrrolizinone (**3**)*

General procedure: A stream of hydrogen chloride was gently passed through a solution of 4.1 mmol of 3-(2-arylpyrrol-yl) propanenitrile (**6**) in 30 mL ether at 0-5°C for 3 h. The solvent was decanted and the precipitate was washed with dry ether (30 mLx 2). 40 mL of water was added, and then 10% aqueous sodium hydroxide was added untill pH 4-4.5. The mixture was stirred at 30-40°C for 1 h, and then heated at 85-90°C for 2 h. After cooling to room temperature, the mixture was extracted with methylene chloride. The combined extracts were washed with water, dried over $MgSO_4$. After removing the solvent, crude product was obtained as a solid. The crude product was purified by recrystallization from ethanol, or column chromatography on silica-gel.

Pharmacological tests

The anti-inflammatory activities were evaluated by the xylene-induced ear edema on mice, and the analgesic activities were evaluated by acetic acid-induced writhing method. The primary results showed most of compounds **3** had anti-inflammatory and/or analgesic activities. Comparison with 5, 6-diaryl-pyrrolizinone derivatives, they had more potential anti-inflammatory and analgesic activities.

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