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Synthesis of Arylsubstituted Imidazolin-2-one Analogues

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Abstract: Herein we reported a one-pot synthesis of arylsubstituted imidazolin-2-ones by the cyclization of α-aminoacetophenone hydrochloride analogues **2** with arylisocyanates **3**. Compared with other known synthetic route, this method resulted in higher yield.

Keywords: One pot synthesis, arylsubstituted imidazolin-2-ones.

Imidazolone, in particular arylsubstituted imidazolin-2-ones have become an attractive target for combinatorial chemistry groups involved in searching pharmacological activitive agents[1]. Some species may be useful as antioxidants *in vivo*[2] and be used as PDE4 inhibitors[3]，also they were found to present at high levels in kidneys of rats with streptozotocin-induced diabetes as novel advanced glycation end products[4].

Several approaches to the synthesis of the class of imidazolin-2-ones have been reported. Such as rearrangement of quinolins *via* an oxidative ring[5], reaction of diaminomaleonitrile with aryl isocyanates[6], cyclizations and subsequently isomerization of N-propargyl carbanilides[7], reaction of α-bromomethyl ketimines with KNCO[8], *etc*. In this context, we wish to report a simple method for the synthesis of arylsubstituted imidazolin-2-ones analogues by reacting α-aminoacetophenones hydrochloride with arylisocyanates.

In the course of the research, unexpectedly, we found that the reaction of α-aminoacetophenone hydrochloride $\mathbf{2a_1}$ with phenylisocyanate $\mathbf{3a_1}$, prepared from aniline and triphosgene, provided 3,4-diphenyl-N-phenyl-imidazolin-2-one-1-carboxamide $\mathbf{4a_1}$ in high yield but 1,5-diarylsubstituted imidazolin-2-one $\mathbf{1a_1}$ could not be obtained even α-aminoacetophenone hydrochloride is in excess (**Scheme 1**). By further research, we found that when R_2 in compound **3** is electron withdrawing group，**4** can be obtained in high yields, and if it is an electron donor group, the mixture of **4** and **1** was obtained. The compounds **1** can be seen as analogues of CA-4[9]. The results are listed in **Table 1**. Compared with other known synthetic methods of arylsubstituted imidazolin-2-ones, this new method is simpler and provides higher yield.

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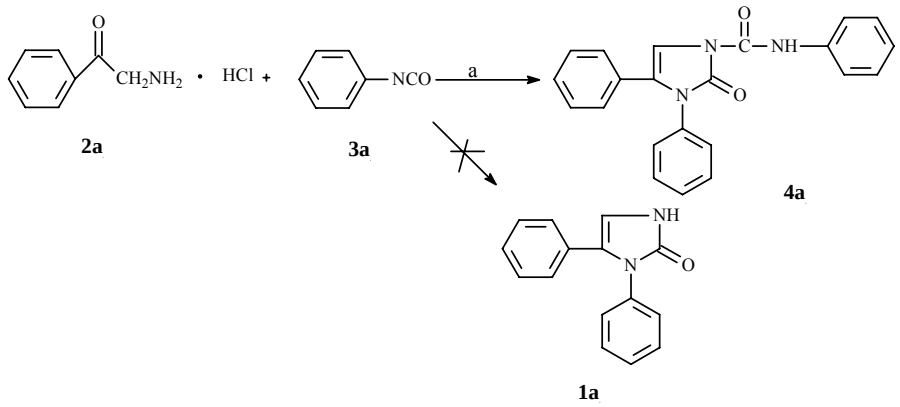
Scheme 1



a) toluene, reflux

The possible mechanism was illustrated in **Scheme 2**. During the reaction, α-aminoacetophenones hydrochloride **2** conjugated with arylisocyanates **3** in the refluxed toluene to generate intermediate **5** , because the nuclephilicity of amino (3') is higher than amino (5'), and the electrophilicity of carbonyl of arylisocyanate is higher than carbonyl (4'), so the intermediate **5** is more easily to react with another molecular of arylisocyanate and provide **4** (path A). The electron donor character and stereo effects are the possible reason for the formation of **1** and **4,** when R_2 are *O*-MeO, *P*-MeO, 3,4,5-triMeO and *O*-Br (path B).

Scheme 2

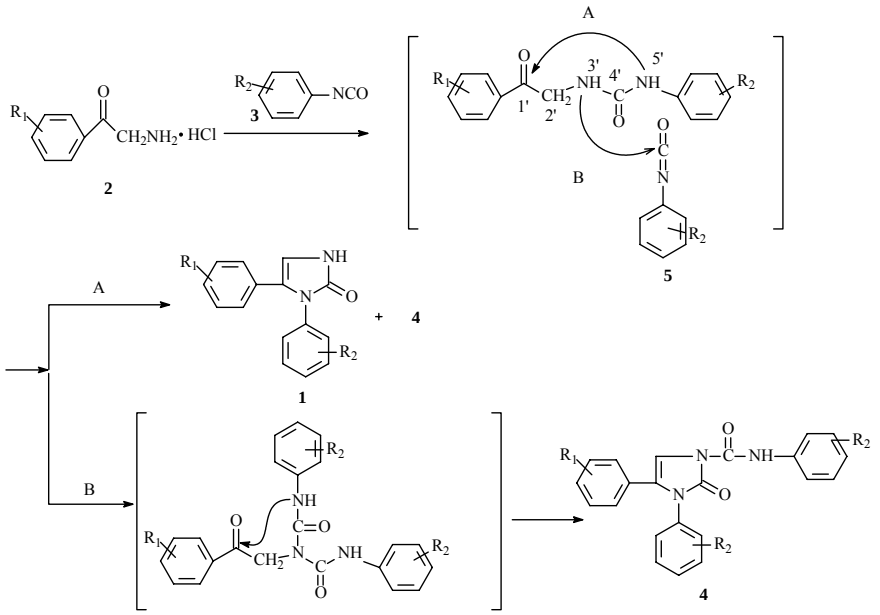


Table 1 The yields of compounds **4a-g** and **1a-g**

Entry	R_1	R_2	Yield(%)	Entry	Yield(%)
4a$_1$	H	H	93.8	**1a$_1$**	/[a]
4a$_2$	4-Cl	H	88.4	**1a$_2$**	/
4a$_3$	4-Br	H	80.2	**1a$_3$**	/
4a$_4$	3,4-2Cl	H	81.5	**1a$_4$**	/
4a$_5$	2,4-2F	H	79.8	**1a$_5$**	/
4a$_6$	4-CH_3O	H	83.5	**1a$_6$**	/
4a$_7$	4-NO_2	H	83.7	**1a$_7$**	/
4b$_1$	H	4-CH_3	84.3	**1b$_1$**	/
4b$_2$	4-Cl	4-CH_3	86.7	**1b$_2$**	/
4b$_3$	4-Br	4-CH_3	87.6	**1b$_3$**	/
4b$_4$	3,4-2Cl	4-CH_3	85.5	**1b$_4$**	/
4b$_5$	2,4-2F	4-CH_3	82.5	**1b$_5$**	/
4b$_6$	4-CH_3O	4-CH_3	80.6	**1b$_6$**	/
4b$_7$	4-NO_2	4-CH_3	79.6	**1b$_7$**	/
4c$_1$	4-CH_3O	4-Cl	75.7[b]	**1c$_1$**	/
4c$_2$	4-Br	4-Cl	78.5	**1c$_2$**	/
4c$_3$	4-Cl	4-Cl	83.3	**1c$_3$**	/
4c$_4$	2,4-2F	4-Cl	80.3	**1c$_4$**	/
4d$_1$	4-Cl	4-CH_3O	60.4	**1d$_1$**	20.5
4d$_2$	4-Br	4-CH_3O	62.5	**1d$_2$**	19.7
4e$_1$	4-CH_3O	2-CH_3O	52.6	**1e$_1$**	33.3
4e$_2$	4-Br	2-CH_3O	55.0	**1e$_2$**	28.6
4f$_1$	4-Cl	2-Br	62.9	**1f$_1$**	19.7
4f$_2$	4-Br	2-Br	61.2	**1f$_2$**	19.7
4f$_3$	4-CH_3O	2-Br	57.1	**1f$_3$**	20.0
4g$_1$	4-Cl	3,4,5-triMeO	52.7	**1g$_1$**	20.4
4g$_2$	4-Br	3,4,5-triMeO	47.8	**1g$_2$**	22.6
4g$_3$	2,4-2F	3,4,5-triMeO	54.7	**1g$_3$**	20.3
4g$_4$	4-CH_3O	3,4,5-triMeO	61.7	**1g$_4$**	15.5

a: not afforded.
b: the yields based on the substituted aniline, from **4c$_1$**(**1c$_1$**) to **4g$_4$**(**1g$_4$**), others based on arylisocyanates, from **4a$_1$** to **4b$_7$**.

General procedure (preparation of 1d$_1$ and 4d$_1$)

4-Methoxyaniline (0.4 g, 3.24 mmol) in dry toluene (4 mL) was added dropwise to a stirred solutin of $(COCl_2)_3$ (0.96 g, 2.91mmol) in dry toluene (4 mL) and cooled in an ice bath. After stirred 1 hr at RT and then refluxed for 4 hr, *p*-chloro-α-aminoacetophenone hydrochloride **2d$_1$** (1.34 g, 6.48 mmol) was added to the mixture directly and then heated under reflux overnight. After removal toluene under reduced pressure, the residue was dissolved in trichloromethane and washed with water and dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, the residue was purified by column chromatography on silica gel using trichloromethane-petroleum ether (1:1) as eluant to afford **1d$_1$** (0.20 g, 20.5%) and **4d$_1$** (0.44 g, 60.4%).

References and Notes

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10. Compound **$4a_1$.** white solid, mp. 168.8-171.3 ℃; ^{1}HNMR($CDCl_3$,δppm) 7.121-7.183 (m, 3H,ArH), 7.245-7.310 (m,5H,ArH), 7.328 (s,1H,CHN), 7.366-7.454 (m,5H,ArH), 7.616- 7.638 (d,2H,J=8.8Hz,ArH), 10.919 (s,1H,PhNH); MS *m/z*:355(M^+). Anal.cacld.for $C_{22}H_{17}N_3O_2$: C 74.35, H 4.82, N 11.82; found C 74.28, H 4.76, N 11.98. Compound **$4a_2$.** white solid,m.p.206.6-208.5 ℃; ^{1}HNMR ($CDCl_3$,δppm) 7.044-7.071 (m,2H,ArH), 7.166 (m,1H, ArH), 7.229-7.286 (m,3H, ArH), 7.334 (s,1H,CHN), 7.364-7.471 (m,6H,ArH), 7.602-7.624 (m,2H,ArH), 10.867 (s,1H,PhNH);.Anal.cacld.for $C_{22}H_{16}ClN_3O_2$: C 67.78, H 4.14, N 10.78; found C 67.49, H 4.08, N 10.76. Compound **$1e_2$**. white solid, ^{1}HNMR($CDCl_3$,δppm) 3.957 (s,3H,OCH_3), 6.937-6.958 (d,1H,J=8.4Hz,ArH), 7.012-7.030 (t,1H,ArH), 7.109-7.133 (t,1H, ArH), 7.442-7.420 (d,2H,J=8.8Hz,ArH), 7.566-7.589 (m,3H,ArH+NC=CH), 8.212- 8.232 (d, 2H,J=8.0Hz,ArH), 10.426 (s,1H,NCONH). MS *m/z*:344(M^+).

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