One-pot facile synthesis of 1,3,4-trisubstituted imidazolin-2-ones

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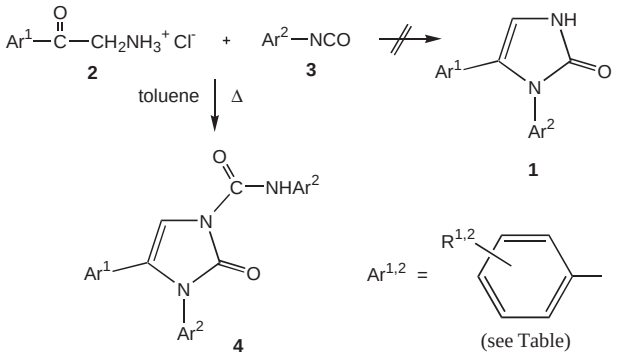
A one-pot synthesis of 1,3,4-trisubstituted imidazolin-2-ones, from the reaction of α-aminoacetophenone hydrochlorides with aryl isocyanates in good yields, is described.

Keywords: α-aminoacetophenones, imidazolin-2-ones, isocyanates

Imidazolin-2-ones have received considerable attention over the past few years for their interesting biological activities. Some species of imidazolin-2-ones become a part of the backbone of the nikkomycins which are isolated from *Streptomyces tendae*[1], and some other imidazolin-2-ones are used as human β_3 adrenergic receptor agonists.[2,3] Recently, imidazolin-2-ones have also proved to be potent PDE4 inhibitors.[4]

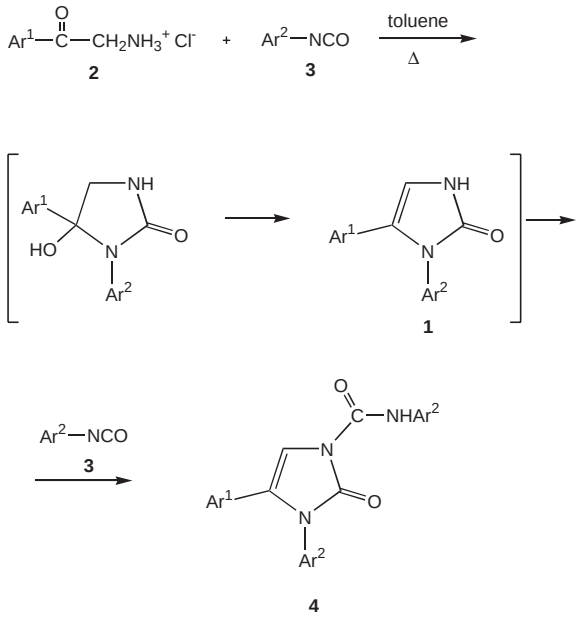
There are several known synthetic methods of imidazolin-2-ones. Among them are the cyclisation and subsequent isomerisation of *N*-propargyl carbanilides,[5] reaction of α-bromomethyl ketimines with potassium cyanate,[6] cyclisation of RNHR' with RNCO,[7] and condensation of *N*-arylphenacylamine oximes with aryl isocyanates.[8] Herein we report a simple and general method for the synthesis of 1,3,4-trisubstituted imidazolin-2-one analogues by reacting α-aminoacetophenone hydrochlorides with aryl isocyanates.

In the course of our research, we found unexpectedly that the reaction of α-aminoacetophenone hydrochloride with phenyl isocyanate provided 2-oxo-*N*,3,4-triphenylimidazoline-1-carboxamide in high yield, rather than the expected 3, 4-disubstituted imidazolin-2-ones (**1**), even when α-aminoacetophenone hydrochloride is present in excess (Scheme 1). To extend the utility of this method, various substituted α-aminoacetophenones were treated with aryl isocyanate, and 1,3,4-trisubstituted imidazolin-2-ones (**4a–n**) were obtained. The results are listed in Table 1. Compared with other known synthetic methods to imidazolin-2-ones, this new method is the most satisfactory of the simple one-pot operations and provides consistently higher yields.



Scheme 1

A possible mechanism for the formation of 1,3,4-trisubstituted imidazolin-2-ones is illustrated in Scheme 2. During the reaction, α-aminoacetophenones **2** combine with aryl isocyanates **3** in the refluxing toluene to generate as an intermediate structure **1**. The NH group of the intermediate **1** is nucleophilic and therefore ready to react with another molecule of the aryl isocyanate to form the 1,3,4-trisubstituted imidazolin-2-ones **4**.



Scheme 2

Experimental

Melting points were obtained on a B-540 Büchi melting point apparatus. Elemental analyses were made with a MOD-1106 elemental analyzer. ^{1}H NMR spectra were recorded on a Brucker AM-400 MHz spectrometer with $SiMe_4$ as internal standard in $CDCl_3$. Mass spectra were made with a HP5989B analyzer (EI, 70eV).

Typical procedure: 4-(4-Chlorophenyl)-2,3-dihydro-2-oxo-N, 3-diphenyl-1H-imidazole-1-carboxamide (**4b**): To a solution of *p*-chloro-α-aminoacetophenone hydrochloride **2b** (0.95 g, 4.62 mmol) in dry toluene (17 ml), phenyl isocyanate 0.5g (4.2 mmol) was added. The mixture was heated under reflux overnight. After removal of toluene under reduced pressure, the residue was dissolved in trichloromethane (20 ml), washed with water, then dried over anhydrous sodium sulfate. After removal of trichloromethane under reduced pressure, the residue was purified by column chromatography on silica gel using trichloromethane – petroleum ether (1 : 1) as eluant to afford **4b** as a white solid (0.72g, 88%). Analytical and spectroscopic properties of compounds **4** are presented in Table 1.

Received 17 September 2003; accepted 15 March 2004
Paper 03/2115

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Table 1 Analytical and spectroscopic data for compounds **4a–n**

	R^1	R^2	Yield/%	M.p./°C	Mol. formula	Calc. (Found) %			MS	^{1}H NMR (δ, ppm)
						C	H	N		
4a	H	H	94	169–171	$C_{22}H_{17}N_3O_2$	74.35 (74.28)	4.82 (4.76)	11.82 (11.98)	355	7.12–7.18 (m, 3H), 7.25–7.31 (m, 5H), 7.33 (s, 1H), 7.37–7.45 (m, 5H), 7.62–7.64 (d, 2H), 10.92 (s, 1H)
4b	4-Cl	H	88	207–209	$C_{22}H_{16}ClN_3O_2$	67.78 (67.49)	4.14 (4.08)	10.78 (10.76)	389	7.04–7.07 (m, 2H), 7.17 (m, 1H), 7.23–7.29 (m, 3H), 7.33 (s, 1H), 7.36–7.47 (m, 6H), 7.60–7.62 (m, 2H), 10.9 (s, 1H)
4c	4-Br	H	80	219–221	$C_{22}H_{16}BrN_3O_2$	60.84 (60.77)	3.71 (3.53)	9.68 (9.74)	433	6.98–7.01 (m, 2H), 7.17 (m, 1H), 7.23–7.25 (m, 2H), 7.34 (s, 1H), 7.37–7.48 (m, 7H), 7.60–7.62 (m, 2H), 10.86 (s, 1H)
4d	3,4-Cl_2	H	81	201–203	$C_{22}H_{15}Cl_2N_3O_2$	62.28 (62.33)	3.56 (3.42)	9.90 (9.78)	423	6.87–6.90 (m, 1H), 7.17 (m, 1H), 7.24 (m, 1H), 7.26–7.27 (m, 2H), 7.32 (s, 1H), 7.37–7.41 (m, 3H), 7.45–7.48 (m, 3H), 7.60–7.62 (m, 2H), 10.82 (s, 1H)
4e	2,4-F_2	H	80	215–217	$C_{22}H_{15}F_2N_3O_2$	67.52 (67.38)	3.86 (3.74)	10.74 (10.59)	391	6.80–6.85 (m, 2H), 7.12–7.17 (m, 2H), 7.21–7.25 (m, 2H), 7.37 (s, 1H), 7.37–7.44 (m, 5H), 7.60–7.65 (d, 2H), 10.90 (s, 1H)
4f	4-CH_3O	H	84	191–192	$C_{23}H_{19}N_3O_3$	71.68 (71.74)	4.97 (4.89)	10.90 (10.76)	385	3.80 (s, 3H), 6.73–6.81 (d, 2H), 7.04–7.06 (d, 2H), 7.16 (m, 1H), 7.24–7.26 (m, 3H), 7.36 (s, 1H), 7.39–7.44 (m, 4H), 7.61–7.63 (d, 2H), 10.93 (s, 1H)
4g	4-NO_2	H	84	222–223	$C_{22}H_{16}N_4O_4$	66.00 (66.13)	4.03 (4.08)	13.99 (14.02)	400	7.19 (m, 1H), 7.25–7.31 (m, 5H), 7.38–7.42 (m, 2H), 7.49–7.51 (m, 3H), 7.53 (s, 1H), 7.60–7.62 (d, 2H), 8.13–8.15 (d, 2H), 10.80 (s, 1H)
4h	H	4-CH_3	84	180	$C_{24}H_{21}N_3O_2$	75.18 (78.17)	5.52 (5.48)	10.96 (10.88)	383	2.35–2.41 (d, 6H), 7.12–7.23 (m, 8H), 7.28–7.30 (m, 3H), 7.31 (s, 1H), 7.49–7.51 (d, 2H), 10.85 (s, 1H)
4i	4-Cl	4-CH_3	87	234–236	$C_{24}H_{20}ClN_3O_2$	68.98 (68.76)	4.82 (4.81)	10.06 (9.92)	417	2.33–2.38 (d, 6H), 7.03–7.05 (d, 2H), 7.08–7.10 (d, 2H), 7.15–7.17 (d, 2H), 7.21–7.24 (m, 4H), 7.29 (s, 1H), 7.45–7.47 (d, 2H), 10.77 (s, 1H)
4j	4-Br	4-CH_3	88	243–244	$C_{24}H_{20}BrN_3O_2$	62.35 (62.06)	4.36 (4.28)	9.09 (9.22)	461	2.33–2.38 (d, 6H), 6.97–6.99 (d, 2H), 7.08–7.10 (d, 2H), 7.15–7.17 (d, 2H), 7.21–7.23 (d, 2H), 7.30 (s, 1H), 7.38–7.40 (d, 2H), 7.45–7.47 (d, 2H), 10.76 (s, 1H)
4k	3,4-Cl_2	4-CH_3	86	195–197	$C_{24}H_{19}Cl_2N_3O_2$	63.73 (63.49)	4.23 (4.18)	9.29 (9.27)	451	2.33–2.39 (d, 6H), 6.85–6.87 (d, 2H), 7.09–7.11 (d, 2H), 7.15–7.17 (d, 2H), 7.23 (s, 1H), 7.29–7.33 (m, 2H), 7.45–7.47 (d, 2H), 8.21–8.22 (m, 2H), 10.73 (s, 1H)
4l	2,4-F_2	4-CH_3	83	208–210	$C_{24}H_{19}F_2N_3O_2$	68.73 (68.58)	4.57 (4.62)	10.02 (10.09)	419	2.33–2.36 (d, 6H), 6.76–6.82 (m, 2H), 7.06–7.10 (t, 3H), 7.15–7.20 (t, 3H), 7.32 (s, 1H), 7.46–7.48 (t, 2H), 10.80 (s, 1H)
4m	4-CH_3O	4-CH_3	81	220	$C_{25}H_{23}N_3O_3$	72.62 (72.48)	5.61 (5.39)	10.16 (10.22)	413	2.35–2.40 (d, 6H), 3.80 (s, 3H), 6.79–6.81 (d, 2H), 7.05–7.07 (d, 2H), 7.11–7.13 (d, 2H), 7.17–7.19 (d, 2H), 7.21–7.22 (d, 2H), 7.23 (s, 1H), 7.48–7.50 (d, 2H), 10.86 (s, 1H)
4n	4-NO_2	4-CH_3	80	233–235	$C_{24}H_{20}N_4O_3$	69.89 (69.82)	4.89 (4.77)	13.58 (13.48)	412	2.36–2.42 (d, 6H), 7.12–7.14 (d, 2H), 7.18–7.20 (d, 2H), 7.26–7.27 (d, 2H), 7.29–7.30 (d, 2H), 7.47–7.49 (d, 2H), 7.51 (s, 1H), 8.12–8.15 (d, 2H), 10.73 (s, 1H)