Synthesis of 2-Arylsubstituted Imidazolone Derivatives

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Since imidazolones have been found to be associated with their various biological activities such as potassium channel opener, phosphodiesterase III/IV inhibition, and crop protection,[1,2] this class of compounds has become a synthetic target for organic and medicinal chemists. Due to increased interest, several synthetic approaches of these compounds have been investigated *via* solution or solid-phase synthesis.[3] Among imidazolones, 2-aminoimidazolone containing the guanidine moiety is particularly an attractive scaffold due to its hydrogen bonding donor and acceptor abilities in the active sites of various proteins. 2-Aminoimidazolones (**i-v**) synthesized up to date are shown in Figure 1[4] and they exhibit various biological activities.[5] Based on this finding, we decided to synthesize new imidazolone derivatives (**vi**) bearing carbon instead of nitrogen at 2-position expecting that compound **vi** would offer different chemical or biological properties compared to 2-aminoimidazolones shown in Figure 1. In this report, we wish to demonstrate the synthesis of 2-arylimidazolone (**vi**) *via* chemoselective addition of carbon nucleophile on variously substituted carbodiimides prepared from natural L-amino acids by using our previous method for construction of 3,4-dihydroquinazoline scaffold.[6]

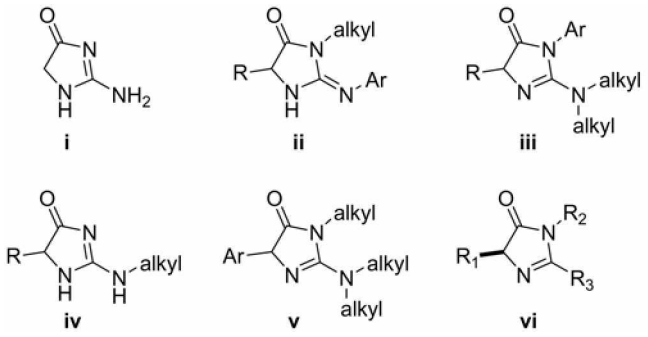
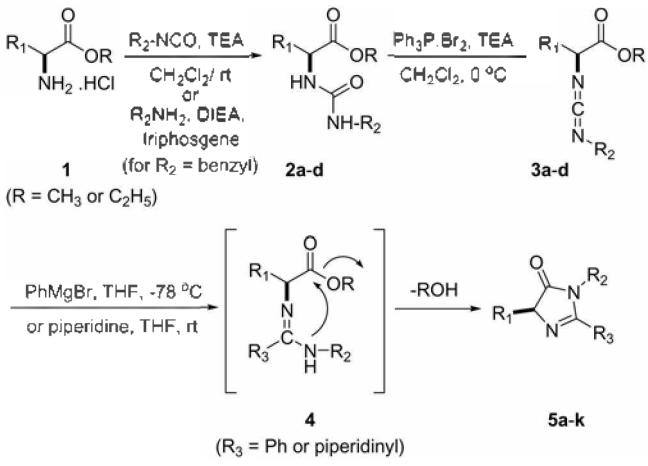


Figure 1. Structures of imidazolone compounds.



Scheme 1. Synthesis of 2-substituted imidazolones.

The complete synthetic route is shown in Scheme 1: Ester of amino acid (**1**) was treated with isocyanate/Et_3N to give urea **2a-c** in 54-82% yields. Since benzylisocyanate was commercially unavailable, compound **2d** was prepared in 84% yield by treating amino acid (**1**) with benzylamine/triphosgene/$^i Pr_2NEt$ (Table 1).[7] Compound **2a-d** were dehydrated with PPh_3-Br_2/TEA to provide the desired carbodiimide **3a-d** in 42-59% yields.[8] Finally, reaction of carbodiimide **3a-d** with Grignard reagent or piperidine resulted in the formation of the corresponding 2-phenylimidazolone **5a** and 2-piperidinylimidazolones **5** (**e**, **g**, **i**, and **k**) *via* tandem chemoselective addition on carbodiimide-cyclization. The results are summarized in Table 1 and 2. In the case of L-phenylalanine (R_1 = benzyl), the reaction of

Table 1. Results for the synthesis of compounds **2** and **3**

Entry	R_1	R_2	Yield (%)	
			2	**3**
a	benzyl	phenyl	82	59
b	H	phenyl	63	42
c	isobutyl	phenyl	54	48
d	isobutyl	benzyl	84	52

Table 2. Results for the synthesis of compounds **5**

Entry	R_1	R_2	R_3	Yield (%)
				5
a	benzyl	phenyl	phenyl	56
b			methyl	–
c			vinyl	–
d			isopropyl	–
e			piperidinyl	75
f	H	phenyl	phenyl	–
g			piperidinyl	>99
h	isobutyl	phenyl	phenyl	–
i			piperidinyl	>99
j	isobutyl	benzyl	phenyl	–
k			piperidinyl	>99

carbodiimide **3a** (R_1 = benzyl, R_2 = phenyl) with phenylmagnesium bromide successfully provided the desired compound **5a** (R_1 = benzyl, R_2 = phenyl, R_3 = phenyl) in 56% yield. However, the reaction with methylmagnesium bromide, vinylmagnesium bromide, and isopropylmagnesium bromide did not afford the corresponding 2-alkyl- or 2-vinylimidazolone. In order to compare with the previous procedures,[4] 2-piperidinylimidazolone **5e** was prepared by reacting compound **3** with piperidine *via* guanidine intermediate **4e** in 75% yield. This result was comparable to the previous procedure which is solid-phase synthesis of 2-aminoimidazolones.[4b]

In the case of L-gylcine and L-leucine, the reaction of carbodiimides **3b** and **3c** (R_1 = H or isobutyl, R_2 = phenyl) with phenylmagnesium bromide did not afford the desired 2-arylimidazolones and only resulted in the decomposition of compound in contrast to the case of L-phenylalanine **5a**. However, the reaction of **3b-d** with piperidine provided 2-aminoimidazolones **5g**, **5i**, and **5k** in quantitative yields, respectively. Compared with the previous papers,[4] our current results have some meaningful points: First, the previous paper (solid-phase synthesis) limits R_1 position to be only aromatic ring, but a hydrogen or alkyl group was also allowed at R_1 position in our result. Secondly, introduction of aromatic group at R_3 position of imidazolone ring may be a first example *via* tandem carbon nucleophilic addition on carbodiimide-cyclization to the best of our knowledge. Therefore, our method is no longer a limitation for introduction of amino-substitution at 2-position.

In conclusion, we have introduced an aromatic group in R_3 position of imidazolone ring and this may be the first example *via* tandem carbon nucleophilic addition on carbodiimide-cyclization to the best of our knowledge. Therefore, our method allows a variety of aromatic ring to be introduced at 2-position and no longer limited to amino-substituent, resulting in a diversity of imidazolone library. In addition, previous reports[4] (solid-phase synthesis) limits R_1 position to be only aromatic ring while our synthetic route allows a hydrogen or alkyl group in this position.

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9. **General procedure for carbodiimide (2a)**: To a suspension of L-phenylalanine ethyl ester HCl salt **1a** (10.0 g, 43.5 mmol) in 200 mL of dried CH_2Cl_2 was added phenylisocyanate (5.7 g, 47.9 mmol, 1.1 equiv.) followed by an addition of triethylamine (5.3 g, 52.2 mmol, 1.2 equiv.) at 0 °C. The reaction mixture was stirred for 5 hr at room temperature and treated with 100 mL of water. The mixture was extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to give solid, which was washed with petroleum ether and dried in vacuo to provide the desired urea compound **2a** (10.6 g, 82%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.06 (m, 10H, Ph), 6.84 (s, 1H, Ph-NH), 5.56 (1H, d, J = 7.9 Hz, CONH), 4.84 (1H, m, CHCO$_2$Et), 4.18 (2H, q, J = 7.2 Hz, CHCO$_2$CH$_2$CH$_3$), 3.14-3.05 (2H, m, PhCH$_2$), 1.26 (3H, t, J = 7.2 Hz, CHCO$_2$CH$_2$CH$_3$). **General procedure for carbodiimide (3a)**: To a solution of urea **2a** (9.5 g, 31.8 mmol) in 200 mL of dried CH_2Cl_2 was added $Ph_3P{\cdot}Br_2$ (20.1 g, 47.6 mmol, 1.5 equiv.) followed by an addition of triethylamine (9.6 g, 95.2 mmol, 3.0 equiv.) at 0 °C and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was treated with 100 mL of water and extracted with CH_2Cl_2. The combined extracts were washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure to give an oily compound, which was purified with column chromatography (Hex.:EtOAc = 6:1) to provide the desired carbodiimide **3a** (3.9 g, 59%) as yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.03 (10H, m, Ph), 4.43 (1H, m, 1H, CHCO$_2$CH$_2$CH$_3$), 4.28 (2H, q, J = 7.1 Hz, CHCO$_2$CH$_2$CH$_3$), 3.32-3.14 (2H, m, PhCH$_2$), 1.30 (J = 7.1 Hz, CHCO$_2$CH$_2$CH$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.2, 139.8, 137.6, 136.6, 129.9, 129.6, 127.6, 125.4, 124.5, 62.5, 61.3, 40.7, 14.6. **General procedure for 2-phenylimidazolone (5a)**: To a stirred solution of carbodiimide **3a** (550 mg, 1.87 mmol) in 20 mL of anhydrous THF was added PhMgBr (2.06 mL, 1 M solution in THF, 2.06 mmol, 1.1 equiv.) under nitrogen atmosphere at −78 °C and then reaction mixture was allowed to warm to 0 °C over 2 hr. After quenching with aqueous NH_4Cl, the reaction mixture was extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give a crude compound, which was purified with column chromatography (Hex.:EtOAc = 5:1) to provide the desired 2-phenylimidazolone **5a** (327 mg, 56%) as yellow solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.17 (13H, m, Ph), 6.57-6.54 (2H, m, Ph), 4.71 (1H, m, CHCO), 3.49 (1H, m, PhCH$_2$), 3.36 (1H, m, PhCH$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.4, 162.2, 135.6, 134.4, 131.1, 130.6, 129.5, 128.8, 128.6, 128.5, 128.3, 127.3, 69.3, 37.8; IR (KBr) 3.58, 2942, 2362, 1738, 1612 cm^{-1}; MS (EI) m/z 326 (M$^+$).