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Original article

A novel and green synthesis of indolone-*N*-amino acid derivatives *via* the Passerini three-component reactions in water

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ABSTRACT

A green Passerini three-component reaction of 2-(4-oxo-4,5,6,7-tetrahydro-1*H*-indol-1-yl)acetic acid with alkyl or aryl isocyanides and aldehydes was reported under aqueous conditions at 35 °C for 1 h, and 21 indolone-*N*-amino acid derivatives were prepared in high yields of 42%–99%. Their structures were characterized by IR, ESI–MS, NMR and elemental analysis, and the possible mechanisms have been also proposed. The highly efficient and eco-friendly method provides a facile access to a library of indolone-*N*-amino acid derivatives for future research on bioactivity screening.

1. Introduction

As an important class of nitrogen-containing heterocycles, pyrroles have been found to possess interesting biological [1], synthetic [2] and optoelectronic properties [3]. Indolones represent a very significant class of fused pyrroles, represented in various natural products [4] and medicinal scaffolds [5] with diverse biological properties including antiplasmodial [6], antimalarial [7], human EP3 receptor antagonistic [8], antiviral [9] and antiproliferative [10] activities. Owing to the favorable intestinal absorption and resistance to glycosidic metabolism [11], the indolone-*N*-amino acid analogs have been developed as selective CRTh2 (DP2) receptor antagonist AZD1981 [12] and anticancer agents [13]. As a consequence, several synthetic methods were reported for the construction of the *N*-aminoacid-indolone derivatives, such as the Paal–Knorr synthesis [14] and [3+2] annulation of arynes [15].

The efficient and selective construction of complicated heterocycles is an ongoing challenge in synthetic chemistry. Accordingly, synthetic approaches such as multicomponent reactions (MCRs) that rapidly and efficiently generate complex multifunctional binding sites have attracted interest because of fewer steps and lower cost are involved [16]. Isocyanides (or isonitriles) have unique reactivity and can react with both nucleophiles and electrophiles at the same atom to form reactive α-adducts. Therefore, the isocyanide-based multicomponent reactions (I-MCRs) [17] have been proven as powerful approaches for the high-throughput synthesis of diverse libraries of potentially bioactive and densely functionalized molecules with high atom economy and convergency in one-pot procedures. Since the reaction of isocyanides, aldehydes and carboxylic acids to generate α-acyloxy carboxamides was discovered by Passerini in 1921, the Passerini three-component reaction (P-3CR) [18] has become a powerful tool in combinatorial chemistry and heterocyclic chemistry [19] for drug discovery as well as natural product synthesis [20].

Nowadays, the green organic reactions are attracting considerable attention in industry and academia due to the environmental and economic benefits. As a safe, readily available, cheap and environmentally benign solvent, water has been used in the development of green organic reactions with the advantages of simplified experimental procedures and unique solvating properties [21]. Therefore, the aqueous MCRs have been successfully utilized to construct γ-iminolactone [22], 3-oxo-3-phenylpropanamid catalyzed by silica nanoparticles [23], benzimidazoles and benzothiazoles [24], thioformamide [25], *a*-(acyloxy)-*a*-(quinolin-4-yl)acetamides [26] and propanamide derivatives [27]. For the rapid design and construction of a pharmacophore-based library of

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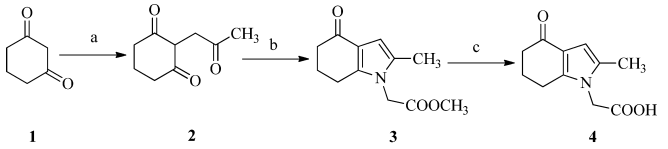


Scheme 1. Synthetic routes for the indolone-*N*-amino acid (**4**). Reagents and conditions: (a) chloroacetone, KOH, H_2O, 20 °C, 6 h; (b) glycine ethyl ester hydrochloride, NaOAc, H_2O, 50 °C, 4 h; and (c) KOH, CH_3OH, H_2O, 40 °C, 3 h; 1.0 mol/L HCl, 0 °C, 5 min.

indolone-*N*-amino acid derivatives, the concept of diversity-oriented methodology of isocyanide-based aqueous Passerini reaction has been adopted in this work.

2. Experimental

Considering the significant bioactivity of indolone-*N*-amino acid derivatives, the 2-(4-oxo-4,5,6,7-tetrahydro-1*H*-indol-1-yl)acetic acid (**4**) was prepared from commercially available 1,3-dicarbonyl compound according to the Barraja's method [28] (Scheme 1). Firstly, the reaction of 1,3-cyclohexanodione (**1**) with chloroacetone in a potassium hydroxide aqueous solution was stirred at 20 °C for 6 h to afford the 1,3-acetonylcyclohexandione (**2**), which could be used without further purification to cyclize to the methyl 2-(2-methyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-1-yl)acetate (**3**) through the Paal–Knorr ring closure reaction [29] using glycine methylester hydrochloride as an amine source. Then, the carboxylic acid component (**4**) of the Passerini reaction is obtained by hydrolyzing **3**.

Initially, the P-3CR of carboxylic acid with various aldehydes and isocyanides was conducted at 35 °C for 2 h in different solvents according to the literature methods [30]. The reaction of 2-(4-oxo-4,5,6,7-tetrahydro-1*H*-indol-1-yl)acetic acid (**4**, 0.1 mmol), *n*-butyl aldehyde (0.15 mmol) and 4-chlorophenyl isocyanide (0.1 mmol) was chosen as a model reaction (Scheme 2). As shown in Table 1, the organic solvents had an obvious influence on the yield of 1-(4-chlorophenylamino)-1-oxopentan-2-yl 2-(2-methyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-1-yl)acetate (**5c**), and toluene, tetrahydrofuran (THF), acetone, *N*,*N*′-dimethylformamide (DMF) and methanol were found to be ineffective (entries 1–5). The use of acetonitrile (CH_3CN) resulted in a low yield of 31%. However, the P-3CR proceeded smoothly in dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$) with higher yields of 75%–78% (entries 6–8). Although these results were satisfying, we attempted the aqueous P-3CR with the aim of establishing greener processes. Fortunately, we achieved an 81% yield of **5c** when the model reaction was carried out in water (entry 9).

In order to acquire the best conditions for the P-3CR, the influence of temperature and time on the model reaction were also investigated. The results indicated that temperatures below 35 °C gave decreased yields (Table 1, entry 10–12), and temperature beyond 35 °C also resulted in poorer yields because of the quick oxidation or hydrolysis of isocyanide (entry 13–16). Therefore, the most appropriate temperature proved to be around 35 °C. Next, we examined the suitable reaction time. It was found that the highest

Table 1
Optimizing the conditions for the Passerini reaction.[a]

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	Toluene	35	2	Trace
2	THF	35	2	Trace
3	Acetone	35	2	Trace
4	DMF	35	2	Trace
5	CH_3OH	35	2	Trace
6	CH_3CN	35	2	31
7	CH_2Cl_2	35	2	75
8	$CHCl_3$	35	2	78
9	H_2O	35	2	81
10	H_2O	5	2	8
11	H_2O	15	2	47
12	H_2O	25	2	73
13	H_2O	45	2	79
14	H_2O	60	2	66
15	H_2O	80	2	58
16	H_2O	100	2	25
17	H_2O	35	0.25	25
18	H_2O	35	0.5	77
19	H_2O	35	1	92
20	H_2O	35	1.5	91
21	H_2O	35	3	76
22	H_2O	35	6	52

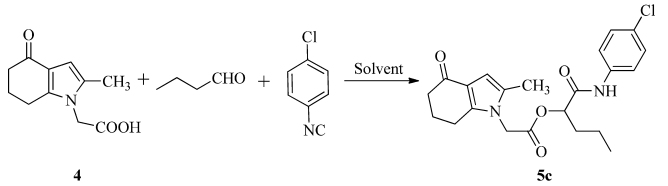
[a] Reactions were carried out using the carboxylic acid (**4**, 0.10 mmol), *n*-butyl aldehyde (0.10 mmol) and 4-chlorophenyl isocyanide (0.10 mmol) in corresponding solvent for appropriate time.
[b] Isolated yields.

yield was achieved under the conditions of 1 h at 35 °C (entry 19). Prolonged reaction time seemed to produce dark by-products and resulted in lower isolated yields (entries 21, 22). Finally, the optimized conditions for the P-3CR were summarized as the follows: the carboxylic acid **4**, an aldehyde and an isocyanide were stirred in water at 35 °C for 1 h.

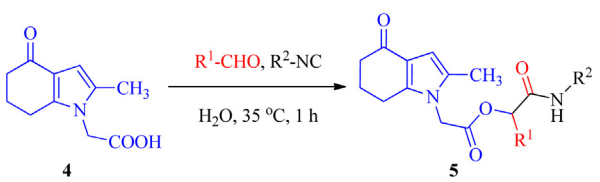
To explore the scope of P-3CR with respect to various substrates, the carboxylic acid (**4**) was examined to react with alkyl or aryl isocyanides and aldehydes in the one-pot procedure, and 21 indolone-*N*-amino acid derivatives (**5**) were efficiently prepared with satisfactory yields of 42%-99% (Scheme 3, Table 2). It is noteworthy that this reaction could proceed smoothly when paraformaldehyde was used. The ethyl 2-isocyanoacetate exhibited similar reactivity to the 4-chlorophenyl isocyanide under the aqueous conditions.

3. Results and discussion

All of the indolone-*N*-amino acid derivatives (**5**) were confirmed by their spectral data. The C=O absorption peaks at 1690–1760 cm^{-1} could be clearly observed in the IR spectra. In the ESI–MS spectrum, the pseudo-molecular ion peak of $(M+H)^+$ or $(M+Na)^+$ were usually observed as the base peak ion for the targeted compounds. In the ^1H NMR spectroscopy, the C(3)–H in the indole ring appeared as a single peak at 6.49–6.22 ppm, and the methylene proton signal of indol-*N*-CH_2 was usually observed as an AB quartet with a coupling constant (*J*) of 17.6 Hz. The proton for O–CH exhibited a triplet or doublet splitting pattern at 5.09–5.28 ppm when the substituent was allyl group for **5b–5g** and



Scheme 2. The model Passerini reaction.



Scheme 3. Synthetic routes for the indolone-*N*-amino acid derivatives (**5**).