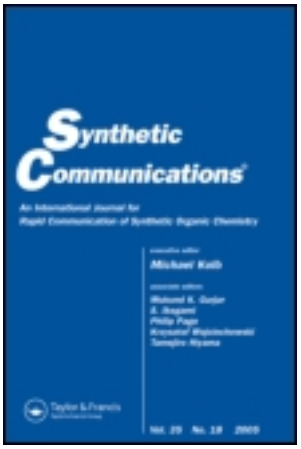

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One-Pot, Three-Component Coupling Reaction: Catalyst-Free Green Synthesis of Novel N-Heteroaryl α-Naphthylglycines

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ONE-POT, THREE-COMPONENT COUPLING REACTION: CATALYST-FREE GREEN SYNTHESIS OF NOVEL *N*-HETEROARYL α-NAPHTHYLGLYCINES

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A series of novel* N-*heteroaryl* α-*arylglycines containing naphthol rings has been prepared by one-pot, three-component condensation reaction of glyoxalic acid, heteroaryl amines and naphthols in water at ambient temperature and under reflux conditions in moderate to high yields. The promising advantages such as removal of organic solvent, no need to catalyst, simplicity of the reaction procedure and easy product separation will be discussed in this article.

Keywords: Glyoxalic acid; heteroaryl amines; naphthols; α-naphthylglycines

INTRODUCTION

Amino acids are among the most important and indispensable materials for the maintenance of human life.[1] In drug discovery, interest in non-proteinogenic α-amino acids [2] is continuously increasing as a result of their potential pharmacological properties and their utility as building blocks in the synthesis of biologically active substances and naturally occurring compounds, such as vancomycin and nocardicin.[3,4]

Several practical approaches to construct amino acid frameworks and their derivatives have been developed by organic/medicinal chemists.[5] Friedel–Crafts type reactions of electron-rich arenes with a glycine cation equivalent are among the most useful tools in achievement of the facile preparation of these α-aromatic amino acid derivatives. However, most of the electrophilic sources employed in the Friedel–Crafts reaction have been limited to imines or imino esters.[6–9] Heaney and co-workers developed an effective preparation of α-aryl-amino acid derivatives using an N,O-acetal, in the presence of a typical silyl chloride, such as Me_3SiCl;

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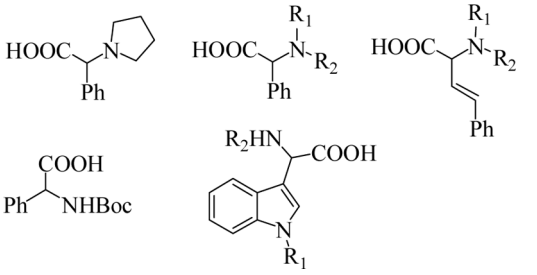


Figure 1. Examples of the synthesized α-arylglycines.

however, most of the reactions required long reaction times to complete.[10] Risch and coworkers[11] demonstrated the aminoalkylation of arenes with benzotriazolyl-substituted *N,N*-aminals in the presence of stoichiometric amounts of $AlCl_3$ and $TiCl_4$, leading to the formation of α-aryl-α-amino acid esters.

The Petasis reaction, or boronic Mannich reaction, involves the three-component coupling of an amine, an aldehyde and an organoboron compound. One of the most important uses of the Petasis reaction is the synthesis of arylglycines employing glyoxylic acid as the aldehyde component and an arylboronic acid as the organoboron derivative.[12–14] This reaction is ideally suited for combinatorial chemistry.[15] In general, this reaction is more efficient with secondary amines and sterically hindered primary amines.[16,17] Examples of the synthesized α-arylglycine derivatives are shown in Fig. 1.[18–20]

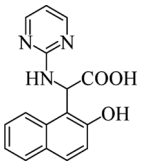
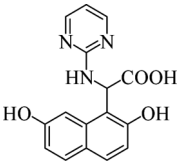
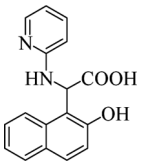
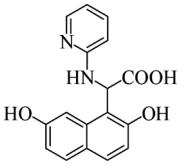
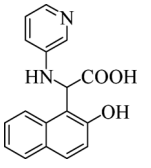
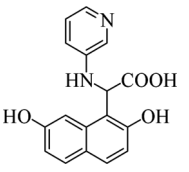
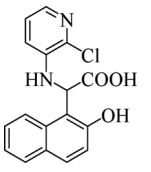
To the best of our knowledge, synthesis of *N*-heteroaryl-2-(2-hydroxynaphthalen-1-yl)glycines and *N*-heteroaryl-2-(2,7-dihydroxynaphthalen-1-yl)glycines via condensation of heteroarylamines, glyoxalic acid and naphthols has not previously been reported in literature. As part of a continuous effort to develop new α-arylglycine derivatives, we report here a convenient one-step synthesis of novel *N*-heteroaryl α-naphthylglycines in water at ambient temperature and under reflux conditions.

RESULTS AND DISCUSSION

We have previously reported a one-pot three-component uncatalyzed quantitative synthesis of new aminonaphthols (Betti bases).[21] One of the benefits of this system is that the reaction proceeded well at room temperature without the requirement of any catalyst in water. Therefore, in this article our synthetic approach is based on the Betti reaction employing glyoxalic acid as the aldehyde component.

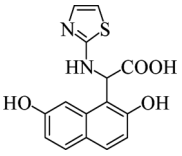
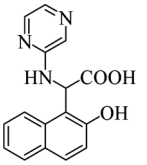
In the beginning, a systematic study was carried out for the synthesis of α-naphthylglycines in water as solvent in the absence of acid catalyst under two coditions: at room temperature and under reflux conditions. Initially, the reaction was conducted using β-naphthol, glyoxalic acid and 2-aminopyrimidine at room temperature, which resulted the desired product 88% yield after 14 h (monitored by a thin-layer chromatography, TLC). With the same substrates, the reaction under reflux conditions, afforded the same product in 80% yield after 2.5 h. Therefore, we decided to examine the other reactions under two conditions and investigated the effects of temperature on the reaction times and yields of products.

Table 1. Synthesis of *N*-heteroaryl α-naphthylglycines in water

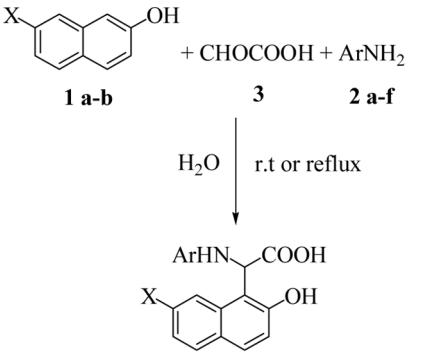
				Method A		
Entry	Amine	Product	**4**	Time/h	Yield (%)	Mp (°C)
1			**4a**	14	88	184–185
2			**4b**	3.5	85	196–198
3			**4c**	17	78	176–178
4			**4d**	4.5	89	179–180
5			**4e**	20	85	170–171
6			**4f**	5	90	159–161
7			**4g**	8	83	200–202

(*Continued*)

Table 1. Continued

Entry	Amine	Product	4	Method A		Mp (°C)
				Time/h	Yield (%)	
8			**4h**	4	78	169–170
9			**4i**	4	75	132–134

One-pot three-component reaction of 2-naphthol (**1a**), 2,7-dihydroxy naphthalene (**1b**), heteroaryl amines (2-aminopyrimidine **2a**, 2-aminopyrazine **2b**, 2-aminopyridine **2c**, 3-aminopyridine **2d**, 2-aminothiazole **2e** and 3-amino-2-chloropyridine **2f**) **2a-f** and aqueous glyoxalic acid (**3**) in water at room temperature (method A) in appropriate times (see Table 1) directly afforded *N*-heteroaryl α-naphthylglycines **4a–i** in moderate to high yields (Scheme 1). Also, these reactions were carried out under reflux conditions (method B). In this procedure, the products **4h** and **4i** not only were formed but also sticky mixtures were obtained. However, these products were obtained at room temperature in 78% and 75% yields, respectively. The results are summarized in Table 1.



Ar = a: 2-pyrimidyl, **b:** 2-pyrazyl, **c:** 2-pyridyl, **d:** 3-pyridyl, **e:** 2-thiazolyl, **f:** 2-chloro-3-pyridyl

1a : X = H, **1b:** X = OH

Scheme 1. Synthesis of α-naphthylglycine derivatives **4**.

After screening two methods, method A has advantages such as efficient, generality and simplicity of the procedure, clean and easy products separation by filtration. But, the formation of some products in this method needs a little longer reaction time. Further studies showed that increasing temperature (method B) did not improve the yields of the products. In this method, after completion of the reaction, water was decanted and the white precipitated product was separated upon addition of ethanol to the mixture. As shown in Table 1, with 2,7-dihydroxynaphthalene, the reaction showed higher rate than 2-naphthol. In addition, when amines with electron poor nature such as 2-aminopyrimidine were used, the reaction proceeded relatively higher rate than other amines. Thus, the naphthols bearing electron-donating and amines contaning withdrawing atoms in ortho position are desirable substrates for these reactions.

To make insight into the reaction mechanism, we initially studied the reaction of 2-naphthol with glyoxalic acid. No reaction progress was observed during several hours. When the iminoacid product obtained from amine condensation with glyoxalic acid was treated with 2-naphthol under the reaction conditions, the corresponding *N*-heteroaryl α-naphthylglycine was obtained. In our one-pot reaction, it might be concluded that iminoacid generated in situ from reaction of amine and glyoxalic acid, reacts with 2-naphthol affording the α-naphthylglycine.

In summary, we described a convenient, efficient and environmentally greener methodology for the synthesis of novel *N*-heteroaryl α-arylglycines containing naphthol rings in water in the absence of acid catalyst at room temperature (method A) and under reflux conditions (method B) in moderate to high yields. In addition to the efficiency and simplicity by method A, this protocol describes generality, clean, low cost procedure and easy products separation for the synthesis of these products. To the best of our knowledge, this is the first report on the synthesis of *N*-heteroaryl α-naphthylglycine derivatives.

EXPERIMENTAL

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker DRX-500 AVANCE spectrometers. Chemical shifts (δ) are reported in ppm and are referenced to the NMR solvent. Mass spectra of the products were obtained with a HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-O-Rapid Heraeus elemental analyzer (Wellesley, MA).

General Procedure for the Synthesis of *N*-Heteroaryl-2-aryl Glycines (Method A)

To a solution of heteroarylamine (5 mmol) and glyoxalic acid (50% aqueous solution) (5 mmol) in water (10 mL) was added β-naphthol or 2,7-dihydroxy naphthalene (5 mmol) and the mixture was stirred for the appropriate times (see Table 1) at ambient temperature. Reaction progress was monitored by TLC. After completion of the reaction, the obtained precipitate was filtered, washed with cold

EtOH, dried and purified by recrystallization from DMSO-H_2O to give colorless crystals of **4a-i**.

General Procedure for the Synthesis of *N*-Heteroaryl-2-aryl Glycines (Method B)

To a solution of heteroarylamine (5 mmol) and glyoxalic acid (50% aqueous solution) (5 mmol) in water (10 mL) was added β-naphthol or 2,7-dihydroxy naphthalene (5 mmol) and the mixture was stirred for the appropriate times (see Table 1) under reflux condition. Reaction progress was monitored by TLC. After completion of the reaction, water was decanted and the white precipitated product was separated upon addition of ethanol (10 mL) to the mixture with stirring, while cooling at 0–5 °C. The precipitate was filtered, washed with cold EtOH, dried and purified by recrystallization from DMSO-H_2O to give colorless crystals of **4a-g**.

***N*-(2-Pyrimidyl)-2-(2-hydroxynaphthalen-1-yl) glycine (4a).** IR (KBr): 3313, 3150–2466, 1712, 1595, 1573, 1531, 1232 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.55 (d, 1H, $J = 8.6$ Hz, methine-H), 6.67 (t, 1H, $J = 4.7$ Hz, pyrimidine-H5), 6.97 (d, 1H, $J = 8.6$ Hz, NH), 7.2–8.09 (m, 6H, naphthalene-H), 8.35 (d, 2H, $J = 4.7$ Hz, pyrimidine-H4 and H6), 10.24 (br, 1H, OH), 12.45 (br, 1H, COOH); ^{1}H NMR (500 MHz, DMSO-d_6 + D_2O): δ 6.53 (s, 1H, methine-H), 6.67 (t, 1H, $J = 4.7$ Hz, pyrimidine-H5), 7.2–8.06 (m, 6H, naphthalene-H), 8.33 (d, 2H, $J = 4.7$ Hz, pyrimidine-H4 and H6);^{13}C NMR (125 MHz, DMSO-d_6): δ 50.60, 111.90, 116.91, 119.08, 123.38, 123.44, 127.57, 129.09, 129.36, 130.36, 133.59, 154.21, 158.88, 162.53, 174.00; MS (EI): m/z 296 $(M+1)^+$, 295 $(M)^+$, 277, 251, 220, 156, 128; Anal. calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.40; N, 14.22. Found: C, 65.15; H, 4.35; N, 14.29.

***N*-(2-Pyrimidyl)-2-(2,7-dihydroxynaphthalen-1-yl) glycine (4b).** IR (KBr): 3396, 3211–2624, 1722, 1635, 1595, 1531, 1458, 1344, 1284, 1228, 1155 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.40 (d, 1H, $J = 8.7$ Hz, methine-H), 6.67 (t, 1H, $J = 4.7$ Hz, pyrimidine-H5), 6.84 (d, 1H, $J = 8.7$ Hz, NH), 6.87–7.67 (m, 5H, naphthalene-H), 8.34 (d, 2H, $J = 4.7$ Hz, pyrimidine-H4 and H6), 9.70 (s, 1H, OH), 10.08 (br, 1H, OH), 12.36 (br, 1H, COOH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 50.77, 105.30, 111.88, 115.09, 115.58, 115.91, 123.84, 130.16, 131.01, 135.37, 154.56, 157.10, 158.92, 162.62, 174.01; MS (EI): m/z 311 $(M)^+$, 293, 264, 248, 200, 172, 144, 115, 95; Anal. calcd. for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.18; N, 13.50. Found: C, 61.68; H, 4.20; N, 13.58.

***N*-(2-Pyridyl)-2-(2-hydroxynaphthalen-1-yl)glycine (4c).** IR (KBr): 3255–2563, 1662, 1625, 1573, 1512, 1442, 1386, 1247, 1164 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.46 (d, 1H, $J = 5.6$ Hz, methine-H), 7.03 (d, 1H, $J = 5.6$ Hz, NH), 6.54, 6.75, 7.14–8.09 (m, 10H, pyridine-H and naphthalene-H), 11.34 (br, 2H, OH and COOH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 50.45, 110.20, 112.97, 117.71, 119.56, 123.36, 123.83, 127.30, 129.25, 129.30, 130.17, 133.73, 137.68, 147.60, 154.33, 158.67, 174.65; MS (EI): m/z 294 $(M)^+$, 276, 250, 184, 156, 144, 128, 115, 94; Anal. calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.76; N, 9.52. Found: C, 69.44; H, 4.72; N, 9.56.

***N*-(2-Pyridyl)-2-(2,7-dihydroxynaphthalen-1-yl)glycine (4d).** IR (KBr): 3249, 3114–2684, 1666, 1625, 1602, 1539, 1487, 1454, 1384, 1307, 1220, 1163 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 6.34 (d, 1H, $J = 6.9$ Hz, methine-H), 6.83 (d, 1H, $J = 6.9$ Hz, NH), 6.53, 6.73, 6.87–8.03 (m, 9H, pyridine-H and naphthalene-H), 9.64 (s, 1H, OH), 10.25 (br, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 50.46, 105.93, 110.09, 112.89, 115.77, 115.80, 115.88, 123.93, 129.97, 130.83, 135.54, 137.55, 147.69, 154.58, 156.87, 158.78, 174.61; MS (EI): m/z 310 $(M)^+$, 292, 236, 200, 172, 165, 144, 137, 115, 94; Anal. calcd. for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.51; N, 9.03. Found: C, 65.84; H, 4.49; N, 9.10.

***N*-(3-Pyridyl)-2-(2-hydroxynaphthalen-1-yl)glycine (4e).** IR (KBr): 3255–2488, 1622, 1573, 1504, 1438, 1377, 1323, 1290, 1253, 1163, 1101 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 5.97 (s, 1H, methine-H), 6.45 (br, 1H, NH), 7.02–8.14 (m, 10H, pyridine-H and naphthalene-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 52.29, 116.39, 118.93, 119.26, 123.36, 124.00, 124.38, 127.29, 129.36, 129.37, 130.39, 133.36, 135.97, 137.62, 144.63, 154.12, 174.30; MS (EI): m/z 294 (M^+), 257, 236, 149, 128, 115, 97; Anal. calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.76; N, 9.52. Found: C, 69.34; H, 4.79; N, 9.58.

***N*-(3-Pyridyl)-2-(2,7-dihydroxynaphthalen-1-yl)glycine (4f).** IR (KBr): 3361–2437, 1620, 1571, 1541, 1377, 1294, 1234, 1197 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 5.79 (s, 1H, methine-H), 6.15 (br, 1H, NH), 6.85–8.10 (m, 9H, pyridine-H and naphthalene-H), 9.62 (s, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 52.44, 106.06, 108.05, 115.48, 115.73, 119.21, 123.97, 124.34, 129.92, 130.18, 135.16, 136.11, 137.72, 144.73, 154.41, 156.46, 174.28; MS (EI): m/z 311 $(M + 1)^+$, 310 $(M)^+$, 292, 262, 236, 199, 151, 128, 115, 94; Anal. calcd. for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.51; N, 9.03. Found: C, 65.75; H, 4.56; N, 9.10.

***N*-(3-Chloro-2-pyridyl)-2-(2-hydroxynaphthalen-1-yl)glycine (4g).** IR (KBr): 3388, 3246–2569, 1704, 1627, 1583, 1490, 1436, 1380, 1288, 1253, 1147 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 6.07–8.19 (m, 11H, methine-H, pyridine-H and naphthalene-H, NH), 10.48 (s, 1H, OH), 13.13 (s, 1H, COOH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 52.15, 118.88, 119.52, 122.75, 123.14, 123.55, 124.68, 127.68, 129.28, 129.62, 130.78, 133.30, 136.94, 136.99, 140.28, 154.34, 173.88; MS (EI): m/z 328 $(M)^+$, 310, 283, 247, 200, 183, 172, 156, 144, 128, 127, 115, 92; Anal. calcd. for $C_{17}H_{13}ClN_2O_3$: C, 62.10; H, 3.95; N, 8.52. Found: C, 62.20; H, 4.02; N, 8.50.

***N*-(2-Thiazolyl)-2-(2,7-dihydroxynaphthalen-1-yl)glycine (4h).** IR (KBr): 3203–2617, 1608, 1517, 1481, 1460, 1375, 1305, 1222, 1164, 1137 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 6.21 (s, 1H, methine-H), 6.61–7.96 (m, 8H, thiazole-H and naphthalene-H, NH), 9.67 (s, 1H, OH), 10.25 (s, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 53.58, 105.84, 107.62, 114.97, 115.72, 115.81, 123.84, 130.25, 130.87, 135.41, 138.81, 154.57, 156.93, 169.30, 173.83; MS (EI): m/z 298 $(M\text{-}18)^+$, 268, 253, 199, 172, 160, 144, 115, 100; Anal. calcd. for $C_{15}H_{12}N_2O_4S$: C, 56.96; H, 3.79; N, 8.86. Found: C, 56.89; H, 3.75; N, 8.90.

***N*-(2-Pyazyl)-2-(2-hydroxynaphthalen-1-yl)glycine (4i).** IR (KBr): 3225–2326, 1649, 1602, 1573, 1533, 1400, 1342, 1197, 1114 cm^{-1}; ^1H NMR (500 MHz,

DMSO-d_6): δ 6.45–8.15 (m, 11H, methine-H, pyrazine-H, NH and naphthalene-H), 10.25 (br, 1H, OH), 12.45 (s, 1H, COOH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 49.70, 109.50, 116.50, 119.09, 123.68, 127.51, 129.13, 129.36, 130.15, 130.42, 133.72, 134.86, 142.01, 154.22, 155.24, 174.14; MS (EI): m/z 295 $(M)^+$, 277, 261, 248, 234, 220, 183, 170, 152, 144, 128, 115, 95; Anal. calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.40; N, 14.23. Found: C, 65.02; H, 4.47; N, 14.29.

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