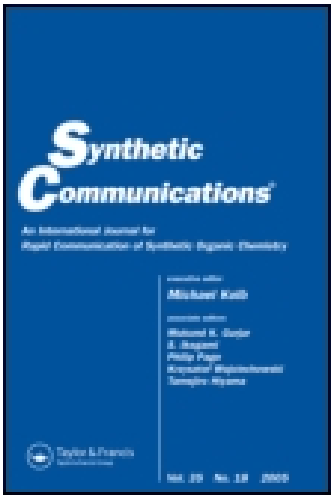

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Efficient Ligand-Free, Palladium-Catalyzed Amidocarbonylation in Ionic Liquids: Facile Synthesis of N-Acyl-α-arylglycines

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Efficient Ligand-Free, Palladium-Catalyzed Amidocarbonylation in Ionic Liquids: Facile Synthesis of *N*-Acyl-α-arylglycines

Qing-Lu Zhao,[1,2] Min Yang,[1] and Lai-Lai Wang[1]
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Abstract: A ligand-free, palladium-catalyzed amidocarbonylation reaction of aromatic aldehyde, acetamide, and CO in ionic liquids $[C_4mim]PF_6$, $[C_6mim]PF_6$, $[C_8mim]PF_6$, and $[C_6mim]BF_4$ as solvents is developed. The yields decreased in the order $[C_6mim]PF_6 > [C_8mim]PF_6 > [C_4mim]PF_6 > [C_6mim]BF_4$, and substrate concentration affected the catalytic activity of amidocarbonylation. The excellent yield with up to 98% in amidocarbonylation of benzaldehyde was obtained using 15 mol% $LiBr \cdot H_2O$ and 6 mol% H_2SO_4 at 80 °C. This reaction could proceed smoothly, resulting in several functionalized *ortho*-, *meta*-, and *para*-substituted *N*-acyl-α-phenylglycines in moderate to good yields, and *o*-tolualdehyde and *m*-tolualdehyde as substrates were amidocarbonylated for the first time in $[C_6mim]PF_6$. A significant dependence of product yield on both substituent position and electronic effect of aromatic aldehyde was observed. The ligand-free synthetic method and convenient separation of the products highlighted the versatility of this newly developed methodology.

Keywords: Amidocarbonylation, aromatic aldehyde, ionic liquids, *N*-acyl-α-arylglycine, palladium

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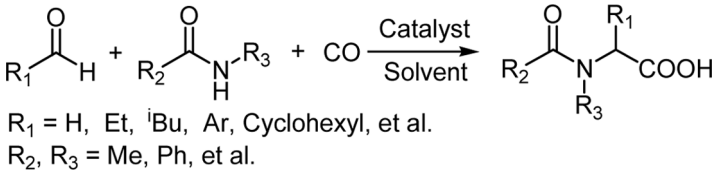


Scheme 1. Amidocarbonylation of aldehydes, amides, and CO.

INTRODUCTION

Transition-metal-catalyzed amidocarbonylation of aldehyde, amide, and carbon monoxide is an efficient multicomponent reaction for the synthesis of *N*-acyl-α-amino acids (Scheme 1),[1–7] which are versatile pharmaceuticals, herbicides, anionic sarcosinate tensides, simple dipeptides such as the sweetener aspartame, important starting materials in peptide synthesis, and intermediates for the production of biologically active agents.[8] Traditionally, cobalt,[1] palladium,[2–5] rhodium, iridium, ruthenium,[6] and platinum[7] catalysts have been applied in this amidocarbonyltion reaction. Recently, palladium has emerged as a preferable catalyst for this reaction because of its higher catalytic activity under relatively mild conditions. Ligand triphenylphosphine and high-boiling-point organic solvent *N*-methylpyrrolidone (NMP, bp 202 °C) are generally used in this homogeneous palladium-catalyzed amidocarbonylation reaction, which complicate the separation of the products.[2–4] In addition, some aldehydes such as indole aldehydes, carbohydratealdehydes, iodo- and bromo-substituted aldehydes, and a few arylacetaldehydes as substrates are not amenable to this amidocarbonylation reaction, and up to 35 mol% of bromide salts as cocatalyst are generally used.[2]

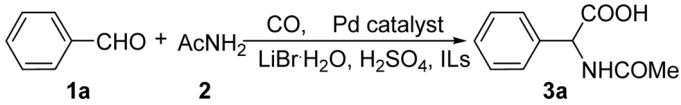
Ionic liquids (ILs), potential green solvents, have successfully replaced the conventional organic solvents in numerous organic and catalytic reactions, such as Friedel–Crafts reaction,[9] Heck reaction,[10] Diels–Alder reaction,[11] allylation,[12] olefin dimerization and oligomerization,[13] hydrogenation,[14] Mannich reaction,[15] and hydroformylation.[16] Moreover, they could simplify product separation and enhance reaction efficiency. Jiang et al. described the amidocarbonylation reaction catalyzed by palladium–phosphine complex in halide anion ILs. However, merely moderate yield (up to 53%) was obtained when aromatic aldehydes were employed as reaction substrates, and hydrophilic halide anion ILs as solvents complicate the manipulation of reaction.[5b] Our aim was to develop environmentally friendly catalytic systems for amidocarbonylation, and the use of ILs $[C_4mim]PF_6$, $[C_6mim]PF_6$, $[C_8mim]PF_6$, and $[C_6mim]BF_4$ as solvents for related endeavors remains

unexplored. Herein, we report our initial studies on phosphine-free, palladium-catalyzed amidocarbonylation of aromatic aldehydes in ionic liquids $[C_4mim]PF_6$, $[C_6mim]PF_6$, $[C_8mim]PF_6$, and $[C_6mim]BF_4$ as solvents, leading to various *N*-acyl-α-arylglycines in moderate to excellent yields with a decreased amount of co-catalyst $LiBr \cdot H_2O$ (15 mol%).

RESULTS AND DISCUSSION

An initial investigation of amidocarbonylation was carried out using benzaldehyde (**1a**) and acetamide (**2**) as probe substrates to optimize reaction conditions, and the results are summarized in Table 1. By using $PdBr_2$ as catalytic precursor and $LiBr \cdot H_2O$ and H_2SO_4 as cocatalysts, the reaction could generate product *N*-acetyl-α-phenylglycine (**3a**) with yield of 71%

Table 1. Palladium-catalyzed amidocarbonylation of benzaldehyde and acetamide in ionic liquids[a]



Entry	Catalyst	LiBr (mol%)	H_2SO_4 (mol%)	Solvent[b]	Substrate concentration ($mol \cdot L^{-1}$)	Temperature (°C)	Yield (%)[c]
1	$PdBr_2$	15	6	$[C_4mim]PF_6$	3.1	80	71
2	$Pd(OAc)_2$	15	6	$[C_4mim]PF_6$	3.1	80	58
3	$PdCl_2$	15	6	$[C_4mim]PF_6$	3.1	80	67
4[d]	$PdBr_2/PPh_3$	15	6	$[C_6mim]PF_6$	3.1	80	11
5	$PdBr_2$	15	6	$[C_6mim]PF_6$	3.1	80	93
6	$PdBr_2$	15	6	$[C_8mim]PF_6$	3.1	80	76
7	$PdBr_2$	15	6	$[C_6mim]BF_4$	3.1	80	49
8	$PdBr_2$	15	6	$[C_6mim]PF_6$	2.3	80	98
9	$PdBr_2$	15	6	$[C_6mim]PF_6$	1.8	80	61
10	$PdBr_2$	10	6	$[C_6mim]PF_6$	2.3	80	48
11	$PdBr_2$	15	3	$[C_6mim]PF_6$	2.3	80	64
12	$PdBr_2$	15	6	$[C_6mim]PF_6$	2.3	60	23
13	$PdBr_2$	15	6	$[C_6mim]PF_6$	2.3	100	57

[a]Reaction conditions: **1a** (30 mmol), **2** (25 mmol), Pd catalytic precursor (0.5 mol%), CO (5 MPa of initial pressure), 12 h.

[b]Abbreviations: $[C_4mim]$ denotes 1-n-butyl-3-methylimidazolium, $[C_6mim]$ denotes 1-n-hexyl-3-methylimidazolium, and $[C_8mim]$ denotes 1-n-octyl-3-methyl imidazolium.

[c]Yield of isolated product.

[d]0.5 mol% $PdBr_2$ and 1 mol% PPh_3 were used.

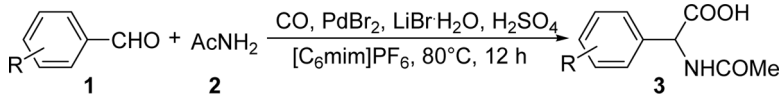
in $[C_4mim]PF_6$ medium (Table 1, entry 1). The result indicated that amidocarbonyltion could be readily carried out in $[C_4mim]PF_6$. It has been known that the amidocarbonylation of benzaldehyde and acetamide under ligand-free condition in ILs $[C_4mim]PF_6$ were not presented by Jiang et al.[5b] Encouraged by our result, we then tested effect of other reaction parameters on reactivity under IL media. Evaluation of palladium salts, such as $PdBr_2$, $Pd(OAc)_2$, and $PdCl_2$, showed that $PdBr_2$ was the most efficient catalyst precursor (Table 1, entries 1–3).

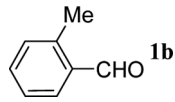
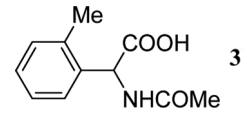
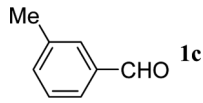
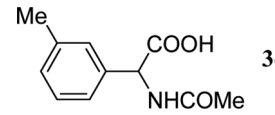
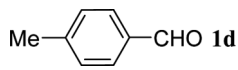
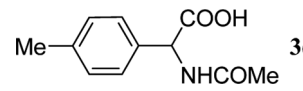
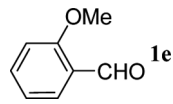
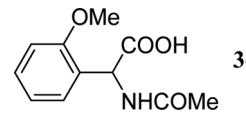
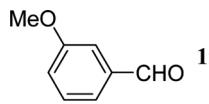
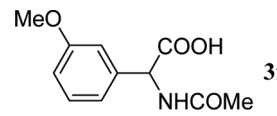
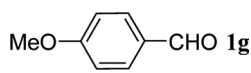
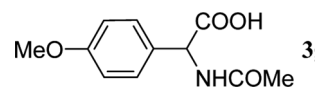
It should be noted that the reaction efficiency was affected by both cationic scaffold and anionic counterpart of ILs. With application of $[C_6mim]PF_6$, $[C_8mim]PF_6$, and $[C_6mim]BF_4$ as media, the yields decreased in the order $[C_6mim]PF_6 > [C_8mim]PF_6 > [C_6mim]BF_4$ (Table 1, entries 5–7). Thus, for the imidazolium-based ILs, hydrophobic $[C_4mim]PF_6$, $[C_6mim]PF_6$, and $[C_8mim]PF_6$ were more suitable for this reaction than hydrophilic $[C_6mim]BF_4$. Similar anion effect of ILs mediun on reaction efficiency has also been known for the carbonylation of aryl halides[17] and copolymerization of styrene and carbon monoxide.[18] The optimum concentration of substrate was 2.3 mol L^{-1} (Table 1, entries 5, 8, and 9). The experimental results showed that substrate concentration had an impact on the catalytic performance of amidocarbonylation. Similar results were observed for Beckmann rearrangement of ketoximes in ionic liquids.[19]

$LiBr \cdot H_2O$ and H_2SO_4 as cocatalysts have an enhancing effect on this reaction. A variation in the amounts of both cocatalysts resulted in substantial change of the yield. The best result was obtained with 15 mol% $LiBr \cdot H_2O$ and 6 mol% H_2SO_4 (Table 1, entries 8, 10, and 11). Finally, it was important to note that ideal reaction temperature appeared to be at 80 °C (Table 1, entries 8, 12, and 13). Considering the almost stoichiometric yield of up to 98%, the effect of other reaction conditions on the reactivity was not further investigated. So far, to our knowledge, it was the highest yield achieved in amidocarbonylation of benzaldehyde (Table 1, entry 8).

Under the optimal reaction conditions, amidocarbonylation of some aromatic aldehydes (**1b–i**) were carried out. As shown in Table 2, several functionalized *ortho*-, *meta*-, and *para*-substituted *N*-acetyl-α-tolylglycines and *N*-acetyl-α-methoxyphenylglycines (**3b–g**) were prepared with moderate to good yields in $[C_6mim]PF_6$ medium. A significant dependence of product yield on both substituent position and electronic effect of aromatic systems was observed, in which *m*-substituted benzaldehydes gave higher yield than *o*- or *p*-substituted ones (Table 2, entries 1–6). However, by employing *o*-chlorobenzaldehyde (**1h**) and *p*-chlorobenzaldehyde (**1i**) as reaction substrate, much lower yields were afforded (Table 2, entries 7 and 8). These results clearly indicate that

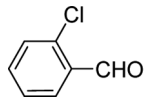
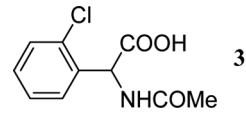
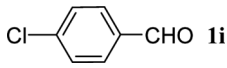
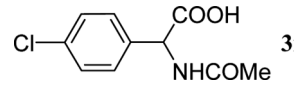
Table 2. Palladium-catalyzed amidocarbonylation of aromatic aldehydes and acetamide in $[C_6mim]PF_6$[a]



Entry	Aldehyde	Product	Yield (%)[b]
1	 **1b**	 **3b**	60
2	 **1c**	 **3c**	83
3	 **1d**	 **3d**	80
4[c]	 **1e**	 **3e**	50
5[c]	 **1f**	 **3f**	60
6[c]	 **1g**	 **3g**	52

(*Continued*)

Table 2. Continued

Entry	Aldehyde	Product	Yield (%)[b]
7	 **1h**	 **3h**	14
8	 **1i**	 **3i**	26

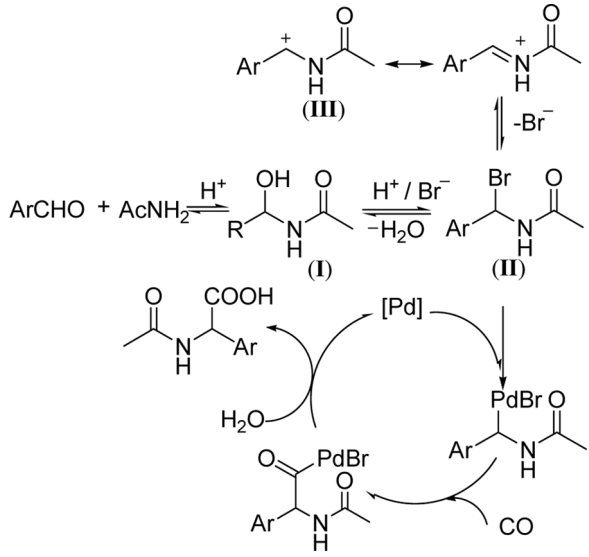
[a]Unless otherwise noted, the reactions were performed with **1** (30 mmol), **2** (25 mmol), $PdBr_2$ (0.5 mol%), H_2SO_4 (6 mol%), and $LiBr \cdot H_2O$ (15 mol%) in 11 mL $[C_6mim]PF_6$ under CO (5 MPa of initial pressure) at 80 °C for 12 h.

[b]Yield of isolated product.

[c]The reaction required 12 mol% H_2SO_4.

benzaldehydes bearing electon-donating substituents react more readily than those with electron-withdrawing groups. This possibly indicates that a better stabilization of an intermediate benzylic cation (**III**, scheme 2) bearing an electron-donating substituent was very important when functionalized aromatic aldehydes (**1b–i**) were used as substrates. It was shown that *o*-tolualdehyde (**1b**) and *m*-tolualdehyde (**1c**) as reaction substrates were first amidocarbonylated by this method. To the best of our knowledge, the amidocarbonylation reaction of **1b** or **1c** in organic solvents has not been reported.

The mechanism for palladium-catalyzed amidocarbonylation of aromatic aldehyde in NMP as solvent had been proposed.[2,3] Reaction of aldehyde with amide generated *N*-(α-hydroxyalkyl)amide (**I**), then nucleophilic substitution of lithium bromide to **I** gave intermediate *N*-(α-bromoalkyl)amide (**II**) in the presence of cocatalysts H_2SO_4. Oxidative addition of **II** to palladium is followed by CO insertion and hydrolysis to yield the product *N*-acyl-α-arylglycine (Scheme 2). Interestingly, several results with $LiBr \cdot H_2O$ and H_2SO_4 as cocatalysts have promoting effects on the reaction; $PdBr_2$ performs the best catalysis among the used catalytic precursors, and benzaldehydes with electron-donating substituents react more efficiently than those bearing electron-withdrawing groups. These are consistent with those in which NMP is solvent. However, it could not be understood why triphenylphosphine as additional ligand had so



Scheme 2. Proposed mechanism for the Pd-catalyzed amidocarbonylation.

much detrimental effect on this reaction in ILs. Further investigation on the question and the reuse of ILs is currently under way in our group.

It is worth pointing out that the separation process of these products turned out to be more convenient using $[C_6mim]PF_6$ than NMP and Jiang's procedure.[2,5] $[C_6mim]PF_6$ is insoluble in water[20]; thus, to treat the produced liquid mixture with aqueous NaOH could produce two phases of liquids. The aqueous phase containing sodium *N*-acyl-α-arylglycinate was adjusted to pH = 2 with 85% phosphoric acid, and the product *N*-acyl-α-arylglycine could be easily precipitated.

In conclusion, we have developed a palladium-catalyzed amidocarbonylation reaction of aromatic aldehyde, acetamide, and CO under ligand-free and IL media. In the absence of any phosphine ligand, the reaction could proceed smoothly with only 15 mol% of $LiBr \cdot H_2O$ as co catalyst. Several functionalized *N*-acyl-α-arylglycines were synthesized by this preparative route to extend the scope of reaction substrates, and up to 98% yield of *N*-acetyl-α-phenylglycine was obtained in $[C_6mim]PF_6$ as solvent, which was the best result achieved in amidocarbonylation of benzaldehyde to date. We believe the ligand-free synthetic method and convenient separation process based on ILs are attractive for many organic chemists working in this and related areas.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 solution on 400 and 100 MHz, respectively, using Bruker AM 400 spectrometer with tetramethylsilane (TMS, $\delta = 0.00$) as internal standard. Proton chemical shifts (δ) and coupling constants (J) were given in parts per million (ppm) and in hertz, respectively. Spin multiplicities were given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). IR spectra were taken with Bruker IFS 120 HR FT-IR spectrometer. MS spectra were obtained on Waters ZQ 4000. All the melting points were determined on an X-4 Electrothermal digital melting-point apparatus and are uncorrected. The ILs used herein were prepared according to the reported procedures.[20] All other reagents were commercially available.

Typical Experimental Procedure

In a 200-mL stainless steel reactor with a magnet-driven propeller stirrer, 30 mmol aromatic aldehyde, 25 mmol acetamide, 0.5 mol% $PdBr_2$, 15 mol% $LiBr \cdot H_2O$, 6 mol% H_2SO_4, and 11 mL ILs were allowed to react at 50 bar of initial CO pressure and 80 °C for 12 h. At the end of this period, the residue gas was released, and 20 mL of dichloromethane was added to the reactor. Treatment of the mixture with 30 mL of aqueous 1.5 mol L^{-1} NaOH formed two phases of liquid. The aqueous phase was extracted with dichloromethane (30 mL × 3) and then adjusted to pH = 2 with 85% phosphoric acid. The white precipitate was filtered off, washed by distilled water, and dried in vacuo. The products were recrystallized from water/methanol mixtures (v/v, 1/1) and characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy.

Data

N-Acetyl-α-phenylglycine (**3a**)[5b]

White solid (4.75 g, 98% yield); mp 199–201 °C. IR (KBr): 3343, 1716, 1601, 1544 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.61$ (d, $J = 7.6$ Hz, 1H), 7.34 (m, 5H), 5.30 (d, $J = 7.6$ Hz, 1H), 1.88 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 172.1$, 169.1, 137.2, 128.5, 128.0, 127.7, 56.3, 22.3. ESI-MS: m/z (%) = 191.9 (85) [M–H], 147.8 (100) [M–COOH].

N-Acetyl-α-(2-tolyl)glycine (**3b**)

White solid (3.1 g, 80% yield); mp 196–197 °C. IR (KBr): 3363, 1740, 1608, 1546 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.57 (d, J = 7.2 Hz, Hz, 1H), 7.19 (m, 4H), 5.25 (d, J = 7.6 Hz, 1H), 2.29 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.1, 169.2, 137.7, 137.1, 128.6, 128.5, 128.3, 124.8, 56.3, 22.3, 21.0. ESI-MS: m/z (%) = 206.1 (97) [M–H], 162.1 (100) [M–COOH], 163.1 (12) [M–H–CH_3CO].

N-Acetyl-α-(3-tolyl)glycine (**3c**)

White solid (4.3 g, 83% yield); mp 202–203 °C. IR (KBr): 3361, 3335, 1704, 1617, 1544 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.80 (s, 1H), 8.54 (d, J = 7.6 Hz, 1H), 7.22 (m, 4H), 5.52 (d, J = 7.6 Hz, 1H), 2.33 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.4, 169.1, 136.3, 136.0, 130.4, 127.9, 127.1, 126.2, 52.8, 22.2, 19.0. ESI-MS: m/z (%) = 206.1 (62) [M–H], 162.1 (100) [M–COOH], 163.1 (12) [M–H–CH_3CO].

N-Acetyl-α-(4-tolyl)glycine (**3d**)[2b]

White solid (4.2 g, 81% yield); mp 226–228 °C. IR (KBr): 3339, 1717, 1546, 1601 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.6 (s, 1H), 8.47 (d, J = 7.60 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.6 Hz, 2H), 5.25 (d, J = 7.2 Hz, 1H), 2.28 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.5, 168.9, 136.9, 134.9, 128.9, 127.5, 56.3, 22.3, 20.7. ESI–MS: m/z (%) = 413.4 (22) [2M–H], 205.8 (100) [M–H], 161.7 (17) [M–COOH].

N-Acetyl-α-(2-methoxyphenyl)glycine (**3e**)[21]

White solid (2.8 g, 50% yield); mp 165–167 °C. IR (KBr): 3358, 1740, 1604, 1531 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.54 (bs, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.30 (m, 2H), 7.01 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 7.6, 7.6 Hz, 1H), 5.63 (d, J = 7.6 Hz, 1H), 3.77 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.3, 169.1, 156.7, 129.3, 128.6, 125.6, 120.4, 111.3, 55.6, 50.3, 22.3. ESI-MS: m/z (%) = 222.2 (70) [M–H], 178.1 (100) [M–COOH], 179.1 (19) [M–H–CH_3CO], 163.0 (18) [M–H–CH_3CONH].

N-Acetyl-α-(3-methoxyphenyl)glycine (**3f**)[2g]

White solid (3.4 g, 60% yield); mp 146–147 °C. IR (KBr): 3343, 1718, 1610, 1587, 1540 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.58 (d, J = 7.6 Hz, 1H), 7.27 (dd, J = 8.4, 8.0 Hz, 1H), 6.92 (m, 3H), 5.28 (d, J = 7.6 Hz, 1H), 3.73 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.0, 169.1, 159.3, 138.7, 129.6, 119.9, 113.4, 113.3, 56.2, 55.1, 22.3. ESI-MS: m/z (%) = 222.2 (58) [M–H], 178.1 (100) [M–COOH], 179.1 (19) [M–H–CH_3CO].

N-Acetyl-α-(4-methoxyphenyl)glycine (**3g**)[2b]

White solid (2.9g, 52% yield); mp 210–212 °C. IR (KBr): 3340, 1717, 1612, 1547, 1516cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.7 (s, 1H), 8.52 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.8 Hz, Hz, 2H), 5.22 (d, J = 7.60 Hz, 1H), 3.73 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.3, 169.0, 160.0, 129.1, 129.0, 113.9, 55.6, 55.2, 22.3. ESI-MS: m/z (%) = 445.4 (12) [2M–H], 219.9 (100) [M–H], 177.8 (27) [M–COOH], 178.8 (10) [M–H–CH_3CO].

N-Acetyl-α-(2-chlorophenyl)glycine (**3h**)[2b,22]

White solid (0.8 g, 14% yield); mp 164–165 °C. IR (KBr): 3360, 1717, 1610, 1537 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 13.01 (s, 1H), 8.68 (d, J = 8.0 Hz, 1H), 7.40 (m, 4H), 5.76 (d, J = 7.6 Hz, 1H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.4, 169.1, 135.4, 133.0, 129.7, 129.5, 129.1, 127.5, 53.1, 22.2. ESI-MS: m/z (%) = 226.2 (18) [M–H], 182.0 (90) [M–COOH], 184.0 (28) [M(^{37}Cl)–COOH].

N-Acetyl-α-(4-chlorophenyl)glycine (**3i**)[2b]

White solid (1.5 g, 26% yield); mp 196–198 °C. IR (KBr): 3339, 1717, 1546, 1601 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 13.0 (s, 1H), 8.67 (d, J = 7.6 Hz, 1H), 7.41 (m, 4H), 5.33 (d, J = 7.60 Hz, 1H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.7, 169.1, 136.4, 132.6, 129.5, 128.5, 55.5, 22.3. ESI-MS: m/z (%) = 453.3 (25) [2M–H], 225.9 (100) [M–H], 181.8 (96) [M–COOH], 183.7 (32) [M(^{37}Cl)–COOH].

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