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Palladium-catalysed carbonylation of 4-substituted 2-iodoaniline derivatives: carbonylative cyclisation and aminocarbonylation

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Abstract—2-Iodoaniline derivatives were used as bifunctional substrates in palladium-catalysed carbonylation. Depending on the substituents, two types of compounds were synthesised: having methyl or hydrogen in 4-position 2-aryl-benzo[*d*][1,3]oxazin-4-one derivatives have been formed, chloro, bromo, cyano or nitro groups in the same position resulted in the formation of dibenzo[*b*,*f*][1,5]-diazocine-6,12-dione derivatives. In the presence of various primary and secondary amines (*tert*-butylamine, amino acid methyl esters) as *N*-nucleophiles 2-keto-carboxamides were obtained as major products in aminocarbonylation reaction with double carbon monoxide insertion.

1. Introduction

Palladium-catalysed carbonylation reactions including amino- and alkoxycarbonylation and carbonylative coupling reactions are widely used in synthetic chemistry.[1,2] Aminocarbonylation plays a special role among these reactions, since those carboxamides which are hardly available in conventional synthetic methods (e.g., with bulky substituents at the amide nitrogen, the application of weak amine nucleophiles) can be synthesised from easily available starting materials. The synthesis of a wide variety of unsaturated carboxamides or aryl carboxamides with various structures has been reported using enol-triflates/iodo-alkenes or aryl triflates/aryl halides as substrates in aminocarbonylation, respectively.[3]

Due to the amino and iodo functionalities, 2-iodoaniline is a versatile building block for organic synthesis. Among them, functionalised iodoaromatics have been applied in many homogeneous catalytic reactions. The allylation of 2-iodoaniline and its consecutive alkoxycarbonylation resulted in the mixture of substituted indol- and 4-oxo-quinoline derivatives.[4] The palladium-catalysed carbonylation of 2-iodoaniline has been used in a multistep reaction for the synthesis of pentacyclic compounds.[5] 2-(2′-Phenyl-ethinyl)-phenol and 2-iodoaniline have been reacted in carbonylation reaction in the presence of $Pd(PPh_3)_4$ resulting in the formation of 2-benzofuranyl-benzo[*d*][1,3]oxazin-4-one derivatives.[6] A carbonylative coupling reaction of 2-iodoaniline and a nucleophile in a zinc complex has been carried out resulting in 3-(2′-amino-benzoyl)-alanine.[7] 3-Keto-2-benzylidene-indol has been synthesised by reacting 2-iodoaniline with phenylacetylene under carbon monoxide in palladium(0)-catalysed reaction.[8] The carbonylative Sonogashira coupling of 2-iodoaniline with 1-octyne resulted in the corresponding 2-amino-aryl-alkinyl ketone in high yield.[9] Various esters possessing enol-triflate moieties and iodo-benzenes have been reacted with 2-iodoaniline in palladium-catalysed carbonylative ring-closure reaction resulting in 2-cycloalkenyl and 2-aryl-benzofuranyl-benzo[*d*]-[1,3]oxazin-4-one derivatives, respectively.[10]

Although 2-iodoaniline derivatives may act both as an iodoarene substrate and as a *N*-nucleophile, to the best of our knowledge, no precedence for their use as a bifunctional substrate has been reported. In this study, catalytic carbonylation on 2-iodoaniline and its 4-substituted derivatives is described.

2. Results and discussion

2.1. Intramolecular aminocarbonylation reactions with 2-iodoaniline derivatives

2-Iodoaniline (**1a**) and its analogues (**1b–f**) were reacted under carbon monoxide pressure (100 bar) in DMF in the presence of in situ generated palladium(0)-triphenylphosphine catalysts *without* adding any further nucleophiles like amines or alcohols (Scheme 1). Palladium(II) acetate was used as catalytic precursor. The formation of neutral

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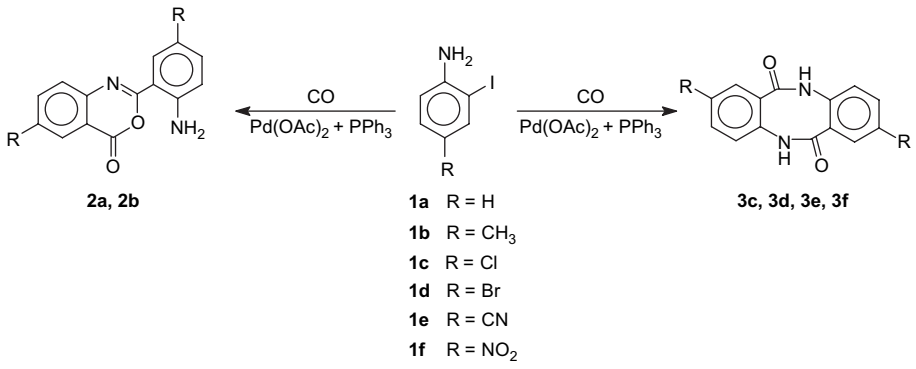


Scheme 1. Carbonylative cyclisation of 2-iodoanilines.

and anionic Pd(0) species from $Pd(OAc)_2/PPh_3$ system has been shown by cyclic voltammetry and ^{31}P NMR spectroscopy.[11–14] The reduction of Pd(II) to Pd(0) is due to PPh_3, which is itself oxidised to triphenylphosphine oxide.

The aim of the work was the application of a substrate family, which possesses both the iodoaryl moiety that can readily be oxidatively added to palladium(0) as well as an amino functionality that can act as a *N*-nucleophile in the product-forming step. The substrates can be divided into two groups according to the chemoselectivity of the reaction. Compounds **1a** and **1b** were transformed to the corresponding 2-aryl-benzo[*d*][1,3]oxazin-4-one derivatives (**2a** and **2b**) via double carbon monoxide insertion, while only one of the amino groups reacts. However, symmetric 5*H*,11*H*-dibenzo[*b*,*f*][1,5]diazocine-6,12-dione ('dianthranilide') type compounds (**3c**–**f**) have been obtained as major product when **1c**–**f** have been used as substrates (Scheme 1). It should be noted that due to extremely low solubilities of the latter dianthranilide-type derivatives and consequently, the difficulty in obtaining good quality NMR spectra, IR and MS spectroscopy play a crucial role in the structure determination. The structures have been proved by the typical vibrations in the ν(CO) region (see Section 4).

The products (**2a**, **2b**, **3c**–**f**) have been obtained with practically complete conversion and isolated in 74–85% yields. High chemoselectivities towards both 2-aryl-benzoxazin-4-ones (**2a**, **2b**) and dibenzo-diazocine-6,12-diones (**3c**–**f**) were obtained. The target compounds were formed with higher than 96% chemoselectivities in both cases. The major strength of these reactions could be their simplicity providing the target compounds without organic side products. The formation of both types of compounds can be rationalised by a simple reaction: two substrates (iodoaniline derivative)+two CO provide the cyclic product. The parent compounds of both families (dianthranilide[15–17] and **2a**[18–20]) are known and there are several conventional synthetic methods for their synthesis. The Beckmann rearrangement of anthraquinone dioxime (yield 85%)[17] and heating of 1,2,3-benzotriazin-4-one in inert solvents (yield 71%)[18] can be considered as high-yielding procedures of preparative importance, respectively.

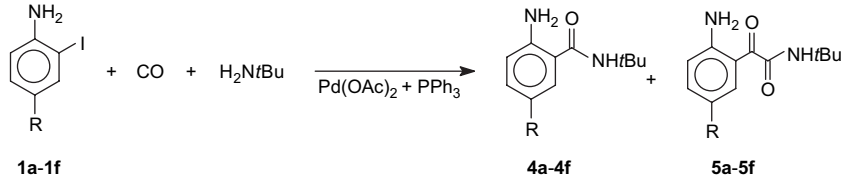
2.2. Aminocarbonylation reactions of 2-iodoaniline derivatives in the presence of primary and secondary amines

The carbonylative dimerisation products (**2a**, **2b**, **3c**–**f**) have been formed only in traces (<5%) in the presence of primary amines. The iodoaniline derivatives (**1a**–**f**) were thus reacted under carbon monoxide pressure (40 bar) in DMF at 50 °C in the presence of $Pd(OAc)_2$ and triphenylphosphine as the in situ catalyst and *tert*-butylamine as nucleophile (Scheme 2, Table 1). The corresponding 2-keto-*tert*-butylcarboxamides

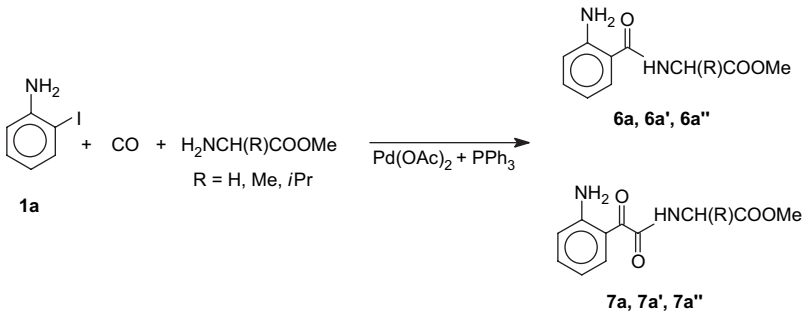
Table 1. Aminocarbonylation of 2-iodoanilines (**1a**–**f**) with primary and secondary amines[a]

Substrate	Amine	t_R[b] [h]	Products[c] [%]	
			Carboxamide	Ketocarboxamide
1a	*t*-BuNH_2	20	0 (**4a**)	100 (**5a**)
1b	*t*-BuNH_2	20	38 (**4b**)	62 (**5b**)
1c	*t*-BuNH_2	20	5 (**4c**)	95 (**5c**)
1d	*t*-BuNH_2	20	0 (**4d**)	100 (**5d**)
1e	*t*-BuNH_2	20	0 (**4e**)	100 (**5e**)
1f	*t*-BuNH_2	20	0 (**4f**)	100 (**5f**)
1a	GlyOMe	70	5 (**6a**)	95 (**7a**)
1a	AlaOMe	70	0 (**6a′**)	100 (**7a′**)
1a	ValOMe	6	0 (**6a″**)	100 (**7a″**)
1a	ProOMe	6	0 (**8a**)	100 (**9a**)
1b	ProOMe	6	0 (**8b**)	100 (**9b**)
1c	ProOMe	6	0 (**8c**)	100 (**9c**)
1f	ProOMe	6	0 (**8f**)	100 (**9f**)

[a] Reaction conditions: 0.025 mmol $Pd(OAc)_2$; 0.05 mmol PPh_3, 1 mmol 2-iodoaniline derivative (**1a**–**f**); 5 mmol *tert*-butylamine (or 1.25 mmol amino acid methylester hydrochloride), 10 ml DMF; 40 bar carbon monoxide, reaction temperature: 50 °C.
[b] Practically complete conversion (>98%) was obtained in all cases.
[c] Determined by GC–MS.

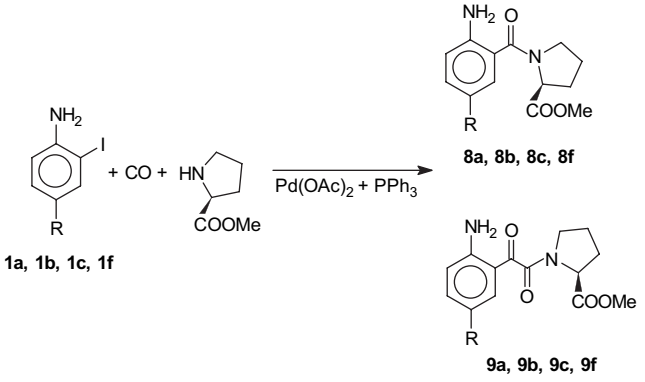


Scheme 2. Aminocarbonylation of 2-iodoanilines with *tert*-butylamine.



Scheme 3. Aminocarbonylation of 2-iodoaniline with amino acid esters as primary amines.

(**5a–f**) were obtained as major products in all cases (Table 1). The amount of the carboxamide in the reaction mixture was the highest (38% yield; **4b**) when **1b** was used as a substrate. Similarly high yields of ketocarboxamides were obtained with glycine methylester, alanine methylester and valine methylester as amine, so methyl *N*-{(2′-amino-phenyl)glyoxyloyl}-glycinate (**7a**), methyl *N*-{(2′-amino-phenyl)glyoxyloyl}-alaninate (**7a′**) and methyl *N*-{(2′-amino-phenyl)-glyoxyloyl}-valinate (**7a″**) were formed by double carbon monoxide insertion, respectively (Scheme 3). The carboxamide formed by single carbon monoxide insertion was detected by GC–MS only in the case of methyl glycinate. Similarly, exclusive ketocarboxamide formation (**9a**, **9b**, **9c**, **9f**) was observed with methyl prolinate as secondary amine (Scheme 4). A similar prevalence of 2-oxo-carboxamides over carboxamides in aminocarbonylation of iodoaromatics has been reported.[21]



Scheme 4. Aminocarbonylation of 2-iodoanilines with methyl prolinate as secondary amine.

3. Conclusions

It has been shown that 2-iodoaniline derivatives can be transformed into two different types of 'dimeric' ring-closure products in palladium-catalysed carbonylation. The reactions need rather severe conditions due to the weak arylamine nucleophile. However, by using various alkylamines for the aminocarbonylation of the same substrates under similar carbonylation conditions, the iodoaryl moiety of iodoanilines reacts exclusively (i.e., the adjacent amino group bound to the aryl ring remained intact). Due to double carbon monoxide insertion, 2-ketocarboxamides of practical interest have been isolated as major products in all cases. As for their potential biological importance, various 2-oxoamides are reported as potent inhibitors of digestive lipases[22–24] and phospholipases A2.[25] Furthermore, 2-oxoamides based on γ-amino acids inhibit Group VIA phospholipase A2 and exhibit interesting in vivo anti-inflammatory and analgesic activity.[26]

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova 400 spectrometer at 400.13 and 100.62 MHz, respectively. Chemical shifts δ are reported in parts per million relative to $CHCl_3$ (7.26 and 77.00 ppm for ^{1}H and ^{13}C, respectively). Elemental analyses were measured on a 1108 Carlo Erba apparatus. Samples of the catalytic reactions were analysed with a Hewlett Packard 5830A gas chromatograph fitted with a capillary column coated with OV-1. The FTIR spectra were taken in KBr pellets using an IMPACT 400 spectrometer (Nicolet) applying a DTGS detector in the region of 400–4000 cm^{-1}, the resolution was 4 cm^{-1}. The amount of the samples was ca. 0.5 mg.

2-Iodoaniline (**1a**) and amino acid esters were purchased from Aldrich. The other substituted 2-iodoanilines (**1b**,[27] **1c**,[27] **1d**,[27] **1e**,[28] **1f**[29]) were synthesised according to the known procedures.

4.2. Aminocarbonylation experiments with 2-iodoaniline derivatives

In a typical experiment, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), 1 mmol iodo substrate (**1a–f**) and 0.5 ml triethyl amine were dissolved in DMF (10 ml) under argon in a 100 ml autoclave. The atmosphere was changed to carbon monoxide and the autoclave was pressurised to 100 bar with carbon monoxide. The reaction was conducted for 140 h upon stirring at 50 °C. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (20 ml) and washed with water (20 ml). The organic phase was thoroughly washed twice with 5% HCl (20 ml), saturated $NaHCO_3$ (20 ml), brine (20 ml), dried over Na_2SO_4 and concentrated to powder-like crystalline material in case of **2a** and **2b**. Due to low solubility of the substituted dianthranilides (**3c–f**), they have been crystallised mainly from the catalytic mixture and washed with ethanol.

4.3. Aminocarbonylation experiments of 2-iodoaniline derivatives with *tert*-butylamine

In a typical experiment, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), 1 mmol iodo substrate (**1a–f**), *tert*-butylamine (0.53 ml, 5 mmol) and 0.5 ml triethyl amine were dissolved in DMF (10 ml) under argon. The homogeneous yellow solution was transferred into a 100 ml autoclave and it was pressurised to 40 bar with carbon monoxide. The reaction was conducted for 20 h upon stirring at 50 °C. A sample of this solution was immediately analysed by GC–MS. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (20 ml) and washed with water (20 ml). The organic phase was thoroughly washed twice with 5% HCl (20 ml), saturated $NaHCO_3$ (20 ml), brine (20 ml), dried over Na_2SO_4 and concentrated to a yellow waxy material or a thick oil. Chromatography (silica, chloroform, than chloroform/ethanol=1:1) yielded the desired compounds as yellow solids.

4.4. Characterisation of the products

4.4.1. 2-(2′-Amino-phenyl)-benzo[*d*][1,3]oxazin-4-one (2a). ^{1}H NMR ($CDCl_3$) δ: 8.21 (dd, 7.9 Hz, 0.9 Hz, 1H); 8.10 (dd, 8.4 Hz, 1.4 Hz, 1H); 7.85 (dt, 7.7 Hz, 1.4 Hz, 1H); 7.57 (d, 8.0 Hz, 1H); 7.45 (t, 7.9 Hz, 1H); 7.26 (dt, 7.9 Hz, 1.4 Hz, 1H); 6.73 (m, 2H); 6.42 (br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$) δ: 159.5; 158.0; 149.8; 146.6; 136.4; 133.8; 129.7; 128.7; 127.9; 126.3; 116.7; 116.5; 110.1. IR (KBr, cm^{-1}): 3439, 3309, 1750, 1742, 1625, 1593, 1550, 1473. MS (*m*/*z*/rel int.): 238 (M^+)/100; 194/17; 120/86; 92/51; 65/30. Anal. Calcd for $C_{14}H_{10}N_2O_2$ (238.25): C, 70.58; H, 4.23; N, 11.76. Found: C, 70.77; H, 4.43; N, 11.48. Yield: 74%. Isolated as pale yellow powder-like crystalline material. Mp 172 °C.

4.4.2. 2-(2′-Amino-4′-methyl-phenyl)-7-methyl-benzo[*d*]-[1,3]oxazin-4-one (2b). ^{1}H NMR ($CDCl_3$) δ: 8.00 (s, 1H); 7.88 (s, 1H); 7.55 (dd, 8.2 Hz, 1.6 Hz, 1H); 7.47 (d, 8.2 Hz, 1H); 7.07 (dd, 8.4 Hz, 1.6 Hz, 1H); 6.63 (d, 8.4 Hz, 1H); 6.25 (br s, 2H, NH_2); 2.46 (s, 3H, CH_3); 2.27 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 159.7; 157.4; 147.3; 144.4; 138.0; 137.8; 134.6; 129.2; 128.3; 126.2; 117.0; 116.5; 110.2; 21.4; 20.2. IR (KBr, cm^{-1}): 3453 (br, diffuse), 1738, 1629, 1620, 1592, 1556, 1492. MS (*m*/*z*/rel int.): 266 (M^+)/100; 222/12; 134/47; 106/28; 77/27. Anal. Calcd for $C_{16}H_{14}N_2O_2$ (266.30): C, 72.17; H, 5.30; N, 10.52. Found: C, 72.02; H, 5.52; N, 10.25. Yield: 85%. Isolated as pale yellow powder-like crystalline material. Mp 191–193 °C.

4.4.3. 2,8-Dichloro-5*H*,11*H*-dibenzo[*b*,*f*][1,5]diazocine-6,12-dione (3c). ^{1}H NMR (DMSO-d_6) δ: 8.30 (s, 2H, Ar-H); 7.30 (d, 8 Hz, 2H, Ar-H); 6.90 (d, 8 Hz, 2H, Ar-H); 6.75 (br s, 2H, CON*H*). IR (KBr, cm^{-1}): 3451 (weak, diffuse), 1680, 1618, 1601, 1492. MS (*m*/*z*/rel int.): 306, 308, 310 (M^+)/15, 10, 2; 153/54; 73/100; 44/67. Anal. Calcd for $C_{14}H_8N_2O_2Cl_2$ (307.14): C, 54.75; H, 2.63; N, 9.12. Found: C, 54.53; H, 2.87; N, 9.01. Yield: 78%. Isolated as yellow powder-like crystalline material. Mp >330 °C (decomposed).

4.4.4. 2,8-Dibromo-5*H*,11*H*-dibenzo[*b*,*f*][1,5]diazocine-6,12-dione (3d). ^{1}H NMR (DMSO-d_6) δ: 7.82 (s, 2H, Ar-H); 7.30 (d, 8 Hz, 2H, Ar-H); 6.62 (d, 8 Hz, 2H, Ar-H); 6.50 (br s, 2H, CON*H*). IR (KBr, cm^{-1}): 3451 (weak, diffuse), 1681, 1612, 1598, 1506, 1487. MS (*m*/*z*/rel int.): 394, 396, 398 (M^+)/28, 55, 27; 197, 199/100, 99; 171/53. Anal. Calcd for $C_{14}H_8N_2O_2Br_2$ (396.04): C, 42.46; H, 2.04; N, 7.07. Found: C, 42.20; H, 1.95; N, 6.89. Yield: 80%. Isolated as yellow powder-like crystalline material. Mp >330 °C (decomposed).

4.4.5. 2,8-Dicyano-5*H*,11*H*-dibenzo[*b*,*f*][1,5]diazocine-6,12-dione (3e). ^{1}H NMR (DMSO-d_6) δ: 8.55 (s, 2H, Ar-H); 7.40 (d, 8 Hz, 2H, Ar-H); 7.11 (s, 2H, CON*H*); 6.69 (d, 8 Hz, 1H, Ar-H). IR (KBr, cm^{-1}): 3455, 3345, 2214, 1621, 1588, 1497. MS (*m*/*z*/rel int.): 288 (M^+)/16; 145/100; 117/29. Anal. Calcd for $C_{16}H_8N_4O_2$ (288.27): C, 66.67; H, 2.80; N, 19.44. Found: C, 66.50; H, 2.94; N, 19.17. Yield: 77%. Isolated as pale yellow powder-like crystalline material. Mp >330 °C (decomposed).

4.4.6. 2,8-Dinitro-5*H*,11*H*-dibenzo[*b*,*f*][1,5]diazocine-6,12-dione (3f). ^{1}H NMR (DMSO-d_6) δ: 8.68 (s, 2H, Ar-H); 7.94 (d, 8 Hz, 2H, Ar-H); 6.86 (br s, 2H, CON*H*); 6.73 (d, 8 Hz, 2H, Ar-H). IR (KBr, cm^{-1}): 3440 (br, diffuse), 1653, 1648, 1622, 1455, 1399. MS (*m*/*z*/rel int.): 382 (M^+)/15; 368/6; 256/12; 213/14; 174/28; 129/35; 97/50; 57/88; 44/93; 43/100. Anal. Calcd for $C_{14}H_8N_4O_6$ (328.24): C, 51.23; H, 2.46; N, 17.07. Found: C, 51.11; H, 2.63; N, 16.87. Yield: 85%. Isolated as orange powder-like crystalline material. Mp >330 °C (decomposed).

4.4.7. *N*-*tert*-Butyl-(2-amino-phenyl)-glyoxylamide (5a). ^{1}H NMR ($CDCl_3$) δ: 8.12 (d, 8.0 Hz, 1H, Ar-H); 7.18 (d, 8 Hz, 1H, Ar-H); 6.65 (br s, 1H, CON*H*); 6.50–6.60 (m, 2H, Ar-H); 6.32 (br s, 2H, N*H*$_2$); 1.38 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$) δ: 190.0; 163.5; 151.8; 135.0; 133.4; 116.3; 115.0; 113.4; 51.0; 27.8. IR (KBr, cm^{-1}): 3440 (br, diffuse), 1693, 1642. MS (*m*/*z*/rel int.): 220 (M^+)/15; 120/100; 93/22; 92/23. Anal. Calcd for $C_{12}H_{16}N_2O_2$ (220.27): C, 65.43; H, 7.32; N, 12.72. Found: C, 65.56; H, 7.60; N, 12.61. Yield: 78%. Isolated as pale brown crystalline material. Mp 155–157 °C.

4.4.8. *N*-*tert*-Butyl-(2-amino-5-methyl-phenyl)-glyoxylamide (5b). ^{1}H NMR ($CDCl_3$) δ: 8.13 (s, 1H, Ar-H); 7.10 (d, 8 Hz, 1H, Ar-H); 6.62 (br s, 1H, CON*H*); 6.55 (d, 8 Hz, 1H, Ar-H); 6.10 (br s, 2H, N*H*$_2$); 2.20 (s, 3H, CH_3); 1.42 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$) δ: 190.1; 163.6; 150.4; 137.3; 133.4; 125.1; 116.9; 114.5; 51.6; 28.5. IR (KBr, cm^{-1}): 3480, 3345 (br, diffuse), 1698, 1652, 1602. MS (*m*/*z*/rel int.): 234 (M^+)/15; 134/100; 107/18; 106/22. Anal. Calcd for $C_{13}H_{18}N_2O_2$ (234.30): C, 66.64; H, 7.74; N, 11.96. Found: C, 66.40; H, 7.83; N, 11.77. Yield: 72%. Isolated as pale brown crystalline material. Mp 165 °C.

4.4.9. *N*-*tert*-Butyl-(2-amino-5-chloro-phenyl)-glyoxylamide (5c). ^{1}H NMR ($CDCl_3$) δ: 8.45 (s, 1H, Ar-H); 7.20 (d, 8 Hz, 1H, Ar-H); 6.70 (br s, 1H, CON*H*); 6.58 (d, 8 Hz, 1H, Ar-H); 6.25 (br s, 2H, N*H*$_2$); 1.40 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$) δ: 190.2; 162.4; 151.2; 138.3; 136.2; 118.6; 115.7; 107.2; 51.7; 28.4. IR (KBr, cm^{-1}): 3490, 3350 (br, diffuse), 1700, 1655, 1605. MS (*m*/*z*/rel int.): 254(256) (M^+)/15(5); 154(156)/100(34); 127/20. Anal. Calcd for $C_{12}H_{15}N_2O_2Cl$ (254.72): C, 56.59; H,

5.94; N, 11.00. Found: C, 56.41; H, 5.73; N, 10.81. Yield: 80%. Isolated as pale brown crystalline material. Mp 169–171 °C.

4.4.10. *N*-*tert*-Butyl-(2-amino-5-bromo-phenyl)-glyoxylamide (5d). ^{1}H NMR ($CDCl_3$) δ: 8.62 (s, 1H, Ar-H); 7.33 (d, 8 Hz, 1H, Ar-H); 6.70 (br s, 1H, CONH); 6.52 (d, 8 Hz, 1H, Ar-H); 6.25 (br s, 2H, NH_2); 1.40 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ: 188.8; 162.6; 150.9; 135.9; 133.1; 120.5; 118.3; 114.9; 51.8; 28.4. IR (KBr, cm^{-1}): 3490, 3350 (br, diffuse), 1690, 1650, 1611. MS (*m*/*z*/rel int.): 300(298) (M^+)/27(26); 200(198)/96(95); 57/100. Anal. Calcd for $C_{12}H_{15}N_2O_2Br$ (299.17): C, 48.18; H, 5.05; N, 9.36. Found: C, 48.05; H, 5.22; N, 9.17. Yield: 83%. Isolated as brown crystalline material. Mp 187–189 °C.

4.4.11. *N*-*tert*-Butyl-(2-amino-5-cyano-phenyl)-glyoxylamide (5e). ^{1}H NMR ($CDCl_3$) δ: 8.95 (s, 1H, Ar-H); 7.42 (d, 8 Hz, 1H, Ar-H); 7.22 (s, 1H, CONH); 6.70 (br s, 2H, NH_2); 6.62 (d, 8 Hz, 1H, Ar-H); 1.43 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ: 188.6; 161.8; 154.4; 140.5; 137.3; 119.0; 117.6; 114.1; 51.9; 28.4. IR (KBr, cm^{-1}): 3480, 3340 (br, diffuse), 2240, 1700, 1652, 1605. MS (*m*/*z*/rel int.): 245 (M^+)/20; 145/65; 118/94; 57/100. Anal. Calcd for $C_{13}H_{15}N_3O_2$ (245.28): C, 63.66; H, 6.16; N, 17.13. Found: C, 63.55; H, 6.37; N, 16.97. Yield: 68%. Isolated as pale brown crystalline material. Mp 170–171 °C.

4.4.12. *N*-*tert*-Butyl-(2-amino-5-nitro-phenyl)-glyoxylamide (5f). ^{1}H NMR ($CDCl_3$) δ: 9.60 (s, 1H, Ar-H); 8.13 (d, 8 Hz, 1H, Ar-H); 7.05 (br s, 2H, NH_2); 6.80 (br s, 1H, CONH); 6.70 (d, 8 Hz, 1H, Ar-H); 1.41 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ: 188.9; 161.7; 156.1; 137.1; 132.3; 130.2; 117.0; 112.5; 52.0; 28.4. IR (KBr, cm^{-1}): 3440 (br, diffuse), 1690, 1653. Anal. Calcd for $C_{12}H_{15}N_3O_4$ (265.27): C, 54.33; H, 5.70; N, 15.84. Found: C, 54.20; H, 5.88; N, 15.67. Yield: 86%. Isolated as orange crystalline material. Mp 219 °C.

4.4.13. Methyl *N*-{(2′-amino-phenyl)glyoxyloyl}-glycinate (7a). ^{1}H NMR ($CDCl_3$) δ: 8.20 (d, 8 Hz, 1H, Ar-H); 7.40 (t, 8 Hz, 1H, Ar-H); 6.62–6.74 (m, 3H, Ar-H+CONH); 6.35 (br s, 2H, NH_2); 4.18 (d, 5.6 Hz, 2H); 3.71 (s, 3H, OCH_3). MS (*m*/*z*/rel int.): 236 (M^+)/21; 208/6; 120/100; 92/28. Anal. Calcd for $C_{11}H_{12}N_2O_4$ (236.23): C, 55.93; H, 5.12; N, 11.86. Found: C, 55.80; H, 5.31; N, 11.69. Yield: 46%. Isolated as waxy yellow material.

4.4.14. Methyl *N*-{(2′-amino-phenyl)glyoxyloyl}-alaninate (7a′). ^{1}H NMR ($CDCl_3$) δ: 8.30 (d, 8 Hz, 1H, Ar-H); 7.43 (t, 8 Hz, 1H, Ar-H); 6.60–6.72 (m, 3H, Ar-H+CONH); 6.23 (br s, 2H, NH_2); 4.60 (qi, 7.5 Hz, 1H, $CHCH_3$); 3.71 (s, 3H, OCH_3); 1.45 (d, 7.5 Hz, 3H, $CHCH_3$). ^{13}C NMR ($CDCl_3$) δ: 188.5; 172.5; 163.3; 151.7; 136.0; 134.1; 132.0; 116.7; 116.0; 52.5; 48.0; 18.0. IR (KBr, cm^{-1}): 3480, 3370 (br, diffuse), 1745, 1688, 1632. MS (*m*/*z*/rel int.): 250 (M^+)/17; 120/100; 92/20. Anal. Calcd for $C_{12}H_{14}N_2O_4$ (250.25): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.30; H, 5.81; N, 10.95. Yield: 48%. Isolated as waxy yellow material.

4.4.15. Methyl *N*-{(2′-amino-phenyl)glyoxyloyl}-valinate (7a″). ^{1}H NMR ($CDCl_3$) δ: 8.25 (d, 8 Hz, 1H, Ar-H); 7.42 (t, 8 Hz, 1H, Ar-H); 6.65–6.75 (m, 3H, Ar-H+CONH); 6.34 (br s, 2H, NH_2); 4.50 (dd, 8.2 Hz, 5.2 Hz, 1H, NHCH); 3.68 (s, 3H, OCH_3); 2.20 (m, 1H, $CH(CH_3)_2$); 0.87 (d, 6.8 Hz, 3H, CH_3); 0.84 (d, 6.8 Hz; 3H, CH_3). MS (*m*/*z*/rel int.): 278 (M^+)/10; 120/100; 92/21. Anal. Calcd for $C_{14}H_{18}N_2O_4$ (278.31): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.32; H, 6.76; N, 10.02. Yield: 48%. Isolated as brown powder-like crystalline material. Mp 121–123 °C.

4.4.16. Methyl *N*-{(2′-amino-phenyl)glyoxyloyl}-prolinate (9a). ^{1}H NMR ($CDCl_3$) δ: 7.70 (d, 8 Hz, 1H, Ar-H); 7.23 (t, 8 Hz, 1H, Ar-H); 6.58–6.70 (m, 2H, Ar-H); 6.35 (br s, 2H, NH_2); 4.60 (m, 1H, $CHCOOCH_3$); 3.76 (s, 3H, OCH_3); 3.40–3.50 (m, 2H, NCH_2); 1.9–2.3 (m, 4H, CH_2CH_2). ^{13}C NMR ($CDCl_3$) δ: 193.2; 172.0; 165.3; 152.0; 136.0; 133.8; 132.0; 116.9; 116.2; 58.0; 52.4; 47.3; 19.3; 14.5. IR (KBr, cm^{-1}): 3480, 3340 (br, diffuse), 1726, 1656. MS (*m*/*z*/rel int.): 276 (M^+)/10; 120/100; 92/20. Anal. Calcd for $C_{14}H_{16}N_2O_4$ (276.29): C, 60.86; H, 5.84; N, 10.14. Found: C, 60.77; H, 5.98; N, 10.02. Yield: 68%. Isolated as yellow powder-like crystalline material. Mp 143 °C.

4.4.17. Methyl *N*-{(2′-amino-5′-methyl-phenyl)glyoxyloyl}-prolinate (9b). ^{1}H NMR ($CDCl_3$) δ: 7.50 (s, 1H, Ar-H); 7.13 (d, 8 Hz, 1H, Ar-H); 6.58 (d, 8 Hz, 1H, Ar-H); 6.15 (br s, 2H, NH_2); 4.63 (m, 1H, $CHCOOCH_3$); 3.80 (s, 3H, OCH_3); 3.40–3.50 (m, 2H, NCH_2); 2.24 (s, 3H, $ArCH_3$); 1.9–2.3 (m, 4H, CH_2CH_2). ^{13}C NMR ($CDCl_3$) δ: 193.3; 171.9; 165.8; 149.8; 137.4; 133.0; 125.5; 116.8; 113.4; 58.0; 52.3; 47.0; 24.6; 20.2. IR (KBr, cm^{-1}): 3490, 3370 (br, diffuse), 1776, 1676. MS (*m*/*z*/rel int.): 290 (M^+)/13; 134/100; 106/22. Anal. Calcd for $C_{15}H_{18}N_2O_4$ (290.32): C, 62.06; H, 6.25; N, 9.65. Found: C, 62.01; H, 6.38; N, 9.47. Yield: 71%. Isolated as yellow crystalline material. Mp 155–157 °C.

4.4.18. Methyl *N*-{(2′-amino-5′-chloro-phenyl)glyoxyloyl}-prolinate (9c). ^{1}H NMR ($CDCl_3$) δ: 7.70 (s, 1H, Ar-H); 7.23 (d, 8 Hz, 1H, Ar-H); 6.62 (d, 8 Hz, 1H, Ar-H); 6.35 (br s, 2H, NH_2); 4.63 (m, 1H, $CHCOOCH_3$); 3.82 (s, 3H, OCH_3); 3.40–3.50 (m, 2H, NCH_2); 1.9–2.3 (m, 4H, CH_2CH_2). ^{13}C NMR ($CDCl_3$) δ: 192.5; 171.9; 165.0; 150.3; 136.0; 132.4; 128.4; 120.8; 118.4; 58.3; 52.2; 47.0; 29.1; 24.4. IR (KBr, cm^{-1}): 3480, 3355 (br, diffuse), 1772, 1674. MS (*m*/*z*/rel int.): 312(310) (M^+)/3(1); 128/100. Anal. Calcd for $C_{14}H_{15}N_2O_4Cl$ (310.74): C, 54.11; H, 4.87; N, 9.02. Found: C, 54.23; H, 4.98; N, 9.17. Yield: 65%. Isolated as yellow crystalline material. Mp 155–156 °C.

4.4.19. Methyl *N*-{(2′-amino-5′-nitro-phenyl)glyoxyloyl}-prolinate (9f). ^{1}H NMR ($CDCl_3$) δ: 8.60 (d, 1.4 Hz, 1H, Ar-H); 8.03 (dd, 1.4 Hz, 8 Hz, 1H, Ar-H); 7.3 (br s, 2H, NH_2); 6.73 (d, 8 Hz, 1H, Ar-H); 4.61 (m, 1H, $CHCOOCH_3$); 3.82 (s, 3H, OCH_3); 3.40–3.50 (m, 2H, NCH_2); 1.9–2.3 (m, 4H, CH_2CH_2). ^{13}C NMR ($CDCl_3$) δ: 192.1; 171.7; 164.2; 156.0; 137.1; 131.4; 131.0; 117.5; 112.0; 58.8; 52.6; 47.0; 29.1; 24.1. IR (KBr, cm^{-1}): 3430, 3300 (br, diffuse), 1722, 1654. MS (*m*/*z*/rel int.): 321 (M^+)/2; 253/9; 128/100. Anal. Calcd for $C_{14}H_{15}N_3O_6$ (321.29): C, 52.34; H, 4.71; N, 13.08. Found: C, 52.22; H, 4.78; N, 13.19. Yield: 58%. Isolated as red-brown powder-like crystalline material. Mp 188–190 °C.

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