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ORIGINAL PAPER

Green synthesis and characterization of novel α-acyloxycarboxamides through three-component reaction between pyridine carbaldehydes, cyclohexyl isocyanide, and benzoic acid derivatives

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Abstract Novel α-acyloxycarboxamides were synthesized and characterized by the Passerini three-component reaction between pyridine carbaldehydes, cyclohexyl isocyanide, and benzoic acid derivatives in water. The reactions were carried out in one pot at room temperature with a quantitative yield. The products were obtained without any need for purification.

Keywords Passerini reaction · Isocyanide · Pyridine carbaldehyde · α-Acyloxycarboxamide

Introduction

The great potential of isocyanides for development of multicomponent reactions lies in the diversity of bond-forming processes available, their functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity often observed [1–9]. In 1921, Passerini pioneered the use of isocyanides and successfully developed a three-component synthesis of α-acyloxycarboxamides by the reaction between carboxylic acid, an aldehyde, and an isocyanide [10–12]. The Passerini reactions involve an oxo component, an isocyanide, and a nucleophile. These reactions are beginning to find utility in the drug discovery process and total syntheses of biologically relevant natural products [13]. As a continuation of our recent studies on isocyanide chemistry [14–18], we report the Passerini multicomponent reaction between pyridine carbaldehydes **1**, cyclohexyl isocyanide (**2**), and benzoic acid derivatives **3**.

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Results and discussion

The pyridine carbaldehydes **1**, cyclohexyl isocyanide (**2**), and benzoic acid derivatives **3** were allowed to react in a 1:1:1 ratio at room temperature in water to yield α-acyloxycarboxamides **4a**–**4o** (Fig. 1; Table 1). The reaction proceeds smoothly and cleanly under mild conditions in water and is therefore considered to be a green chemistry method. The products were obtained without any further purification with a quantitative yield in one-pot reactions. The products were crystallized from an ethanol/water mixture. The structures of the products were deduced from their elemental analyses and IR, ^{1}H NMR, and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **4a** exhibited distinct signals arising from $-CH_2$ of cyclohexyl (δ = 0.86–2.32 ppm), –N–CH (3.76–3.79 ppm), –CH–O (6.39 ppm), –NH (6.78–6.81 ppm), and aromatic –CH (7.24–8.58 ppm).

The ^{13}C NMR spectrum of **4a** indicated 16 distinct resonances arising from $-CH_2$ of cyclohexyl (δ = 24.6–32.8 ppm), –N–CH (48.4 ppm), C–O (76.0 ppm), aromatic carbons (122.0–155.2 ppm), CO of an ester (165.2 ppm), and CO of an amide (165.9 ppm). The IR spectrum showed a symmetric absorption at 3,270 cm^{-1} attributed to the –NH, three absorptions at 3,062, 2,954, and 1,726 cm^{-1} attributed to the C=O of the ester, an absorption at 1,689 cm^{-1} attributed to the C=O of

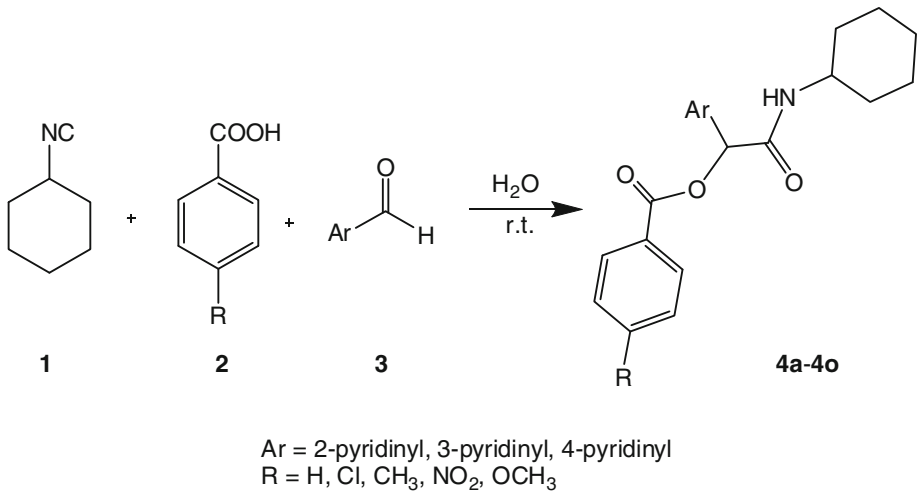

Fig. 1 Preparation of α-acyloxycarboxamides **4a–4o** from pyridine carbaldehydes **1**, cyclohexyl isocyanide (**2**), and benzoic acid derivatives **3** in water

Table 1 Conditions and yield of reactions for synthesis of α-acyloxycarboxamides **4a–4o**

Entry	Products	R	Pyridine carbaldehyde	Reaction time/h	Yield/%
1	**4a**	H	2-Pyridine	2	95
2	**4b**	Cl	2-Pyridine	1	96
3	**4c**	CH_3	2-Pyridine	1	96
4	**4d**	NO_2	2-Pyridine	1	99
5	**4e**	OCH_3	2-Pyridine	1	96
6	**4f**	H	3-Pyridine	2	95
7	**4g**	Cl	3-Pyridine	1	96
8	**4h**	CH_3	3-Pyridine	1	96
9	**4i**	NO_2	3-Pyridine	1	99
10	**4j**	OCH_3	3-Pyridine	1	96
11	**4k**	H	4-Pyridine	2	95
12	**4l**	Cl	4-Pyridine	1	96
13	**4m**	CH_3	4-Pyridine	1	96
14	**4n**	NO_2	4-Pyridine	1	99
15	**4o**	OCH_3	4-Pyridine	1	96

the amide, and three absorptions at 1,552, 1,272, and 1,114 cm^{-1} attributed to the C–O.

A reasonable mechanism for the formation of compounds **4a–4o** is shown in Fig. 2. The acid **3** protonates pyridine carbaldehyde **1** to form an intermediate which is then attacked by the isocyanide **2** leading to formation of **4** [19] (Fig. 2).

Experimental

Starting materials and solvents were purchased from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The reactions were monitored by TLC and NMR techniques, which indicated that there were no side products. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were measured on a Perkin-Elmer RXI FT-IR spectrometer. ^1H and ^{13}C NMR spectra ($CDCl_3$) were recorded on a Bruker Avance spectrometer at 250.0 and 62.9 MHz, respectively. Elemental analyses were performed by using a Perkin-Elmer 2400(II) CHN/O analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. The TLC plates were prepared from Merck silica gel powder.

*General procedure for the synthesis of **4a–4o***

Isocyanide **2** (0.2 mmol) was added to a magnetically stirred solution of pyridine carbaldehyde **1** (0.2 mmol) and benzoic acid derivative **3** (0.2 mmol) in 5 cm^3 water at room temperature over 10 min. The mixture was stirred for the time specified in Table 1 at room temperature after which time single spot products were obtained by TLC. The solvent was removed under reduced pressure and the products were purified by plate thin-layer liquid chromatography and then crystallized.

α-Benzoyloxy-N-cyclohexylpyridine-2-acetamide (**4a**, $C_{20}H_{22}N_2O_3$)

White powder, yield 95%; m.p.: 154–155 °C; IR (KBr): $\bar{\nu}$ = 3,270 (NH), 3,062, 2,954, 1,726 (C=O of ester), 1,689 (C=O of amide), 1,552, 1,272, 1,114 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.86–2.32 (m, 10H, 5 CH_2 of cyclohexyl), 3.76–3.79 (m, 1H, N–CH), 6.39 (s, 1H, CH–O), 6.78–6.81 (d, J = 7.24 Hz, 1H, NH), 7.24–8.58 (m, 9H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.58, 24.63, 25.47, 32.70, 32.76, 48.42, 76.03, 121.95, 123.49, 128.25, 129.34, 129.95, 133.50, 137.21, 149.11, 155.20, 165.18, 165.90 ppm.

α-(4-Chlorobenzoyloxy)-N-cyclohexylpyridine-2-acetamide (**4b**, $C_{20}H_{21}ClN_2O_3$)

White powder, yield 96%; m.p.: 211–213 °C; IR (KBr): $\bar{\nu}$ = 3,305 (NH), 3,071, 2,937, 1,735 (C=O of ester), 1,664

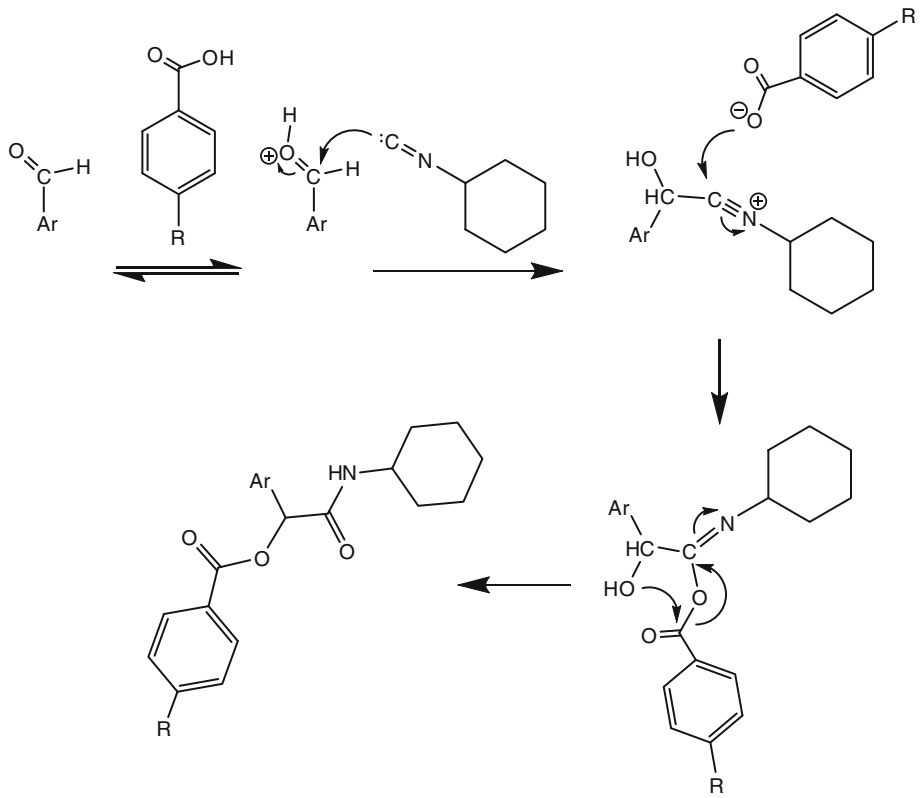

Fig. 2 Proposed mechanism for the formation of compounds **4a–4o**

(C=O of amide), 1,547, 1,265, 1,246 (C–O), 1,117 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.82–2.37$ (m, 10H, 5 CH_2 of cyclohexyl), 3.85–3.89 (m, 1H, N–CH), 6.17 (s, 1H, CH–O), 6.76–6.79 (d, $J = 7.24$ Hz, 1H, NH), 7.22–8.05 (m, 8H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.55$, 24.60, 25.47, 32.67, 32.73, 48.95, 76.05, 121.95, 122.08, 128.24, 128.65, 131.05, 136.92, 138.01, 151.18, 155.20, 165.28, 167.90 ppm.

N-Cyclohexyl-α-(4-methylbenzoyloxy)pyridine-2-acetamide (**4c**, $C_{21}H_{24}N_2O_3$)

White powder, yield 96%; m.p.: 216–217 °C; IR (KBr): $\bar{\nu} = 3{,}351$ (NH), 3,067, 2,986, 1,724 (C=O of ester), 1,677 (C=O of amide), 1,557, 1,273, 1,257 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.87–1.73$ (m, 10H, 5 CH_2 of cyclohexyl), 2.17 (s, 3H, CH_3), 3.95–4.09 (m, 1H, N–CH), 6.22 (s, 1H, CH–O), 6.65–6.66 (d, $J = 7.24$ Hz, 1H, NH), 7.25–8.38 (m, 8H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.42$, 24.56, 24.60, 25.37, 32.67, 32.76, 49.05, 75.85, 121.85, 122.97, 126.84, 127.95, 128.85, 137.31, 137.90, 149.99, 155.30, 165.58, 166.90 ppm.

N-Cyclohexyl-α-(4-nitrobenzoyloxy)pyridine-2-acetamide (**4d**, $C_{20}H_{21}N_3O_5$)

White powder, yield 99%; m.p.: 245–246 °C; IR (KBr): $\bar{\nu} = 3{,}316$ (NH), 3,075, 2,936, 1,736 (C=O of ester), 1,673 (C=O of amide), 1,548, 1,531, 1,347 (NO), 1,269, 1,251 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.13–2.16$ (m, 10H, 5 CH_2 of cyclohexyl), 3.75–3.77 (m, 1H, N–CH), 6.34 (s, 1H, CH–O), 6.82–6.84 (d, $J = 7.24$ Hz, 1H, NH), 7.24–8.60 (m, 8H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.50$, 24.57, 25.43, 32.64, 32.72, 48.59, 76.52, 121.33, 123.65, 131.09, 134.87, 137.39, 149.18, 150.79, 154.59, 163.54, 165.14 ppm.

N-Cyclohexyl-α-(4-methoxybenzoyloxy)pyridine-2-acetamide (**4e**, $C_{21}H_{24}N_2O_4$)

White powder, yield 96%; m.p.: 231–232 °C; IR (KBr): $\bar{\nu} = 3{,}280$ (NH), 3,085, 2,960, 1,730 (C=O of ester), 1,665 (C=O of amide), 1,556, 1,447, 1,260, 1,122, 1,091 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.11–2.10$ (m, 10H, 5 CH_2 of cyclohexyl), 3.76–3.80 (m, 1H, N–CH), 3.87 (s, 3H, O–CH_3), 6.31 (s, 1H, CH–O), 6.72–6.75 (d, $J = 7.24$ Hz, 1H, NH), 6.93–8.58 (m, 8H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.58$, 24.63, 25.48, 32.73, 32.78, 48.36, 55.47, 75.84, 113.78, 121. 66, 122.00, 123.07, 132.05, 137.18, 149.15, 155.43, 163.81, 164.84, 166.12 ppm.

α-Benzoyloxy-N-cyclohexylpyridine-3-acetamide (**4f**, $C_{20}H_{22}N_2O_3$)

White powder, yield 95%; m.p.: 155–157 °C; IR (KBr): $\bar{\nu} = 3{,}226$ (NH), 3,044, 2,961, 1,721 (C=O of ester), 1,688 (C=O of amide), 1,550, 1,265, 1,112 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.86–2.32$ (m, 10H, 5 CH_2 of cyclohexyl), 3.76–3.79 (m, 1H, N–CH), 6.39 (s, 1H, CH–O), 6.78–6.81 (d, $J = 7.24$ Hz, 1H, NH), 7.24–8.58 (m, 9H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.58$, 24.64,

25.49, 32.71, 32.76, 48.42, 75.34, 121.95, 128.22, 129.04, 129.85, 133.25, 133.63, 136.59, 148.98, 155.20, 165.18, 165.90 ppm.

α-(4-Chlorobenzoyloxy)-N-cyclohexylpyridine-3-acetamide (**4g**, $C_{20}H_{21}ClN_2O_3$)
White powder, yield 96%; m.p.: 213–215 °C; IR (KBr): $\bar{\nu}$ = 3,279 (NH), 3,099, 2,963, 1,732 (C=O of ester), 1,667 (C=O of amide), 1,560, 1,447, 1,261, 1,112 (C–O), 1,103 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.04–2.26 (m, 10H, 5 CH_2 of cyclohexyl), 3.26–3.30 (m, 1H, N–CH), 5.77 (s, 1H, CH–O), 6.10 (s, 1H, NH), 7.44–8.77 (m, 8H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.55, 24.62, 25.43, 32.69, 32.73, 48.74, 75.35, 121.95, 128.25, 128.29, 131.14, 133.15, 134.59, 138.63, 149.38, 153.20, 165.18, 167.73 ppm.

N-Cyclohexyl-α-(4-methylbenzoyloxy)pyridine-3-acetamide (**4h**, $C_{21}H_{24}N_2O_3$)
White powder, yield 96%; m.p.: 217 °C; IR (KBr): $\bar{\nu}$ = 3,283 (NH), 3,087, 2,986, 1,736 (C=O of ester), 1,661 (C=O of amide), 1,559, 1,414, 1,262, 1,094 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.04–1.75 (m, 10H, 5 CH_2 of cyclohexyl), 2.07 (s, 3H, CH_3), 3.35 (m, 1H, N–CH), 5.80 (s, 1H, CH–O), 6.08 (s, 1H, NH), 7.20–8.35 (m, 8H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 21.42, 24.56, 24.66, 25.50, 32.70, 32.76, 47.85, 75.24, 123.58, 126.80, 127.75, 128.93, 133.29, 136.39, 137.84, 149.68, 155.30, 165.18, 166.91 ppm.

N-Cyclohexyl-α-(4-nitrobenzoyloxy)pyridine-3-acetamide (**4i**, $C_{20}H_{21}N_3O_5$)
White powder, yield 99%; m.p.: 247–249 °C; IR (KBr): $\bar{\nu}$ = 3,313 (NH), 3,073, 2,936, 1,733 (C=O of ester), 1,656 (C=O of amide), 1,540, 1,260 (NO_2), 1,099, 1,037 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.08–2.49 (m, 10H, 5 CH_2 of cyclohexyl), 3.24–3.36 (m, 1H, N–CH), 5.75 (s, 1H, CH–O), 6.15 (s, 1H, NH), 7.97–8.79 (m, 8H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.50, 24.61, 25.42, 32.76, 32.82, 48.49, 75.52, 121.33, 122.77, 131.36, 133.55, 134.06, 136.79, 148.48, 152.09, 153.59, 163.64, 165.24 ppm.

N-Cyclohexyl-α-(4-methoxybenzoyloxy)pyridine-3-acetamide (**4j**, $C_{21}H_{24}N_2O_4$)
White powder, yield 96%; m.p.: 231–232 °C; IR (KBr): $\bar{\nu}$ = 3,297 (NH), 3,089, 2,929, 1,734 (C=O of ester), 1,658 (C=O of amide), 1,559, 1,448, 1,265, 1,117 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.11–2.10 (m, 10H, 5 CH_2 of cyclohexyl), 3.76–3.80 (m, 1H, N–CH), 3.87 (s, 3H, O–CH_3), 6.31 (s, 1H, CH–O), 6.72–6.75 (d, J = 7.24 Hz, 1H, NH), 6.93–8.50 (m, 8H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.58, 24.63, 25.70, 32.70, 32.78, 48.36, 55.47, 77.41, 113.78, 121.28, 122.97, 131.98, 133.35, 136.69, 148.62, 153.19, 163.71, 164.84, 166.32 ppm.

α-Benzoyloxy-N-cyclohexylpyridine-4-acetamide (**4k**, $C_{20}H_{22}N_2O_3$)
White powder, yield 95%; m.p.: 155–157 °C; IR (KBr): $\bar{\nu}$ = 3,287 (NH), 3,087, 2,931, 1,735 (C=O of ester), 1,658 (C=O of amide), 1,559, 1,265, 1,118 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.86–2.32 (m, 10H, 5 CH_2 of cyclohexyl), 3.76–3.79 (m, 1H, N–CH), 6.29 (s, 1H, CH–O), 6.78–6.81 (d, J = 7.24 Hz, 1H, NH), 7.24–8.58 (m, 9H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.59, 24.67, 25.49, 32.73, 32.76, 48.42, 77.56, 121.95, 128.12, 129.15, 129.90, 132.93, 149.02, 155.20, 165.18, 165.90 ppm.

α-(4-Chlorobenzoyloxy)-N-cyclohexylpyridine-4-acetamide (**4l**, $C_{20}H_{21}ClN_2O_3$)
White powder, yield 96%; m.p.: 213–215 °C; IR (KBr): $\bar{\nu}$ = 3,277 (NH), 3,095, 2,963, 2,928, 1,732 (C=O of ester), 1,660 (C=O of amide), 1,562, 1,261, 1,093 (C–O), 1,029 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.82–2.37 (m, 10H, 5 CH_2 of cyclohexyl), 3.21–3.26 (m, 1H, N–CH), 5.30 (s, 1H, CH–O), 6.75–6.78 (d, J = 7.24 Hz, 1H, NH), 7.22–8.08 (m, 8H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.59, 24.68, 25.65, 32.69, 32.75, 48.49, 77.69, 122.40, 128.32, 128.50, 131.44, 138.82, 149.23, 150.59, 165.50, 166.50 ppm.

N-Cyclohexyl-α-(4-methylbenzoyloxy)pyridine-4-acetamide (**4m**, $C_{21}H_{24}N_2O_3$)
White powder, yield 96%; m.p.: 216–218 °C; IR (KBr): $\bar{\nu}$ = 3,281 (NH), 3,086, 2,962, 1,734 (C=O of ester), 1,660 (C=O of amide), 1,559, 1,260, 1,091 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.11–2.08 (m, 10H, 5 CH_2 of cyclohexyl), 2.39 (s, 3H, CH_3), 3.30–3.35 (m, 1H, N–CH), 5.75 (s, 1H, CH–O), 6.06 (s, 1H, NH), 7.35–8.62 (m, 8H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 20.56, 24.58, 24.64, 25.60, 32.70, 32.78, 48.49, 77.56, 121.40, 127.21, 127.80, 128.35, 141.84, 149.23, 155.15, 163.50, 164.46 ppm.

N-Cyclohexyl-α-(4-nitrobenzoyloxy)pyridine-4-acetamide (**4n**, $C_{20}H_{21}N_3O_5$)
White powder, yield 99%; m.p.: 242–243 °C; IR (KBr): $\bar{\nu}$ = 3,313 (NH), 3,073, 2,936, 1,733 (C=O of ester), 1,656 (C=O of amide), 1,540, 1,260 (N=O), 1,099, 1,037 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.03–2.06 (m, 10H, 5 CH_2 of cyclohexyl), 3.35–3.47 (m, 1H, N–CH), 5.84 (s, 1H, CH–O), 6.25 (s, 1H, NH), 7.24–8.60 (m, 8H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.50, 24.58, 25.00, 32.68, 32.72, 48.59, 77.42, 120.97, 121.33, 131.00, 134.06, 149.23, 152.09, 154.20, 163.54, 165.14 ppm.

N-Cyclohexyl-α-(4-methoxybenzoyloxy)pyridine-4-acetamide (**4o**, $C_{21}H_{24}N_2O_4$)
White powder, yield 96%; m.p.: 236–237 °C; IR (KBr): $\bar{\nu}$ = 3,289 (NH), 3,095, 2,963, 1,733 (C=O of ester), 1,663 (C=O of amide), 1,561, 1,447, 1,262, 1,123 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.11–2.10 (m, 10H, 5 CH_2 of cyclohexyl), 3.76–3.80 (m, 1H, N–CH), 3.87 (s, 3H,

O–CH_3), 6.31 (s, 1H, CH–O), 6.72–6.75 (d, $J = 7.24$ Hz, 1H, NH), 6.93–8.50 (m, 8H, arom CH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.58$, 24.63, 24.95, 32.69, 32.78, 48.36, 55.47, 77.41, 112.71, 121.33, 123.17, 132.25, 149.23, 150.43, 155.43, 163.81, 166.12 ppm.

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