

FULL PAPER

Synthesis of novel 2-(alkyl/arylamino)-2-oxo-1-(quinolin-4-yl)ethyl cinnamates through three-component reaction between an isocyanide, quinoline-4-carbaldehyde and cinnamic acid derivatives

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Passerini reactions of an isocyanide, quinoline-4-carbaldehyde, and cinnamic acid derivatives in water proceed at room temperature giving 2-(alkyl/aryl amino)-2-oxo-1-(quinolin-4-yl)ethyl cinnamate derivatives in quantitative yield. The reactions are one-pot, and the products did not require any purification. This procedure offers significant advantages such as operational simplicity, mild reaction conditions, enhanced rates, cleaner reaction profiles, ease of isolation of products, and H₂O as a medium, making it a valuable protocol for synthesizing these compounds.

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KEYWORDS

Multicomponent reactions (MCRs); Passerini reactions; quinoline-4-carbaldehyde; isocyanide; cinnamic acid derivatives.

Introduction

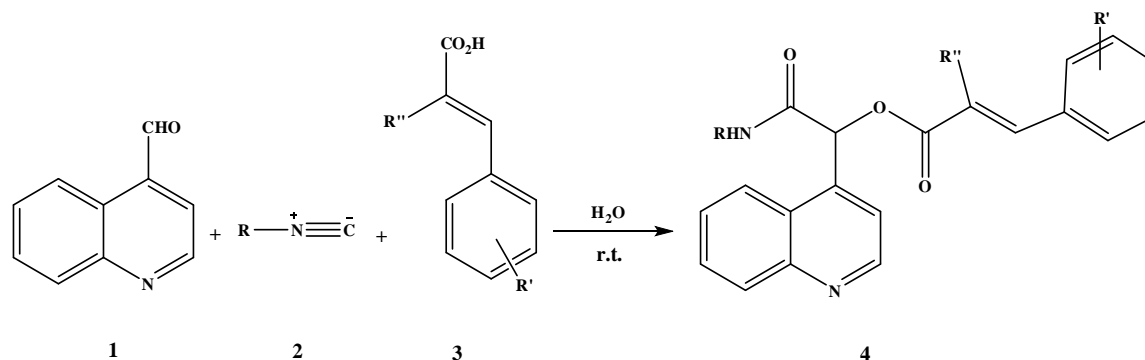
Recently, multicomponent reactions (MCRs) have been considered a superior synthetic strategy [1-4]. MCRs, reactions involving at least three starting materials in a one-pot reaction, remain the most efficient method of rapidly introducing molecular diversity [5-9]. As such, they have found widespread use in organic and diversity-oriented synthesis by their ability to access highly functionalized molecules in simple and straightforward one-step transformation [10]. Compared with the conventional organic reactions, MCRs are advantageous in being highly convergent and requiring minimum time and effort to achieve structural complexity. Thus, MCRs are accepted as green chemical processes. Among the known multicomponent reactions to date, the most valuable reactions are those based on isocyanides. Isocyanide-based

multicomponent reactions (abbreviated to IMCRs by Ugi and Dömling) [11-13], introduced in 1921 by Passerini [14], followed by Ugi and others, are the most explored and well-studied [15]. IMCRs, under their synthetic potential, their inherent atom efficiency, convergent nature, ease of implementation, and the generation of molecular diversity, have attracted much attention [16-20]. IMCRs are particularly interesting because they are more versatile and diverse than the remaining MCRs.

The great potential of isocyanides for developing 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 [21-23]. The Passerini reactions involve an oxo component, an isocyanide, and a nucleophile. The Passerini reactions are beginning to find

utility in the drug discovery process and total syntheses of biologically relevant natural products [24-27]. The quinoline scaffold is found in most drugs commonly used to treat malaria [28]. In connection with our recent

interest in isocyanide chemistry [29-37], we report the Passerini multicomponent reaction between quinoline-4-carbaldehyde **1**, an isocyanide **2**, and cinnamic acid derivatives **3** (Scheme 1).



SCHEME 1 Preparation of 2-(alkyl/aryl amino)-2-oxo-1-(quinolin-4-yl)ethyl cinnamates **4a-4y** from 4-quinolinecarboxaldehyde **1**, isocyanide derivatives **2**, and cinnamic acid derivatives **3** in H₂O

Experimental

General

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The methods used to follow the reactions are TLC and NMR. TLC and NMR indicated that there is no side product. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Jasco 6300 FTIR spectrometer. ¹H and ¹³C NMR spectra (CDCl₃) were recorded on a BRUKERDRX-250AVANCE and BRUKERDRX-400AVANCE spectrometers at 250.0 and 400 MHz, for ¹H spectra, and at 62.5 and 100 MHz, for ¹³C spectra. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. Preparative layer chromatography (PLC) plates were prepared from Merck silica gel (F₂₅₄) powder.

General procedure for the preparation of compound 4

Isocyanide **2** (0.2 mmol) was added to a magnetically stirred solution of quinoline-4-

carbaldehyde **1** (0.2 mmol) and cinnamic acid derivatives **3** (0.2 mmol) in H₂O (5 mL) at room temperature over 5 min. The mixture was stirred for the time specified in Table 1 at room temperature, after which time TLC obtained single spot products. The solvent was removed under reduced pressure and the products were purified by crystallization. The characterization data of the compounds are given below.

Results and discussion

The quinoline-4-carbaldehyde **1**, isocyanide derivatives **2**, and cinnamic acid derivatives **3** were allowed to react in a 1:1:1 ratio at room temperature in H₂O to yield 2-(alkyl/aryl amino)-2-oxo-1-(quinolin-4-yl)ethyl cinnamates **4a-4y** (Scheme 1 and Table 1). The reaction proceeds smoothly and cleanly under mild conditions in H₂O and is considered an almost waste-free method. The products were crystallized from MeOH/H₂O or EtOH/H₂O, without any further purification, in quantitative yield in one-pot reactions.

A plausible mechanism for the formation of compounds **4a-4y** is shown in Scheme 2. The acid **2** protonates carboxaldehyde **1** to form an

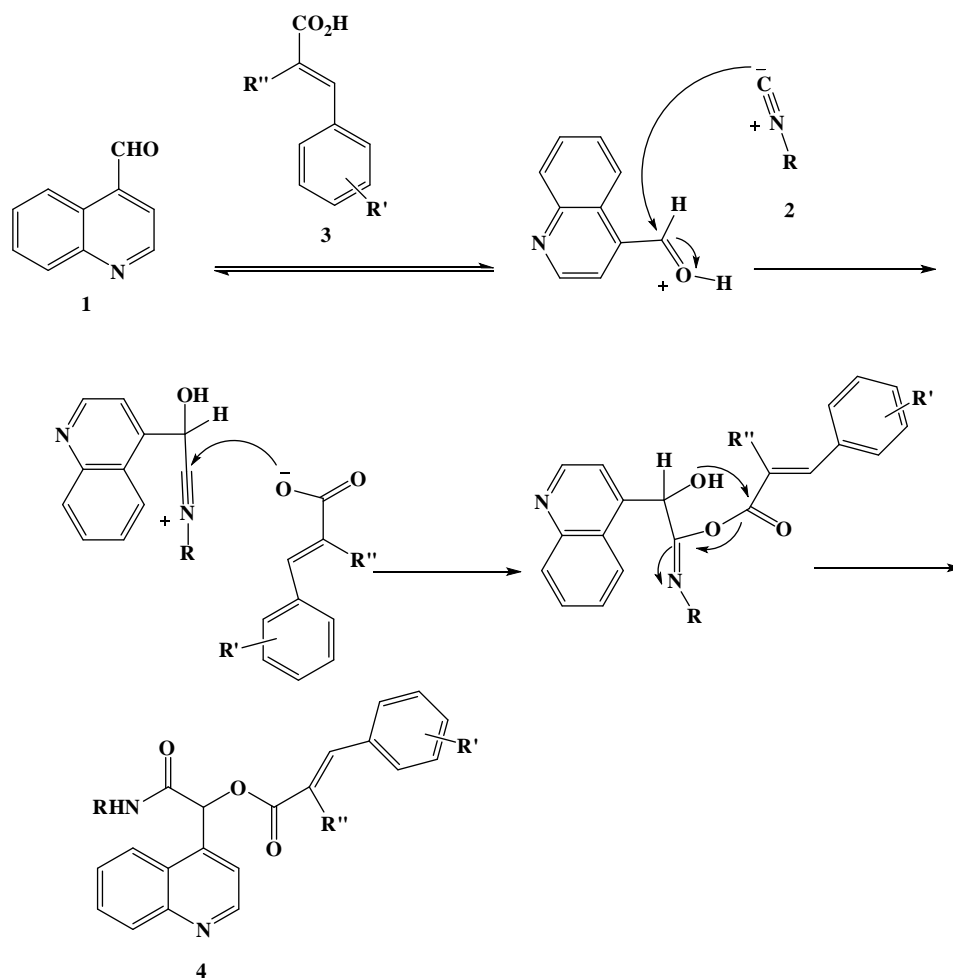
intermediate, which is then attacked by the isocyanide **3**, leading to the formation of **4** (Scheme 2) [38].

Since there is no noticeable difference between the yield of the products, the substituents R and R' have not considerably influenced the output of the reactions because these substituents are not very strong electron donor or withdrawing groups. Substituent R' is far from the center of reaction.

The structures of the products were deduced from their IR, ¹H, and ¹³C NMR, and mass spectra. For example, the ¹H NMR spectrum of **4l** exhibited distinct signals arising from -CH₃ (δ= 0.919 ppm), CH₂ (1.30-1.36 ppm), CH₂ (1.50-1.55 ppm), N-CH₂ (3.32-3.37 ppm), -NH (6.47 ppm), -C=CH (6.52 ppm, ³J = 16 Hz), -CH-O (6.94 ppm), HC=C- (7.78 ppm, ³J = 16 Hz), and 10 aromatic -CH (7.09-8.97 ppm) (Figure 1).

TABLE 1 Conditions and yield of reactions for synthesis of α-acyloxycarboxamides **4a-4y**

4	R	'R	"R	Time/h	Yield%
4a	Cyclohexyl	3-Cl	H	1	97
4b	Cyclohexyl	4-F	H	1	96
4c	Cyclohexyl	4-Me	H	1	97
4d	Cyclohexyl	3-MeO	H	1	95
4e	Cyclohexyl	H	Me	1	92
4f	t-buthyl	3-Cl	H	1	98
4g	t-buthyl	4-F	H	1	96
4h	t-buthyl	4-Me	H	1	97
4i	t-buthyl	3-MeO	H	1	95
4j	t-buthyl	H	Me	1	94
4k	n-buthyl	3-Cl	H	1	98
4l	n-buthyl	4-F	H	1	95
4m	n-buthyl	4-Me	H	1	96
4n	n-buthyl	3-MeO	H	1	97
4o	n-buthyl	H	Me	1	95
4p	benzyl	3-Cl	H	1	92
4q	benzyl	4-Me	H	1	91
4r	2,6-dimethylphenyl	3-Cl	H	3	96
4s	2,6-dimethylphenyl	4-F	H	3	95
4t	2,6-dimethylphenyl	4-Me	H	3	94
4u	2,6-dimethylphenyl	3-MeO	H	3	92
4v	2,6-dimethylphenyl	H	Me	3	90
4w	tosylmethyl	3-Cl	H	1	92
4x	tosylmethyl	4-F	H	1	93
4y	tosylmethyl	4-Me	H	1	92



SCHEME 2 Proposed mechanism for the formation of compounds 4a-4y

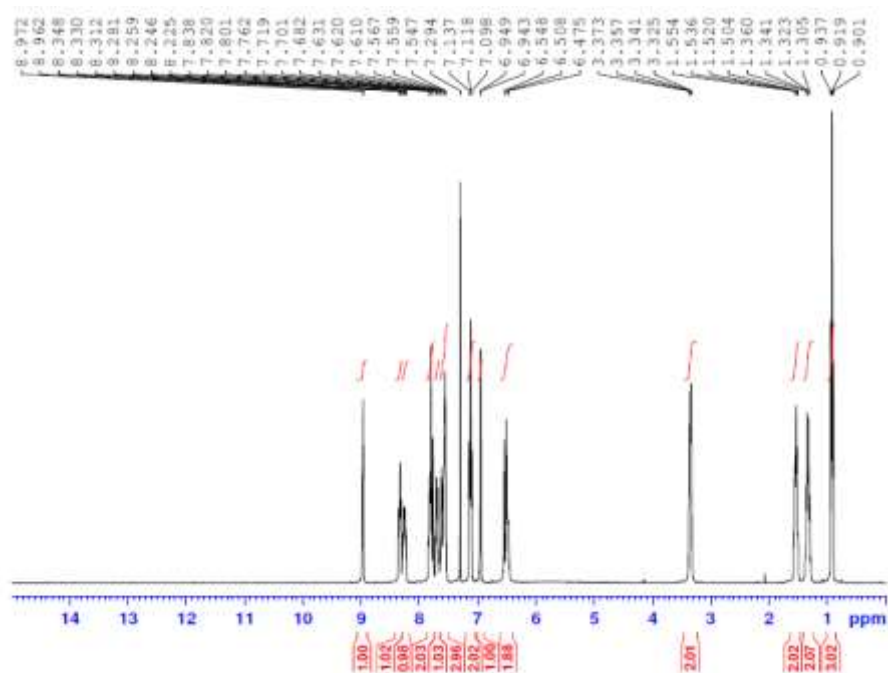


FIGURE 1 ¹H NMR spectrum of compound 4l

The ^{13}C NMR spectrum of 4l indicated 27 distinct resonances arising from $-\text{CH}_3$ ($\delta=13.7$ ppm), CH_2 (20.0 ppm), CH_2 (31.4 ppm), $\text{N}-\text{CH}_2$ (39.4 ppm), $\text{C}-\text{O}$ (72.1 ppm), aromatic carbons (115.8-149.5 ppm), $\text{C}=\text{O}$ of an ester (165.0 ppm), $\text{C}-\text{F}$ (d, $\delta=163.0, 165.55$ ppm, $^1J=251$ Hz), and $\text{C}=\text{O}$ of an amide (167.0 ppm).

The IR spectrum of 4l revealed asymmetric absorption at 3285 cm^{-1} attributed to the $-\text{NH}$, an absorption at 1736 cm^{-1} attributed to the $\text{C}=\text{O}$ of the ester, and absorption at 1636 cm^{-1} attributed to the $\text{C}=\text{O}$ of the amide. The mass spectrum of 4l displayed a molecular ion peak at m/z : 406 value.

(E)-2-(cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(3-chlorophenyl)acrylate (4a)

Colorless Crystals, yield (97%); m.p.: 170-172°C; IR (KBr) (ν_{max} , cm^{-1}): 3306, 3064, 2931, 2853, 1728, 1631, 1550, 1251, 1089. ^1H NMR (400 MHz, CDCl_3) δ (ppm) : 1.16-1.96 (m, 10 H, cyclohexane), 3.80-3.89 (m, 1H, N-CH), 6.27 (d, $J=8$ Hz, N-H), 6.57 (d, $J=16$ Hz, C=CH), 6.91 (s, 1H, CH-O), 7.75 (d, $J=16$ Hz, HC=C), 7.29-8.97 (m, 10 arom. H). ^{13}C NMR (100MHz, CDCl_3) δ (ppm): 24.7 - 32.8 (5 CH_2), 48.7 (N-CH), 72.2 (CH-O), 116.6 (C=C), 145.9 (C=C), 120.0, 124.0, 127.4, 129.3, 129.5, 129.9, 132.2, 137.0 (10 arom. CH), 126.1, 141.7, 148.2, 149.6, 164.9, 166.1 (7 C). MS, m/z (%): 449 (21), 323 (32), 278 (12), 158 (100), 137 (12), 102 (12), 83 (10), 55 (18).

(E)-2-(cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(4-fluorophenyl)acrylate (4b)

Colorless Crystals, yield (96%); m.p.: 175-177°C; IR (KBr) (ν_{max} , cm^{-1}): 3271, 3070, 2929, 2853, 1724, 1637, 1598, 1231, 1158, 1095, 829. ^1H NMR (400 MHz, CDCl_3) δ (ppm) : 1.16-1.95 (m, 10 H, cyclohexane), 3.80-3.89 (m, 1H, N-CH), 6.28 (d, $J=8$ Hz, N-H), 6.52 (d, $J=16$ Hz, C=CH), 6.92 (s, 1H, CH-O), 7.74 (d, $J=16$ Hz, HC=C), 7.10-8.97 (m, 10 arom. H). ^{13}C NMR (100MHz, CDCl_3) δ (ppm): 24.7-32.9 (5 CH_2), 48.6 (N-CH), 72.1 (CH-O), 116.1 (C=C), 146.1 (C=C), 115.8, 116.3, 120.0, 124.1, 126.2, 127.5,

129.8, 129.9, 130.3, 130.4, 149.5 (10 arom. CH), 130.0, 130.0, 141.9, 148.1, 163.0, 165.0, 165.5, 166.1 (7 C).

(E)-2-(cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-p-tolylacrylate (4c)

Colorless Crystals, yield (97%); m.p.: 168-170°C; IR (KBr) (ν_{max} , cm^{-1}): 3308, 3082, 2929, 2851, 1713, 1644, 1596, 1551, 1273, 1158, 1061. ^1H NMR (400 MHz, CDCl_3) δ (ppm) : 1.16-1.96 (m, 10 H, cyclohexane), 2.41 (s, Me), 3.80-3.89 (m, 1H, N-CH), 6.32 (d, $J=8$ Hz, N-H), 6.55 (d, $J=16$ Hz, C=CH), 6.93 (s, 1H, CH-O), 7.68 (d, $J=16$ Hz, HC=C), 7.22-8.97 (m, 10 arom. H). ^{13}C NMR (100MHz, CDCl_3) δ (ppm): 21.5 (CH_3), 24.7-32.9 (5 CH_2), 48.6 (N-CH), 71.9 (CH-O), 114.8 (C=C), 147.6 (C=C), 119.9, 124.2, 128.4, 129.7, 131.0, 141.7, 147.6, 149.5 (10 arom. CH), 126.2, 127.4, 129.9, 142.2, 148.0, 165.2, 166.2 (7C).

(E)-2-(cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(3-methoxyphenyl)acrylate (4d)

White Crystals, yield (95%); m.p.: 167-169°C; IR (KBr) (ν_{max} , cm^{-1}): 3280, 3082, 2929, 2851, 1716, 1655, 1559, 1257, 1051. ^1H NMR (400 MHz, CDCl_3) δ (ppm) : 1.39-1.94 (m, 10 H, cyclohexane), 3.86 (s, 1H, N-CH), 3.86 (s, 3H, OMe), 6.30 (d, $J=8$ Hz, N-H), 6.58 (d, $J=16$ Hz, C=CH), 7.01 (s, 1H, CH-O), 7.78 (d, $J=16$ Hz, HC=C), 7.08-8.97 (m, 10 arom. H). ^{13}C NMR (100MHz, CDCl_3) δ (ppm): 24.7-32.8 (5 CH_2), 48.6 (N-CH), 55.3 (OMe), 72.1 (CH-O), 113.2 (C=C), 147.4 (C=C), 116.3, 116.8, 120.0, 121.0, 124.1, 127.4, 129.8, 130.0, 135.1, 159.9 (10 arom. CH), 126.2, 129.9, 141.8, 148.2, 149.7, 165.0, 166.2 (7 C).

(E)-2-(cyclohexylamino)-2-oxo-1-(quinolin-4-yl)ethyl 2-methyl-3-phenylacrylate (4e)

Colorless Crystals, yield (92%); m.p.: 165-167°C; IR (KBr) (ν_{max} , cm^{-1}): 3281, 3088, 2929, 2852, 1708, 1654, 1561, 1238, 1109. ^1H NMR (250 MHz, CDCl_3) δ (ppm): 1.16-1.90 (m, 10 H, cyclohexane), 2.17 (s, 3H, Me), 3.80-3.84 (m, 1H, N-CH), 6.12 (d, $J=8$ Hz, N-H), 6.83 (s, 1H,

CH-O), 7.51-7.73 (m, 1H, HC=C), 7.24-8.93 (m, 11 arom. H). ¹³C NMR (62.5 MHz, CDCl₃) δ (ppm): 14.1 (Me), 24.5-32.7 (5 CH₂), 48.5 (N-CH), 72.7 (CH-O), 150.0 (C=C), 124.0, 127.2, 128.4, 128.8, 129.5, 129.7, 130.2, 141.0, 120.1 (11 arom. CH), 135.1, 137.2, 141.2, 148.7, 161.1, 166.3, 166.8 (7 C).

(E)-2-(tert-butylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(3-chlorophenyl)acrylate (4f)

Colorless Crystals, yield (98%); m.p.: 157-159°C; IR (KBr) (ν_{max}, cm⁻¹): 3318, 3065, 2974, 1720, 1670, 1549, 1265, 1060. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.40 (s, 9 H, 3Me), 6.16 (s, N-H), 6.59 (d, *J*=16 Hz, C=CH), 6.83 (s, 1H, CH-O), 7.73 (d, *J*=16 Hz, HC=C), 7.29-8.98 (m, 10 arom. H). ¹³C NMR (100MHz, CDCl₃) δ (ppm): 28.3 (3 Me), 52.0 (N-C), 72.4 (CH-O), 117.6 (C=C), 145.7 (C=C), 120.0, 124.0, 126.6, 127.5, 127.9, 129.9, 130.3, 130.8, 149.6 (10 arom. CH), 126.2, 135.0, 135.5, 141.9, 148.2, 164.7, 166.0 (7C).

(E)-2-(tert-butylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(4-fluorophenyl)acrylate (4g)

Colorless Crystals, yield (96%); m.p.: 177-179°C; IR (KBr) (ν_{max}, cm⁻¹): 3428, 3068, 2963, 2928, 1731, 1638, 1507, 1237, 1043. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.40 (s, 9 H, 3Me), 6.16 (s, N-H), 6.51 (d, *J*=16 Hz, C=CH), 6.83 (s, 1H, CH-O), 7.77 (d, *J*=16 Hz, HC=C), 7.09-8.98 (m, 10 arom. H). ¹³C NMR (100MHz, CDCl₃) δ (ppm): 28.6 (3 Me), 52.0 (N-C), 72.2 (CH-O), 116.1 (C=C), 146.1 (C=C), 115.8, 116.3, 120.0, 124.0, 127.5, 129.9, 130.0, 130.3, 130.4, 149.6 (10 arom. CH), 115.8, 126.2, 142.0, 148.2, 163.0, 165.0, 165.5, 166.2 (7C).

*(E)-2-(tert-butylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-*p*-tolylacrylate (4h)*

Colorless Crystals, yield (97%); m.p.: 159-161°C; IR (KBr) (ν_{max}, cm⁻¹): 3535, 3284, 2969, 2918, 1728, 1540, 1327, 1146. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.40 (s, 9 H, 3Me), 2.39 (s, 3H, Me), 6.25 (s, N-H), 6.53 (d, *J*=16 Hz, C=CH), 6.83 (s, 1H, CH-O), 7.77 (d, *J*=16 Hz,

HC=C), 7.21-8.96 (m, 10 arom. H). ¹³C NMR (100MHz, CDCl₃) δ (ppm): 21.5 (Me), 28.6 (3 Me), 52.0 (N-C), 72.1 (CH-O), 114.9 (C=C), 147.5 (C=C), 119.9, 124.1, 127.4, 128.4, 129.7, 129.8, 129.9, 141.7, 149.7 (10 arom. CH), 126.3, 131.0, 142.1, 148.2, 165.2, 166.3 (7C).

(E)-2-(tert-butylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(3-methoxyphenyl)acrylate (4i)

White Crystals, yield (95%); m.p.: 151-153°C; IR (KBr) (ν_{max}, cm⁻¹): 3314, 3065, 2964, 2836, 1722, 1549, 1456, 1365, 1050. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.40 (s, 9 H, 3Me), 3.85 (s, 3H, OMe), 6.19 (s, N-H), 6.57 (d, *J*=16 Hz, C=CH), 6.84 (s, 1H, CH-O), 7.77 (d, *J*=16 Hz, HC=C), 6.98-8.97 (m, 10 arom. H). ¹³C NMR (100MHz, CDCl₃) δ (ppm): 28.6 (3 Me), 52.0 (N-C), 55.3 (OMe), 72.1 (CH-O), 113.2 (C=C), 147.4 (C=C), 116.3, 116.8, 119.9, 121.1, 124.1, 127.5, 130.0, 130.0, 135.0, 159.9 (10 arom. CH), 126.3, 129.7, 142.4, 147.9, 149.4, 165.0, 166.1 (7C).

(E)-2-(tert-butylamino)-2-oxo-1-(quinolin-4-yl)ethyl 2-methyl-3-phenylacrylate (4j)

Colorless Crystals, yield (94%); m.p.: 152-154°C; IR (KBr) (ν_{max}, cm⁻¹): 3325, 3059, 2967, 2928, 1713, 1510, 1241, 1108. ¹H NMR (250 MHz, CDCl₃) δ (ppm): 1.32 (s, 9 H, 3Me), 2.16 (s, 3H, Me), 6.05 (s, N-H), 6.75 (s, 1H, CH-O), 7.50-7.73 (m, 1H, HC=C), 7.24-8.93 (m, 11 arom. H). ¹³C NMR (62.5 MHz, CDCl₃) δ (ppm): 14.1 (Me), 28.6 (3 Me), 51.9 (N-C), 72.7 (CH-O), 150.0 (C=C), 120.1, 123.9, 127.2, 128.4, 128.8, 129.5, 129.7, 130.3, 141.0 (11 arom. CH), 121.1, 127.0, 135.1, 141.4, 148.7, 166.8 (7C).

(E)-2-(butylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(3-chlorophenyl)acrylate (4k)

Colorless Crystals, yield (98%); m.p.: 147-149°C; IR (KBr) (ν_{max}, cm⁻¹): 3296, 3088, 2956, 2929, 2870, 1716, 1660, 1564, 1200, 1053. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 0.918 (t, *J*=7.2 Hz, Me), 1.28-1.40 (m, 2H, CH₂), 1.49-1.57 (m, 2H, CH₂), 3.28-3.40 (m, 2H, N-CH₂),

6.45 (s, N-H), 6.60 (d, $J=16$ Hz, C=CH), 6.93 (s, 1H, CH-O), 7.74 (d, $J=16$ Hz, HC=C), 7.29-8.96 (m, 10 arom. H). ^{13}C NMR (100MHz, CDCl_3) δ (ppm): 13.7 (Me), 20.0 (CH_2), 31.5 (CH_2), 39.5 (N- CH_2), 72.2 (CH-O), 117.5 (C=C), 145.8 (C=C), 119.9, 124.1, 126.6, 127.6, 127.9, 130.1, 130.3, 130.9, 135.1, 135.5 (10 arom. CH), 126.1, 129.7, 142.0, 147.9, 149.3, 164.7, 166.8 (7C).

(E)-2-(butylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(4-fluorophenyl)acrylate (4l)

Colorless Crystals, yield (95%); m.p.: 149-151°C; IR (KBr) (ν_{max} , cm^{-1}): 3285, 3068, 2954, 2930, 2872, 1736, 1636, 1508, 1138, 980. ^1H NMR (400 MHz, CDCl_3) δ (ppm) : 0.919 (t, $J=7.2$ Hz, Me), 1.30-1.36 (m, 2H, CH_2), 1.50-1.55 (m, 2H, CH_2), 3.32-3.37 (m, 2H, N- CH_2), 6.47 (s, N-H), 6.52 (d, $J=16$ Hz, C=CH), 6.94 (s, 1H, CH-O), 7.78 (d, $J=16$ Hz, HC=C), 7.09-8.97 (m, 10 arom. H). ^{13}C NMR (100MHz, CDCl_3) δ (ppm): 13.7 (Me), 20.0 (CH_2), 31.4 (CH_2), 39.4 (N- CH_2), 72.1 (CH-O), 115.8 (C=C), 146.1 (C=C), 115.8, 116.1, 116.3, 119.9, 124.1, 127.5, 129.8, 19.9, 130.3, 130.4, 149.5 (10 arom. CH), 126.1, 130.0, 141.8, 148.1, 163.0, 165.0, 165.5, 167.0 (7C). MS, m/z (%): 407 (4), 307 (40), 262 (20), 247 (2), 166 (4), 149 (100), 121 (23), 101 (22), 57 (13).

(E)-2-(butylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-p-tolylacrylate (4m)

Colorless Crystals, yield (96%); m.p. 144-146°C; IR (KBr) (ν_{max} , cm^{-1}): 3295, 2956, 2929, 2870, 1727, 1659, 1509, 1250, 1151. ^1H NMR (400 MHz, CDCl_3) δ (ppm) : 0.92 (t, $J=7.2$, Me), 1.30-1.39 (m, 2H, CH_2), 1.45-1.58 (m, 2H, CH_2), 2.41 (s, Me), 3.33-3.38 (m, 2H, N- CH_2), 6.51 (s, N-H), 6.55 (d, $J=16$ Hz, C=CH), 6.97 (s, 1H, CH-O), 7.80 (d, $J=16$ Hz, HC=C), 7.22-8.97 (m, 10 arom. H). ^{13}C NMR (100MHz, CDCl_3) δ (ppm): 13.1 (Me), 20.0 (CH_2), 21.5 (Me), 31.5 (CH_2), 39.3 (N- CH_2), 71.9 (CH-O), 114.7 (C=C), 147.6 (C=C), 119.7, 124.2, 128.4, 129.8, 131.0, 141.7, 149.1 (10 arom. CH), 126.2, 127.6, 129.4, 130.1, 165.2, 167.0 (7C).

(E)-2-(butylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(3-methoxyphenyl)acrylate (4n)

Colorless Crystals, yield (97%); m.p.: 147-149°C; IR (KBr) (ν_{max} , cm^{-1}): 3288, 3091, 2955, 2869, 1722, 1563, 1157, 1094. ^1H NMR (250 MHz, CDCl_3) δ (ppm) : 0.88 (t, $J=7.2$ Hz, Me), 1.25-1.34 (m, 2H, CH_2), 1.44-1.53 (m, 2H, CH_2), 3.27-3.35 (m, 2H, N- CH_2), 3.81 (s, 3H, OMe), 6.40 (s, N-H), 6.54 (d, $J=16$ Hz, C=CH), 6.90 (s, 1H, CH-O), 7.75 (d, $J=16$ Hz, HC=C), 6.93-8.92 (m, 10 arom. H). ^{13}C NMR (62.5 MHz, CDCl_3) δ (ppm): 13.6 (Me), 19.9 (CH_2), 31.4 (CH_2), 39.4 (N- CH_2), 55.3 (OMe), 72.1 (CH-O), 113.2 (C=C), 147.3 (C=C), 116.3, 116.7, 119.8, 121.0, 123.9, 127.3, 129.6, 130.0, 130.2, 149.9 (10 arom. CH), 126.0, 135.0, 141.2, 148.7, 159.9, 165.0, 167.1 (7C).

(E)-2-(butylamino)-2-oxo-1-(quinolin-4-yl)ethyl 2-methyl-3-phenylacrylate (4o)

Colorless Crystals, yield (95%); m.p.: 141-143°C; IR (KBr) (ν_{max} , cm^{-1}): 3295, 3090, 2956, 2869, 1711, 1671, 1213, 1105. ^1H NMR (250 MHz, CDCl_3) δ (ppm) : 0.85 (t, $J=7$ Hz, Me), 1.19-1.31 (m, 2H, CH_2), 1.41-1.49 (m, 2H, CH_2), 2.16 (s, 3H, Me), 3.24-3.32 (m, 2H, N- CH_2), 6.38 (s, N-H), 6.85 (s, 1H, CH-O), 7.52-7.58 (m, 1H, HC=C), 7.24-8.91 (m, 11 arom. H). ^{13}C NMR (62.5 MHz, CDCl_3) δ (ppm): 13.6 (Me), 14.1 (Me), 19.9 (CH_2), 31.4 (CH_2), 39.4 (N- CH_2), 72.7 (CH-O), 149.9 (C=C), 120.0, 124.0, 127.3, 128.4, 128.9, 129.6, 129.7, 130.2, 141.0 (11 arom. CH), 126.0, 127.0, 135.1, 148.8, 166.8, 167.2 (7C).

(E)-2-(benzylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(3-chlorophenyl)acrylate (4p)

White Crystals, yield (92%); m.p.: 175-177°C; IR (KBr) (ν_{max} , cm^{-1}): 3288, 3088, 3023, 1720, 1659, 1562, 1324, 1188. ^1H NMR (250 MHz, CDCl_3) δ (ppm): 4.42-4.60 (m, 2 H, benzyl), 6.54 (d, $J=16$ Hz, C=CH), 6.57-6.63 (m, 1H, NH), 6.95 (s, 1H, CH-O), 7.68 (d, $J=16$ Hz, HC=C), 7.21-8.93 (m, 15 arom. H). ^{13}C NMR (62.5 MHz, CDCl_3) δ (ppm): 43.6 (CH_2), 72.4 (CH-O), 117.5

(C=C), 145.8 (C=C), 120.0, 123.9, 126.5, 127.4, 127.7, 127.8, 127.9, 128.8, 129.7, 130.2, 130.3, 130.8, 149.9 (15 arom. CH), 125.9, 135.0, 135.5, 137.3, 140.8, 164.6, 167.0 (8C).

(E)-2-(benzylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-p-tolylacrylate (4q)

White Crystals, yield (91%); m.p.: 166-168°C; IR (KBr) (ν_{\max} , cm^{-1}): 3284, 3083, 3030, 2922, 1714, 1660, 1629, 1311, 1159, 1060. ^1H NMR (250 MHz, CDCl_3) δ (ppm) : 2.16 (s, 3 H, Me), 4.42-4.60 (m, 2H, benzyl), 6.48 (d, $J=15.75$ Hz, C=CH), 6.76 (d, $J=4$ Hz, N-H), 6.95 (s, 1H, CH-O), (d, $J=16$ Hz, C=CH), 7.74 (d, $J=15.75$ Hz, HC=C), 7.16-8.91 (m, 15 arom. H). ^{13}C NMR (62.5 MHz, CDCl_3) δ (ppm) : 21.5 (Me), 43.5 (CH₂), 72.1 (CH-O), 114.8 (C=C), 149.9 (C=C), 119.9, 124.0, 127.3, 127.7, 128.3, 128.8, 129.6, 129.7, 130.2, 141.6, 147.5 (15 arom. CH), 126.0, 131.0, 137.4, 141.1, 148.7, 159.2, 165.2, 167.3 (8C).

(E)-2-(2,6-dimethylphenylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(3-chlorophenyl)acrylate (4r)

Colorless Crystals, yield (96%); m.p.: 191-193°C; IR (KBr) (ν_{\max} , cm^{-1}): 3265, 3031, 2978, 2921, 1719, 1667, 1530, 1265, 1200, 1060. ^1H NMR (250 MHz, CDCl_3) δ (ppm) : 2.1 (s, 6 H, 2 Me), 6.62 (d, $J=15$ Hz, C=CH), 7.024 (s, 1H, CH-O), 7.53(s, N-H), 7.71(d, $J=15$ Hz, HC=C), 7.067-8.98 (m, 13 arom. H). ^{13}C NMR (62.5 MHz, CDCl_3) δ (ppm): 18.2 (2 Me), 72.7 (CH-O), 117.5 (C=C), 150.0 (C=C), 119.7, 124.0, 126.5, 127.5, 127.7, 128.0, 128.3, 129.8, 130.2, 130.8, 145.8 (13 arom. CH), 125.8, 132.3, 135.0, 135.3, 135.5, 140.7, 148.7, 164.9, 165.3 (10 C).

(E)-2-(2,6-dimethylphenylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(4-fluorophenyl)acrylate (4s)

Colorless Crystals, yield (95%); m.p.: 202-204°C; IR (KBr) (ν_{\max} , cm^{-1}): 3250, 3040, 2921, 1728, 1598, 1509, 1231, 1158, 1052, 829. ^1H NMR (250 MHz, CDCl_3) δ (ppm) : 2.07(s, 6H, 2Me), 6.53 (d, $J=16$ Hz, C=CH), 6.83 (s, 1H, CH-

O), 7.53 (s, N-H), 7.70 (d, $J=16$ Hz, HC=C), 6.85-9.02 (m, 13 arom. H). ^{13}C NMR (62.5 MHz, CDCl_3) δ (ppm): 18.2 (2 Me), 72.5 (CH-O), 115.6 (C=C), 149.6 (C=C), 116.0, 116.2, 116.4, 119.7, 124.1, 127.6, 128.3, 129.7, 130.0, 130.2, 130.3, 130.4, 146.3 (13 arom. CH), 115.9, 117.5, 127.8, 132.3, 135.3, 141.4, 144.8, 148.2, 165.2, 165.4 (10 C).

(E)-2-(2,6-dimethylphenylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-p-tolylacrylate (4t)

White Crystals, yield (94%); m.p.: 184-186°C; IR (KBr) (ν_{\max} , cm^{-1}): 3248, 3027, 2955, 2920, 1732, 1636, 1537, 1307, 1205, 1153, 1054. ^1H NMR (250 MHz, CDCl_3) δ (ppm) : 2.06 (s, 6 H, 2Me), 2.36 (s, 3H, Me), 6.56 (d, $J=16$ Hz, C=CH), 6.97 (s, 1H, CH-O), 7.58 (s, N-H), 7.72 (d, $J=16$ Hz, HC=C), 7.00-8.98 (m, 13 arom. H). ^{13}C NMR (62.5 MHz, CDCl_3) δ (ppm): 18.2 (2 Me), 21.5 (Me), 72.4 (CH-O), 114.7 (C=C), 149.7 (C=C), 119.7, 124.2, 127.5, 127.7, 128.2, 128.2, 128.4, 129.6, 129.7, 129.9, 135.3, 141.7, 147.6 (13 arom. CH), 117.0, 126.0, 131.0, 132.4, 141.4, 145.8, 148.2, 165.4, 165.6 (10 C).

(E)-2-(2,6-dimethylphenylamino)-2-oxo-1-(quinolin-4-yl)ethyl 3-(3-methoxyphenyl)acrylate (4u)

White Crystals, yield (92%); m.p.: 179-181°C; IR (KBr) (ν_{\max} , cm^{-1}): 3250, 3030, 3000, 2942, 1710, 1667, 1578, 1294, 1158, 1050, 974. ^1H NMR (250 MHz, CDCl_3) δ (ppm) : 2.06 (s, 6 H, 2Me), 3.82 (s, 3H, OMe), 6.59 (d, $J=16$ Hz, C=CH), 6.94 (s, 1H, CH-O), 7.58 (s, N-H), 7.73 (d, $J=16$ Hz, HC=C), 6.95-8.97 (m, 13 arom. H). ^{13}C NMR (62.5 MHz, CDCl_3) δ (ppm): 18.2 (2Me), 55.3 (OMe), 72.5 (CH-O), 113.2 (C=C), 149.9 (C=C), 116.3, 116.9, 119.7, 121.0, 124.1, 127.4, 127.7, 128.2, 130.0, 130.2, 135.3, 147.4 (13 arom. CH), 125.9, 129.8, 132.4, 135.0, 140.9, 148.6, 159.9, 165.2, 165.5 (10 C).

(E)-2-(2,6-dimethylphenylamino)-2-oxo-1-(quinolin-4-yl)ethyl 2-methyl-3-phenylacrylate (4v)

White Crystals, yield (90%); m.p.: 173-175°C; IR (KBr) (ν_{\max} , cm^{-1}): 3260, 3023, 2978, 2921,

1708, 1669, 1533, 1246, 1110. ^1H NMR (250 MHz, CDCl_3) δ (ppm) : 2.06 (s, 6 H, 2Me), 2.18 (s, 3H, Me), 6.99 (s, 1H, CH-O), 7.59 (s, N-H), 7.76-7.87 (m, 1H, HC=C), 7.01-8.98 (m, 14 arom. H). ^{13}C NMR (62.5 MHz, CDCl_3) δ (ppm): 14.2 (Me), 18.2 (2Me), 73.2 (CH-O), 119.8 (C=C), 150.0 (C=C), 124.1, 126.9, 127.4, 127.7, 128.2, 128.5, 128.9, 129.7, 130.2, 141.3 (14 arom. CH), 125.9, 132.4, 135.1, 135.3, 140.9, 148.6, 165.6, 167.0 (9 C).

(E)-2-oxo-1-(quinolin-4-yl)-2-(tosylmethylamino)ethyl 3-(3-chlorophenyl)acrylate (4w)

Yellow Crystals, yield (92%); m.p.: 214-216°C; IR (KBr) (ν_{max} , cm^{-1}): 3420, 3062, 2924, 1729, 1701, 1638, 1425, 1317, 1146, 1086. ^1H NMR (250 MHz, CDCl_3) δ (ppm) : 2.15 (s, 3 H, Me), 4.58-4.97 (m, 2H, CH_2), 6.58 (d, $J=16$ Hz, C=CH), 6.77 (s, 1H, CH-O), 6.83 (d, $J=7.75$ Hz, N-H), 7.66 (d, $J=16$ Hz, HC=C), 7.22-8.95 (m, 14 arom. H). ^{13}C NMR (62.5 MHz, CDCl_3) δ (ppm): 21.5 (Me), 60.1 (CH_2), 71.9 (CH-O), 117.3 (C=C), 149.9 (C=C), 119.2, 124.2, 126.6, 127.3, 128.0, 128.2, 129.6, 129.7, 130.1, 130.7, 140.2, 145.9 (14 arom. CH), 125.5, 132.8, 134.9, 135.4, 145.4, 148.5, 155.8, 164.6, 166.9 (9 C).

(E)-2-oxo-1-(quinolin-4-yl)-2-(tosylmethylamino)ethyl 3-(4-fluorophenyl)acrylate (4x)

Yellow Crystals, yield (93%); m.p.: 208-210°C; IR (KBr) (ν_{max} , cm^{-1}): 3429, 3080, 2949, 1731, 1704, 1599, 1511, 1319, 1283, 1145, 1086. ^1H NMR (250 MHz, CDCl_3) δ (ppm) : 2.17 (s, 3 H, Me), 4.55-4.95 (m, 2H, CH_2), 6.51 (d, $J=15.75$ Hz, C=CH), 6.79 (s, 1H, CH-O), 6.88 (d, $J=8$ Hz, N-H), 7.70 (d, $J=16$ Hz, HC=C), 7.01-8.95 (m, 14 arom. H). ^{13}C NMR (62.5 MHz, CDCl_3) δ (ppm): 21.4 (Me), 59.9 (CH_2), 71.7 (CH-O), 115.4 (C=C), 149.9 (C=C), 116.0, 116.3, 119.0, 124.1, 128.3, 129.6, 129.7, 130.1, 130.3, 130.5 (14 arom. CH), 119.5, 125.5, 127.3, 132.9, 140.2, 145.4, 164.5, 166.9 (9 C).

(E)-2-oxo-1-(quinolin-4-yl)-2-(tosylmethylamino)ethyl 3-*p*-tolylacrylate (4y):

Yellow Crystals; m.p.: 196-198°C; yield: 92%. IR (KBr) (ν_{max} , cm^{-1}): 3429, 3037, 2949, 1731, 1702, 1636, 1504, 1317, 1283, 1156, 1088. ^1H NMR (250 MHz, CDCl_3) δ (ppm) : 2.18 (s, 3 H, Me), 2.37 (s, 3 H, Me), 4.54-4.92 (m, 2H, CH_2), 6.54 (d, $J=16$ Hz, C=CH), 6.79 (s, 1H, CH-O), 6.89 (d, $J=8$ Hz, N-H), 7.76 (d, $J=16$ Hz, HC=C), 7.00-8.94 (m, 14 arom. H). ^{13}C NMR (62.5 MHz, CDCl_3) δ (ppm): 21.5 (2 Me), 59.8 (CH_2), 71.5 (CH-O), 114.4 (C=C), 149.9 (C=C), 119.0, 124.2, 127.3, 128.3, 128.4, 129.6, 129.7, 130.1, 147.9 (14 arom. CH), 125.7, 130.9, 133.0, 140.3, 141.7, 145.3, 165.0, 166.9 (9 C).

Conclusion

We believe that the reported method offers a mild, simple, efficient, and one-pot synthetic method to prepare novel 2-(alkyl/aryl amino)-2-oxo-1-(quinolin-4-yl)ethyl cinnamates by the Passerini three-component reaction. The reaction proceeds smoothly and cleanly under mild conditions, and no side reactions were observed. The products were obtained in excellent yields. Their ease of work-up, high yields, mild reaction conditions, and H_2O as a medium make it a valuable protocol for synthesizing these compounds.

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