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SYNTHESIS OF 2-SUBSTITUTED 3,4-DIHYDROQUINAZOLINE DERIVATIVES *VIA* REGIOSELECTIVE ADDITION OF A CARBON NUCLEOPHILE TO A CARBODIIMIDE

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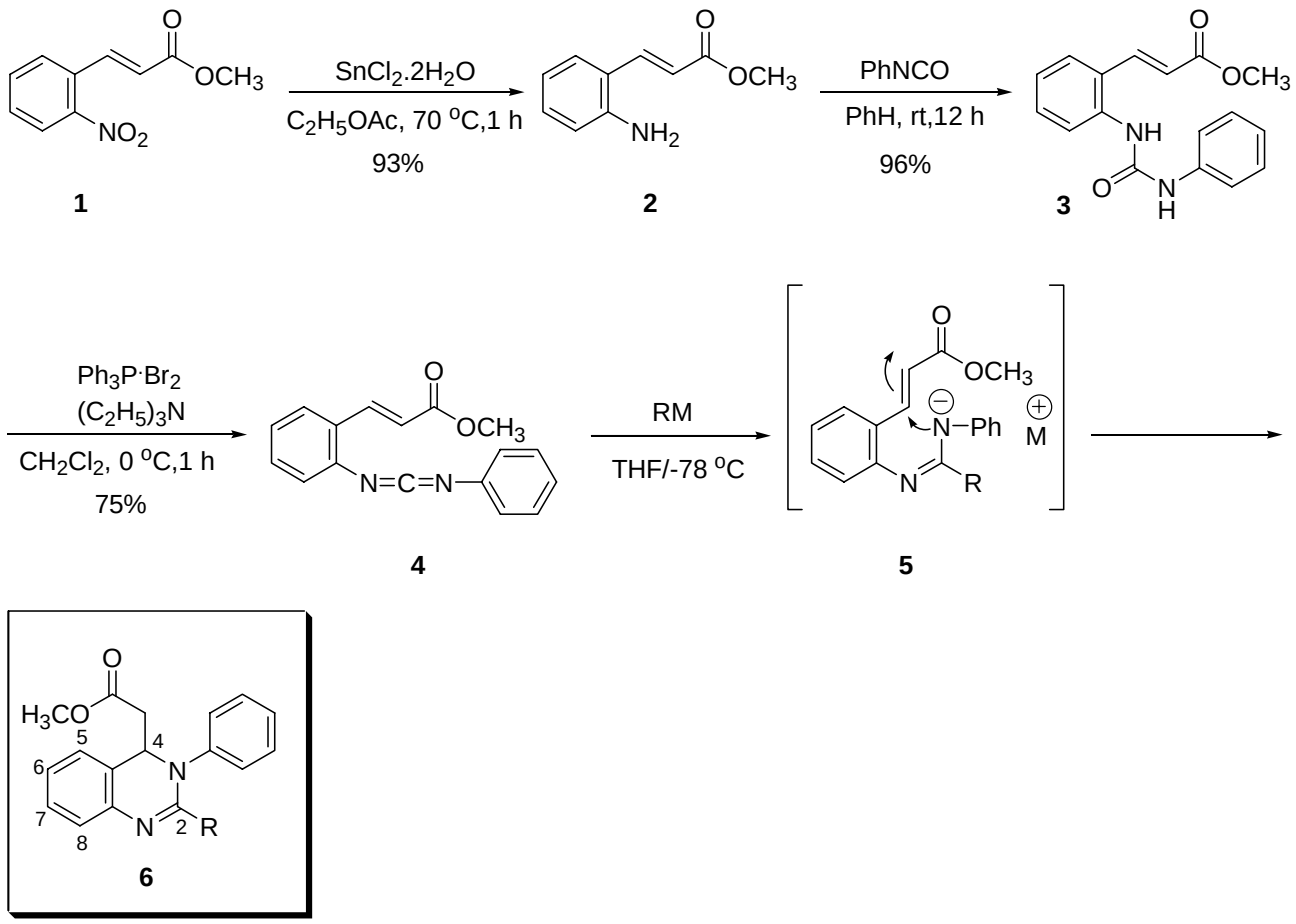
Abstract- Synthesis of 2-alkyl or phenyl-substituted 3,4-dihydroquinazoline derivatives (**6**) is described *via* regioselective carbon nucleophilic addition (RMgBr and RM) to a carbodiimide (**4**) followed by intramolecular conjugate addition.

Quinazoline and its related skeletons have attracted the interests of medicinal chemists as an important class of heterocyclic scaffolds occurring in a large number of bioactive molecules for a variety of biological targets.[1] As a result, a number of quinazoline compounds have been prepared by various research groups such as the Molina, Xin and Saito groups.[2-4] A number of methods for synthesis of quinazoline and quinazolinone compounds have been reported.[5] Among them, Molina's carbodiimide approach has been a general route and most of these reactions have used heteroatom nucleophiles such as amine, thiol and alcohol for electrocyclization.[6] Surprisingly, no reports of carbon nucleophiles used for the addition into the heterocumulene of carbodiimide exist. Therefore, we now report the first example of 2-alkyl- or aryl-substituted 3,4-dihydroquinazolines (**6**) *via* regioselective addition of various carbon

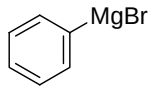
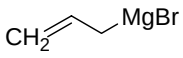
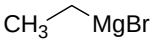
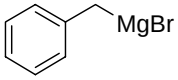
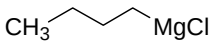
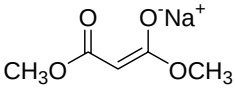
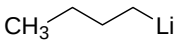
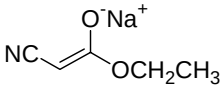
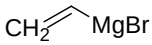
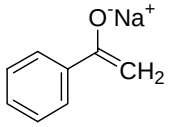
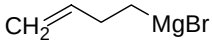
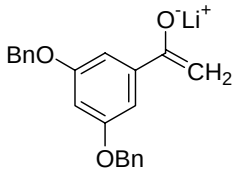
nucleophiles (Grignard reagents and metal enolates) to a carbodiimide (**4**) followed by intramolecular conjugate addition of the resulting amine species (**5**) to an α,β-unsaturated ester as shown in Scheme 1.



Scheme 1. Synthesis of 2-substituted 3,4-dihydroquinazoline derivatives

Carbodiimide (**4**), intermediate of this reaction, was prepared in 75% yield by the reaction of phenylurea (**3**) with $Ph_3P{\cdot}Br_2$ and $(C_2H_5)_3N$ instead of more general route using aza-Wittig reaction condition.[7] The phenylurea (**3**) was prepared in two steps (89% yield) starting from methyl 2-nitrocinnamate (**1**) according to a published procedure.[8] We tried the reaction of carbodiimide (**4**) with three types of carbon nucleophiles, Grignard reagents (Table 1, Entries 1-3 and 5-8), alkyllithium (Entry 4), and metal enolates (Entries 9-12), to examine the scope and limitation of the reaction. The results are summarized in Table 1.

Table 1. Reaction of Carbodiimide (4) with Carbon Nucleophiles.

Entry	RM	Condition	Product (Yield, %)[a]	Entry	RM	Condition	Product (Yield, %)[a]
1		- 78 ^{o}C/ 30 min	**6a** (81)	**7**		- 78 ^{o}C/ 30 min	**6g** (-)[b]
2		- 78 ^{o}C/ 30 min	**6b** (60)	**8**		- 78 ^{o}C/ 30 min	**6h** (-)[b]
3		- 78 ^{o}C/ 30 min	**6c** (58)	**9**[c]		- 78 to 0^{o}C/ 30 min	**6i** (60)
4		- 78 ^{o}C/ 30 min	**6d** (-)[b]	**10**[c]		- 78 to 0^{o}C/ 30 min	**6j** (86)
5		- 78 ^{o}C/ 30 min	**6e** (50)	**11**[c]		- 78 to 0 ^{o}C/ 30 min	**6k** (32)
6		- 78 ^{o}C/ 30 min	**6f** (65)	**12**[d]		- 78 to 0^{o}C/ 30 min	**6l** (20)

[a] Isolated yield; [b] Many products without major components from TLC analysis; [c] NaH was used as a base; [d] LiHMDS was used as a base.

First, some of Grignard reagents (Entries 1-3 and 5-6) were found to be effective in regioselective addition to the carbodiimide group to generate 2-substituted 3,4-dihydroquinazoline compounds (**6a-c, 6e** and **6f**) in moderate to good yields (50 to 81%). Phenylmagnesium bromide (Entry 1) gave a higher yield of product (**6a**, 81%) than other Grignard reagents (Entries 2-3 and 5-6) tried. Two allylic-type Grignard reagents (Entries 7 and 8: allylmagnesium bromide and benzylmagnesium bromide) did not give the expected products. This failure was probably due to a stabilized six-membered cyclic transition state as was reported earlier (Figure 1). [9] Simple *n*-butyllithium (Entry 4), as a third type of carbon nucleophile, also gave a complicated mixture. This result implies non-selective addition of this carbon nucleophile due to its plausible high reactivity, when compared to the successful result of *n*-butylmagnesium chloride (Entry 3; 58% yield of **6c**).

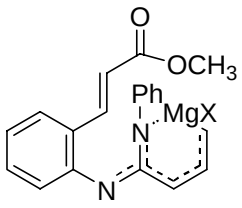


Figure 1. A supposed cyclic transition state of allylic-type Grignard reagent.

Secondly, metal enolates (Entries 9-12) as a second type of carbon nucleophile underwent the tandem nucleophilic addition-conjugate addition to provide the desirable products (**6i-l**) in 20 to 86% yields. Sodium ethyl cyanoacetate (Entry 10) gave the highest yield of product (**6j**, 86%), followed by sodium methyl malonate (**6i**, 60%) and sodium acetophenoxide (**6k**, 32%). The results imply that the yields of these reactions are dependent on the relative reactivities of the corresponding enolates. On the other hand, lithium 3,5-dibenzyloxyacetophenoxide, a functionalized enolate (Entry 12), provided the product (**6l**) in 20% yield, but its sodium enolate failed to give the desired cyclized product. The spectroscopic data (^{1}H- and ^{13}C-NMR spectroscopy) show that all compounds (**6i-l**) obtained from reactions with enolates exclusively exist in enol forms *via* intramolecular hydrogen bonding interaction at the equilibrium state as shown in Figure 2.

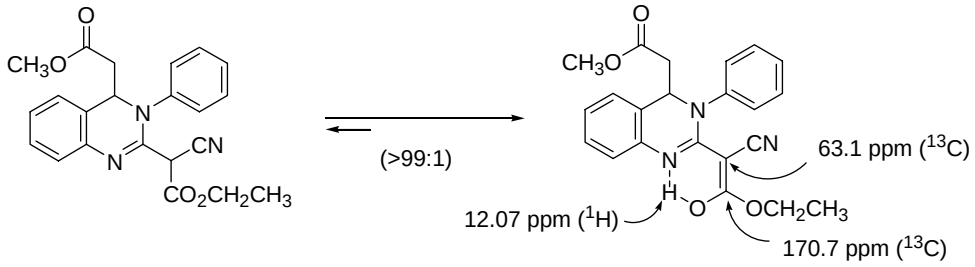


Figure 2. Enol form of compound (6j) at equilibrium state.

In summary, 2-alkyl- or phenyl-substituted 3,4-dihydroquinazoline derivatives (**6**) could efficiently be synthesized *via* the regioselective addition of carbon nucleophiles with carbodiimides followed by

intramolecular conjugate addition. This procedure allowed the construction of new type of 3,4-dihydroquinazoline derivatives with a set of diverse substituents at C-2 position. With other isocyantes instead of phenyl isocyante, 3,4-dihydroquinazoline derivatives containing various substituents at N-3 position could be also obtained.

EXPERIMENTAL

Mps were determined on a Thomas-Hoover capillary melting apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer 16F-PC FT-IR and MIDAC 101025 using a potassium bromide pellet. ^{1}H NMR spectra were recorded on a Varian Unity Plus 300 (300 MHz) spectrometer or on a Brucker Avance 300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Varian Unity Plus 300 (75 MHz) spectrometer. The chemical shifts are reported in ppm (δ) relative to tetramethylsilane. Low and high-resolution FABMS (positive ion mode) mass spectra were determined on a JEOL 700 mass spectrometer. TLC was carried out by pre-coated silica gel (E. Merck Kiesegel 60F_{254} layer thickness 0.25 mm). Flash column chromatography was performed with Merck Kiesegel 60 Art 9385 (230 - 400 mesh). All solvents used were purified according to standard procedures.

Preparation of methyl 2-nitrocinnamate (1)

To a solution of 2-nitrocinnamic acid (1.99 g, 10.3 mmol) in methanol (100 mL) was added concentrated sulfuric acid (0.17 mL, 3.06 mmol) at rt. After the solution was refluxed for 12 h, the solution was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent and column chromatography (ethyl acetate/hexane = 1:5) of the residue gave methyl 2-nitrocinnamate (**1**) (2.07 g, 97%) as a yellow solid: mp 75 °C (ethyl acetate-hexane); IR (KBr) 1718, 1636, 1520, 1432, 1346, 1198, 974, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 15.9 Hz, 1H, -C<u>H</u>=CH-CO_2CH_3), 8.03 (d, *J* = 7.5 Hz, 1H, aromatic), 7.70-7.63 (m, 2H, aromatic), 7.56 (m, 1H, aromatic), 6.37 (d, *J* = 15.9 Hz, 1H,

-CH=C<u>H</u>-CO_2CH_3), 3.83 (s, 3H, -OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 148.6, 140.4, 133.9, 130.9, 130.7, 129.4, 125.2, 123.1, 52.3.

Preparation of methyl 2-aminocinnamate (2)

To a solution of methyl 2-nirocinnamate (**1**) (0.202 g, 0.975 mmol) in EtOAc (20 mL) was added $SnCl_2 \cdot 2H_2O$ (1.11 g, 4.87 mmol) at rt, and then the solution was refluxed for 1 h. After cooling, the pH of the solution was made slightly basic by addition of aqueous $NaHCO_3$. The mixture was filtered with Celite 545 and extracted with EtOAc three times. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent and column chromatography (ethyl acetate/hexane = 1:5) of the residue gave methyl 2-nitrocinnamate (**2**) (0.161 g, 93%) as a yellow solid: mp 67 °C (ethyl acetate-hexane); IR (KBr) 3365, 2364, 1704, 1622, 1330, 1198, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 15.9 Hz, 1H, -C<u>H</u>=CH-CO_2CH_3), 7.40 (d, *J* = 7.5 Hz, 1H, aromatic), 7.19 (t, *J* = 7.2 Hz, 1H, aromatic), 6.78 (t. *J* = 7.8 Hz, 1H, aromatic), 6.72 (d, *J* = 7.5 Hz, 1H, aromatic), 6.38 (d, *J* = 15.9 Hz, 1H, -CH=C<u>H</u>-CO_2CH_3), 4.02 (br, 2H, -NH_2), 3.82 (s, 3H, -OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 145.9, 140.6, 131.6, 128.3, 120.1, 119.2, 117.9, 117.0, 51.9.

Preparation of phenyl-substituted urea (3)

To a solution of methyl 2-aminocinnamate (**2**) (6.35 g, 35.8 mmol) in benzene (150 mL) was added dropwise phenyl isocyanate (5.12 g, 43.0 mmol) at rt, and then the solution was stirred for 12 h. The precipitate was filtered and washed with ether to give pure phenyl-substituted urea (**3**) (10.2 g, 96%) as a white solid: mp 184 °C (ether); IR (KBr) 3346, 3278, 1724, 1650, 1548, 1322, 1172, 758, 672 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.94 (s, 1H, -NH-CO-), 8.49 (s, 1H, -NH-CO-), 7.89 (d, *J* = 15.9 Hz, 1H, -C<u>H</u>=CH-CO_2CH_3), 7.76 (d, *J* = 7.8 Hz, 2H, aromatic), 7.46 (d, *J* = 8.4 Hz, 2H, aromatic), 7.39 (t, *J* = 8.1 Hz, 1H, aromatic), 7.28 (t, *J* = 7.8 Hz, 2H, aromatic), 7.12 (t, *J* = 7.5 Hz, 1H, aromatic), 6.97 (t, *J* = 7.8 Hz, 1H, aromatic), 6.58 (d, *J* = 15.3 Hz, 1H, -CH=C<u>H</u>-CO_2CH_3), 3.73 (s, 3H, -OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.4, 153.5, 140.5, 140.3, 138.5, 131.4, 129.5, 127.8, 126.8, 124.6, 124.4, 122.7,

119.5, 118.9, 52.2.

Preparation of phenyl-substituted carbodiimide (4)

To a solution of phenyl-substituted urea (**3**) (6.04 g, 20.4 mmol) and triethylamine (6.19 g, 61.2 mmol) in CH_2Cl_2 (100 mL) was added portionwise dibromotriphenylphosphine (12.9 g, 30.6 mmol) at 0 °C. The resulting mixture was stirred for 1 h at the same temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent and column chromatography (ethyl acetate/hexane = 1:10) of the residue gave phenyl-substituted carbodiimide (**4**) (4.26 g, 75%) as a white solid: mp 54 °C (ethyl acetate-hexane); IR (KBr) 2142, 1716, 1484, 1172, 756, 592 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 16.2 Hz, 1H, -C<u>H</u>=CH-CO_2CH_3), 7.56 (d, *J* = 7.8 Hz, 1H, aromatic), 7.36-7.29 (m, 3H, aromatic), 7.25 (d, *J* = 7.8 Hz, 1H, aromatic), 7.20-7.13 (m, 4H, aromatic), 6.52 (d, *J* = 16.2 Hz, 1H, -CH=C<u>H</u>-CO_2CH_3), 3.80 (s, 3H, -OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 140.5, 138.4, 138.0, 134.3, 131.3, 129.8, 129.0, 127.8, 126.1, 126.0, 125.9, 124.6, 119.6, 52.0.

***A Typical Procedure of 2-Phenyl-3,4-dihydroquinazoline* (6a)**

To a solution of carbodiimide (**4**) (0.911 g, 3.27 mmol) in THF (50 mL) was added dropwise 3.0 *M* phenylmagnesium bromide in ether (2.62 mL, 7.58 mmol) at -78 °C with stirring under an atmosphere of argon. After stirring for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc three times. Evaporation of the solvent and column chromatography (ethyl acetate/hexane = 1:5) of the residue gave 2-phenyl-3,4-dihydroquinazoline (**6a**) (0.942 g, 81%) as a white solid: mp 117 °C (ethyl acetate-hexane); IR (KBr) 3062, 2948, 1738, 1536, 1374, 1164, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77-7.74 (m, 2H, aromatic), 7.50 (d, *J* = 7.2 Hz, 1H, aromatic), 7.31 (t, *J* = 7.8 Hz, 1H, aromatic), 7.24-7.21 (m, 3H, aromatic), 7.15-7.03 (m, 4H, aromatic), 6.96 (d, *J* = 7.8 Hz, 2H, aromatic), 6.90 (t, *J* = 7.2 Hz, 1H, aromatic), 5.38 (t, *J* = 7.2 Hz, 1H, -CH_2-C<u>H</u>-N-), 3.67 (s, 3H, -OCH_3), 2.89 (dd, *J* = 4.8 and 8.1 Hz, 1H, -CO-CH_2-), 2.69 (dd, *J* = 6.6 and 15.1 Hz, 1H, -CO-CH_2-); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 171.5, 154.9, 145.4, 142.1, 136.3, 130.4, 130.0, 129.2, 128.9, 128.5, 126.5, 126.3, 125.3, 125.1, 124.4, 123.6, 59.4, 52.1, 40.8; HRMS (FAB, M+H) Calcd for $C_{23}H_{21}N_2O_2$ 357.1603, found 357.1626. **6b** (oil): IR (KBr) 2946, 1734, 1562, 1486, 1240, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.8 Hz, 2H, aromatic), 7.17-7.08 (m, 5H, aromatic), 6.94 (m, 1H, aromatic), 6.86 (d, *J* = 7.2 Hz, 1H, aromatic), 5.02 (t, *J* = 7.2 Hz, 1H, -CH_2-C<u>H</u>-N-), 3.45 (s, 3H, -OCH_3), 2.68-2.54 (m, 2H , -CO-CH_2-), 2.34-2.15 (m, 2H, -C<u>H</u>$_2$-CH_3), 1.00 (t, *J* = 7.8 Hz, 3H, -CH_2-C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 159.7, 143.9, 141.9, 130.0, 129.0, 127.3, 127.0, 125.3, 125.3, 124.6, 124.2, 59.4, 52.2, 41.5, 28.9, 12.3; HRMS (FAB, M+H) Calcd for $C_{19}H_{21}N_2O_2$ 309.1603, found 309.1613. **6c** (oil): IR (KBr) 2956, 2362, 1734, 1560, 1486, 1240, 764, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.6 Hz, 2H, aromatic), 7.31-7.20 (m, 5H, aromatic), 7.08 (m, 1H, aromatic), 6.98 (d, *J* = 7.5 Hz, 1H, aromatic), 5.14 (dd, *J* = 5.8 and 7.3 Hz, 1H, -CH_2-C<u>H</u>-N-), 3.59 (s, 3H, -OCH_3), 2.81-2.67 (m, 2H, -CO-CH_2-), 2.34 (m, 2H, -C<u>H</u>$_2$-CH_2-CH_2-CH_3), 1.54 (m, 2H, -CH_2-C<u>H</u>$_2$-CH_2-CH_3), 1.23 (m, 2H, -CH_2-CH_2-C<u>H</u>$_2$-CH_3), 0.78 (t, *J* = 7.3 Hz, 3H, -CH_2-CH_2-CH_2-C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 159.0, 144.0, 141.9, 129.9, 129.0, 127.3, 127.1, 125.3, 125.3, 124.6, 124.2, 59.4, 52.2, 41.6, 35.4, 30.2, 22.9, 14.1; HRMS (FAB, M+H) Calcd for $C_{21}H_{25}N_2O_2$ 337.1916, found 337.1888. **6e** (oil): IR (KBr) 2948, 1732, 1540, 1244, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.27 (m, 4H, aromatic), 7.19-7.08 (m, 4H, aromatic), 7.02 (d, 1H, *J* = 7.6 Hz, aromatic), 6.31 (dd, 1H, *J* = 2.1 and 16.8 Hz, -CH=C<u>H</u>$_2$), 6.20 (dd, 1H, *J* = 9.9 and 16.8 Hz, -C<u>H</u>=CH_2), 5.48 (dd, 1H, *J* = 2.1 and 10.0 Hz, -CH=C<u>H</u>$_2$), 5.26 (dd, 1H, *J* = 6.3 and 7.7 Hz, -N-C<u>H</u>-CH_2-CO_2CH_3), 3.64 (s, 3H, -OCH_3), 2.80 (dd, 1H, *J* = 6.3 and 14.9 Hz, -N-CH-C<u>H</u>$_2$-CO_2CH_3), 2.72 (dd, 1H, *J* = 7.8 and 15.0 Hz, -N-CH-C<u>H</u>$_2$-CO_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 152.4, 143.9, 141.7, 132.8, 129.5, 128.9, 125.8, 125.7, 125.2, 124.7, 124.5, 124.2, 58.7, 52.1, 41.0; HRMS (FAB, M+H) Calcd for $C_{19}H_{19}N_2O_2$ 307.1447, found 307.1443. **6f** (oil): IR (KBr) 2948, 1734, 1562, 1486, 1240, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.37 (m, 2H, aromatic), 7.31-7.21 (m, 5H, aromatic), 7.08 (td, *J* = 2.4 and 6.7 Hz, 1H, aromatic), 6.98 (d, *J* = 7.2 Hz, 1H, aromatic), 5.70 (m, 1H, -CH_2-CH_2-C<u>H</u>=CH_2), 5.15 (dd, *J* = 5.7 and 7.5 Hz, 1H, -CH_2-C<u>H</u>-N-), 4.98-4.89 (m, 2H, -CH_2-CH_2-CH=C<u>H</u>$_2$), 3.59 (s, 3H, -OCH_3), 2.81-2.67 (m, 2H, -CO-CH_2-), 2.53-2.32 (m, 4H, -C<u>H</u>$_2$-C<u>H</u>$_2$-CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ

171.1, 157.7, 143.9, 141.9, 137.7, 129.9, 129.0, 127.2, 126.9, 125.3, 124.6, 124.3, 115.6, 59.4, 52.2, 41.7, 34.9, 31.9; HRMS (FAB, M+H) Calcd for $C_{21}H_{23}N_2O_2$ 335.1760, found 335.1761. **6i**: mp 153 °C (ethyl acetate-hexane); IR (KBr) 3072, 2950, 1720, 1562, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.23 (s, 1H, -OH), 7.35-7.23 (m, 5H, aromatic), 7.14-7.04 (m, 4H, aromatic), 5.27 (dd, *J* = 5.4 and 9.3 Hz, 1H, -CH_2-C<u>H</u>-N-), 3.70 (s, 3H, -OCH_3), 3.43 (s, 6H, C<u>H</u>$_3$O-CO-CH-CO-OC<u>H</u>$_3$), 3.10 (dd, *J* = 5.4 and 16.2 Hz, 1H, -CO-CH_2-), 2.87 (dd, *J* = 9.3 and 15.9 Hz, 1H, -CO-CH_2-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 168.9, 157.4, 144.7, 133.3, 131.7, 129.4, 129.3, 128.2, 126.0, 125.8, 124.3, 124.1, 116.4, 59.4, 52.2, 51.3, 39.4; HRMS (FAB, M+H) Calcd for $C_{22}H_{23}N_2O_6$ 411.1556, found 411.1554. **6j**: mp 179 °C (ethyl acetate-hexane); IR (KBr) 3100, 2980, 2362, 2206, 1722, 1570, 1284, 1132, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.07 (s, 1H, -OH), 7.42-7.23 (m, 6H, aromatic), 7.13-7.10 (m, 3H, aromatic), 5.19 (dd, *J* = 6.6 and 8.3 Hz, 1H, -CH_2-C<u>H</u>-N-), 4.23 (q, *J* = 7.1 Hz, 2H, -O-C<u>H</u>$_2$-CH_3), 3.72 (s, 3H, -OCH_3), 3.01 (dd, *J* = 6.5 and 15.1 Hz, 1H, -CO-CH_2), 2.80 (dd, *J* = 8.4 and 15.1 Hz, 1H, -CO-CH_2-), 1.31 (t, *J* = 7.1 Hz, 3H, -O-CH_2-C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.7, 158.9, 144.1, 132.6, 130.2, 129.8, 127.6, 126.4, 125.4, 125.3, 123.7, 117.5, 116.5, 63.1, 61.1, 60.7, 52.8, 40.7, 14.9; HRMS (FAB, M+H) Calcd for $C_{22}H_{22}N_3O_4$ 392.1610, found 392.1613. **6k**: mp 124 °C (ethyl acetate-hexane); IR (KBr) 3100, 2948, 1736, 1572, 1202, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 14.11 (s, 1H, -OH), 7.66-7.62 (m, 2H, aromatic), 7.53-7.48 (m, 2H, aromatic), 7.44-7.39 (m, 3H, aromatic), 7.37-7.28 (m, 4H, aromatic), 7.12-7.09 (m, 2H, aromatic), 7.03 (m, 1H, aromatic), 5.20 (s, 1H, a vinyl proton of the enol), 5.14 (dd, *J* = 5.1 and 8.1 Hz, 1H, -CH_2-C<u>H</u>-N-), 3.57 (s, 3H, -OCH_3), 2.98-2.84 (m, 2H, -CO-CH_2-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.1, 170.6, 157.0, 141.8, 141.1, 134.3, 130.4, 130.3, 129.6, 128.5, 128.3, 128.2, 126.9, 126.1, 123.5, 122.0, 116.3, 79.6, 59.0, 52.2, 40.2; HRMS (FAB, M+H) Calcd for $C_{25}H_{23}N_2O_3$ 399.1709, found 399.1707. **6l** (oil): IR (KBr) 3400, 3032, 2946, 1736, 1572, 1154, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 14.10 (s, 1H, -OH), 7.52-7.47 (m, 2H, aromatic), 7.43-7.28 (m, 14H, aromatic), 7.12-7.01 (m, 3H, aromatic), 6.92 (d, *J* = 2.1 Hz, 2H, aromatic), 6.23 (t, *J* = 2.2 Hz, 1H, aromatic), 5.15-5.11 (m, 2H, a vinyl proton of the enol and -CH_2-C<u>H</u>-N-), 5.01 (s, 4H, 2 x -OCH_2Ph), 3.56 (s, 3H, -OCH_3), 2.97-2.83 (m, 2H, -CO-CH_2-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 170.2, 159.6, 156.8, 143.3, 141.4, 136.7, 133.9, 130.0,

129.3, 128.5, 128.3, 128.0, 127.7, 127.6, 125.8, 123.2, 121.7, 115.9, 105.6, 104.1, 79.5, 70.1, 58.7, 51.9, 39.9; HRMS (FAB, M+H) Calcd for $C_{39}H_{35}N_2O_5$ 611.2546, found 611.2542.

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