Solvent-free Synthesis of 1,2-Disubstituted Derivatives of 1,2-Dihydroisoquinoline, 1,2-Dihydroquinoline and 1,2-Dihydropyridine

Rahimeh Hajinasiri and Sobhan Rezayati

Chemistry Department, Qaemshahr Branch, Islamic Azad University, Qaemshahr, I. R. Iran

Reprint requests to Dr. Rahimeh Hajinasiri. Fax: +981232240091. Tel.: +981232145117.
E-mail: rhmhajinasiri@yahoo.com

Z. Naturforsch. **2013**, *68b*, 818 – 822 / DOI: 10.5560/ZNB.2013-3095
Received March 7, 2013

A one-pot and efficient approach to the synthesis of dialkyl 2-[1-[(alkoxycarbonyl)anilino]-2(1*H*)-(isoquinolin-2-yl) (or -quinolin-1-yl or -pyridin-1-yl)]-2-butenedioates is described. This method involves a three-component reaction between isoquinoline, quinoline or pyridine, dialkyl acetylenedicarboxylates and *N*-phenylcarbamates under solvent-free conditions, without using any catalyst and at room temperature. The mild reaction conditions and good yields of the products exhibit the synthetic advantage of this method.

Key words: 1,2-Dihydroisoquinoline, Solvent-free, Phenylcarbamate, 1,2-Dihydroquinoline, 1,2-Dihydropyridine

Introduction

The enlargement of green environmentally compassionate synthetic procedures has been a topic of considerable concern over the past few years both in academia and in industry [1]. Especially, solvent-free reactions and reactions in water are of increasing interest. The replacement of conventional solvents with water or under solvent-free conditions, is one of the most interesting basic approaches along these lines. The isoquinoline skeleton is found in a large number of naturally occurring and synthetic biologically active heterocyclic compounds [2, 3]. In particular, 1,2-dihydroisoquinoline derivatives act as delivery systems that transport drugs through the otherwise highly impermeable blood-brain barrier [4, 5]. Isoquinoline derivatives also exhibit sedative [6], antidepressant [7, 8], antitumor, and antimicrobial activities [9 – 11]. Here we describe an efficient one-pot and method for the synthesis of 1,2-disubstituted 1,2-dihydroisoquinoline derivatives *via* the reaction of isoquinoline (**1**), a dialkyl acetylenedicarboxylate **3** and a *N*-phenylcarbamate **2** under solvent-free conditions at room temperature (Scheme 1).

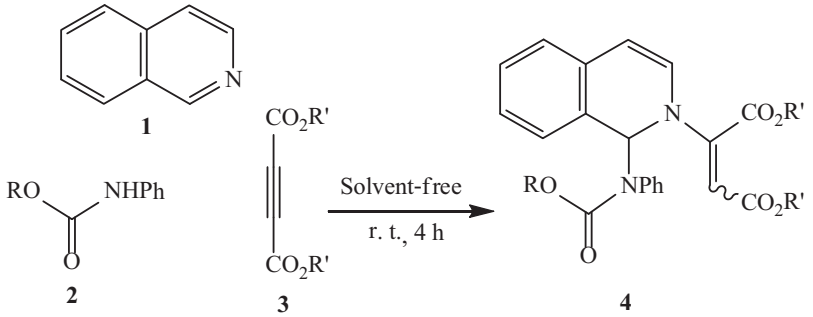
Results and Discussion

The reaction of isoquinoline (**1**), *N*-phenylcarbamates **2**, and dialkyl acetylenedicarboxylates **3** proceeds smoothly under solvent-free conditions at room temperature to produce dialkyl 2-[1-[(alkoxycarbonyl)anilino]-2(1*H*)-isoquinolin-2-yl]-2-butenedioate derivatives **4** in 75 – 85 % yield (Scheme 1).

The structures of the compounds were apparent from the ^{1}H NMR, ^{13}C NMR and IR spectra which are in agreement with the proposed formulae. The ^{1}H NMR spectrum of **4a** showed all expected signals at δ = 1.00, 1.73 and 4.16 ppm for the propyl moiety, two singlets at δ = 3.70 and 3.83 ppm for two methoxy groups and a singlet at δ = 6.80 ppm for the olefinic poroton, along with characteristic signals for the isoquinoline and phenyl moieties. The proton-decoupled ^{13}C NMR spectrum of **4a** showed 21 signals in agreement with the proposed structure.

A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that the initial event is the formation of a 1 : 1 zwitterionic intermediate **5** from isoquinoline and dialkyl acetylenedicarboxylate [12] which is subsequently protonated by the *N*-phenylcarbamates **2** and then attacked by the conjugate base of the carbamate to produce **4** (Scheme 2).

Under similar conditions, the reaction of quinoline and pyridine with dialkyl acetylenedicarboxylates in the presence of *N*-phenylcarbamate led to dialkyl 2-[1-[(alkoxycarbonyl)anilino]-2(1*H*)-quinolin-1-yl]-2-butenedioates **7** and dialkyl 2-[1-[(alkoxycar-

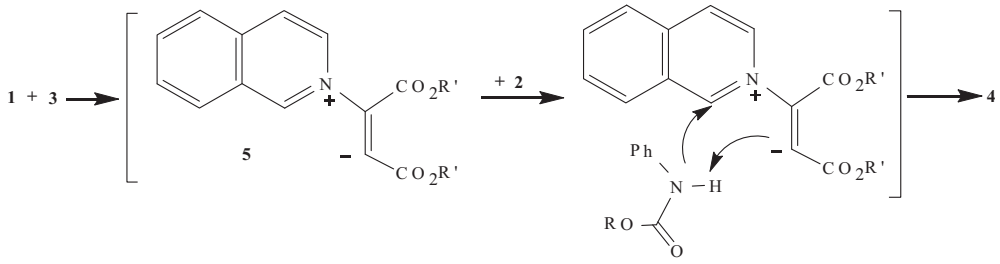


2a: R = *n*-Pr
2b: R = *i*-Pr
2c: R = cyclohexyl

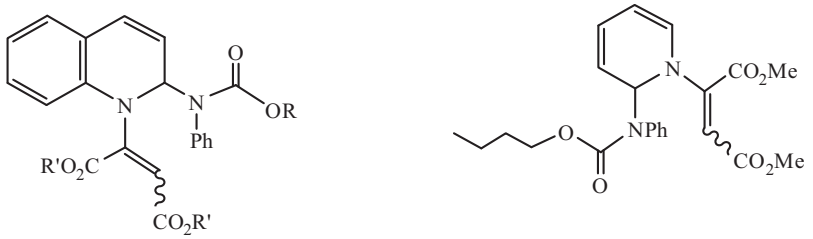
3a: R' = Me
3b: R' = Et

4a: R = *n*-Pr, R' = Me
4b: R = *n*-Pr, R' = Et
4c: R = R = *i*-Pr, R' = Me
4d: R = *i*-Pr, R' = Et
4e: R = cyclohexyl, R' = Me
4f: R = cyclohexyl, R' = Et

Scheme 1. Synthesis of compounds **4a**–**f**.



Scheme 2. Possible mechanism for the formation of compounds **4**.



7a: R = *n*-Bu, R' = Me
7b: R = *i*-Pr, R' = Et
7c: R = *n*-Pr, R' = Et
7d: R = Et, R' = Et

Scheme 3. Derivatives of 1,2-dihydroquinoline and 1,2-dihydropyridine.

bonyl)anilino]-2(1*H*)-pyridin-1-yl]-2-butenedioates **8** in 78 – 90 % yield (Scheme 3).

Conclusion

In conclusion, we have described a convenient one-pot route for the synthesis of 1,2-disubstituted nitrogen-containing heterocycles, by reaction of isoquinoline, quinoline or pyridine, *N*-phenylcarbamates and dialkyl acetylenedicarboxylates under solvent-free condition and at r. t. The advantages of our work are that the reaction is performed under solvent-free and mild condition, without using a catalyst.

Experimental Section

General

^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker FT-500 spectrometer in $CDCl_3$, and tetramethylsilane (TMS) was used as an internal standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicolet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4 % of the calculated values. Acetylenic ester, isoquinoline, quinoline and pyridine were obtained from Fluka and were used without further purification.

*General procedure for the preparation of compounds **4a–f**, **7a–d** and **8***

To a magnetically stirred mixture of an *N*-phenylcarbamate **2** (2 mmol) and a dialkyl acetylenedicarboxylate **3** (2 mmol) was slowly added isoquinoline (**1**) (or quinoline or pyridine) (2 mmol), and the reaction mixture was stirred for 4 h at r. t. After completion of the reaction as indicated by TLC, the residue was purified by chromatography over silica gel (Merck, 230 – 400 mesh) using an *n*-hexane-AcOEt mixture (5 : 1) as eluant, to afford the pure adducts.

*Dimethyl 2-[1-[(propoxycarbonyl)anilino]-2(1H)-isoquinolin-2-yl]-2-butenedioate (**4a**)*

Yellow oil, yield: 0.67 g (75 %). – IR (KBr): ν = 1736 (C=O), 2980 (CH) cm^{-1}. – ^{1}H NMR: δ = 1.00 (t, ^3J = 7.1 Hz, CH_3), 1.73 (sixtet, ^3J = 7.2 Hz, CH_2), 3.70 (s, OCH_3), 3.83 (s, OCH_3), 4.16 (t, ^3J = 7.0 Hz, CH_2), 6.80 (s, CH), 7.08 (d, ^3J = 7.3 Hz, CH), 7.09 (d, ^3J = 7.3 Hz, CH), 7.32 – 7.50 (m, 10 CH) ppm. – ^{13}C NMR: δ = 11.0 (Me), 23.0 (CH_2), 51.5 (OMe), 52.0 (OMe), 67.6 (CH_2), 68.2 (CH), 93.6 (CH), 106.5 (CH), 118.6 (CH), 123.3 (CH), 123.7 (CH), 128.8 (2CH), 129.1 (2CH), 129.3 (CH), 132.4 (C), 136.3 (C), 138.1 (C), 140.5 (C), 154.8 (C=O), 163.8 (C=O), 167.8 (C=O) ppm. – EI-MS: $m/z(\%)$ = 450 (2) [M]$^+$, 435 (5), 407 (40), 391 (54), 363 (42), 307 (38). – Anal. for $C_{25}H_{26}N_2O_6$ (450.48): calcd. C 66.65, H 5.82; found C 66.66, H 5.84.

*Diethyl 2-[1-[(propoxycarbonyl)anilino]-2(1H)-isoquinolin-2-yl]-2-butenedioate (**4b**)*

Yellow oil, yield: 0.74 g (78 %). – IR (KBr): ν = 1734 (C=O), 2985 (CH) cm^{-1}. – ^{1}H NMR: δ = 1.02 (t, ^3J = 7.2 Hz, CH_3), 1.22 (t, ^3J = 7.1 Hz, CH_3), 1.24 (t, ^3J = 7.1 Hz, CH_3), 1.74 (sixtet, ^3J = 7.0 Hz, CH_3), 4.15 (q, ^3J = 7.1 Hz, CH_2), 4.16 (q, ^3J = 7.2 Hz, CH_2), 4.21 (t, ^3J = 7.0 Hz, CH_2), 6.81 (s, CH), 7.07 (d, ^3J = 7.3 Hz, CH), 7.09 (d, ^3J = 7.4 Hz, CH), 7.10 – 7.80 (m, 10CH) ppm. – ^{13}C NMR: δ = 10.1 (Me), 14.0 (Me), 14.1 (Me), 22.3 (CH_2), 61.1 (CH_2), 62.3 (CH_2), 66.8 (CH_2), 68.3 (CH), 93.8 (CH), 105.1 (CH), 118.6 (CH), 123.3 (CH), 124.0 (CH), 128.5 (2CH), 128.9 (2CH), 129.0 (CH), 132.5 (C), 136.3 (C), 138.0 (C), 138.1 (C), 154.8 (C=O), 163.8 (C=O), 167.8 (C=O) ppm. – EI-MS: $m/z(\%)$ = 478 (2) [M]$^+$, 449 (34), 405 (38), 391 (45), 307 (33). – Anal. for $C_{27}H_{30}N_2O_6$ (476.54): calcd. C 67.77, H 6.32; found C 66.73, H 6.34.

*Dimethyl 2-[1-[(isopropoxycarbonyl)anilino]-2(1H)-isoquinolin-2-yl]-2-butenedioate (**4c**)*

Yellow oil, yield: 0.72 g (80 %). – IR (KBr): ν = 1731 (C=O), 2982 (CH) cm^{-1}. – ^{1}H NMR: δ = 1.23 (d, ^3J = 6.7 Hz, CH_3), 1.30 (d, ^3J = 6.7 Hz, CH_3), 3.70 (s, OCH_3), 3.83 (s, OCH_3), 4.99 – 5.05 (m, CH), 6.80 (s, CH), 7.08 (d, ^3J = 7.3 Hz, CH), 7.09 (d, ^3J = 7.3 Hz, CH), 7.32 – 7.54 (m, 10CH) ppm. – ^{13}C NMR: δ = 21.8 (2Me), 52.0 (OMe), 53.1 (OMe), 68.2 (CH), 70.6 (CH), 94.0 (CH), 107.1 (CH), 118.5 (CH), 123.5 (CH), 128.8 (2CH), 129.1 (2CH), 129.2 (CH), 132.5 (C), 136.1 (C), 138.2 (C), 139.1 (C), 153.2 (C=O), 164.2 (C=O), 167.8 (C=O) ppm. – EI-MS: $m/z(\%)$ = 450 (2) [M]$^+$, 435 (5), 407 (40), 391 (54), 363 (42), 307 (38). – Anal. for $C_{25}H_{26}N_2O_6$ (450.50): calcd. C 66.65, H 5.82; found C 66.66, H 5.81.

*Diethyl 2-[1-[(isopropoxycarbonyl)anilino]-2(1H)-isoquinolin-2-yl]-2-butenedioate (**4d**)*

Yellow oil, yield: 0.76 g (80 %). – IR (KBr): ν = 1732 (C=O), 2984 (CH) cm^{-1}. – ^{1}H NMR: δ = 1.22 (d, ^3J = 6.3 Hz, CH_3), 1.24 (d, ^3J = 6.3 Hz, CH_3), 1.30 (t, ^3J = 6.5 Hz, CH_3), 1.34 (t, ^3J = 6.3 Hz, CH_3), 4.13 (q, ^3J = 6.5 Hz, CH_2), 4.26 (q, ^3J = 6.5 Hz, CH_2), 5.00 – 5.08 (m, CH), 6.80 (s, CH), 7.07 (d, ^3J = 7.3 Hz, CH), 7.09 (d, ^3J = 7.3 Hz, CH), 7.20 – 7.42 (m, 10 CH) ppm. – ^{13}C NMR: δ = 14.0 (Me), 14.1 (Me), 21.8 (2Me), 60.6 (CH_2), 61.1 (CH_2), 67.7 (CH), 70.6 (CH), 94.1 (CH), 106.2 (CH), 118.5 (CH), 123.2 (CH), 124.0 (CH), 128.5 (2CH), 129.0 (2CH), 129.2 (CH), 132.4 (C), 138.1 (C), 140.5 (C), 140.6 (C), 153.2 (C=O), 164.2 (C=O), 167.8 (C=O) ppm. – EI-MS: $m/z(\%)$ = 478 (2) [M]$^+$, 449 (34), 405 (35), 391 (46), 307 (38). – Anal. for $C_{27}H_{30}N_2O_6$ (478.54): calcd. C 67.77, H 6.32; found C 67.78, H 6.30.

*Dimethyl 2-[1-[(cyclohexoxycarbonyl)anilino]-2(1H)-isoquinolin-2-yl]-2-butenedioate (**4e**)*

Yellow oil, yield: 0.83 g (85 %). – IR (KBr): ν = 1734 (C=O), 2986 (CH) cm^{-1}. – ^{1}H NMR: δ = 1.60 – 1.65 (m, CH_2), 1.72 – 1.80 (m, 2CH_2), 1.94 – 2.00 (m, 2CH_2), 3.70 (s, OCH_3), 3.83 (s, OCH_3), 4.80 (m, CH), 6.80 (s, CH), 7.06 (d, ^3J = 7.3 Hz, CH), 7.08 (d, ^3J = 7.3 Hz, CH), 7.06 – 7.52 (m, 10 CH) ppm. – ^{13}C NMR: δ = 23.4 (2CH_2), 25.4

(CH_2), 32.0 ($2CH_2$), 52.0 (OMe), 53.1 (OMe), 73.7 (CH), 75.3 (CH), 94.1 (CH), 107.3 (CH), 118.5 (CH), 123.2 (CH), 124.2 (CH), 128.5 (2CH), 129.0 (2CH), 129.1 (CH), 132.4 (C), 136.3 (C), 138.5 (C), 139.2 (C), 153.1 (C=O), 164.2 (C=O), 166.7 (C=O) ppm. – EI-MS: $m/z(\%) = 490$ (2) $[M]^+$, 475 (5), 431 (25), 407 (35), 347 (38), 323 (38). – Anal. for $C_{28}H_{30}N_2O_6$ (490.55): calcd. C 68.56, H 6.16; found C 68.54, H 6.15.

*Diethyl 2-[1-[(cyclohexoxycarbonyl)anilino]-2(1H)-isoquinolin-2-yl]-2-butenedioate (**4f**)*

Yellow oil, yield: 0.81 g (78 %). – IR (KBr): $\nu = 1735$ (C=O), 2989 (CH) cm^{-1}. – ^1H NMR: $\delta = 1.31$ (t, $^3J = 6.3$ Hz, CH_3), 1.41 (t, $^3J = 6.9$ Hz, CH_3), 1.60 – 1.65 (m, CH_2), 1.72 – 1.80 (m, $2CH_2$), 1.94 – 2.00 (m, $2CH_2$), 4.11 (q, $^3J = 7.1$ Hz, CH_2), 4.22 (q, $^3J = 7.1$ Hz, CH_2), 4.77 – 4.80 (m, CH), 6.80 (s, CH), 7.07 (d, $^3J = 7.3$ Hz, CH), 7.09 (d, $^3J = 7.3$ Hz, CH), 7.14 – 7.65 (m, 10 CH) ppm. – ^{13}C NMR: $\delta = 23.4$ ($2CH_2$), 25.3 (CH_2), 31.0 ($2CH_2$), 61.0 (CH_2), 62.2 (CH_2), 66.6 (CH), 70.6 (CH), 94.0 (CH), 106.3 (CH), 118.7 (CH), 123.3 (CH), 124.0 (CH), 128.5 (2CH), 129.0 (2CH), 129.1 (CH), 132.0 (C), 136.1 (C), 138.4 (C), 139.0 (C), 153.1 (C=O), 164.2 (C=O), 166.8 (C=O) ppm. – EI-MS: $m/z(\%) = 518$ (2) $[M]^+$, 489 (5), 445 (35), 391 (38). – Anal. for $C_{30}H_{34}N_2O_6$ (518.60): calcd. C 69.48, H 6.61; found C 69.47, H 6.62.

*Dimethyl 2-[1-[(butoxycarbonyl)anilino]-2(1H)-quinolin-2-yl]-2-butenedioate (**7a**)*

Yellow oil, yield: 0.74 g (80 %). – IR (KBr): $\nu = 1735$ (C=O), 2985 (CH) cm^{-1}. – NMR data for the major isomer (63 %): ^1H NMR: $\delta = 0.94$ (t, $^3J = 7.2$ Hz, CH_3), 1.52 – 1.54 (m, CH_2), 1.68 – 1.71 (m, CH_2), 3.86 (s, OCH_3), 4.11 (s, OCH_3), 4.26 (t, $^3J = 6.9$ Hz, CH_2), 6.80 (s, CH), 7.10 – 7.33 (m, 11 CH) ppm. – ^{13}C NMR: $\delta = 14.1$ (Me), 22.7 (CH_2), 31.5 (CH_2), 52.6 (OMe), 52.9 (OMe), 68.2 (CH_2), 103.9 (CH), 115.9 (CH), 119.2 (CH), 120.3 (CH), 124.2 (CH), 127.0 (2CH), 127.1 (C), 127.3 (CH), 128.0 (2CH), 131.0 (CH), 132.3 (CH), 136.8 (C), 138.9 (C), 145.6 (C), 154.5 (C=O), 164.2 (C=O), 166.4 (C=O) ppm. – NMR data for the minor isomer (37 %): ^1H NMR: $\delta = 0.92$ (t, $^3J = 7.2$ Hz, CH_3), 1.54 – 1.57 (m, CH_2), 1.72 – 1.74 (m, CH_2), 3.95 (s, OCH_3), 4.00 (s, OCH_3), 4.02 (t, $^3J = 6.8$ Hz, CH_2), 7.01 (s, CH), 7.34 – 7.83 (m, 11 CH) ppm. – ^{13}C NMR: $\delta = 14.0$ (Me), 23.0 (CH_2), 31.4 (CH_2), 52.9 (OMe), 53.1 (OMe), 68.5 (CH_2), 104.0 (CH), 116.1 (CH), 119.3 (CH), 120.5 (CH), 124.3 (CH), 127.2 (2CH), 127.3 (C), 127.5 (CH), 128.1 (2CH), 131.3 (CH), 132.6 (CH), 137.0 (C), 140.1 (C), 145.9 (C), 154.6 (C=O), 164.3 (C=O), 166.7 (C=O) ppm. – EI-MS: $m/z(\%) = 464$ (2) $[M]^+$, 449 (5), 405 (35), 321 (15), 363 (38). – Anal. for $C_{26}H_{28}N_2O_6$ (464.51): calcd. C 67.23, H 6.08; found C 67.25, H 6.06.

*Diethyl 2-[1-[(isopropoxycarbonyl)anilino]-2(1H)-quinolin-1-yl]-2-butenedioate (**7b**)*

Yellow oil, yield: 0.74 g (78 %). – IR (KBr): $\nu = 1734$ (C=O), 2986 (CH) cm^{-1}. – ^1H NMR: $\delta = 1.23$ (d, $^3J = 6.5$ Hz, CH_3), 1.24 (d, $^3J = 6.5$ Hz, CH_3), 1.32(t, $^3J = 6.5$ Hz, CH_3), 1.34 (t, $^3J = 6.5$ Hz, CH_3), 4.15 (q, $^3J = 6.9$ Hz, CH_2), 4.27 (q, $^3J = 6.9$ Hz, CH_2), 5.01 – 5.06 (m, CH), 6.78 (s, CH), 7.07 (d, $^3J = 7.3$ Hz, CH), 7.09 (d, $^3J = 7.3$ Hz, CH), 7.00 – 7.28 (m, 11 CH) ppm. – ^{13}C NMR: $\delta = 13.9$ (Me), 14.0 (Me), 21.5 (2Me), 60.4 (CH_2), 61.0 (CH_2), 67.8 (CH), 68.7 (CH), 108.0 (CH), 115.9 (CH), 119.1 (CH), 120.1 (CH), 124.0 (CH), 126.9 (2CH), 127.1 (C), 127.3 (CH), 127.9 (2CH), 130.9 (CH), 132.5 (CH), 136.5 (C), 138.9 (C), 145.5 (C), 154.3 (C=O), 164.0 (C=O), 166.0 (C=O) ppm. – EI-MS: $m/z(\%) = 478$ (2) $[M]^+$, 449 (5), 405 (40), 391 (54), 307 (38). – Anal. for $C_{27}H_{30}N_2O_6$ (478.54): calcd. C 67.77, H 6.32; found C 67.76, H 6.31.

*Diethyl 2-[1-[(propoxycarbonyl)anilino]-2(1H)-quinolinyl]-2-butenedioate (**7c**)*

Yellow oil, yield: 0.81 g (85 %). – IR (KBr): $\nu = 1732$ (C=O), 2983 (CH) cm^{-1}. – ^1H NMR: $\delta = 1.43$ (t, $^3J = 6.3$ Hz, CH_3), 1.44 (t, $^3J = 6.2$ Hz, CH_2), 1.46 (t, $^3J = 6.2$ Hz, CH_2), 1.64 (sixtet, $^3J = 6.4$ Hz, CH_2), 4.42 (t, $^3J = 6.2$ Hz, CH_2), 4.43 (q, $^3J = 6.3$ Hz, CH_2), 4.46 (q, $^3J = 6.2$ Hz, CH_2), 5.33 (s, CH), 7.25 (d, $^3J = 7.5$ Hz, CH), 7.38 – 7.80 (m, 10 CH), 9.40 (d, $^3J = 7.5$ Hz, CH) ppm. – ^{13}C NMR: $\delta = 11.0$ (Me), 14.1 (Me), 14.2 (Me), 19.1 (CH_2), 61.1 (CH_2), 61.7 (CH_2), 64.8 (CH_2), 68.2 (CH), 108.0 (CH), 115.9 (CH), 119.1 (CH), 120.1 (CH), 124.0 (CH), 126.9 (2CH), 127.1 (C), 127.3 (CH), 127.9 (2CH), 130.9 (CH), 132.5 (CH), 136.5 (C), 138.9 (C), 145.5 (C), 154.3 (C=O), 164.0 (C=O), 166.0 (C=O) ppm. – EI-MS: $m/z(\%) = 478$ (2) $[M]^+$, 449 (34), 405 (38), 391 (45), 307 (33). – Anal. for $C_{27}H_{30}N_2O_6$ (476.54): calcd. C 67.77, H 6.32; found C 66.76, H 6.33.

*Diethyl 2-[1-[(ethoxycarbonyl)anilino]-2(1H)-quinolin-1-yl]-2-butenedioate (**7d**)*

Yellow oil, yield: 0.78 g (85 %). – IR (KBr): $\nu = 1735$ (C=O), 2982 (CH) cm^{-1}. – ^1H NMR: $\delta = 1.23$ (t, $^3J = 6.3$ Hz, CH_3), 1.30 (t, $^3J = 6.3$ Hz, CH_3), 1.31 (t, $^3J = 6.3$ Hz, CH_3), 4.14 (q, $^3J = 7.1$ Hz, CH_2), 4.16 (q, $^3J = 7.1$ Hz, CH_2), 4.93 (q, $^3J = 7.1$ Hz, CH_2), 6.82 (s, CH), 7.04 – 7.30 (m, 11 CH) ppm. – ^{13}C NMR: $\delta = 14.0$ (Me), 14.5 (Me), 14.7 (Me), 59.3 (CH_2), 60.0 (CH_2), 60.1 (CH_2), 68.2 (CH_2), 68.9 (CH), 108.0 (CH), 115.9 (CH), 119.1 (CH), 120.1 (CH), 124.0 (CH), 126.9 (2CH), 127.1 (C), 127.3 (CH), 127.9 (2CH), 130.9 (CH), 132.5 (CH), 136.5 (C), 138.9 (C), 145.5 (C), 154.3 (C=O), 164.0 (C=O), 166.0 (C=O) ppm. – EI-MS: $m/z(\%) = 464$ (2) $[M]^+$, 435

(5), 391(60), 377 (38), 293 (38). – Anal. for $C_{26}H_{28}N_2O_6$ (464.51): calcd. C 67.22, H 6.07; found C 67.23, H 6.07.

*Dimethyl 2-[1-[(butoxycarbonyl)anilino]-2(1H)-pyridin-1-yl]-2-butenedioate (**8a**)*

Yellow oil, yield: 0.74 g (90 %). – IR (KBr): ν = 1732 (C=O), 2986 (CH) cm^{-1}. NMR data for the major isomer (63 %): ^{1}H NMR: $\delta = 0.93$ (t, $^3J = 7.2$ Hz, CH_3), 1.45 – 1.49 (m, CH_2), 1.58 – 1.62 (m, CH_2), 3.67 (s, OCH_3), 3.98 (s, OCH_3), 4.13 (t, $^3J = 6.8$ Hz, CH_2), 6.80 (s, CH), 7.16 – 7.38 (m, 10 CH) ppm. – ^{13}C NMR: δ = 14.1 (Me), 19.0 (CH_2), 31.4 (CH_2), 51.7 (OMe), 53.0 (OMe), 64.6 (CH_2), 67.4 (CH), 104.1 (CH), 106.6 (CH), 119.1 (CH), 124.0 (CH), 125.9 (CH), 128.1 (2CH), 129.8 (2CH), 135.1(C), 148.0 (CH), 152.9 (C=O), 161.0 (C=O), 164.4 (C=O) ppm. NMR data for the minor isomer (37 %): ^{1}H NMR: $\delta = 0.91$ (t, $^3J = 7.2$ Hz, CH_3), 1.49 – 1.53 (m, CH_2), 1.63 – 1.64 (m, CH_2), 3.68 (s, OCH_3), 3.83 (s, OCH_3), 4.19 (t, $^3J = 6.8$ Hz, CH_2), 7.10 (s, CH), 7.40 – 7.58 (m, 10CH) ppm. – ^{13}C NMR: δ = 13.7 (Me), 19.2 (CH_2), 31.9 (CH_2), 52.0 (OMe), 53.1 (OMe), 64.9 (CH_2), 66.6 (CH), 103.8 (CH), 105.9 (CH), 118.9 (CH), 123.8 (CH), 125.7 (CH), 128.5 (2CH), 129.3 (2CH), 134.9 (C), 147.7 (CH), 152.1 (C=O), 164.9 (C=O), 165.6 (C=O) ppm. – EI-MS: $m/z(\%) = 414$ (2) $[M]^+$, 399 (5), 355 (35), 327 (38). – Anal. for $C_{22}H_{26}N_2O_6$ (414.45): calcd. C 63.76, H 6.32; found C 67.78, H 6.34.

[1] P. T. Anastas, J. C. Warner, *Green Chemistry*, Oxford University Press, Oxford **1998**.
[2] K. W. Bentley, *Nat. Prod. Rep.* **2001**, *18*, 148.
[3] J. P. Michael, *Nat. Prod. Rep.* **2002**, *19*, 742.
[4] E. Pop, W. M. Wu, E. Shek, N. Bodor, *J. Med. Chem.* **1989**, *32*, 1774.
[5] M. M. Sheha, N. A. A El-Koussi, H. Farag, *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 47.
[6] E. Lukevics, I. Segal, A. Zablotskaya, S. Germane, *Molecules* **1997**, *2*, 180.
[7] B. E. Maryanoff, D. F. McComsey, J. F. Gardocki, R. P. Shank, M. J. Costanzo, S. O. Nortey, C. R. Schneider, P. E. Setler, *J. Med. Chem.* **1987**, *30*, 1433.
[8] K. L. Sorgi, C. A. Maryanoff, D. F. McComsey, D. W. Graden, B. E. Maryanoff, *J. Am. Chem. Soc.* **1990**, *112*, 3567.
[9] H. J. Knjlker, S. Agarwal, *Tetrahedron Lett.* **2005**, *46*, 1173.
[10] J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669.
[11] M. Nassiri, R. Heydari, N. Hazeri, S. M. Habibi-Khorassani, M. Maghsoodlou, F. J. Milani, *Arkivoc* **2010**, 61.
[12] M. Nassiri, R. Heydari, N. Hazeri, S. M. Habibi-Khorassani, M. Maghsoodlou, F. J. Milani, *J. Chem. Res.* **2010**, *34*, 365.