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SELECTIVE 1,2- VS 1,4-ADDITION OF *N*-ARYLPHOSPHAZENES TO β,γ-UNSATURATED α-KETOESTERS. SYNTHESIS OF QUINOLINECARBOXYLATES[#]

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Abstract – Selective conjugate reaction (1,4-addition) of *N*-arylphosphazenes derived from triphenylphosphine to α,β-unsaturated carbonyl compounds yielded 2-quinolinecarboxylates. However, when more reactive phosphazene species derived from trimethylphosphine were used, selective reaction with the carbonyl carbon (1,2-addition) occurred and *N*-aryl-1-azadienes were obtained. Thermal 6π-azaelectrocyclization of these 1-azadienes afforded 4-quinolinecarboxylates.

INTRODUCTION

Quinoline ring systems have been a subject of interest during the last 120 years due to its wide occurrence in natural products, frequently showing biological activity.[1] Since the XVII century the quinoline derived alkaloid quinine (**I**) has been widely used to combat malaria and in the XX century quinine (**I**) was replaced by its stereoisomer quinidine (**II**), which nowadays has been substituted by the more efficient synthetic alkaloids chloroquine (**III**), quinacrine, or primaquine.

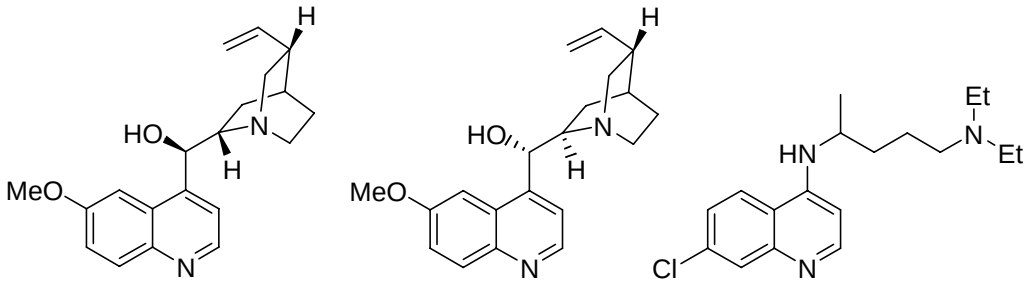
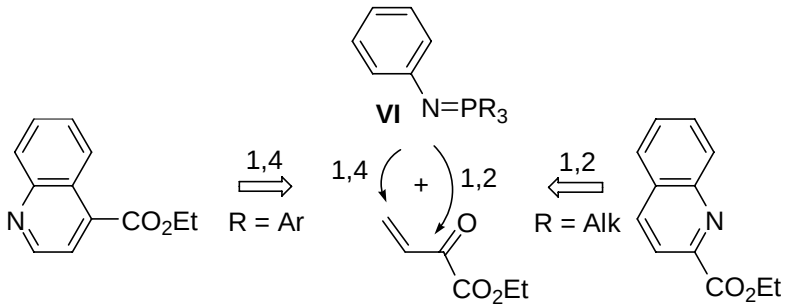


Figure 1. Quinoline derived antimalarial alkaloids.

[#] Dedicated to Prof. Steven M. Weinreb on the occasion of his 65th Birthday.

Moreover, besides the antimalarial[2] applications, a large variety of quinolines have displayed other potent pharmaceutical properties such as anti-inflammatory,[3a] antiasthmatic,[3b] antibacterial,[3c] antihypertensive,[3d] or for the treatment of tuberculosis[3e] or Parkinson's disease[3f] and a substantial number of molecules owning quinoline ring structures have been extensively used as general building blocks in organic synthesis.[4] There are numerous methods for the preparation of quinolines. Most of the classical syntheses, developed in the latter XIX century, are based in reactions between amines and carbonyl compounds,[5] but these methods only tolerate access to quinolines with low diversity in the substituents and more recently a huge branch of more versatile synthesis have been developed.[6]

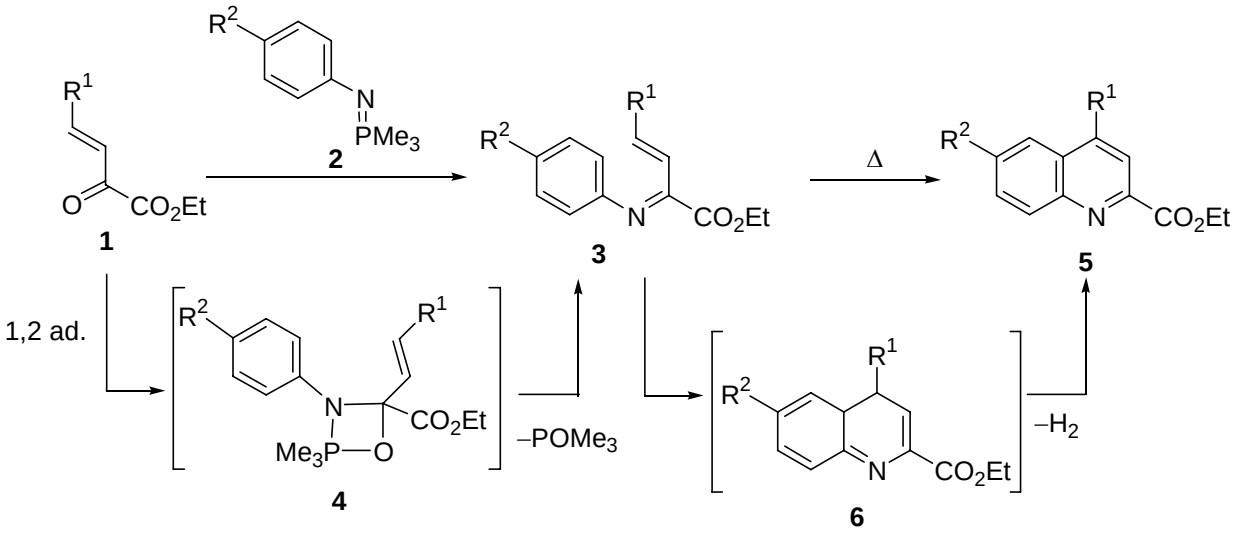
In this context, we have reported the synthesis 4-aminoquinolines[7] from enamines and isocyanates as well as of phosphorylated quinolines[8] from arylamines and functionalized carbonyl compounds and continuing with our interest in the synthesis and reactivity of six membered heterocycles and especially of quinolines, we report here the preparation of quinolinecarboxylates (**IV**) and (**V**), which are selectively generated either by 1,4- or 1,2-addition of *N*-aryl (R = Ar) or *N*-alkyl (R = Alk) phosphazenes (**VI**) to α,β-unsaturated carbonylic compounds (**VII**) (Scheme 1).



Scheme 1. Retrosynthesis of quinolines (**IV)** and (**V**).

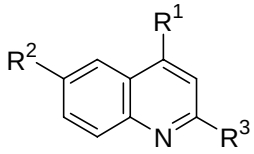
RESULTS AND DISCUSSION

Recently, we reported the synthesis of 1-azadienes derived from α-amino acids through aza-Wittig reaction of *N*-arylphosphazenes with β,γ-unsaturated α-ketoesters.[9] The preparation of 1-azadienes derived from α-amino acids (**3**) is assumed to occur trough nucleophilic 1,2-addition of *N*-aryl *P*-trimethylphosphazenes (**2**) to α,β-unsaturated carbonyl compounds (**1**), formation of a 4-membered oxazaphosphetane intermediates (**4**), and subsequent elimination of phosphine oxide in a typical aza-Wittig reaction mechanism[10] (Scheme 2). These heterodienes (**3**) can be used for the preparation of functionalized quinolines. Thus, when *N*-aryl 1-azadienes (**3**) were heated, quinoline-carboxylates (**5**) were obtained in good yields (Scheme 2, Table 1, Entries 1-2 and 5-6).



Scheme 2. Synthesis of 2-quinolinecarboxylates from *N*-aryl-1-azadienes (**1**).

Table 1. Quinolines (**5**) and (**10**) synthesized.



Entry	Comp	R^1	R^2	R^3	% Yield	
					1,2-ad[a]	1,4-ad[b]
1	**5a**	*p*-NO_2-C_6H_4	Me	CO_2Et	83	-
2	**5b**	*p*-NO_2-C_6H_4	MeO	CO_2Et	85	-
3	**10a**	CO_2Et	Me	*p*-NO_2-C_6H_4	-	79
4	**10b**	CO_2Et	MeO	*p*-NO_2-C_6H_4	-	79
5	**5c(10c)**	CO_2Et	Me	CO_2Et	80	83
6	**5d(10d)**	CO_2Et	MeO	CO_2Et	79	83

(a) From 1-azadienes (**3**); (b) From β,γ-unsaturated α-ketoesters (**1**).

Quinolines (**5**) were fully characterized by ^{1}H NMR, ^{13}C NMR, EIMS and IR spectroscopy. Characteristic signals for quinoline (**5a**) in ^{1}H and ^{13}C NMR spectra were assigned on the basis of COSY, DEPT and HETCOR experiments. ^{1}H NMR spectrum shows two doublets at δ = 8.31 and 7.70 ppm with a coupling constant $^3J_{HH}$ = 8.6 Hz, corresponding respectively to the aromatic H-8 and H-7 of the quinoline ring and other two singlets at δ = 8.09 ppm for H-3 and δ = 7.54 ppm for H-5. ^{13}C NMR spectrum shows four signals for the CH of the quinoline ring at δ = 132.7, 131.1, 123.5 and 121.1 ppm, corresponding to C-7, C-8, C-5 and C-3, respectively, as well as three signals for the three substituted quaternary carbons at δ = 146.9, 144.2, and 139.8 for C-2, C-4 and C-6, respectively. 2D NMR

experiments were carried out with quinoline (**5a**) in order to determine unambiguously the position of the substituents in the quinoline ring. For quinoline (**5a**) a correlation was observed between the aromatic CH of the *p*-NO_2-C_6H_4 substituent and the C-4 in the ring (Figure 2, *vide infra*). Formation of these quinolines (**5**) derived from α-amino esters can be explained through 6π-azaelectrocyclization[11] of azadienes (**3**) followed by spontaneous oxidation of the resulting dihydroquinoline intermediate (**6)** (Scheme 2, *vide supra*).

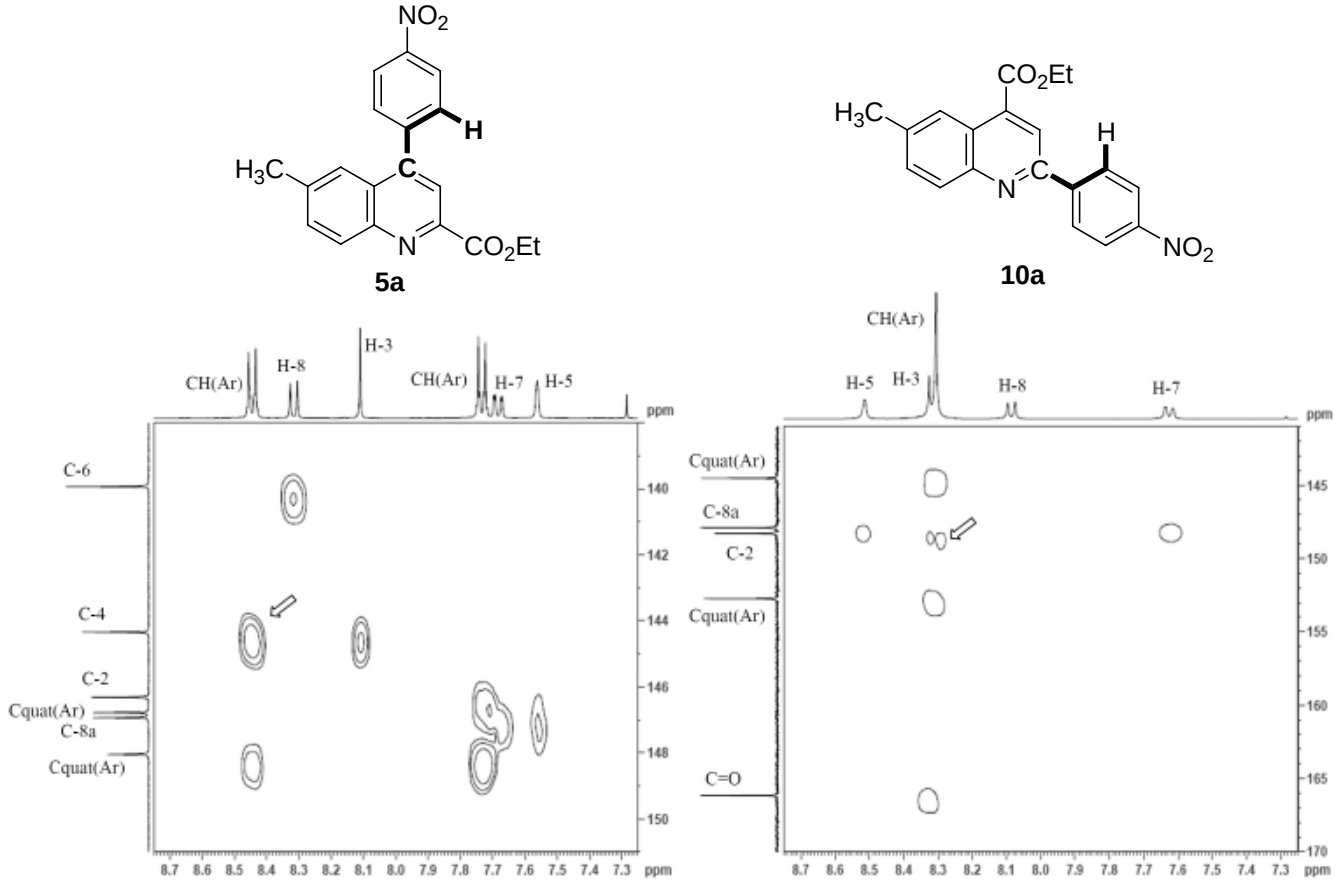
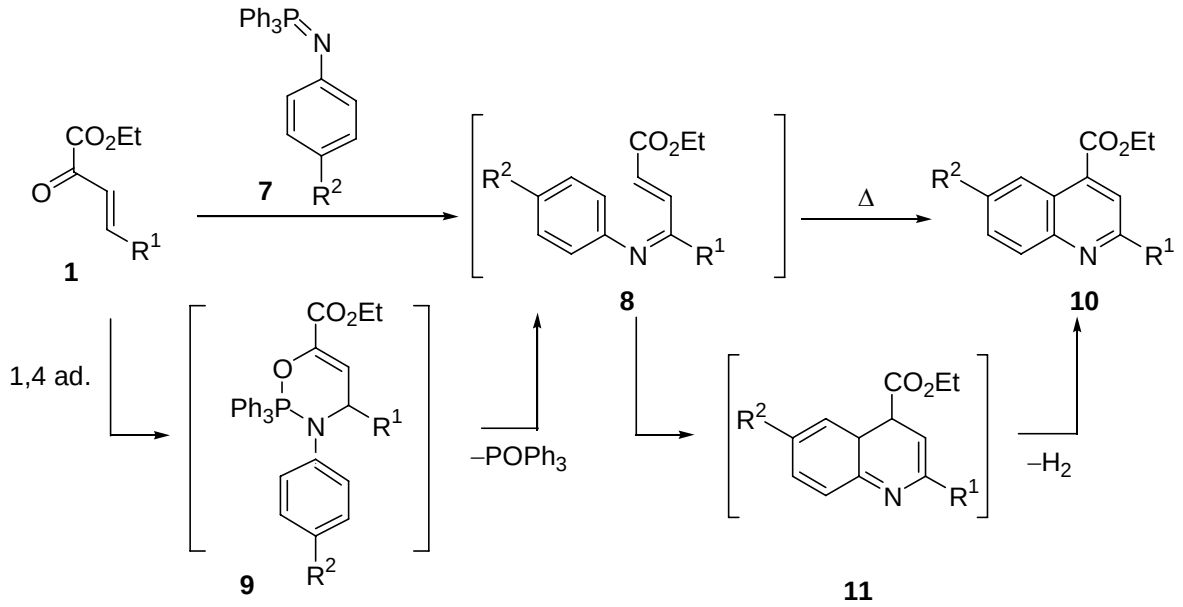


Figure 2. HMBC correlations for quinolines (**5a**) and (**10a**).

These results prompted us to explore, whether quinolines with the carboxylic group in position 4 could be also obtained from carbonyl derivative (**1**) and other phosphazenes, since the reactivity of phosphazenes as nucleophiles decreases when they are derived from trialkylphosphine, dialkylarylphosphine, alkyldiarylphosphine or triarylphosphine.[10] Thus, no reaction of *N*-aryl *P*-triphenylphosphazene (**7**) with functionalized carbonyl compound (**1**) (R^1 = *p*-NO_2-C_6H_4) was observed at room temperature. However, when α-ketoesters (**1**) and *N*-aryl *P*-triphenylphosphazene (**7**) were heated in refluxing chloroform, quinolines (**10**) were obtained in good yields (Scheme 3, Table 1, Entries 3-6). Quinolines (**10**) were characterized by ^{1}H NMR, ^{13}C NMR, EIMS and IR spectroscopy. 2D-NMR experiments were also carried out with quinoline (**10a**) and the correlation between the *p*-NO_2-C_6H_4 substituent and C-2 of the

quinoline ring was observed (Figure 2, *vide supra*), which is consistent with proposed structure for 4-quinolinecarboxylate (**10a**). The regioselective preparation of quinolines (**10**) could be explained by initial formation of the 6-membered oxazaphosphetane (**9**) through 1,4-addition of the phosphazene species (**7**) to the α,β-unsaturated carbonylic compound (**1**) and elimination of phosphine oxide to afford the non isolated 1-azadiene (**8**) and subsequent 6π-azaelectrocyclization with spontaneous oxidation of the dihydroquinoline intermediate (**11**) to yield quinolines (**10**).



Scheme 3. Synthesis of 4-quinoline-carboxylates from *N*-aryl phosphazenes (**7**) and ketoesters (**1**).

In conclusion, the results reported here involve an easy synthesis of substituted 2- and 4-quinolines. Thermal 6π-azaelectrocyclization of functionalized *N*-aryl 1-azadienes (**3**) gives 2-quinoline-carboxylates (**5**), while the addition of *N*-aryl *P*-triphenylphosphazenes (**7**) to α,β-unsaturated carbonyl compounds (**1**) affords 4-quinoline-carboxylates (**10**). 1,2- *versus* 1,4-addition of the phosphazene species to α,β-unsaturated ketones can be selectively performed by switching the methyl substituents by aryl substituents in the phosphazene group.

EXPERIMENTAL

General. Chemicals were purchased from Aldrich or Acros. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) spectra were recorded on

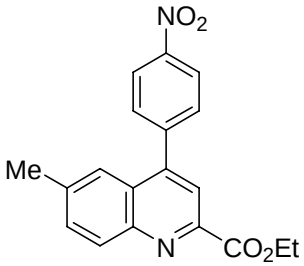
a Varian VXR 300 MHz spectrometer using $CDCl_3$ or CD_3OD solutions with TMS as an internal reference (δ = 0.00 ppm). Mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on a Hewlett Packard 5971 or 5973 spectrometer. Infrared spectra (IR) were taken on a Nicolet IRFT Magna 550 spectrometer, and were obtained as solids in KBr. Elemental analyses were performed in a LECO CHNS-932 apparatus. β,γ-unsaturated α-ketoesters (**1**)[12] and 1-azadienes (**3**)[9] were synthesized according to literature procedures.

General procedure for the synthesis of quinolines (5) and (10).

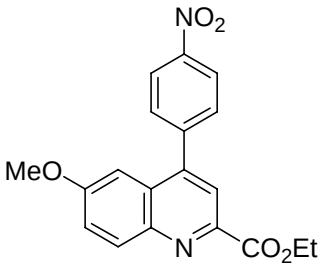
Procedure A: a solution of 1-azadiene (**3**) (1 mmol) in xylene (3 mL) was stirred and refluxed until TLC indicated the disappearance of the starting material (24 to 48 h.). The resulting solution was concentrated under reduced pressure and the crude residue was purified by crystallization from Et_2O.

Procedure B: a solution of β,γ-unsaturated α-keto ester (**1**) (1 mmol) and the corresponding *N*-aryl phosphazene derived from triphenylphosphine (**7**) (1 mmol) in $CHCl_3$ (3 mL) was stirred and refluxed until TLC indicated the disappearance of the carbonylic compound (**1**) (24 to 48 h.). The solvent was then removed under reduced pressure and the crude residue was purified by chromatography (SiO_2, AcOEt / hexanes 1:3).

2-Ethoxycarbonyl-6-methyl-4-*p*-nitrophenylquinoline (5a): Synthesized according to the general procedure A with ethyl 4-*p*-nitrophenyl-2-*p*-tolylimino-(*E*)-3-butenoate (338 mg, 1 mmol), affording 303 mg (83 %) of **5a** as a yellow solid. mp 203–204 ºC (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.43 (d, $^3J_{HH}$ = 7.2 Hz, 2 H, 2 CH_{ar}), 8.31 (d, $^3J_{HH}$ = 8.6 Hz, 1 H, CH_{quin}), 8.09 (s, 1 H, CH_{quin}), 7.72 (d $^3J_{HH}$ = 7.2 Hz, 2 H, 2 CH_{ar}), 7.70 (d, $^3J_{HH}$ = 8.6 Hz, 1 H, CH_{quin}), 7.54 (s, 1 H, CH_{quin}), 4.58 (q, $^3J_{HH}$ = 7.0 Hz, 2 H, CH_2O), 2.51 (s, 3 H, CH_3), 1.50 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.2 (C=O), 148.0 (C_{quat}), 146.9 (C_{quat}), 146.7 (C_{quat}), 146.2 (C_{quat}), 144.2 (C_{quat}), 139.8 (C_{quat}), 132.7 (CH), 131.1 (CH), 130.5 (2 CH), 126.9 (C_{quat}), 123.8 (2 CH), 123.5 (CH), 121.1 (CH), 62.3 (CH_2O), 22.0 (CH_3), 14.3 (CH_3). FTIR (KBr): ν_{max} (cm^{-1}): 1722 (C=O st. ester). EIMS m/z (amu): 336 (M^+, 3), 264 ($M^+ - CO_2Et$, 100). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C 67.85, H 4.79, N 8.33. Found: C 67.80, H 4.83, N 8.27.



2-Ethoxycarbonyl-6-methoxy-4-*p*-nitrophenylquinoline (5b): Synthesized according to the general procedure A with ethyl 2-*p*-methoxyphenylimino-4-*p*-nitrophenyl-(*E*)-3-butenoate (354 mg, 1 mmol), affording 311 mg (85 %) of **5b** as a yellow solid. mp 203–204 ºC (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.54 (d, $^3J_{HH}$ = 7.2 Hz, 2 H, 2 CH_{ar}), 8.53 (d, $^3J_{HH}$ = 8.5 Hz, 1 H, CH_{quin}), 8.28 (s, 1 H, CH_{quin}), 7.74 (d $^3J_{HH}$ = 7.2 Hz, 2 H, 2 CH_{ar}), 7.75 (d, $^3J_{HH}$ = 8.5 Hz, 1 H, CH_{quin}), 7.32 (s, 1 H, CH_{quin}), 4.54 (q, $^3J_{HH}$ = 7.0 Hz, 2 H, CH_2O), 3.91 (s, 3 H,



CH_3O), 1.47 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.0 (C=O), 160.8 (C_{quat}), 148.1 (C_{quat}), 146.7 (C_{quat}), 146.5 (C_{quat}), 146.1 (C_{quat}), 144.0 (C_{quat}), 132.7 (CH), 131.2 (CH), 130.2 (2 CH), 126.5 (C_{quat}), 144.0 (2 CH), 123.4 (CH), 121.1 (CH), 62.2 (CH_2O), 56.0 (CH_3), 14.5 (CH_3). FTIR (KBr): ν_{max} (cm^{-1}): 1719 (C=O st. ester). EIMS m/z (amu): 352 (M^+, 66), 279 ($M^+ - CO_2Et$, 100). Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.80; H, 4.61; N, 7.98.

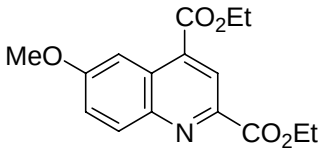
4-Ethoxycarbonyl-6-methyl-2-*p*-nitrophenylquinoline (10a): Synthesized according to the general procedure B with ethyl 4-*p*-nitrophenyl-2-oxo-3-butenoate (249 mg, 1 mmol) and *N*-(*p*-tolyl)-*P*,*P*,*P*-triphenylphosphine imide (440 mg, 1.2 mmol), affording 272 mg (79 %) of **10a** as a yellow solid. mp 163–164 ºC (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.50 (s, 1 H, CH_{quin}), 8.32–8.28 (m, 5 H, 2 CH_{ar} + CH_{quin}), 8.08 (d, $^3J_{HH}$ = 8.7 Hz, 1 H, CH_{quin}), 7.61 (dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 1.7 Hz, 1 H, CH_{quin}), 4.53 (q, $^3J_{HH}$ = 7.2 Hz, 2 H, CH_2O), 2.57 (s, 3 H, CH_3), 1.49 (t, $^3J_{HH}$ = 7.2 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.9 (C=O), 152.4 (C_{quat}), 148.1 (C_{quat}), 147.7 (C_{quat}), 144.2 (C_{quat}), 139.0 (C_{quat}), 135.5 (C_{quat}), 132.4 (CH), 130.0 (CH), 127.7 (2 CH), 124.3 (C_{quat}), 124.2 (CH), 123.7 (2 CH), 119.5 (CH), 61.9 (CH_2O), 22.1 (CH_3), 14.2 (CH_3). FTIR (KBr) ν_{max} (cm^{-1}): 1716 (C=O st. ester). EIMS m/z (amu): 336 (M^+, 100), 263 ($M^+ - CO_2Et$, 55). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C 67.85, H 4.79, N 8.33. Found: C 67.89, H 4.74, N 8.28.

4-Ethoxycarbonyl-6-methoxy-2-*p*-nitrophenylquinoline (10b): Synthesized according to the general procedure B with ethyl 4-*p*-nitrophenyl-2-oxo-3-butenoate (249 mg, 1 mmol) and *N*-(*p*-methoxyphenyl)-*P*,*P*,*P*-triphenylphosphine imide (460 mg, 1.2 mmol), affording 281 mg (79 %) of **10b** as a yellow solid. mp 163–164 ºC (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 1 H, CH_{quin}), 8.35–8.23 (m, 5 H, 4 CH_{ar} + CH_{quin}), 8.00 (d, $^3J_{HH}$ = 8.7 Hz, 1 H, CH_{quin}), 7.73 (dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 1.7 Hz, 1 H, CH_{quin}), 4.58 (q, $^3J_{HH}$ = 7.2 Hz, 2 H, CH_2O), 3.96 (s, 3 H, CH_3O), 1.46 (t, $^3J_{HH}$ = 7.2 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.7 (C=O), 161.0 (C_{quat}), 152.2 (C_{quat}), 148.2 (C_{quat}), 147.5 (C_{quat}), 144.0 (C_{quat}), 135.5 (C_{quat}), 132.4 (CH), 129.8 (CH), 127.5 (2 CH), 124.4 (C_{quat}), 124.0 (CH), 123.7 (2 CH), 119.4 (CH), 61.8 (CH_2O), 54.9 (CH_3O), 14.2 (CH_3). FTIR (KBr) ν_{max} (cm^{-1}): 1716 (C=O st. ester). EIMS m/z (amu): 352 (M^+, 100), 279 ($M^+ - CO_2Et$, 45). Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.73; H, 4.54; N, 7.92.

2,4-Diethoxycarbonyl-6-methylquinoline (5c/10c): Synthesized according to the general procedure A with ethyl 4-ethoxycarbonyl-4-*p*-tolylimino-(*E*)-2-butenoate (289 mg, 1 mmol), affording 234 mg (80 %) of **5c/10c** as a white solid. Synthesized according to the general procedure B with ethyl *(E)*-4-ethoxycarbonyl-4-oxo-2-butenoate (200 mg, 1 mmol) and *N*-(*p*-tolyl)-*P*,*P*,*P*-triphenylphosphine imide (440 mg, 1.2 mmol), affording 243

mg (83 %) of **5c/10c** as a white solid. mp 109–110 ºC (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.57 (s, 1 H, CH_{quin}), 8.55 (d, $^4J_{HH}$ = 1.8 Hz, 1 H, CH_{quin}), 8.19 (d, $^3J_{HH}$ = 8.7 Hz, 1 H, CH_{quin}), 7.62 (dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 1.8 Hz, 1 H, CH_{quin}), 4.53 (q, $^3J_{HH}$ = 7.0 Hz, 2 H, CH_2O), 4.49 (q, $^3J_{HH}$ = 7.2 Hz, 2 H, CH_2O), 2.57 (s, 3 H, CH_3), 1.47 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, CH_3), 1.45 (t, $^3J_{HH}$ = 7.2 Hz, 3 H, CH_3).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.9 (C=O), 165.0 (C=O), 147.4 (C_{quat}), 146.8 (C_{quat}), 140.8 (C_{quat}), 135.5 (C_{quat}), 132.7 (CH), 131.0 (CH), 126.3 (C_{quat}), 124.3 (CH), 122.1 (CH), 62.4 (CH_2O), 62.0 (CH_2O), 22.3 (CH_3), 14.3 (CH_3), 14.2 (CH_3). FTIR (KBr) ν_{max} (cm^{-1}): 1719 (C=O st. ester). EIMS m/z (amu): 287 (M^+, 8), 214 ($M^+ - CO_2Et$, 100). Anal. Calcd for $C_{16}H_{17}NO_4$: C 66.89, H 5.96, N 4.88. Found: C 66.95, H 5.91, N 4.91.

2,4-Diethoxycarbonyl-6-methoxyquinoline (5d/10d): Synthesized according to the general procedure A with ethyl 4-ethoxycarbonyl-4-*p*-methoxyphenylimino-(*E*)-2-butenoate (305 mg, 1 mmol), affording 245 mg (79 %) of **5d/10d** as a white solid. Synthesized according to the general procedure B with ethyl *(E)*-4-ethoxycarbonyl-4-oxo-2-butenoate (200 mg, 1 mmol) and *N*-(*p*-methoxyphenyl)-*P*,*P*,*P*-triphenylphosphine imide (460 mg, 1.2 mmol), affording 252 mg (83 %) of **5d/10d** as a white solid. mp 112–113 ºC (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 1 H, CH_{quin}), 8.26 (d, $^4J_{HH}$ = 2.7 Hz, 1 H, CH_{quin}), 8.22 (d, $^3J_{HH}$ = 9.3 Hz, 1 H, CH_{quin}), 7.44 (dd, $^3J_{HH}$ = 9.3 Hz, $^4J_{HH}$ = 2.7 Hz, 1 H, CH_{quin}), 4.54 (q, $^3J_{HH}$ = 7.0 Hz, 2 H, CH_2O), 4.49 (q, $^3J_{HH}$ = 7.2 Hz, 2 H, CH_2O), 3.98 (s, 3 H, CH_3O), 1.48 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, CH_3), 1.47 (t, $^3J_{HH}$ = 7.2 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.9 (C=O), 165.1 (C=O), 160.9 (C_{quat}), 145.2 (C_{quat}), 144.9 (C_{quat}), 133.7 (C_{quat}), 132.8 (CH), 128.3 (C_{quat}), 123.8 (CH), 123.0 (CH), 103.0 (CH), 62.3 (CH_2O), 61.9 (CH_2O), 55.7 (CH_3O), 14.4 (CH_3), 14.3 (CH_3). FTIR (KBr) ν_{max} (cm^{-1}): 1712 (C=O st. ester) EIMS m/z (amu): 303 (M^+, 12), 230 ($M^+ - CO_2Et$, 100). Anal. Calcd for $C_{16}H_{17}NO_5$: C 63.36, H 5.65, N 4.62. Found: C 63.30, H 5.68, N 4.58.



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