Synthesis of Multisubstituted 1,4-Dihydrobenzoxazin-2-ones Through a One-pot Nucleophilic *N*-Alkylation/*C*-alkylation of Cyclic α-Iminoesters

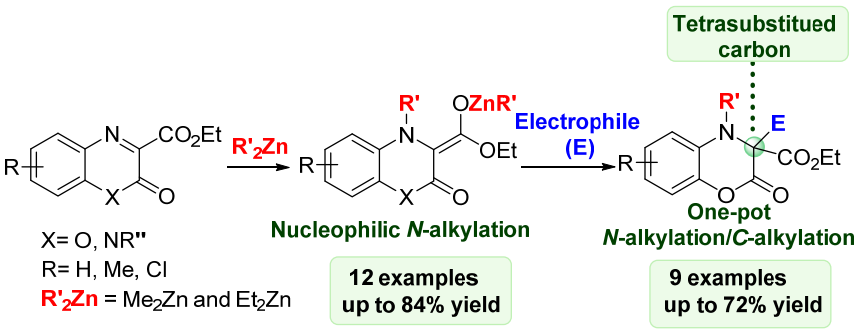
Lode De Munck[a]
Carlos Vila*[a]
Carolina Pons [a]
José R. Pedro*[a]

[a] Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 50, 46100 Burjassot, València (Spain)

carlos.vila@uv.es;

jose.r.pedro@uv.es

Click here to insert a dedication.



Received:
Accepted:
Published online:
DOI:

Abstract Herein we described a nucleophilic *N*-alkylation of 2-oxobenzoxazine-2-carboxylates with organozinc reagents with good selectivities and moderate to good yields. Moreover, the synthesis of multisubstituted 1,4-dihydrobenzoxazines-2-ones bearing a tetrasubstituted carbon atom is described via a one-pot *N*-alkylation/C-alkylation reactions

Key words dihydrobenzoxazinone, umpolung, zinc, tetrasubstituted carbon, one-pot reaction, cyclic α-iminoesters

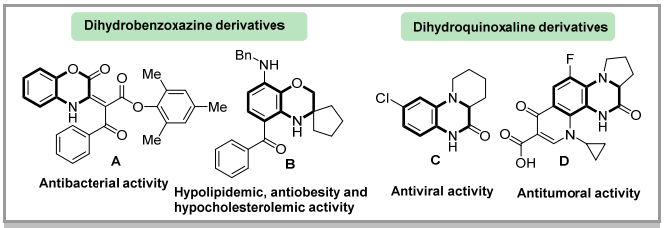
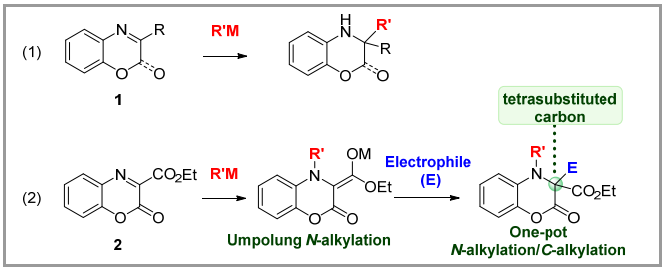


Figure 1 Biologically active dihydrobenzoxazine and dihydroquinoxaline derivatives

1,4-Benzoxazines derivatives are an important class of heterocyclic compounds present in numerous natural products, which have played crucial roles in the area of medicinal chemistry over the past decades because of their widespread range of biological and pharmaceutical activities.[1] Examples of dihydrobenzoxazine derivatives with biological activities are the compound **A** with antibacterial propierties[2] or the compound **B** that shows hypolipidemia, antiobesity and hypocholesterolemic activity.[3] A related skeleton is that of 1,4-quinoxaline which also exhibits important biological activities.[4] So compound **C** shows antiviral activity[5] and compound **D** presents antitumor activity.[6] Consequently, the synthesis of new 1,4-benzoxazine (and also 1,4-quinoxaline) derivatives has been and continues to be attracting the attention of synthetic organic chemists and medicinal chemists.

Traditional methods for building the skeleton of 1,4-benzoxazines and 1,4-quinoxalines use 2-nitrophenols, 2-aminophenols or benzene-1,2-diamines as starting materials,[7] although recently several transition-metal catalysed reactions have been described.[8] Alternatively the modification of substituents on the 1,4-benzoxazines have been carried out, particularly by the addition of nucleophilic reagents to cyclic imines[9] (reaction 1, Scheme 1). We envisioned that the installation of one additional electron-withdrawing group at C-3 position as in **2** (Scheme 1) will lead to a highly polarized C=N double bond,[10,11] that could be considered as an efficient way to induce umpolung of the imine functionality. However, considering the system as a whole, it would be an α,β-unsaturated ester that would undergo conjugate addition at the nitrogen atom of the imine functionality. In any case it would be a nucleophilic alkylation at the nitrogen atom of the imine group. Moreover the intermediate metal enolate obtained in this nucleophilic *N*-alkylation reaction could experience a subsequent C-C bond formation by reaction with an alkylating reagent. In the literature,[12-15] several successfully examples for the regioselective *N*-alkylation of acyclic α-imino esters have been described by the groups of Shimizu,[13a-d,14a-i] Kozlowski,[13e-g] and others.[15] However, the *N*-alkylation of the cyclic α-imino esters such **2** has been scarcely studied, despite its synthetic

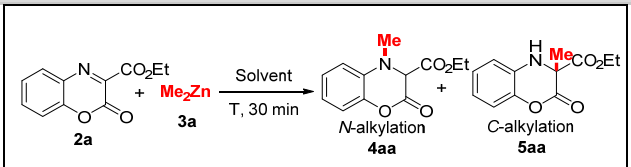
potential.[16,17] Herein, we present our efforts toward the nucleophilic *N*-alkylation of 2-oxobenzoxazine-2-carboxylates with organozinc reagents. Furthermore, we report the synthesis of multisubstituted 1,4-dihydrobenzoxazin-2-ones bearing a quaternary carbon atom by one-pot *N*-alkylation followed by a *C*-alkylation of the enolate produced with alkyl halides.



Scheme 1 Organometallic additions to benzoxazinone derivatives

Our studies began with the optimization of the reaction conditions for the *N*-alkylation step, using ethyl 2-oxo-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (**2a**) as a model substrate and Me_2Zn as the organozinc reagent. As shown in Table 1, we started the optimization process with the screening of various solvents (CH_2Cl_2, toluene and THF, entries 1-3) at room temperature, obtaining the best yield of the *N*-alkylation product **4aa** when CH_2Cl_2 was used. Next, different temperatures of Me_2Zn addition reaction were evaluated. The best yield of product **4aa** (66%) was obtained when Me_2Zn was added at 0 °C and then the reaction mixture was allowed to reach room temperature (entry 4).

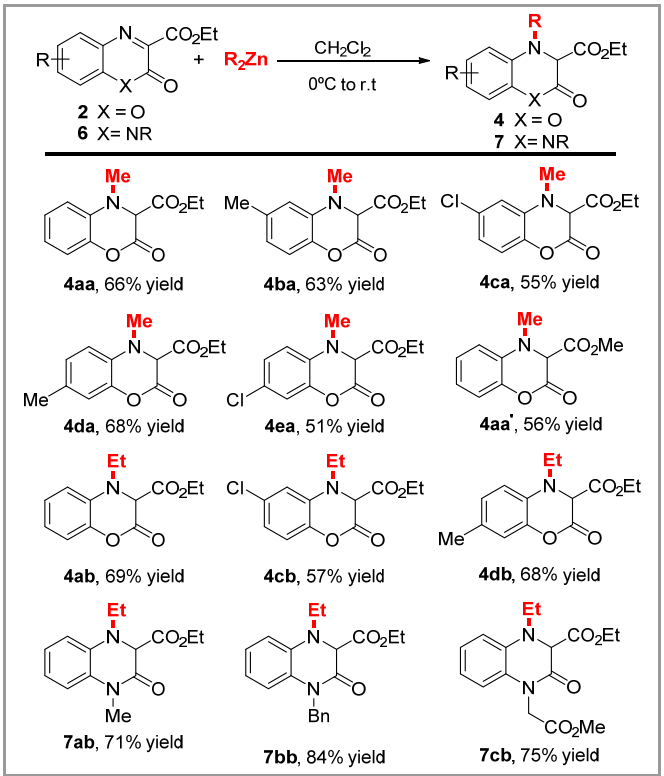
Table 1 Optimization of reaction conditions for the *N*-alkylation step.[a]



Entry	Me_2Zn	solvent	T (°C)	**4aa** (%)[b]	**5aa** (%)[b]
1	2 eq.	CH_2Cl_2	rt	60	5
2	2 eq.	toluene	rt	45	9
3	2 eq.	THF	rt	36	-
4	2 eq.	CH_2Cl_2	0°C to rt	66	10
5	2 eq.	CH_2Cl_2	-78°C to rt	54	7

[a] Reaction conditions:**2a** (0.15 mmol), **3a** 2M in toluene (0.30 mmol). [b] Yield after column chromatography.

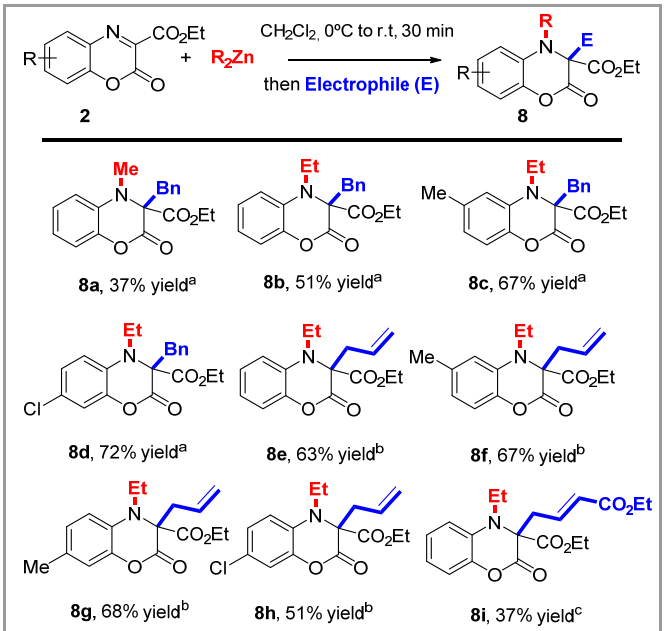
Under the best reaction conditions (Table 1, entry 4), the scope of the reaction was evaluated using differently substituted ethyl 2-oxo-benzoxazine-3-carboxylates **2** (Scheme 2). Electron-donating groups at the 6 or 7 positions of the arene ring of the benzoxazine, were well tolerated and the corresponding *N*-alkylated products **4ba** and **4da** were gained with good yields. However, when chlorine atoms were installed at position 6 or 7, the corresponding products were obtained with lower yields. When the reaction was quenched with MeOH, a transesterification reaction was observed and the corresponding methyl 4-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (**4aa'**) was obtained in 56% yield. After study of the *N*-alkylation with Me_2Zn, we tested the reaction with Et_2Zn. The corresponding *N*-alkylation products **4ab**, **4cb** and **4db**, were obtained with slightly better yields than when Me_2Zn was used as organometallic reagent. Very recently, Shimizu has developed the *N*-alkylation of quinoxaline derivatives with Grignard reagents.[16] Therefore, we also decided to examine the addition of dialkylzinc reagents to ethyl 3-oxo-3,4-dihydroquinoxaline-2-carboxylate derivatives **6** bearing different *N*-protecting groups such as methyl, benzyl or CH_2CO_2Me. When the reaction was performed with Et_2Zn,[18] the desired *N*-alkylated products **7ab**, **7bb** and **7cb** were obtained with good yields (71-84% yields).



Scheme 2 Scope of the *N*-alkylation reaction.

To increase the synthetic applicability of the *N*-alkylation of benzoxazines and quinoxaline derivatives, we attempted the alkylation of the enolates formed after the initial addition of the organozinc reagent. In this manner, a tandem *N*-alkylation/*C*-alkylation reaction would be possible for the one-pot three component coupling reaction providing dihydrobenzoxazine derivatives with a tetrasubstituted carbon atom. For this purpose, after the addition of the organozinc reagent, benzyl bromide or allyl bromide (5 equivalents) were added to quench the reaction mixture. The corresponding enolate generated after the addition of Et_2Zn was found more reactive than the one formed from Me_2Zn. The corresponding Et_2Zn-enolate was trapped with benzyl bromide, affording the corresponding product **8b** with 51% yield. On the other hand, product **8a**, obtained from Me_2Zn-enolate, was gained with lower yield (37%). The corresponding *N,C*-dialkylated products **8c** and **8d**, with different substitution pattern in the aromatic ring of the benzoxazine skeleton, were gained with better yields (67% and 72%, respectively). Furthermore, we tested allyl bromide as electrophile for trapping the enolate. The corresponding allyl

substituted products (**8e-8h**) were obtained with good yields. Our efforts for a tandem *N*-alkylation/*C*-alkylation reaction with quinoxaline derivatives were unsuccessful, due to the lack of reactivity of the corresponding zinc-quinoxaline enolate. Finally, when we tested ethyl (*E*)-4-iodobut-2-enoate as electrophile, poor conversion to compound **8i** was achieved. In order to increase the conversion we tried different additives, but all the attempts fail. Therefore, the α,β-unsaturated ester **8i** with a benzoxazine skeleton, was synthesized from the corresponding lithium enolate prepared from compound **4ab** and LDA in THF, and trapped with ethyl (*E*)-4-iodobut-2-enoate.



Scheme 3 Scope for the one-pot *N*-alkylation/*C*-alkylation reactions. [a] BnBr was used as electrophile. [b] AllylBr was used as electrophile. [c] Ethyl (*E*)-4-iodobut-2-enoate was used as electrophile

In summary, we have developed one-pot synthesis of multisubstituted dihydrobenzoxazin-2-ones using a tandem *N*-alkylation/C-alkylation process. The reaction proceeds through a nucleophilic addition of organozinc reagents to the nitrogen of the benzoxazine derivative. The resulting zinc-enolate can be trapped with electrophiles to form dihydrobenzoxazin-2-ones with a tetrasubstituted carbon atom with moderate to good yields. This methodology provides a straightforward procedure for the synthesis of a variety of pharmacologically and synthetically useful nitrogen heterocycles.

The experimental section has no title; please leave this line here.

Reactions were carried out under nitrogen in test tubes or round bottom flasks oven-dried overnight at 120 °C. Dicloromethane and toluene were distilled from CaH_2. THF was distilled from sodium benzophenone ketyl. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for ^1H and at 75 MHz for ^{13}C NMR using residual non-deuterated solvent as internal standard ($CHCl_3$: δ 7.26 and 77.0 ppm). Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a AB SCIEX Triple TOF™ spectrometer equipped with an electrospray source with a capillary voltage of 4.5 kV(ESI). Ethyl 2-oxo-2*H*-benzo[*b*][1,4]oxazine-3-carboxylates **2** and ethyl 3-oxo-3,4-dihydroquinoxaline-2-carboxylates **5** were prepared from the corresponding aminophenol or the corresponding benzene-1,2-diamine as described in the literature.[9i, 19]

Procedure for the nucleophilic *N*-alkylation of benzoxazinones

To a solution of benzoxazinone **2** (0.15 mmol) in dichloromethane (2 mL) at 0°C, a 2M Me_2Zn solution in toluene /1M Et_2Zn solution in hexanes **3** (0.3 mmol) is added dropwise under nitrogen atmosphere. After addition, the reaction is placed at room temperature and is stirred till completion (TLC, ±30 minutes). The reaction is quenched with aqueous solution of Rochelle salt (5 mL), extracted with dichloromethane (3x15 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting product is purified by flash column chromatography on silica (hexane:ethyl acetate), obtaining product **4**.

Ethyl 4-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (4aa)

Yield: 23.4 mg (66%); brown oil

IR (neat): 1769, 1683, 1502, 1282, 1200, 1013, 745 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.18 – 7.00 (m, 2H), 6.93 – 6.78 (m, 2H), 4.65 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.05 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 165.43 (C), 160.55 (C), 141.16 (C), 133.45 (C), 125.52 (CH), 120.16 (CH), 116.48 (CH), 112.94 (CH), 64.94 (CH), 62.36 (CH_2), 36.43 (CH_3), 13.9 (CH_3).

HRMS (ESI$^+$): m/z 236.0918 [M + H]$^+$, $C_{12}H_{14}NO_4$ requires 236.0923.

Ethyl 4,6-dimethyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (4ba)

Yield: 23.6 mg (63%); green oil.

IR (neat): 1767, 1682, 1508, 1208, 1016, 750 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 6.92 (d, *J* = 8.1 Hz, 1H), 6.71 – 6.58 (m, 2H), 4.62 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.03 (s, 3H), 2.33 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 165.55 (C), 160.63 (C), 139.15 (C), 135.29 (C), 133.09 (C), 120.58 (CH), 116.11 (CH), 113.52 (CH), 64.95 (CH), 62.30 (CH_2), 36.38 (CH_3), 21.29 (CH_3), 13.96 (CH_3).

HRMS (ESI$^+$): m/z 250.1076 [M + H]$^+$, $C_{13}H_{16}NO_4$ requires 250.1079.

Ethyl 6-chloro-4-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (4ca)

Yield: 22.3 mg (55%); orange oil.

IR (neat): 1777, 1728, 1500, 1202, 1036, 837, 806 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 6.96 (d, *J* = 8.5 Hz, 1H), 6.84 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.80 (d, *J* = 2.3 Hz, 1H), 4.63 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.03 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 165.05 (C), 159.70 (C), 139.62 (C), 134.43 (C), 130.77 (C), 119.82 (CH), 117.37 (CH), 113.11 (CH), 64.54 (CH), 62.65 (CH_2), 36.48 (CH_3), 13.99 (CH_3).

HRMS (ESI$^+$): m/z 270.0517 [M + H]$^+$, $C_{12}H_{13}ClNO_4$ requires 270.0533.

Ethyl 4,7-dimethyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (4da)

Yield: 25.6 mg (68%); brown oil.

IR (neat): 1755, 1740, 1506, 1213, 1178, 1043, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 6.91 (ddd, *J* = 8.1, 1.8, 0.8 Hz, 1H), 6.86 (dd, *J* = 1.9, 0.7 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 4.61 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.02 (s, 3H), 2.28 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 165.6 (C), 160.8 (C), 141.0 (C), 131.0 (C), 130.0 (C), 125.9 (CH), 117.0 (CH), 112.7 (CH), 65.0 (CH_3), 62.3 (CH_2), 36.4 (CH), 20.5 (CH_3), 14.0 (CH_3).

HRMS (ESI$^+$): m/z 250.1077 [M + H]$^+$, $C_{13}H_{16}NO_4$ requires 250.1079.

Ethyl 7-chloro-4-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (4ea)

Yield: 20.7 mg (51%); red oil.

IR (neat): 1769, 1734, 1500, 1195, 1013, 956, 850, 802, 690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (dt, *J* = 5.6, 2.2 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 1H), 4.64 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.03 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 165.09 (C), 159.75 (C), 141.22 (C), 132.29 (C), 125.36 (C), 124.84 (CH), 116.83 (CH), 113.62 (CH), 64.66 (CH_2), 62.59 (CH), 36.53 (CH_3), 13.99 (CH_3).

HRMS (ESI$^+$): m/z 270.0523 $[M + H]^+$, $C_{12}H_{13}ClNO_4$ requires 270.0533.

Ethyl 4-ethyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (4ab)

Yield: 25.8 mg (69%); brown oil.

IR (neat): 1770, 1674, 1499, 1266, 1206, 1017, 747 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 7.10 – 7.00 (m, 1H), 6.93 – 6.81 (m, 2H), 4.77 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.60 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.29 (dq, *J* = 14.4, 7.2 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 165.99 (C), 161.00 (C), 141.35 (C), 132.83 (C), 125.37 (CH), 120.03 (CH), 116.69 (CH), 113.34 (CH), 62.29 (CH), 62.17 (CH_2), 43.39 (CH_2), 13.91 (CH_3), 12.30 (CH_3).

HRMS (ESI$^+$): m/z 250.1067 $[M + H]^+$, $C_{13}H_{16}NO_4$ requires 250.1079.

Ethyl 6-chloro-4-ethyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (4cb)

Yield: 24.3 mg (57%); red oil.

IR (neat): 1778, 1734, 1501, 1189, 1131, 1046, 836, 804 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 (dd, *J* = 8.1, 0.8 Hz, 1H), 6.89 – 6.80 (m, 2H), 4.77 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.55 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.28 (dq, *J* = 13.6, 7.3 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ165.6 (C), 160.2 (C) , 139.8 (C), 133.8 (C), 130.7 (C), 119.7 (CH), 117.6 (CH), 113.4 (CH), 62.6 (CH_2), 61.8 (CH), 43.5 (CH_2), 14.0 (CH_3), 12.2 (CH_3).

HRMS (ESI$^+$): m/z 284.0689 $[M + H]^+$, $C_{13}H_{15}ClNO_4$ requires 284.0684.

Ethyl 4-ethyl-7-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (4db)

Yield: 26.9 mg (68%); red oil.

IR (neat): 1770, 1679, 1512, 1295, 1199, 1150, 1021, 801 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (ddd, *J* = 8.1, 1.8, 0.7 Hz, 1H), 6.87 (d, *J* = 1.3 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 4.73 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.57 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.25 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.28 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 4H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 166.14 (C), 161.30 (C), 141.31 (C), 130.39 (C), 130.02 (C), 125.84 (CH), 117.22 (CH), 113.29 (CH), 62.29 (CH_2), 62.23 (CH), 43.45 (CH), 20.47 (CH_3), 13.97 (CH_3), 12.36 (CH_3).

HRMS (ESI$^+$): m/z 264.1229 $[M + H]^+$, $C_{14}H_{18}NO_4$ requires 264.1236.

Procedure for *N*-alkylation/transesterification of benzoxazinone

To a solution of benzoxazinone **2a** (0.15 mmol) in dichloromethane (2 mL) at 0°C, a 2M Me_2Zn solution in toluene **3a** (0.3 mmol) is added dropwise under nitrogen atmosphere. After addition, the reaction is placed at room temperature and is stirred for 30 minutes. Dry methanol (3 mmol) is added to the reaction and the resulting mixture is stirred till completion (TLC, ±30 minutes). The reaction is quenched with Rochelle salt (5 mL), extracted with dichloromethane (3x15 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting product is purified by flash column chromatography on silica (hexane:ethyl acetate), obtaining product **4aa'**

Methyl 4-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (4aa')

Yield: 18.6 mg (56%); brown oil.

IR (neat): 1773, 1726, 1504, 1215, 1195, 1023, 740 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): 7.13 (td, *J* = 7.7, 1.5 Hz, 1H), 7.05 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.97 – 5.88 (m, 2H), 4.69 (s, 1H), 3.69 (s, 3H), 3.05 (s, 3H).

^{13}C NMR (75MHz, $CDCl_3$): 166.0 (C), 160.3 (C), 141.0 (C), 133.3 (C), 125.6 (CH), 120.2 (CH), 116.5 (CH), 113.0 (CH), 64.8 (CH), 53.0 (CH_3), 36.4 (CH_3).

HRMS (ESI$^+$): 222.0760 $[M + H]^+$, $C_{11}H_{12}NO_4$ requires 222.0766.

Procedure for the nucleophilic *N*-alkylation of quinoxalinones

To a solution of quinoxalinone **4** (0.15 mmol) in dichloromethane (2 mL) at 0 °C, a 1M Et_2Zn solution in hexanes **3b** (0.3 mmol) is added dropwise under nitrogen atmosphere. After addition, the reaction is placed at room temperature and is stirred till completion (TLC, ±30 minutes). The reaction is quenched with Rochelle salt (5 mL), extracted with dichloromethane (3x15 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting product is purified by flash column chromatography on silica (hexane:ethyl acetate), obtaining product **7.**

Ethyl 1-ethyl-4-methyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-2-carboxylate (7ab)

Yield: 27.9 mg (71%); yellow oil.

IR (neat): 1699, 1390, 1242, 1148, 764, 663 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 – 7.01 (m, 1H), 6.96 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.90 – 6.79 (m, 2H), 4.67 (s, 1H), 4.09 (qd, *J* = 7.1, 2.8 Hz, 2H), 3.58 (dd, *J* = 13.7, 6.9 Hz, 1H), 3.42 (s, 3H), 3.26 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 167.89 (C), 162.17 (C), 135.36 (C), 129.24 (C), 124.06 (CH), 119.24 (CH), 114.90 (CH), 112.54 (CH), 64.40 (CH), 61.65 (CH_2), 43.64 (CH_2), 29.47 (CH_3), 14.06 (CH_3), 12.34 (CH_3).

HRMS (ESI$^+$): m/z 263.1389 $[M + H]^+$, $C_{14}H_{19}N_2O_3$ requires 263.1396.

Ethyl 4-benzyl-1-ethyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-2-carboxylate (7bb)

Yield: 42.6 mg (84%); clear oil.

IR (neat): 1727, 1671, 1506, 1405, 1200, 1004, 741, 720, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 – 7.14 (m, 5H), 7.01 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H), 6.84 (dt, *J* = 8.0, 1.4 Hz, 2H), 6.73 (ddd, *J* = 8.2, 7.3, 1.3 Hz, 1H), 5.75 – 5.50 (m, 1H), 4.77 (s, 1H), 4.73 (d, *J* = 16.2 Hz, 1H), 4.14 (qd, *J* = 7.1, 0.8 Hz, 2H), 3.63 (dq, *J* = 14.1, 7.1 Hz, 1H), 3.35 (dq, *J* = 13.5, 7.2 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 167.90 (C), 162.30 (C), 136.58 (C), 135.38 (C), 128.81 (C), 128.69 (CH), 127.14 (CH), 126.25 (CH), 124.14 (CH), 119.39 (CH), 115.74 (CH), 112.79 (CH), 64.33 (CH), 61.69 (CH_2), 46.51 (CH_2), 43.82 (CH_2), 14.07 (CH_3), 12.46 (CH_3).

HRMS (ESI$^+$): m/z 339.1704 $[M + H]^+$, $C_{20}H_{23}N_2O_3$ requires 339.1709.

Ethyl 1-ethyl-4-(2-methoxy-2-oxoethyl)-3-oxo-1,2,3,4-tetrahydroquinoxaline-2-carboxylate (7cb)

Yield: 36.1 mg (75%); yellow oil.

IR (neat): 1733, 1674, 1396, 1289, 1216, 1194, 1012, 744 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 – 6.98 (m, 1H), 6.91 – 6.77 (m, 2H), 6.72 (dd, *J* = 8.0, 1.3 Hz, 1H), 4.96 (d, *J* = 17.5 Hz, 1H), 4.71 (s, 1H), 4.45 (d, *J* = 17.5 Hz, 1H), 4.11 (qd, *J* = 7.1, 1.1 Hz, 2H), 3.75 (s, 3H), 3.59 (dt, *J* = 14.1, 7.0 Hz, 1H), 3.30 (dq, *J* = 14.4, 7.2 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 168.35 (C), 167.36 (C), 162.27 (C), 135.42 (C), 128.16 (C), 124.40 (CH), 119.41 (CH), 114.39 (CH), 113.09 (CH), 64.12 (CH), 61.72 (CH2), 52.44 (CH_3), 44.01 (CH_2), 43.82 (CH_2), 13.97 (CH_3), 12.35 (CH_3).

HRMS (ESI$^+$): m/z 321.1450 $[M + H]^+$, $C_{16}H_{21}N_2O_5$ requires 321.1451.

Procedure for *N*-alkylation/*C*-alkylation of benzoxazinones

To a solution of benzoxazinone **2** (0.15 mmol) in dichloromethane (2 mL) at 0°C, a 2M Me_2Zn solution in toluene /1M Et_2Zn solution in hexanes **3** (0.3 mmol) is added dropwise under nitrogen atmosphere. After addition, the reaction is placed at room temperature and is stirred for 30 minutes. After 30 minutes, the electrophile (0.75 mmol) is introduced in the reaction, which is stirred at room temperature till completion (TLC). The reaction is quenched with Rochelle salt (5 mL), extracted with

dichloromethane (3x15 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting product is purified by flash column chromatography on silica (hexane:ethyl acetate), obtaining product **8a-8h**.

Ethyl 3-benzyl-4-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (8a)

Yield: 18.1 mg (37%); yellow oil.

IR (neat): 1757, 1738, 1499, 1272, 1218, 1181, 1018, 742, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.21 – 7.09 (m, 5H), 7.00 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 6.81 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.74 – 6.59 (m, 2H), 4.32 – 4.13 (m, 2H), 3.72 (d, *J* = 15.0 Hz, 1H), 3.50 (d, *J* = 15.0 Hz, 1H), 2.89 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 167.43 (C), 163.76 (C), 139.57 (C), 134.09 (C), 133.01 (C), 130.00 (CH), 128.27 (CH), 127.14 (CH), 125.36 (CH), 119.03 (CH), 116.03 (CH), 111.94 (CH), 71.79 (C), 62.58 (CH_2), 37.73 (CH_2), 32.48 (CH_3), 13.96 (CH_3).

HRMS (ESI^+): m/z 326.1389 $[M + H]^+$, $C_{19}H_{20}NO_4$ requires 326.1392.

Ethyl 3-benzyl-4-ethyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (8b)

Yield: 26.0 mg (51%); yellow oil.

IR (neat): 1753, 1736, 1499, 1235, 1203, 1045, 735, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.12-7.08 (m, 5H), 6.98 (ddd, *J* = 8.1, 7.4, 1.6 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.72 – 6.58 (m, 2H), 4.27 (qd, *J* = 7.1, 1.7 Hz, 2H), 3.62 (d, *J* = 14.8 Hz, 1H), 3.51 – 3.25 (m, 2H), 3.19 – 3.02 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 168.2 (C), 164.1 (C), 139.6 (C), 133.9 (C), 131.4 (CH), 130.3 (C), 128.2 (CH), 127.1 (CH), 125.3 (CH), 118.6 (CH), 116.3 (CH), 112.1 (CH), 72.3 (C), 62.6 (CH_2), 40.8 (CH_2), 38.6 (CH_2), 13.9 (CH_3), 12.3 (CH_3).

HRMS (ESI^+): m/z 340.1548 $[M + H]^+$, $C_{20}H_{22}NO_4$ requires 340.1549.

Ethyl 3-benzyl-4,6-dimethyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (8c)

Yield: 35.5 mg (67%); clear oil.

IR (neat): 1755, 1740, 1506, 1234, 1213, 1078, 1043, 799, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.09 (m, 5H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.52 – 6.40 (m, 2H), 4.25 (qd, *J* = 7.2, 1.9 Hz, 2H), 3.63 (d, *J* = 14.8 Hz, 1H), 3.43 (d, *J* = 14.7 Hz, 1H), 3.47 – 3.27 (m, 1H), 3.09 (dq, *J* = 14.2, 7.1 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 168.3 (C), 164.2 (C), 137.7 (C), 134.9 (C), 134.1 (C), 131.1 (C), 130.3 (CH), 128.1 (CH), 127.1 (CH), 119.2 (CH), 116.0 (CH), 112.8 (CH), 72.3 (C), 62.6 (CH_2), 40.8 (CH_2), 38.5 (CH_2), 21.4 (CH_3), 13.9 (CH_3), 12.42 (CH_3).

HRMS (ESI^+): m/z 354.1709 $[M + H]^+$, $C_{21}H_{24}NO_4$ requires 354.1705.

Ethyl 3-benzyl-7-chloro-4-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (8d)

Yield: 40.4 mg (72%); yellow oil.

IR (neat): 1763, 1744, 1497, 1264, 1240, 1042, 1021, 795, 746, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.16 – 7.01 (m, 5H), 6.94 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.52 (d, *J* = 8.8 Hz, 1H), 4.28 (qd, *J* = 7.1, 3.1 Hz, 2H), 3.61 (d, *J* = 14.7 Hz, 1H), 3.46 (s, 1H), 3.47 – 3.28 (m, 1H), 3.10 (dq, *J* = 14.3, 7.1 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 167.8 (C), 163.6 (C), 139.6 (C), 133.6 (C), 130.3 (C), 130.2 (CH), 128.3 (CH), 127.3 (CH), 125.0 (CH), 123.0 (C), 116.6 (CH), 112.7 (CH), 72.2 (C), 62.8 (CH_2), 40.9 (CH_2), 38.8 (CH_2), 13.9 (CH_3), 12.1 (CH_3).

HRMS (ESI^+): m/z 374.1165 $[M + H]^+$, $C_{20}H_{21}ClNO_4$ requires 374.1159.

Ethyl 3-allyl-4-ethyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (8e)

Yield: 27.3 mg (63%); brown oil.

IR (neat): 1762, 1739, 1498, 1271, 1215, 1130, 1020, 744, 660 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.12 – 7.07 (m, 1H), 7.06 – 6.99 (m, 1H), 6.85 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.85 – 6.75 (m, 1H), 4.12 (qd, *J* = 7.1, 1.4 Hz, 1H), 3.45 (dq, *J* = 14.4, 7.2 Hz, 2H), 3.28 (dd, *J* = 14.9, 7.0 Hz, 1H), 3.26 – 3.11 (m, 1H), 3.00 – 2.85 (m, 1H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 168.2 (C), 163.6 (C), 140.6 (C), 132.5 (C), 131.1 (CH), 125.3 (CH), 120.2 (CH_2), 119.6 (CH), 116.6 (CH), 113.4 (CH), 70.8 (C), 62.3 (CH_2), 40.1 (CH_2), 36.9 (CH_2), 13.9 (CH_3), 13.0 (CH_3).

HRMS (ESI^+): m/z 290.1385 $[M + H]^+$, $C_{16}H_{20}NO_4$ requires 290.1392.

Ethyl 3-allyl-4-ethyl-6-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (8f)

Yield: 30.5 mg (67%); red oil.

IR (neat): 1761, 1739, 1506, 1277, 1215, 1180, 1077, 925, 802 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 6.89 (d, *J* = 8.0 Hz, 1H), 6.63 (ddd, *J* = 8.0, 1.8, 0.7 Hz, 1H), 6.63 – 6.54 (m, 1H), 5.87 – 5.69 (m, 1H), 5.22 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.15 (dq, *J* = 10.2, 1.4 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.43 (dq, *J* = 14.4, 7.1 Hz, 1H), 3.34 – 3.22 (m, 1H), 3.17 (ddt, *J* = 15.1, 6.4, 1.6 Hz, 1H), 2.90 (ddt, *J* = 15.1, 7.5, 1.2 Hz, 1H), 2.32 (s, 3H), 1.19 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 168.3 (C), 163.6 (C), 138.5 (C), 135.0 (C), 132.1 (C), 131.2 (CH), 120.1 (CH), 120.1 (CH_2), 116.2 (CH), 114.0 (CH), 70.8 (C), 62.3 (CH_2), 40.1 (CH_2), 36.9 (CH_2), 21.4 (CH_3), 13.9 (CH_3), 13.0 (CH_3).

HRMS (ESI^+): m/z 304.1550 $[M + H]^+$, $C_{17}H_{22}NO_4$ requires 304.1549.

Ethyl 3-allyl-4-ethyl-7-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (8g)

Yield: 30.9 mg (68%); orange oil.

IR (neat): 1762, 1738, 1511, 1273, 1229, 1144, 1020, 802 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 6.88 (ddd, *J* = 8.2, 1.9, 0.8 Hz, 1H), 6.84 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 5.90 – 5.70 (m, 1H), 5.22 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.16 (dq, *J* = 10.2, 1.4 Hz, 1H), 4.11 (qd, *J* = 7.2, 0.9 Hz, 2H), 3.42 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.32 – 3.21 (m, 1H), 3.22 – 3.12 (m, 1H), 2.90 (ddt, *J* = 15.1, 7.4, 1.2 Hz, 1H), 2.27 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 168.3 (C), 163.8 (C), 140.6 (C), 131.3 (CH), 130.1 (C), 129.6 (C), 125.7 (CH), 120.0 (CH_2), 117.1 (CH), 113.5 (CH), 70.8 (C), 62.2 (CH_2), 40.1 (CH_2), 36.7 (CH_2), 20.4 (CH_3), 13.9 (CH_3), 13.1(CH_3).

HRMS (ESI^+): m/z 304.1550 $[M + H]^+$, $C_{17}H_{22}NO_4$ requires 304.1549..

Ethyl 3-allyl-7-chloro-4-ethyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (8h)

Yield: 24.8 mg (51%); orange oil.

IR (neat): 1770, 1740, 1494, 1273, 1218, 1147, 1077, 858, 801 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.08 – 7.01 (m, 2H), 6.71 (d, *J* = 8.5 Hz, 1H), 5.76 (dddd, *J* = 16.7, 10.2, 7.5, 6.4 Hz, 1H), 5.29 – 5.13 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.43 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.33 – 3.23 (m, 1H), 3.18 (ddt, *J* = 15.2, 6.4, 1.4 Hz, 1H), 2.92 (ddt, *J* = 15.1, 7.4, 1.1 Hz, 1H), 1.18 (t, *J* = 6.9Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 167.8 (C), 162.9 (C), 140.7 (C), 131.4 (C), 130.8 (CH), 125.1 (CH), 124.2 (C), 120.5 (CH_2), 116.9 (CH), 114.1 (CH), 70.7 (C), 62.5 (CH_2), 40.2 (CH_2), 36.9 (CH_2), 13.9 (CH_3), 12.78 (CH_3).

HRMS (ESI^+): m/z 324.1003 $[M + H]^+$, $C_{16}H_{19}ClNO_4$ requires 324.1003.

Ethyl (*E*)-3-(4-ethoxy-4-oxobut-2-en-1-yl)-4-ethyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-3-carboxylate (8i)

To a solution of product **4ab** (0.1 mmol) in THF (1 mL) at -78 °C, LDA 2M in THF (1.2 mmol) is added and the reaction is stirred for half an hour at -78°C. After half an hour, ethyl (*E*)-4-iodobut-2-enoate is added at -78 °C and is allowed to reach room temperature. The reaction is stirred till completion (TLC). The reaction is quenched with saturated aqueous solution of ammonium chloride (5 mL), extracted with dichloromethane (3x15 mL), dried over anhydrous magnesium sulfate and concentrated

under reduced pressure. The resulting product is purified by flash column chromatography on silica (hexane:ethyl acetate), obtaining product **8i**.

Yield: 20.1 mg (37%); orange oil.

IR (neat): 1763, 1730, 1716, 1497, 1263, 1215, 1187, 1130, 1092, 1037, 746 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.10 (ddd, *J* = 8.1, 7.4, 1.6 Hz, 1H), 7.06 – 7.02 (m, 1H), 6.94 – 6.71 (m, 3H), 5.98 (dt, *J* = 15.7, 1.5 Hz, 1H), 4.24 – 4.05 (m, 4H), 3.54 – 3.18 (m, 3H), 3.06 (ddd, *J* = 15.6, 7.8, 1.4 Hz, 1H), 1.30 – 1.16 (m, 6H), 1.09 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 167.7 (C), 165.6 (C), 163.2 (C), 140.7 (CH), 140.7 (C), 132.2 (C), 126.0 (CH), 125.5 (CH), 120.1 (CH), 116.7 (CH), 113.7 (CH), 70.3 (C), 62.6 (CH_2), 60.5 (CH_2), 40.3 (CH_2), 35.0 (CH_2), 14.2 (CH_3), 13.8 (CH_3), 12.9 (CH_3).

HRMS (ESI^+): m/z 362. 1587 $[M + H]^+$, $C_{19}H_{24}NO_6$ requires 362,1598.

Acknowledgments

Financial support from the MINECO (Gobierno de España; CTQ2013-47494-P) and from Generalitat Valenciana (ISIC2012/001) is gratefully acknowledged. L. M. thanks the Generalitat Valenciana for predoctoral grant. C.V. thanks MINECO for a JdC contract.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

References

(1) (a) Ilaš, J.; Anderluh, P. Š.; Dolenc, M. S.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325. (b) Achari, B.; Mandal, S. B.; Dutta, P. K.; Chowdhury, C. *Synlett*, **2004**, 2449. (c) Patel, M.; McHush, R. J.; Corodva, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Trainor, G. L.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1729. (d) Pamerla, M.; Reddy, D. R. S.; Battula, S.; Bodipati N.; Murthy, Y. L. N. *Med. Chem. Res.*, **2015**, *24*, 611. (e) Bouyssou, T.; Casarosa, P.; Naline, E.; Pestel, S.; Konetzki, I.; Devillier, P.; Schnapp, A. *J. Pharmacol. Exp. Ther*., **2010**, *334*, 53. (f) Liu, C.; Tan, J. L.; Xiao, S. Y.; Liao, J. F.; Zou, G. R.; Ai, X. X.; Chen, J. B.; Xiang, Y.; Yang, Q.; Zuo, H. *Chem. Pharm. Bull*., **2014**, *62*, 915. (g) Combs, D. W.; Rampulla, M. S.; Bell, S. C.; Klaubert, D. H.; Tobia, A. J.; Falotico, R.; Haertlein, B.; Lakas-Weiss, C.; Moore, J. B. *J. Med. Chem*., **1990**, *33*, 380. (h) Blass, B. *ACS Med. Chem. Lett.*, **2013**, *4*, 1020. (i) Ilaš, J.; Jakopin, Ž.; Borštnar, T.; Stegnar, M.; Kikelj, D. *J. Med. Chem*., **2008**, *51*, 5617. (j) Moffett, R. B. *J. Med. Chem*., **1966**, *9*, 475.

(2) Miles, D. H.; Petrovna, K. O.; Naser, S.; Yurjevich, S. S.; Goun, E. A.; Michailovich, S. V. *US Pat.*, **2003**, *6*, 649, 610.

(3) Lestage, P.; Lockhart, B.; Fleury, M. B.; Largeron, M. *WO Patent Appl.*, **2003**, 03033481.

(4) (a) Sanna, P.; Carta, A.; Loriga, M.; Zanetti, S. Sechi, L. *Il Farmaco*, **1999**, 54, 161. (b) Balzarini, J.; De Clercq, E.; Carbonez, A.; Burt, V.; Kleim, J.-P. *AIDS Res. Hum. Retroviruses*, **2000**, *16*, 517. (c) Goldfarb, D. S. *U.S. Pat. Appl. Publ*, US20090163545A120090625, **2009**.

(5) Tanimori, S.; Nishimira, T.; Kirihata, M. *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 4119.

(6) Abu Shuheil, M. Y.; Hassuneh, M. R.; Al-Hiari, Y. M.; Qaisi, A. M.; El-Abadelah, M. M. *Heterocycles*, **2007**, *71*, 2155.

(7) (a) Achari, A.; Mandal, S. B.; Dutta, P. K.; Chowdhury, C. *Synlett* **2004**, *14*, 2449. (b) Li, X.; Liu, N.; Zhang, H.; Knudson, S. E.; Slayden, R. A.; Tonge, P. J. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 6306. (b) Semenova, T. D.; Krasnykh, O. P. *Russ. J. Org. Chem*., **2005**, *41*, 1222. (c) Zykova, S. S. Karmanova, O. G. *Pharm. Chem. J*., **2015**, *49*, 362. (d) Venable, J. D.; Kindrachuk, D. E.; Peterson, M. L.; Edwards, J. P. *Tetrahedron Lett*., **2010**, *51*, 337. (e) Koz'minykh, O.; Goncharov, V. I.; Koz'minykh, E. N. *Russ. J. Org. Chem*., **2006**, *42*, 1715. (f) Yao, Q.-C.; Wu, D.-E.; Ma, R.-Z.; Xia, M. *J. Organomet. Chem*., **2013**, *743*, 1. (g) López-Iglesias, M.; Busto, E.; Gotor, V.; Gotor-Fernández, V. *J. Org. Chem*. **2015**, *80*, 3815. (h) Konda, S.; Raparti, S.; Bhaskar, K.; Munaganti, R. K.; Guguloth, V.; Nagarapu, L.; Akkewar, D. M. *Bioorg. Med. Chem. Lett.*, **2015**, *25*, 1643. (i) Nguyen, K. M. H.; Schwendimann, L.; Gressens, P.; Largeron, M. *Org. Biomol. Chem.*, **2015**, *13*, 3749. (j) Ramesh, C.; Raju, B. R.; Kavala, V.; Kuo, C.-W.; Yao, C.-F. *Tetrahedron* **2011**, *67*, 1187.

(8) (a) Alapour, S.; Ramjugernathand, D.; Koorbanally, N. A. *RSC Adv*., **2015**, *5*, 83576. (b) Liu, Z.-T.; Wang, Y.-H.; Zhu, F.-L.; Hu, X.-P. *Org. Lett*., **2016**, *18*, 1190. (c) Li, D.; Ma, H.; Yu, W. *Adv. Synth. Catal*., **2015**, ***357***, 3696. (d) Balalaie, S.; Bararjanian, M.; Hosseinzadeh, S.; Rominger, F.; Bijanzadeh, H. R.; Wolf, E. *Tetrahedron*, **2011**, *67*, 7294. (e) Tanimori, S.; Inaba, U.; Kato, Y.; Ura, H.; Kashiwagi, H.; Nishimura, T.; Kirihata, M. *Res. Chem. Intermed*., **2014**, *40*, 2157. (f) Luo, X.; Chenard, E.; Martens, P.; Cheng, Y.-X.; Tomaszewski, M. J. *Org. Lett*., **2010**, *12*, 3574. (g) Luo, X.; Chenard, E.; Martens, P.; Srikanth, Y.- G.; Ramakrishna, K. V. S.; Sharma, G. V. M. *Org. Lett*., **2015**, *17*, 4576.

(9) (a) Lou, H.; Wang, Y.; Jin, E.; Lin, X. *J. Org. Chem.*, **2016**, *81*, 2019. (b) Wu, L.-L.; Xiang, Y.; Yang, D.-C.; Guanand, Z.; He, Y.-H. *Catal. Sci. Technol*., **2016**, *6*, 3963. (c) Wang, Y.-Q.; Zhang, Y.; Pan, K.; You, J.; Zhao, J. *Adv. Synth. Catal.* **2013**, ***355***, 3381. (d) Shinkevich, E. Y.; Novikov, M. S.; Khlebnikov, A. F.; *Synthesis* **2007**, 225. (e) Banzatti, C.; Heidempergher, F.; Melloni, P. *J. Hetererocyclic Chem*. **1983**, *20*, 259. (f) Shao, P.-L.; Liao, J.-Y.; Ho, Y. A.; Zhao, Y. *Angew. Chem. Int. Ed*. **2014**, *53*, 5435. (g) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *Synlett*, **2004**, *14*, 2597. (h) Xue, Z.-Y.; Jiang, Y.; Peng, X.-Z.; Yuan, W.-C.; Zhang, X.-M. *Adv. Synth. Catal.* **2010**, *352*, 2132. (i) Yu, J.-S.; Zhou, J. *Org. Biomol. Chem*., **2015**, *13*, 10968. (j) Kano, T.; Takechi, R.; Kobayashi, R.; Maruoka, K. *Org. Biomol. Chem*., **2014**, *12*, 724. (k) Kano, T.; Song, S.; Kubota, Y. Maruoka, K. *Angew. Chem. Int. Ed*. **2012**, *51*, 1191.

(10) For pioneering works of Kagan, see: (a) Fiaud, J.-C.; Kagan, H. B. *Tetrahedron Lett*. **1970**, *11*, 1813. (b) Fiaud, J.-C.; Kagan, H. B. *Tetrahedron Lett*. **1971**, *12*, 1019.

(11) For selected *C*-selective alkylation of α-imino esters, see: (a) Münster, P.; Steglich, W. *Synthesis* **1987**, 223. (b) Ermert, P.; Meyer, J.; Stucki, C.; Schneebeli, J.; Obrecht, J.-P. *Tetrahedron Lett.* **1988**, ***29***, 1265. (c) Calí, P.; Begtrup, M. *Synthesis* **2002**, 63. (d) Chiev, K. P.; Roland, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2205. (e) Basra, S.; Fennie, M. W.; Kozlowski, M. C. *Org. Lett*. **2006**, *8*, 2659. (f) Mitani, M.; Tanaka, Y.; Sawada, A.; Misu, A.; Matsumoto, Y. *Eur. J. Org. Chem*. **2008**, 1383. (g) Lin, L.; Fu, X.; Ma, X.; Zhang, J.; Wang, R. *Synlett* **2012**, 2559. (h) Hatano, M.; Yamashita, K.; Mizuno, M.; Ito, O.; Ishihara, K. *Angew. Chem. Int. Ed*. **2015**, *54*, 2707. (i) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778.

(12) For a review see: (a) Dickstein, J. S.; Kozlowski, M. C. *Chem. Soc. Rev*. **2008**, *37*, 1166. For accounts, see: (b) Shimizu, M.; Hachiya, I.; Mizota, I. *Chem. Commun*. **2009**, 874. (c) Koyama, K.; Mizata, I.; Shimizu, M. *Pure Appl. Chem*. **2014**, *86*, 755.

(13) With Grignard reagents: (a) Niwa, Y.; Takayama, K.; Shimizu, M. *Bull. Chem. Soc. Jpn*., **2002**, *75*, 1819. (b) Niwa, Y.; Takayama, K.; Shimizu, M. *Tetrahedron Lett*. **2001**, *42*, 5473. (c) Mizota, I.; Matsuda, Y.; Kamimura, S.; Tanaka, H.; Shimizu, M. *Org. Lett.* **2013**, *15*, 4206. (d) Mizota, I.; Maeda, T.; Shimizu, M. *Tetrahedron* **2015**, *71*, 5793. (e) Dickstein, J. S.; Fennie, M. W.; Norman, A. L.; Paulose, B. J.; Kozlowski, M. C. *J. Am. Chem. Soc*. **2008**, *130*, 15794. (f) Curto, J. M.; Dickstein, J. S.; Berritt, S.; Kozlowski, M. C. *Org. Lett.* **2014**, *16*, 1948. (g) Curto, J. M.; Kozlowski, M. C. *J. Org. Chem*. **2014**, *79*, 5359. (h) Mizutani, Y.; Tanimoto, H.; Morimoto, T.; Nishiyama, Y.; Kakiuchi, K. *Tetrahedron Lett.* **2012**, *53*, 5903. (h) Tanaka, H.; Mizota, I.; Shimizu, M. *Org. Lett*. **2014**, *16*, 2276. (i) Hatano, M.; Yamashita, K.; Ishihara, K. *Org. Lett*. **2015**, *17*, 2412. (j) Yoo, S.-E.; Gong, Y.-D. *Heterocycles* **1997**, *45*, 1251.

(14) With organoaluminium reagents: (a) Niwa, Y.; Shimizu, M. *J. Am. Chem. Soc.* **2003**, *125*, 3720. (b) Shimizu, M.; Takao, Y.; Katsurayama, H.; Mizota, I. *Asian J. Org. Chem.* **2013**, *2*, 130. (c)

Sano, T.; Mizota, I.; Shimizu, M. *Chem. Lett.* **2013**, *42*, 995. (d) Mizota, I.; Tanaka, K.; Shimizu, M. *Tetrahedron Lett.* **2012**, *53*, 1847. (e) Shimizu, M.; Niwa, Y. *Tetrahedron Lett.* **2001**, *42*, 2829. (f) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415.

(15) With organozinc reagents: (a) van Vliet, M. R. P.; Jastrzebski, J.; Klaver, W. J.; Goubitz, K.; van Koten, G. *Recl. Trav. Chim. Pays-Bas*, **1987**, *106*, 132. (b) van der Steen, F. H.; Kleijn, H.; Jastrzebski, T. B. H.; van Koten, G. *J. Org. Chem*., **1991**, *56*, 5147. (c) Uneyama, K.; Yan, F.; Hirama, S.; Katagiri, T. *Tetrahedron Lett.* **1996**, *37*, 2045.

(16) For a recently tandem *N*-alkylation/*C*-alkylation of quinoxalinone derivatives using Grignard reagents, see: Miyamaru, S.; Umezu, K.; Ito, A.; Shimizu, M. *Eur. J. Org. Chem*. **2015**, 3327.

(17) For a *C*-selective alkylation of cyclic α-imino esters: Harwood, L. M.; Vines, K. J.; Drew, M. G. B. *Synlett* **1996**, 1051.

(18) When we tried the *N*-alkylation of quinoxaline derivatives with Me_2Zn, full conversion was not achieved obtaining a mixture of approximately (1:1, starting material: product that was difficult to purify by column chromatography.

(19) Li, D.; Ma, H.; Yu, W.; *Adv. Synth. Catal.* **2015**, 357, 3696.