JOC The Journal of Organic Chemistry

Article

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Original Mitsunobu-Triggered Sequence Involved in a One-Pot Domino Process toward Tetracyclic Systems Bearing a Bis-*N*,*O*-acetal Junction

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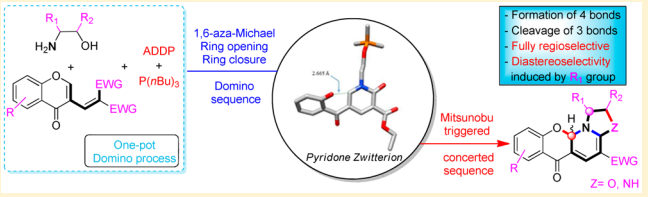
Supporting Information

ABSTRACT: Herein is reported an efficient, one-pot domino process through a 1,6-aza-Michael addition-triggered sequence and an original Mitsunobu-type concerted sequence for the synthesis of tetracyclic systems containing a bis-*N*,*O*-acetal junction. This methodology led to the construction of four new bonds, the cleavage of three C−O bonds, and the generation of an asymmetric center. Mitsunobu activation afforded final ring closure involving the creation of two bonds, which remains unprecedented among reported Mitsunobu-type sequences. The latter occurred in a regioselective fashion at the challenging C_6-position of 2-pyridone intermediates. In the case of adequately substituted enantiopure amino alcohols, up to 95:5 of diastereoisomeric excess was achieved. Computational studies allowed the discrimination of a favored pathway for Mitsunobu sequence and supported the regioselectivity as well as the diastereoselectivity observed for this step.



INTRODUCTION

The late 20th and early 21st centuries have witnessed an unprecedented increase of powerful tools such as domino sequences[1,2] and multicomponent[3,4] reactions to access architecturally complex molecular frameworks. This modern conception of organic chemistry is quickly replacing traditional stepwise approaches to meet environmental and economic demands, in particular for the high-throughput screening of novel scaffolds of biological interest.

Fundamental named reactions have reached a privileged place in this new branch of research as they frequently are involved or even combined[5] in such processes. Among these, Michael addition,[6] Knoevenagel condensation,[7] Mannich reaction,[8] Claisen rearrangement,[9] or Diels−Alder reaction[10] are widely used. Remarkable metal-catalyzed reactions such as Heck[11] or metathesis[12] coupling reactions also have emerged in a wide range of domino sequences to achieve molecular complexity. Nevertheless, a few popular reactions among this restricted elite group still remain disregarded despite their high synthetic relevance.

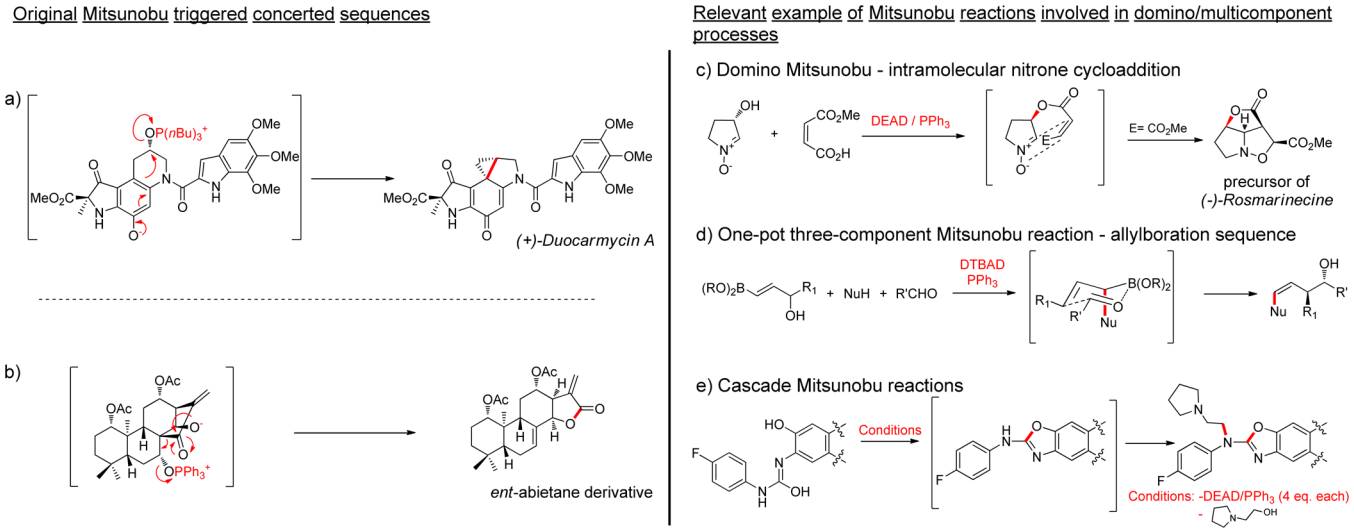
Mitsunobu coupling is a commonly known essential reaction in organic synthesis.[13] Its broad synthetic versatility makes it a powerful strategy for the construction of novel C−O,[14] C−N,[15] C−S,[16] or C−C[17] bonds. Interesting Mitsunobu-triggered concerted sequences which could be incorporated in domino strategies have been reported in the literature (Scheme 1, examples a and b). Among the few examples known, one has been reported by Boger et al. in the last step of the total synthesis of (+)-duocarmycin A[18] to allow the pivotal cyclopropanation reaction (Scheme 1, example a). More recently, Takeya and co-workers also proposed an interesting rearrangement under Mitsunobu activation for efficient transformation of 7,14-dihydroxy-*ent*-kaurene diterpenoids, commonly found in *Rabdosia* plant species, into *ent*-abietanes (Scheme 1, example b).[19]

However, Mitsunobu activation remains too rarely involved in domino processes or multicomponent reactions. The first relevant example has been reported by Goti et al. in the total synthesis of (−)-rosmarinecine (Scheme 1, example c).[20] The ring-fused tricyclic precursor of this bioactive alkaloid was achieved by an elegant domino Mitsunobu intramolecular nitrone cycloaddition process. Comparatively, Greshock et al. later reported a Mitsunobu-triggered biomimetic pathway involving Diels−Alder cycloaddition for the total synthesis of D,L-stephacidin A.[21] More recently, Berrée and co-workers described the first and unique Mitsunobu transformation

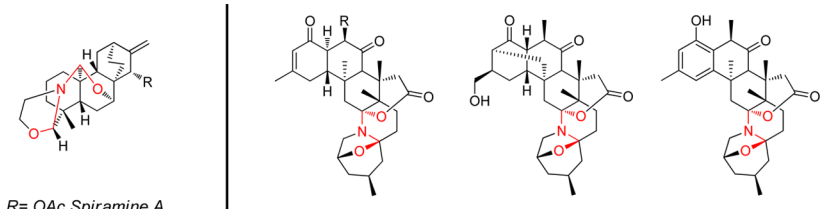
Received: June 24, 2016
Published: September 7, 2016

DOI: 10.1021/acs.joc.6b01523
J. Org. Chem. 2016, 81, 8837−8849

Scheme 1. Modern Applications of Mitsunobu Activation in Domino/Multicomponent/Concerted Sequences



Scheme 2. Representative Structures of Spiramine and Zoanthamine Alkaloids

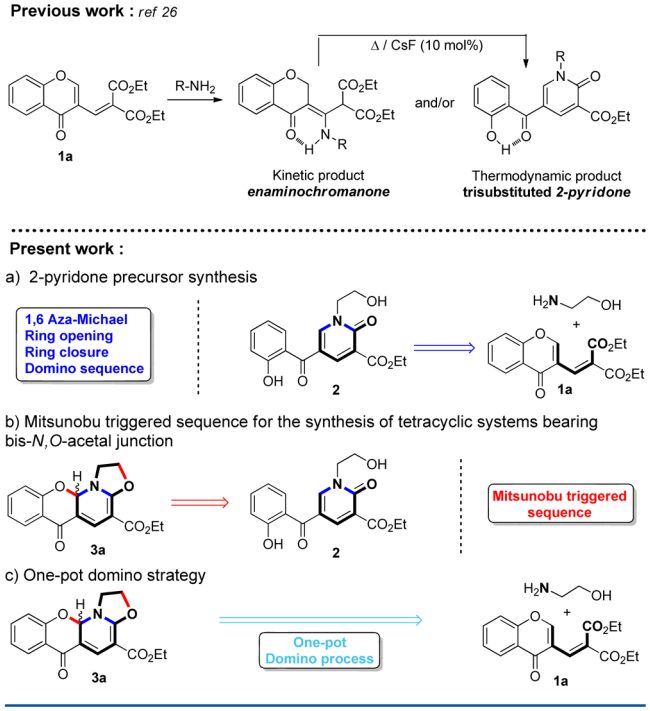


involved in a one-pot multicomponent reaction (Scheme 1, example d)[22] to provide enamides and enol benzoates. Finally, cascade/tandem sequences involving consecutive Mitsunobu activations also were studied by Yan et al. (Scheme 1, example e)[23] and Ganesan et al.[24] among two other groups.[25]

Driven by the high efficiency of such strategies and in keeping with our previous work (Scheme 3),[26] we envisioned to develop a one-pot domino aza-Michael/Mitsunobu process to access tetracyclic frameworks bearing bis-*N,O*-acetal junction. This atypical junction is found in structurally complex bioactive natural products such as spiramine[27] and zoanthamine[28] alkaloids (Scheme 2).

In this work, starting from adequately *N*-substituted 2-pyridone, we anticipated that Mitsunobu activation could be an attractive solution to achieve bis-*N,O*-acetal junction (Scheme 3, example b), allowing in situ generation of a leaving group on the alcohol moiety and phenolic group deprotonation. This activation would not be incompatible with experimental conditions for 2-pyridone intermediate synthesis (Scheme 3, example a)[26] and would thus be suitable for the envisioned one-pot domino strategy (Scheme 3, example c). Moreover, easy access to a large panel of amino alcohols and Michael acceptors bearing the chromone core offers an interesting flexibility in terms of reaction scope. Mitsunobu-triggered final ring closure would lead to the intramolecular formation of two new bonds which has not been reported so far in Mitsunobu-type sequences.

Scheme 3. Domino Strategy for the Synthesis of Nitrogen-Fused Oxazolopyridines Analogues

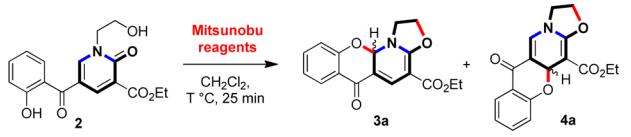


RESULTS AND DISCUSSION

We started to investigate the Mitsunobu sequence on the 2-pyridone derivative **2** (Table 1) as a model substrate synthesized from **1a** according to our previous work.[26] Different conditions were screened, and the results are summarized in Table 1.

DOI: 10.1021/acs.joc.6b01523
J. Org. Chem. 2016, 81, 8837−8849

Table 1. Screening of Experimental Conditions for Mitsunobu Activation



entry	diazo reagent (1.6 equiv)	PR_3 (1.6 equiv)	T (°C)	conv[a] (%) (yield, %)[b]	ratio (**3a**:**4a**)
1[c]	DEAD	PPh_3	rt	79 (0)[d]	1:0
2	DEAD	PPh_3	rt	100 (0)[d]	1:0
3[e]	ADDM	$P(n\text{-Bu})_3$	rt	100 (86)	1:0
4	ADDM	$P(n\text{-Bu})_3$	40	100 (88)	1:0
5[f]	DDQ	$P(n\text{-Bu})_3$	40	0	
6	ADDP	$P(n\text{-Bu})_3$	40	100 (92)	1:0
7	DCAD	$P(n\text{-Bu})_3$	40	100 (91)	1:0
8[f]	ADDP	$P(OEt)_3$	40	0	
9[f]	ADDP	$P(cy)_3$	40	0	
10[f]	ADDP	$P(p\text{-mp})_3$[g]	40	0	
11[h]			40	0	

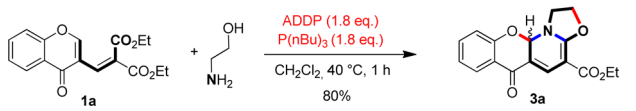
[a]Determined by ^{1}H NMR spectroscopy. [b]Isolated yield. [c]Reaction carried out for 1 h in the presence of 1.3 equiv of each Mitsunobu reagent. [d]Product **3a** was inseparable from Mitsunobu byproducts. [e]The reaction appeared to be non-reproducible. [f]The reaction was carried out for 1 h. [g]$P(p\text{-mp})_3$: tris(4-methoxyphenyl)phosphine. [h]Reaction carried out in the presence of 1.1 equiv of NEt_3 as a base.

The usual Mitsunobu system (DEAD (diethyl azodicarboxylate)/PPh_3) was tested in a first attempt. We were pleased to observe that full conversion into the desired compound **3a** was achieved in only 25 min at ambient temperature (entry 2) when 1.6 equiv of each Mitsunobu reagent was used. Moreover, the reaction proceeded regioselectively at the C_6-position of the 2-pyridone ring since no traces of **4a** were detected. Unfortunately, oxazolopyridine product appeared to be nonisolable from residual dihydro-diethyl azodicarboxylate (DEAD-H_2) and triphenylphosphine oxide formed during the Mitsunobu reaction.

In the past few years, recurrent post purification problems of Mitsunobu reactions have led to the emergence of a new generation of Mitsunobu reagents (both phosphines and azidocarboxylates),[29] devised to facilitate reaction workup. We thus turned our attention to ADDM (azodicarbonyl dimorpholide),[30] DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone),[31] ADDP (1,1′-(azodicarbonyl)dipiperidine),[32] and DCAD (di-*p*-chlorobenzyl azidocarboxylate).[33] The latter have been proven to be at least as efficient as DEAD, and their dihydro analogues more easily removable by column chromatography due to their higher polarity.[29] Satisfactorily, replacing DEAD/PPh_3 by ADDM/$P(n\text{-Bu})_3$ afforded the expected product in 86% isolated yield (entry 3). We then decided to carry out the reaction at 40 °C as the latter was irreproducible depending on ambient temperature variation. The Mitsunobu sequence was positively affected by increasing temperature since compound **3a** was isolated in 88% yield (entry 4). Unfortunately, when ADDM was replaced by DDQ the reaction was negatively impacted as no conversion was observed (entry 5). To conclude the screening on diazo reagents, ADDP and DCAD were tested without significant changes observed in the reaction profile in comparison to ADDM (entries 6 and 7). ADDP was finally chosen as the most convenient azido reagent mainly due to its easier and cheaper access in comparison to DCAD. Different phosphines were finally compared to $P(n\text{-Bu})_3$, but none of them afforded the desired compound (entries 8−10). Only starting material was fully recovered. It can be mentioned that addition of $P(n\text{-Bu})_3$ in the corresponding resulting mixtures afforded full conversion into **3a**, indicating that all tested phosphines did not react with ADDP.

Having established optimal reaction conditions for a Mitsunobu-triggered sequence, we then tested their efficiency in a one-pot domino process starting from substrate **1a** (Scheme 4).

Scheme 4. One-Pot Domino Sequence under Optimized Mitsunobu Conditions



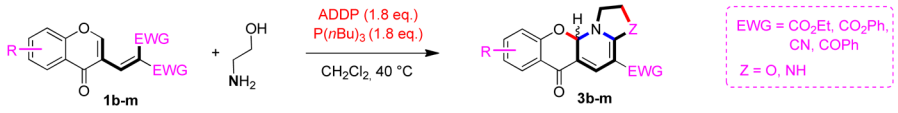
Pleasingly, starting from ethanolamine, Michael acceptor **1a**, and 1.8 equiv of each Mitsunobu reagent, the reaction led to the desired nitrogen-fused oxazolopyridine **3a** in full conversion and satisfactory 80% isolated yield.

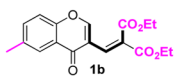
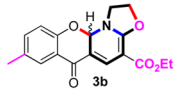
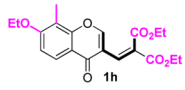
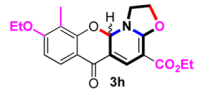
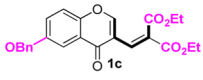
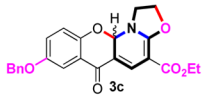
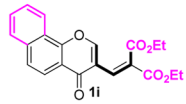
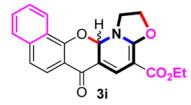
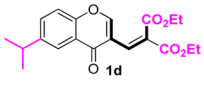
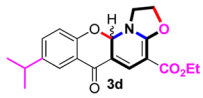
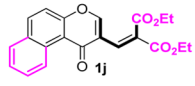
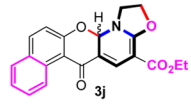
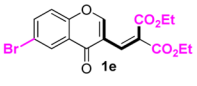
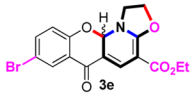
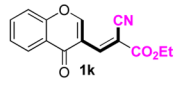
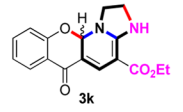
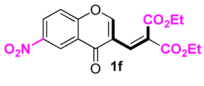
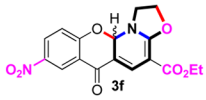
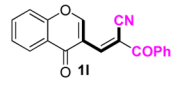
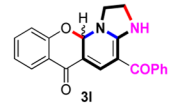
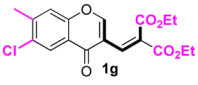
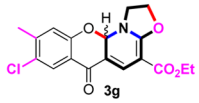
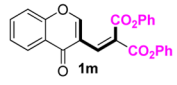
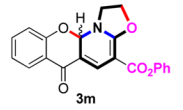
Scope and limitations of the reaction were then investigated on different chromone acceptors reacting with diversified amino alcohols. As could be anticipated, depending on the chromone moiety substitution, phenolate reactivity of the zwitterionic 2-pyridone intermediate directly impacted the Mitsunobu sequence (Table 2).

Electron-donating groups (EDG) enhancing phenol nucleophilicity, such as 5-substituted methylchromone or benzyloxychromone, afforded the corresponding oxazolopyridines **3b** and **3c**, respectively, in 83% and 88% isolated yields (entries 1 and 2). High reactivity was also observed for 5-substituted isopropylchromone, although **3d** was isolated in 69% yield (entry 3). On the other hand, when phenol group nucleophilicity was weakened, the reaction was negatively impacted. A strong electron-withdrawing group (EWG) such as a nitro group in the *para* position prevented the Mitsunobu−domino sequence. Only the zwitterionic 2-pyridone intermediate was indeed observed after 2 h of reaction time. Comparatively, 5-bromo-substituted *α,β*-unsaturated chromone afforded the desired product **3e** in a modest 38% isolated yield. In this case, the decrease of phenolate reactivity also led to an incomplete conversion from the corresponding 2-pyridone zwitterionic intermediate since the latter was detected in the reaction mixture at the end of the reaction. In a second attempt, an extra equivalent of ADDP/$P(n\text{-Bu})_3$ was added to the reaction media after 1 h of reaction time in order to shift the equilibrium in favor of the oxazolopyridine derivative. However, no significant improvement was observed since **3e** was isolated in 54% yield. The domino process was then investigated with diverse electronic-withdrawing groups on the Michael acceptor moiety. Interestingly, in the case of nonsymmetrical Michael acceptors bearing cyano/ester or cyano/ketone groups, excellent chemoselectivity was achieved in favor of imidazopyridine derivatives since **3k** and **3l** were obtained in, respectively, 93:7 and >99:1 ratios. This chemoselectivity could be explained by the higher reactivity of the cyano group in the first ring-closure step of the domino process and the presence of an intramolecular hydrogen bond involved in the formed imidazopyridine stabilization. It is worth mentioning that in the latter cases the Mitsunobu sequence led to the formation of one C−O bond and one C−N bond. The structure of **3l** was confirmed by X-ray diffraction

DOI: 10.1021/acs.joc.6b01523
J. Org. Chem. 2016, 81, 8837−8849

Table 2. Impact of Michael Acceptor Substitution on Domino Process



Entry	Michael acceptor	Product	Time (min)	Yield (%)	Entry	Michael acceptor	Product	Time (min)	Yield (%)[a]
1	 1b	 3b	40	83	7	 1h	 3h	60	41
2	 1c	 3c	40	88	8	 1i	 3i	70	45
3	 1d	 3d	40	69	9	 1j	 3j	50	71
4	 1e	 3e	60	38 (54)[b]	10	 1k	 3k	50	63[d]
5	 1f	 3f	120	0[c]	11	 1l	 3l	40	69
6	 1g	 3g	60	60	12	 1m	 3m	40	81

[a]Isolated yield. [b]Achieved by addition of an extra 1 equiv of Mitsunobu reagents in the reaction mixture after 1 h of reaction time. [c]The reaction stopped at the zwitterionic 2-pyridone stage. [d]Only 7% of conversion into the corresponding cyano oxazolopyridine was observed by ^{1}H NMR.

analysis (CCDC 1477526) (Figure 1). One molecule of dichloromethane appeared to be trapped in each asymmetric unit of the crystal matrix.

Figure 1. X-ray structure of **3l** (asymmetric unit in thermal ellipsoid representation with 50% of probability).

On the other hand, in the case of keto ester or nitro ester Michael acceptors, no chemoselectivity was observed since the desired oxazolopyridines were obtained in moderate to low ratios among complex mixtures of unidentified byproducts. Finally, dibenzoate substituents afforded the desired compound **3m** in 81% isolated yield. Interestingly, no competitive intermolecular Mitsunobu reaction was observed. The latter could have occurred with a phenol group released in the ring-closure step.

The investigation was then focused on the amino alcohol moiety (Table 3). It was anticipated that substitution in the α-position of the nitrogen atom with sterically hindered groups might have an influence on the formed asymmetric center stereocontrol. Gratifyingly, good diastereoselectivity was achieved with a variety of enantiopure 2-substituted ethanolamines. Hindered substituents such as methyl or ethyl groups afforded desired compounds **3n** and **3o** in good yields and satisfactory >80:20 and >85:15 diastereoisomeric excess (Table 3, entries 1 and 2). Surprisingly, the isopropyl group did not enhance diastereoisomeric excess. The best result was obtained for the phenyl group, which afforded the desired compound **3r** in 75% yield and >95:5 diastereoselectivity (Table 3, entry 5).

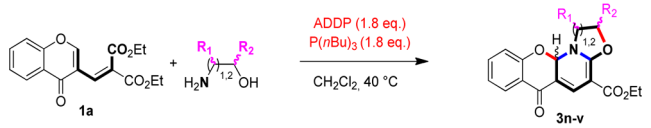
Absolute configurations of **3n** and **3r** asymmetric centers were determined by NOESY experiments (Scheme 5). The results show that H_a and H_b are *trans*-oriented in both cases. Consequently, absolute configurations of the new asymmetric centers were assigned as (*S*)-isomers.

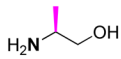
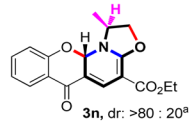
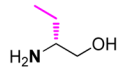
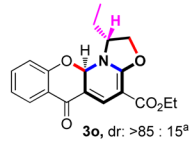
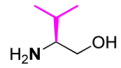
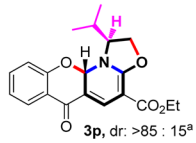
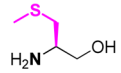
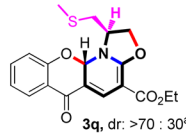
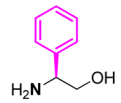
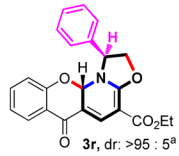
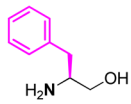
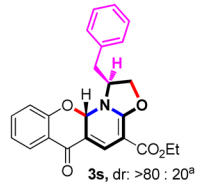
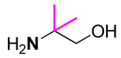
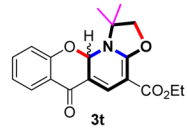
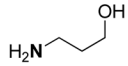
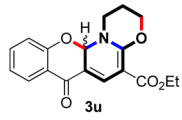
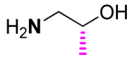
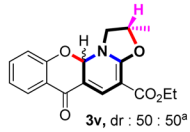
Finally, when 2-(benzyl)ethanolamine was used, the corresponding dihydro-oxazolopyridine **3s** was obtained in 77% yield and >80:20 diastereoisomeric excess (Table 3, entry 6).

The Mitsunobu sequence was less tolerant to secondary alcohols since compound **3v** was isolated in 35% yield (entry 9). As could be envisioned, this substitution did not have any influence on asymmetric center stereocontrol. In the case of tertiary alcohol, no conversion into targeted product was observed. The presence of a dimethyl group in the α-position of the nitrogen atom enhanced the reactivity of the Mitsunobu sequence by the Thorpe−Ingold effect.[34] Nevertheless, besides the desired oxazolopyridine, the steric hindrance of **3t** led to a substantial proportion of kinetic enaminochromanone side product as reported in our previous work involving primary amines and Michael acceptors.[26] The latter explains the moderate 52% of isolated yield observed for **3t**. In the case of

DOI: 10.1021/acs.joc.6b01523
J. Org. Chem. 2016, 81, 8837−8849

Table 3. Impact of Amino Alcohol Substitution on Domino Process



Entry	Amino alcohol	Product	Time (min)	Yield (%)[b]
1		 **3n**, dr: >80 : 20[a]	60	84
2		 **3o**, dr: >85 : 15[a]	60	77
3		 **3p**, dr: >85 : 15[a]	60	67
4		 **3q**, dr: >70 : 30[a]	60	69
5		 **3r**, dr: >95 : 5[a]	60	75
6		 **3s**, dr: >80 : 20[a]	60	77
7		 **3t**	40	52[c]
8		 **3u**	120	0[d]
9		 **3v**, dr : 50 : 50[a]	60	35

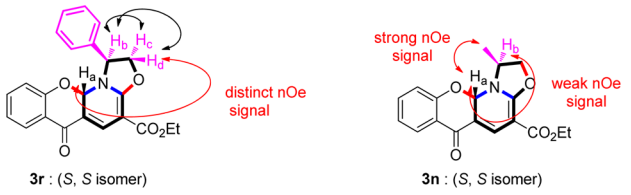
[a]Ratio determined by ^{1}H NMR spectroscopy. [b]Isolated yield. [c]Enaminochromanone kinetic product was observed in the crude mixture. [d]The reaction stopped at the zwitterionic 2-pyridone stage.

the cyclohexyl group, only enaminochromanone was observed in the crude mixture after 2 h of reaction time. Finally, a 6-membered oxazino ring was attempted, but surprisingly, the domino process stopped at the zwitterionic 2-pyridone stage.

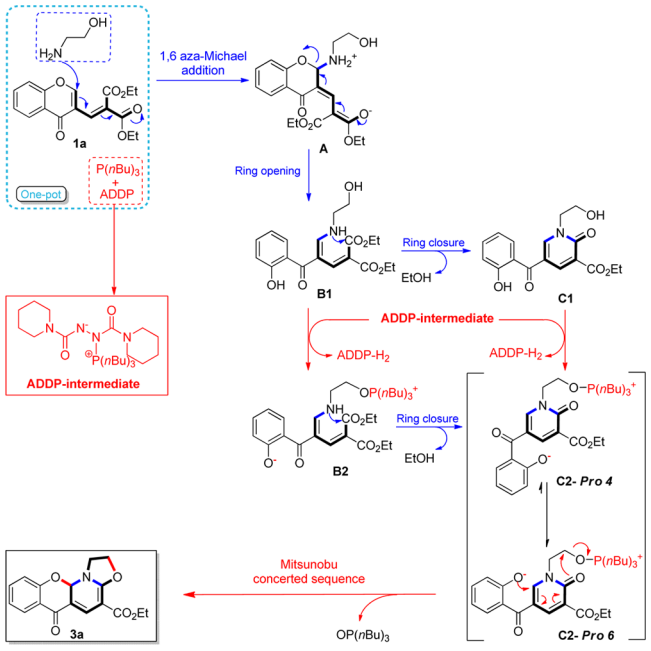
A plausible mechanism in accordance with previous work and DFT calculations is depicted in Scheme 6. The domino process would be initiated by a 1,6-aza-Michael addition of primary amino alcohols onto chromone acceptors leading first to a nonisolable intermediate **A**. The latter would then undergo a ring-opening step to provide **B1**. At this stage, the **C2** (in **Pro4** vs **Pro6** conformation) intermediate would be accessed via two competitive pathways, both of them involving a ring-closure step

DOI: 10.1021/acs.joc.6b01523
J. Org. Chem. 2016, 81, 8837−8849

Scheme 5. NOESY Interactions for 3n and 3r



Scheme 6. Plausible Mechanism of the Domino Process

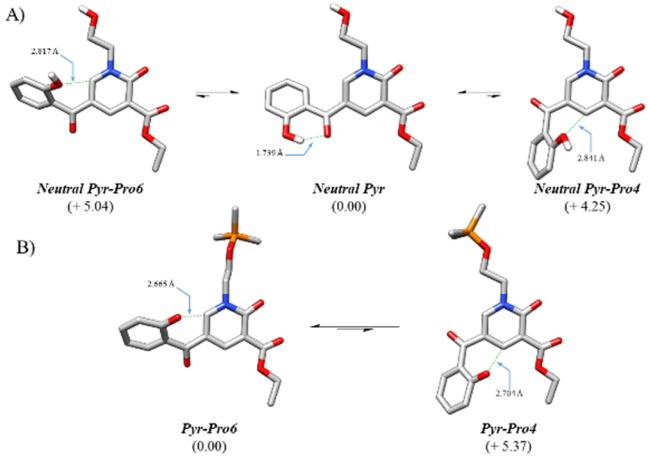


(**B1** to **C1** or **B2** to **C2**) and the generation of zwitterion species by active Mitsunobu reagent (**B1** to **B2** or **C1** to **C2**). Finally, 2-pyridone zwitterion **C2** in the favorable **Pro6** conformation would undergo a regioselective Mitsunobu-triggered sequence to allow final ring closure to afford the desired tetracyclic nitrogen-bridged dihydro-oxazolopyridines.

Mechanistic Study by DFT Calculations. To support the proposed mechanism of the Mitsunobu concerted sequence, a complete DFT investigation was conducted using state of the art M06-2X functional at the 6-31G(d,p) level of theory. The solvent effect was taken into account using the PCM (polarizable continuum model) formalism during optimization and frequency calculations.[35] As further specified, the domino process involves a first step leading to the formation of the 2-pyridone zwitterion intermediate followed by the intramolecular Mitsunobu triggered sequence, yielding tetracyclic nitrogen-bridged dihydro-oxazolopyridines.

a. Selectivity at C_6- vs C_4-Position. From the first step of the one-pot process, the formation of *N*-(hydroxyethyl)-2-pyridone (**2** ≡ **Pyr**) could be anticipated. In order to reduce the computational cost of the study and to simplify the system, we assumed the use of trimethylphosphine instead of *n*-tributylphosphine. At this point, two positions (C_4 and C_6) of zwitterionic **Pyr** could be involved in the intramolecular addition of the phenolate moiety. Therefore, the regioselectivity should be influenced by the conformational preference of zwitterionic **Pyr** and then by the energetic barrier level of the cyclization process. The nature of **Pyr** (neutral or zwitterionic) appeared to have an important impact on conformational preference. Concerning the neutral state **Neutral Pyr**, the existence of an intramolecular H-bonding greatly stabilizes the structure and thus strongly influences the orientation of different conformers (Scheme 7,

Scheme 7. Conformational Analysis of 2-Pyridone Intermediates at the Neutral (A) and Zwitterionic State (B) Calculated at the PCM/M06-2X/6-31G(d,p) Level of Theory[36]



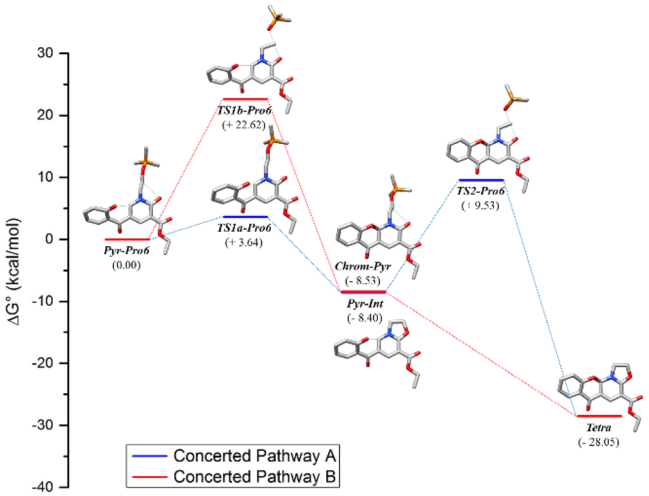
A). This affirmation is supported by the high relative free Gibbs energy computed for the two other C_6 (**Neutral Pyr-Pro6**) and C_4 (**Neutral Pyr-Pro4**) conformers, respectively, of 5.04 and 4.25 kcal/mol.

On the other hand, when zwitterionic **Pyr** was considered (negative charge on the phenolic moiety and positive charge on the phosphonium), the conformational analysis of **Pyr** indicated two conformers characterized by a tight distance between the phenoxide moiety and C_6 (**Pyr-Pro6**) or C_4 (**Pyr-Pro4**) positions of the 2-pyridone ring. The computed Boltzmann distribution definitively shows that **Pyr-Pro6** is quasi-exclusively favored (relative $\Delta G°$ of +5.37 kcal/mol calculated for **Pyr-Pro4** conformer at room temperature, Scheme 7, B). Moreover, calculations clearly revealed that the distance between reactive centers for **Pyr-Pro6** (2.665 Å) is slightly closer than for **Pyr-Pro4** (2.704 Å) (see the SI). These results are in perfect agreement with the regioselectivity observed experimentally.

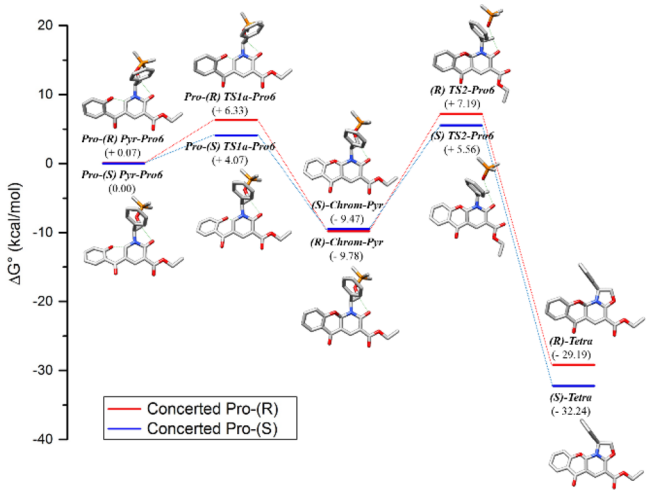
b. Concerted Path A vs Path B for Mitsunobu Sequence. DFT calculations were pursued with the study of the Mitsunobu sequence pathway and the localization of possible transition states and intermediates involved in this process leading to the final tetracyclic product (**Tetra**) and the release of trimethylphophine oxide byproduct (**TMP**). Herein, from the **Pyr-Pro6** transition state, two different concerted pathways can be hypothesized. On the one hand, a concerted pathway A in which the phenoxide ion of **Pyr-Pro6** induces a nucleophilic attack at the C_6-position of 2-pyridone ring could be envisioned. The latter leads to a chromenopyridone intermediate (**Chrom-Pyr**) that then undergoes a nucleophilic substitution of the phosphonium group by the oxygen of the 2-pyridone carbonyl group to form final **Tetra** (Scheme 8; also see the SI). On the other hand, another plausible concerted pathway B also was taken into account. The latter is initiated by the formation of the dihydro-oxazole ring from **Pyr-Pro6**, probably due to the impulse of nitrogen atom electron's lone pair, which generates a furtive pyridinium intermediate (**Pyr-Int**). Finally, **Pyr-Int** reacts in a barrierless fashion to yield final **Tetra** product since

DOI: 10.1021/acs.joc.6b01523
J. Org. Chem. 2016, 81, 8837–8849

Scheme 8. Energetic Profiles of Mitsunobu Sequence Computed at the PCM/M062X/6-31G(d,p) Level of Theory[36]



Scheme 9. Comparison of Pro-(*R*) and Pro(*S*) Concerted Mechanism A of Mitsunobu Sequence Calculated at the PCM/M06-2X/6-31G(d,p) Level of Theory[36]



several attempts failed to localize any transition state (Scheme 8; also see the SI). The overall process from **Pyr-Pro6** to **Tetra** was calculated to be exothermic with a free Gibbs energy variation of −28.05 kcal/mol (see the SI).

According to these calculations, it was assumed that the Mitsunobu-triggered sequence follows the concerted pathway A since the **TS1a-Pro6** transition state (+3.64 kcal/mol) is highly favored over **TS1b-Pro6** (+22.62 kcal/mol) regarding its lower activation barrier (Scheme 8). Moreover, the computed interatomic distance of transition states **TS1a-Pro6** (2.089 Å) and **Pyr-Int** (2.495 Å) also supported the proposed mechanism (Scheme SI 1). As calculations proved that concerted pathway A is greatly favored, the latter was applied on the β-substituted amino alcohols in order to justify the diastereoselectivity observed in these cases.

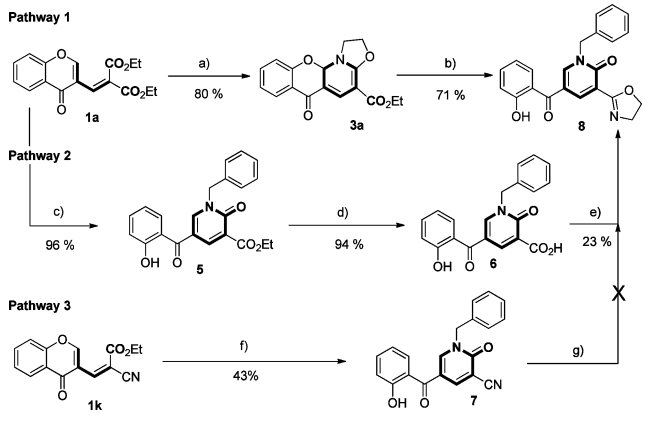
c. Diastereoselectivity. Since the best diastereoselectivity was observed (>95:5) for the 2-pyridone derivative bearing an (*S*)-1-amino-2-phenylethanol moiety, the latter was chosen as the model structure.[37]

First, transition states (**TS1a-Pro6**) implying phenolate nucleophilic attack at the C_6-position were calculated to be significantly different in terms of energy with +6.33 and +4.07 kcal/mol for Pro-(*R*) and Pro-(*S*) processes, respectively (Scheme 9; also see the SI). The calculated difference in terms of energy barriers ($\Delta\Delta G^{\ddagger}$ of 2.19 kcal/mol) favors the Pro-(*S*) process and can explain the diastereoselectivity observed when the Curtin−Hammett principle is applied.[38] Moreover, taking into account the last step of the Mitsunobu sequence characterized by a second transition state (**TS2-Pro6**), the computed free Gibbs energy barrier for Pro-(*S*) (+15.03 kcal/mol) is also favored over the Pro-(*R*) (+16.97 kcal/mol) process. Finally, when considering pathway A, the Pro-(*S*) process was modeled to be more favorable in terms of energy, and these theoretical results are correlated to the experimentally observed diastereoselectivity for **3r**. Despite this good correlation between both aspects, Pro-(*R*) and Pro-(*S*) processes were also computed through the concerted pathway B. Indeed, from a chemical point of view the latter was first considered as more plausible to control the newly formed stereogenic center through the furtive chiral oxazolopyridinium intermediate (**Pyr Int**). Nevertheless, the calculations did not support this hypothesis since this pathway remains improbable regarding the high activation barriers required (+19.71 kcal/mol for Pro-(*R*) and +19.12 kcal/mol for Pro-(*S*)). Moreover, in this case, no significant differences were highlighted in terms of free Gibbs energy barriers that could explain the diastereoselectivity observed ($\Delta\Delta G^{\ddagger}$ of 0.66 kcal/mol; see the SI).

As a final conclusion of the calculations section, the Mitsunobu-triggered sequence pathway was elucidated by DFT calculations. This domino sequence follows the concerted pathway A in a remarkable C_6-regioselective and diastereoselective fashion.

An interesting application that underlines the potential of this methodology is pointed out in Scheme 10. It was shown that the resulting tetracyclic systems could be useful synthetic intermediates to access a new class of *N*,3,5-trisubstituted 2-pyridones bearing an oxazoline group at the C_3-position. As illustrated in

Scheme 10. Application of the Developed Methodology[a]



[a]Key: (a) ethanolamine (1.05 equiv), ADDP/P*n*(Bu)$_3$ (1.8 equiv each), CH_2Cl_2, 40 °C, 40 min; (b) benzylamine (1.2 equiv), CH_2Cl_2, 40 °C, 40 h; (c) benzylamine (1.05 equiv), CsF (10 mol %), CH_2Cl_2, 40 °C, 1 h; (d) Ac_2O/HCl (37%) (3:1), 90 °C, h; (e) ethanolamine (1.00 equiv), PPh_3 (3 equiv), Et_3N (3 equiv), CCl_4 (4 equiv), MeCN/Pyr, rt, 14 h; (f) benzylamine (1.05 equiv), CsF (10 mol %), EtOH, 60 °C, 2 h; (g) ethanolamine (2.00 equiv), $ZnCl_2$ (0.50 equiv), chlorobenzene, reflux, 16 h.

DOI: 10.1021/acs.joc.6b01523
J. Org. Chem. 2016, 81, 8837−8849

Scheme 10 (pathway 1), the treatment of compound **3a** with benzylamine afforded 2-pyridone **8** in 71% yield. It is proposed that the latter was achieved through the addition of benzylamine at the C_{11a}-position of **3a** followed by a ring-opening/aza-Claisen rearrangement/ring-closure sequence. The oxazoline group could thus have been introduced at the C_3-position in two steps in 57% overall yield starting from Michael acceptor **1a**.

On the other hand, classical reported methodologies appeared to be much less efficient to access **8** starting from carboxylic acid[39] or cyano precursors.[40] The latter was synthesized in three steps in 21% overall yield via pathway 2, while the cyano group failed to provide **8** through pathway 3 (Scheme 10).

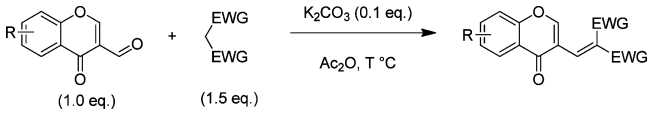
CONCLUSION

In conclusion, an original Mitsunobu-triggered sequence has been successfully developed and incorporated in a global domino process for the generation of an interesting class of tetracyclic systems bearing an atypical bis-*N*,*O*-acetal junction. This powerful one-pot methodology operates under mild conditions and has demonstrated its tolerance to a large scope of Michael acceptors and readily available racemic or chiral amino alcohols. The concerted mechanism proposed for the Mitsunobu-triggered sequence was corroborated by experimental and theoretical mechanism studies. From a synthetic point of view, Mitsunobu activation has shown its significant value in incorporation in domino strategies. Furthermore, this is the first time that the Mitsunobu reaction has led to the formation of two bonds. Ultimately, it was demonstrated that the formed tetracyclic nitrogen-bridged dihydro-oxazolopyridines can be useful synthetic intermediates to access a new class of *N*,3,5-trisubstituted 2-pyridones of biological interest.

EXPERIMENTAL SECTION

General Details. Unless otherwise specified, reagents and starting materials were purchased from traditional suppliers and were used without further purification. Reactions were carried out in standard glassware. NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C in deuterated chloroform ($CDCl_3$) at room temperature, using TMS as internal standard (δ = 0). High-resolution ESI mass spectra were measured on a Q-TOF System spectrometer. Column chromatographic purifications were performed using Si_2O (40−63 μm) as the solid phase and a mixture of dichloromethane/ethyl acetate or cyclohexane/ethyl acetate as the eluent. Melting points were recorded on a Scientific Analyzer SMP 10 apparatus and are uncorrected. Infrared spectra were performed neat on an FT-IR spectrophotometer, and only broad or strong signals are reported.

General Procedure for α,β-Unsaturated Chromone Synthesis (1). Michael acceptors bearing the chromone core were prepared by an



improved method according to Ghosh's procedure.[41] To a previously stirred solution of malonate derivative (1.5 equiv) and K_2CO_3 (0.1 equiv) in acetic anhydride, the appropriate 3-formylchromone was added, and the mixture was heated at adequate temperature until no starting material was observed (TLC analysis). After being cooled at room temperature or at 0 °C, the precipitate formed was filtered and washed with cyclohexane to afford the corresponding Michael acceptors.

*Diethyl 2-[(4-oxo-4H-chromen-3-yl)methylene]malonate (**1a**):* white powder (precipitation in Ac_2O); R_f = 0.31, eluent (ethyl acetate/cyclohexane 1:4); mp = 112−114 °C, 5.00 g scale reaction (in 15 mL of Ac_2O) for 3h at 90 °C, 8.81 g was isolated, 97% yield; IR (ν_{max}/cm^{-1}) 1716, 1650, 1632, 1460, 1213; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.34 (s, 1H), 8.26 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.79 (s, 1H), 7.71 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.50−7.42 (m, 2H), 4.34 (2 × q, *J* = 7.2 Hz, 4H), 1.50 (t, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 175.1, 165.9, 163.9, 156.4, 155.9, 134.3, 133.1, 128.12, 126.4, 126.0, 123.8, 119.1, 118.2, 61.8, 61.8, 14.1, 14.0. Physical and NMR spectral data are in accordance with those previously reported.[41]

*Diethyl 2-((6-methyl-4-oxo-4H-chromen-3-yl)methylene)-malonate (**1b**):* pale yellow powder (precipitation in cold Ac_2O); R_f = 0.33, eluent (ethyl acetate/cyclohexane 3:7); mp = 67−69 °C, 5.00 g scale reaction (in 15 mL of Ac_2O) for 3 h at 90 °C, 5.90 g was isolated, 67% yield; IR (ν_{max}/cm^{-1}) 1715, 1654, 1620, 1481, 1201; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.26 (s, 1H), 7.97 (s, 1H), 7.73 (s, 1H), 7.47 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 4.29 (2 × q, *J* = 7.1 Hz, 4H), 2.42 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 175.1, 165.9, 163.9, 156.4, 154.1, 136.0, 135.4, 133.2, 127.9, 125.5, 123.3, 118.8, 117.9, 61.7, 61.4, 20.9, 14.1, 14.0. Physical and NMR spectral data are in accordance with those previously reported.[41]

*Diethyl 2-((6-(benzyloxy)-4-oxo-4H-chromen-3-yl)methylene)-malonate (**1c**):* yellow powder (precipitation in Ac_2O); R_f = 0.40, eluent (ethyl acetate/cyclohexane 1:9); mp = 130−132 °C, 0.20 g scale reaction (in 4 mL of Ac_2O) for 1 h at 90 °C, 0.27 g was isolated, 90% yield; IR (ν_{max}/cm^{-1}) 1724, 1687, 1658, 1483, 1450, 1220; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.30 (s, 1H), 7.78 (s, 1H), 7.70 (d, *J* = 2.6 Hz, 1H), 7.31−7.49 (m, 7H), 5.15 (s, 2H), 4.32 (qx2, *J* = 7.3 Hz, 4H), 1.32 (t × 2, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 174.9, 165.9, 163.9, 156.6, 156.2, 150.8, 136.0, 133.2, 128.7 (×2), 128.3, 128.0, 127.7 (×2), 124.7, 124.4, 119.7, 118.3, 106.7, 70.7, 61.7 (×2), 14.1, 14.0; HRMS (ESI$^+$) calcd for $C_{24}H_{23}O_7$ $[M + H]^+$ 423.1444, found 423.1427

*Diethyl 2-((6-isopropyl-4-oxo-4H-chromen-3-yl)methylene)-malonate (**1d**):* pale yellow powder (precipitation in Ac_2O at 0 °C); R_f = 0.65, eluent (ethyl acetate/cyclohexane 3:7); mp = 59−61 °C, 1.00 g scale reaction (in 4 mL of Ac_2O) for 3 h at 90 °C, 1.45 g was isolated, 88% yield; IR (ν_{max}/cm^{-1}) 1723, 1658, 1604, 1487, 1463, 1243; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.30 (d, *J* = 1.0 Hz, 1H), 8.08 (d, *J* = 2.4 Hz, 1H), 7.78 (d, *J* = 1.0 Hz, 1H), 7.58 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 4.33 (dq, *J* = 10.1, 7.1 Hz, 4H), 3.04 (hept, *J* = 6.9 Hz, 1H), 1.40−1.28 (m, 6H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 175.3, 165.9, 163.9, 156.3, 154.3, 147.0, 133.3, 133.1, 127.9, 123.5, 123.1, 118.8, 118.1, 61.7 (×2), 33.8, 23.9 (×2), 14.1, 14.0; HRMS (ESI$^+$) calcd for $C_{20}H_{23}O_6$ $[M + H]^+$ 359.1495, found 359.1508.

*Diethyl 2-((6-bromo-4-oxo-4H-chromen-3-yl)methylene)-malonate (**1e**):* white powder (precipitation in cold Ac_2O); R_f = 0.56, eluent (ethyl acetate/cyclohexane 4:6); mp = 89−91 °C, 1.00 g scale reaction (in 4 mL of Ac_2O) for 2 h at 90 °C, 1.34 g was isolated, 89% yield; IR (ν_{max}/cm^{-1}) 1720, 1643, 1610, 1456, 1235; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.34−8.38 (m, 1H), 8.32 (s, 1H), 7.79 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.72 (s, 1H), 7.39 (d, *J* = 8.9 Hz, 1H), 4.33 (2 × q, *J* = 7.1 Hz, 4H), 1.33 (2 × t, *J* = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 173.8, 165.7, 163.7, 156.5, 154.6, 137.3, 132.5, 128.9, 128.7, 125.0, 120.2, 119.5, 119.2, 61.9 (×2), 14.1, 14.0; HRMS (ESI$^+$) calcd for $C_{17}H_{16}BrO_6$ $[M + H]^+$ 395.0130, found 395.0138.

*Diethyl 2-((6-nitro-4-oxo-4H-chromen-3-yl)methylene)malonate (**1f**).* pale yellow powder (precipitation in Ac_2O); R_f = 0.66, eluent (ethyl acetate/cyclohexane 1:1); mp = 158−160 °C, 3.50 g scale reaction (in 10 mL of Ac_2O) for 2 h, 3.86 g was isolated, 67% yield; IR (ν_{max}/cm^{-1}) 1720, 1657, 1626, 1531, 1465, 1345, 1202; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.11 (d, *J* = 2.7 Hz, 1H), 8.55 (dd, *J* = 9.2, 2.8 Hz, 1H), 8.40 (d, *J* = 1.0 Hz, 1H), 7.70 (d, *J* = 1.0 Hz, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 4.34 (qx2, *J* = 7.1 Hz, 4H), 1.35 (t × 2, *J* = 7.1, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 173.7, 165.5, 163.5, 158.6, 156.5, 145.2, 131.6, 129.8, 128.6, 123.8, 123.0, 120.1, 119.8, 62.0 (×2), 14.1, 14.0; HRMS (ESI$^+$) calcd for $C_{17}H_{16}NO_8$ $[M + H]^+$ 362.0876, found 362.0886.

*Diethyl 2-((6-chloro-7-methyl-4-oxo-4H-chromen-3-yl)-methylene)malonate (**1g**):* colorless crystals (crystallization in Ac_2O); R_f = 0.80, eluent (ethyl acetate/cyclohexane 1:1); mp = 140−142 °C, 1.00 g scale reaction (in 4 mL of Ac_2O) for 2 h at 90 °C, 1.17 g was isolated, 71% yield; IR (ν_{max}/cm^{-1}) 1723, 1646, 1616, 1556, 1458, 1375, 1189; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.29 (d, *J* = 1.0 Hz, 1H), 8.20 (s, 1H), 7.74 (d, *J* = 1.0 Hz, 1H), 7.37 (d, *J* = 0.9 Hz, 1H), 4.34 (2 ×

DOI: 10.1021/acs.joc.6b01523
J. Org. Chem. 2016, 81, 8837−8849

q, J = 7.1 Hz, 4H), 2.52 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 174.0, 165.8, 163.8, 156.3, 154.1, 143.7, 132.7, 132.7, 128.4, 126.0, 122.8, 120.0, 119.0, 61.8 (×2), 20.9, 14.1, 14.0; HRMS (ESI$^+$) calcd for $C_{18}H_{18}ClO_6$ $[M + H]^+$ 365.0792, found 365.0805.

*Diethyl 2-((7-ethoxy-8-methyl-4-oxo-4H-chromen-3-yl)-methylene)malonate (**1h**):* white solid (precipitation in Ac_2O); R_f = 0.80, eluent (ethyl acetate/cyclohexane 1:1); mp = 101−102 °C, 0.63 g scale reaction (in 2 mL of Ac_2O) for 3 h at 90 °C, 0.83 g was isolated, 82% yield; IR (ν_{max}/cm^{-1}) 1723, 1656, 1616, 1460, 1240; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.32 (d, J = 1.0 Hz, 1H), 8.08 (d, J = 8.9 Hz, 1H), 7.80 (d, J = 1.0 Hz, 1H), 6.99 (d, J = 8.9 Hz, 1H), 4.34 (2 × q, J = 7.1 Hz, 4H), 4.19 (q, J = 7.0 Hz, 2H), 2.30 (s, 3H), 1.49 (t, J = 7.0 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 175.1, 166.1, 164.0, 161.3, 156.3, 155.1, 133.5, 127.5, 124.8, 118.2, 117.4, 114.4, 110.0, 64.5, 61.7, 61.7, 14.8, 14.2, 14.0, 8.1; HRMS (ESI$^+$) calcd for $C_{20}H_{23}O_7$ $[M + H]^+$ 375.1444, found 375.1458.

*Diethyl 2-((4-oxo-4H-benzo[h]chromen-3-yl)methylene)-malonate (**1i**):* beige powder (precipitation in cold Ac_2O); R_f = 0.52, eluent (ethyl acetate/cyclohexane 1:2); mp = 140−142 °C, 4.00 g scale reaction (in 15 mL of Ac_2O) for 4h, 4.73 g was isolated, 73% yield; IR (ν_{max}/cm^{-1}) 1718, 1648, 1569, 1510, 1367, 1206; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.51 (s, 1H), 8.45 (d, J = 7.9 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.85 (s, 1H), 7.65−7.82 (m, 3H), 4.36 (2 × q, J = 7.2 Hz, 4H), 1.34 (2 × t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 175.0, 165.9, 163.8, 155.5, 153.5, 136.0, 133.0, 129.7, 128.5, 128.2, 127.5, 126.1, 123.7, 122.2, 120.9, 120.3, 120.2, 61.8, 61.8, 14.2, 14.0. Physical and NMR spectral data are in accordance with those previously reported.[42]

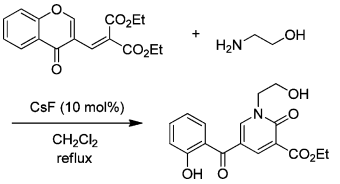
*Diethyl 2-((1-oxo-1H-benzo[f]chromen-2-yl)methylene)-malonate (**1j**):* pale yellow powder (precipitation in cold Ac_2O); R_f = 0.77, eluent (ethyl acetate/cyclohexane 1:1); mp = 84−86 °C, 4.00 g scale reaction (in 10 mL of Ac_2O) for 5 h, 5.10 g was isolated, 78% yield; IR (ν_{max}/cm^{-1}) 1715, 1654, 1591, 1514, 1440, 1218; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.94 (d, J = 8.4 Hz, 1H), 8.33 (s, 1H), 8.02−8.11 (m, 1H), 7.84−7.95 (m, 2H), 7.70−7.82 (m, 1H), 7.57−7.69 (m, 1H), 7.40−7.53 (m, 1H), 4.35 (2 × q, J = 7.2 Hz, 4H), 1.34 (2 × t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 176.7, 165.9, 163.8, 157.2, 153.8, 136.1, 133.5, 130.8, 130.4, 129.6, 128.3, 128.3, 127.1, 127.0, 121.4, 117.3, 117.1, 61.8, 61.8, 14.2, 14.0; HRMS (ESI$^+$) calcd for $C_{21}H_{19}O_6$ $[M + H]^+$ 367.1182, found 367.1194.

*Ethyl 2-cyano-3-(4-oxo-4H-chromen-3-yl)acrylate (**1k**):* orange powder (precipitation in cold Ac_2O); R_f = 0.77, eluent (ethyl acetate/cyclohexane 1:1); mp = 128−130 °C, 3.00 g scale reaction (in 8 mL of Ac_2O) for 5 h at room temperature, 3.23 g was isolated, 70% yield; IR (ν_{max}/cm^{-1}) 2221, 1726, 1654, 1605, 1557, 1450, 1274; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.17 (d, J = 0.9 Hz, 1H), 8.67 (d, J = 0.9 Hz, 1H), 8.30 (ddd, J = 8.0, 1.7, 0.5 Hz, 1H), 7.79 (ddd, J = 8.7, 7.2, 1.7 Hz, 1H), 7.60−7.49 (m, 2H), 4.41 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 174.5, 161.5, 158.3, 155.8, 145.7, 134.9, 126.6, 126.5, 123.6, 118.6, 117.8, 115.4, 103.6, 62.9, 14.2. Physical and NMR spectral data are in accordance with those previously reported.[41]

*2-Benzoyl-3-(4-oxo-4H-chromen-3-yl)acrylonitrile (**1l**):* white powder (precipitation in Ac_2O followed by column chromatography); R_f = 0.31, eluent (ethyl acetate/cyclohexane 1:4); mp = 140−142 °C, 500 mg scale reaction (in 1 mL of Ac_2O) for 2 h at room temperature, 507 mg was isolated, 58% yield; IR (ν_{max}/cm^{-1}) 2220, 1729, 1616, 1560, 1463; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.25 (s, 1H), 8.41 (s, 1H), 8.28 (dd, J = 7.9, 1.7 Hz, 1H), 7.88 (d, J = 7.2 Hz, 2H), 7.84−7.77 (m, 1H), 7.71−7.64 (m, 1H), 7.61−7.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 188.5, 174.7, 158.1, 155.9, 146.0, 135.4, 135.0, 133.6, 129.4 (×2), 128.8 (×2), 126.7, 126.5, 123.5, 118.6, 118.1, 116.4, 110.9; HRMS (ESI$^+$) calcd for $C_{19}H_{12}NO_3$ $[M + H]^+$ 302.0817, found 302.0823.

*Diphenyl 2-((4-oxo-4H-chromen-3-yl)methylene)malonate (**1m**):* yellow powder (precipitation in cold Ac_2O); R_f = 0.77, eluent (ethyl acetate/cyclohexane 1:1); mp = 123−124 °C, 3.00 g scale reaction (in 8 mL of Ac_2O) for 5 h at room temperature, 3.23 g was isolated, 70% yield: IR (ν_{max}/cm^{-1}) 1756, 1725, 1661, 1614, 1485, 1461, 1239; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.48 (s, 1H), 8.34 (d, J = 7.9 Hz, 1H), 7.99 (s, 1H), 7.76 (t, J = 7.9 Hz, 1H), 7.57−7.41 (m, 6H), 7.39−7.24 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 174.7, 163.9, 162.7, 158.1, 155.8, 150.6, 150.6, 136.2, 134.5, 129.6 (×2), 129.6 (×2), 126.9, 126.6, 126.3, 126.2 (×2), 123.8, 121.7 (×2), 121.5 (×2), 118.9, 118.2; HRMS (ESI$^+$) calcd for $C_{25}H_{17}O_6$ $[M + H]^+$ 413.1025, found 413.1031.

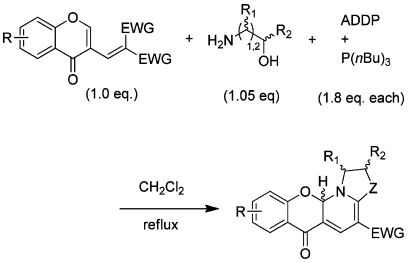
General Procedure for Pyridone Synthesis (2).



To a previously stirred solution containing α,β-unsaturated chromone and CsF (10.0 mol %) in dichloromethane was added the corresponding amine (1.05 equiv). The reaction mixture was stirred under reflux until full consumption of substrates was observed (followed by TLC). After concentration under reduced pressure, the resulting mixture yielded pure *N*,3,5-trisubstituted pyridin-2-one after purification on silica gel column chromatography.

*Ethyl 5-(2-hydroxybenzoyl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (**2**):* pale yellow powder (column chromatography); R_f = 0.24, eluent (ethyl acetate/dichloromethane 1:1); mp = 146−148 °C, 1.00 g scale reaction (in 5 mL of CH_2Cl_2) for 1 h, 0.75 g was isolated, 71% yield; IR (ν_{max}/cm^{-1}) 3448, 1722, 1625, 1530, 1341, 1218; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 11.39 (s, 1H), 8.53 (d, J = 2.7 Hz, 1H), 8.34 (d, J = 2.7 Hz, 1H), 7.62 (dd, J = 8.0, 1.6 Hz, 1H), 7.51 (ddd, J = 8.7, 7.2, 1.6 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.20 (t, J = 4.9 Hz, 2H), 4.02−3.92 (m, 2H), 3.43 (t, J = 5.2 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 194.4, 163.9, 162.4, 159.1, 148.6, 144.1, 136.4, 131.8, 119.3, 119.2, 118.7, 118.6, 115.3, 61.6, 59.9, 53.4, 14.2; HRMS (ESI$^+$) calcd for $C_{17}H_{18}NO_6$ $[M + H]^+$ 332.1134, found 332.1142.

General Procedure for Tetracyclic Nitrogen Fused Tetrahydro-oxazolopyridine Synthesis (3).



To a previously stirred solution containing α,β-unsaturated chromones under reflux in dichloromethane were added the corresponding amine (1.05 equiv), ADDP (1.8 equiv), and P(n-Bu)$_3$. The reaction mixture was stirred under reflux until full consumption of substrates was observed (followed by TLC). The resulting mixtures yielded pure tetrahydro-oxazolopyridines derivatives after purification on silica gel column chromatography.

*Ethyl 6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]-pyridine-4-carboxylate (**3a**):* bright yellow amorphous solid (column chromatography); R_f = 0.53, eluent (ethyl acetate/dichloromethane 1:1); mp = 168−169 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 40 min, 79 mg isolated, 80% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1657, 1616, 1460, 1279; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.97 (dd, J = 7.8, 1.7 Hz, 1H), 7.93 (s, 1H), 7.50 (ddd, J = 8.3, 7.2, 1.8 Hz, 1H), 7.10 (ddd, J = 8.1, 7.3, 1.1 Hz, 1H), 6.95 (dd, J = 8.3, 1.1 Hz, 1H), 6.57 (s, 1H), 4.98−4.89 (m, 1H), 4.84 (q, J = 9.2 Hz, 1H), 4.35−4.26 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.79 (q, J = 9.5 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 179.9, 163.7, 163.5, 155.3, 136.0, 135.6, 127.6, 123.9, 122.6, 117.8, 110.6, 86.6, 81.5, 69.5, 59.8, 45.1, 14.5; HRMS (ESI$^+$) calcd for $C_{17}H_{16}NO_5$ $[M + H]^+$ 314.1028, found 314.1033.

*Ethyl 8-methyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]-oxazolo[3,2-a]pyridine-4-carboxylate (**3b**):* bright yellow amorphous solid (column chromatography); R_f = 0.46, eluent (ethyl acetate/dichloromethane 1:1); mp = 91−92 °C, 100 mg scale reaction (in 3 mL

DOI: 10.1021/acs.joc.6b01523
J. Org. Chem. 2016, 81, 8837−8849

of CH_2Cl_2) for 40 min, 82 mg isolated, 83% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1657, 1616, 1487, 1463, 1279; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.92 (s, 1H), 7.75 (d, J = 1.9 Hz, 1H), 7.31 (dd, J = 8.3, 1.9 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.52 (s, 1H), 4.97−4.88 (m, 1H), 4.83 (q, J = 9.2 Hz, 1H), 4.33−4.26 (m, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.77 (q, J = 9.5 Hz, 1H), 2.33 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.1, 163.7, 163.5, 153.3, 136.6, 135.8, 132.2, 127.3, 123.5, 117.6, 110.8, 86.5, 81.3, 69.5, 59.8, 45.1, 20.5, 14.5; HRMS (ESI$^+$) calcd for $C_{18}H_{18}NO_5$ [M + H]$^+$ 328.1185, found 328.1191.

*Ethyl 8-(benzyloxy)-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]-oxazolo[3,2-a]pyridine-4-carboxylate (**3c**):* bright yellow amorphous solid (column chromatography); R_f = 0.41, eluent (ethyl acetate/dichloromethane 1:1); mp = 199−200 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 40 min, 87 mg isolated, 88% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1655, 1616, 1486, 1241; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.94 (s, 1H), 7.51 (d, J = 3.1 Hz, 1H), 7.47−7.34 (m, 5H), 7.17 (dd, J = 8.9, 3.2 Hz, 1H), 6.90 (d, J = 8.9 Hz, 1H), 6.50 (s, 1H), 5.08 (s, 2H), 4.97−4.88 (m, 1H), 4.88−4.76 (m, 1H), 4.32−4.26 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.76 (q, J = 9.5 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 179.9, 163.7, 163.5, 154.1, 149.8, 136.6, 136.1, 128.6 (×2), 128.1, 127.6 (×2), 124.9, 124.1, 119.1, 110.5, 109.8, 86.5, 81.5, 70.6, 69.5, 59.8, 45.1, 14.5; HRMS (ESI$^+$) calcd for $C_{24}H_{22}NO_6$ [M + H]$^+$ 420.1447, found 420.1453.

*Ethyl 8-isopropyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]-oxazolo[3,2-a]pyridine-4-carboxylate (**3d**):* bright yellow amorphous solid (column chromatography); R_f = 0.60, eluent (ethyl acetate/dichloromethane 1:1); mp = 84−86 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 40 min, 67 mg was isolated, 68% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1655, 1616, 1486, 1461, 1241; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.92 (s, 1H), 7.82 (d, J = 2.3 Hz, 1H), 7.37 (dd, J = 8.5, 2.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.53 (s, 1H), 4.98−4.77 (m, 2H), 4.34−4.25 (m, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.77 (q, J = 9.4 Hz, 1H), 2.92 (hept, J = 6.9 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.26 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.2, 163.8, 163.5, 153.5, 143.3, 135.7, 134.2, 124.8, 123.5, 117.7, 110.9, 86.5, 81.4, 69.4, 59.8, 45.1, 33.4, 23.9, 23.9, 14.5; HRMS (ESI$^+$) calcd for $C_{20}H_{22}NO_5$ [M + H]$^+$ 356.1498, found 356.1505.

*Ethyl 8-bromo-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]-oxazolo[3,2-a]pyridine-4-carboxylate (**3e**):* bright yellow amorphous solid (column chromatography); R_f = 0.33, eluent (ethyl acetate/dichloromethane 1:1); mp = 193−194 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 38 mg isolated, 38% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1657, 1618, 1488, 1459, 1247; ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.08 (d, J = 2.4 Hz, 1H), 7.96 (s, 1H), 7.57 (dd, J = 8.7, 2.6 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.57 (s, 1H), 5.01−4.80 (m, 2H), 4.35−4.26 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.81 (q, J = 9.5 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 178.6, 163.6, 163.5, 154.1, 138.2, 136.9, 130.2, 125.2, 119.9, 115.4, 109.6, 86.8, 81.9, 69.5, 59.9, 45.1, 14.5; HRMS (ESI$^+$) calcd for $C_{17}H_{15}BrNO_5$ [M + H]$^+$ 392.0134, found 392.0136.

*Ethyl 8-chloro-9-methyl-6-oxo-1,2,6,11a-tetrahydrochromeno-[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (**3g**):* bright yellow amorphous solid (column chromatography); R_f = 0.469 eluent (ethyl acetate/dichloromethane 1:1); mp = 192−193 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 59 mg isolated, 60% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1655, 1615, 1497, 1475, 1268; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.89 (s, 1H), 7.86 (s, 1H), 6.83−6.79 (m, 1H), 6.49 (s, 1H), 4.97−4.78 (m, 2H), 4.29−4.23 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.77 (q, J = 9.4 Hz, 1H), 2.36 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 178.7, 163.6, 163.5, 153.5, 144.6, 136.3, 128.7, 127.2, 122.8, 120.0, 109.9, 86.8, 81.6, 69.5, 59.8, 45.1, 20.8, 14.5; HRMS (ESI$^+$) calcd for $C_{18}H_{17}ClNO_5$ [M + H]$^+$ 362.0795, found 362.0801.

*Ethyl 9-ethoxy-10-methyl-6-oxo-1,2,6,11a-tetrahydrochromeno-[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (**3h**):* bright yellow amorphous solid (column chromatography); R_f = 0.37, eluent (ethyl acetate/dichloromethane 1:1); mp = 193−194 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 41 mg isolated, 41% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1653, 1611, 1518, 1497, 1267; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.90 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 6.54 (s, 1H), 4.98−4.81 (m, 2H), 4.32 (td, J = 9.3, 6.2 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.13 (q, J = 7.0 Hz, 2H), 3.82 (q, J = 9.3 Hz, 1H), 2.10 (s, 3H), 1.46 (t, J = 7.0 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 179.9, 163.8, 163.2, 162.8, 154.3, 134.7, 126.4, 117.5, 114.0, 111.0, 106.1, 86.7, 81.2, 69.3, 64.1, 59.7, 45.0, 14.8, 14.5, 8.1; HRMS (ESI$^+$) calcd for $C_{20}H_{22}NO_6$ [M + H]$^+$ 372.1447, found 372.1453.

*Ethyl 6-oxo-1,2,6,13a-tetrahydrobenzo[7,8]chromeno[3,2-e]-oxazolo[3,2-a]pyridine-4-carboxylate (**3i**):* bright yellow amorphous solid (column chromatography); R_f = 0.48, eluent (ethyl acetate/dichloromethane 1:1); mp = 128−129 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 44 mg isolated, 45% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1652, 1617, 1489, 1463, 1239; ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.21 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.98 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.66−7.60 (m, 1H), 7.57−7.50 (m, 2H), 6.76 (s, 1H), 5.03−4.90 (m, 2H), 4.55−4.43 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.91 (q, J = 9.4 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.0, 163.7, 163.3, 152.7, 137.5, 129.3, 128.1, 126.2, 124.7, 122.8, 122.6, 122.2, 118.6, 110.3, 87.6, 81.6, 76.8, 69.5, 59.9, 45.2, 14.5; HRMS (ESI$^+$) calcd for $C_{21}H_{18}NO_5$ [M + H]$^+$ 364.1185, found 364.1188.

*Ethyl 6-oxo-1,2,6,13a-tetrahydrobenzo[5,6]chromeno[3,2-e]-oxazolo[3,2-a]pyridine-4-carboxylate (**3j**):* bright yellow amorphous solid (column chromatography); R_f = 0.38, eluent (ethyl acetate/dichloromethane 1:1); mp = 91−92 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 70 mg isolated, 71% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1657, 1616, 1486, 1463, 1279; ^1H NMR (300 MHz, $CDCl_3$) δ_H 9.39 (dd, J = 8.7, 1.0 Hz, 1H), 7.97 (s, 1H), 7.94 (d, J = 9.0 Hz, 1H), 7.77 (dd, J = 8.1, 1.6 Hz, 1H), 7.65 (ddd, J = 8.6, 6.9, 1.5 Hz, 1H), 7.45 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.06 (d, J = 8.9 Hz, 1H), 6.51 (s, 1H), 4.98−4.89 (m, 1H), 4.84 (q, J = 9.0, 8.4 Hz, 1H), 4.34−4.27 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.78 (q, J = 9.4 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.5, 163.8, 163.2, 156.1, 137.1, 131.8, 130.0, 129.2, 128.3, 126.6, 125.1, 118.3, 116.2, 111.7, 86.4, 81.4, 76.7, 69.5, 59.8, 45.0, 14.5; HRMS (ESI$^+$) calcd for $C_{21}H_{18}NO_5$ [M + H]$^+$ 364.1185, found 364.1192.

*Ethyl 6-oxo-2,3,6,11a-tetrahydro-1H-chromeno[3,2-e]imidazo-[1,2-a]pyridine-4-carboxylate (**3k**):* bright yellow amorphous solid (column chromatography); R_f = 0.16, eluent (ethyl acetate/dichloromethane 1:1); mp = 183−184 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 78 mg isolated, 67% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1648, 1607, 1558, 1501, 1478, 1462, 1360; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.98 (dd, J = 7.8, 1.8 Hz, 1H), 7.95 (s, 1H), 7.86 (bs, 1H), 7.45 (ddd, J = 8.6, 7.2, 1.8 Hz, 1H), 7.08 (td, J = 7.6, 1.1 Hz, 1H), 6.94 (dd, J = 8.2, 1.0 Hz, 1H), 6.31 (s, 1H), 4.30−4.22 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.91 (t, J = 8.5 Hz, 2H), 3.75−3.57 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 179.7, 166.8, 159.0, 155.7, 135.2, 134.8, 127.5, 124.3, 122.2, 117.7, 108.2, 86.2, 80.5, 59.6, 46.3, 42.8, 14.6; HRMS (ESI$^+$) calcd for $C_{17}H_{17}N_2O_4$ [M + H]$^+$ 313.1188, found 313.1194.

*4-Benzoyl-2,3-dihydro-1H-chromeno[3,2-e]imidazo[1,2-a]-pyridin-6(11aH)-one (**3l**):* bright yellow amorphous solid (column chromatography); R_f = 0.25, eluent (ethyl acetate/dichloromethane 1:1); mp = 219−221 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 50 min, 79 mg isolated, 69% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1726, 1643, 1553, 1469, 1463, 1362; ^1H NMR (300 MHz, $CDCl_3$) δ_H 9.42 (s, 1H), 7.96 (dd, J = 7.8, 1.8 Hz, 1H), 7.76 (s, 1H), 7.56−7.39 (m, 6H), 7.10 (td, J = 7.5, 1.1 Hz, 1H), 6.98 (dd, J = 8.3, 1.0 Hz, 1H), 6.32 (s, 1H), 4.32 (td, J = 9.6, 6.5 Hz, 1H), 4.12−3.89 (m, 2H), 3.85−3.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 191.4, 179.9, 160.2, 155.9, 139.5, 136.7, 135.1, 130.3, 128.4 (×2), 127.9 (×2), 127.6, 124.1, 122.5, 117.7, 109.2, 91.6, 85.4, 45.9, 43.1; HRMS (ESI$^+$) calcd for $C_{21}H_{17}N_2O_3$ [M + H]$^+$ 345.1239, found 345.1240.

*Phenyl 6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (**3m**):* bright yellow amorphous solid (column chromatography); R_f = 0.44, eluent (ethyl acetate/dichloromethane 1:1); mp = 123−124 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 40 min, 71 mg isolated, 81% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1661, 1613, 1522, 1500, 1469, 1284,

DOI: 10.1021/acs.joc.6b01523
J. Org. Chem. 2016, 81, 8837−8849

1266; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.06 (s, 1H), 7.98 (dd, J = 7.8, 1.8 Hz, 1H), 7.52 (ddd, J = 8.6, 7.5, 1.8 Hz, 1H), 7.40−7.33 (m, 2H), 7.20 (t, J = 7.4 Hz, 1H), 7.15−7.08 (m, 3H), 6.98 (d, J = 8.2 Hz, 1H), 6.57 (s, 1H), 4.90 (td, J = 9.1, 5.3 Hz, 1H), 4.81 (q, J = 9.1 Hz, 1H), 4.29 (td, J = 9.4, 6.2 Hz, 1H), 3.79 (q, J = 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 179.9, 164.1, 162.1, 155.4, 150.9, 135.8, 135.5, 129.2 (×2), 127.6, 125.3, 123.8, 122.7, 122.0 (×2), 117.9, 111.2, 86.4, 80.6, 69.7, 45.2; HRMS (ESI$^+$) calcd for $C_{21}H_{16}NO_5$ $[M + H]^+$ 362.1028, found 362.1033.

(1S,11aS)-Ethyl 1-methyl-6-oxo-1,2,6,11a-tetrahydrochromeno-[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (**3n**): bright yellow amorphous solid (column chromatography); R_f = 0.40, eluent (ethyl acetate/dichloromethane 1:1); mp = 71−72 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 87 mg isolated, 84% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1658, 1610, 1509, 1460, 1280. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.97 (dd, J = 7.8, 1.8 Hz, 1H), 7.93 (s, 1H), 7.50 (ddd, J = 8.4, 7.2, 1.8 Hz, 1H), 7.10 (ddd, J = 8.1, 7.3, 1.1 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.65 (s, 1H), 4.91 (t, J = 8.5 Hz, 1H), 4.66−4.54 (m, 1H), 4.48 (dd, J = 8.8, 5.8 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.47 (d, J = 6.3 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.3, 163.8, 162.9, 155.2, 135.8, 135.6, 127.6, 123.9, 122.6, 117.8, 110.5, 83.4, 81.5, 76.0, 59.8, 51.4, 15.2, 14.5; HRMS (ESI$^+$) calcd for $C_{18}H_{18}NO_5$ $[M + H]^+$ 328.1185, found 328.1190.

(1R)-Ethyl 1-ethyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]-oxazolo[3,2-a]pyridine-4-carboxylate (**3o**): bright yellow amorphous solid (column chromatography); R_f = 0.49, eluent (ethyl acetate/dichloromethane 1:1); mp = 61−62 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 83 mg isolated, 77% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1659, 1613, 1508, 1458, 1282. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.97 (dd, J = 7.8, 1.8 Hz, 1H), 7.94 (s, 1H), 7.49 (ddd, J = 8.7, 7.2, 1.8 Hz, 1H), 7.13−7.06 (m, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.62 (s, 1H), 4.85 (t, J = 8.9 Hz, 1H), 4.60 (dd, J = 9.0, 5.4 Hz, 1H), 4.56−4.39 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.10−1.87 (m, 1H), 1.80−1.68 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.4, 163.8, 163.3, 155.2, 135.8, 135.6, 127.7, 124.0, 122.6, 117.8, 110.4, 83.7, 81.3, 73.6, 59.8, 56.1, 21.3, 14.5, 8.0; HRMS (ESI$^+$) calcd for $C_{19}H_{20}NO_5$ $[M + H]^+$ 342.1375, found 342.1348.

(1S)-Ethyl 1-isopropyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (**3p**): bright yellow amorphous solid (column chromatography); R_f = 0.52, eluent (ethyl acetate/dichloromethane 1:1); mp = 65−66 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 75 mg isolated, 67% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 2963, 1660, 1614, 1509, 1459, 1284. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.01 (dd, J = 7.8, 1.8 Hz, 1H), 7.97 (s, 1H), 7.55−7.47 (m, 1H), 7.16−7.09 (m, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.63 (s, 1H), 4.80−4.62 (m, 2H), 4.56−4.48 (m, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.42 (hept, J = 6.9, 3.3 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.4, 163.8, 163.4, 155.3, 135.9, 135.6, 127.8, 124.0, 122.6, 117.8, 110.4, 83.9, 81.1, 70.0, 59.8, 59.7, 24.7, 18.0, 14.5, 14.2; HRMS (ESI$^+$) calcd for $C_{20}H_{22}NO_5$ $[M + H]^+$ 356.1498, found 356.1507.

(1R)-Ethyl 1-((methylthio)methyl)-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (**3q**): bright yellow amorphous solid (column chromatography); R_f = 0.51, eluent (ethyl acetate/dichloromethane 1:1); mp = 68−69 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 81 mg isolated, 69% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 2977, 1658, 1612, 1509, 1460, 1282. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.01 (dd, J = 7.9, 1.8 Hz, 1H), 7.95 (s, 1H), 7.52 (ddd, J = 8.6, 7.3, 1.8 Hz, 1H), 7.17−7.10 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.72 (s, 1H), 5.03−4.87 (m, 1H), 4.82 (dd, J = 9.3, 4.9 Hz, 1H), 4.77−4.66 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.02 (dd, J = 13.5, 3.4 Hz, 1H), 2.81 (dd, J = 13.5, 8.1 Hz, 1H), 2.21 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.2, 163.7, 163.1, 155.1, 135.8, 135.7, 127.8, 124.0, 122.7, 117.7, 110.7, 84.0, 81.6, 74.1, 59.9, 54.5, 33.2, 16.1, 14.5; HRMS (ESI$^+$) calcd for $C_{19}H_{20}NO_5S$ $[M + H]^+$ 374.1057, found 374.1062.

(1S,11aS)-Ethyl 1-benzyl-6-oxo-1,2,6,11a-tetrahydrochromeno-[3,2-e]oxazolo[3,2-a]pyridine-4-carboxylate (**3r**): bright yellow amorphous solid (column chromatography); R_f = 0.55, eluent (ethyl acetate/dichloromethane 1:1); mp = 83−84 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 97 mg isolated, 75% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1657, 1617, 1488, 1460, 1279; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.96 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.48−7.40 (m, 4H), 7.38−7.32 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.15 (s, 1H), 5.44 (dd, J = 9.1, 5.4 Hz, 1H), 5.17 (t, J = 9.2 Hz, 1H), 4.82 (dd, J = 9.3, 5.4 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.4, 163.9, 162.9, 155.3, 135.6, 135.4, 134.2, 130.0, 129.8 (×2), 127.6, 127.5 (×2), 123.9, 122.5, 117.8, 111.2, 83.9, 81.4, 76.9, 59.9, 59.6, 14.6; HRMS (ESI$^+$) calcd for $C_{23}H_{20}NO_5$ $[M + H]^+$ 390.1341, found 390.1346.

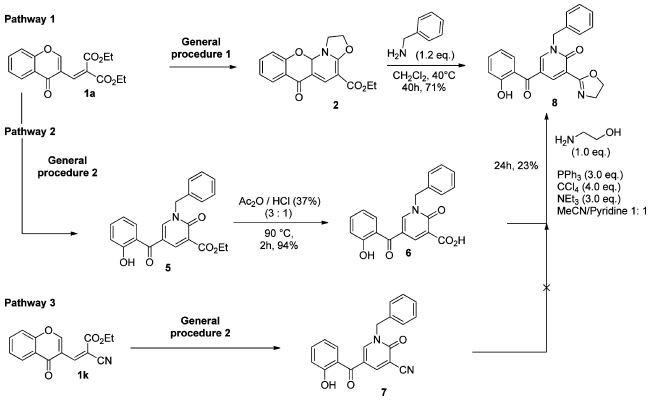
(1S)-Ethyl 6-oxo-1-phenyl-1,2,6,11a-tetrahydrochromeno[3,2-e]-oxazolo[3,2-a]pyridine-4-carboxylate (**3s**): bright yellow amorphous solid (column chromatography); R_f = 0.57, eluent (ethyl acetate/dichloromethane 1:1); mp = 65−66 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 99 mg isolated, 77% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1661, 1615, 1509, 1460, 1279. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.02 (dd, J = 7.8, 1.7 Hz, 1H), 7.97 (s, 1H), 7.58−7.49 (m, 1H), 7.41−7.30 (m, 3H), 7.23 (d, J = 6.7 Hz, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.76 (s, 1H), 4.82−4.73 (m, 1H), 4.73−4.60 (m, 2H), 4.23 (q, J = 7.1 Hz, 2H), 3.38 (dd, J = 13.7, 4.1 Hz, 1H), 2.79 (dd, J = 13.6, 9.0 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.3, 163.7, 163.1, 155.2, 135.8, 135.7, 134.3, 129.3, 129.2, 129.1, 129.0, 127.8, 127.7, 124.0, 122.7, 117.8, 110.7, 83.9, 81.6, 73.7, 59.8, 56.3, 35.1, 14.5; HRMS (ESI$^+$) calcd for $C_{24}H_{22}NO_5$ $[M + H]^+$ 404.1498, found 404.1503.

Ethyl 1,1-dimethyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]-oxazolo[3,2-a]pyridine-4-carboxylate (**3t**): bright yellow amorphous solid (column chromatography); R_f = 0.47, eluent (ethyl acetate/dichloromethane 1:1); mp = 188−189 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 56 mg isolated, 52% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1653, 1607, 1488, 1459, 1278; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.98 (dd, J = 7.8, 1.7 Hz, 1H), 7.91 (s, 1H), 7.50 (ddd, J = 8.7, 7.3, 1.8 Hz, 1H), 7.16−7.07 (m, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.71 (s, 1H), 4.54 (d, J = 8.7 Hz, 1H), 4.45 (d, J = 8.7 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.73 (s, 3H), 1.52 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.5, 163.9, 163.5, 155.5, 135.6, 127.7, 124.1, 122.6, 117.9, 111.3, 84.5, 81.8, 81.1 (×2), 61.8, 59.8, 27.1, 22.3, 14.5; HRMS (ESI$^+$) calcd for $C_{19}H_{20}NO_5$ $[M + H]^+$ 342.1341, found 342.1348.

(2S)-Ethyl 2-methyl-6-oxo-1,2,6,11a-tetrahydrochromeno[3,2-e]-oxazolo[3,2-a]pyridine-4-carboxylate (**3v**): bright yellow amorphous solid (column chromatography); R_f = 0.52, eluent (ethyl acetate/dichloromethane 1:1); mp = 78−79 °C, 100 mg scale reaction (in 3 mL of CH_2Cl_2) for 1 h, 36 mg isolated, 35% yield; product sensitive to $CDCl_3$ acidity; IR (ν_{max}/cm^{-1}) 1658, 1609, 1516, 1489, 1460, 1279. Diastereoisomer 1: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.97 (dd, J = 7.8, 1.8 Hz, 1H), 7.94 (s, 1H), 7.49 (ddd, J = 8.6, 7.3, 1.8 Hz, 1H), 7.10 (ddd, J = 8.0, 7.3, 1.1 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.53 (s, 1H), 5.35−5.16 (m, 1H), 4.37 (t, J = 8.9 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.87 (d, J = 8.5 Hz, 1H), 1.69 (t, J = 6.5 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 179.9, 163.7, 163.3, 155.3, 136.2, 135.6, 127.6, 123.9, 122.6, 117.8, 110.4, 86.7, 81.4, 79.4, 59.7, 51.7, 20.0, 14.5. Diastereoisomer 2: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.97 (dd, J = 7.8, 1.8 Hz, 1H), 7.95 (s, 1H), 7.49 (ddd, J = 8.6, 7.3, 1.8 Hz, 1H), 7.10 (ddd, J = 8.0, 7.3, 1.1 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.53 (s, 1H), 5.35−5.16 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.87 (d, J = 8.5 Hz, 1H), 3.36 (t, J = 9.4 Hz, 1H), 1.69 (t, J = 6.5 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.0, 163.7, 163.1, 155.3, 136.1, 135.6, 127.6, 123.9, 122.6, 117.8, 110.2, 86.4, 81.3, 79.1, 59.7, 50.9, 20.5, 14.5; HRMS (ESI$^+$) calcd for $C_{18}H_{18}NO_5$ $[M + H]^+$ 328.1185, found 328.1186.

DOI: 10.1021/acs.joc.6b01523
J. Org. Chem. 2016, 81, 8837−8849

Synthetic Pathways for Access to 3-dihydrooxazolopyridin-2-one (8).



*Ethyl 1-Benzyl-5-(2-hydroxybenzoyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (**5**).* Synthesized according to general procedure 2 using 1.05 equiv of benzylamine and 1.0 equiv of **1a**: pale orange powder (precipitation in cold diethyl ether): R_f = 0.36, eluent (ethyl acetate/cyclohexane 1:1); mp = 120−122 °C, 0.50 g scale reaction (in 5 mL of CH_2Cl_2) for 1 h, 0.57 g was isolated, 95% yield; IR (ν_{max}/cm^{-1}) 3444, 1727, 1650, 1624, 1540, 1340, 1238; ^{1}H NMR (300 MHz, CDCl $_3$) δ_H 8.53 (d, J = 2.6 Hz, 1H), 8.15 (d, J = 2.7 Hz, 1H), 7.52 (ddd, J = 8.5, 7.3, 1.6 Hz, 1H), 7.43−7.35 (m, 6H), 7.08 (d, J = 8.4 Hz, 1H), 6.90−6.83 (m, 1H), 5.25 (s, 2H), 4.40 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 194.3, 164.1, 162.6, 158.7, 146.2, 143.6, 136.4, 134.8, 131.4, 129.3 (×2), 128.9, 128.8 (×2), 120.4, 119.0, 118.9, 118.6, 115.9, 61.7, 53.3, 14.3; HRMS (ESI$^+$) calcd for $C_{22}H_{20}NO_5$ [M + H]$^+$ 378.1341, found 378.1336.

*1-Benzyl-5-(2-hydroxybenzoyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid (**6**).* A solution of **5** (1.14 g, 3.02 mmol) in 6 mL of Ac_2O/HCl (37%) was heated to 90 °C. After complete consumption of starting material (2 h), the reaction media was allowed to cool at room temperature. The formed precipitate was filtrated and washed with cyclohexane to yield pure compound **6** as a white powder: R_f = 0.36, eluent (ethyl acetate/cyclohexane 1:1); mp = 201−203 °C, 1.01 g was isolated, 94% yield; IR (ν_{max}/cm^{-1}) 3418, 2958, 1722, 1610, 1467, 1439; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.39 (s, 1H), 8.92 (d, J = 2.6 Hz, 1H), 8.50 (d, J = 2.6 Hz, 1H), 7.50−7.32 (m, 7H), 7.10−6.90 (m, 2H), 5.40 (s, 2H); ^{13}C NMR (75 MHz, DMSO): δ_C 191.4, 164.8, 163.0, 156.3, 149.1, 144.8, 135.9, 133.9, 130.7, 129.2 (×2), 128.5 (x3), 124.8, 119.9, 118.9, 117.2, 117.1, 53.6; HRMS (ESI$^+$) calcd for $C_{20}H_{16}NO_5$ [M + H]$^+$ 350.1028, found 350.1034.

*1-Benzyl-5-(2-hydroxybenzoyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**7**).* Synthesized according to general procedure 2 using 1.05 equiv of benzylamine and 1.0 equiv of **1k**: white powder (column chromatography): R_f = 0.38, eluent (ethyl acetate/cyclohexane 1:1); mp = 89−91 °C, 400 mg scale reaction (in 4 mL of EtOH) for 2 h, 211 mg was isolated, 43% yield; IR (ν_{max}/cm^{-1}) 3054, 2230, 1731, 1660, 1622, 1541, 1337, 1251; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 11.19 (s, 1H), 8.22 (d, J = 2.6 Hz, 1H), 8.18 (d, J = 2.6 Hz, 1H), 7.55 (ddd, J = 8.6, 7.2, 1.7 Hz, 1H), 7.46−7.37 (m, 5H), 7.36−7.31 (m, 1H), 7.08 (dd, J = 8.4, 1.1 Hz, 1H), 6.93−6.86 (m, 1H), 5.25 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 193.1, 162.6, 158.9, 146.6, 146.5, 137.0, 133.9, 131.1, 129.5 (×2), 129.3, 128.9 (×2), 119.3, 119.1, 118.1, 116.6, 114.6, 105.3, 53.8; HRMS (ESI$^+$) calcd for $C_{20}H_{15}N_2O_3$ [M + H]$^+$ 331.1083, found 331.1106.

*1-Benzyl-3-(4,5-dihydrooxazol-2-yl)-5-(2-hydroxybenzoyl)-pyridin-2(1H)-one (**8**).* Pathway 1: To a solution of **3a** (120 mg, 0.38 mmol) in dichloromethane (3 mL) was added benzylamine (46 μL, 0.42 mmol), and the reaction mixture was heated to reflux. After complete consumption of starting material (40 h), the reaction mixture was allowed to cool at room temperature and was concentrated under vacuum. Selective precipitation in cold diethyl ether afforded pure compound **8** as a white powder: R_f = 0.14, eluent (ethyl acetate/dichloromethane 9:1); mp = 175−177 °C, 102 mg isolated, 71% yield. Pathway 2: To a solution of **5** (300 mg, 0.84 mmol), ethanolamine (50 μL, 0.84 mmol), Et_3N (0.35 mL, 2.52 mmol), and CCl_4 (0.33 mL, 3.36 mmol) in MeCN/pyridine (2 mL, 1:1) was added dropwise a solution of PPh_3 (511 mg, 2.52 mmol) in MeCN/pyridine (2 mL, 1:1). The mixture was stirred at room temperature for 18 h and then concentrated under reduced pressure. The residue was then dissolved in diethyl ether and basified to pH 8−9 with concentrated aqueous NH_4OH solution. The organic layer was separated, and the organic phase was extracted with diethyl ether (three times). The combined extracts were dried ($MgSO_4$) and evaporated. Purification by column chromatography afforded pure compound **8** as a white powder: R_f = 0.14, eluent (ethyl acetate/dichloromethane 9:1); mp = 175−177 °C, 42 mg isolated, 23% yield; IR (ν_{max}/cm^{-1}) 1673, 1632, 1541, 1291, 1247; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 11.37 (s, 1H), 8.41 (d, J = 2.7 Hz, 1H), 8.12 (d, J = 2.7 Hz, 1H), 7.49 (ddd, J = 8.6, 7.2, 1.7 Hz, 1H), 7.46−7.34 (m, 6H), 7.05 (dd, J = 8.4, 1.1 Hz, 1H), 6.86 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H), 5.24 (s, 2H), 4.36 (td, J = 9.4, 1.3 Hz, 2H), 4.13 (td, J = 9.4, 1.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 194.5, 162.5, 160.8, 158.7, 144.8, 141.4, 136.4, 135.0, 131.5, 129.2 (×2), 128.9 (×2), 128.8, 119.0, 118.8, 118.6, 117.7, 116.1, 67.0, 55.8, 53.5; HRMS (ESI$^+$) calcd for $C_{22}H_{19}N_2O_4$ [M + H]$^+$ 375.1345, found 375.1347.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01523.

Experimental procedures, product characterization data including ^{1}H and ^{13}C NMR spectra, and quantum chemical calculation details (PDF)

Single-crystal X-ray diffraction data for compound **3l** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the "Ministère de l'Enseignement Supérieur et de la Recherche" and "Région Haute Normandie" for a Graduate Fellowship awarded to T.L. We are grateful to CS of the University of Le Havre for research facilities.

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DOI: 10.1021/acs.joc.6b01523
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DOI: 10.1021/acs.joc.6b01523
J. Org. Chem. 2016, 81, 8837−8849