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Rhodium(III)-Catalyzed *ortho*-Alkylation of Phenoxy Substrates with Diazo Compounds via C−H Activation: A Case of Decarboxylative Pyrimidine/Pyridine Migratory Cyclization Rather than Removal of Pyrimidine/Pyridine Directing Group

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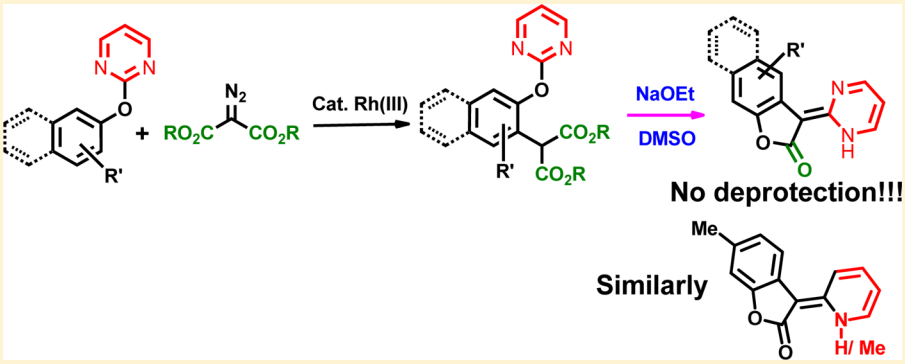
Supporting Information



ABSTRACT: An efficient Rh(III)-catalyzed *ortho*-alkylation of phenoxy substrates with diazo compounds has been achieved for the first time using pyrimidine or pyridine as the directing group. Furthermore, bis-alkylation has also been achieved using *para*-substituted phenoxypyrimidine and 3 mol equiv of the diazo ester. The *ortho*-alkylated derivatives of phenoxy products possessing the ester functionality undergo *decarboxylative pyrimidine/pyridine migratory cyclization* (rather than deprotection of pyrimidine/pyridine group) using 20% NaOEt in EtOH affording a novel class of 3-(pyrimidin-2(1*H*)-ylidene)benzofuran-2(3*H*)-ones and 6-methyl-3-(pyridin-2(1*H*)-ylidene)benzofuran-2(3*H*)-one. The *ortho*-alkylated phenoxypyridine possessing ester functionality also undergoes decarboxylative pyridine migratory cyclization using MeOTf/NaOMe in toluene providing 6-methyl-3-(1-methylpyridin-2(1*H*)-ylidene)benzofuran-2(3*H*)-one.

INTRODUCTION

Phenols are ubiquitous structural motifs found in a wide range of natural products, pharmaceuticals, polymers, and agrochemicals.[1] In addition to these, phenols and their derivatives (e.g., aryl-triflates, -pivalates -carbamates, and sulfamates) are widely used as coupling partners in cross-coupling reactions.[2] Given the synthetic and economic potential of the phenol/phenoxy derivatives, much recent attention has been devoted to functionalize C−H bonds on phenoxy substrates. Thus, during the past few years, phenols,[3] siloxides/silanols,[4] phenoxy esters,[5] carbamates,[6] and 2-phenoxypyridines[7] have been successfully utilized as versatile substrates for C−H functionalization. In addition, 2-phenoxypyrimidines are also used as substrates for *ortho*-acetoxylation and arylation.[8] Despite the fact that many C−H functionalization reactions are reported on phenoxy substrates, to the best of our knowledge, *ortho*-alkylation of phenoxy precursors using diazo compounds has not been reported so far. Recently, several research groups have described *ortho*-alkylation/annulation reactions using diazo compounds in the presence of rhodium(III),[9] iridium(III),[10] or cobalt(III)[11] catalysts. In continuation to our studies on C−H functionalization,[12] we describe herein a Rh(III)-catalyzed *ortho*-alkylation of phenoxy substrates using 2-phenoxypyrimidine/2-phenoxypyridine as substrates. Interestingly, while trying to remove the directing group, we observed a novel case of decarboxylative pyrimidine/pyridine migratory cyclization (*rather than deprotection*) furnishing 3-(pyrimidin-2(1*H*)-ylidene)benzofuran-2(3*H*)-ones, 6-methyl-3-(pyridin-2(1*H*)-ylidene)benzofuran-2(3*H*)-one and 6-methyl-3-(1-methylpyridin-2(1*H*)-ylidene)-benzofuran-2(3*H*)-one. We believe that this observation is important since pyrimidine/pyridine groups are widely used removable directing groups with no reported case of such a rearrangement/migration.

RESULTS AND DISCUSSION

We began our studies by using 2-phenoxypyrimidine **1a** and diethyl diazomalonate **2a** as model substrates for the reaction. Pleasingly, we isolated the *ortho*-alkylated product **3a** in 30% yield when we treated 2-phenoxypyrimidine **1a**, with diethyl

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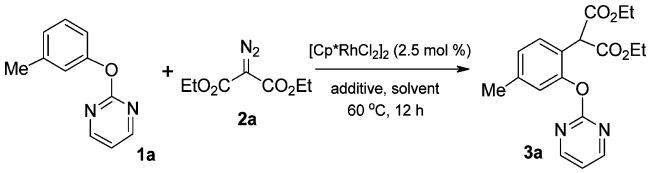
diazomalonate **2a** in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol %), NaOAc (30 mol %) in MeOH solvent at 60 °C for 12 h (Table 1, entry 1). Encouraged by this, we screened various additives and solvents to get the optimal yield of the product **3a**. Among the additives screened (entries 2−7), $AgSbF_6$ enhanced yield of the product to 65%. After adding PivOH (20 mol %) as coadditive along with $AgSbF_6$, drastic improvement in the yield of the product (78%) was observed with complete consumption of the starting material, 2-phenoxypyrimidine **1a** (entry 8). However, the reaction using PivOH itself as additive, in the absence of $AgSbF_6$ led to decreased in the yield (46%) of the product (entry 9). A brief examination of solvents revealed that MeOH is a good solvent for this reaction (entries 10−16). On the basis of these, the optimal reaction conditions for the present reaction are 2-phenoxypyrimidine (1 equiv), α-diazo carbonyl compound (1.2 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (20 mol %) in MeOH solvent at 60 °C for 12 h.

Table 1. Optimization Study for the [Rh]-Catalyzed Alkylation with Diazo Compounds[a]



entry	additive	solvent	yield (%)[b]
1	NaOAc	MeOH	30
2	AgOAc	MeOH	51
3	Ag_2CO_3	MeOH	23
4	AgOTf	MeOH	42
5	AgF_2	MeOH	20
6	$AgBF_4$	MeOH	54
7	$AgSbF_6$	MeOH	65
8	**$AgSbF_6$/PivOH (20 mol %)**	**MeOH**	**78**
9	PivOH	MeOH	46
10	$AgSbF_6$/PivOH (20 mol %)	EtOH	61
11	$AgSbF_6$/PivOH (20 mol %)	TFA	15
12	$AgSbF_6$/PivOH (20 mol %)	DCE	21
13	$AgSbF_6$/PivOH (20 mol %)	PEG	Trace
14	$AgSbF_6$/PivOH (20 mol %)	toluene	25[c]
15	$AgSbF_6$/PivOH (20 mol %)	dioxane	40[c]
16	$AgSbF_6$/PivOH (20 mol %)	*t*AmOH	52[c]

[a]Reaction conditions: **1a** (0.3 mmol), α-diazo ester **2a** (0.36 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), additive (10 mol %), solvent (3 mL), 60 °C (oil bath temperature). [b]Isolated yield. [c]At 110 °C.

After having the optimized reaction conditions in hand, the scope of the carbenoid functionalization was subsequently explored with respect to phenoxy precursors and diazocarbonyl compounds (Scheme 1). Initially, the unsubstituted 2-phenoxypyrimidine **1m** was tested under these conditions, but here we isolated mono- and bis-C−H functionalization products in an overall yield of 79% in the ratio 3:1, respectively. The reaction using substrates bearing electron donating groups (-OMe, -Me) or electron withdrawing groups (-F, $-CF_3$) proceeded smoothly affording the *ortho*-alkylated phenoxy derivatives in good yields. Bromo and chloro functional groups (cf. **1c−d**) were well tolerated, thus paving the way for further transformations. *ortho*-Substituted phenoxy precursors also underwent carbenoid coupling smoothly providing the alkylated derivatives **3h** and **3i** in good yields. In particular, substrate bearing 2-alkynyl substituent (**1j**) was also compatible giving good yield (68%) of the alkylated product **3j**. We were pleased to find that those bearing 2-naphthyl substituents at the α-position (**1k** and **1l**) also worked well and the products **3k** and **3l** were obtained in 74% and 70% yields, respectively. But in the case of 1-naphthyl substituted precursor **1n**, two regio-isomeric products (**3n** and **3n′**) were formed in equal ratio. We were able to separate both the isomers through column chromatography. This reaction is interesting in that it paves a way for the substitution at C-8 position of 1-naphthol. The scope of the diazo substituents was further investigated by using α-diazomalonates bearing Me and *i*-Pr substituents; in both the cases the *ortho*-alkylated products **3o** and **3p** were isolated in excellent yields.

We were also successful in achieving bis-alkylation in some cases by increasing the amount of diazomalonate to 3 mol equiv with respect to phenoxy substrates (Scheme 2). Thus, we have synthesized three bis-alkylated products **4a−4c** in good yields.

Removal of the pyrimidine directing group from the *ortho*-alkylated phenoxy pyrimidines (**3a−p** and **4a−c**), can lead to free phenol derivatives, which are useful for further transformations. For this purpose, we conducted the reaction of **3a** with 20% NaOEt in EtOH using DMSO solvent at 110 °C (Scheme 3). After careful examination of the product, we found that the novel decarboxylative rearranged product **5a** involving pyrimidyl group migration was formed instead of free phenol derivative. The structure of **5a** was confirmed by using X-ray crystallography (Figure S2) that clearly reveals an NH···O(C) type H-bonded dimer. This product seems to be the result of an unusual rearrangement. The generality of this rearrangement was examined by employing phenoxy derivatives (**3b−g**) and naphthalene derivatives **3k−l**; in all the cases good to excellent yields of such decarboxylatively rearranged/cyclized products (**5a−i**) were isolated.[13] We also isolated compounds **A−B**; although IR/HRMS data were consistent with these, we could not obtain sharp signals in the $^1H/^{13}C$ NMR spectra of these. We tried an alternative method for removing the pyrimidine directing group, by treating *ortho*-alkylated phenoxy pyrimidine **3a** with MeOTf/toluene at 100 °C to form the corresponding pyridinium salt. Subsequently, the crude pyridinium salt was refluxed in Na/MeOH solution for 30 min gave the same decarboxylative rearranged product **5a** in 64% yield; we did not observe any pyrimidine cleaved free phenol derivative.

In view of the importance of the 2-phenoxypyridine skeleton in pharmaceuticals,[14] we have also checked the generality of our catalytic conditions by choosing 2-phenoxypyridine substrates. Thus the reaction of 2-pehoxypyridine substrates **6** with different diazo compounds **2** under the above catalytic conditions (Scheme 4) afforded good yields of the corresponding *ortho*-alkylated 2-phenoxy pyridines (**7a−c**) that proves the generality of our catalytic system.

As our initial object was the synthesis of *ortho*-alkylated free phenol derivatives, we attempted some reactions for the removal of the pyridine directing group also. First, we tried the reaction of *ortho*-alkylated 2-phenoxy pyridine **7a** with 20% NaOEt in DMSO solvent at 110 °C. Under these conditions, we obtained the decarboxylative rearranged product **8** (Scheme 5a). We also attempted a reaction for removing the pyridine directing group following a previously reported procedure.[7] As shown in Scheme 5b, the reaction of *ortho*-alkylated 2-phenoxy pyridine **7a** with MeOTf in toluene, and subsequent treatment with Na/MeOH under reflux conditions afforded only decarboxylative rearranged product **9.** The structure of the compound **9** was confirmed by

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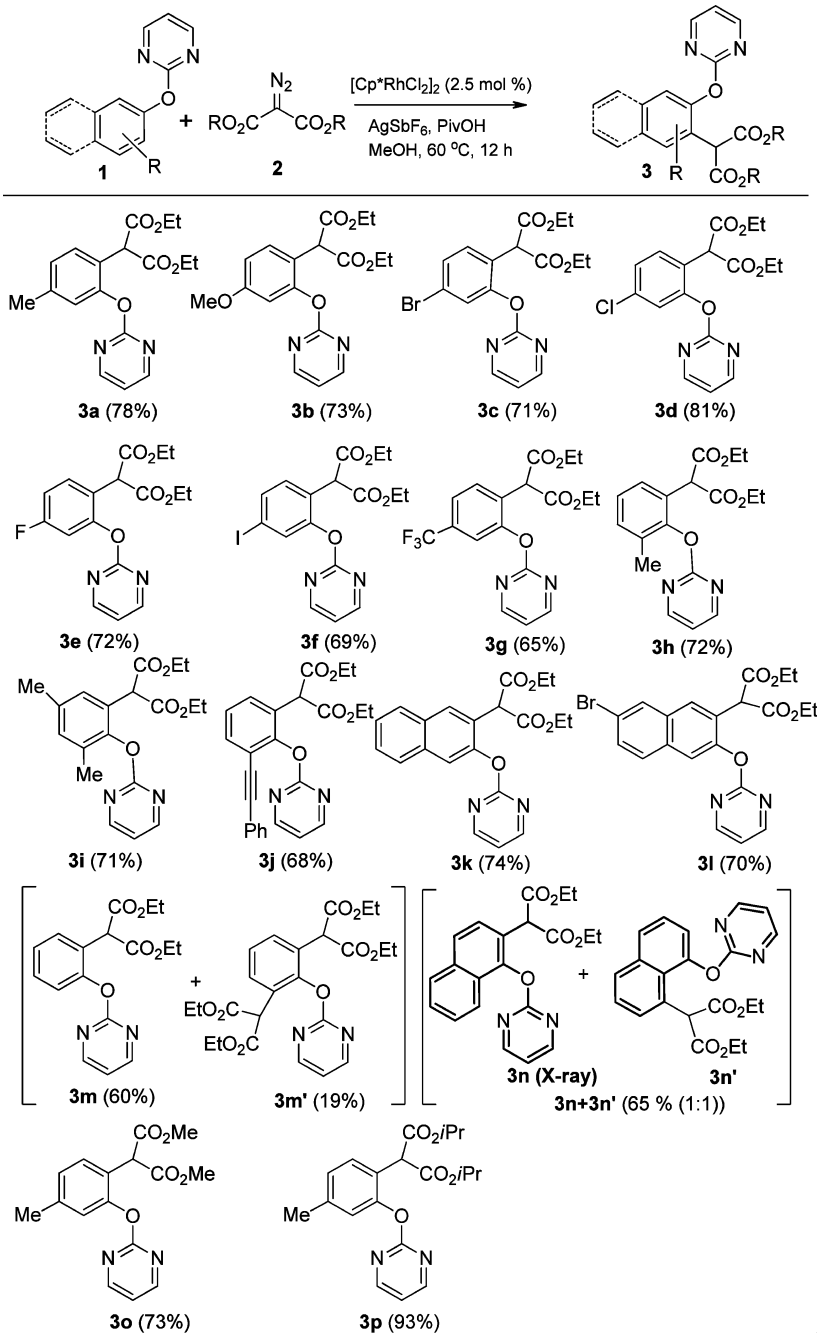
Scheme 1. Scope of the Rh(III)-Catalyzed C−H Alkylation of Phenoxy Substrates[a,b]



[a]Reaction conditions: Phenoxy substrate **1** (0.3 mmol), diazo compound **2** (0.36 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (20 mol %), MeOH (3 mL) at 60 °C (oil bath temperature) for 12 h. [b]Isolated yields with column chromatography.

using X-ray crystallography. We did not obtain any free phenolic derivative under these conditions.

On the basis of the literature precedents on Rh(III)-catalyzed C−H functionalization of aromatic compounds using α-diazo compounds,[9,12f] a plausible pathway is depicted in Scheme 6. Initially, pyrimidine nitrogen undergoes coordination to the active dicationic Rh(III) species $[Rh(Cp^*)][SbF_6]^{2-}$ followed by *ortho* C−H bond cleavage results in the formation of six-membered rhodacycle intermediate **I** with the loss of one of the $[SbF_6]^-$ as $HSbF_6$. Then, coordination of diazo compound to rhodium in intermediate **I** followed by the elimination of N_2 affords the metal-carbenoid intermediate **III** via the intermediate **II**. Subsequently, migratory insertion of the carbene into the Rh−C bond gives intermediate **IV**, which upon protonation delivers the alkylated product by regenerating the active Rh(III) catalyst.

A plausible pathway for the decarboxylative pyrimidine migratory cyclization product **5a** is shown in Scheme 7. Initially, sodium ethoxide abstracts a proton from *ortho*-alkylated phenoxy precursor **V** which is followed by migration of pyrimidine group leading to the anion **VI**. Elimination of ethoxide (possibly as ethanol) followed by base hydrolysis and elimination of CO_2 results in **5a** via **VII** and **VIII**. A similar reaction sequence may be operative in the formation of compounds **8**−**9**.

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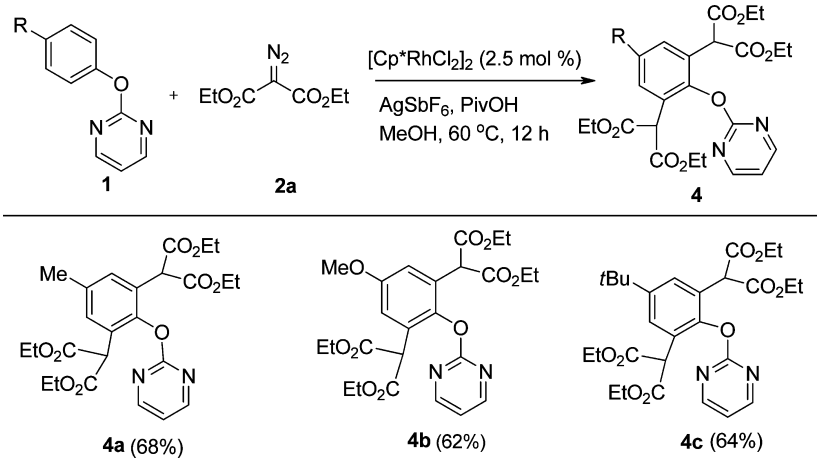
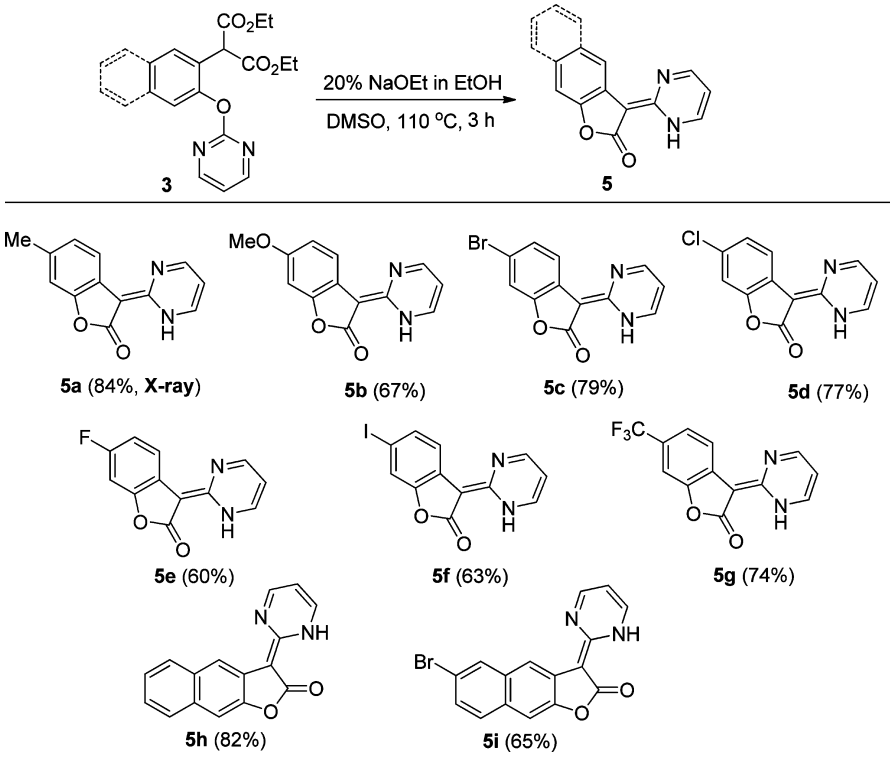
Scheme 2. Scope of the Rh(III)-Catalyzed Double C−H Alkylation of Phenoxy Precursors with Diazomalonate (2a)[a,b]

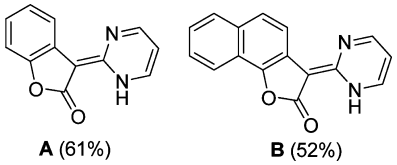


[a]Reaction conditions: Substrate **1** (0.3 mmol), diazo compound **2a** (0.9 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (20 mol %), MeOH (3 mL) at 60 °C (oil bath temperature) for 12 h. [b]Isolated yields after column chromatography.

Scheme 3. Base Promoted Decarboxylative Migratory Cyclization Products[a]



[a]Reaction conditions: *ortho*-alkylated phenoxypyrimidine **3** (0.15 mmol), 20% NaOEt in EtOH (20 mol %), DMSO (2 mL) at 110 °C (oil bath temperature) for 3 h. Isolated yields after column chromatography.



CONCLUSIONS

In summary, we have developed the first Rh(III)-catalyzed *ortho*-alkylation of phenoxy derivatives with α-diazo esters using 2-phenoxypyrimidines/pyridines as substrates. The salient features of this catalytic system include mild catalytic conditions, large functional group compatibility, high product yields, and environmentally benign N_2 gas as the sole byproduct. More interestingly, we have also discovered a new decarboxylative pyrimidine migrated cyclization products in our attempt to remove (deprotect) the pyrimidine directing group. We believe that possibility of this type of reaction should be borne in mind

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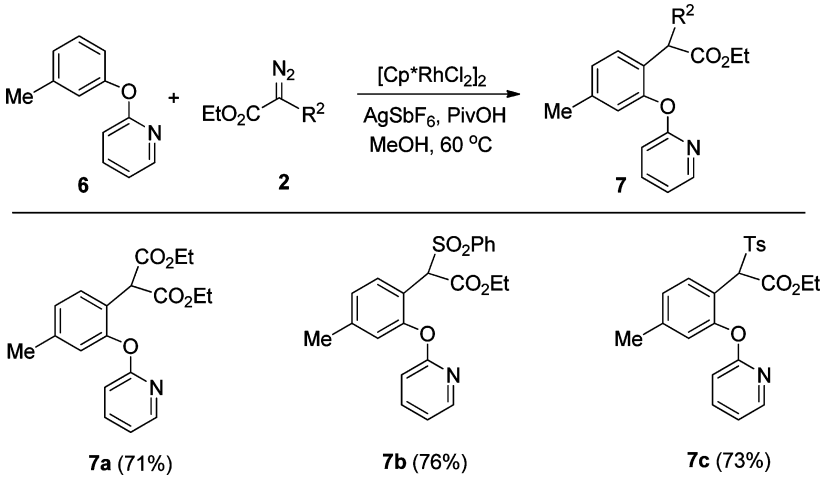
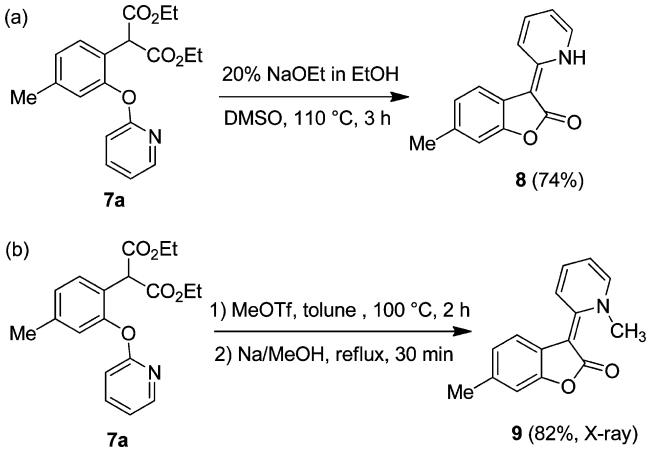
Scheme 4. Scope of the Rh(III)-Catalyzed C−H Alkylation of 2-Phenoxypyridines with Diazo Compounds[a,b]



[a]Reaction conditions: Phenoxypyridine **6** (0.3 mmol), diazo compound **2** (0.36 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (20 mol %), MeOH (3 mL) at 60 °C (oil bath temperature) for 12 h. [b]Isolated yields after column chromatography.

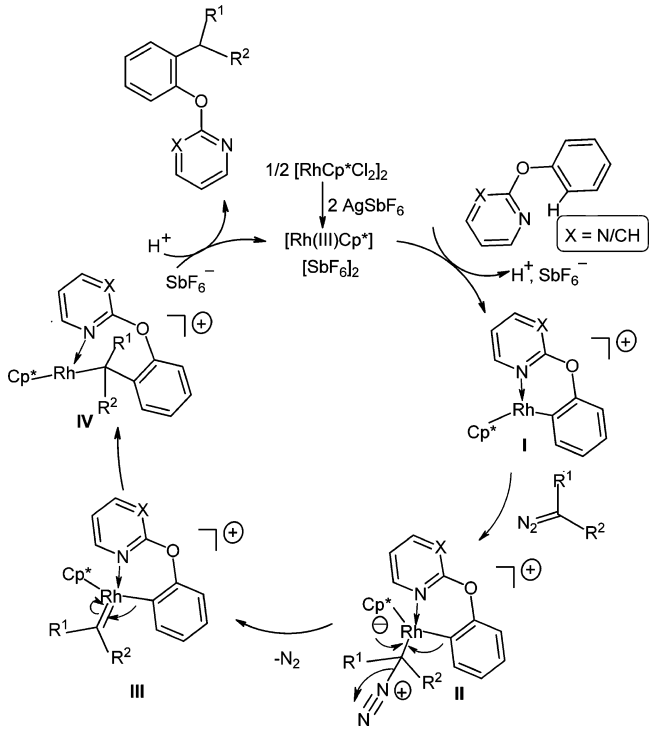
Scheme 5. Attempted Reactions for the Removal of Pyridine Directing Group[a]



[a]Reaction conditions: *ortho*-alkylated phenoxypyridine **7a** (0.50 mmol), MeOTf (0.88 mmol) PhMe (20 mL) at 100 °C (oil bath temperature) for 3 h, Na (12 mmol), MeOH (20 mL) at 80 °C for 30 min. Isolated yields after column chromatography.

while using the pyrimidine directing group that is widely used in C−H functionalization reactions.

Scheme 6. Plausible Pathway for the *ortho*-C−H Functionalization of Phenoxy Substrates



EXPERIMENTAL SECTION

General Methods. Chemicals were purified when required according to standard procedures.[15] All reactions, unless stated otherwise, were performed in a dry nitrogen atmosphere. ^1H and ^{13}C NMR spectra were recorded using 5 mm tubes on 400 MHz NMR spectrometer with field strengths 400 and 100 MHz, respectively or on 500 MHz NMR spectrometer with field strengths 500 and 125 MHz, respectively in $CDCl_3$/DMSO-d_6 solution with shifts referenced to $SiMe_4$ ($\delta = 0$). All J values are in Hz. Infrared spectra were recorded neat or by using KBr pellets on a FT/IR spectrometer. Melting points were determined by using a local hot-stage melting point apparatus and are uncorrected. For TLC, glass micro slides were coated with silica-gel-GF_{254} (mesh size 75 μ) and spots were identified using iodine or UV chamber as appropriate. For column chromatography, silica gel of 100−200 mesh size was used. Mass spectra were recorded using HRMS (ESI-TOF analyzer) equipment. X-ray data were collected at 298 K using Mo Kα (λ = 0.710 73 Å) radiation. Structures were solved and refined using standard methods.[16] CCDC nos. 1511133−1511134 and 1525099.

I. Synthesis of Precursors. All the 2-phenoxypyrimdine,[7a] 2-phenoxypyridine,[7b] and diazo substrates[17] were synthesized by following the known procedures. Among these, 2-((6-bromonaphthalen-2-yl)oxy)pyrimidine precursor **1l** is new.

Compound 1l. Yield 1.96 g (82%, white solid): mp 94−98 °C; IR (KBr, cm^{-1}) 2953, 1562, 1397, 1299, 1237, 1195, 1139, 968, 891, 632 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.04 (s, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.89 (s, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.65 (s, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.39 (dd, J = 9.0 and 8.5 Hz, 1H), 7.08 (dd, J = 7.0 and 4.5 Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 165.3, 159.8, 150.8, 132.5, 132.3, 129.9, 129.9$_1$, 129.3, 128.7, 122.7, 119.4, 118.3, 116.4; HRMS (ESI) calcd for $C_{14}H_9BrN_2O$ [M^+ + H] m/z 300.9976 and 302.9956, found 300.9976 and 302.9956.

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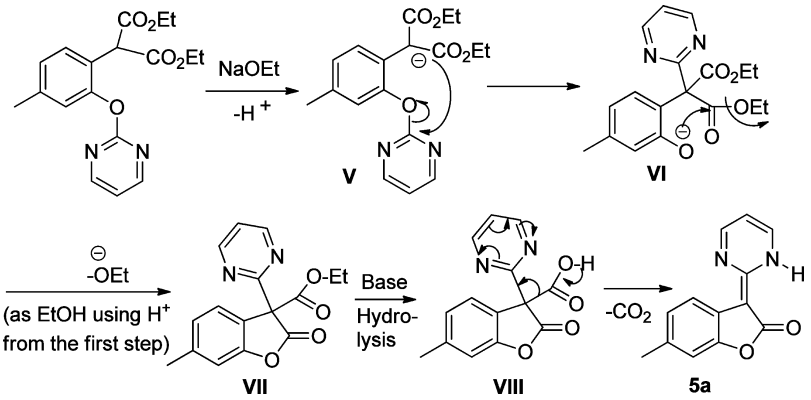
Scheme 7. Plausible Reaction Pathway for Migratory Cyclization



ii. General Procedure for the [Rh]-Catalyzed Reaction of Phenoxy Precursors with Diazo Compounds. A mixture of phenoxypyrimidine/pyridine (0.3 mmol), diazo compound (0.36 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %) and PivOH (20 mol %)) was taken in a Schlenk tube [under ambient conditions; no inert atmosphere needed]. To this, MeOH (3 mL) was added and the contents stirred at 60 °C (oil bath temperature) for 12 h. After cooling to rt, the reaction mixture was extracted with DCM (3 × 20 mL). The combined organic phase was washed with brine solution (20 mL), dried over anh. Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (4:1) mixture as the eluent.

iii.a. General Procedure for the Synthesis of Migratory Cyclization Products from *ortho*-Alkylated Phenoxypyrimidines/Phenoxypyridines. A mixture of *ortho*-alkylated phenoxypyrimidine [or **7a**] (0.15 mmol) and 20% NaOEt in EtOH (20 mol %) in DMSO (2 mL) was stirred for 3 h at 110 °C (oil bath temperature), then cooled and 2 N HCl (10 mL) was added. This was diluted with EtOAc (3 × 10 mL) and washed with brine solution (20 mL), dried over anh. Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (2:3) mixture as the eluent. We have tried an alternative method for removing the pyrimidine directing group by treating *ortho*-alkylated phenoxy pyrimidine **3a** with MeOTf/toluene at 100 °C. Subsequently, this mixture was heated under reflux in Na/MeOH solution for 30 min to give the same decarboxylative rearranged product **5a**. But the yield was better from the first method using NaOEt. We also tried the removal of pyrimidine directing group by treating compound **3a** with N_2H_4/TFA in EtOH at 140 °C,[18] but did not observe any product formation. We also conducted the reaction of compound **3a** with Et_3SiH in TFA at 50 °C for 2 h, followed by the treatment with N_2H_4/AcOH in MeOH at rt for 12−24 h.[19] In this case also, there was no reaction.

iii.b. General Procedure for the Synthesis of Migratory Cyclization Products from *ortho*-Alkylated Phenoxypyridines. A mixture of *ortho*-alkylated phenoxypyridine (0.50 mmol) in 20 mL toluene and added MeOTf (0.88 mmol) under N_2 was stirred for 2 h at 100 °C (oil bath temperature).Then the reaction mixture was cooled, and solvent removed by evaporation. The residue was dissolved in dry methanol (5 mL). To this, NaOMe (12 mmol Na in 15 mL of methanol) under N_2 was added, the mixture was heated at 80 °C for 30 min, then cooled and solvent was removed by evaporation. The resulting mixture was extracted with DCM (3 × 10 mL) and washed with brine solution (20 mL), dried over anh. Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (3:2) mixture as the eluent.

Compound ***3a***. Yield 0.080 g (78%, white solid); mp 80−84 °C; IR (KBr) 3052, 2975, 1731, 1567, 1408, 1304, 1145, 1041, 811, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 4.8 Hz, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 7.06 (t, J = 4.8 Hz, 1H), 7.01 (s, 1H), 4.93(s, 1H), 4.20−4.10 (m, 4H), 2.39 (s, 3H), 1.20 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 165.2, 159.7, 150.5, 139.8, 130.2, 127.0, 122.8$_3$, 122.7$_5$, 116.3, 61.7, 51.0, 21.2, 13.9; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_5$ $[M^+ + H]$ m/z 345.1450, found 345.1449.

Compound ***3b***. Yield 0.079 g (73%, gummy liquid); IR (neat) 3068, 2981, 1742, 1573, 1501, 1408, 1030, 816, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 4.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 1H), 7.07 (t, $J \sim$ 4.8 Hz, 1H), 6.89 (dd, J = 8.5 and 2.5 Hz, 1H), 6.74 (d, J = 3.0 Hz, 1H), 4.88 (s, 1H), 4.19−4.10 (m, 4H), 3.80 (s, 3H), 1.19 (t, $J \sim$ 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 165.1, 160.4, 159.8, 151.5, 131.2, 117.9, 116.5, 112.1, 108.1, 61.7, 55.5, 50.7, 14.0; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_6$ $[M^+ + H]$ m/z 361.1400, found 361.1401.

Compound ***3c***. Yield 0.087 g (71%, white solid); mp 74−78 °C; IR (KBr) 3063, 2975, 1748, 1567, 1403, 1299, 1036, 921, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 4.8 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 8.4 and 1.6 Hz, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.10 (t, $J \sim$ 4.8 Hz, 1H), 4.95 (s, 1H), 4.21−4.12 (m, 4H), 1.20 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 164.8, 159.9, 151.2, 131.8, 129.2, 125.9, 122.4, 116.9, 62.0, 51.0, 14.0; HRMS (ESI) calcd for $C_{17}H_{17}BrN_2O_5Na$ $[M^+ + Na]$ and $[M^+ + Na + 2]$ m/z 431.0219 and 433.0198, found 431.0217 and 433.0197.

Compound ***3d***. Yield 0.088 g (81%, white solid); mp 68−72 °C; IR (KBr) 3057, 2992, 1748, 1573, 1403, 1304, 1025, 926, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 4.8 Hz, 2H), 7.61 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.24 (s, 1H), 7.11 (t, $J \sim$ 4.6 Hz, 1H), 4.96 (s, 1H), 4.21−4.12 (m, 4H), 1.21 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 164.7, 159.8, 151.1, 134.6, 131.5, 126.3, 124.5, 122.9, 116.8, 62.0, 50.8, 13.9; HRMS (ESI) calcd for $C_{17}H_{18}ClN_2O_5$ $[M^+ + H]$ and $[M^+ + H + 2]$ m/z 365.0905 and 367.0875, found 365.0904 and 367.0887.

Compound ***3e***. Yield 0.075 g (72%, gummy liquid); IR (neat) 2986, 1753, 1573, 1474, 1419, 1238, 1096, 789 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 4.8 Hz, 2H), 7.37−7.31(m, 1H), 7.17 (t, $J \sim$ 5.0 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 7.05−7.00 (m, 1H), 5.65 (s, 1H), 4.29−4.21 (m, 4H), 1.33 (t, J = 7.2 Hz, 3H), 1.24 (t, $J \sim$ 7.0 Hz, 3H); ^{13}C NMR (100 MHz) δ 169.6, 166.2, 161.3 (d, $J_{(C-F)}$ = 247.5 Hz), 157.2, 152.8, 150.2 (d, $J_{(C-F)}$ = 6.6 Hz), 129.2 (d, $J_{(C-F)}$ = 10.1 Hz), 119.3, 118.4 (d, $J_{(C-F)}$ = 3.3 Hz), 118.2, 118.1, 113.3 (d, $J_{(C-F)}$ = 22.4 Hz), 64.9, 61.7, 51.1, 14.2, 14.0; HRMS (ESI) calcd for $C_{17}H_{18}FN_2O_5$ $[M^+ + H]$ m/z 349.1200, found 349.1199.

Compound ***3f***. Yield 0.094 g (69%, gummy liquid); IR (neat) 2982, 1732, 1567, 1479, 1407, 1391, 1293, 1216, 1154, 1030, 911, 844, 808 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 4.5 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.55 (s, 1H), 7.38 (d, J = 8.5 Hz 1H), 7.09 (t, J = 5.0 Hz, 1H), 4.93 (s, 1H), 4.19−4.10 (m, 4H), 1.19 (t, J = 7.0 Hz, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 164.8, 159.9, 151.0, 135.1, 132.0, 131.6, 125.8, 116.8, 93.6, 62.0, 51.0, 14.0; HRMS (ESI) calcd for $C_{17}H_{18}IN_2O_5$ $[M^+ + H]$ m/z 457.0261, found 457.0260.

Compound ***3g***. Yield 0.078 g (65%, gummy liquid); IR (neat) 2986, 1734, 1562, 1408, 1299, 1041, 942, 767 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, J = 5.0 Hz, 2H), 7.80 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.49 (s, 1H), 7.12 (t, $J \sim$ 4.8 Hz, 1H), 5.04 (s, 1H), 4.22−4.13 (m, 4H), 1.21 (t, J = 7.0 Hz, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 164.8, 159.9, 150.9, 131.7 (qrt, $J_{(C-F)}$ = 33.2 Hz), 131.4, 129.8,

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124.6, 122.6 (qrt, $J_{(C-F)} \sim 4.0$ Hz), 122.4, 119.9 (qrt, $J_{(C-F)} \sim 3.6$ Hz), 117.0, 62.2, 51.2, 14.0; HRMS (ESI) calcd for $C_{18}H_{18}F_3N_2O_5$ $[M^+ + H]$ m/z 399.1169, found 399.1165.

Compound ***3h***. Yield 0.074 g (72%, gummy liquid); IR (neat) 2981, 1731, 1573, 1468, 1403, 1304, 1041, 899, 762 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 4.8 Hz, 2H), 7.48 (dd, $J \sim 7.4$ Hz, 1H), 7.29−7.24 (m, 2H), 7.05 (t, $J \sim 4.8$ Hz, 1H), 4.94 (s, 1H), 4.19−4.09 (m, 4H), 2.15 (s, 3H), 1.19 (t, $J \sim 7.4$ Hz, 6H);^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 164.7, 159.9, 149.3, 131.3, 131.2, 128.1, 126.2, 126.1, 116.2, 61.8, 51.4, 16.8, 14.0; HRMS (ESI) calcd for $C_{18}H_{20}N_2O_5Na$ $[M^+ + Na]$ m/z 367.1270, found 367.1274.

Compound ***3i***. Yield 0.076 g (71%, white solid); mp 76−80 °C; IR(KBr) 3046, 2992, 1731, 1567, 1408, 1310, 1255, 1030, 740 cm^{-1}; ^{1}HNMR (400 MHz,$CDCl_3$) δ 8.56 (d, J = 4.8 Hz, 2H), 7.27 (s, 1H), 7.09 (s, 1H), 7.04 (t, $J \sim 4.8$ Hz, 1H), 4.89 (s, 1H), 4.19−4.08 (m, 4H), 2.37 (s, 3H), 2.11 (s, 3H), 1.19 (t, $J \sim 7.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 164.8, 159.9, 147.0, 135.5, 132.1, 130.7, 128.4, 125.6, 116.1, 61.7, 51.3, 21.1, 16.6, 14.0; HRMS (ESI) calcd for $C_{19}H_{22}N_2O_5Na$ $[M^+ + Na]$ m/z 381.1427, found 381.1428.

Compound ***3j***. Yield 0.088 g (68%, gummy liquid); IR (neat) 3052, 2975, 1759, 1731, 1578, 1496, 1452, 1397, 1288, 1140, 1036, 899, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 4.8 Hz, 2H), 7.67 (dd, $J \sim 7.8$ Hz and ~1.4, 1H), 7.60 (dd, J = 7.6 Hz and 1.6, 1H), 7.33 (t, $J \sim 7.8$ Hz, 1H), 7.29−7.24 (m, 3H), 7.22−7.19 (m, 2H), 7.04 (t, J = 4.8 Hz, 1H), 5.11 (s, 1H), 4.22−4.14 (m, 4H), 1.21 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 165.0, 159.7, 151.7, 133.0, 131.5, 130.6, 128.5, 128.2, 126.8, 125.8, 122.8, 118.0, 116.4, 95.1, 84.6, 62.0, 51.2, 14.0; HRMS (ESI) calcd for $C_{25}H_{23}N_2O_5$ $[M^+ + H]$ m/z 431.1608, found 431.1605.

Compound ***3k***. Yield 0.084 g (74%, white solid); mp 94−98 °C; IR (KBr) 3057, 2981, 1742, 1567, 1507, 1397, 1299, 1145, 1036, 921, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 4.8 Hz, 2H), 8.13 (s, 1H), 7.92−7.90 (m, 1H), 7.81−7.79 (m, 1H), 7.68 (s, 1H), 7.51−7.49 (m, 2H), 7.08 (t, J = 4.8 Hz, 1H) 5.09 (s, 1H), 4.24−4.14 (m, 4H), 1.22 (t, $J \sim 7.0$ Hz, 6H);^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 165.4, 159.8, 148.6, 133.6, 131.4, 130.3, 128.3, 127.3, 127.0, 125.9, 125.3, 119.4, 116.5, 61.9, 51.8, 14.0; HRMS (ESI) calcd for $C_{21}H_{20}N_2O_5Na$ $[M^+ + Na]$ m/z 403.1270, found 403.1276.

Compound ***3l***. Yield 0.096 g (70%, white solid); mp 84−88 °C; IR (KBr) 3046, 2981, 1742, 1578, 1501, 1408, 1370, 1299, 1025, 915, 800 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 4.8 Hz, 2H), 8.08 (s, 1H), 8.04 (s, 1H), 7.68−7.66 (m, 2H), 7.59−7.57 (m, 1H), 7.10 (t, $J \sim 4.6$ Hz, 1H), 5.07 (s, 1H), 4.24−4.14 (m, 4H), 1.22 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 165.2, 159.9, 148.9, 132.4, 132.1, 130.3$_4$, 130.2$_6$, 129.5, 129.0, 126.6, 119.9, 119.5, 116.7, 62.1, 51.7, 14.0; HRMS (ESI) calcd for $C_{21}H_{20}BrN_2O_5$ $[M^+ + H]$ and $[M^+ + H + 2]$ m/z 459.0556 and 461.0535, found 459.0558 and 461.0535.

Compound ***3m***. Yield 0.059 g (60%, along with **3m′**; total 79%, white solid); mp 78−82 °C; IR (KBr) 3052, 2981, 1742, 1573, 1408, 1030, 910, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 4.8 Hz, 2H), 7.65−7.63 (m, 1H), 7.41−7.32 (m, 2H), 7.20 (d, J = 8.4 Hz, 1H), 7.06 (t, J = 4.8 Hz, 1H), 5.00 (s, 1H), 4.18−4.10 (m, 4H), 1.19 (t, J = 7.2 Hz, 6H);^{13}C NMR (100 MHz) δ 167.7, 165.1, 159.8, 150.7, 130.5, 129.4, 125.9, 125.8, 122.4, 116.5, 61.8, 51.3, 13.9; HRMS (ESI) calcd for $C_{17}H_{18}N_2O_5Na$ $[M^+ + Na]$ m/z 353.1114, found 353.1118.

Compound ***3m′***. Yield 0.019 g (19%, along with **3m**, total 79%, gummy liquid); IR (neat) 3068, 2975, 1726, 1573, 1414, 1052, 734, 701 cm^{-1}; ^{1}H NMR (500 MHz) δ 8.52 (d, J = 4.5 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.06 (t, J = 5.0 Hz, 1H), 4.89 (s, 2H), 4.16−4.06 (m, 8H), 1.17 (t, J = 7.0 Hz, 12H); ^{13}C NMR (125 MHz) δ 167.5, 164.9, 159.8, 148.9, 130.7, 126.6, 126.2, 116.7, 61.9, 51.5, 14.0; HRMS (ESI) calcd for $C_{24}H_{29}N_2O_9$ $[M^+ + H]$ m/z 489.1874, found 489.1864.

Compound ***3n***. Yield 0.039 g (34%, combined yield along with **3n′** is 65%, white solid); mp 92−96 °C; IR (KBr) 3068, 2981,1737,1578,1414, 1299, 1030, 904, 805, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.8 Hz, 2H), 7.92−7.75 (m, 4H), 7.54−7.45 (m, 2H), 7.05 (t, J = 4.8 Hz, 1H), 5.17 (s, 1H), 4.20−4.14 (m, 4H), 1.20 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz) δ 167.7, 165.5, 159.9, 146.6, 134.4, 128.0, 127.2, 126.7$_1$, 126.6$_8$, 126.6, 126.0, 122.4, 122.1, 116.4, 61.8, 51.4, 13.9; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_5$ $[M^+ + H]$ m/z 381.1451, found 381.1455. This compound was crystallized from dichloromethane.

Compound ***3n′***. Yield 0.034 g (31%, combined yield along with **3n** is 65%, gummy liquid); IR (neat) 3052, 2986, 1759, 1573, 1425, 1364, 1101, 1025, 877, 740 cm^{-1}; ^{1}H NMR (400 MHz) δ 8.73 (d, J = 4.4 Hz, 2H), 7.88 (t, $J \sim 5.0$ Hz, 2H), 7.79 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.56−7.49 (m, 2H), 7.20−7.18 (m, 1H), 5.85 (s, 1H), 4.38−4.26 (m, 4H), 1.43 (t, $J \sim 7.0$ Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H);^{13}C NMR (100 MHz) δ 170.2, 167.1, 157.3, 153.2, 144.8, 134.0, 127.9, 127.2, 126.9, 126.8, 126.6, 126.2, 125.4, 121.3, 119.4, 65.2, 61.6, 54.4, 14.2, 14.1; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_5$ $[M^+ + H]$ m/z 381.1451, found 381.1454.

Compound ***3o***. Yield 0.069 g (73%, gummy liquid); IR (neat) 3140, 2948, 1742, 1622, 1567, 1507, 1402, 1140, 1019, 959, 882, 812 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 2H), 7.51 (d, J = 6.0 Hz, 1H), 7.16 (d, J = 3.6 Hz, 1H), 7.08−7.02 (m, 2H), 4.97 (s, 1H), 3.69 (s, 6H), 2.39 (s, 3H); ^{13}C NMR (100 MHz) δ 168.3, 165.2, 159.8, 150.5, 140.1, 130.2, 127.1, 123.0, 122.5, 116.4, 52.8, 50.8, 21.3; HRMS(ESI) calcd for $C_{16}H_{17}N_2O_5$ $[M^+ + H]$ m/z 317.1138, found 317.1137.

Compound ***3p***. Yield 0.104 g (93%, white solid); mp 84−88 °C; IR (neat) 2981, 2931, 1726, 1567, 1403, 1309, 1101, 800, 657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, J = 4.8 and 1.2 Hz, 2H), 7.54 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.06−7.03 (m, 1H), 7.00 (s, 1H), 5.02−4.99 (m, 2H), 4.87 (s, 1H), 2.38 (s, 3H), 1.22 (d, J = 6.0 Hz, 6H), 1.15 (d, J = 6.0 Hz, 6H); ^{13}CNMR (100 MHz) δ 167.4, 165.3, 159.8, 157.3, 150.6, 139.7, 130.3, 126.9, 123.0, 122.8, 119.2, 116.3, 69.3, 51.2, 21.5$_7$, 21.5$_5$, 21.3; HRMS (ESI) calcd for $C_{20}H_{24}N_2O_5Na$ $[M^+ + Na]$ m/z 395.1583, found 395.1582.

Compound ***4a***. Yield 0.102 g (68%, white solid); mp 78−82 °C; IR (KBr) 2981, 1737, 1578, 1485, 1403, 1370, 1036, 816, 740 cm^{-1};^{1}H NMR(400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.8 Hz, 2H), 7.45 (s, 2H), 7.05 (t, J = 4.8 Hz, 1H), 4.84 (s, 2H), 4.18−4.02 (m, 8H), 2.42 (s, 3H), 1.17 (t, $J \sim 7.0$ Hz, 12H);^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 164.9, 159.7, 146.6, 135.8, 131.1, 125.9, 116.5, 61.8, 51.3, 21.3, 13.9; HRMS (ESI) calcd for $C_{25}H_{31}N_2O_9$ $[M^+ + H]$ m/z 503.2030, found 503.2030.

Compound ***4b***. Yield 0.096 g (62%, gummy liquid); IR (neat) 3074, 2975, 1731, 1611, 1573, 1468, 1364, 1036, 899, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.8 Hz, 2H), 7.19 (s, 2H), 7.04 (t, J = 4.8 Hz, 1H), 4.84 (s, 2H), 4.16−4.04 (m, 8H), 3.84 (s, 3H), 1.17 (t, $J \sim 7.0$ Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 165.1, 159.8, 156.9, 142.6, 127.1, 116.6, 115.9, 61.8, 55.7, 51.5, 13.9; HRMS (ESI) calcd for $C_{25}H_{31}N_2O_{10}$ $[M^+ + H]$ m/z 519.1979, found 519.1980.

Compound ***4c***. Yield 0.104 g (64%, gummy liquid); IR (neat) 3074, 2964, 1731, 1578, 1414, 1299, 1030, 897, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 4.8 Hz, 2H), 7.65 (s, 2H), 7.05 (t, J = 4.8 Hz, 1H), 4.87 (s, 2H), 4.17−4.07 (m, 8H), 1.38 (s, 9H), 1.19 (t, $J \sim 7.0$ Hz, 12H); ^{13}C NMR (100 MHz) δ 167.7, 165.0, 159.8, 148.6, 146.6, 127.8, 125.5, 116.5, 61.8, 51.6, 34.8, 31.4, 14.0; HRMS (ESI) calcd for $C_{28}H_{37}N_2O_9$ $[M^+ + H]$ m/z 545.2499, found 545.2497.

Compound ***5a***. Yield 0.028 g (84%, red solid); mp 250−254 °C; IR (neat) 3096, 2915, 2855, 2367, 1814, 1677, 1600, 1430, 1315, 1183, 1090, 975, 800 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (br s, 1H), 8.83 (br s, 1H), 8.32 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 6.95 (s, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.80 (t, $J \sim 5.6$ Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.9, 153.7, 148.1, 131.2, 123.7, 123.2, 118.5, 109.4, 108.5, 81.9, 79.1, 21.1; HRMS (ESI) calcd for $C_{13}H_{11}N_2O_2$ $[M^+ + H]$ m/z 227.0820, found 227.0821. This compound was crystallized from acetonitrile.

Compound ***5b***. Yield 0.024 g (67%, red solid); mp 242−246 °C; IR (neat) 3107, 2915, 2860, 1808, 1688, 1605, 1496, 1309, 1205, 1112, 1002, 800 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.68 (br s, 1H), 8.65 (d, J = 4.8 Hz, 1H), 8.32 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 6.75 (d, J = 5.4 Hz, 1H), 6.69 (dd, J = 8.4 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR(125 MHz, DMSO-d_6) δ 169.9, 155.7, 153.3, 148.7, 119.2, 119.0, 108.4, 108.2, 96.3, 81.6, 79.1, 55.4; HRMS (ESI) calcd for $C_{13}H_{11}N_2O_3$ $[M^+ + H]$ m/z 243.0770, found 243.0768.

Compound ***5c***. Yield 0.035 g (79%, red solid); mp 252−256 °C; IR (neat) 2920, 2849, 2367, 1682, 1594, 1255, 1156, 1084, 811, 773 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (br s, 1 H), 8.64 (s, 2H), 7.80−7.71 (m, 1H), 7.30−7.21 (m, 1H), 7.07−6.84 (m, 2H);^{13}C NMR (125

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MHz, DMSO-d_6) δ 172.5, 169.6, 154.9, 148.8, 130.9, 125.8, 124.5, 120.3, 112.3, 110.2, 81.7; HRMS (ESI) calcd for $C_{12}H_8BrN_2O_2$ [M^+ + H] and [M^+ + H + 2] m/z 290.9769 and 292.9749, found 290.9764 and 292.9746.

Compound ***5d***. (Purity ca. 95%[13]): Yield 0.028 g (77%, red solid); mp 260−264 °C; IR (neat) 3096, 2920, 2844, 1688, 1594, 1540, 1425, 1205, 1085, 970, 849, 778 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (br s, 1H), 8.92 (br s, 1H), 8.4 (br s, 1H), 7.75 (d, J = 6.4 Hz, 1H), 7.23 (s, 1H), 7.12 (d, J = 6.4 Hz, 1H), 6.91(t, J = 4.0 Hz,1H);^{13}C NMR (125 MHz, DMSO-d_6) δ 169.8, 158.5, 154.6, 148.6, 126.2, 126.1, 122.9, 119.8, 109.9, 109.7, 81.7, 79.5; HRMS (ESI) calcd for $C_{12}H_7ClN_2O_2Na$ [M^+ + Na] and [M^+ + Na + 2] m/z 269.0094 and 271.0064, found 269.0090 and 271.0074.

Compound ***5e***. Yield 0.021 g (60%, yellow solid); mp 214−218 °C; IR (KBr) 2920, 2848, 1675, 1603, 1536, 1428, 1314, 1262, 1226, 1190, 1092, 1009, 808, 767 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.40 (br s, 1H), 8.75−8.67 (m, 2H), 7.00 (s, 2H), 6.94−6.93 (m, 1H), 6.89−6.87 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1, 158.9, 157.5, 154.6 (d, $J_{(C-F)}$ = 25 Hz), 152.5, 149.7, 123.0, 114.1 (d, $J_{(C-F)}$ = 20 Hz), 110.9 (d, $J_{(C-F)}$ = 21.8 Hz), 110.6, 106.0, 81.1; HRMS (ESI) calcd for $C_{12}H_8FN_2O_2$ [M^+ + H] m/z 231.0570, found 231.0571.

Compound ***5f***. Yield 0.032 g (63%, red solid); mp 212−216 °C; IR (KBr) 3090, 2915, 1676, 1598, 1536, 1464, 1304, 1200, 1092, 953, 777 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.87 (br s, 1 H), 8.81 (br s, 1H), 8.37 (br s, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.46 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 6.91 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.5, 154.7, 148.9, 131.7, 127.1, 120.9, 117.6, 110.1, 84.5, 81.8; HRMS (ESI) calcd for $C_{12}H_8IN_2O_2$ [M^+ + H] m/z 338.9630, found 338.9623.

Compound ***5g***. Yield 0.031 g (74%, yellow solid); mp 290−294 °C; IR (KBr) 3079, 2931, 2844, 2362, 1677, 1600, 1534, 1430, 1326, 1189, 1002, 920, 789 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.10 (br s, 1H), 8.71 (br s, 2H), 7.92 (d, J = 7.5 Hz 1H), 7.43−7.41 (m, 2H), 7.01 (t, J = 5.0 Hz 1H); ^{13}CNMR (125 MHz, DMSO-d_6) δ 169.3, 155.0, 147.2, 131.2, 126.0, 123.8, 121.2 (d, $J_{(C-F)}$ = 30.8 Hz), 119.6, 118.2, 110.5, 105.2, 81.4, 79.1; HRMS (ESI) calcd for $C_{13}H_8F_3N_2O_2$ [M^+ + H] m/z 281.0538, found 281.0537.

Compound ***5h***. Yield 0.032 g (82%, red solid); mp 262−266 °C; IR (KBr) 2931, 2860, 1693, 1594, 1435, 1315, 1249, 1178, 959, 855 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.97 (br s, 1H), 8.71 (d, J = 5.0 Hz, 1H), 8.18 (s, 1H), 7.84 (m, 2H), 7.55 (s, 1H), 7.37−7.31 (m, 2H), 6.92 (t, J = 5.0, Hz,1H); ^{13}C NMR δ 170.1, 157.2, 148.2, 130.7, 129.8, 127.9, 127.3, 126.9, 124.0, 123.5, 115.1, 109.4, 104.0, 81.1; HRMS (ESI) calcd for $C_{16}H_{11}N_2O_2$ [M^+ + H] m/z 263.0820, found 263.0822.

Compound ***5i***. Yield 0.033 g (65%, red solid); mp 276−280 °C; IR (KBr) 2960, 2854, 1691, 1593, 1459, 1402, 1319, 1211, 1113, 1004, 958, 886, 772 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.74 (br s, 2H), 8.14−8.09 (m, 2H), 7.80−7.78 (m, 1H), 7.58 (s, 1H), 7.41 (d, J = 8.0 Hz,1H), 6.97−6.940 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.4, 155.9, 154.7, 148.9, 132.5, 130.0, 129.4, 129.0, 128.8, 126.7, 117.5, 114.6, 110.2, 104.7, 81.5; HRMS (ESI) calcd for $C_{16}H_{10}BrN_2O_2$ [M^+ + H] and [M^+ + H + 2] m/z 340.9925 and 342.9905, found 340.9926 and 342.9908.

Compound ***A***.[13] Yield 0.019 g (61%, red solid); mp 206−210 °C; IR (neat) 3096, 2915, 1676, 1593, 1536, 1443, 1293, 1200, 1077, 968, 849, 777 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_9N_2O_2$ [M^+ + H] m/z 213.0664, found 213.0666.

Compound ***B***.[13] Yield 0.020 g (52%, red solid); mp 230−234 °C; IR (neat) 2920, 2848, 1794, 1561, 1406, 1293, 1122, 1066, 967, 802, 678 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{11}N_2O_2$ [M^+ + H] m/z 263.0820, found 263.0822.

Compound ***7a***. Yield 0.080 g (78%, gummy liquid); IR (neat) 2957, 2905, 1758, 1567, 1505, 1463, 1257, 1092, 1014, 798 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.68 (m, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz 1H), 7.01- 6.99 (m, 1H), 6.93 (s, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.94 (s, 1H), 4.19−4.10 (m, 4H), 2.34 (s, 3H), 1.19 (t, J = 7.2 Hz, 6H); ^{13}CNMR (125 MHz) δ 168.2, 163.5, 151.7, 147.7, 139.7, 139.5, 130.0, 126.2, 122.9, 122.3, 118.6, 111.3, 61.7, 51.4, 21.2, 14.0; HRMS (ESI) calcd for $C_{19}H_{21}NO_5Na$ [M^+ + Na] m/z 366.1318, found 366.1316.

Compound ***7b***. Yield 0.092 g (75%, gummy liquid); IR (neat) 3054, 2987, 1737, 1567, 1422, 1324, 1148, 1019, 683 cm^{-1}; ^{1}H NMR (500 MHz) δ 8.15 (dd, J = 5.0 and 4.5 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.69−7.66 (m, 1H), 7.58 (d, J = 8.1 Hz,, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.04−7.00 (m, 2H), 6.82 (s, 1H), 6.76 (d, J = 8.5 Hz, 1H), 5.65 (s, 1H), 4.20−4.09 (m, 2H), 2.33 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz) δ 164.6, 162.9, 152.7, 147.7, 141.4, 139.6, 137.7, 134.0,130.9, 129.6, 128.7, 125.8, 121.5, 119.1, 117.3, 111.8, 67.3, 62.4, 21.4, 13.9; HRMS (ESI) calcd for $C_{22}H_{21}NO_5SNa$ [M^+ + Na] m/z 434.1030, found 434.1034.

Compound ***7c***. Yield 0.093 g (73%, gummy liquid); IR (neat) 3060, 2926, 1742, 1572, 1422, 1329, 1148, 1019, 812, 657 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.69−7.66 (m, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.04−7.01 (m, 2H), 6.84 (s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.64 (s, 1H), 4.18−4.12 (m, 2H), 2,42 (s, 3H), 2.33 (s, 3H), 1.18 (t, J = 7.0 Hz, 3H); ^{13}CNMR (100 MHz) δ 164.7, 163.0, 152.7, 147.7, 145.0, 141.3, 139.6, 134.8, 130.9, 129.7, 129.3, 125.8, 121.5, 119.0, 117.5, 111.8, 67.2, 62.4, 21.7, 21.5, 13.9; HRMS (ESI) calcd for $C_{23}H_{24}NO_5S$ [M^+ + H] m/z 426.1375, found 426.1378.

Compound ***8*** *[Method iii(a) Was Used]*. Yield 0.025 g (74%, red solid); mp 182−186 °C; IR (neat) 2915, 2848, 1681, 1646, 1595, 1435, 1333, 1228, 1108, 964, 785 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.70 (s, 1H), 7.73 (s, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.03 (s, 1H), 6.97 (d, J = 7.5 Hz, 1H), 6.64 (t, J = 6.0 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 149.4, 148.8, 139.6, 135.2, 131.8, 123.5, 119.0, 116.3, 111.7, 110.7, 81.8, 21.5; HRMS (ESI) calcd for $C_{14}H_{12}NO_2$ [M^+ + H] m/z 226.0868, found 226.0867.

Compound ***9*** *[Method iii(b) Was Used]*. Yield 0.098 g (82%, red solid); mp 120−124 °C; IR (neat) 2923, 2831, 1675, 1623, 1512, 1396, 1269, 1164, 1107, 932, 762 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 6.5 Hz, 1H), 7.57 (t, J = 7.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.98 (s, 1H), 6.89−6.83 (m, 2H), 4.08 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 153.3, 149.5, 141.5, 136.9, 131.5, 126.6, 126.3, 122.5, 115.7, 114.4, 110.3, 82.9, 46.8, 21.5; HRMS (ESI) calcd for $C_{15}H_{13}NO_2Na$ [M^+ + Na] m/z 262.0844, found 262.0845.

Crystal Data. *Compound* ***3m***. $C_{21}H_{20}N_2O_5$, M = 380.39, Monoclinic, Space group $C2/c$, a = 16.953(2), b = 10.6145(14), c = 22.394(3) Å, V = 3827.2(8) Å^3, α = 90, β = 108.248(5), γ = 90, Z = 8, μ = 0.095 mm^{-1}, data/restraints/parameters: 4431/0/255, R indices (I > 2σ(I)): $R1$ = 0.0582, $wR2$ (all data) = 0.1802. CCDC No. 1511133.

Compound ***5a***. $C_{13}H_{10}N_2O_2$, M = 226.23, Monoclinic, Space group $C2/c$, a = 23.0446(19), b = 6.2463(5), c = 15.0567(12) Å, V = 2138.3(3) Å^3, α = 90, β = 93.350(4), γ = 90, Z = 8, μ = 0.097 mm^{-1}, data/restraints/parameters: 1872/0/159, R indices (I > 2σ(I)): $R1$ = 0.0379, $wR2$ (all data) = 0.1063. CCDC No. 1511134.

Compound ***9***. $C_{15}H_{13}NO_2$, M = 239.26, Monoclinic, Space group $C2/c$, a = 25.879(2), b = 7.4025(6), c = 13.146(1) Å, V = 2514.0(4) Å^3, β = 93.350(4), Z = 8, μ = 0.084 mm^{-1}, data/restraints/parameters: 2190/0/165, R indices (I > 2σ(I)): $R1$ = 0.0658, $wR2$ (all data) = 0.1820. CCDC No. 1525099.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02693.

Figures giving ORTEP drawings as shown by X-ray crystallography, and copies of ^{1}H/^{13}C NMR spectra of all new products (PDF)

Crystal data (CIF)

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Notes

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(13) In a few cases (e.g., **5c** and **A**–**B**), although TLC indicated a pure product, we were not able to get good line-like $^{13}C/^{1}H$ spectra. However, the HRMS data were clear-cut. It is possible that these compounds show tautomeric behavior, but we have not investigated this in the current work.

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