One-pot synthesis of dihydrobenzisoxazoles from hydroxylamines, acetylenedicarboxylates, and arynes via in situ generation of nitrones

Pan Li, Chunrui Wu, Jingjing Zhao, Yang Li, Weichao Xue, and Feng Shi

Abstract: Aryne [3 + 2] cycloaddition with nitrones generated in situ from the addition of hydroxylamines to acetylenedicarboxylates affords moderate to good yields of dihydrobenzisoxazoles. This reaction extends the current scope of aryne cycloaddition to include in situ generated nitrones and produces functionalized dihydrobenzisoxazoles with a quaternary center.

Key words: nitrone, aryne, dipolar cycloaddition, reactive intermediate, dihydrobenzisoxazole.

Résumé : La cycloaddition [3 + 2] d'aryne à des nitrones générées in situ par l'addition d'hydroxylamines à des acétylènecarboxylates conduit à la formation avec des rendements allant de modérés à bons de dihydrobenzisoxazoles. Cette réaction prolonge la plage d'application des réactions de cycloadditions à des arynes de façon à inclure des nitrones générées in situ et à produire des dihydrobenzisoxazoles fonctionnalisés avec un centre quaternaire.

Mots-clés : nitrone, aryne, cycloaddition dipolaire, intermédiaire réactif, dihydrobenzisoxazole.

[Traduit par la Rédaction]

Introduction

In recent years, the [3 + 2] dipolar cycloaddition of arynes with various 1,3-dipoles has become resurgent[1–7] with the development of the Kobayashi aryne precursor,[8] 2-(trimethylsilyl)aryl triflates. Among the stable and isolable dipoles, diazo compounds[2] and azides[3] have received heavy investigation. However, another equally stable and isolable 1,3-dipole, nitrone, has not been thoroughly studied.

Nitrone cycloaddition with arynes affords dihydrobenzisoxazole derivatives, which are known synthetic intermediates and exhibit antimicrobial activities.[9] Because of the limited availability and few synthetic routes, the bioactivity of dihydrobenzisoxazole derivatives remains underinvestigated. It is thus not hard to envisage that aryne cycloaddition would represent a useful synthetic route for dihydrobenzisoxazoles and potentially allow for the construction of libraries around this privileged scaffold, given the relatively easy access to nitrones from readily available starting materials.[10]

Curiously, the investigation of aryne–nitrone cycloaddition has paid little attention to the scope of nitrones, but significant attention to the scope of arynes. In fact, almost every precursor of aryne has been studied in the context of cycloaddition with nitrones, including 1-aminobenzotriazoles (with $Pb(OAc)_4$),[11] 2-halophenyl triflates (with BuLi),[12] diazotized anthranilic acid,[13] benzoxadisilole derivatives (with $PhI(OAc)_2$ then fluoride),[14] and the Kobayashi precursor (with fluoride).[15] However, in most reports, only one or two nitrones were examined. The substitution pattern and functional group compatibility have been poorly explored. To the best of our knowledge, to date, only three reports have focused on the structural modification of nitrones,[12b,15] and regretfully only one has employed nitrones equipped with functional groups.[15a]

This deficiency can be partially ascribed to the fact that nitrones can be hard to work with. Conventional column chromatography is difficult to use with functionalized nitrones because of the high polarity they possess. Thus, to expand the scope of nitrones in the cycloaddition with arynes, alternative protocols have to be sought. In one attempt, Kivrak and Larock[16] employed oxaziridines in the aryne cycloaddition, which possibly act as a nitrone precursor. However, this strategy is largely limited to *N-tert*-butyl oxaziridines. We hypothesized that in situ generation of nitrones would solve the concerning issue of their isolation and purification, and hence accommodate complex structures and functional groups. The same strategy has been used by us and others in the cycloaddition of arynes with other dipoles,[17] but not yet with nitrones.

Hydroxylamine (**2**)[18] is the usual starting material for the preparation of nitrones. Although the most widely used route involves condensation with carbonyl compounds, electron-poor alkynes[19] (**1**), such as dimethyl acetylenedicarboxylate (DMAD), and allenes[20] have also been used to afford nitrones (**3**) via a Michael addition–tautomerization process (Scheme 1).

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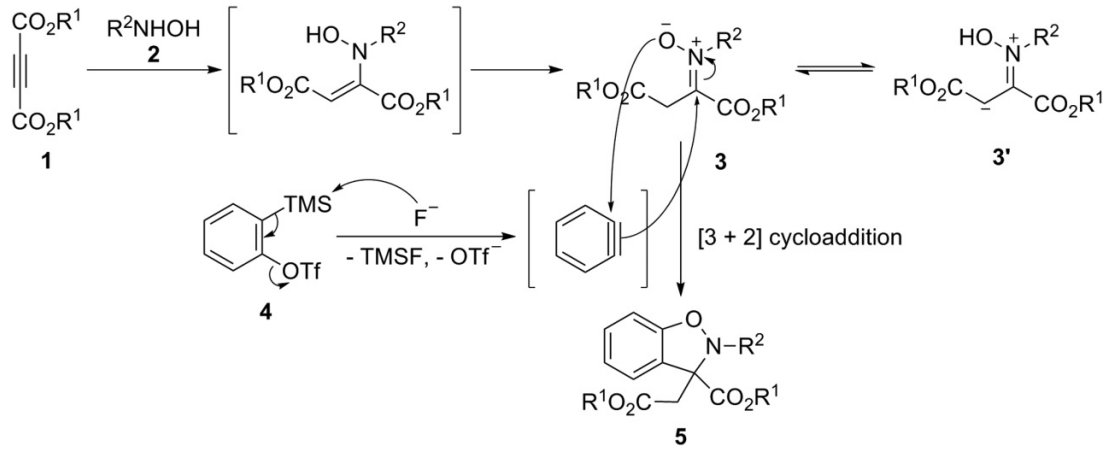
Scheme 1. Generation of nitrones from hydroxylamines and acetylenedicarboxylates.



Therefore, the treatment of a mixture of hydroxylamines and electron-poor alkynes with the Kobayashi aryne precursor in the presence of a fluoride source would lead to the in situ generation of both nitrones and arynes, and allow for a subsequent cycloaddition in a one-pot, three-component manner.[21]

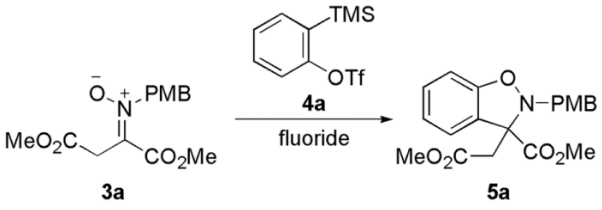
Results and discussion

We first isolated nitrone **3a** from the reaction of DMAD (**1a**) with *N*-(4-methoxybenzyl)hydroxylamine (**2a**) and subjected it to different reaction conditions with benzyne precursor **4a** (Table 1). Both CsF (Table 1, entry 1) and tetrabutylammonium fluoride (TBAF; Table 1, entries 4 and 5) proved effective fluoride sources, and the optimal conditions involved MeCN as the solvent at a slightly elevated temperature of 50 °C (Table 1, entry 1). The yield of this reaction was only moderate, despite a fairly clean thin-layer chromatography (TLC). The lost mass is mostly ascribed to some unidentifiable polar side products at the baseline of the TLC, and charging more benzyne precursor failed to provide a higher yield. The structure of **5a** was characterized by extensive NMR techniques, including heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC; see the Supplementary data). Note that nitrone **3a** contains an active methylene group, which may tautomerize to **3′** (Scheme 1) and react with arynes in a known σ-bond cleavage process.[22] This side product was not isolated, indicating that **3** reacted largely as the nitrone tautomer.

Next, we moved to the one-pot reaction conditions. We were pleased to find that the nitrone formation was very fast. As long as CsF (or TBAF) was added last, by the time we weighed out CsF (or withdrew TBAF solution from the bottle) the reaction between **1a** and **2a** was complete at room temperature (rt). This is an important observation as it may largely eliminate the potential cycloaddition of **3** with **1** as well as the *N*- or *O*-arylation of **2** with arynes. Under these conditions, **5a** was still isolated in a 58% yield (Table 2, entry 1), indicating no apparent loss of yield in the one-pot, three-component protocol. In addition, microwave irradiation afforded a 64% yield of the desired product.

We then started to examine the scope and limitation of this protocol (Table 2). First, different arynes were tested (Table 2, entries 2 and 3). The symmetrical dimethoxybenzyne afforded

Table 1. Reaction optimization.



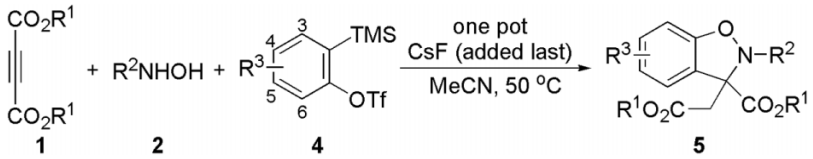
Entry	Fluoride	Solvent	*T* (°C)	Time (h)	Yield (%)[a]
1	CsF	MeCN	50	3	64
2	CsF	MeCN	rt	16	29
3	CsF	THF	70	16	9
4	TBAF	MeCN	rt	16	40
5	TBAF	THF	rt	16	46

Note: All reactions were carried out on a 0.4 mmol scale in 4 mL of solvent. **3a/4a**/fluoride = 1:1.2:2. rt, room temperature; THF, tetrahydrofuran; TBAF, tetrabutylammonium fluoride; PMB, *p*-methoxybenzyl; TMS, trimethylsilyl; Tf, trifluoromethanesulfonyl.

[a]Isolated yields.

the desired product **5b** in a moderate 46% yield (Table 2, entry 2), and the unsymmetrical 3-methoxybenzyne gave a single regioisomer in a 40% yield (Table 2, entry 3). This regioselectivity was similarly observed by Suzuki and co-workers[12a] and Larock and co-workers[15a] in their earlier studies. A range of hydroxylamines were examined next. As can be seen, hydroxylamines derived from aromatic aldehydes (Table 2, entries 4 and 5), an aromatic ketone (Table 2, entry 7), aliphatic aldehydes (Table 2, entries 8 and 9), and an aliphatic ketone (Table 2, entry 10) all afforded moderate to good yields of the corresponding products. Halogen, ether, and ester functional groups were well-tolerated. However, we noticed that the hydroxylamine derived from 4-cyanobenzaldehyde (**2d**) only afforded a complex mixture (Table 2, entry 6). Detailed study revealed that this nitrone was unstable under the reaction conditions and quickly decomposed upon exposure to CsF. Lastly, the replacement of DMAD with its analogues was also partly successful, as diethyl acetylenedicarboxylate (**1b**)

Table 2. Reaction scope.



1 2 4 5

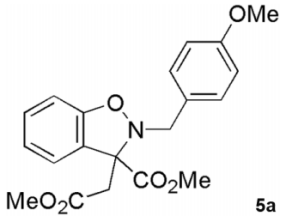
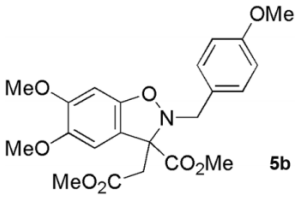
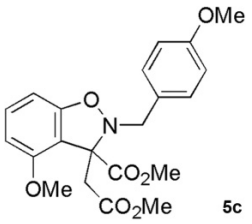
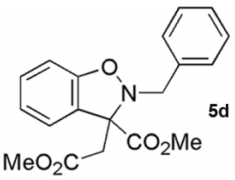
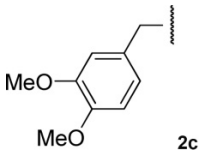
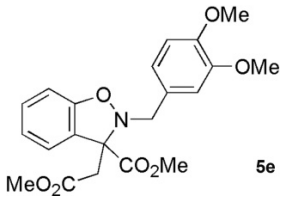
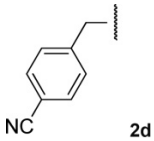
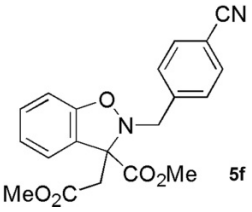
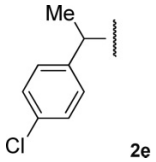
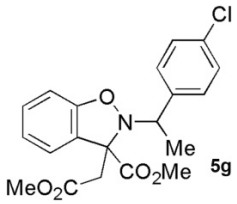
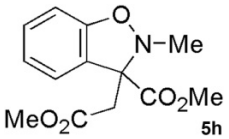
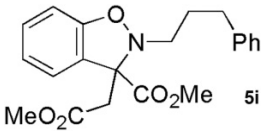
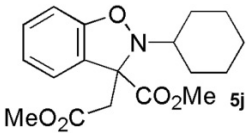
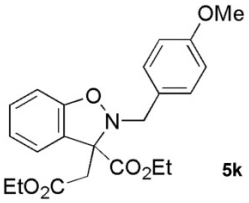
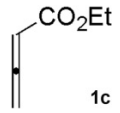
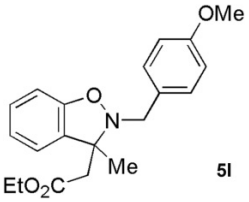
Entry	R^1 (**1**)	R^2 (**2**)	R^3 (**4**)	Product	Yield (%)[a]
1	Me (**1a**)	PMB (**2a**)	H (**4a**)	 **5a**	58[b]
2	Me (**1a**)	PMB (**2a**)	4,5-$(MeO)_2$ (**4b**)	 **5b**	46
3	Me (**1a**)	PMB (**2a**)	3-MeO (**4c**)	 **5c**	40[c]
4	Me (**1a**)	Bn (**2b**)	(**4a**)	 **5d**	46
5	Me (**1a**)	 **2c**	H (**4a**)	 **5e**	49
6	Me (**1a**)	 **2d**	H (**4a**)	 **5f**	Mixture

Table 2 (*concluded*).

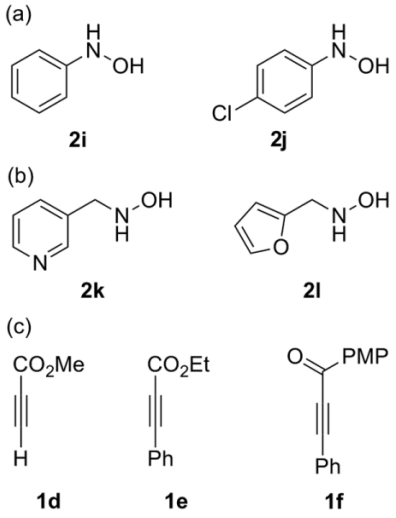
Entry	R^1 (**1**)	R^2 (**2**)	R^3 (**4**)	Product	Yield (%)[a]
7	Me (**1a**)	 **2e**	H (**4a**)	 **5g**	74 (1.8:1 dr)[d]
8	Me (**1a**)	Me (**2f**)	H (**4a**)	 **5h**	76[e]
9	Me (**1a**)	$Ph(CH_2)_3$ (**2g**)	H (**4a**)	 **5i**	64
10	Me (**1a**)	Cy (**2h**)	H (**4a**)	 **5j**	90
11	Et (**1b**)	PMB (**2a**)	H (**4a**)	 **5k**	75
12	 **1c**	PMB (**2a**)	H (**4a**)	 **5l**	36

Note: All reactions were carried out on a 0.4 mmol scale in 4 mL of MeCN for 3 h. PMB, *p*-methoxybenzyl; Cy, cyclohexyl; Bn, benzyl.
[a]Isolated yields.
[b]The use of microwave irradiation (100 W max, 80 °C, 30 min + 30 min) conditions afforded a 64% yield.
[c]The regiochemistry was analogously assigned by comparison with literature results (refs. 12a and 15a) and analysis of the ^{1}H NMR spectroscopy.
[d]The diastereomeric ratio (dr) was determined by crude ^{1}H NMR spectroscopy.
[e]The hydroxylamine was supplied as an HCl salt, and 1.2 equiv of Cs_2CO_3 was added to neutralize the acid.

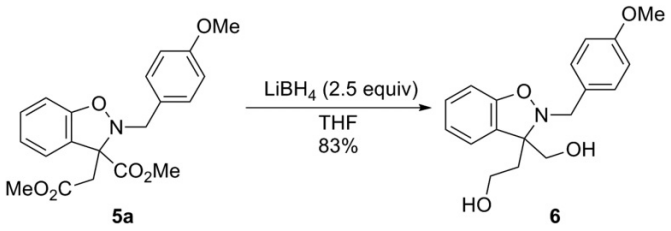
afforded a 75% yield of **5k** (Table 2, entry 11). An electron-poor allene (**1c**) could also smoothly afford **5l** in an unoptimized 36% yield (Table 2, entry 12). Thus, the one-pot three-component protocol could furnish dihydrobenzisoxazoles with three different handles for possible manipulation. Regretfully, the yields and the mass balance of some reactions remained less than satisfactory.

This protocol poses some limitations (Fig. 1). For example, *N*-arylhydroxylamines, such as **2i** and **2j**, react with DMAD reversibly[23,24] and thus *N*-aryldihydrobenzisoxazole derivatives are not accessible via this approach. Additionally, some hydroxylamines derived from heteroaromatic aldehydes, such as **2k** and **2l**, are unstable and not successfully employed either. It thus appears that the currently described protocol is more suitable for nonbenzylic aliphatic hydroxylamines (such as in Table 2, entries 8–10). Lastly, alkynes with only one electron-withdrawing group, such as **1d**, **1e**, and **1f**, are not sufficiently reactive to generate nitrones. To date, all attempts to employ

Fig. 1. Limitation of the protocol. (*a*) Hydroxylamines that form nitrones reversibly. (*b*) Unstable hydroxylamines. (*c*) Alkynes with insufficient reactivity.



Scheme 2. Reduction of the diester.



hydrazines in place of hydroxylamines to afford azomethine imine intermediates in situ have not been successful.

The stereochemistry in entry 7 (Table 2) was particularly worth mentioning. In Larock and co-workers' report,[15a] a cyclic nitrone with an embedded chiral center provided good diastereoselectivity. Since previous reports have indicated that nitrones employed in our chemistry are stereochemically defined (C=N bond adopting *E* geometry),[25] we were curious about the level of diastereoselectivity of the reaction involving nitrone **5g** in an open-chain A1,3 strain context. The experiment revealed a very modest level of stereoseletivity of 1.8:1, indicating that acyclic stereocontrol[26] in nitrone–aryne cycloaddition is difficult. A similar cycloaddition with alkenes in the literature provided an agreeable modest level of diastereoselectivity.[25]

As a useful extension of this protocol, the two ester groups can be further manipulated. For example, the simple reduction of **5a** using $LiBH_4$ afforded the corresponding diol **6** in an 83% yield (Scheme 2). Unfortunately, reduction with SmI_2 only afforded a complex mixture.

In summary, we have developed a one-pot protocol for the efficient synthesis of functionalized dihydrobenzisoxazoles from hydroxylamines, acetylenedicarboxylates, and arynes via in situ generation of nitrones. The protocol not only circumvents the necessity to isolate nitrones and thus is pot efficient, but also works with a different scope of nitrones. The stability of the hydroxylamines and nitrones poses the biggest limitation to the current method.[27]

Experimental section

All reagents purchased from commercial sources were used as received. THF and MeCN were distilled from Na/benzophenone and CaH_2, respectively. The silica gel for column chromatography was supplied as 300–400 mesh from Haiyang Chemicals (Qingdao, China).[28] Powdered CsF was used as received and stored in a dessicator.

All melting points are uncorrected. The ^1H and ^{13}C NMR spectra were referenced to the residual solvent signals (7.26 ppm for ^1H and 77.0 ppm for ^{13}C in $CDCl_3$).

General procedure

To an oven-dried 10 mL round-bottom flask equipped with a stirrer was added 0.48 mmol of the aryne precursor (1.2 equiv), followed by 0.4 mmol of the hydroxylamine. Dry MeCN (2 mL) was added and the mixture was stirred until it became homogeneous. A solution of dialkyl acetylenedicarboxylate (0.4 mmol) in MeCN (2 mL) was added dropwise, followed by 0.8 mmol of solid CsF (2 equiv) in one portion. The reaction mixture was stirred at 50 °C and monitored by TLC. Upon completion, the reaction mixture was poured into brine and extracted three times with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether / EtOAc) to afford the dihydrobenzisoxazoles.

Compound 5a

Slightly yellow solid; mp 126–127 °C. R_f = 0.43 (petroleum ether / EtOAc, 4:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.39 (dd, J = 7.6, 1.0 Hz, 1H), 7.36–7.31 (m, 2H), 7.25–7.19 (m, 1H), 6.96 (td, J = 7.5, 0.9 Hz, 1H), 6.92–6.87 (m, 2H), 6.77 (d, J = 8.1 Hz, 1H), 4.18 and 4.10 (ABq, J = 13.8 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H), 3.38 and 3.14 (ABq, J = 16.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 169.3. 159.0, 156.1, 130.0, 129.6, 128.9, 127.3, 125.0, 121.5, 113.7, 108.2, 74.3, 56.8, 55.2, 52.8, 51.8, 41.2. HR-MS electrospray ionization (ESI)) calcd for $C_{20}H_{22}NO_6$ (M + H): 372.1442; found: 372.1440.

Compound 5b

Slightly yellow oil. R_f = 0.23 (petroleum ether / EtOAc, 2:1). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.32 (d, J = 8.7 Hz, 2H), 6.95 (s, 1H), 6.89 (d, J = 8.7 Hz, 2H), 6.39 (s, 1H), 4.13 and 4.04 (ABq, J = 13.7 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H), 3.36 and 3.10 (ABq, J = 16.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 169.5, 159.0, 150.6, 150.6, 144.1, 130.0, 128.9, 117.0, 113.7, 108.4, 93.1, 74.9, 56.8, 56.7, 56.0, 55.2, 52.8, 51.8, 41.4. HR-MS (ESI) calcd for $C_{22}H_{26}NO_8$ (M + H): 432.1653; found: 432.1653.

Compound 5c

Colorless oil. R_f = 0.49 (petroleum ether / EtOAc, 4:1). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37 (m, 2H), 7.15 (t, J = 8.2 Hz, 1H), 6.92–6.83 (m, 2H), 6.43 (d, J = 8.1 Hz, 1H), 6.36 (dd, J = 8.1, 0.5 Hz, 1H), 4.30 and 4.20 (ABq, J = 13.8 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.63 (s, 3H), 3.45 and 3.28 (ABq, J = 15.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 169.3, 159.0, 157.3, 155.6, 130.9, 130.0, 129.3, 114.2, 113.7, 103.4, 100.8, 74.2, 57.5, 55.6, 55.2, 52.6, 51.6, 39.0. HR-MS (ESI) calcd for $C_{21}H_{24}NO_7$ (M + H): 402.1547; found: 402.1545.

Compound 5d

Colorless oil. R_f = 0.52 (petroleum ether / EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46–7.31 (m, 6H), 7.26–7.21 (m, 1H), 6.97 (td, J = 7.5, 0.9 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.28 and 4.20 (ABq, J = 14.0 Hz, 2H), 3.83 (s, 3H), 3.69 (s, 3H), 3.41 and 3.18 (ABq, J = 16.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 169.3, 156.1, 136.9, 129.6, 128.7, 128.3, 127.5, 127.3, 124.9, 121.5, 108.2, 74.4, 57.3, 52.9, 51.9, 41.2. HR-MS (ESI) calcd for $C_{19}H_{20}NO_5$ (M + H): 342.1336; found: 342.1332.

Compound 5e

Colorless oil. R_f = 0.30 (petroleum ether / EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, J = 7.1 Hz, 1H), 7.22 (td, J = 7.80, 1.0 Hz, 1H), 6.98–6.92 (m, 3H), 6.85 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 4.22 and 4.06 (ABq, J = 13.8 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 3.38 and 3.14 (ABq, J = 16.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 169.3, 156.1, 148.8, 148.4, 129.6, 129.3, 127.3, 125.0, 121.5, 121.0, 111.8, 110.9, 108.2, 74.4, 57.1, 55.84, 55.78, 52.9, 51.9, 41.2. HR-MS (ESI) calcd for $C_{21}H_{24}NO_7$ (M + H): 402.1547; found: 402.1549.

Compound 5g

Slightly yellow oil. R_f = 0.59 (petroleum ether / EtOAc, 4:1). This compound was obtained as a mixture of diastereomers. A very small quantity of the major isomer could be purified and characterized as such: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34–7.22 (m, 6H), 6.96 (td, J = 7.6, 0.9 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 4.40 (q, J = 6.6 Hz, 1H), 3.57 (s, 3H), 3.48 (s, 3H), 3.27 and 2.81 (ABq, J = 16.7 Hz, 2H), 1.43 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 168.8, 156.4, 140.9, 133.2, 129.5, 129.2, 128.4, 128.3, 125.5, 121.5, 107.7, 74.7, 61.6, 52.6, 51.6, 42.4, 22.0. HR-MS (ESI) calcd for $C_{20}H_{21}ClNO_5$ (M + H): 390.1103; found: 390.1100. The minor isomer could not be purified.

Compound 5h

The reaction was performed in the presence of 1.2 equiv of Cs_2CO_3. The product was as slightly yellow oil. R_f = 0.41 (petroleum ether / EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 (dd, J = 7.6, 0.9 Hz, 1H), 7.25–7.19 (m, 1H), 6.97–6.91 (m, 1H), 6.80 (d, J = 8.1 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.24 and 3.09 (ABq, J = 16.8 Hz, 2H), 2.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 169.4, 156.1, 129.8, 126.8, 125.2, 121.7, 108.2, 74.7, 52.9, 52.0, 40.6, 40.2. HR-MS (ESI) calcd for $C_{13}H_{16}NO_5$ (M + H): 266.1023; found: 266.1019.

Compound 5i

Slightly yellow oil. R_f = 0.40 (petroleum ether / EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (dd, J = 7.6, 0.8 Hz, 1H), 7.30–7.25 (m, 2H), 7.21–7.16 (m, 4H), 6.94 (td, J = 7.6, 0.8 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 3.26 and 3.04 (ABq, J = 16.7 Hz, 2H), 3.07–3.01 (m, 1H), 2.93–2.86 (m, 1H), 2.74 (t, J = 7.7 Hz, 2H), 2.11–2.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 169.3, 156.0, 141.7, 129.6, 128.4, 128.3, 127.4, 125.8, 125.1, 121.5, 108.0, 74.5, 52.8, 52.4, 51.8, 40.5, 32.9, 29.4. HR-MS (ESI) calcd for $C_{21}H_{24}NO_5$ (M + H): 370.1649; found: 370.1646.

Compound 5j

Slightly yellow oil. R_f = 0.54 (petroleum ether / EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 (dd, J = 7.6, 0.8 Hz, 1H), 7.23–7.17 (m, 1H), 6.90 (td, J = 7.5, 0.9 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 3.78 (s, 3H), 3.61 (s, 3H), 3.36 and 3.03 (ABq, J = 16.2 Hz, 2H), 3.07 (tt, J = 10.7, 3.2 Hz, 1H), 1.91–1.48 (m, 6H), 1.36–1.06 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 170.1, 156.7, 129.4, 128.2, 124.3, 121.0, 107.1, 73.7, 62.9, 52.9, 51.7, 41.6, 31.3, 29.8, 25.6, 25.4, 25.1. HR-MS (ESI) calcd for $C_{18}H_{24}NO_5$ (M + H): 334.1649; found: 334.1649.

Compound 5k

Slightly yellow oil. R_f = 0.49 (petroleum ether/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (dd, J = 7.6, 1.0 Hz, 1H), 7.37–7.33 (m, 2H), 7.22 (td, J = 8.0, 1.3 Hz, 1H), 6.98–6.93 (m, 1H), 6.92–6.89 (m, 2H), 6.77 (d, J = 8.0 Hz, 1H), 4.37–4.09 (m, 6H), 3.81 (s, 3H), 3.38 and 3.12 (ABq, J = 16.5 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.8, 168.7, 159.0, 156.1, 130.0, 129.5, 129.1, 127.5, 125.0, 121.3, 113.7, 108.1, 74.3, 61.9, 60.8, 56.7, 55.2, 41.4, 14.0 (overlapped signal). HR-MS (ESI) calcd for $C_{22}H_{26}NO_6$ (M + H): 400.1755; found: 400.1750.

Compound 5l

Colorless oil. R_f = 0.39 (petroleum ether/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.33 (m, 2H), 7.21–7.15 (m, 2H), 6.97–6.89 (m, 3H), 6.79–6.76 (m, 1H), 4.14–4.05 (m, 2H), 4.06 and 3.90 (ABq, J = 13.6 Hz, 2H), 3.81 (s, 3H), 2.80 (s, 2H), 1.73 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 158.9, 155.6, 132.5, 130.0, 129.6, 128.6, 122.9, 121.2, 113.8, 108.5, 68.3, 60.4, 55.3, 55.2, 44.4, 20.6, 14.1. HR-MS (ESI) calcd for $C_{20}H_{24}NO_4$ (M + H): 342.1700; found: 342.1699.

Compound 6

To an oven-dried 10 mL round-bottom flask equipped with a stirrer was added **5a** (93 mg, 0.25 mmol). Dry THF (3 mL) was added and the solution was cooled to 0 °C. A $LiBH_4$ solution (2 mol/L in THF, 0.35 mL, 0.7 mmol, 2.5 equiv) was added dropwise. The reaction mixture was stirred at rt overnight. Glycerol (1 mL) was added and the mixture was stirred for 2 h before being poured into brine. It was extracted three times with EtOAc, and the combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography to afford **6** as a slightly yellow oil. R_f = 0.25 (petroleum ether/EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35–7.32 (m, 2H), 7.23–7.17 (m, 1H), 7.08 (dd, J = 7.5, 0.8 Hz, 1H), 6.98–6.95 (m, 1H), 6.93–6.89 (m, 2H), 6.77 (d, J = 8.0 Hz, 1H), 4.25 and 4.20 (ABq, J = 13.9 Hz, 2H), 3.91–3.69 (m, 4H), 3.80 (s, 3H), 2.26–2.03 (m, 2H), OH protons show a br at ~3.0. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.0, 156.1, 130.1, 129.2 (2C), 128.5, 122.9, 121.4, 113.9, 108.3, 73.9, 65.2, 58.9, 55.2, 54.9, 34.7. HR-MS (ESI) calcd for $C_{18}H_{22}NO_4$ (M + H): 316.1543; found: 316.1541.

Supplementary data

Supplementary data are available with the manuscript through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2012-0199.

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