Tetrahedron xxx (2013) 1–10

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Construction of spiro[indoline]oxindoles through one-pot thermal-induced [3+2] cycloaddition/silica gel-promoted fragmentation sequence between isatin ketonitrones and electron-deficient alkynes

Hai-Bin Yang, Yin Wei *, Min Shi *,†

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

ARTICLE INFO

Article history:
Received 30 January 2013
Received in revised form 11 March 2013
Accepted 15 March 2013
Available online xxx

Keywords:
Isatin ketonitrone
[3+2] Cycloaddition
Silica gel
C–C bond cleavage
Spiro[indoline]oxindoles

ABSTRACT

One-pot thermal-induced [3+2] cycloaddition/silica gel-promoted fragmentation sequence between isatin ketonitrones and electron-deficient alkynes affords spiro[indoline]oxindoles in moderate to excellent yields along with good diastereoselectivities. The detailed mechanism of silica gel-promoted fragmentation has been clarified by experiment and DFT calculations.

1. Introduction

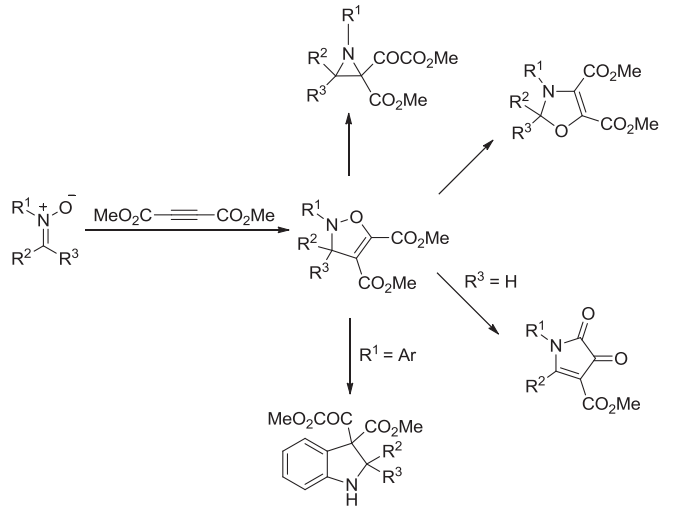
Spirooxindoles are privileged structural motifs found in many alkaloids and unnatural biologically active compounds.[1] Inspired by these important scaffolds, a variety of synthetic methods for producing spirooxindoles, especially applications to natural product synthesis, have been investigated over the last decade.[2]

In organic chemistry much attention has been focused on the syntheses and reactions of nitrones because of their importance as synthetic tools.[3] In fact, many reports have appeared on the use of nitrone as reagents, especially in the 1,3-dipolar cycloaddition reactions in which nitrones occupy a uniquely important position due to their synthetic significance.[4] However, to the best of our knowledge, there are a few reports on cycloadditions of isatin ketonitrones[5] because isatin ketonitrones are hard to be prepared by simple condensation reaction between isatin and arylhydroxylamine.[6] During our ongoing investigations on the cycloaddition reactions using isatin derivatives,[7] we discovered that trifluoroacetic acid can efficiently promote the condensation of isatin with *N*-arylhydroxylamine, affording a variety of isatin ketonitrones in good yields under mild conditions. Therefore, we attempted to use isatin ketonitrones as substrates to prepare some novel spirooxindoles, subsequently enriching the structural motifs of spirooxindole cores.

In general, nitrones react energetically with electron-deficient alkynes, such as acetylenedicarboxylate to form 4-isoxazoline as intermediates and products.[8] However, 4-isoxazolines, due to the presence of a weak nitrogen–oxygen bond and the carbon–carbon π system, undergo many types of rearrangements to afford different heterocycles, such as 2-acylaziridine,[9] 4-oxazoline,[10] 1*H*-pyrrole-2,3-dione,[11] and indoline[12] (Scheme 1). The type of rearrangements depends on the substituents of R^1, R^2, and R^3. Among these heterocycles, 2-acylaziridine is unstable and can rearrange to azomethine ylides through C–C bond cleavage, which is different from those of simple aziridines, which usually undergo C–N bond cleavage.[13] Tsuge and co-workers have reported that 2-acylaziridine generated by treating nitrone with acetylenedicarboxylate (DMAD) can be trapped by intramolecular alkene linkage to construct pyrrolidine structural motif (Scheme 2, Eq. 1).[14] Recently, Zhang and co-workers have disclosed that aziridine can react with electron-rich alkene in the presence of Lewis acid through C–C cleavage of aziridine.[15] Inspired by these results, we envisioned that the combination of isatin ketonitrone **1a**, DMAD **2a**, and dihydropyran **3** in the presence of Lewis acid or upon

* Corresponding authors. E-mail address: Mshi@mail.sioc.ac.cn (M. Shi).
† Fax: +86 21 64166128.

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.03.062



Scheme 1. The generation of 4-oxazoline via [3+2] cycloaddition between nitrone and electron-deficient alkyne and the related rearrangement.

difficulty in analyzing spectroscopic data of the crude product (low diastereoselectivity) and purification, we decided to adopt a strategy of adding silica gel to the reaction mixture after completion of thermal-induced [3+2] cycloaddition. This strategy offered an efficient and stereoselective access to construct 2-spiroindoline, which is a privileged structural motif found in many alkaloids and unnatural biologically active compounds. The closely related structural motif is mytragynine pseudoindoxyl **2**, which is a potent anti-viral agent that displays promising anticancer properties (Fig. 1).[16] Although radical dearomatising spirocyclisation onto C-2

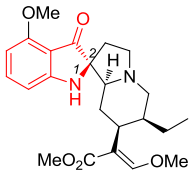
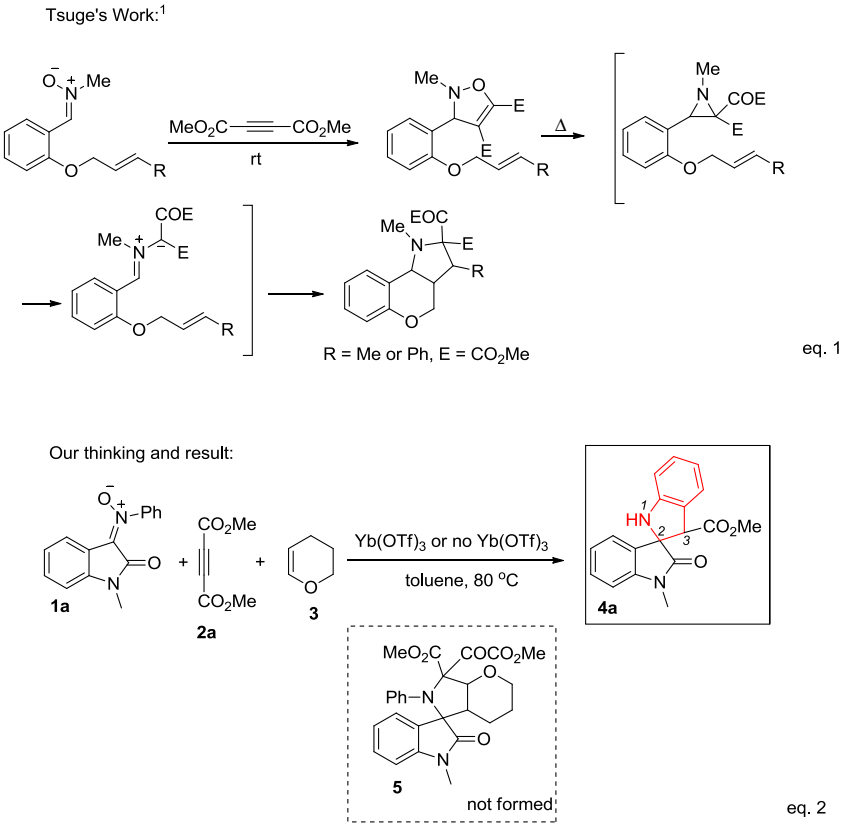


Fig. 1. The structure of mytragynine pseudoindoxyl.



Scheme 2. Our original thinking and the experimental result.

heating may produce product **5**. After examining the reaction outcome, interestingly, product **4a** was obtained in good yield along with good diastereoselectivity rather than the anticipated product **5**, and dihydropyran **3** did not participate in the reaction (Scheme 2, Eq. 2). On the basis of analyzing ^{1}H NMR spectroscopic data, we found that compound **4a** purified by flash chromatography (silica gel) was different from the crude product obtained by removing the solvent in vacuo, thus we thought that silica gel must promote some transformation of the crude product. Due to the position of indole can afford this structural motif, this synthetic procedure must use toxic Bu_3SnH or air-sensitive SmI_2 and is unsuitable for substrate containing halides (Br or I).[17] Moreover, C-3 position of the product obtained by radical dearomatising spirocyclisation onto C-2 position of indole cannot be functionalized, which is unfavorable to a diversity-oriented synthetic strategy. Herein, further exploration of methodologies for synthesizing this structural motif is highly desirable and we wish to report our results in this context.

Please cite this article in press as: Yang, H.-B.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.03.062

2. Results and discussion

Initial studies using nitrone **1a** as the substrate were aimed at determining the reaction outcome and subsequently optimizing the reaction conditions. The results are summarized in Table 1. We found that compound **4a** was formed in 61% yield along with 11:1 diastereoselectivity when 200 mg of 300–400 mesh silica gel was subjected to the resulting mixture at 80 °C for 2 h after **1a** (1.0 equiv) and **2a** (1.5 equiv) were stirred in 1,2-dichloroethane (DCE) at 60 °C for 12 h (Table 1, entry 1). The structure of compound **4a** was confirmed by NMR spectroscopic data and X-ray diffraction. The ORTEP drawing is shown in Fig. 2 and the CIF data are presented in the Supplementary data.[18] The examination of solvent effects using **1a** (1.0 equiv) and **2a** (1.5 equiv) as substrates revealed that toluene was the solvent of choice, giving the desired product **4a** in 62% yield along with 12:1 dr value (Table 1, entries 2–8). The temperature has significant influence in this reaction. Screening of the reaction temperature revealed that 80 °C gave the best result with respect to yield as well as diastereoselectivity and carrying out the reaction at 100 °C afforded **4a** in 35% yield along with 9:1 dr value (Table 1, entries 9 and 11). When nitrone **1a**, electron-deficient alkyne **2a**, 4 Å MS, and 300–400 mesh silica gel were stirred together in 1 mL of toluene at 80 °C for 12 h instead of adding silica gel stepwise, compound **4a** was obtained in 60% yield along with 10:1 dr value (Table 1, entry 10). Increasing the ratio of **1a**/**2a** to 1:3 (3.0 equiv of **2a** was used) indicated that the reaction proceeded smoothly to afford **4a** in 90% yield along with 14:1 dr value (Table 1, entry 12). Because the intermediate could be completely transformed to compound **4a** with 200 mg silica gel under the mild conditions and the low price of silica gel, we did not further investigate the effect of the ratio of silica gel to this reaction. Thus, we have established the optimal reaction conditions for this reaction: after **1a** (1.0 equiv) and **2a** (3.0 equiv) were stirred in toluene at 80 °C for 12 h, 200 mg of 300–400 mesh silica gel was added to the resulting mixture and the reaction mixture was then further stirred at 80 °C for 2 h.

With these optimal conditions in hand, we examined the substrate generality of this reaction to the substituted isatin-derived nitrones and the results are shown in Table 2. The

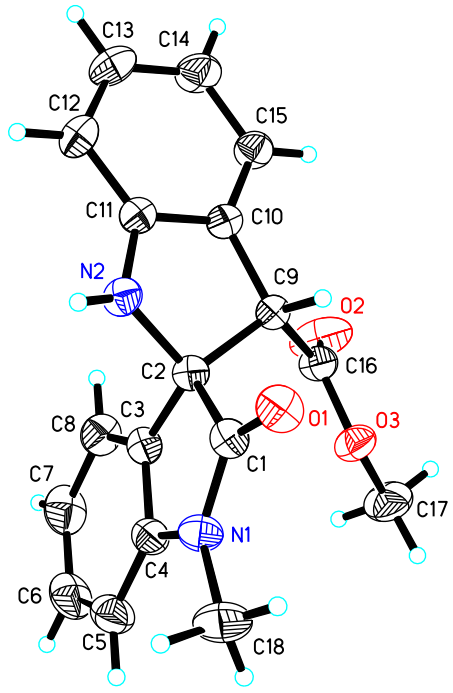
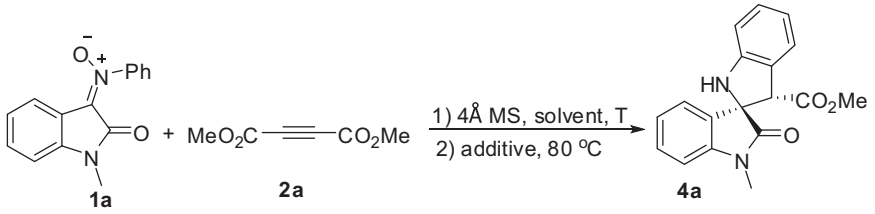


Fig. 2. ORTEP drawing of compound **4a**.

configuration for the major diastereoisomers of products is the same as that for compound **4a**. As for isatin ketonitrones, regardless of whether R^1 is electron-withdrawing group (Cl) or moderately electron-donating group (Me), the corresponding products **4b**,**c** could be obtained in good yields along with good diastereoselectivities (Table 2, entries 1 and 2). In the cases of substrates **1d**–**f**, the reactions proceeded smoothly to furnish the desired products **4d**–**4f** in higher yields for electron-donating group (product **4d**, R^2=Me, R^1=R^3=H) substituted isatin ketonitrones and higher diastereoselectivities for electron-withdrawing group (product **4e** or **4f**, R^2=Cl or Br, R^1=R^3=H) substituted isatin

Table 1
Optimization of the reaction conditions



Entry[a]	**1a**/**2a**	Solvent	Temp (°C)	Additive	dr[b]	Yield[c] (%)
1	1:1.5	DCE	60	Silica gel	11:1	61
2	1:1.5	DMF	60	Silica gel	—	<1
3	1:1.5	Ethanol	60	Silica gel	8:1	39
4	1:1.5	Dioxane	60	Silica gel	7:1	32
5	1:1.5	Toluene	60	Silica gel	12:1	62
6	1:1.5	Acetonitrile	60	Silica gel	13:1	45
7	1:1.5	n-Hexane	60	Silica gel	10:1	35
8	1:1.5	Chloroform	60	Silica gel	12:1	47
9	1:1.5	Toluene	80	Silica gel	14:1	78
10[d]	1:1.5	Toluene	80	Silica gel	10:1	60
11	1:1.5	Toluene	100	Silica gel	9:1	35
12	**1:3**	**Toluene**	**80**	**Silica gel**	**14:1**	**90**

Bold signifies optimal conditions.

[a] Nitrone **1a** (0.1 mmol), alkyne **2a** (×mmol), and 4 Å MS (100 mg) were stirred in 1 mL of solvent. After 12 h, 200 mg of 300–400 mesh silica gel was added and the resulting mixtures were stirred for 2 h at 80 °C.

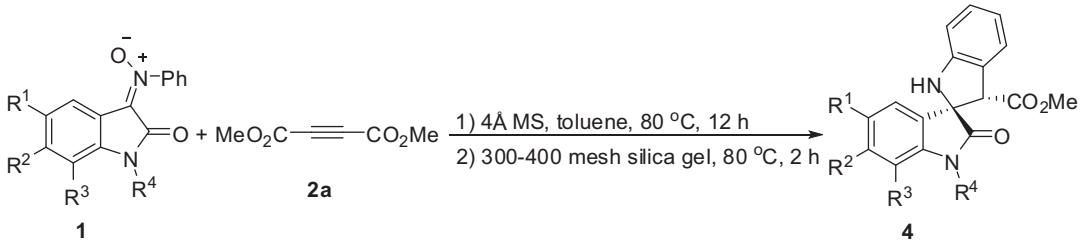
[b] The dr values were determined by ^{1}H NMR spectroscopic data of the crude products.

[c] Isolated yields.

[d] Nitrone **1a**, alkyne **2a**, 4 Å MS (100 mg), and 300–400 mesh silica gel (200 mg) were stirred in 1 mL of toluene.

Please cite this article in press as: Yang, H.-B.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.03.062

Table 2
Scope of one-pot thermal-induced [3+2] cycloaddition/silica gel-promoted fragmentation sequence to the substituted isatins derived nitrones



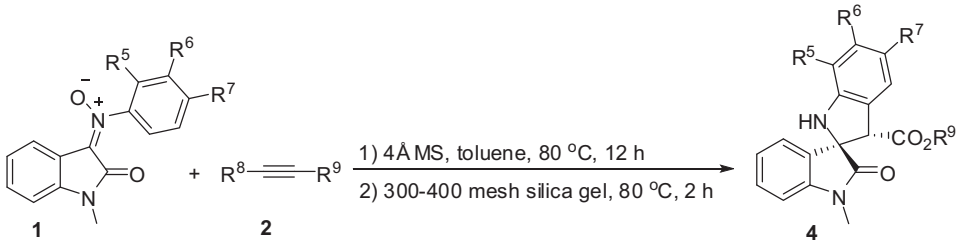
Entry[a]	$R^1/R^2/R^3/R^4$	dr[b]	Yield[c] (%)
1	**1b**, Me/H/H/Me	17:1	**4b**, 70
2	**1c**, Cl/H/H/Me	14:1	**4c**, 73
3	**1d**, H/Me/H/Me	15:1	**4d**, 72
4	**1e**, H/Cl/H/me	25:1	**4e**, 62
5	**1f**, H/Br/H/Me	25:1	**4f**, 64
6	**1g**, H/H/Cl/Me	9:1	**4g**, 87
7	**1h**, H/H/F/me	8:1	**4h**, 76
8	1i, H/H/H/Bn	15:1	**4i**, 78
9	1j, H/H/H/H	10:1	**4j**, 62

[a] Nitrone **1a** (0.1 mmol), alkyne **2a** (3 mmol), and 4 Å MS (100 mg) were stirred in 1 mL of toluene. After 12 h, 200 mg of 300–400 mesh silica gel was added and the resulting mixtures were stirred for 2 h at 80 °C.
[b] The dr values were determined by ^{1}H NMR spectroscopic data of the crude products.
[c] Isolated yields.

ketonitrones (Table 2, entries 3–5). As for isatin ketonitrones with electron-withdrawing group R^3, such as Cl and F, the reactions proceeded efficiently to afford the corresponding products **4g**,**h** in increased yields, albeit with slightly lower diastereoselectivities (Table 2, entries 6 and 7). Changing the N-PG (PG=Protecting Group) to Bn produced the corresponding product **4i** in 78% yield along with 15:1 diastereoselectivity and substrate **1j** having no protecting group (PG=H) afforded the desired product **4j** in 62% yield along with 10:1 diastereoselectivity. The yield and diastereoselectivity for substrate **1i** are better than those of substrate **1j**, indicating that the protecting group could improve the reaction outcomes (Table 2, entries 8 and 9).

We next investigated the effects of the substituted phenylhydroxylamine derived nitrones and electron-deficient alkynes to this reaction and the results are shown in Table 3. It was found that whether R^5 is an electron-withdrawing group (Cl) or a moderately electron-donating group (Me), the corresponding products **4k**,**l** could be formed in moderate yields along with good dr values (Table 3, entries 1 and 2). Compared with substrate **1n** having an electron-withdrawing group (Cl), the reaction could give better results in terms of yield and diastereoselectivity for substrate **1m** having electron-donating group (Me) (Table 3, entries 3 and 4). Interestingly, when R^7 is an electron-withdrawing group (Br), the corresponding product **4o** was obtained in excellent yield along with 14:1 dr value (Table 3, entry 5). Subsequently, a variety of electron-deficient alkynes were tested for this reaction sequence with isatin ketonitrone **1a**. The reaction proceeded smoothly for electron-deficient alkyne **2b** to afford **4p** in 78% yield and 21:1 dr

Table 3
Scope of one-pot thermal-induced [3+2] cycloaddition/silica gel-promoted fragmentation sequence to the substituted phenylhydroxylamine derived nitrones and electron-deficient alkynes



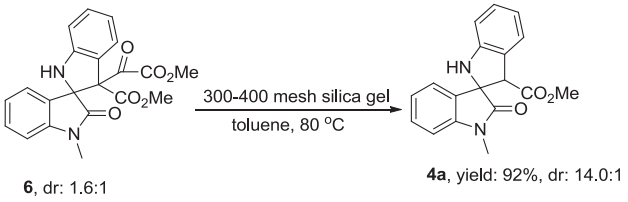
Entry[a]	$R^5/R^6/R^7$	R^8/R^9	dr[b]	Yield[c] (%)
1	**1k**, Me/H/H	**2a**, CO_2Me/CO_2Me	13:1	**4k**, 71
2	**1l**, Cl/H/H	**2a**, CO_2Me/CO_2Me	18:1	**4l**, 67
3	**1m**, H/Me/H	**2a**, CO_2Me/CO_2Me	15:1	**4m**, 63
4	**1n**, H/Cl/H	**2a**, CO_2Me/CO_2Me	8:1	**4n**, 57
5	**1o**, H/H/Br	**2a**, CO_2Me/CO_2Me	14:1	**4o**, 93
6	**1a**, H/H/H	**2b**, CO_2Et/CO_2Et	21:1	**4p**, 78
7	**1a**, H/H/H	**2c**, H/CO_2Me	17:1	**4a**, 94
8	**1a**, H/H/H	**2d**, H/COMe	15:1	**4q**, 69

[a] Nitrone **1a** (0.1 mmol), alkyne **2a** (3 mmol), and 4 Å MS (100 mg) were stirred in 1 mL of toluene. After 12 h, 200 mg of 300–400 mesh silica gel was added and the resulting mixtures were stirred for 2 h at 80 °C.
[b] The dr values were determined by ^{1}H NMR spectroscopic data of the crude products.
[c] Isolated yields.

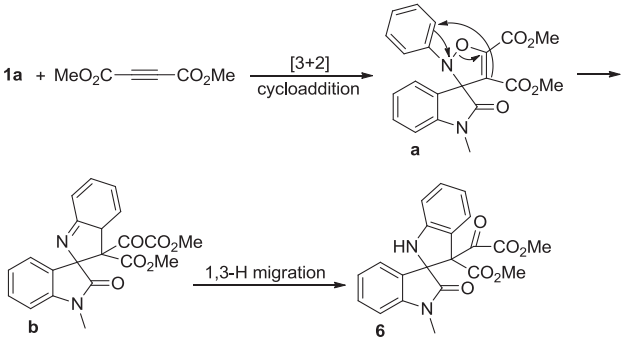
Please cite this article in press as: Yang, H.-B.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.03.062

value (Table 3, entry 6). In the case of substrate **2c**, the reaction also proceeded smoothly to furnish the corresponding product **4a** in better yield and diastereoselectivity as compared with that of substrate **1a** and electron-deficient alkyne **2a** (Table 3, entry 7). It was noteworthy that but-3-yn-2-one could be also subjected to this reaction, providing **4q** in 69% yield and 15:1 dr value (Table 3, entry 8).

To elucidate the detailed mechanism, the crude product before treating with silica gel was purified by recrystallization using diethyl ether. On the basis of carefully analyzing ^{1}H NMR spectroscopic data and ^{13}C NMR spectroscopic data, the crude product before treating with silica gel has been identified as compound **6** along with 1.6:1 dr value, and HRMS data further support our judgment. Treatment of compound **6** with 300–400 mesh silica gel in toluene at 80 °C for 12 h can furnish compound **4a** in 92% yield along with 14:1 diastereoselectivity, strongly supporting that compound **6** is a key intermediate to the formation of compound **4a** (Scheme 3). On the basis of the mechanism proposed by Maruoka and co-workers,[12] a plausible mechanism is tentatively outlined in Scheme 4 to explain the formation of compound **6**. The reaction is initiated by the formation of 4-isoxazoline **a** via the [3+2] cycloaddition between isatin ketonitrone **1a** and electron-deficient alkyne, which rearranges to give intermediate **b** because of the weak nitrogen–oxygen bond and the carbon–carbon π system. Subsequently intermediate **b** would isomerize into compound **6** via 1,3-proton transfer.

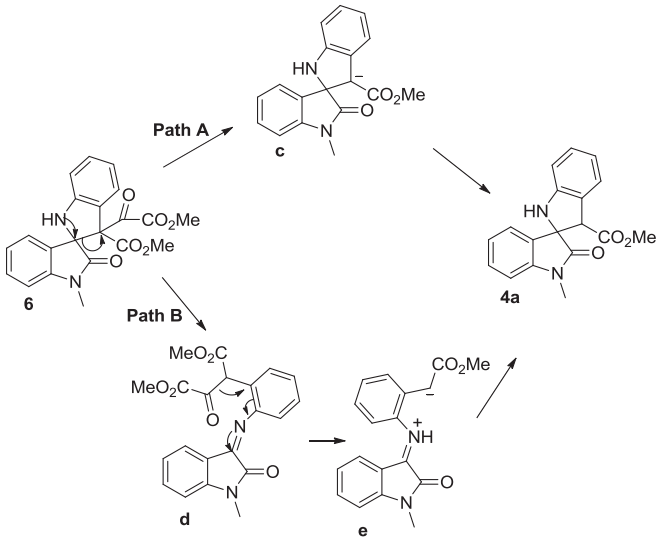


Scheme 3. The isolation of compound **6** and the further transformation.



Scheme 4. The proposed reaction mechanism for the reaction between isatin-derived nitrone and electron-deficient alkyne.

However, to the best of our knowledge, there is no previous report on the silica gel-promoted C–C bond cleavage at the α-position of 2-oxoacetate. The proton-catalyzed pathway was excluded because we found that Brønsted acids, such as trifluoromethane sulfonic acid (CF_3SO_3H, 0.4 equiv) and methanesulfonic acid (CH_3SO_3H, 0.4 equiv), showed no catalytic activity for the transformation of **1a** to **4a**. Two possible mechanisms are proposed to explain the transformation of compound **6** to compound **4a** in Scheme 5. Initially, carbonyl group of compound **6** is attacked by weak nucleophilic silyl-hydroxyl group of silica gel to afford

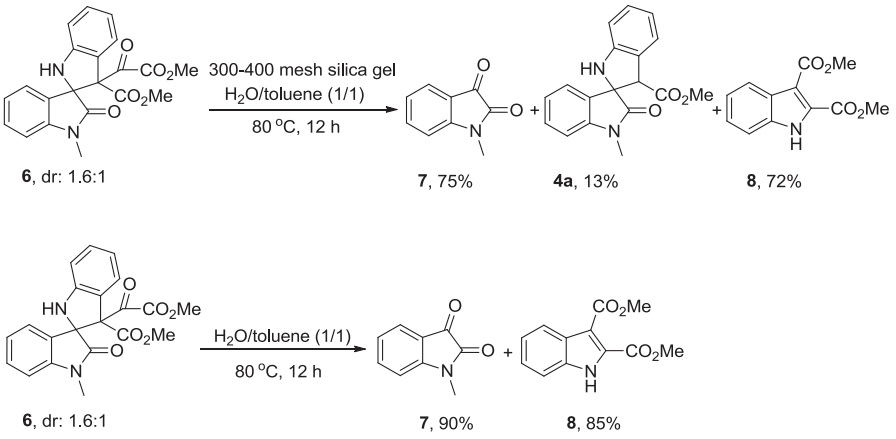


Scheme 5. The proposed reaction mechanism for silica gel-promoted C–C bond cleavage at the α-position of 2-oxoacetate.

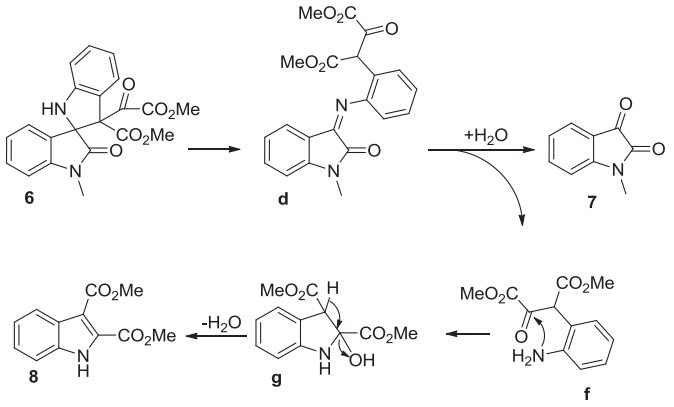
carbanion **c**, which accepts one proton to form compound **4a** from silica gel. Due to the change of the dr value from compound **6** to compound **4a**, this mechanism cannot be a concerted process (Path A). In the other pathway, the ring-opening of indoline via retro-Mannich reaction process gives intermediate **d**, which subsequently eliminates 2-oxoacetate at the aid of Si–OH of silica gel to give intermediate **e** and then intermediate **e** undergoes intramolecular annulation to afford product **4a** (Path B).

To testify the existence of imine intermediate **d**, water is added to trap imine intermediate **d** and the results are shown in Scheme 6. Stirring compound **6** and 300–400 mesh silica gel in water/toluene (1:1) at 80 °C for 12 h can provide *N*-methyl isatin in 75% yield and 2,3-disubstituted indole **8** in 70% yield along with **4a** in 13% yield, indicating that compound **6** can be easily transformed to imine. However, compound **6** can be also transformed to *N*-methyl isatin **7** in 90% yield under the same condition without the addition of silica gel, indicating that the formation of imine intermediate **d** did not require the participation of silica gel. A plausible reaction mechanism for the formation of compound **8** is shown in Scheme 7. The hydrolysis of imine intermediate **d** gives the corresponding compound **7** and intermediate **f**, which is transformed to 2,3-disubstituted indole **8** via intermediate **g** through intramolecular dehydration condensation between amine group and carbonyl group.

To understand clearly the detailed mechanism of silica gel-promoted fragmentation, we have theoretically investigated the reaction pathways as shown in Scheme 5 (for details, see Supplementary data). All calculations have been performed at the B3LYP/6-31G(d) level of theory with Gaussian 09 program.[19] To take the effect of the silica gel into account, two silicic acid molecules ($H_6Si_2O_7$) were used to simulate the silica gel surface contacting with reaction system.[20,21] The path **A** shown in Scheme 5 was ruled out since the suggested intermediates and transition states could not be located. The relative energies of intermediates and transitional states along the suggested path **B** are shown in Scheme 8. The compound **6** initially undergoes the intramolecular proton-transfer via transition state **TS1** with an energy barrier of 25.3 kcal/mol, giving the imine intermediate **d**. Then, the hydrogen atom of the hydroxyl groups in silicic acid is hydrogen-bonded to the nitrogen atom of intermediate **d** to form a loose complex **10**. Subsequently, the silicic acid is deprotonated to obtain the intermediate **11** via **TS2** with an energy barrier of 33.6 kcal/mol. The deprotonated silicic



Scheme 6. The trap of intermediate **d** by H_2O.



Scheme 7. The proposed mechanism for the formation of compound **8**.

acid subsequently promotes C–C bond cleavage through **TS3** to give the intermediate **12**, which undergoes the intramolecular annulation to form the product complex **13** and then affords the separated products.

3. Conclusion

In summary, we have developed a novel one-pot thermal-induced [3+2] cycloaddition/silica gel-promoted fragmentation sequence between isatin ketonitrones and electron-deficient alkynes, leading to spiro[indoline]oxindoles in moderate to excellent yields with good dr values. The unique structure of these products may be useful for potential drug discovery. This is the first example on silica gel-promoted elimination of 2-oxoacetate and the detailed mechanism of silica gel-promoted fragmentation has been clarified by experimental and theoretical investigations. Current efforts are in progress to apply this new methodology to synthesize biologically active products.

4. Experimental section

4.1. General remarks

^1H and ^{13}C NMR spectra were recorded at 400 (or 300) MHz, respectively. HRMS spectra were recorded by ESI method. The employed solvents were dried up by standard methods when necessary. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure.

4.2. General procedure for the one-pot thermal-induced [3+2] cycloaddition/silica gel-promoted fragmentation sequence between isatin ketonitrones and electron-deficient alkynes

Isatin ketonitrone **1** (0.1 mmol, 1.0 equiv), electron-deficient alkyne **2** (0.3 mmol, 3.0 equiv), and 4 Å MS (100 mg) were stirred in toluene (1.0 mL) at 80 °C. After 12 h, 200 mg of 300–400 mesh silica gel was added and the resulting mixtures were stirred for 2 h. The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography (SiO_2) to give the corresponding products **4** in moderate to good yields.

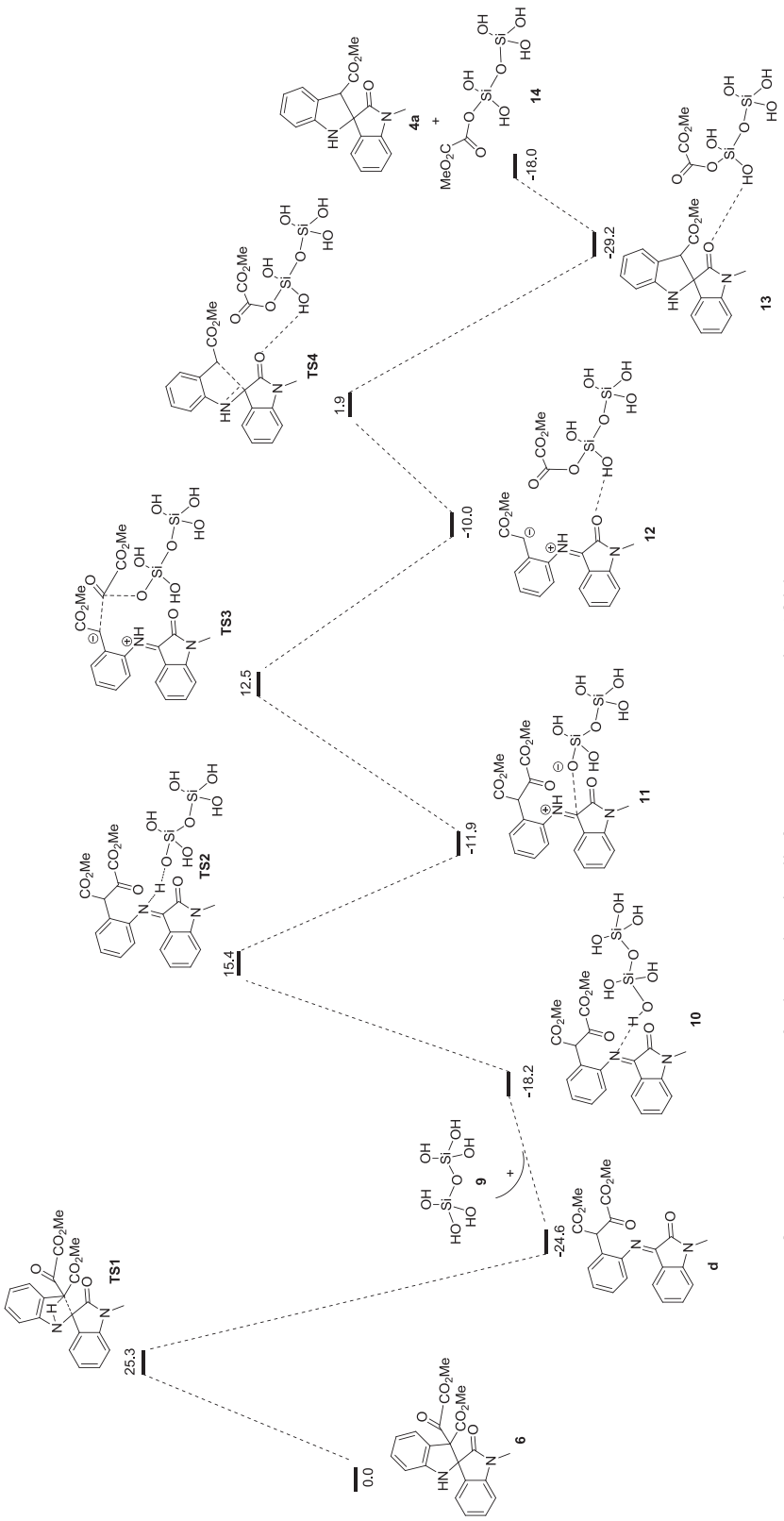
Compound **1a**: Yield: 73%. A yellow solid. Mp: 160–162 °C. IR (neat) ν 3059, 3021, 1695, 1608, 1467, 1373, 1328, 1098, 1080, 983 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.18 (s, 3H), 6.84 (d, J=7.6 Hz, 1H), 7.15 (td, J=7.6, 0.8 Hz, 1H), 7.43 (td, J=7.6, 1.2 Hz, 1H), 7.46–7.55 (m, 5H), 8.47 (dd, J=7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.0, 107.9, 118.0, 123.1, 123.6, 125.1, 129.0, 130.6, 132.2, 134.6, 142.0, 146.4, 159.5; HRMS (MALDI) calcd for $C_{15}H_{12}N_2O_2$ requires (M^++H): 253.0977, Found: 253.0976.

Compound **1b**: Yield: 82%. A red solid. Mp: 190–192 °C. IR (neat) ν 3063, 3010, 2911, 1694, 1612, 1538, 1483, 1299, 1101, 1008, 930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 2.39 (s, 3H), 3.16 (s, 3H), 6.74 (d, J=8.0 Hz, 1H), 7.23 (d, J=8.0 Hz, 1H), 7.45–7.55 (m, 5H), 8.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.0, 26.0, 107.7, 118.0, 123.7, 125.7, 129.0, 130.6, 132.6, 132.7, 134.9, 140.0, 146.4, 159.6; HRMS (MALDI) calcd for $C_{16}H_{14}N_2O_2$ requires (M^++H): 267.1134, Found: 267.1132.

Compound **1c**: Yield: 59%. A red solid. Mp: 210–212 °C. IR (neat) ν 3108, 3084, 3019, 1701, 1536, 1471, 1290, 1234, 1101, 1076, 994 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.19 (s, 3H), 6.78 (d, J=8.4 Hz, 1H), 7.40 (dd, J=8.0, 1.6 Hz, 1H), 7.46–7.58 (m, 5H), 8.48 (d, J=2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.1, 108.8, 119.1, 123.6, 124.8, 128.5, 129.0, 130.9, 131.6, 133.9, 140.3, 146.2, 159.1; HRMS (MALDI) calcd for $C_{15}H_{11}ClN_2O_2$ requires (M^++H): 287.0587, Found: 287.0587.

Compound **1d**: Yield: 86%. A red solid. Mp: 214–216 °C. IR (neat) ν 3032, 2916, 2857, 1701, 1614, 1454, 1378, 1244, 1078, 923 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.45 (s, 3H), 3.18 (s, 3H), 6.68 (s, 1H), 6.97 (d, J=7.8 Hz, 1H), 7.45–7.54 (m, 5H), 8.35 (d, J=8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 22.5, 25.9, 108.9, 115.5, 123.6, 123.7, 124.9, 128.9, 130.4, 134.5, 142.3, 143.4, 146.3, 159.7; HRMS (MALDI) calcd for $C_{16}H_{14}N_2O_2$ requires (M^++H): 267.1134, Found: 267.1136.

Please cite this article in press as: Yang, H.-B.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.03.062



Gas-phase enthalpy profile (ΔH_{298} (kcal/mol)). Calculated at B3LYP/6-31G(d) level.

Scheme 8. The reaction energy profile for path **B**.

Compound **1e**: Yield: 78%. A red solid. Mp: 218–220 °C. IR (neat) ν 3056, 3015, 1702, 1601, 1531, 1479, 1371, 1284, 1238, 1107, 1072, 995 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.16 (s, 3H), 6.84 (s, 1H), 7.11 (d, J=8.4 Hz, 1H), 7.46–7.57 (m, 5H), 8.38 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.1, 108.7, 116.5, 122.9, 123.6, 125.7, 129.0, 130.8, 133.7, 137.7, 142.9, 146.2, 159.3; HRMS (MALDI) calcd for $C_{15}H_{11}ClN_2O_2$ requires (M^++H): 287.0587, Found: 287.0578.

Compound **1f**: Yield: 99%. A red solid. Mp: 233–235 °C. IR (neat) ν 3060, 2927, 1701, 1599, 1285, 1104, 1060, 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.17 (s, 3H), 7.01 (d, J=1.6 Hz, 1H), 7.28 (dd, J=8.4, 1.6 Hz, 1H), 7.46–7.56 (m, 5H), 8.32 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.1, 111.5, 116.9, 123.6, 125.9, 126.0, 129.0, 130.8, 132.2, 133.9, 142.9, 146.3, 159.3; HRMS (MALDI) calcd for $C_{15}H_{11}BrN_2O_2$ requires (M^++H): 331.0082, Found: 331.0062.

Compound **1g**: Yield: 64%. A red solid. Mp: 237–240 °C. IR (neat) ν 3053, 2953, 1702, 1599, 1535, 1450, 1370, 1316, 1110, 1056, 989 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.56 (s, 3H), 7.06 (dd, J=8.4, 7.6 Hz, 1H), 7.34 (dd, J=8.4, 1.2 Hz, 1H), 7.44–7.47 (m, 2H), 7.50–7.58 (m, 3H), 8.48 (dd, J=8.0, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 29.2, 115.4, 120.6, 123.3, 123.6, 123.8, 129.0, 130.8, 133.6, 134.1, 137.6, 146.5, 159.7; HRMS (MALDI) calcd for $C_{15}H_{11}ClN_2O_2$ requires (M^++H): 287.0587, Found: 287.0581.

Compound **1h**: Yield: 59%. A red solid. Mp: 170–172 °C. IR (neat) ν 3051, 2937, 1706, 1626, 1548, 1461, 1372, 1230, 791 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 3.99–3.40 (m, 3H), 7.03–7.19 (m, 2H), 7.45–7.59 (m, 5H), 8.29 (dd, J=7.5, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 28.6 (d, J_{C-F}=5.3 Hz), 120.0 (d, J_{C-F}=19.1 Hz), 120.6 (d, J_{C-F}=1.6 Hz), 120.9 (d, J_{C-F}=2.9 Hz), 123.6, 123.7, 128.2 (d, J_{C-F}=9.2 Hz), 129.0, 130.8, 134.1, 146.2, 147.1 (d, J_{C-F}=242.6 Hz), 159.2; ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$) δ −136.87 (br s, 1F); HRMS (MALDI) calcd for $C_{15}H_{11}FN_2O_2$ requires (M^++H): 271.0883, Found: 271.0875.

Compound **1i**: Yield: 75%. A yellow solid. Mp: 208–210 °C. IR (neat) ν 3067, 3030, 2939, 1696, 1605, 1541, 1463, 1258, 1162, 948, 871 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 4.87 (s, 2H), 6.76 (d, J=7.8 Hz, 1H), 7.11 (t, J=7.5 Hz, 1H), 7.24–7.34 (m, 6H), 7.51–7.53 (m, 5H), 8.50 (d, J=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 43.7, 108.9, 118.2, 123.1, 123.7, 125.1, 127.3, 127.7, 128.8, 129.0, 130.7, 132.1, 134.4, 135.4, 141.3, 146.4, 159.5; HRMS (MALDI) calcd for $C_{21}H_{16}N_2O_2$ requires (M^++H): 329.1290, Found: 329.1280.

Compound **1j**: Yield: 62%. A yellow solid. Mp: 258–260 °C. IR (neat) ν 3149, 3066, 3028, 2828, 1701, 1539, 1459, 1351, 1256, 1237, 1139, 925, 857 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, TMS) δ 6.90 (d, J=7.6 Hz, 1H), 7.07 (td, J=7.6, 0.8 Hz, 1H), 7.40 (td, J=7.6, 1.2 Hz, 1H), 7.49–7.59 (m, 5H), 8.28 (d, J=7.6 Hz, 1H), 10.8 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS) δ 109.8, 118.4, 121.9, 124.0, 124.2, 128.8, 130.2, 132.4, 134.5, 141.0, 146.4, 160.0; HRMS (MALDI) calcd for $C_{14}H_{10}N_2O_2$ requires (M^++H): 239.0821, Found: 239.0806.

Compound **1k**: Yield: 47%. A yellow solid. Mp: 156–158 °C. IR (neat) ν 3079, 2927, 1702, 1606, 1468, 1375, 1244, 1093, 985 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.27 (s, 3H), 3.17 (s, 3H), 6.86 (d, J=7.5 Hz, 1H), 7.16 (t, J=7.5 Hz, 1H), 7.25 (d, J=7.8 Hz, 1H), 7.31–7.46 (m, 4H), 8.50 (d, J=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 16.4, 25.9, 107.9, 117.4, 123.0, 123.3, 125.0, 126.7, 129.9, 131.1, 131.2, 132.1, 135.0, 142.1, 145.9, 159.2; HRMS (MALDI) calcd for $C_{16}H_{14}N_2O_2$ requires (M^++H): 267.1134, Found: 267.1120.

Compound **1l**: Yield: 80%. A yellow solid. Mp: 210–212 °C. IR (neat) ν 3097, 3065, 3023, 2935, 1697, 1608, 1467, 1376, 1297, 1108, 987 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.17 (s, 3H), 6.86 (d, J=8.0 Hz, 1H), 7.16 (td, J=7.6, 0.8 Hz, 1H), 7.39–7.48 (m, 4H), 7.44 (dd, J=7.2, 1.2 Hz, 1H), 8.47 (dd, J=8.4, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 25.9, 108.1, 117.1, 123.1, 125.1, 125.3, 127.4, 127.9, 130.3, 131.0, 132.6, 135.6, 142.4, 144.0, 159.1; HRMS (MALDI) calcd for $C_{15}H_{11}ClN_2O_2$ requires (M^++H): 287.0587, Found: 287.0589.

Compound **1m**: Yield: 63%. A red solid. Mp: 162–164 °C. IR (neat) ν 3056, 2928, 1702, 1607, 1469, 1375, 1327, 1096, 1023, 985, 873 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 2.43 (s, 3H), 3.18 (s, 3H), 6.84 (d, J=8.0 Hz, 1H), 7.14 (t, J=7.6 Hz, 1H), 7.25–7.27 (m, 2H), 7.33–7.44 (m, 3H), 8.46 (d, J=7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.3, 26.0, 107.9, 118.0, 120.7, 123.0, 124.0, 125.0, 128.7, 131.3, 132.1, 134.5, 139.3, 142.0, 146.4, 159.5; HRMS (MALDI) calcd for $C_{16}H_{14}N_2O_2$ requires (M^++H): 267.1134, Found: 267.1138.

Compound **1n**: Yield: 99%. A yellow solid. Mp: 209–211 °C. IR (neat) ν 3072, 2935, 1704, 1605, 1541, 1468, 1327, 1243, 1103, 987, 898 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.19 (s, 3H), 6.85 (d, J=7.6 Hz, 1H), 7.15 (td, J=7.6, 0.8 Hz, 1H), 7.37 (dd, J=7.6, 2.0 Hz, 1H), 7.42–7.53 (m, 4H), 8.44 (dd, J=7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.0, 108.1, 117.7, 122.0, 123.2, 124.2, 125.2, 130.0, 130.7, 132.5, 134.6, 134.8, 142.2, 146.8, 159.3; HRMS (MALDI) calcd for $C_{15}H_{11}ClN_2O_2$ requires (M^++H): 287.0587, Found: 287.0593.

Compound **1o**: Yield: 58%. A yellow solid. Mp: 212–214 °C. IR (neat) ν 3093, 3055, 2927, 1698, 1677, 1606, 1466, 1243, 1095, 1067, 1013, 982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 3.19 (s, 3H), 6.85 (d, J=7.8 Hz, 1H), 7.15 (t, J=7.5 Hz, 1H), 7.37 (d, J=8.4 Hz, 2H), 7.44 (t, J=7.5 Hz, 1H), 7.64 (d, J=8.4 Hz, 2H), 8.44 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 26.0, 108.1, 117.8, 123.2, 124.8, 125.1, 125.4, 132.2, 132.5, 134.7, 142.1, 145.0, 159.4; HRMS (MALDI) calcd for $C_{15}H_{11}BrN_2O_2$ requires (M^++H): 331.0082, Found: 331.0079.

Compound **4a**: Yield: 28 mg, 90%. A white solid. Mp: 187–189 °C. IR (neat) ν 3365, 3049, 2957, 1747, 1708, 1608, 1487, 1467, 1375, 1203, 1006, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.28 (s, 3H), 3.30 (s, 3H), 4.11 (br s, 1H), 4.79 (s, 1H), 6.74 (d, J=8.0 Hz, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.92 (t, J=7.6 Hz, 1H), 7.05 (d, J=7.2 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 7.30 (t, J=7.6 Hz, 1H), 7.39 (d, J=7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 26.6, 51.6, 56.2, 70.9, 108.1, 110.3, 120.1, 122.9, 123.0, 123.4, 126.3, 128.7, 130.0, 142.9, 149.5, 169.1, 176.9; HRMS (MALDI) calcd for $C_{18}H_{16}N_2O_3$ requires (M^++H): 309.1239, Found: 309.1243.

Compound **4b**: Yield: 23 mg, 70%. A white solid. Mp: 163–165 °C. IR (neat) ν 3365, 3051, 2953, 1747, 1710, 1604, 1467, 1364, 1198, 1170, 1106, 809 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.19 (s, 3H), 3.27 (s, 3H), 3.29 (s, 3H), 4.12 (s, 1H), 4.77 (s, 1H), 6.74 (d, J=7.8 Hz, 2H), 6.86 (s, 1H), 6.92 (t, J=7.8 Hz, 1H), 7.09 (d, J=7.5 Hz, 1H), 7.18 (t, J=7.8 Hz, 1H), 7.39 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 20.8, 26.7, 51.6, 56.3, 71.0, 107.9, 110.4, 120.2, 123.6, 123.7, 126.3, 128.75, 128.79, 130.3, 132.7, 140.6, 149.5, 169.2, 176.9; HRMS (MALDI) calcd for $C_{19}H_{18}N_2O_3$ requires (M^++H): 323.1396, Found: 323.1385.

Compound **4c**: Yield: 25 mg, 73%. A white solid. Mp: 180–182 °C. IR (neat) ν 3358, 3056, 2953, 1747, 1708, 1609, 1487, 1467, 1351, 1204, 1103, 1009, 932 cm^{-1}; ^1H NMR (400 MHz, actone-d_6) δ 3.31 (s, 3H), 3.39 (s, 3H), 4.68 (s, 1H), 5.11 (s, 1H), 6.83 (d, J=7.6 Hz, 1H), 6.95 (t, J=7.6 Hz, 1H), 6.98 (d, J=2.4 Hz, 1H), 7.04 (d, J=8.4 Hz, 1H), 7.27 (t, J=8.0 Hz, 1H), 7.39 (d, J=7.6 Hz, 1H), 7.45 (dd, J=8.4, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 26.8, 51.9, 56.4, 70.8, 109.2, 110.5, 120.5, 123.1, 123.4, 126.3, 128.2, 129.0, 130.0, 130.4, 141.6, 149.0, 168.9, 176.5; HRMS (MALDI) calcd for $C_{18}H_{15}ClN_2O_3$ requires (M^++H): 343.0849, Found: 343.0854.

Compound **4d**: Yield: 23 mg, 72%. A white solid. Mp: 244–246 °C. IR (neat) ν 3362, 2903, 1708, 1608, 1484, 1467, 1374, 1318, 1285, 1263, 1093, 1016, 873 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.35 (s, 3H), 3.27 (s, 3H), 3.31 (s, 3H), 4.08 (s, 1H), 4.75 (s, 1H), 6.67 (s, 1H), 6.70–6.74 (m, 2H), 6.88–6.94 (m, 2H), 7.17 (t, J=7.8 Hz, 1H), 7.38 (d, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 21.9, 26.6, 51.7, 56.2, 70.9, 109.1, 110.4, 120.2, 122.9, 123.4, 123.6, 125.8, 126.3, 128.7, 140.5, 143.1, 149.5, 169.3, 177.3; HRMS (MALDI) calcd for $C_{19}H_{18}N_2O_3$ requires (M^++H): 323.1396, Found: 323.1385.

Compound **4e**: Yield: 21 mg, 62%. A white solid. Mp: 190–192 °C. IR (neat) ν 3288, 3048, 2951, 1741, 1723, 1608, 1595, 1492, 1376, 1200, 1068, 1001 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.27 (s, 3H),

Please cite this article in press as: Yang, H.-B.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.03.062

3.35 (s, 3H), 4.11 (s, 1H), 4.76 (s, 1H), 6.73 (d, *J*=7.6 Hz, 1H), 6.85 (s, 1H), 6.89 (t, *J*=9.6 Hz, 2H), 6.96 (t, *J*=8.8 Hz, 1H), 7.17 (t, *J*=8.0 Hz, 1H), 7.38 (d, *J*=7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.8, 51.9, 56.3, 70.5, 109.0, 110.4, 120.4, 122.7, 123.2, 124.1, 126.4, 127.1, 128.9, 135.9, 144.3, 149.2, 169.0, 176.9; HRMS (MALDI) calcd for $C_{18}H_{15}ClN_2O_3$ requires (M^++H): 343.0849, Found: 343.0844.

Compound **4f**: Yield: 25 mg, 64%. A white solid. Mp: 195–198 °C. IR (neat) ν 3292, 3048, 1740, 1722, 1605, 1592, 1374, 1200, 1174, 1093, 999 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 3.26 (s, 3H), 3.35 (s, 3H), 4.14 (s, 1H), 4.75 (s, 1H), 6.72 (d, *J*=7.8 Hz, 1H), 6.89–6.94 (m, 2H), 7.00–7.05 (m, 2H), 7.17 (t, *J*=7.5 Hz, 1H), 7.38 (d, *J*=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 26.8, 51.9, 56.2, 70.6, 110.4, 111.8, 120.4, 123.2, 123.7, 124.3, 125.7, 126.3, 127.7, 128.9, 144.3, 149.2, 169.0, 176.7; HRMS (MALDI) calcd for $C_{18}H_{15}BrN_2O_3$ requires (M^++H): 387.0344, Found: 387.0338.

Compound **4g**: Yield: 33 mg, 87%. A white solid. Mp: 170–172 °C. IR (neat) ν 3375, 3054, 2957, 1745, 1717, 1605, 1459, 1320, 1205, 1106, 794, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.35 (s, 3H), 3.66 (s, 3H), 4.15 (br s, 1H), 4.78 (s, 1H), 6.72 (d, *J*=7.6 Hz, 1H), 6.81 (t, *J*=7.6 Hz, 1H), 6.89–6.95 (m, 2H), 7.17 (t, *J*=7.6 Hz, 1H), 7.21 (dd, *J*=8.0, 1.2 Hz, 1H), 7.39 (d, *J*=7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 30.1, 51.8, 56.7, 70.4, 110.4, 115.6, 120.4, 121.4, 123.2, 123.8, 126.4, 128.9, 131.7, 132.3, 138.8, 149.2, 168.9, 177.3; HRMS (MALDI) calcd for $C_{18}H_{15}ClN_2O_3$ requires (M^++H): 343.0849, Found: 343.0844.

Compound **4h**: Yield: 74 mg, 76%. A white solid. Mp: 197–200 °C. IR (neat) ν 3370, 3058, 2957, 1745, 1715, 1628, 1608, 1465, 1371, 1241, 1208, 1013, 901 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.34 (s, 3H), 3.48 (d, *J*=2.4 Hz, 3H), 4.24 (br s, 1H), 4.74 (s, 1H), 6.71 (d, *J*=8.0 Hz, 1H), 6.80–6.85 (m, 2H), 6.89 (t, *J*=7.2 Hz, 1H), 6.99–7.04 (m, 1H), 7.15 (t, *J*=7.6 Hz, 1H), 7.38 (d, *J*=7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 29.1 (d, *J*=5.6 Hz), 51.7, 56.5, 70.8 (d, *J*=1.9 Hz), 110.3, 117.9 (d, *J*=18.9 Hz), 118.8 (d, *J*=3.0 Hz), 120.2, 123.1, 123.6 (d, *J*=6.3 Hz), 126.3, 128.8, 129.3 (d, *J*=8.5 Hz), 131.7 (d, *J*=2.6 Hz), 147.4 (d, *J*=243.2 Hz), 149.2, 168.9, 176.6; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$) δ −135.86–135.80 (m, 1F); HRMS (MALDI) calcd for $C_{18}H_{15}FN_2O_3$ requires (M^++H): 327.1145, Found: 327.1144.

Compound **4i**: Yield: 30 mg, 78%. A white solid. Mp: 133–136 °C. IR (neat) ν 3335, 3055, 3032, 2949, 1717, 1608, 1484, 1465, 1434, 1170, 1011, 918 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.11 (s, 3H), 4.19 (br s, 1H), 4.70 (d, *J*=16.0 Hz, 1H), 4.87 (s, 1H), 5.24 (d, *J*=16.0 Hz, 1H), 6.74 (d, *J*=7.6 Hz, 2H), 6.85 (t, *J*=7.6 Hz, 1H), 6.92 (t, *J*=7.6 Hz, 1H), 7.03 (d, *J*=7.6 Hz, 1H), 7.14–7.20 (m, 2H), 7.27–7.31 (m, 1H), 7.34 (t, *J*=7.6 Hz, 2H), 7.40–7.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 44.3, 51.4, 56.1, 70.9, 109.2, 110.4, 120.3, 123.0, 123.1, 123.5, 126.5, 127.6, 127.8, 128.7, 128.8, 128.9, 130.0, 135.5, 142.0, 149.4, 169.1, 177.1; HRMS (MALDI) calcd for $C_{24}H_{20}N_2O_3$ requires (M^++H): 385.1552, Found: 385.1553.

Compound **4j**: Yield: 18 mg, 62%. A white solid. Mp: 205–208 °C. IR (neat) ν 3347, 3156, 3096, 2951, 1749, 1706, 1602, 1465, 1171, 1112, 872 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.31 (s, 3H), 4.24 (br s, 1H), 4.79 (s, 1H), 6.73 (d, *J*=8.0 Hz, 1H), 6.85–6.94 (m, 3H), 7.02 (d, *J*=7.2 Hz, 1H), 7.16–7.22 (m, 2H), 7.40 (d, *J*=7.2 Hz, 1H), 9.45 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 51.7, 56.1, 71.5, 110.46, 110.49, 120.3, 122.9, 123.38, 123.41, 126.4, 128.8, 129.1, 130.1, 140.3, 149.4, 169.2, 179.9; HRMS (MALDI) calcd for $C_{17}H_{14}N_2O_3$ requires (M^++Na): 317.0902, Found: 317.0901.

Compound **4k**: Yield: 23 mg, 71%. A white solid. Mp: 169–172 °C. IR (neat) ν 3298, 3054, 2951, 2853, 1714, 1610, 1598, 1466, 1375, 1209, 1089, 1030, 1013, 924 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.14 (s, 3H), 3.28 (s, 3H), 3.30 (s, 3H), 3.97 (br s, 1H), 4.80 (s, 1H), 6.83–6.87 (m, 2H), 6.91 (td, *J*=7.6, 0.8 Hz, 1H), 7.01 (d, *J*=7.6 Hz, 1H), 7.04 (dd, *J*=7.6, 0.8 Hz, 1H), 7.24 (d, *J*=7.6 Hz, 1H), 7.30 (td, *J*=7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 16.6, 26.7, 51.6, 56.6, 70.8, 108.1, 119.7, 120.4, 122.9, 123.0, 123.8, 129.2, 129.7, 130.1, 143.0, 148.1, 169.2, 177.1; HRMS (MALDI) calcd for $C_{19}H_{18}N_2O_3$ requires (M^++H): 323.1396, Found: 323.1392.

Compound **4l**: Yield: 23 mg, 67%. A white solid. Mp: 222–225 °C. IR (neat) ν 3281, 2953, 2864, 1742, 1715, 1607, 1465, 1207, 1092, 1020, 912 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.28 (s, 3H), 3.30 (s, 3H), 4.38 (br s, 1H), 4.84 (s, 1H), 6.82–6.87 (m, 2H), 6.85 (dd, *J*=7.6, 0.8 Hz, 1H), 6.94 (td, *J*=7.2, 0.8 Hz, 1H), 7.17 (dt, *J*=7.6, 1.0 Hz, 1H), 7.28 (d, *J*=7.6 Hz, 1H), 7.32 (td, *J*=7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.7, 51.8, 56.8, 70.7, 108.3, 115.4, 120.9, 123.07, 123.13, 124.6, 124.8, 128.2, 128.6, 130.4, 142.9, 146.6, 168.6, 176.3; HRMS (MALDI) calcd for $C_{18}H_{15}ClN_2O_3$ requires (M^++H): 343.0849, Found: 343.0836.

Compound **4m**: Yield: 20 mg, 63%. A white solid. Mp: 150–152 °C. IR (neat) ν 3329, 2946, 2922, 1719, 1707, 1609, 1470, 1428, 1350, 1248, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 2.31 (s, 3H), 3.27 (s, 3H), 3.28 (s, 3H), 4.07 (br s, 1H), 4.73 (s, 1H), 6.56 (s, 1H), 6.73 (d, *J*=7.8 Hz, 1H), 6.84 (d, *J*=7.8 Hz, 1H), 6.91 (t, *J*=7.8 Hz, 1H), 7.06 (d, *J*=7.5 Hz, 1H), 7.24–7.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 21.5, 26.6, 51.6, 56.1, 71.0, 108.1, 111.2, 120.7, 121.1, 122.9, 123.1, 125.9, 128.9, 130.0, 138.9, 143.0, 149.7, 169.4, 177.0; HRMS (MALDI) calcd for $C_{19}H_{18}N_2O_3$ requires (M^++H): 323.1396, Found: 323.1388.

Compound **4n**: Yield: 20 mg, 57%. A white solid. Mp: 248–250 °C. IR (neat) ν 3400, 2948, 1748, 1478, 1471, 1436, 1346, 1179, 1021, 927, 914 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.27 (s, 3H), 3.28 (s, 3H), 4.24 (br s, 1H), 4.68 (s, 1H), 6.70 (s, 1H), 6.84–6.87 (m, 2H), 6.92 (t, *J*=7.6 Hz, 1H), 7.04 (d, *J*=7.2 Hz, 1H), 7.26–7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.7, 51.7, 55.6, 71.2, 108.3, 110.4, 120.0, 122.0, 123.06, 123.08, 127.1, 128.2, 130.3, 134.5, 142.9, 150.7, 168.8, 176.4; HRMS (MALDI) calcd for $C_{18}H_{15}ClN_2O_3$ requires (M^++H): 343.0849, Found: 343.0838.

Compound **4o**: Yield: 36 mg, 93%. A white solid. Mp: 205–208 °C. IR (neat) ν 3324, 2952, 2933, 1724, 1708, 1610, 1470, 1246, 1099, 1016, 873 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.28 (s, 3H), 3.29 (s, 3H), 4.16 (br s, 1H), 4.74 (s, 1H), 6.60 (d, *J*=8.4 Hz, 1H), 6.85 (d, *J*=7.6 Hz, 1H), 6.93 (td, *J*=8.0, 0.8 Hz, 1H), 7.05 (d, *J*=7.6 Hz, 1H), 7.25–7.28 (m, 1H), 7.31 (td, *J*=7.6, 1.6 Hz, 1H), 7.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.7, 51.8, 55.9, 71.2, 108.3, 111.5, 112.0, 123.0, 123.1, 125.7, 128.3, 129.4, 130.3, 131.6, 142.9, 148.6, 168.5, 176.4; HRMS (MALDI) calcd for $C_{18}H_{15}BrN_2O_3$ requires (M^++H): 387.0344, Found: 387.0345.

Compound **4p**: Yield: 25 mg, 78%. A white solid. Mp: 145–147 °C. IR (neat) ν 3395, 3050, 1744, 1714, 1608, 1462, 1376, 1322, 1187, 1092, 1033, 793 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.76 (t, *J*=7.2 Hz, 3H), 3.29 (s, 3H), 3.75 (q, *J*=7.2 Hz, 2H), 4.15 (br s, 1H), 4.76 (s, 1H), 6.72 (d, *J*=7.8 Hz, 1H), 6.83–6.93 (m, 3H), 7.03 (d, *J*=7.5 Hz, 1H), 7.16 (t, *J*=7.8 Hz, 1H), 7.30 (t, *J*=7.8 Hz, 1H), 7.43 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 13.4, 26.6, 55.8, 60.5, 70.9, 108.1, 110.3, 120.1, 122.9, 123.5, 126.4, 128.6, 128.8, 130.0, 143.0, 149.4, 168.5, 176.9; HRMS (MALDI) calcd for $C_{19}H_{18}N_2O_3$ requires (M^++H): 323.1396, Found: 323.1385.

Compound **4q**: Yield: 20 mg, 69%. A white solid. Mp: 154–156 °C. IR (neat) ν 3344, 3052, 2923, 1708, 1608, 1484, 1467, 1349, 1090, 780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.81 (s, 3H), 3.32 (s, 3H), 4.12 (br s, 1H), 4.78 (s, 1H), 6.75 (d, *J*=8.1 Hz, 1H), 6.87–6.98 (m, 3H), 7.06 (d, *J*=7.2 Hz, 1H), 7.18 (t, *J*=7.8 Hz, 1H), 7.25 (d, *J*=9.0 Hz, 1H), 7.33 (t, *J*=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 26.7, 29.8, 63.6, 70.6, 108.6, 110.5, 120.3, 123.5, 124.2, 124.3, 126.6, 128.0, 128.8, 130.4, 142.6, 149.6, 177.4, 203.1; HRMS (MALDI) calcd for $C_{18}H_{16}N_2O_2$ requires (M^++H): 293.1290, Found: 293.1281.

Compound **6**: A yellow solid. Mp: 88–95 °C. IR (neat) ν 3339, 2952, 1736, 1713, 1607, 1484, 1469, 1258, 1098, 1037, 983, 908 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.21 (s, 3H) (minor isomer), 3.26 (s, 3H), 3.50 (s, 3H) (minor isomer), 3.59 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H) (minor isomer), 4.03 (br s, 1H), 6.82–7.07 (m, 5H), 7.23–7.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.4, 26.5, 52.4, 52.97,

Please cite this article in press as: Yang, H.-B.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.03.062

53.01, 53.1, 70.7, 72.49, 72.54, 74.4, 108.4, 111.5, 111.8, 120.8, 120.9, 122.5, 123.0, 123.4, 124.0, 124.1, 124.5, 126.3, 126.4, 126.7, 128.9, 130.0, 130.2, 130.3, 130.7, 143.2, 143.9, 150.0, 150.4, 160.2, 160.7, 166.5, 168.1, 174.4, 174.5, 186.1, 186.4; HRMS (MALDI) calcd for $C_{21}H_{18}N_2O_6$ requires (M^++H): 395.1243, Found: 395.1239.

Compound **8**: This is a known compound.[1] ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.98 (s, 3H), 3.99 (s, 3H), 7.27 (t, J=8.4 Hz, 1H), 7.37 (t, J=8.4 Hz, 1H), 7.45 (d, J=8.4 Hz, 1H), 8.06 (d, J=8.4 Hz, 1H), 9.55 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 51.9, 52.7, 111.9, 122.6, 122.7, 125.9, 126.8, 128.0, 134.8, 161.4, 164.6; HRMS (MALDI) calcd for $C_{12}H_{11}NO_4$ requires (M^++H): 234.0766, Found: 234.0756.

Acknowledgements

We thank the Shanghai Municipal Committee of Science and Technology (11JC1602600), National Basic Research Program of China (973)-2009CB825300, and the National Natural Science Foundation of China for financial support (21072206, 21102166, 20672096, 20872162, 20672127, 21121062, and 20732008).

Supplementary data

^{1}H NMR and ^{13}C NMR spectroscopic and analytic data of isatin ketonitrones **1a**–**o**, products **4a**–**q**, and intermediate **6** as well as the X-ray data of compound **4a** are included in the Supplementary data. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.03.062.

References and notes

1. For a review, see: Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.
2. For reviews, see: (a) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003; (b) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36; (c) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127; (d) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.
3. (a) Holzapfel, C. W.; Crous, R. *Heterocycles* **1988**, *68*, 1337; (b) Kiguchi, T.; Shirakawa, M.; Ninomiya, I.; Naito, T. *Chem. Pharm. Bull.* **1996**, *66*, 1282; (c) Hamer, J.; Macaluso, A. *Chem. Rev.* **1966**, *66*, 673; (d) Delpierre, G. R.; Lamchen, M. *Quart. Rev.* **1965**, *19*, 329.
4. (a) Breuer, E. In *The Chemistry of Functional Group, Supplement F, Part 1*; Patai, S., Ed.; John Wiley: New York, NY, 1982; p 659; (b) Black, D. S.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205; (c) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley: New York, NY, 1986; Vol. 2, p 83; (d) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH,: New York, NY, 1988; (e) Tamura, O.; Mita, N.; Gotanda, K.; Yamada, K.; Nakano, T.; Katagiri, R.; Sakamoto, M. *Heterocycles* **1997**, *66*, 95; (f) Chiacchio, U.; Casuscelli, F.; Corsaro, A.; Rescifina, A.; Romeo, G.; Uccella, N. *Tetrahedron* **1996**, *50*, 6671; (g) Brandi, A.; Cardona, F.; Cicchi, S. *Chem.—Eur. J.* **2009**, *15*, 7808; (h) Padwa, A.; Bur, S. *Tetrahedron* **2007**, *63*, 5341; (i) Bur, S.; Padwa, A. *Adv. Heterocycl. Chem.* **2007**, *94*, 1; (j) Merino, P.; Mannucci, V.; Tejero, T. *Eur. J. Org. Chem.* **2008**, 3943; (k) Merino, P.; Delso, I.; Tejero, T. *Eur. J. Org. Chem.* **2008**, 2929.
5. (a) Shuji, K.; Takashi, T. *Chem. Lett.* **1995**, 49; (b) Mehrdad, M.; Faraji, L.; Jadidi, K.; Eslami, P.; Sureni, H. *Monatsh. Chem.* **2011**, *142*, 917; (c) Pei, C.-K.; Jiang, Y.; Shi, M. *Eur. J. Org. Chem.* **2012**, 4206.
6. Aurich, H. G.; Weiss, W. *Tetrahedron* **1976**, *32*, 159.
7. (a) Guan, X.-Y.; Wei, Y.; Shi, M. *Chem.—Eur. J.* **2011**, *16*, 13617; (b) Zhang, X.-C.; Cao, X.-H.; Wei, Y.; Shi, M. *Chem. Commun.* **2011**, 1548; (c) Zhang, X.-C.; Cao, X.-H.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 1142; (d) Cao, S.-H.; Zhang, X.-C.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2011**, 2668; (e) Liu, Z.; Gu, P.; Shi, M. *Org. Lett.* **2011**, *13*, 2314; (f) Wang, D.; Jiang, J.-J.; Zhang, R.; Shi, M. *Tetrahedron: Asymmetry* **2011**, *22*, 1133; (g) Zhao, M.-X.; Zhang, Z.-W.; Chen, M.-X. *Eur. J. Org. Chem.* **2011**, 3001; (h) Deng, H.-P.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 3348; (i) Lian, Z.; Shi, M. *Eur. J. Org. Chem.* **2012**, 581; (j) Lian, Z.; Wei, Y.; Shi, M. *Tetrahedron* **2012**, *68*, 2401; (k) Yang, H.-B.; Guan, X.-Y.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2012**, 2792.
8. (a) Takeuchi, Y. *Adv. Heterocycl. Chem.* **1977**, *21*, 207; (b) Freeman, J. P. *Chem. Rev.* **1983**, *83*, 261.
9. Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K.; Sklarz, B. *J. Am. Chem. Soc.* **1968**, *90*, 5325.
10. Damavandy, J. A.; Jones, R. A. Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 712.
11. Huisgen, R.; Seidl, H.; Bruning, I. *Chem. Ber.* **1969**, *102*, 1102.
12. Tomioka, Y.; Nagahiro, C.; Nomura, Y.; Maruoka, H. *J. Heterocycl. Chem.* **2003**, *40*, 121.
13. (a) Unhureanu, I.; Klotz, P.; Mann, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4615; (b) Wender, P. A.; Strand, D. *J. Am. Chem. Soc.* **2009**, *131*, 7528; (c) Yadav, V. K.; Sriramurthy, V. *J. Am. Chem. Soc.* **2005**, *127*, 16366; (d) Munegumi, T.; Azumaya, I.; Kato, T.; Masu, H.; Saito, S. *Org. Lett.* **2006**, *8*, 379.
14. Tsuge, O.; Ueno, K.; Kanemasa, S. *Chem. Lett.* **1986**, 797.
15. Li, L.; Wu, X.-X.; Zhang, J.-L. *Chem. Commun.* **2011**, 5049.
16. (a) Takayama, H.; Hurihara, M.; Subhadhisakul, S.; Kitajima, M.; Aimi, N.; Sakai, S. I. *Heterocycles* **1996**, *42*, 87; (b) Takayama, H.; Ishikawa, H.; Kurihara, M.; Kitajima, M.; Aimi, N.; Ponglux, D.; Koyama, F.; Matsumoto, K.; Moriyama, T.; Yamamoto, L. T.; Watanabe, K. *J. Med. Chem.* **2002**, *45*, 1949.
17. Kyei, A. S.; Tchabanenko, K.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron Lett.* **2004**, *45*, 8931.
18. The crystal data of **4a** have been deposited in CCDC with number 865933. Empirical Formula: $C_{18}H_{16}N_2O_3$; Formula Weight: 308.33; Crystal Color, Habit: colorless; Crystal Dimensions: 0.360×0.258×0.160 mm; Crystal System: monoclinic; Lattice parameters: a=12.0894(12) Å, b=8.4383(8) Å, c=15.2650(14) Å, α=90°, β=92.784(2)°, γ=90°, V=1555.4(3) Å^3; Space group: $P2(1)/n$; Z=4; D_{calcd}=1.317 g/cm^3; F_{000}=648; Final R indices [$I>2\sigma(I)$] $R1$=0.0491, $wR2$=0.1183
19. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision A.1*; Gaussian: Wallingford CT, 2009.
20. For computational studies on the silica gel participated reactions, see: Shao, L.-X.; Li, Y.-X.; Shi, M. *Chem.—Eur. J.* **2007**, *13*, 862.
21. Jiao, N.; Shi, Z.-S.; Zhang, C.; Li, S.; Pan, D.-L.; Ding, S.-T.; Cui, Y.-X. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572.