DOI: 10.1002/ejoc.200801259

Synthesis of Polysubstituted 3-Iodopyrans by Electrophilic Cyclization

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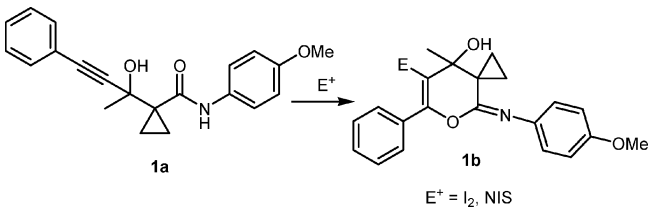
Keywords: Iodine / Cyclization / Oxygen heterocycles / Alkynes

A variety of polysubstituted 3-iodopyrans were readily prepared in good to excellent yield under mild reaction conditions by the reaction of alkynyl carboxamides with ICl, I_2, and NIS. The products obtained from this process are versatile materials that can be used to construct other complex functionalized pyran structures of importance. The occurrence of the pyranyl group in both natural products and pharmaceuticals confers important value to this study.

Introduction

Substituted pyrans are ubiquitous building blocks in natural products having important biological activities.[1] One of strategies used frequently for the synthesis of these heterocycles conjoins carbon nucleophiles with monosaccharide-based starting materials.[2] Though highly valuable, this approach for pyran assembly is generally restricted to certain nucleophilic structural types.[1a,2f] Recently, the electrophilic cyclization of aryl-substituted alkynes has provided an extremely useful route for the synthesis of a wide variety of heterocyclic and carbocyclic compounds.[3] The reported works have shown the electrophilic cyclization of functionally substituted alkynes to be an efficient approach of generating benzo[*b*]thiophenes,[4] benzofurans,[5] bicyclic β-lactams,[6] cyclic carbonates,[7] 2,3-dihydropyrroles and pyrroles,[8] furans,[9] furopyridines,[10] indoles,[11] isochromenes,[12] isocoumarins and α-pyrones,[13] isoquinolines and naphthyridines,[14] isoxazoles,[15] oxazoles,[16] naphthalenes,[17] polycyclic romatics,[18] quinolines,[3b] indoles,[19] and chromones[20] under mild reaction. As a result of the importance of heterocycles as pharmacologically active molecules, the development of new synthetic approaches using mild reaction conditions remains an active research area. Our work in this field has led to the development of methods for the synthesis of polysubstituted furans and other heterocyclic compounds via an ammonium ylide and Pd-catalyzed routes.[21] Very recently, we completed the electrophilic cyclization of various propargylic oxirane compounds and I_2 and explored an efficient route to highly substituted iodofurans under mild reaction conditions.[22] This successful electrophilic cyclization strategy encouraged us to develop a simple methodology for the synthesis of other oxygen- or nitrogen-containing heterocyclic compounds. On the basis of a similar approach, we devised, therefore, a new process that makes the facile electrophilic cyclization of alkynyl carboxamides with ICl, I_2, and NIS possible (Scheme 1). Because the obtained pyrans contain several active functional groups, such as a three-membered ring, hydroxy and iodine groups, etc., this method is thus particularly valuable for the construction of complex pyran-type compounds.



Scheme 1.

Results and Discussion

Herein, we wish to report our results on the electrophilic cyclization of alkynyl carboxamides to polysubstituted pyrans. This chemistry generally produces the desired pyrans in good to excellent yield under very mild reaction conditions. The iodide products can be further extended to complex polysubstituted pyran compounds by a Pd-catalyzed coupling reaction.

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Our investigations began with the reaction of compound **1a** in CH_3CN under typical iodocyclization conditions (I_2 with an excess amount of $NaHCO_3$). For all cases in which CH_3CN, MeOH, and $CHCl_3$ were used as the solvent, **1a** remained unchanged even during a prolonged time (24 h) at room temperature (Table 1, Entries 1–3). By changing the solvent to THF, the corresponding pyran was isolated in 41% yield under the above conditions (Table 1, Entry 4). The structure of the product was discerned by spectroscopic analysis and further confirmed by X-ray diffraction to be 3-iodopyran **1a** (Figure 1).[23] Apparently, the product was the unexpected conjugated iminolactone rather than the usual lactam, which was similar to the reported result by Hashmi et al.[24] In the presence of K_2CO_3 and Cs_2CO_3, only 24 and 35% yield of the product was obtained, respectively (Table 1, Entries 5 and 6). In an attempt to utilize the stronger *t*BuOK base, the reaction failed (Table 1, Entry 7). Although $NaHCO_3$ is indispensable in the THF reaction system, a higher yield was still obtained when CH_2Cl_2 was used as the solvent (Table 1, Entry 8). This indicated that the solvent played an important role in this process. To our delight, in the case of a base-free reaction, the most satisfactory result was observed in CH_2Cl_2 (Table 1, Entry 9). To explore the scope of our electrophilic cyclization strategy, the reactions of ylamide **1a** with other common electrophiles (NIS ICl, NBS) in CH_2Cl_2 at room temperature were also studied (Table 1, Entries 10–13). However, the results are distinct for the above electrophiles. Yields of 60 and 65% of the corresponding iodine-containing pyran were obtained when NIS was used as the electrophile in both cases (with or without excess $NaHCO_3$), respectively (Table 1, Entries 10 and 11). Disappointingly, none of the desired iodine- or bromine-containing product was observed when ICl or NBS was used (Table 1, Entries 12 and 13). Thus, we chose the following optimized reaction conditions for all subsequent electrophilic cyclizations: a mixture of alkynyl carboxamide (0.25 mmol) and NIS (2 equiv.) in CH_2Cl_2 (3 mL) stirred at room temperature for an appropriate amount of time.

Table 1. Iodocyclization of **1a** under various conditions.

Entry	Solvents	E	Base	Yield [%][a]
1	CH_3CN	I_2	$NaHCO_3$	NR
2	MeOH	I_2	$NaHCO_3$	NR
3	$CHCl_3$	I_2	$NaHCO_3$	NR
4	THF	I_2	$NaHCO_3$	41
5	THF	I_2	K_2CO_3	24
6	THF	I_2	Cs_2CO_3	35
7	THF	I_2	*t*BuOK	NR
8	CH_2Cl_2	I_2	$NaHCO_3$	45
9	CH_2Cl_2	I_2	–	58
10	CH_2Cl_2	NIS	–	65
11	CH_2Cl_2	NIS	$NaHCO_3$	60
12	CH_2Cl_2	NBS	$NaHCO_3$	NR
13	CH_2Cl_2	ICl	–	NR

[a] Isolated yield.

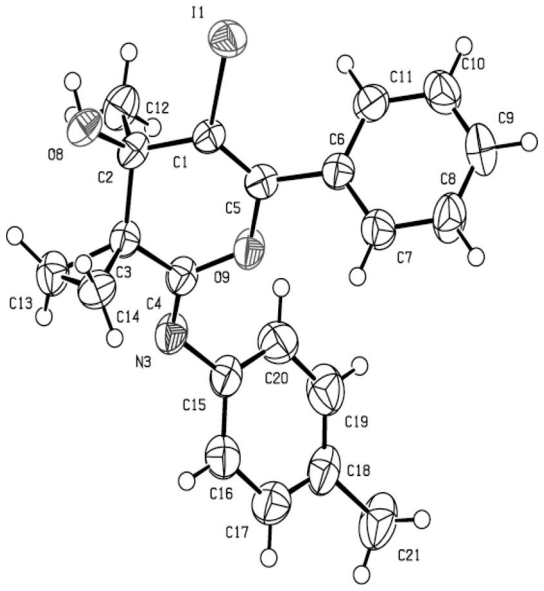
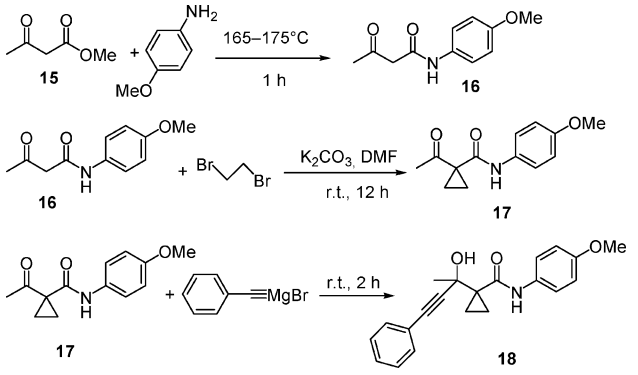


Figure 1. 3-Iodopyran **1a**.

To test the generality of this chemistry, alkynyl carboxamides bearing different substituents on the nitrogen atom and the carbon–carbon triple bond were prepared in three steps as depicted in Scheme 2: (1) starting substituted 3-oxobutanamides **15** were synthesized by the reaction of ethyl acetoacetate with different anilines;[25] (2) a three-membered ring was successfully introduced into the 3-oxobutanamides by using 1,2-dibromoethane;[26] (3) the phenylacetylene was added dropwise into a solution of the Grignard reagent derived from bromoethane, followed by the addition of 1-acetylcyclopropanecarboxamide **17** to obtain finally the expected adducts.[25] The resulting pent-4-ynamides were then allowed to react under the standard electrophilic cyclization conditions to afford the corresponding polysubstituted pyran products in good to excellent yield. The results are summarized in Table 2. The iodocyclization of both *N*-phenyl- and *N*-(4-methoxyphenyl)-substituted pent-4-ynamides (**2a**, **3a**) by using NIS generated the corresponding 3-iodopyrans in 72 and 76% yield, respectively, with only a trace amount of side products (Table 2, Entries 2 and 3). Excellent results were obtained with *N*-(4-methylphenyl) substrate **4a** (Table 2, Entry 4). In general, introducing electron-withdrawing groups on the *N*-aromatic ring significantly increased the yields and decreased the reaction times (Table 2, Entries 5–8). It is worthy to note that the presence of a strong electron-withdrawing *p*-NO_2 group on the *N*-aromatic moiety markedly lowered the yield of the corresponding cyclization product (Table 2, Entry 5). The best result obtained was for *N*-(4-chlorophenyl) substrate **6a** (Table 2, Entry 6), which gave 95% yield of the product in only 5 h. The reaction also proceeded with a naphthyl substituent on the nitrogen atom. Thus, substrate **9a** was smoothly converted into the

corresponding 3-iodopyran **9b** in 79% yield (Table 2, Entry 9). The product was also obtained when the α-position of the carbonyl compound was substituted with an alkyl group. In contrast, substituents in the α-position of the carbonyl group have an important effect on the efficiency of the iodocyclization process. In comparison to the yield of 93% (Table 2, Entry 4), 5-butyl-3-iodopyran can be synthesized in a moderate 70% yield by the cyclization of corresponding adduct **1a** (Table 2, Entry 10).



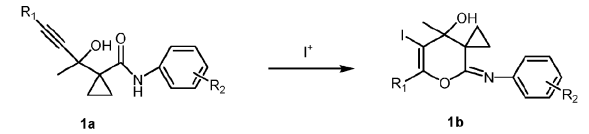
Scheme 2.

We continued to elucidate the scope of the reaction by examining the effect of various substituents on the alkyne terminus. In comparison to the reaction of substrate **1a**, the adducts containing electron-withdrawing groups (Cl, Br) in the *para* position of the aromatic ring on the distal end of the carbon–carbon triple bond were only isolated in ca. 80% yield (Table 2, Entries 11 and 12). Cyclization with NIS still proceeded when the terminus of the carbon–carbon triple bond was substituted with an alkyl group. Therefore, 2-propyl-3-iodopyran **13b** and 2-butyl-3-iodopyran **14b** can be synthesized in 83 and 75% yield, respectively (Table 2, Entries 13 and 14).

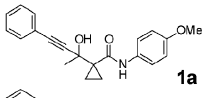
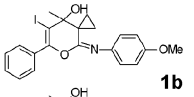
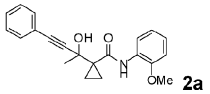
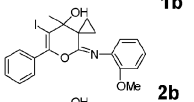
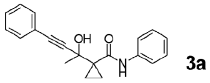
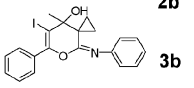
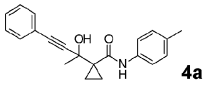
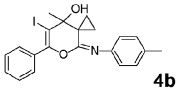
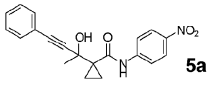
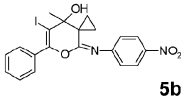
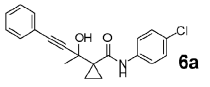
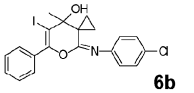
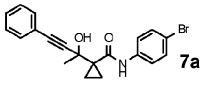
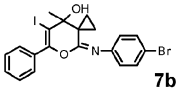
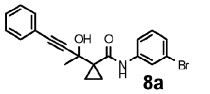
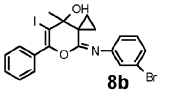
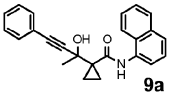
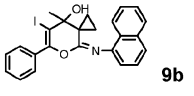
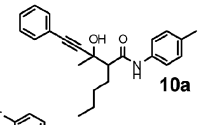
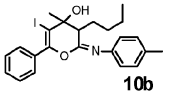
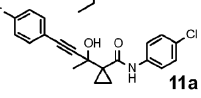
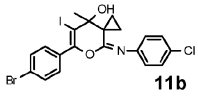
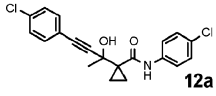
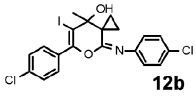
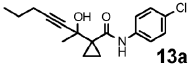
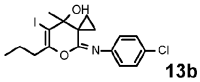
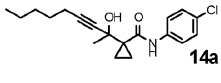
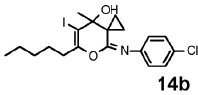
We believe that this approach to 3-iodopyrans should prove very useful for the synthesis of additional highly substituted pyrans (Scheme 3). As mentioned in the introduction, the presence of the iodide functional group on the pyran ring provides an opportunity for further functionalization. For example, product **7b** underwent Sonogashira coupling with phenyl acetylene to afford polysubstituted pyran **7c** in 76% yield (Scheme 3).

On the basis of the results obtained above, we propose the following mechanism for this process (Scheme 4): (1) coordination of the carbon–carbon triple bond to NIS or attack of the iodine cation on the triple bond to generate iodonium intermediate **A**; (2) intramolecular nucleophilic attack of the oxygen of the carboxamides group on the activated iodonium intermediate to produce pyran salt **B**; (3) deprotonation of **B** to afford product **C**, promoted by the iodide nucleophile present in the reaction mixture.

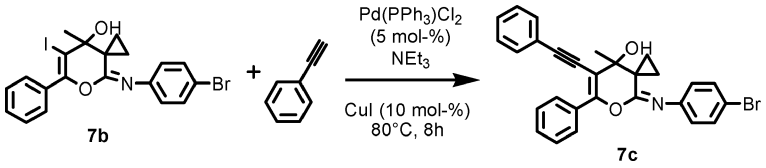
Table 2. Iodocyclization of cyclization of alkynyl carboxamides to polysubstituted pyrans.



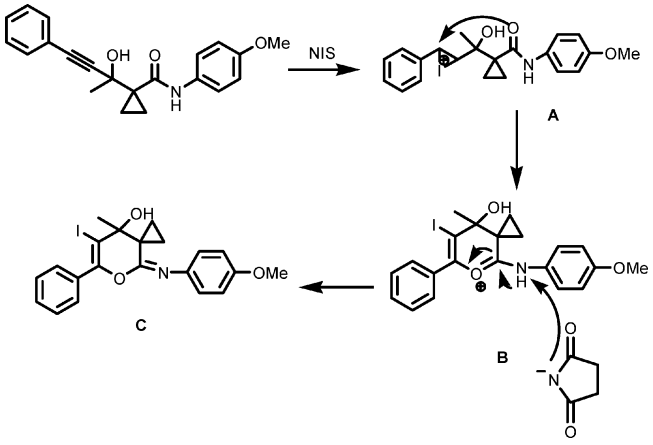
1a 1b

Entry	Adduct	Time [h]	Product	Yield [%][a]
1	 1a	12	 1b	6
2	 2a	12	 2b	72
3	 3a	15	 3b	61
4	 4a	8	 4b	93
5	 5a	12	 5b	80
6	 6a	5	 6b	95
7	 7a	5	 7b	92
8	 8a	5	 8b	89
9	 9a	8	 9b	79
10	 10a	24	 10b	70
11	 11a	12	 11b	81
12	 12a	12	 12b	80
13	 13a	13	 13b	83
14	 14a	15	 14b	75

[a] Isolated yields.



Scheme 3.



Scheme 4.

Conclusions

In summary, we have developed a new approach to the formation of polysubstituted 3-iodopyrans. The process showed considerable synthetic advantages in terms of mild reaction conditions, the simplicity of the reaction procedure, and good to excellent yields. Iodocyclization of alkynyl carboxamides followed by palladium-catalyzed coupling afforded products with an increased molecular complexity and has provided a powerful tool for the preparation of a wide range of functionalized and polysubstituted pyrans. Further work based on the three-membered ring to extend this method for the synthesis of complex active molecular structures is in progress.

Experimental Section

General: Commercially available reagents and solvents were used without further purification. Melting points were determined with a microscopic apparatus and are uncorrected. Column chromatography was carried out on silica gel. ^{1}H NMR spectra were recorded with a 400 MHz spectrometer in $CDCl_3$ by using TMS as the internal standard. ^{13}C NMR spectra were recorded with a 100 MHz spectrometer in $CDCl_3$. Mass spectra were recorded with a HP5998 MS spectrometer by using the EI method. IR spectra were recorded with an FTIR spectrometer and only the major peaks are reported. All new compounds were further characterized by element analysis.

Compound 1b: Colorless solid; m.p. 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93–1.00 (m, 1 H), 1.09–1.16 (m, 1 H), 1.36–1.43 (m, 1 H), 1.51 (s, 3 H), 1.55–1.84 (m, 1 H), 2.03 (s, 2 H), 7.28 (s, 1 H), 3.73 (s, 3 H), 6.80–6.85 (m, 3 H), 6.94–7.00 (m, 1 H), 7.22–7.27 (m, 3 H), 7.38–7.41 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.15, 13.47, 27.05, 27.50, 55.57, 69.73, 89.42, 111.07, 120.52, 122.03, 124.19, 127.66, 129.26, 129.30, 135.06, 135.45, 149.99, 156.29 ppm. IR (KBr): $\tilde{\nu}$ = 3284, 2923, 1537, 1097, 752, 511 cm^{-1}. $C_{21}H_{20}INO_3$ (461.1): calcd. C 54.68, H 4.37, N 3.04; found C 54.65, H 4.32, N 3.09.

Compound 2b: Colorless solid; m.p. 82–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–1.05 (m, 1 H), 1.06–1.12 (m, 1 H), 1.35–1.41 (m, 4 H), 1.73–1.80 (m, 1 H), 2.02 (s, 1 H), 3.69 (s, 3 H), 6.75–6.79 (m, 2 H), 6.98–7.02 (m, 2 H), 7.22–7.35 (m, 3 H), 7.48–7.51 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.25, 13.48, 27.16, 27.74, 55.29, 69.63, 89.64, 113.61, 124.29, 127.82, 129.35, 129.42, 135.09, 138.13, 147.63, 153.89, 156.18 ppm. IR (KBr): $\tilde{\nu}$ = 3426, 1680, 1503, 1241, 1069, 696 cm^{-1}. $C_{21}H_{20}INO_3$ (461.1): calcd. C 54.68, H 4.37, N 3.04; found C 54.64, H 4.34, N 3.02.

Compound 3b: Colorless solid; m.p. 85–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89–0.96 (m, 1 H), 1.08–1.15 (m, 1 H), 1.38–1.44 (m, 1 H), 1.47 (s, 3 H), 1.74–1.81 (m, 1 H), 1.93 (s, 1 H), 6.94–7.03 (m, 3 H), 7.19–7.25 (m, 2 H), 7.27–7.31 (m, 3 H), 7.44–7.48 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.32, 13.69, 27.22, 27.61, 69.64, 89.63, 122.30, 123.79, 127.77, 128.40, 129.34, 129.46, 134.90, 145.48, 147.58, 154.85 ppm. IR (KBr): $\tilde{\nu}$ = 3331, 1689, 1225, 755, 550 cm^{-1}. $C_{20}H_{18}INO_2$ (431.0): calcd. C 55.70, H 4.21, N 3.25; found C 55.73, H 4.24, N 3.28.

Compound 4b: Colorless solid; m.p. 135–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–1.06 (m, 1 H), 1.07–1.13 (m, 1 H), 1.36–1.42 (m, 1 H), 1.46 (s, 3 H), 1.73–1.80 (m, 1 H), 1.90 (s, 1 H), 2.26 (m, 3 H), 6.88–6.91 (d, J = 6.0 Hz, 2 H), 7.01–7.03 (d, J = 4.0 Hz, 2 H), 7.30–7.34 (m, 3 H), 7.46–7.50 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.28, 13.56, 20.86, 27.21, 27.70, 69.65, 89.62, 122.54, 127.79, 128.98, 129.39, 133.32, 135.06, 142.57, 147.68, 154.33 ppm. IR (KBr): $\tilde{\nu}$ = 3559, 2972, 1680, 1069, 733, 537 cm^{-1}. $C_{21}H_{20}INO_2$ (445.0): calcd. C 56.64, H 4.53, N 3.15; found C 56.68, H 4.56, N 3.12.

Compound 5b: Colorless solid; m.p. 178–179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96–1.01 (m, 1 H), 1.06–1.22 (m, 1 H), 1.50–1.54 (m, 4 H), 1.74–1.80 (m, 1 H), 2.04 (s, 1 H), 6.96–6.98 (m, 2 H), 7.31–7.33 (d, J = 4.0 Hz, 3 H), 7.40–7.42 (m, 2 H), 8.0–8.1 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.87, 14.67, 27.27, 27.49, 69.30, 90.58, 122.37, 124.43, 127.98, 129.13, 129.76, 134.39, 143.79, 147.21, 152.52, 157.24 ppm. IR (KBr): $\tilde{\nu}$ = 3504, 1684, 1339, 1066, 732, 521 cm^{-1}. $C_{20}H_{17}IN_2O_4$ (476.0): calcd. C 50.44, H 3.60, N 5.88; found C 50.37, H 3.68, N 5.82.

Compound 6b: Yellow crystal; m.p. 88–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–1.07 (m, 1 H), 1.08–1.15 (m, 1 H), 1.39–1.44 (m, 4 H), 1.46–1.79 (m, 1 H), 1.94 (s, 1 H), 6.86–7.15 (m, 2 H), 7.16–7.23 (m, 2 H), 7.31–7.34 (m, 3 H), 7.43–7.47 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.45, 13.93, 27.21, 27.59, 69.51, 89.96, 123.81, 127.89, 128.45, 128.99, 129.26, 129.58, 134.75, 144.01, 147.45, 155.56 ppm. IR (KBr): $\tilde{\nu}$ = 3563, 1679, 1486, 1069, 733, 524 cm^{-1}. $C_{20}H_{17}ClINO_2$ (465.0): calcd. C 51.58, H 3.68, N 3.01; found C 51.51, H 3.73, N 3.08.

Compound 7b: Colorless solid; m.p. 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89–0.94 (m, 1 H), 1.09–1.14 (m, 1 H), 1.40–1.46 (m, 4 H), 1.73–1.78 (m, 1 H), 1.92 (s, 1 H), 6.82–6.84

(m, 2 H), 7.31–7.34 (m, 5 H), 7.43–7.46 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.49, 13.96, 27.23, 27.62, 69.50, 90.01, 116.80, 124.23, 127.91, 129.27, 129.60, 131.41, 134.77, 144.55, 147.48, 155.54 ppm. IR (KBr): $\tilde{\nu}$ = 3432, 1679, 1483, 1068, 733, 520 cm^{-1}. $C_{20}H_{17}BrINO_2$ (508.9): calcd. C 47.09, H 3.36, N 2.75; found C 47.05, H 3.39, N 2.81.

Compound 8b: Colorless solid; m.p. 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89–0.94 (m, 1 H), 1.10–1.15 (m, 1 H), 1.41–1.46 (m, 4 H), 1.73–1.78 (m, 1 H), 1.96 (s, 1 H), 6.84–6.87 (m, 1 H), 7.05–7.09 (t, J = 8.0 Hz, 1 H), 7.12–7.16 (m, 2 H), 7.31–7.33 (m, 3 H), 7.46–7.49 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.52, 14.09, 27.23, 27.54, 69.52, 89.94, 121.14, 121.93, 125.50, 126.69, 127.87, 129.30, 129.61, 129.71, 134.61, 147.02, 147.36, 156.11 ppm. IR (KBr): $\tilde{\nu}$ = 3559, 1678, 1067, 734, 477 cm^{-1}. $C_{20}H_{17}BrINO_2$ (508.9): calcd. C 47.09, H 3.36, N 2.81; found C 47.06, H 3.32, N 2.72.

Compound 9b: Colorless solid; m.p. 125–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.88 (m, 1 H), 1.08–1.13 (m, 1 H), 1.20–1.26 (m, 2 H), 1.51–1.59 (m, 4 H), 1.92 (s, 1 H), 1.95–2.00 (m, 1 H), 6.98–6.99 (d, J = 2.0 Hz, 1 H), 7.17–7.23 (m, 3 H), 7.29–7.35 (m, 2 H), 7.41–7.44 (m, 2 H), 7.51–7.53 (d, J = 4.0 Hz, 1 H), 7.76–7.78 (m, 1 H), 7.89 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.64, 14.34, 27.45, 27.88, 69.65, 89.61, 116.61, 123.37, 123.68, 125.29, 125.52, 125.73, 127.63, 127.69, 127.86, 129.30, 129.40, 134.03, 134.76, 142.00, 147.64, 155.61 ppm. IR (KBr): $\tilde{\nu}$ = 3558, 1683, 1071, 775, 569 cm^{-1}. $C_{24}H_{20}INO_2$ (481.0): calcd. C 59.89, H 4.19, N 2.91; found C 59.85, H 4.23, N 2.98.

Compound 10b: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82–0.86 (m, 2 H), 0.87–0.93 (m, 3 H), 1.42–1.51 (m, 2 H), 1.53 (s, 3 H), 1.62–1.65 (m, 2 H), 2.01–2.13 (m, 1 H), 2.30 (s, 3 H), 2.96–2.99 (m, 1 H), 6.94–6.96 (d, J = 8.0 Hz, 2 H), 7.06–7.08 (d, J = 4.0 Hz, 2 H), 7.32–7.33 (d, J = 2.0 Hz, 2 H), 7.41–7.44 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.96, 20.90, 22.65, 26.34, 29.11, 29.44, 50.05, 88.17, 120.58, 122.39, 127.88, 127.95, 129.07, 129.46, 129.55, 133.79, 142.41, 147.70, 153.62 ppm. IR (neat): $\tilde{\nu}$ = 3452, 1026, 865, 532 cm^{-1}. $C_{23}H_{26}INO_2$ (475.1): calcd. C 58.11, H 5.51, N 2.95; found C 58.13, H 5.54, N 2.90.

Compound 11b: Colorless solid; m.p. 80–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.87 (m, 3 H), 1.02–1.04 (m, 1 H), 1.05–1.27 (m, 8 H), 1.30–1.42 (m, 2 H), 1.66–1.77 (m, 1 H), 1.79 (s, 1 H), 2.43–2.44 (d, J = 2.0 Hz, 1 H), 6.82–6.84 (d, J = 2.0 Hz, 2 H), 7.20–7.22 (d, J = 4.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.39, 13.85, 13.93, 22.27, 25.86, 27.30, 27.64, 30.68, 35.60, 68.81, 88.96, 123.50, 128.42, 128.81, 144.42, 149.60, 156.14 ppm. IR (KBr): $\tilde{\nu}$ = 3389, 2923, 1678, 1090, 1002, 838, 517 cm^{-1}. $C_{20}H_{16}BrClINO_2$ (542.1): calcd. C 44.11, H 2.96, N 2.57; found C 44.25, H 2.89, N 2.64.

Compound 12b: Colorless solid; m.p. 98–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82–0.84 (m, 1 H), 0.85–0.89 (m, 3 H), 1.02–1.07 (m, 1 H), 1.30–1.35 (m, 4 H), 1.42–1.47 (m, 2 H), 1.64–1.71 (m, 1 H), 1.75 (s, 1 H), 6.83–6.85 (m, 2 H), 7.20–7.23 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.38, 10.24, 13.12, 13.23, 13.92, 15.46, 19.73, 19.80, 27.32, 27.67, 27.74, 37.45, 37.67, 68.81, 89.32, 123.52, 128.45, 144.42, 149.37, 156.06 ppm. IR (KBr): $\tilde{\nu}$ = 3555, 2965, 1679, 997, 837, 516 cm^{-1}. $C_{20}H_{16}Cl_2INO_2$ (498.1): calcd. C 48.03, H 3.22, N 2.80; found C 48.11, H 3.29, N 2.83.

Compound 13b: Colorless solid; m.p. 121–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91–0.94 (m, 1 H), 1.09–1.14 (m, 1 H), 1.40–1.46 (m, 4 H), 1.72–1.78 (m, 1 H), 1.94 (s, 1 H), 6.85–6.87 (d, J = 4.0 Hz, 2 H), 7.17–7.19 (m, 2 H), 7.31–7.33 (m, 2 H), 7.45–7.47 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.52, 14.02, 27.21, 27.53, 69.54, 90.48, 123.66, 123.88, 128.53, 129.12, 130.88, 131.20, 133.65, 143.96, 146.51, 155.28 ppm. IR (KBr): $\tilde{\nu}$ = 3558, 1223, 786, 456 cm^{-1}. $C_{20}H_{17}ClINO_2$ (465.7): calcd. C 51.58, H 3.68, N 3.01; found C 51.49, H 3.61, N 3.12.

Compound 14b: Colorless solid; m.p. 88–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–0.94 (m, 2 H), 1.09–1.15 (m, 1 H), 1.40–1.46 (m, 5 H), 1.73–1.78 (m, 1 H), 1.87 (s, 1 H), 6.85–6.87 (m, 2 H), 7.17–7.19 (m, 2 H), 7.29–7.31 (m, 2 H), 7.38–7.40 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.52, 14.04, 27.24, 27.56, 69.52, 90.87, 123.73, 127.41, 128.55, 129.21, 129.33, 129.56, 129.72, 133.84, 136.46, 143.92, 146.16, 155.18 ppm. IR (KBr): $\tilde{\nu}$ = 3532, 1249, 711, 488 cm^{-1}. $C_{19}H_{23}ClINO_2$ (459.1): calcd. C 49.64, H 5.04, N 3.05; found C 49.49, H 5.13, N 3.11.

Compound 7c: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.89 (m, 1 H), 0.97–1.02 (m, 1 H), 1.13–1.18 (m, 1 H), 1.42–1.57 (m, 1 H), 1.62 (s, 3 H), 1.63–2.34 (m, 1 H), 2.34 (s, 1 H), 6.88–6.90 (d, J = 4.0 Hz, 2 H), 7.25–7.40 (m, 5 H), 7.40–7.43 (m, 3 H), 7.82–7.84 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.61, 13.59, 27.01, 27.94, 67.82, 83.50, 98.19, 106.81, 116.72, 122.81, 124.00, 127.56, 127.95, 128.03, 128.49, 129.31, 129.75, 131.22, 131.54, 132.44, 144.99, 150.91, 155.61 ppm. IR (neat): $\tilde{\nu}$ = 3562, 1682, 1111, 691, 527 cm^{-1}. $C_{28}H_{22}BrNO_2$ (483.2): calcd. C 69.43, H 4.58, N 2.89; found C 69.52, H 4.51, N 2.83.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra, elemental analysis data.

Acknowledgments

The authors thank the NSF (NSF-20621091) and the "Hundred Scientist" from the Chinese Academy of Sciences for the financial support of this work.

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Received: December 18, 2008
Published Online: March 24, 2009

