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A Divergent Synthesis of γ-Iminolactones, Dihydroquinolin-2-ones, and γ-Lactames from β-Hydroxymethylcyclopropanylamides

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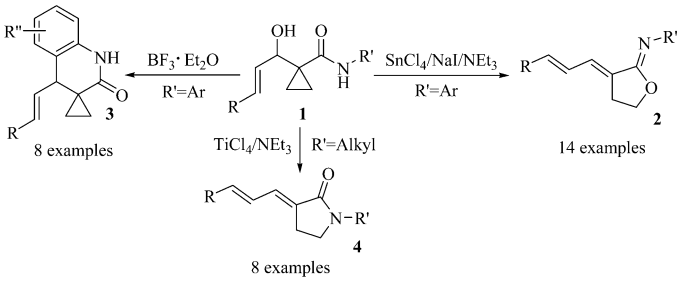
Received July 10, 2007



γ-Iminolactones **2**, dihydroquinolin-2-ones **3**, and γ-lactames **4** have been synthesized starting from β-hydroxymethylcyclopropanylamides **1**, mediated by $SnCl_4$/NaI/NEt_3, BF_3·OEt_2, and $TiCl_4$/NEt_3. The corresponding products **2**, **3**, and **4** were produced, respectively, in high to excellent yields.

Introduction

Cyclopropanes are extremely versatile building blocks in organic synthesis owing to their ready accessibility and good reactivity.[1,2] Since the first report by Cloke in 1929 that cyclopropyl ketones can be transformed into dihydrofuran derivatives,[3] the synthetic applications of cyclopropyl ketones have been well studied.[4] Comparatively, although the studies on the synthetic utility of cyclopropyl amides are relatively few, some interesting results[5] including the ring-expansion products like the *N*-substituted pyrrolidin-2-ones have been obtained.[5a] Recently, we developed new strategies for the preparation of furo[2,3-*b*]quinolines and highly substituted pyridin-2(1*H*)-ones through a novel $SnCl_4$-mediated tandem ring-opening/recyclization reaction[6a] and the Vilsmeier−Haack reaction,[6b] respectively, starting from the easily available 1-acyl-*N*-arylcyclopropanecarboxamides.[6] Due to our interest in the synthetic applications of cyclopropyl amides,[5,6] in this paper, the Lewis acid mediated highly selective reactions of β-hydroxymethylcyclopropanylamides **1**, which can lead to γ-iminolactones **2**, dihydroquinolin-2-ones **3**, and γ-lactames **4**, are reported (Scheme 1).

β-Hydroxymethylcyclopropanylamides **1** have the structure characters of both cyclopropyl amides[5,6] and cyclopropyl carbinol. On treatment with an acid, cyclopropyl carbinyl cation intermediate could be formed from cyclopropyl carbinol. This carbocation will undergo either ring expansion to give a

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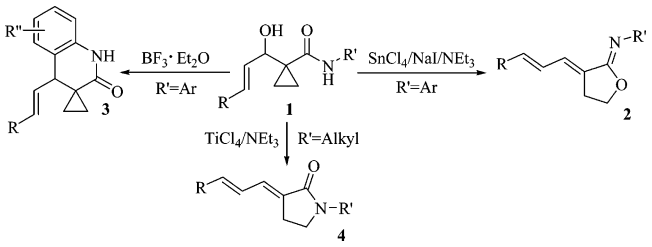
10.1021/jo701495s CCC: $37.00
Published on Web 09/18/2007

SCHEME 1. The Lewis Acid Mediated Reactions of *β*-Hydroxymethylcyclopropanylamides 1



cyclobutyl cation[7] or ring cleavage to give a homoallyl cation[8] to relieve ring strain. Recently, the ring-cleavage pathway of cyclopropyl carbinol through stabilization of the homoallyl cation by a silylmethyl function was efficiently utilized for the synthesis of multiply substituted tetrahydropyran rings.[9] Lewis acids have been used as catalysts for an enormous variety of organic reactions, for example, alkene alkylation and dimerization,[10] formation and hydrolysis of acetals,[11] Friedel−Crafts reactions,[12] aldol and related reactions,[13] and electrocyclic reactions.[14] Recent reports show that Lewis acid-mediated halogenative ring-opening of cyclopropyl carbinol substrates offered a practical, useful, and versatile method for the stereoselective synthesis of substituted olefins.[15] In our recent research, the cyclopropyl carbinol substrates, *β*-hydroxymethylcyclopropanylamides **1**, showed divergent behavior with respect to the Lewis acid catalyst. As a result, in the presence of $SnCl_4$, $TiCl_4$, and $BF_3{\cdot}OEt_2$, a series of ring-opening/*N*- or *O*-annulation and Friedel−Crafts alkylation products were obtained in high to excellent yields, respectively, as described in Scheme 1.

Results and Discussion

In our initial studies, the 1-(1-hydroxyethyl)-*N*-(2-methoxyphenyl)cyclopropanecarboxamide (**5**), prepared by reducing 1-acetyl-*N*-(2-methoxyphenyl)cyclopropanecarboxamide[6] with sodium borohydride,[16] was selected as the substrate (Scheme 2). Unfortunately, it was found that no reaction occurred upon treatment of **5** with Lewis acids, such as $SnCl_4{\cdot}5H_2O$, $TiCl_4$, and $BF_3{\cdot}OEt_2$ in acetonitrile. However, the $SnCl_4{\cdot}5H_2O$ mediated reaction of (*E*)-1-(1-hydroxy-3-phenylallyl)-*N*-(2-methoxyphenyl)cyclopropanecarboxamide (**1a**) (obtained by the sodium borohydride reduction of 1-cinnamoyl-*N*-(2-methoxyphenyl)-cyclopropanecarboxamide,[16] which was prepared by the condensation of 1-acetyl-*N*-(2-methoxyphenyl)cyclopropanecarboxamide with benzaldehyde)[17] provided a ring-opened product **6** in 43% yield, an intramolecular Friedel−Crafts alkylation product dihydroquinolin-2-one **3a** in 41% yield, and a ring-opened/recylization product *γ*-iminolactone[18] **2a** in 6% yield, respectively, in acetonitrile for 0.5 h (Scheme 2). With the aim to improve the yield of **2a** (according to our previous work regarding the *O*-annulation of 2-(2-chloroethyl)-*N*-(2-methoxyphenyl)-3-oxobutanamide),[6a] 2.0 equiv of NaI[19] was added to the $SnCl_4{\cdot}5H_2O$ mediated reaction of **1a** in acetonitrile for 1 h, then NEt_3 (3.0 equiv) was added and reacted for another 1 h. To our delight, **2a** was obtained in 78% isolated yield (Table 1, entry 1). In addition, our experiments showed that a small amount of $SnCl_4{\cdot}5H_2O$ (for example, 0.5 equiv) was not efficient (Table 1, entry 2). Other Lewis acids, including $TiCl_4$, $FeCl_3$, and $AlCl_3$, gave **2a** in relatively lower yields (Table 1, entries 3−5). The reaction could be carried out in DMF, THF, xylene, and dichloroethane but with lower yields of **2a** (Table 1, entries 7−10). Interestingly, **3a** was obtained as the major product (in yield of 52%) for the $BF_3{\cdot}OEt_2$ mediated reaction of **1a** (Table 1, entry 6). Therefore, selecting $BF_3{\cdot}OEt_2$ as the Lewis acid, we tried to improve the yield of **3a** by changing the solvent system and reaction temperature without the activation of NaI (Table 1, entries 11 and 12). Mediated by $BF_3{\cdot}OEt_2$, the reaction of **1a** exclusively afforded **3a** in 70% isolated yield within 15 min with dicholormethane as the solvent at room temperature (Table 1, entry 12). It is noteworthy that both *γ*-iminolactone **2a** and dihydroquinolin-2-one **3a** could be obtained in high yields from the same substrate **1a** (Table 1, entries 1 and 12). In fact, selective synthesis has been a formidable challenge in organic synthesis, especially controlled highly selective synthesis

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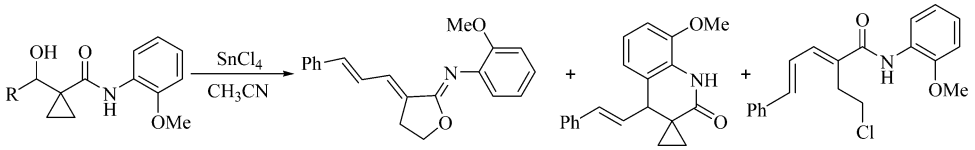
SCHEME 2



1a: R=trans PhCH=CH; **5**: R=Me **2a** **3a** **6**

TABLE 1. Lewis Acid Mediated Transformation of 1a to 2a and 3a[a]

entry	reagent (equiv)	solvent	time (h)	yield[b] (%) 2a	3a
1	$SnCl_4 \cdot 5H_2O$ (1.0)/NaI (2.0)	acetonitrile	2.0	78	0
2	$SnCl_4 \cdot 5H_2O$ (0.5)/NaI (2.0)	acetonitrile	2.0	43	17
3	$TiCl_4$ (1.0)/NaI (2.0)	acetonitrile	1.5	51	5
4	$FeCl_3$ (1.0)/NaI (2.0)	acetonitrile	5.5	34	0
5	$AlCl_3$ (1.0)/NaI (2.0)	acetonitrile	2.0	62	10
6	$BF_3 \cdot OEt_2$ (1.0) /NaI (2.0)	acetonitrile	0.5	19	52
7	$SnCl_4 \cdot 5H_2O$ (1.0)/NaI (2.0)	DMF	2.0	27[c]	0
8	$SnCl_4 \cdot 5H_2O$ (1.0)/NaI (2.0)	THF	2.0	35	28
9	$SnCl_4 \cdot 5H_2O$ (1.0)/NaI (2.0)	xylene	2.0	41	11
10	$SnCl_4 \cdot 5H_2O$ (1.0)/NaI (2.0)	dichloroethane	2.0	34	46
11	$BF_3 \cdot OEt_2$ (1.0)	dicholorethane	0.25	0	57
12	$BF_3 \cdot OEt_2$ (1.0)	dicholormethane	0.25	0	70[d]

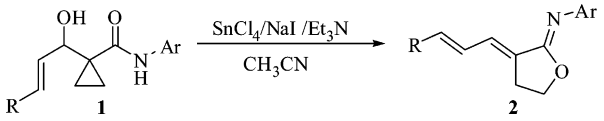
[a] The reactions were carried out in solvent (6 mL) with **1** (1.0 mmol), NEt_3 (3.0 mmol), and Lewis acid, with or without NaI (2.0 mmol) at 60 °C. [b] Isolated yield. [c] 65% of **1a** was recovered. [d] The reaction was performed at room temperature.

derived from the same starting materials.[20] Therefore, this divergent method for the synthesis of γ-iminolactone **2a** and dihydroquinolin-2-one **3a** from β-hydroxymethylcyclopropanylamides **1** was studied in detail.

With the optimized reaction conditions in hand (Table 1, entries 1 and 12), the scope of the transformations was then evaluated. Thus, a series of β-hydroxymethyl-*N*-arylcyclopropanylamides **1b**−**n**[16] were subjected to the optimized conditions described in Table 1, entry 1, and the results are summarized in Table 2. The substrates **1b**−**n** (with both electron-donating and electron-withdrawing group(s) on the aryl ring) underwent the ring-opened/recylization reaction smoothly to afford the corresponding γ-iminolactones **2b**−**n** in good to high yields with the reaction time of 2−3.5 h (Table 2, entries 1−13). The structures of the γ-iminolactones were further determined by the X-ray diffraction of **2e** (see the Surpporting Information, Figure S1), in which *N*-aryl orientated toward the oxygen atom of the ring.

The Friedel−Crafts alkylation reaction of **1a** could also be expanded. As shown in Table 3, substrates β-hydroxymethyl-*N*-arylcyclopropanylamides **1** with one or two electron-donating group(s) on either or both aryl ring(s) were reactive and the corresponding dihydroquinolin-2-ones **3** were obtained in high yields (Table 3, entries 1−3 and 5−7) leaving the cyclopropane ring intact. In the case of precursor **1e** with an electron-withdrawing chloro group on an aryl ring, the desired product **3e** was obtained in good yields (Table 3, entry 4). Recently,

TABLE 2. Synthesis of γ-Iminolactones 2 from β-Hydroxymethyl-*N*-arylcyclopropanylamides 1[a]

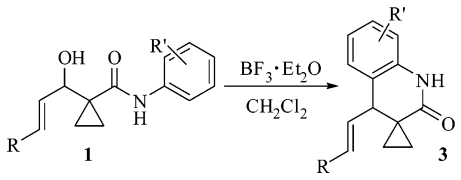


1 **2**

entry	β-hydroxymethyl-*N*-arylcyclopropanylamides 1	R	Ar	time (h)	product 2	yield[b] (%)
1	**1b**	PhCH=CH	2-$MeOC_6H_4$	2.0	**2b**	64
2	**1c**	4-$MeOC_6H_4$	2-$MeOC_6H_4$	2.5	**2c**	84
3	**1d**	4-MeC_6H_4	2-$MeOC_6H_4$	3.0	**2d**	82
4	**1e**	4-ClC_6H_4	2-$MeOC_6H_4$	3.5	**2e**	71
5	**1f**	4-$MeOC_6H_4$	2,4-$Me_2C_6H_3$	3.5	**2f**	85
6	**1g**	4-$MeOC_6H_4$	2-MeC_6H_4	3.0	**2g**	82
7	**1h**	4-$MeOC_6H_4$	Ph	3.0	**2h**	84
8	**1i**	4-MeC_6H_4	Ph	3.0	**2i**	79
9	**1j**	2-furyl	4-$EtOC_6H_4$	2.0	**2j**	75
10	**1k**	4-ClC_6H_4	4-$EtOC_6H_4$	3.0	**2k**	87
11	**1*l***	3-$MeOC_6H_4$	4-$EtOC_6H_4$	3.0	**2*l***	91
12	**1m**	2-ClC_6H_4	4-$EtOC_6H_4$	2.5	**2m**	88
13	**1n**	Ph	4-ClC_6H_4	3.5	**2n**	67

[a] The reactions were carried out in acetonitrile (6 mL) with **1** (1.0 mmol), $SnCl_4 \cdot 5H_2O$ (1.0 mmol), NaI (2.0 mmol), and NEt_3 (3.0 mmol) at 60 °C. [b] Isolated yield.

TABLE 3. Synthesis of Dihydroquinolin-2-ones 3 from β-Hydroxymethyl-*N*-arylcyclopropanylamides 1[a]



1 **3**

entry	β-hydroxymethyl-*N*-arylcyclopropanylamides 1	R	R′	time (min)	product 3	yield[b] (%)
1	**1b**	PhCH=CH	2-MeO	15	**3b**	79
2	**1c**	4-$MeOC_6H_4$	2-MeO	10	**3c**	83
3	**1d**	4-MeC_6H_4	2-MeO	5	**3d**	79
4	**1e**	4-ClC_6H_4	2-MeO	25	**3e**	50
5	**1f**	4-$MeOC_6H_4$	2,4-Me_2	15	**3f**	80
6	**1g**	4-$MeOC_6H_4$	2-Me	20	**3g**	78
7	**1h**	4-$MeOC_6H_4$	H	15	**3h**	72

[a] The reactions were carried out in dichloromethane (6 mL) with **1** (1.0 mmol) and $BF_3 \cdot OEt_2$ (1.0 mmol) at room temperature. [b] Isolated yield.

some reports showed that the spirotryprostatin core could be efficiently constructed by the MgI_2-mediated ring expansion reaction of a spiro[cyclopropane-1,3′-oxindole] with an aldimine;[21] such investigations, i.e., the synthetic transformations of dihydroquinolin-2-ones **3** via cyclopropane ring-opening pathway, are currently under way in our laboratory.

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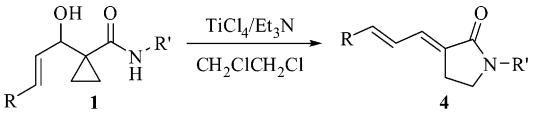
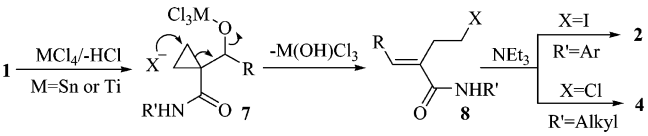
TABLE 4. Synthesis of γ-Lactames 4 from β-Hydroxymethyl-*N*-alkylcyclopropanylamides 1[a]



entry	β-hydroxymethyl-*N*-alkylcyclopropanylamides 1	R	R′	time (h)	product 4	yield[b] (%)
1	**1o**	Ph	Me	1.6	**4a**	94
2	**1p**	2-thienyl	Me	1.0	**4b**	83
3	**1q**	4-ClC_6H_4	Me	3.5	**4c**	86
4	**1r**	4-MeC_6H_4	Me	2.1	**4d**	87
5	**1s**	4-$MeOC_6H_4$	Me	2.0	**4e**	76
6	**1t**	4-MeC_6H_4	n-Pr	2.3	**4f**	84
7	**1u**	Ph	n-Pr	2.0	**4g**	87
8	**1v**	Ph	Bn	3.3	**4h**	91

[a] The reactions were carried out in 1,2-dichloroethane (6 mL) with **1** (1.0 mmol), $TiCl_4$ (0.5 mmol), and NEt_3 (3.0 mmol) at room temperature to 60 °C. [b] Isolated yield.

SCHEME 3. Proposed Mechanisms for the Synthesis of γ-Iminolactones 2 and γ-Lactames 4



Interestingly, when the reaction of β-hydroxymethyl-*N*-alkylcyclopropanylamide **1o** (in which R′ is a methyl instead of an aryl group as in **1a**−**n**) was carried out under the above optimal reaction conditions (Table 1, entry 1) for 6 h, instead of an *O*-attack annulation product γ-iminolactone **2o**, an *N*-attack annulation product γ-lactame **4a** was obtained in 37% isolated yield. Under otherwise identical conditions as described (Table 1, entry 1) and with 1,2-dichloroethane as the solvent, **4a** was obtained in 82% isolated yield in 4.5 h. It was found that in the case when only $SnCl_4 \cdot 5H_2O$ was employed (without NaI), γ-lactame **4a** was obtained in 80% isolated yield. Gratifyingly, the higher yield of **4a** (94%) was achieved within 1.5 h when $TiCl_4$ (0.5 equiv) was selected to promote the reaction with 1,2-dichloroethane as the solvent (Table 4, entry 1). As expected, the transformation of **1o** to **4a** could be expanded. Under the optimized conditions (Table 4, entry 1), the reactions of β-hydroxymethyl-*N*-alkylcyclopropanylamides **1p**−**v**[16] were performed and the desired γ-lactames **4b**−**h** were produced in high to excellent yields (Table 4, entries 2−8). In a study on coupling-cyclization reactions of 2,3-allenamides with organic halides by Ma and co-workers,[18d] the *O*- or *N*-attack selectivity was attributed to the steric hindrance at the 4-positions of 2,3-allenamides. In our experiments, steric effects of the substituent on the nitrogen atom may play an important role for the highly selective formation of the related annulation products, γ-iminolactones **2** or γ-lactames **4**.

On the basis of all of the above results, plausible mechanisms for the formation of γ-iminolactones **2** and γ-lactames **4** from β-hydroxymethylcyclopropanylamides **1** are presented in Scheme 3. The overall transformations may involve the $SnCl_4$/NaI or $TiCl_4$ initiated reaction of **1** to provide a ring-opened intermediate **8**, which was followed by either an intramolecular *N*-annulation or *O*-annulation to produce γ-lactames **4** or γ-iminolactones **2** in the presence of NEt_3, respectively, depending in a large part on the steric effects of the substituent (R′) on the nitrogen atom. When R′ is a large group, such as an aryl group, *O*-annulation is preferred. Whereas *N*-annulation is preferred when R′ is a relatively smaller group, such as Me, *n*-Pr, and Bn. In addition, compared with an oxygen atom, the relatively higher nucleophilicity of the nitrogen atom made the transformation from **8** to **4** proceeded more efficiently even in the absence of NaI.

Conclusion

In summary, a divergent synthesis of γ-iminolactones **2**, dihydroquinolin-2-ones **3**, and γ-lactames **4** from β-hydroxymethylcyclopropanylamides **1** in high to excellent yields under mild reaction conditions has been developed. Through an efficient one-pot ring-opened/*O*- or *N*-annulation process, $SnCl_4$/NaI/NEt_3 mediated reactions of β-hydroxymethyl-*N*-arylcyclopropanylamides **1a**−**n** provided γ-iminolactones **2a**−**n** and $TiCl_4$/NEt_3 mediated reactions of β-hydroxymethyl-*N*-alkylcyclopropanylamides **1o**−**v** gave γ-lactames **4a**−**h**, respectively. This high *O*/*N*-attack selectivity may be directed by the steric effect of the substituent on the nitrogen atom in the amide moiety. Mediated by $BF_3 \cdot OEt_2$, dihydroquinolin-2-ones **3a**−**h** could also be efficiently prepared from β-hydroxymethyl-*N*-arylcyclopropanylamides **1a**−**h** via an intramolecular Friedel−Crafts alkylation reaction. Further synthetic applications for γ-iminolactones **2** and dihydroquinolin-2-ones **3** are in progress.

Experimental Section

General procedure for the synthesis of 2 (with 2a as an example): To a solution of substrate **1a** (323 mg, 1.0 mmol) in acetonitrile (6.0 mL) was added $SnCl_4 \cdot 5H_2O$ (350 mg, 1.0 mmol) and NaI (300 mg, 2.0 mmol). The mixture was stirred at 60 °C for 1 h, then NEt_3(0.41 mL, 3.0 mmol) was added. After an additional 1 h, the reaction mixture was poured into cold water (50 mL), extracted with dichloromethane (6 × 8 mL), and dried over with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by a shot flash silica gel column chromatography to give compound **2a** (238 mg, 78%) as yellow crystals (eluent: ethyl ether/petroleum ether = 1/4). Compound **2a**: mp 142−143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.98−3.01 (m, 2H), 3.91 (s, 3H), 4.32 (t, *J* = 7.5 Hz, 2H), 6.65−6.73 (m, 2H), 6.95−6.96 (m, 2H), 7.06−7.07 (m, 1H), 7.23−7.38 (m, 4H), 7.54 (d, *J* = 7.5 Hz, 2H), 8.73−8.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.0, 54.6, 66.5, 110.4, 119.3, 121.7, 123.2, 124.3, 125.4, 125.9, 126.5, 126.8, 127.3, 132.2, 135.4, 135.9, 150.5, 156.4; IR (KBr, cm^{-1}) 3426, 1731, 1650, 1550, 1327, 1288, 1222, 1136, 1066, 961, 857, 749, 689; MS calcd *m*/*z* 305.1, found 306.1 $[(M + 1)]^+$. Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.61; H, 6.29; N, 4.62.

General procedure for the synthesis of 3 (with 3a as an example): To a solution of substrate **1a** (323 mg, 1.0 mmol) in dichloromethane (6.0 mL) was added $BF_3 \cdot OEt_2$ (1.0 mmol, 0.12 mL) at room temperature. The mixture was stirred for 15 min (monitored by TLC). The reaction mixture was then poured into cold water (50 mL), extracted with dichloromethane (6 × 8 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by a shot flash silica gel column chromatography to give compound **3a** (214 mg, 70%) as white crystals (eluent: ethyl ether/petroleum ether = 1/3). Compound **3a**: mp 129−130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86−0.89 (m, 1H), 0.91−0.95 (m, 1H), 1.12−1.16 (m, 1H), 1.69−1.73 (m, 1H), 3.10 (d, *J* = 6.5 Hz, 1H), 3.89 (s, 3H), 6.23−6.28 (m, 1H), 6.34 (d, *J* = 16 Hz, 1H), 6.78−6.83 (m, 2H), 6.99−7.02 (m, 1H), 7.19−7.32 (m, 5H), 7.95 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.9, 16.6, 22.7, 46.9, 54.5, 108.0, 118.8, 121.6, 123.8, 124.4, 125.1, 126.2, 127.2, 127.8, 129.2, 135.5, 144.6, 170.6; IR

(KBr, cm^{-1}) 3194, 1679, 1492, 1387, 1075, 1023, 925, 841, 734; MS calcd *m*/*z* 305.1, found 306.1 $[(M + 1)]^+$;. Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.73; H, 6.24; N, 4.57.

General procedure for the synthesis of 4 (with 4a as an example): To a solution of substrate **1o** (231 mg, 1.0 mmol) in 1,2-dichloroethane (6 mL) was added $TiCl_4$ (0.5 mmol, 0.054 mL) for 20 min at room temperature then NEt_3 (0.41 mL, 3.0 mmol) at 60 °C. After an additional 80 min, the reaction mixture was poured into cold water (50 mL), extracted with dichloromethane (6 × 8 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by a shot flash silica gel column chromatography to give compound **4a** (201 mg, 94%) as white crystals (eluent: ethyl ether/petroleum ether = 1/1). Compound **4a**: mp 150−151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.87−2.91 (m, 2H), 2.97 (s, 3H), 3.47 (t, J = 7.5 Hz, 2H), 6.80−6.85 (m, 2H), 7.03−7.05 (m, 1H), 7.26−7.28 (m, 1H), 7.32−7.35 (m, 2H), 7.45−7.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 30.5, 46.9, 124.4, 127.1, 128.7, 129.0, 129.3, 132.2, 137.0, 138.0, 169.1; IR (KBr, cm^{-1}) 2881, 1671, 1634, 1291, 1134, 1058, 977, 754; MS calcd *m*/*z* 213.1, found 214.1 $[(M + 1)]^+$. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.67; H, 7.11; N, 6.46.

Acknowledgment. Financial support of this research by the Ministry of Education of China (106064), the NNSFC (20672019), Science Foundation for Yong Teachers of Northeast Normal University (20060301), and analysis and testing foundation of Northeast Normal University is greatly acknowledged.

Supporting Information Available: Experimental details and full characterization data, copies of ^{1}H and ^{13}C NMR spectra for compounds **1a**−**v**, **2a**−**n**, **3a**−**h**, **4a**−**h**, **5**, and **6**, and CIF data for **2e**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701495S