Synthesis of Heterocycle-Annulated Medium-Sized Oxacycles and Lactone Derivative by Intramoleculer Heck Reaction

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Received 20 April 2009

Abstract: An efficient and convergent methodology for the highly strained medium-sized oxacyclic compounds and lactone derivatives has been developed via palladium-catalyzed intramoleculer Heck reaction.

Key words: intramoleculer Heck reaction, palladium acetate, 8-*exo*-trig, eight-membered oxacycle, lactone

In recent years, tremendous interest[1] has been shown in the application of transition-metal-mediated protocols for the construction of heterocyclic systems. Besides its synthetic utility, transition-metal chemistry involving heteroatom-containing compounds is of interest from the mechanistic point of view,[2] and this is attributed to the unique characteristics derived from the heteroatom present in the substrates.[3]

As a part of our ongoing research project on the synthesis of heterocyclic compounds, we recently reported the first example[4] of the palladium-catalyzed unusual [1,3]-aryloxy shift followed by a cycloisomerization, leading to potentially bioactive heterocyclic systems. We also reported the first example[5] of eight-membered sulfur heterocycles from a sulfone ester tether precursor by the palladium-mediated Heck reaction. Moreover, most recently we have also reported the synthesis[6] of eight-membered azocine derivatives by catalyzed aza-Claisen rearrangement[7] and intramoleculer Heck reaction sequences. In continuation to our work on the palladium chemistry,[8] we intended to extend the intramoleculer Heck cyclization leading to ultimate synthesis of the medium-sized heterocyclic compounds by varying the heterocyclic core moiety as the smallest unit.

Usually, medium-sized heterocycles are regarded as an exceedingly important group of compounds, the structural basic units of which are regularly found in the framework of a variety of natural products.[9] Principally, eight- and nine-membered heterocycles are constituents of a number of compounds with increased pharmacological properties.[10] Large number of medium rings containing oxygen or nitrogen atom(s) in medicinally interesting compounds continue to insure that they are important synthetic targets for organic chemists. The synthetic routes for the construction of medium-sized heterocycles involving direct ring closure are often slow[11] and inhibited by an unfavorable entropy and enthalpy (the strain exerted in so many medium rings) and also transannular interaction.[12] Today, palladium chemistry occupies a special place amongst the so far reported intramoleculer cyclization strategy of both applied and academic interests.[13] The aforesaid finding inspired us to undertake a study of the formation of medium-sized oxa-heterocycles by the application of palladium-mediated intramoleculer Heck reaction, and herein we report the results.

Intramoleculer Heck reaction may undergo cyclization via two modes[14] such as *exo*-trig and/or *endo*-trig. Entropy and enthalpy factors[15] as well as transannular interaction play an important role in the cyclization. The *exo*-trig mode is favorable for small to common ring-forming reactions, and the *endo*-trig mode is favorable only for large ring-forming reactions. In the case of a medium ring-forming reaction, both *exo*- and *endo*-trig mode may occur, depending on the nature of the alkene present in the Heck precursor. The Heck reaction usually proceed through *endo*-trig mode of cyclization with an alkene having a Michael type of olefinic fragment.[16]

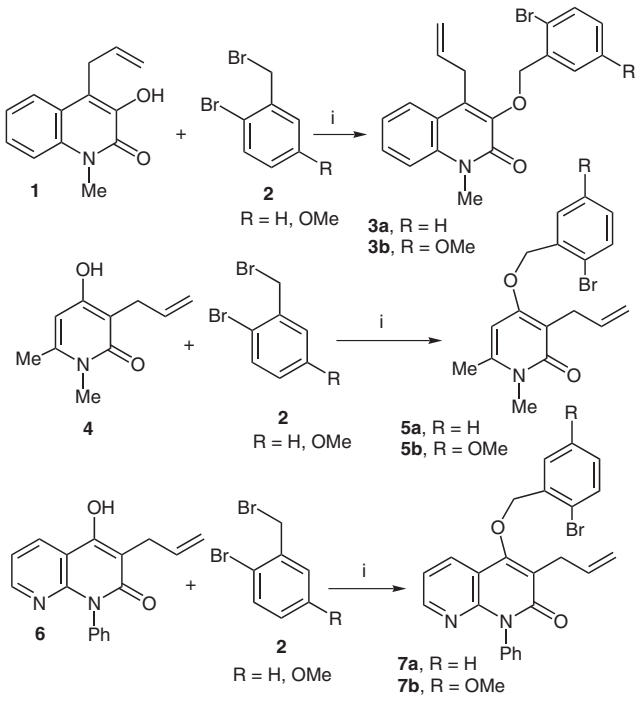
The precursors **3**, **5**, and **7** for our present investigation were prepared in 60–80% yields by classical allylation of **1**, **4**, and **6** with either 2-bromobenzyl bromide **2a** or 2-bromo-5-methoxybenzyl bromide **2b** in dry acetone in the presence of anhydrous K_2CO_3 and a small amount of sodium iodide[17] (Scheme 1).

We next attempted palladium-catalyzed intramolecular Heck reaction with these substrates. To this end, the first experiment was carried out with **3a** as a model substrate. Initially, the substrate **3a** was allowed to react in dry DMF in the presence of $Pd(OAc)_2$ (10 mol%) as the catalyst, anhydrous potassium acetate as the base and in conjunction with TBAB at 95 °C for three hours under nitrogen atmosphere to give the corresponding cyclized product **8a**[18] in 46% yield (Scheme 2, entry 1, Table 1).

However, when the same reaction was performed for a longer period (6 h), pleasingly the yield of the cyclized product was increased considerably (57%, entry 2, Table 1).

When the same reaction was conducted by changing the catalytic composition from entry 1 to entry 3 in Table 1, the yield of the product was maximum (71%), that is, the catalyst $Pd(PPh_3)_4$ has exhibited better catalytic activity over the commonly used $Pd(OAc)_2$ catalyst as evident

SYNLETT 2009, No. 13, pp 2083–2088
Advanced online publication: 16.07.2009
DOI: 10.1055/s-0029-1217702; Art ID: G10109ST



Scheme 1 *Reagents and conditions*: (i) dry acetone, K_2CO_3, NaI, reflux.

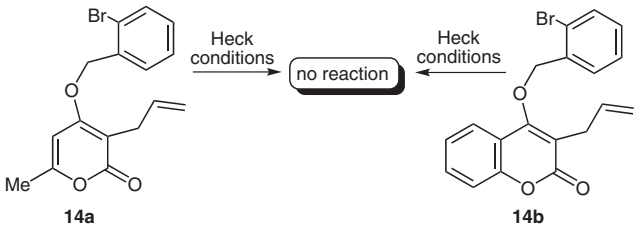
from the shorter reaction time and better yield of the product. We have also examined other reaction conditions (entry 4–6, Table 1) and DMF is found to be the solvent of choice; KOAc is the most resourceful base, though it is the nucleophilic in nature yet it plays a vital role in this reaction. $Pd(PPh_3)_4$ is the suitable catalyst.

It is well known[19] that the additions of silver carbonate or thallium salts cleanly suppressed the double bond isomerization and accelerate the cyclization, possibly by removing halide ions strongly attached to Pd from a coordination sphere to generate a cationic Pd catalyst, making the insertion easier and faster. Therefore, we performed the Heck reaction in the presence of Ag_2CO_3 in place of KOAc. Unfortunately, we could not achieve any new result. However, the formation of **8a** in only 35% yield was observed (Table 1, entry 7 and 8). We have also conducted the Heck reaction using the IL-mediated[20] systems under different conditions, but no reaction occurred (Table 1, entry 11 and 12). Interestingly, when the reaction was carried out in DMF–H_2O[21] (7:2), the product **8a** was obtained in 46% yield. However, the reaction did not proceed at all when carried out in water alone (Table 1, entry 10). Compound **8a** was characterized from its elemental analysis and spectral data.[18]

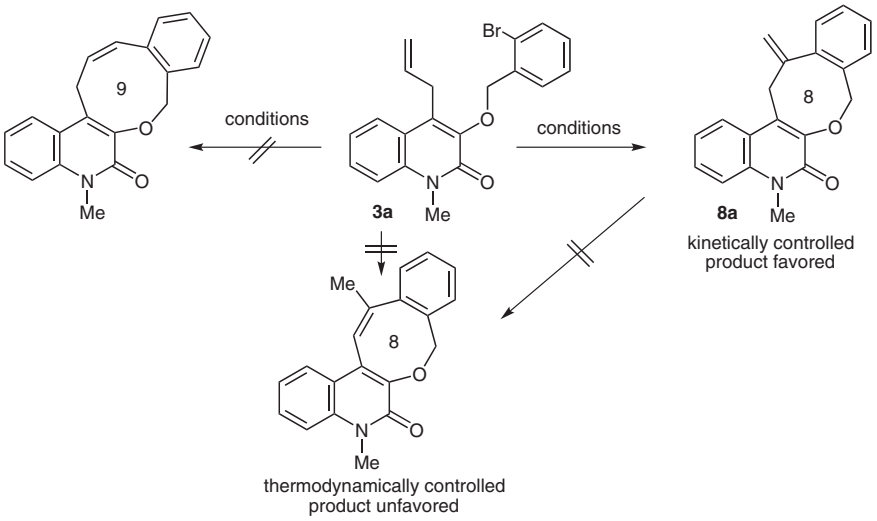
We next turned our attention to other heterocyclic substrates for Heck cyclization. Substrate **3b** was treated under the optimized conditions: $Pd(PPh_3)_4$, TBAB, KOAc, DMF, 95 °C to give the Heck product **8b** in 49% yield. However, by changing the reaction conditions (entry 14, Table 1) we have successfully obtained an excellent yield (84%) of **8b**. Longer reaction time slightly improved the yield of **8b** to 87% (entry 15).

We have also extended this protocol to other heterocyclic systems such as 4-hydroxypyridone (**4**), 4-hydroxyazanaphthyridine (**7**), 4-hydroxypyrone (**14a**), and 4-hydroxycoumarin (**14b**) systems. When Heck reactions were carried out with these systems each precursor smoothly underwent cyclization leading to the formation of the corresponding *exo*-Heck (kinetically controlled) product in good to excellent yields except for **7b** and **14a**,**b** (Scheme 3).

In the case of substrate **7b**, the Heck reaction performed under the conditions shown in Table 1, entry 1, afforded exclusively the *endo*-Heck cyclization product **10b**[22]



Scheme 3



Scheme 2

Table 1 Screening and Optimization of the Heck Reactions

Entry	Conditions	Prod.	Yield (%)
1	$Pd(OAc)_2$, TBAB, KOAc, DMF, 95 °C, 3 h	**8a**	46
2	$Pd(OAc)_2$, TBAB, KOAc, DMF, 95 °C, 6 h	**8a**	57
3	$Pd(PPh_3)_4$, TBAB, KOAc, DMF, 95 °C, 2 h	**8a**	71
4	$Pd(PPh_3)_2Cl_2$, TBAB, KOAc, DMF, 95 °C, 6 h	**8a**	<5
5	$Pd(OAc)_2$, TBAB, KOAc, THF, 70 °C, 12 h	**8a**	0
6	$Pd(OAc)_2$, TBAB, KOAc, MeCN, 70 °C, 12 h	**8a**	0
7	$Pd(OAc)_2$, TBAB, Ag_2CO_3, DMF, 120 °C, 4 h	**8a**	35
8	$Pd(PPh_3)_4$, TBAB, Ag_2CO_3, DMF, 120 °C, 4 h	**8a**	22
9	$Pd(OAc)_2$, TBAB, KOAc, DMF–H_2O, 120 °C, 6 h	**8a**	46
10	$Pd(OAc)_2$, TBAB, KOAc, H_2O, 120 °C, 12 h	**8a**	n.r.[b]
11	$Pd(OAc)_2$, TBAB, KOAc, IL,[a] 120 °C, 6 h	**8a**	n.r.[b]
12	$Pd(OAc)_2$, KOAc, IL,[a] 120 °C, 6 h	**8a**	n.r.[b]
13	$Pd(PPh_3)_4$, TBAB, KOAc, DMF, 95 °C, 2 h	**8b**	49
14	$Pd(OAc)_2$, TBAB, KOAc, DMF, 110 °C, 3.5 h	**8b**	84
15	$Pd(OAc)_2$, TBAB, KOAc, DMF, 120 °C, 6 h	**8b**	87
16	$Pd(OAc)_2$, TBAB, KOAc, DMF, 95 °C, 5 h	**9a**	54
17	$Pd(OAc)_2$, TBAB, KOAc, DMF, 120 °C, 5 h	**9a**	69
18	$Pd(OAc)_2$, TBAB, KOAc, DMF, 85 °C, 5 h	**9b**	34
19	$Pd(OAc)_2$, TBAB, KOAc, DMF, 120 °C, 5 h	**9b**	59
20	$Pd(OAc)_2$, TBAB, KOAc, DMF, 95 °C, 3.5 h	**10a**	73
21	$Pd(OAc)_2$, TBAB, KOAc, DMF, 120 °C, 5 h	**10b**	51
22	$Pd(OAc)_2$, TBAB, KOAc, DMF, 100 °C, 3–12 h	**12**	0
23	$Pd(PPh_3)_4$, TBAB, KOAc, DMF, 110 °C, 2–12 h	**12**	0
24	$Pd(PPh_3)_2Cl_2$, TBAB, KOAc, DMF, 130 °C, 2–12 h	**12**	0
25	$Pd(PPh_3)_2Cl_2$, TBAB, KOAc, DMF, 130 °C, 2–12 h	**12**	0
26	$Pd(PPh_3)_2Cl_2$, TBAB, NaOAc, DMA, 130 °C, 2 h	**12**	43

[a] IL = ionic liquid [N-alkylated imidazolium ion, alkyl group = $(CH_2)_{11}Me$].
[b] n.r. = no reaction.

through a 9-*endo*-trig mode of cyclization. Formation of nine-membered products is quite difficult compared to the eight-membered products. Yet in this system the nine-membered oxa-heterocyclic product was obtained exclusively in 51% yield. However, we are unable to provide any rationalization for this cyclization.

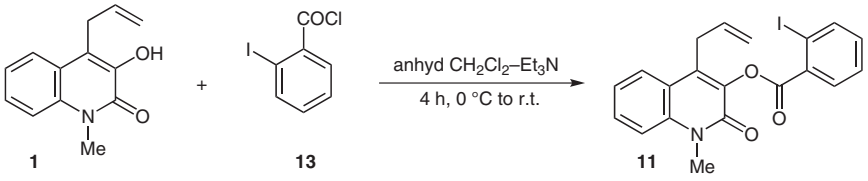
Heck reactions of the substrates **14a**,**b** were carried out under several (different) reaction conditions. The entire starting materials disappeared giving a complex mixture from which no product could be isolated as the substrate lactones **14a**,**b** are base sensitive.

Recently, Guy et al.[23] attempted the synthesis of medium-sized lactone derivatives from the highly activated Heck precursors. However, their attempts to synthesize medium-sized lactone derivatives by palladium-catalyzed Heck reaction failed. In fact, it is very difficult to construct this type of lactone derivatives perhaps due to the lack of a satisfactory synthetic procedure. In general, Heck reactions are carried out in the presence of a strong base, and therefore, the reaction medium becomes basic in nature making the synthesis of the lactones by the application of the Heck reaction a great challenge. Keeping this in mind, we have attempted to synthesize medium-sized lactone derivatives. For this purpose, the starting material **11** was prepared as depicted in Scheme 4. The reaction of the acid chloride **13** (prepared from 2-iodobenzoic acid and thionyl chloride in CH_2Cl_2) with 4-allyl-3-hydroxy-*N*-methylquinolone in CH_2Cl_2–Et_3N at 0 °C to room temperature for four hours afforded the Heck precursor **11**.

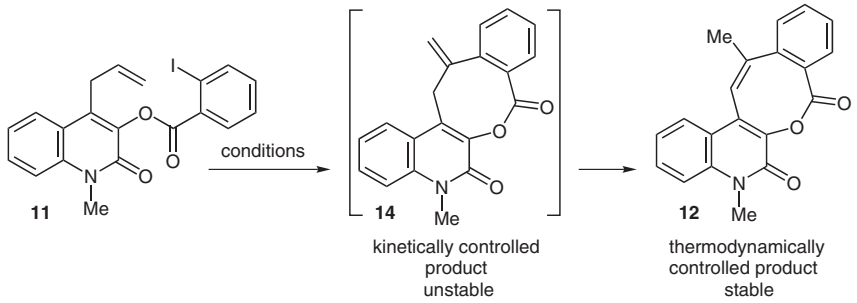
Attempted synthesis of the lactone from its precursor **11** using the reaction conditions shown in Table 1, entries 22–25 miserably failed, and the starting material remained unchanged. Consequently, we altered the reaction conditions, and when we performed the same reaction under the conditions described in Scheme 5, Table 1, entry 26, we were delighted to obtain the corresponding lactone derivative **12** in 43% yield. The cyclized product was formed via 8-*exo*-trig mode of cyclization followed by a double-bond isomerization.

Here it is noteworthy that the final product **12** is a thermodynamically controlled one because the kinetically controlled exocyclic product **14** isomerizes to **12** under these reaction conditions. The results of the Heck reactions are presented in Table 2.

In short, we have developed important synthetic protocols for the synthesis of heterocycle-annulated medium-sized ring compounds including the lactone derivative which is quite difficult to synthesize via this type of Heck protocol. The developed method is simple, straightforward, and high-yielding. The cyclization mode and related chemistry is also attractive. We are continuing this work, and a full account will be communicated later.



Scheme 4



Scheme 5

Table 2 Results of Heck Reactions

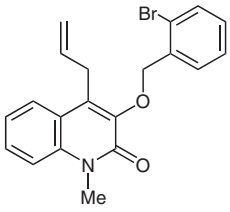
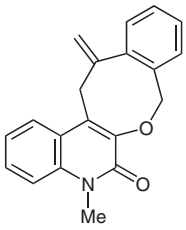
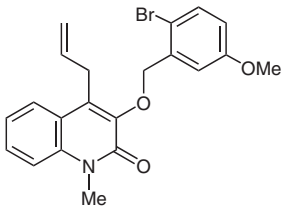
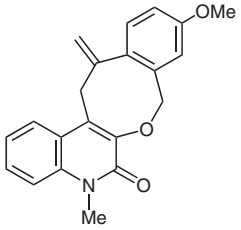
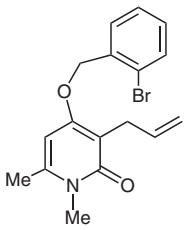
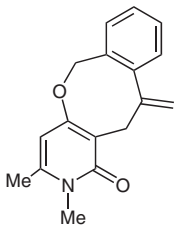
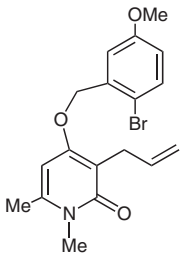
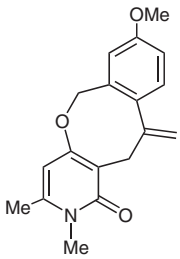
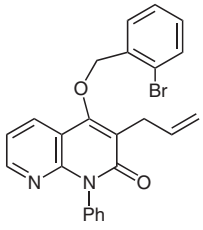
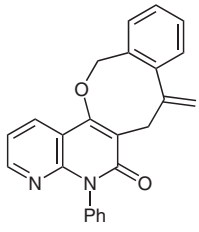
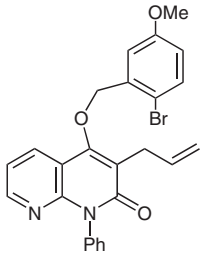
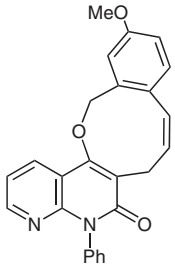
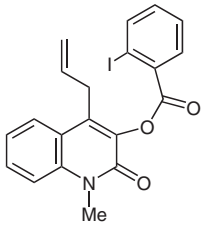
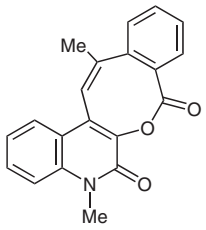
Entry	Substrate	Optimized conditions	Products	Yield (%)
1	 **3a**	$Pd(PPh_3)_4$, TBAB, KOAc, DMF, 95 °C, 2 h	 **8a**	71
2	 **3b**	$Pd(OAc)_2$, TBAB, KOAc, DMF, 120 °C, 6 h	 **8b**	87
3	 **5a**	$Pd(OAc)_2$, TBAB, KOAc, DMF, 120 °C, 5 h	 **9a**	69
4	 **5b**	$Pd(OAc)_2$, TBAB, KOAc, DMF, 95 °C, 3.5 h	 **9b**	59
5	 **7a**	$Pd(OAc)_2$, TBAB, KOAc, DMF, 95 °C, 3.5 h	 **10a**	73

Table 2 Results of Heck Reactions (continued)

Entry	Substrate	Optimized conditions	Products	Yield (%)
6	 **7b**	$Pd(OAc)_2$, TBAB, KOAc, DMF, 120 °C, 5 h	 **10b**	51
7	 **11**	$Pd(PPh_3)_2Cl_2$, TBAB, NaOAc, DMA, 130 °C, 2 h	 **12**	43

Acknowledgment

We thank the CSIR (New Delhi) and the DST (New Delhi) for financial assistance. Two of us (B.C and R.N.D) are grateful to the CSIR and the UGC, respectively, for fellowships.

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(18) **General Procedure for the Synthesis of the Compound by Heck Reaction**
A mixture of **3a** (70 mg, 0.182 mmol), TBAB (147 mg, 0.455 mmol), and dry KOAc (26 mg, 0.265 mmol) was taken in dry DMF (10 mL). $Pd(OAc)_2$ (10 mol%, 4.1 mg) was added, and the mixture was stirred on an oil bath at 110 °C for ca. 2 h. The reaction mixture was cooled, DMF was removed under reduced pressure, H_2O (3 mL) was added and extracted with EtOAc (3 × 20 mL) and washed with H_2O (2 × 20 mL), followed by brine (20 mL). The organic layer was dried (Na_2SO_4), and the solvent was distilled off to furnish a viscous mass which was purified by column chromatography over silica gel. Elution of the column with 20% EtOAc–hexane afforded the product **8a**. Similarly, other compounds were synthesized.
Compound **8a**: white solid, mp 174 °C. IR (KBr): 2918, 2899, 1643, 1600 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.66 (s, 3 H, NCH_3), 4.02 (s, 2 H,=CCH_2), 5.17 (s, 1 H, =CH_a), 5.42 (s, 1 H, =CH_b), 5.48 (s, 2 H, OCH_2), 7.12–7.19 (m, 4 H, ArH), 7.20 (t, 1 H, *J* = 7.88 Hz, ArH), 7.25 (d, 1 H, *J* = 5.2 Hz, ArH), 7.43 (t, 1 H, *J* = 7.80 Hz, ArH), 7.65 (d, 1 H, *J* = 7.96 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.67, 36.98, 73.86, 114.17, 114.26, 120.53, 122.31, 123.83, 127.86, 128.37, 128.45, 128.65, 128.69, 133.47, 133.93, 137.01, 141.33, 143.94, 148.03, 159.00. MS (TOF MS ES+): *m/z* = 326.13 [M + Na^+]. Anal. Calcd (%) for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.29; H, 5.77; N, 4.57.

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(22) The spectral data, especially NMR studies, showed that the OCH_2 protons appears as two separate singlets which is further supported by the DEPT experiment. DEPT contains two extra methylene groups due to the rapid interconversion of the existing possible conformers.
Compound **10b**: yellow solid, mp 250 °C. IR (KBr): 2941, 2838, 1647, 1625 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.45–3.61 (m, 2 H, =CHCH_2), 3.80 (s, 3 H, OCH_3), 4.89 (s, 1 H, OCH_a), 5.44 (s, 1 H, OCH_b), 6.74 (d, 1 H, *J* = 11.4 Hz, =CH_a), 7.11–7.15 (m, 1 H, =CH_b), 7.19–7.22 (m, 5 H, ArH), 7.43–7.54 (m, 4 H, ArH), 8.23 (d, 1 H, *J* = 7.5 Hz, ArH), 8.46 (d, 1 H, *J* = 3.2 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.6, 59.4, 109.2, 112.6, 112.7, 115.1, 119.2, 125.3, 125.8, 128.5, 128.9, 129.5, 136.0, 136.7, 138.8, 138.3, 154.1, 154.7, 159.8, 172.5, 194.6. (TOF MS ES+): *m/z* = 419.08 [M + Na]. Anal. Calcd (%) for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07. Found: C, 75.81; H, 5.03; N, 7.21.

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