Palladium-Catalyzed Amino-Heck Reaction of γ,δ–Unsaturated Ketone *O*-Diethylphosphinyloximes: A New Synthesis of Substituted Pyrroles and Indoles

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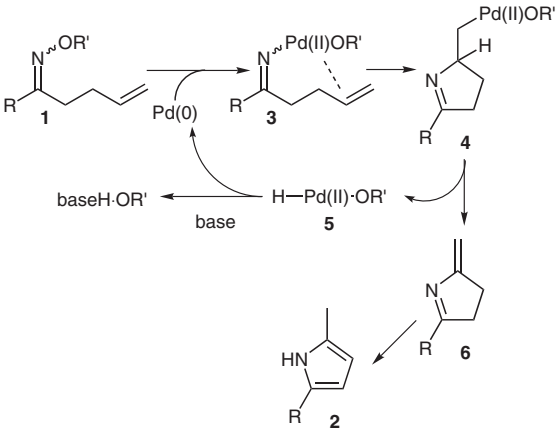
Dedicated to Professor Hsing-Jang Liu on his 65th birthday

Abstract: γ,δ-Unsaturated ketone *O*-diethylphosphinyloximes, readily prepared from the corresponding ketones, were used as starting materials for the intramolecular amino-Heck reactions. In the presence of a catalytic amount of $Pd(PPh_3)_4$ in DBU, cyclization reactions occurred preferentially via a 5-*exo* fashion to afford a variety of 2-substituted 5-methyl-1*H*-pyrroles and several indole derivatives in moderate to high yields.

Key words: amino-Heck reaction, oximes, pyrroles, heterocycles, palladium

Recently, the intramolecular amino-Heck reactions of ketone oxime derivatives have drawn much attention as a new synthetic strategy for the preparation of aza-heterocycles.[1–6] For example, under palladium-catalyzed reaction conditions, a series of γ,δ-unsaturated *O*-pentafluorobenzoyloximes and *O*-methylsulfonyloximes have been reported to undergo cyclization reactions to produce substituted pyrroles.[1a,5] The accepted mechanism for such transformation is depicted in Scheme 1 as exemplified by the conversion of oxime **1** into 2-substituted 5-methyl-1*H*-pyrrole **2**. The process is initiated by the oxidative addition of Pd(0) species to **1** to form an alkylideneaminopalladium(II) intermediate **3**. With the complexation of the palladium(II) to the γ,δ-double bond, **3** successively cyclizes in a 5-*exo* mode to afford a σ-complex **4**. Subsequent β-elimination reaction of intermediate **4** provides a hydride–palladium complex **5** as well as 2-methylene-3,4-dihydro-2*H*-pyrrole **6** which is supposed to isomerize into **2**. Meanwhile, a base-promoted elimination reaction of **5** leads to the regeneration of Pd(0) species. According to the literature reports, these reactions were frequently complicated by undesired Beckmann rearrangement, especially when sulfonyloximes were used as substrates.[1a] In addition, some oxime precursors were shown to be unstable upon chromatographic purification, making their routine preparation and application in synthesis problematic.[1a] Furthermore, in some cases, the isomerization of 3,4-dihydro-2*H*-pyrroles into pyrroles (**6** → **2**, Scheme 1) did not occur spontaneously under catalytic conditions,[5] and therefore an additional step involving the acidic reaction conditions was required to effect the isomerization. Due to these limitations, the development of more effective oxime derivatives for the cyclization process appears to be necessary. Herein, we wish to report the first examples of palladium-catalyzed intramolecular amino-Heck reaction of hitherto unexplored γ,δ-unsaturated *O*-diethylphosphinyloximes.



Scheme 1 Proposed mechanism for the amino-Heck reactions of γ,δ-unsaturated oxime derivatives

This new protocol, as described below, provides an entry into a variety of 2-substituted 5-methyl-1*H*-pyrroles as well as several substituted indoles. Moreover, the investigations also allowed us to find some interesting aspects on the regiochemistry of the cyclization process, which have not been revealed by earlier studies.

Initial experiments focused on the cyclization of 1-phenyl-4-penten-1-one *O*-diethylphosphinyloxime (**1a**), which could be readily prepared from benzaldehyde as outlined in Scheme 2. Addition of but-3-enyl magnesium bromide to benzaldehyde afforded alcohol **7**, which was then oxidized to ketone **8** by pyridinium dichromate (PDC) as the oxidizing agent. Treatment of **8** with hydroxylamine hydrochloride ($NH_2OH·HCl$) and sodium acetate (NaOAc) in methanol[7] yielded an *O*-hydroxy-oxime intermediate. Without purification, this compound was subsequently subjected to a coupling reaction with commercially available diethyl cholorophosphate [$(EtO)_2POCl$] by using sodium hydride (NaH) as a base to afford **1a** as a mixture of two isomers in 81% yield (*E*/*Z* = 87:13) after chromato-

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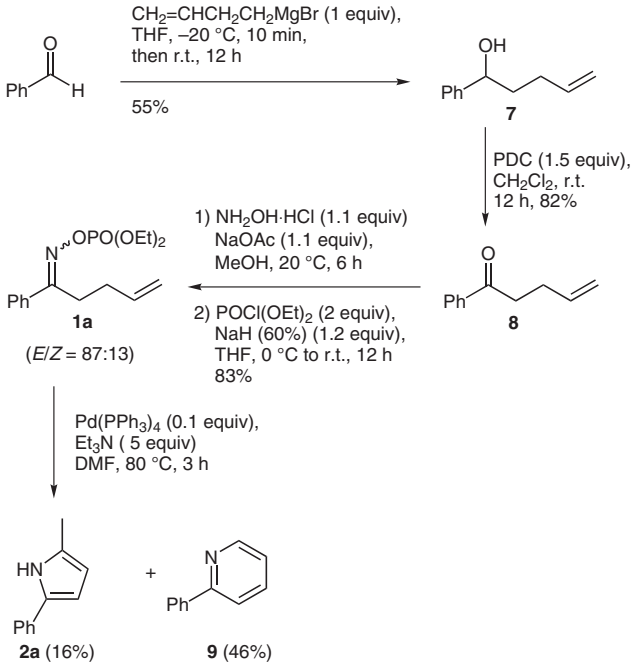
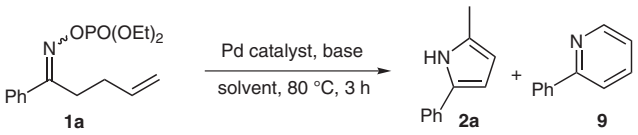
graphic purification on silica gel. Initially, the cyclization reaction of **1a** was performed by using the catalytic conditions [$Pd(PPh_3)_4$ (0.1 equiv), Et_3N (5 equiv), DMF (0.02 M), 80 °C, 3 h] as previously described for 1-phenyl-4-penten-1-one *O*-pentafluorobenzoyloxime.[5] After three hours, the desired product **2a** was observed to form in 16% conversion, together with 46% of 2-phenylpyridine (**9**) and 20% of recovered **1a**. The formation of **9** could be resulted from the 6-*endo* cyclization followed by the dehydrogenation of the resulting dihydropyridine intermediate.[8] Given the same reaction conditions, the regioselectivity in our case stands in marked contrast to that of the reactions previously reported for 1-phenyl-4-penten-1-one *O*-penta-fluorobenzoyloxime and *O*-methylsulfonyloxime,[5] in which the cyclization proceeded exclusively in a 5-*exo* pathway to give a mixture of **2a** and 5-methylidene-2-phenyl-3,4-dihydro-2*H*-pyrrole, and the latter compound could be isomerized into **2a** upon the treatment with chlorotrimethylsilane (TMSCl). To our knowledge, the reaction in Scheme 2 represents the first example of producing pyridinyl derivative from γ,δ-unsaturated ketone oxime derivatives in the absence of a β-acetoxy or alkoxy group or an α,β-double bond, the functionalities so far having shown to be indispensable for generating **9** and its analogues.[1a,9] We speculated that the regiochemical bias observed in our case may be attributed to the unique coordination nature and/or the steric effect of the diethylphosphinyl group. Currently, the studies to disclose the mechanistic intricacies of the regiochemistry are being carried out by us. Additionally, it was found that the stereochemistry of **1a** did not have any influence on the outcome of the cyclization since similar results were obtained when the reactions were carried out independently with the separated *E*,*Z*-isomers.[10] Consequently, we used isomeric mixtures for all of the subsequent investigations.



Scheme 2 Preparation and palladium-catalyzed cyclization of **1a**

We envisaged that the yield of **2a** could be improved with the adjustment of reaction conditions. To this end, several other catalytic systems were screened as illustrated in Table 1 (entries 1–7). The results in Table 1 suggested that the ratio between **2a** and **9** was almost not affected by the increased concentration of **1a** (Table 1, entry 2). Moreover, the use of $Pd(OAc)_2$ combined with Ph_3P also had no significant impact on the ratio (Table 1, entry 3).

Table 1 Optimization of the Reaction Conditions for **2a**



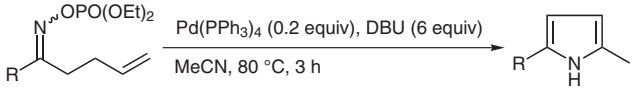
Entry	Conditions[a,b]	Yield (%)[c]		Ratio of **2a/9**
		2a	**9**	
1	$Pd(PPh_3)_4$ (0.1 equiv), Et_3N (5 equiv), DMF (0.02 M)	16	46	26:74
2	$Pd(PPh_3)_4$ (0.1 equiv), Et_3N (5 equiv), DMF (0.05 M)	11	35	24:76
3	$Pd(OAc)_2$ (0.1 equiv), Ph_3P (0.4 equiv), Et_3N (5 equiv), DMF (0.02 M)	8	17	32:68
4	$Pd(PPh_3)_4$ (0.1 equiv), Et_3N (5 equiv), MeCN (0.02 M)	13	3	81:19
5	$Pd(PPh_3)_4$ (0.2 equiv), Et_3N (5 equiv), MeCN (0.02 M)	70	6	92:8
6	$Pd(PPh_3)_4$ (0.2 equiv), K_2CO_3 (5 equiv), MeCN (0.02 M)	19	1	95:5
7[d]	$Pd(PPh_3)_4$ (0.2 equiv), DBU (6 equiv), MeCN (0.02 M)	90	10	90:10

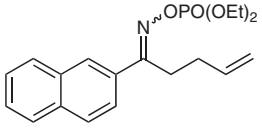
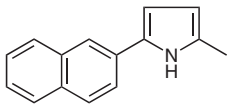
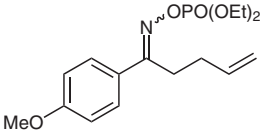
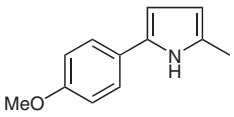
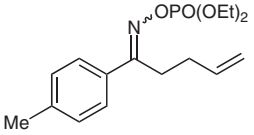
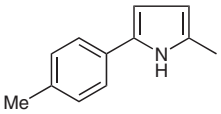
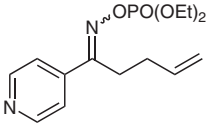
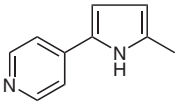
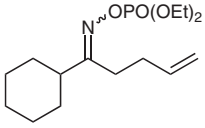
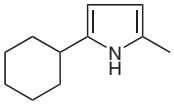
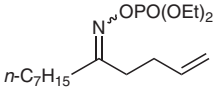
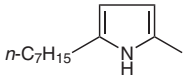
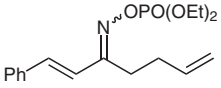
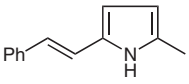
[a] All reactions were performed using one equivalent of **1a**.
[b] Molar concentration refers to that of **1a**.
[c] Isolated yields of purified products.
[d] Using 6 equiv of DBU gave more consistent results than using 5 equiv.

However, as indicated in entry 4, the ratio between **2a** and **9** could be dramatically increased by changing the solvent from DMF to MeCN. Besides, based on the result in entry 4, it was further observed that the yield of **2a** and the ratio between **2a** and **9** could be both improved with the increased loadings of $Pd(PPh_3)_4$ (0.1 equiv → 0.2 equiv; Table 1, entry 5). In addition to the solvents and the catalysts, we also examined two other bases. As shown in entry 6, the use of K_2CO_3 to replace Et_3N resulted in a higher **2a/9** ratio (95:5) but a poorer yield of **2a** (19%) compared with those given in entry 5. Eventually, we found that 90% yield of **2a**, higher than that in the previously reported case,[5] could be obtained when DBU was employed as a base (Table 1, entry 7). The catalytic system indicated in entry 7 [$Pd(PPh_3)_4$ (0.2 equiv), DBU (6 equiv), MeCN (0.02 M)] was then considered the method of choice and consequently applied into a variety of oxime substrates as given in Table 2.

Substrates **1b–h** in Table 2 were similarly prepared in comparable yields from the corresponding aldehydes as that for **1a**.[11] Under the catalytic conditions,[12] most of these compounds (**1b–g**) underwent the cyclization smoothly to provide the corresponding pyrroles in good to high yields (40–90%; Table 2, entries 1–6). In most of the

Table 2 Pd(0)-Catalyzed Amino-Heck Cyclization of 1-Substituted 4-Penten-1-one *O*-Diethylphosphinyloximes

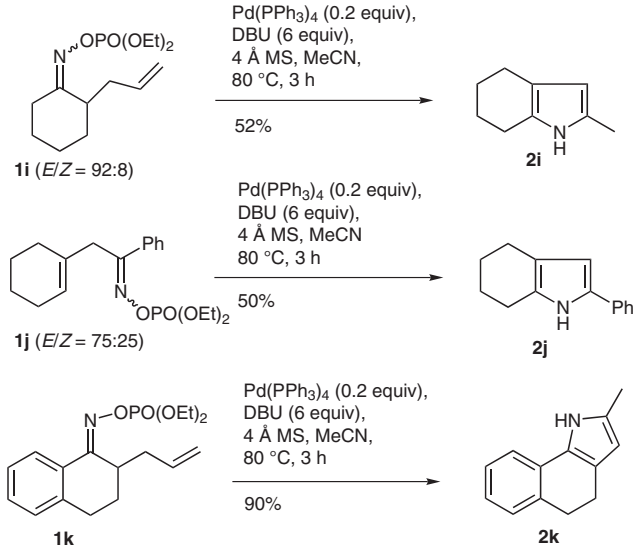


Entry[a]	Substrate[b]	Product[c]	Yield (%)[d]
1	 **1b** (*E*/*Z* = 93:7)	 **2b**	90
2[e]	 **1c** (*E*/*Z* = 70:30)	 **2c**	50
3[e]	 **1d** (*E*/*Z* = 95:5)	 **2d**	60
4[e]	 **1e** (*E*/*Z* = 83:17)	 **2e**	55
5[e]	 **1f** (*E*/*Z* = 69:31)	 **2f**	61
6[e]	 **1g** (*E*/*Z* = 50:50)	 **2g**	40
7[e]	 **1h** (*E*/*Z* = 78: 22)	 **2h**	32

[a] All reactions were carried out using 1 equiv of **1b–h** in a 0.02 M solution.
[b] The *E*/*Z* ratio was determined based on ^1H NMR spectrum.
[c] For characterizations, see: ref. 18 and 19.
[d] Isolated yield.
[e] After optimization, 90 mg of MS 4 Å were used for 1 mmol of oxime.

cases, the addition of a small amount of MS 4 Å to the reaction mixtures was required in order to suppress the formation of ketones derived from the hydrolysis of the oximes[1a,6] (Table 2, entries 2–6).[13] The substituted pyridines arising from the 6-*endo* cyclization were isolated as the major side products (5–25%) in entries 1–6. However, the attempt to cyclize **1h** under the reaction conditions produced **2h** only in a moderate yield (32%) even in the presence of molecular sieves (Table 2, entry 7), along with 30% of the ketone and 19% of the substituted pyridine. It was worthwhile to note that in all cases examined, no trace of products was seen resulting from Beckmann rearrangement, a competitive reaction which was frequently encountered in other reported cases.[1a,5]

The synthetic versatility of the current protocol was further demonstrated by the synthesis of a few 2-substituted indoles from substrates **1i–k**,[14] prepared, respectively, from 2-allyl-cyclohexanone,[15] 2-cyclohex-1-enyl-1-phenyl-ethanone,[16] and 2-allyl-3,4-dihydro-2*H*-naphthalen-1-one[17] following the procedure given in Scheme 1. Upon the subjection to the reaction conditions,[13] these substrates cyclized efficiently to provide **2i–k** in good to high yields (50–90%) as the sole regioisomers (Scheme 3).



Scheme 3 Preparation of **2i–k** via palladium-catalyzed cyclization of diethylphosphinyloximes **1i–k**

The products **2a–k** were all purified by flash chromatography on aluminum oxide. The spectral data (^{1}H NMR, ^{13}C NMR) of the known compounds (**2a–f**,**h–k**) were found to be in good agreement with those reported in the literatures.[18] For **2g**, several spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, MS) were used to establish its structure.[19]

As described above, under the catalytic conditions developed by us, a wide variety of γ,δ-unsaturated *O*-diethylphosphinyloximes could undergo the intramolecular amino-Heck reactions preferentially in a 5-*exo* pathway to afford the substituted pyrroles and the indoles in moderate to high yields. The oxime precursors were all readily prepared and stable enough for chromatographic purification on silica gel. Furthermore, it should be noted that most of these phosphinyloximes may also potentially serve as the substrates for the generation of substituted pyridines provided with suitable catalytic conditions favoring 6-*endo* cyclization. At the present time, the studies to find such reaction conditions and the application of the protocol into the preparation of other types of heterocyclic compounds are ongoing in our group.

Acknowledgment

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References and Notes

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(10) The configurations the *E*,*Z*-isomers were tentatively assigned based on the chemical shifts of the α-methylene protons on the ^{1}H NMR spectrum.
(11) **General Procedure for the Preparation of Diethylphosphinyloximes from the Corresponding Ketones**
To a solution of 1-phenylpent-4-en-1-one (**8**, 317 mg, 1.98 mmol) in MeOH (8 mL), NaOAc (179 mg, 2.18 mmol) and $NH_2OH{\cdot}HCl$ (152 mg, 2.18 mmol) were successively added. The reaction mixture was stirred at 20 °C for 6 h, then diluted with CH_2Cl_2 (30 mL) and washed sequentially with H_2O (2 × 10 mL) and sat. NaCl aq soln (10 mL). After dried over anhyd Na_2SO_4 and concentrated at ambient temperature, the crude hydroxyoxime was dissolved in anhyd THF (13 mL). The solution was cooled to 0 °C and added with NaH (60%, 95 mg, 2.38 mmol). Stirring was continued at 0 °C for another 20 min under N_2, before $(EtO)_2POCl$ (0.61 mL, 3.96 mmol) was added dropwise in 3 min. The reaction mixture was allowed to warm to r.t. and continued to stir for 12 h. After concentration, the crude residue was subjected to chromatographic purification on silica gel (hexane–EtOAc = 5:1 and 1:1) to afford **1a** as a mixture of two isomers (*E*/*Z* = 87:13, 513 mg, 83%).
1-Phenyl-4-penten-1-one *O*-diethylphosphinyloxime (**1a**): IR (neat): 2983, 1276, 1034, 919 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (*Z*-isomer) = 1.30 (td, J_1 = 7.1 Hz, J_2 = 0.7 Hz, 6 H), 2.24 (td, J_1 = 7.2 Hz, J_2 = 6.9 Hz, 2 H), 2.74 (br t, *J* = 7.6 Hz, 2H), 4.10–4.19 (m, 4 H), 4.96–5.09 (m, 2 H), 5.70–5.83 (m, 1 H), 7.31–7.37 (m, 2 H), 7.37–7.48 (m, 3 H); δ (*E*-

isomer) = 1.38 (td, J_1 = 7.1 Hz, J_2 = 0.7 Hz, 6 H), 2.32 (td, J_1 = 7.8 Hz, J_2 = 6.4 Hz, 2 H), 2.95 (br t, J = 7.9 Hz, 2 H), 4.21–4.34 (m, 4 H), 5.00 (br d, J = 11.5 Hz, 1 H), 5.04 (br d, J = 17.1 Hz, 1 H), 5.82 (dm, J = 17.1 Hz, 1 H), 7.37–7.45 (m, 3 H), 7.65 (br d, J = 7.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*Z*-isomer) = 16.1 (d, J = 6.1 Hz), 30.2, 34.7, 64.5 (d, J = 5.5 Hz), 115.8, 127.5, 128.3, 129.6, 132.1, 136.5, 166.9 (d, J = 13.0 Hz); δ (*E*-isomer) = 16.2 (d, J = 6.3 Hz), 27.0, 30.5, 64.6 (d, J = 6.0 Hz), 115.8, 127.1, 128.7, 130.5, 133.6, 136.6, 166.7 (d, J = 13.4 Hz). HRMS–FAB: *m/z* calcd for $C_{15}H_{23}O_4NP$ $[M + H]^+$: 312.1365; found: 312.1357.

(12) **Typical Procedure of the Amino-Heck Reaction for 1a**
Under a nitrogen atmosphere, $Pd(PPh_3)_4$ (89 mg, 0.08 mmol) and DBU (356 mg, 2.34 mmol) were sequentially added to a solution of **1a** (120 mg, 0.39 mmol) in anhyd MeCN (19.3ml) at r.t. The resulting yellow suspension was quickly warmed to 80 °C and continued to stir for 3 h. The mixture was then filtrated through a Celite pad, washed with EtOAc and concentrated. The chromatographic purification of the crude products on aluminum oxide (hexane–EtOAc = 30:1, 10:1, and 5:1) provided **2a** in 90% yield (55 mg) and **9** in 10% yield (6 mg).
5-Methyl-2-phenyl-1*H*-pyrrole (**2a**): IR (neat): 3399, 774, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 5.99 (m, 1 H), 6.44 (t, J = 3.0 Hz, 1 H), 7.19 (t, J = 7.3 Hz, 1 H), 7.36 (t, J = 7.8 Hz, 2 H), 7.45 (br d, J = 8.2 Hz, 2 H), 8.13 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2, 106.2, 108.0, 123.4, 125.7, 128.9, 129.1, 130.8, 133.0. LRMS (MALDI): *m/z* calcd for $C_{11}H_{11}N$ $[M]^+$: 157.1; found: 157.0.
2-Phenylpyridine (**9**): IR (neat): 1735, 1266, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.26 (m, 1 H), 7.40–7.52 (m, 3 H), 7.70–7.79 (m, 2 H), 8.00 (d, J = 7.3 Hz, 2 H), 8.70 (d, J = 4.7 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 120.6, 122.1, 126.9, 128.8, 129.0, 136.7, 139.4, 149.7, 157.5. LRMS (MALDI): *m/z* calcd. for $C_{11}H_{10}N$ $[M + H]^+$: 156.1; found: 156.1.

(13) The reactions were performed similarly as indicated in ref. 12 except for adding 4 Å MS (90 mg/1 mmol) to the solution of oxime before $Pd(PPh_3)_4$ and DBU were introduced.

(14) The *E*/*Z* ratios were tentatively assigned based on ^{1}H NMR spectra.

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(19) As an unknown compound, the spectral data of 2-(1-heptyl)-5-methyl-1*H*-pyrrole (**2g**) are as follows: IR (neat): 3373, 2925, 2854, 765 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.9 Hz, 3 H), 1.22–1.39 (m, 8 H), 1.54–1.66 (m, 2 H), 2.25 (s, 3 H), 2.55 (t, J = 7.7 Hz, 2 H), 5.76 (br s, 1 H), 5.77 (br s, 1 H), 7.56 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 14.1, 22.6, 27.8, 29.1, 29.4, 29.8, 31.8, 104.8, 105.6, 125.8, 131.6. HRMS–FAB: *m/z* calcd for $C_{12}H_{20}N$ $[M – H]^+$: 178.1596; found: 178.1600.