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Palladium-catalyzed addition of R_2NH to double bonds. Synthesis of α-amino tetrahydrofuran and pyran rings

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Abstract—Efficient addition of R^1R^2NH to unsaturated heterocycles has been achieved using palladium catalysts. The methodology was applied to the synthesis of a number of α-amino tetrahydrofurans and pyrans. Nature of amine, ring size and catalyst were found to affect the reaction. Mechanistic aspects of the reactions were explored by deuterium labelling experiments. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The formation of a carbon–nitrogen bond through the direct addition of an N–H bond across an unsaturated bond has long been a challenge to synthetic chemists.[1,2] In our quest to find efficient air and moisture stable metal catalysts for hydroamination reactions under pH neutral conditions, we were particularly attracted by a report in which bis(triphenylphosphite)palladium(II) dithiocyanate catalyzed the hydroamination of morpholine to 2,3-dihydrofuran in 45 turnovers.[3]

The synthesis of α-amino tetrahydrofuran and pyran rings are particularly interesting as 5- and 6-membered functionalised heteroatom rings are found in many nucleosides[4–6] and glycolipids[7] that have interesting biological activities. These molecules are prepared generally from one of two routes: Substitution of a halide or hydroxyl group by an amine, or the hydroamination of a double bond in the presence of an acid or base.[8,9] These methods are limited by the nucleophilicity of the amine, and involve equilibrium processes that lead to modest yields. They also often require fairly harsh reaction conditions, making them unsuitable for the synthesis of fragile molecules.

The idea of employing a palladium catalyst to effect the formation of these molecules is particularly interesting, as the methodology offers hydroamination reactions at pH neutral conditions. As far as we are aware, there is no work reported in the area, so we decided to initiate a study to explore the scope and limitations of the reaction.

Keywords: C–N bond formation; homogeneous catalysis; palladium; amination.

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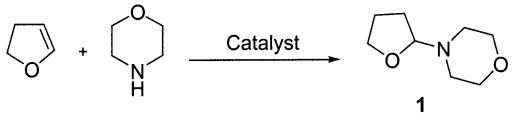
2. Results and discussion

A number of palladium(II) precursors were screened for the reaction between morpholine and 2,3-dihydrofuran (Table 1). We found that the addition of phosphorus ligands is unnecessary and that $K_2Pd(SCN)_4$ is a good catalyst (entry 4); the reaction occurred cleanly at ambient temperature and yielded the desired product regiospecifically. The combination of palladium and thiocyanate seems to imbue special activity, as yields dropped quite dramatically when thiocyanate was substituted by other anions (entries 5–7). Entries 1 and 8 confirm definite involvement of palladium in the process. The thiocyanate anion is envisaged to have an important role, even though its precise coordination mode and function is not known. The addition of excess KSCN to the reaction mixture improves the catalytic turnover, which suggests that this rather unusual anion acts, at least, to stabilize important reaction intermediates.

Table 1. Effect of different catalysts



1

Entry	Catalyst	Time (h)	Temperature (°C)	Yield[a] (%)
1	None	12	80	0
2	$Pd\{P(OPh)_3\}_2(SCN)_2$	12	20	86
3	$Pd(PPh_3)_2(SCN)_2$	12	20	90
4	$K_2Pd(SCN)_4$	12	20	91
5	$Pd(NCMe)_2Cl_2$	16	20	26
6	$Pd(OAc)_2$	16	20	46
7	PdI_2	14	20	29
8	KSCN	24	20	0

Reaction conditions: 2.9 mmol of amine to 2.5 mL of dihydrofuran, substrate/catalyst=45.

[a] Isolated yields.

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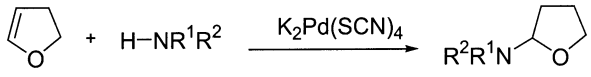
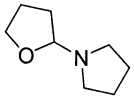
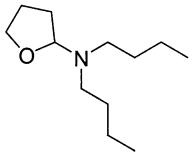
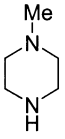
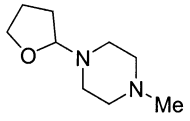
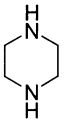
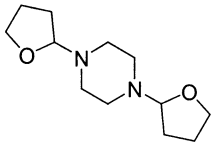
Table 2. Hydroamination of 2,3-dihydrofuran



Entries	Amine	Product	Time (h)	Temperature (°C)	Yield[a] (%)
1		 **2**	16	80	83
2	Bu_2NH	 **3**	16	80	75
3		 **4**	12	20	92
4		 **5**	14	60	75[b]

Reaction conditions: as before. Reaction times are unoptimised (duration of an overnight experiment).
[a] Isolated yields of compounds estimated to be >95% pure by ^{1}H NMR.
[b] Substrate/catalyst=11.25.

The reaction is equally applicable to other secondary alkyl amines, which required no more than gentle or moderate heating (Table 2). The reactions were again regiospecific, giving α-amino substituted tetrahydrofuran as the only observable product. The yields are generally high compared to previously reported methods. For example, under basic conditions, 2,3-dihydrofuran reacts with morpholine and pyrrolidine to give **2** and **3**, in 60 and 45% yields, respectively.[10] However, the reaction only seems to work with secondary alkyl amines, as the use of aryl amines (aniline and *N*-methyl aniline) leads to a mixture of unidentifiable products.

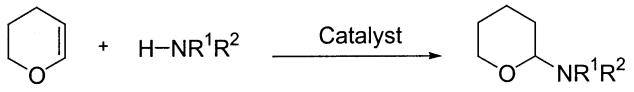
In contrast, the corresponding hydroamination reactions of 2,3-dihydropyran take longer, and occur only at elevated temperatures (Table 3). The yields of these reactions are mostly very high, and seem to be limited by the volatility of the amine (entries **3** and **4**). It is interesting to note that while the phosphine-ligated $[Pd(PPh_3)_2(SCN)_2]$ complex failed to induce any reaction between morpholine and dihydropyran, the introduction of primary and secondary arylamines to the unsaturated pyran ring is possible (entries **5** and **6**). For the latter reactions, the addition of triphenylphosphine ligand was necessary to stabilize the catalyst over the prolonged reaction period and also led to cleaner products. The reaction with aniline gave **10** as the major product, whereas the formation of the methyl substituted **11** was slower and required higher temperature, suggesting that the steric demand imposed by the amine is an important factor.

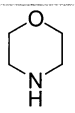
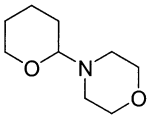
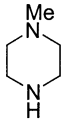
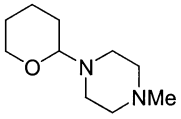
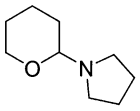
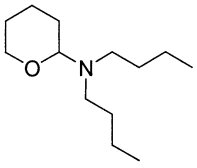
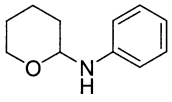
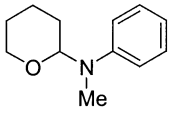
2.1. Mechanism of the catalytic reaction

The reactions did not appear to be acid-catalysed as sulfuric and *p*-toluenesulfonic acids failed to induce *any* reaction between morpholine and 2,3-dihydropyran, even after heating at 60°C for 24 h.

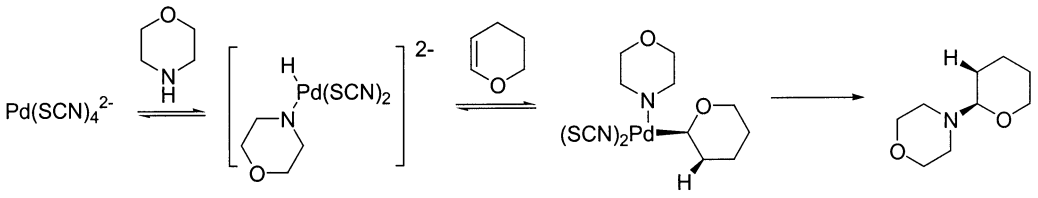
Although transition metal catalysed hydroamination reactions via double bond activation has been proposed,[11] we did not observe any interaction between $K_2Pd(SCN)_4$ and dihydropyran. However, successive addition of measured quantities of morpholine to a solution of $K_2Pd(SCN)_4$ indicated, tentatively, by ^{1}H NMR spectroscopy, the formation of a fluxional and equilibrating mixture of complexes corresponding to a bis(morpholine) palladium dithiocyanate stoichiometry—this seems to agree with the result of a previous study, where a palladium complex with the same stoichiometry has also been proposed as the resting state of an intramolecular hydroamination reaction.[12] We thus

Table 3. Hydroamination of 3,4-dihydro-2H-pyran



Entry	Amine	Product	Catalyst[a]	Time (h)	Temp (°C)	Yield[b] (%)
1		 **6**	**A**	12	80	98
2		 **7**	**A**	12	80	96
3		 **8**	**A**	16	70	52
4	Bu_2NH	 **9**	**A**	16	100	82
5	$PhNH_2$	 **10**	**B**	40	80	74
6	PhNHMe	 **11**	**B**	48	100	84

Reaction conditions as before.
[a] Catalyst **A**: $K_2Pd(SCN)_4$; **B**: $Pd(PPh_3)_2(SCN)_2$.
[b] Isolated yields.



Scheme 1. Proposed mechanism.

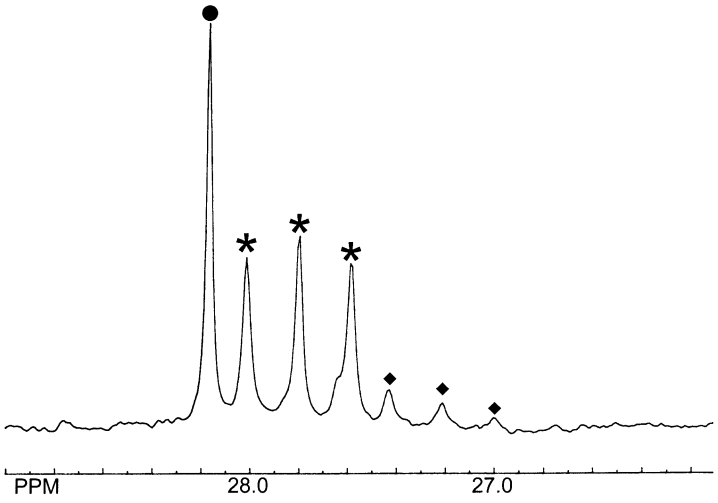
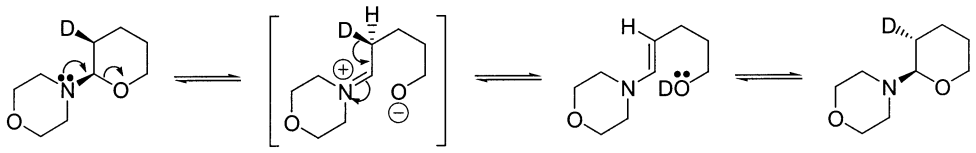


Figure 1. Isotopic-labeling experiment. $^{13}C-\{^1H\}$ NMR spectrum showing the resonance due to C3: ●6 (singlet); ∗*D*-6 (triplet); ◆ D_2-6 (quintet, partially obscured). The $^{13}C-\{^1H\}$ NMR spectrum was acquired with suitably long relaxation delays to minimize noe effects.



Scheme 2. Ring opening and closure via an enamine intermediate.

suggest a mechanism that involves transient hydridopalladium complexes (Scheme 1). The proposal is supported by the known regiochemistry of Pd–H insertion to unsaturated furan rings.[13]

To investigate the mode of N–H addition, catalytic hydroamination reaction of 2,3-dihydropyran was performed with 1-*deuterio*-morpholine in 10 molar excess of the pyran. Integration of the corresponding ^1H signals of the resultant product revealed that there is an apparent *absence of exactly one proton at the C3 position*. This observation strengthens our belief that an oxonium intermediate is not involved in the reaction, as this will invariably lead to deuterium being incorporated into dihydropyran, which was present in excess.

On closer inspection, the ^{13}C NMR spectrum of the same sample revealed the presence of the mono-deuterio compound, as well as di-hydro and di-deuterio isomers of **6** (Fig. 1). This was confirmed by the analysis of the parent peaks of the three isomers by mass spectrometry, which revealed an equal distribution of all three isomers: *m/z* (FAB): 171 (no deuterium, 77.5%), 172 (one deuterium, 100%) and 173 (two deuteriums, 83.9%), which is roughly 1:1:1 (taking into account ^{13}C isotopic distribution). This led us to suspect that the product undergoes an intermolecular exchange process, which leads to the scrambling of the deuterium isotope. Indeed, when a solution of **6** was heated to 60°C in methanol-d^4, we observed a slow incorporation of deuterium label onto C-3 as the intensity of the H-3 signal decreased.

Thus we propose the operation of a ring-opening process as depicted in Scheme 2. The process is akin to the mutarotation process (anomeric effect) of tetrahydropyran derivatives,[14,15] and is a fairly common phenomenon for glycosylamines and amides.[7] In this case the tetrahydropyran ring opens and closes via an enamine intermediate, leading to the scrambling of deuterium labels at C-3. Note that in the reaction mixture this process will be occurring in the presence of an excess of dihydropyran. As no deuterium label was lost from the product, it rules out the involvement of an oxonium intermediate.

3. Conclusion

In conclusion, a range of α-alkylamine tetrahydrofurans, as well as α-alkyl and α-arylamino-tetrahydropyrans can be synthesized under pH neutral conditions by a hydroamination reaction catalysed by palladium thiocyanate complexes. The α-aminotetrahydropyran rings are found to undergo rapid reversible ring opening in solution. Further applications of the reaction are currently being investigated.

4. Experimental

4.1. General

Proton and carbon NMR spectra were recorded for solutions in deuteriochloroform, using Bruker AM360 or AMX400 spectrometers. ^1H NMR data of known compounds are in agreement with reported values, which were quoted accordingly. The chemical shifts are in parts per million (δ ppm), unless otherwise stated, referenced to TMS (δ 0). The coupling constants are in Hertz (J Hz). The following abbreviations are used: s—singlet, t—triplet,

q—quartet, m—multiplet, d—doublet, br—broad. Melting points were determined on an Electrothermal Gallenhamp melting point apparatus and are uncorrected. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded using the FAB technique by the Mass Spectrometry Service within The University of London's Intercollegiate Research Services (ULIRS). Mass data are reported in mass units (*m*/*z*), and values in brackets show the relative intensity from the base peak (as 100%).

4.1.1. Potassium *tetrakis*(thiocyanate)palladium(II).[16] The compound was prepared by a modified procedure: $PdCl_2(NCMe)_2$ (0.26 g, 1.0 mmol) was added to a solution of potassium thiocyanate (0.39 g, 4.0 mmol) in acetone (15 mL), and the reaction mixture was refluxed for 30 min. The product crystallized as a red solid upon cooling. It was collected by filtration, and washed with acetone (2×5 mL). A second crop of product was obtained by slow evaporation of the filtrate. Yield 0.41 g (99%). ν_{max} (KBr disc)[18] ν(C≡N) 2122, 2093 cm^{-1}.

4.2. Typical experimental procedure (Table 1, entry 3)

To a mixture of 2,3-dihydrofuran (2.5 mL, 33 mmol) and morpholine (250 mg, 2.9 mmol) was added potassium *tetrakis*(thiocyanate)palladium(II) (26 mg, 0.06 mmol). The reaction mixture was stirred at 20°C overnight. The volatile reagents were then removed under reduced pressure, and petroleum ether (40–60, 30 mL) was added to the residue. The precipitate was removed by filtration, and the filtrate concentrated under reduced pressure. The crude product was purified by distillation to give **1** (410 mg, 91% yield).

4.2.1. 4-(Tetrahydrofuran-2-yl)-morpholine, 1. Colourless oil. bp 56°C/0.6 Torr (lit.[10] 76–77°C/4 Torr). ν_{max} (liquid film) 2954, 1454, 1261, 1040 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.75–2.00 (m, 4H), 2.50 (m, 2H), 2.70 (m, 2H), 3.65 (m, 4H), 3.70 (m, 1H), 3.83 (m, 1H), 4.50 (br. m, 1H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 25.9, 28.4, 48.5, 67.4, 68.3, 96.3.

4.2.2. 1-(Tetrahydrofuran-2-yl)-pyrrolidine, 2. Colourless oil. bp 65–67°C/4.5 Torr (lit.[10] 90–93°C/34 Torr). ν_{max} (liquid film) 2061, 1467, 1352, 1003 cm^{-1}. ^{1}H NMR[10] (360 MHz, $CDCl_3$) δ: 1.68–1.98 (m, 8H), 2.63–2.74 (m, 4H), 3.73–3.85 (m, 2H), 4.69 (t, *J*=5.8 Hz, 1H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 23.8, 25.4, 29.9, 47.8, 67.8, 93.4.

4.2.3. Dibutyl-(tetrahydrofuran-2-yl)-amine, 3. Colourless oil. bp 67–69°C/0.7 Torr (lit.[10] 112–115°C/12 Torr). ν_{max} (liquid film) 2953, 1465, 1376 cm^{-1}. ^{1}H NMR[10] (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*=7 Hz, 6H), 1.23–1.46 (m, 8H), 1.62–1.94 (m, 4H), 2.54 (m, 4H), 3.60–3.89 (2H, m), 4.81 (t, *J*=6.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.4, 21.0, 25.9, 29.4, 31.6, 50.0, 67.4, 95.6.

4.2.4. 1-Methyl-4-(tetrahydrofuran-2-yl)-piperazine, 4. Colourless oil. bp 75–77°C/1.8 Torr. ν_{max} (liquid film) 2936, 1455, 1371, 1286 cm^{-1}. At ambient temperature the methine proton and carbon signals were very broad in the NMR spectra, probably due to conformational ring flip of the nitrogen heterocycle. The signals sharpened at higher temperature (334 K). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.72–1.88 (m, 4H), 2.17 (s, 3H), 2.20–2.40 (m, 4H), 2.41–2.60 (m, 2H), 2.65–2.71 (m, 2H), 3.65 (dd, *J*=6, 13 Hz, 1H), 3.76 (dd, *J*=7, 13 Hz, 1H), 4.48 (t, *J*=5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, 298 K) δ: 25.9, 28.7, 46.4, 48.0 (br.), 55.5, 68.3, 96.0. HRMS calculated for $C_9H_{18}N_2O$ 170.1419, observed 170.1431.

4.2.5. 1,4-Bis-(tetrahydrofuran-2-yl)-piperazine, 5. Colourless crystalline solid. mp 77–78°C. ν_{max} (Nujol) 2902, 1461, 1376 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.73–1.96 (m, 8H), 2.48–2.57 (m, 4H), 2.67–2.79 (m, 4H), 3.66–3.73 (m, 2H), 3.76–3.83 (m, 2H), 4.50–4.56 (m, 2H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 25.6, 28.4, 47.7, 68.0, 95.7. Found: C, 63.65; H, 9.80; N, 12,25. $C_{12}H_{22}N_2O_2$ requires C, 63.70; H, 9.80; N, 12.40%. HRMS calculated for $C_{12}H_{22}N_2O_2$ 226.1682, observed 226.1680.

4.2.6. 4-(Tetrahydropyran-2-yl)-morpholine, 6. Clear oil. bp 58–60°C/0.8 Torr (lit.[17] 111.5°C/12 Torr). ν_{max} (liquid film) 2943, 2849, 1453, 1008 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.40–1.70 (m, 5H), 1.81–1.95 (m, 1H), 2.58 (m, 2H), 2.86 (m, 2H), 3.43 (m, 1H), 3.62–3.74 (m, 4H), 3.77 (m, 1H), 3.98 (dd, *J*=3, 11 Hz, 1H). ^{13}C NMR (90.5 MHz, $CDCl_3$, 298 K) δ: 23.4, 25.7, 28.3, 48.1, 67.2, 67.4, 93.6.

4.2.7. 1-Methyl-4-(tetrahydropyran-2-yl)-piperazine, 7. Clear oil. bp 76–78°C/1 Torr ν_{max} (liquid film) 2936, 1456, 1373, 1009 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33–1.51 (m, 5H), 1.77 (m, 1H), 2.16 (s, 3H), 2.20–2.42 (m, 4H), 2.46–2.57 (m, 2H), 2.71–2.83 (m, 2H), 3.31 (m, 1H), 3.68 (m, 1H), 3.86 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 23.8, 26.2, 28.9, 46.5, 47.9, 55.8, 67.8, 93.8. HRMS calculated for $C_{10}H_{20}N_2O$ 184.1575, observed 184.1582.

4.2.8. 1-(Tetrahydropyran-2-yl)-pyrrolidine, 8. Clear oil. bp 58–59°C/2.2 Torr (lit.[17] 85.5°C/9.5 Torr). ν_{max} (liquid film) 2042, 1448, 1290, 1072 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40–1.51 (m, 4H), 1.61–1.80 (m, 6H), 2.63–2.69 (m, 2H), 2.75–2.81 (m, 2H), 3.33 (m, 1H), 3.85–3.90 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 23.4, 24.0, 25.8, 31.0, 47.2, 66.8, 90.5.

4.2.9. Dibutyl-(tetrahydropyran-2-yl)-amine, 9. Clear oil. bp 65–66°C/0.4 Torr (lit.[17] 119.5–120°C/10.5 Torr). ν_{max} (liquid film) 2933, 1465, 1376, 1076 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.89 (t, *J*=7 Hz, 6H), 1.21–1.70 (m, 13H), 1.81–1.90 (m, 1H), 2.50–2.60 (m, 2H), 2.62–2.74 (m, 2H), 3.37 (m, 1H), 3.95 (m, 2H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 14.0, 20.5, 24.3, 26.5, 30.5, 31.8, 50.1, 67.7, 92.5.

4.2.10. Phenyl-(tetrahydropyran-2-yl)-amine, 10. Colourless crystalline solid. mp 73–74°C, bp 112–114°C/5 Torr (lit.[17] 114°C/5 Torr). ν_{max} (Nujol) 3350, 2970, 1604, 1376 cm^{-1}. ^{1}H NMR[18] (360 MHz, $CDCl_3$) δ: 1.45–1.72 (m, 4H), 1.86–1.95 (m, 2H), 3.56 (m, 1H), 3.99 (m, 1H), 4.28–4.30 (br. d, 1H), 4.69 (dd, *J*=2, 9 Hz, 1H), 6.72–6.80 (m, 3H), 7.19 (dd, *J*=7, 8 Hz, 2H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 23.0, 25.3, 31.8, 65.8, 82.4, 113.9, 118.7, 129.2, 145.5.

4.2.11. Methyl-phenyl-(tetrahydropyran-2-yl)-amine, 11. Pale yellow oil. bp 94–98°C/0.4 Torr (lit.[19] 101°C/0.5 Torr). ν_{max} (liquid film) 2941, 1599, 1503 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ: 1.53–2.07 (m, 6H), 3.03 (s, 3H), 3.65 (m, 1H), 4.12 (m, 1H), 4.81 (m, 1H), 6.89 (t, J=7 Hz, 1H), 6.98 (d, J=9 Hz, 2H), 7.32 (dd, J=7, 9 Hz, 2H). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 24.2, 25.7, 30.0, 32.5, 67.7, 89.0, 115.4, 118.8, 129.0, 149.9.

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