Palladium-Catalyzed Cyclization of *N*-*n*-Butyl, *N*-(*o*-Iodobenzyl)-3-butenamides: Six- versus Seven- and Eight-membered Ring Formation

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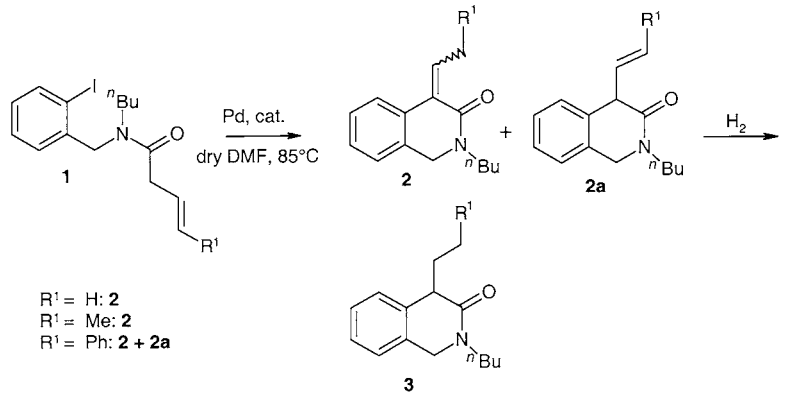
Abstract: The regiochemistry of the palladium-catalyzed annulation of *N*-*n*-butyl, *N*-(*o*-iodobenzyl)-3-butenamides **1** can be dramatically varied by addition of water to the reaction mixture. In anhydrous DMF **1** lead to 6-membered ring formation, while in aqueous DMF 7/8-membered rings were formed. The water effect was also observed in MeCN and THF.

Key words: palladium catalysis, cyclization, medium-sized rings, regioselectivity, water

Palladium-catalyzed intramolecular arylation of a carbon-carbon double bond has become an important and general tool in the synthesis of carbo- and heterocycles.[1] Being interested into benzazepine and benzodiazepine synthesis by metal-catalysed seven-membered ring formation from properly *o*-substituted iodoarenes,[2] we carried out a study on palladium-catalyzed intramolecular cyclisation of *N*-*n*-butyl, *N*-(*o*-iodophenylmethyl)amides (**1**) of organic acid (3-butenoic, 3-pentenoic, 4-phenyl-3-butenoic acid) chlorides, respectively. In the presence of $Pd(OAc)_2/Ph_3P$ as a catalyst, *n*-Bu_4NOAc as a base in dry DMF[3] at 85 °C compounds **1** underwent 6-membered ring cyclization leading to (*E*)-(*Z*)-1,4-dihydro-2*H*-isoquinolin-3-one derivatives **2** (1/1, molar ratio). In the case of R^1 = Ph, the isomer (*E*)-**2a** was also obtained in addition to **2** *E* and *Z* (1/1/1, molar ratio) (Scheme 1 and Table 1, entries 1, 3, 5).[4] They were catalytically hydrogenated to **3**[4] in the presence of Pd/C (Scheme 1).

Surprisingly, the regioselectivity of annulation changed dramatically if water was present in the reaction mixture. With a DMF–water mixture (10/1, v/v) the reaction proceeded through *exo* and *endo* insertion of the terminal carbon-carbon double bond leading to 7- and 8-membered ring formation (Scheme 2). In particular, compounds **1** (R^1 = H, Me) led to the isomeric 1*H*-2-benzazepin-3-one derivatives **4**, **4a** and dihydro-2*H*-2-benzazocin-3-ones **5** and **5a** (Table 1, entries 2, 4). With **1** (R^1 = Me) 2-benzazepine derivative **4b** bearing a vinyl substituent on C-5 carbon atom was also obtained. Compound **1** (R^1 = Ph) transformed regioselectively into **4**, **4a** (entry 6). Particularly in the cases of R^1 = H, Me the mixture of isomeric Heck products turned out to be difficult to separate by flash chromatography. Base treatment of the crude obtained from **1** (*t*-BuOK, DMF, 80 °C, 18 h) allowed the transformation into the thermodynamically more stable compounds **4a** and **5a** (Scheme 2), which could be separated and characterized.[5]

Remarkably, the yields of *endo* cyclization products steadily decrease with more sterically hindered R^1 groups, as shown by comparing *exo*/*endo* (**4**/**5**) product ratios obtained with R^1 = H (62/38), R^1 = Me (87/13) and R^1 = Ph (100/0).



Scheme 1 6-Membered ring cyclization products obtained in anhydrous DMF

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Table 1 Palladium-Catalyzed Cyclization of **1**[a]

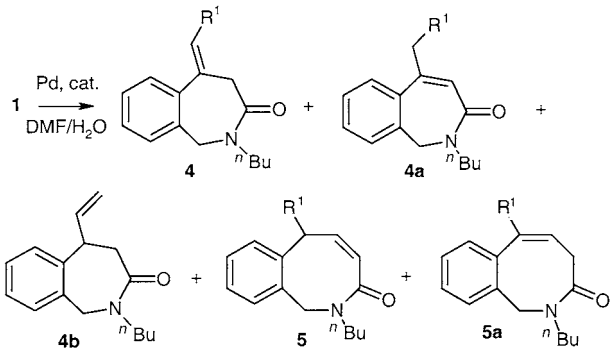
	Substrate **1**	Solvent	Time (h)	Yield[b] (%)	Product ratio[c] **2**–**2a**/**4**–**4a**/**5**–**5a**
1	R^1 = H	DMF	2	60	100/–/–
2	R^1 = H	DMF/H_2O[d]	2	87[e]	–/62/38
3	R^1 = Me	DMF	20	49[f]	96/4/–
4	R^1 = Me	DMF/H_2O[d]	2.5	76[e]	–/87/13[g]
5	R^1 = Ph	DMF	2	50	100/–/–
6	R^1 = Ph	DMF/H_2O[d]	2.5	62[e]	–/100/–
7	R^1 = H	MeCN	2.5	55	90/4/6
8	R^1 = H	MeCN/H_2O[d]	3	85	–/72/28
9	R^1 = Ph	MeCN	3	52	100/–/–
10	R^1 = Ph	MeCN/H_2O[d]	2.5	73	–/100/–
11	R^1 = H	THF	20[h]	62	100/–/–
12	R^1 = H	THF	5[h]	n.d.	100/–/–[i]
13	R^1 = H	THF/H_2O[d]	5[h]	72	9/68/23
14	R^1 = Ph	THF	3[h]	58	100/–/–
15	R^1 = Ph	THF/H_2O[d]	4[h]	66	–/100/–
16	R^1 = H	DMF	2	62[j]	30/30/40
17	R^1 = H	DMF	1	53[k]	–/35/65

[a] Reactions were run with 10% mol $Pd(OAc)_2$, 20% mol Ph_3P, 2.5 equiv *n*-Bu_4NOAc, [**1**] = 0.05 M, at 85 °C (unless otherwise indicated) for the time required for complete conversion of **1**.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis of the crude.
[d] 10/1, v/v.
[e] Isolated yield after *t*-BuOK treatment of the crude, in DMF at 80 °C for 18 h.
[f] 6% of the starting material was recovered.
[g] Determined by ^1H NMR analysis of the crude, after *t*-BuOK treatment.
[h] At reflux.
[i] ^1H NMR analysis of the reaction mixture after 5h showed the presence of (*E*)-(*Z*)-**2** (15%), and *iso*-**1** (85%).
[j] Reaction was run with 2.5 mol% of Herrmann catalyst.[9]
[k] Reaction was run with 2.5 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$ and 10 mol% of (*o*-Tol)$_3$P, at 65 °C.

Independently of the substituents (R^1 = H, Me, Ph) substrates **1** show a similar behaviour in DMF, both under anhydrous and aqueous conditions. The palladium-catalyzed annulations of the model compounds **1** (R^1 = H, Ph), were also carried out in other solvents such as MeCN and THF. Under anhydrous conditions 6-membered ring cyclization was largely or completely favoured (entries 7, 9, 11, 14), whereas the addition of water caused highly or completely selective 7-/8-membered ring formation (entries 8, 10, 13, 15). Under dry conditions the reactions proceeded with lower yields due to alteration of the first products formed.

A reasonable hypothesis to account for these results is that the reaction of **1** proceeded through different pathways depending on double bond isomerization. If no isomerization of **1** occurs the reaction proceeds through the well established pathway of oxidative addition to palladium(0) followed by ring closure and H-elimination to afford seven and eight-membered rings **4**–**4b** and **5**–**5a**. If **1** first isomerizes to *iso*-**1**, six-membered rings **2** and **2a** are formed (Scheme 3).

To prove this point *iso*-**1** (R^1 = H) was synthesized and treated with $Pd(OAc)_2/Ph_3P$ as catalyst, *n*-Bu_4NOAc as a base in anhydrous DMF. The reaction gave **2**, isolated in 56% yield. This implies an intramolecular reaction of the Pd-C bond with the double bond carbon α to the carbonyl group. Apparently, the intramolecular 6-ring formation makes up for the unfavorable electronic situation[1] (Scheme 3).



R^1 = H: **4** + **4a** + **5** + **5a**
R^1 = Me: **4** + **4a** + **4b** + **5** + **5a**
R^1 = Ph: **4** + **4a**

Scheme 2 7-, 8-Membered ring cyclization products obtained in aqueous DMF. With R^1 = Me a 2-benzazepine derivative bearing a vinyl substituent on the C-5 carbon atom (**4b**) also formed

The question now arises whether the isomerization of **1** is base-catalyzed or proceeds at the level of the palladium complex resulting from oxidative addition, probably through an η^3-allylpalladium complex.[6] Our experiments support the first hypothesis. Compounds **1** (R^1 = H, Me) treated with *n*-Bu_4NOAc at 85 °C under anhydrous conditions and in the absence of palladium catalyst, isomerized into the thermodynamically more stable compounds *iso*-**1**. No evidence of *iso*-**1** (R^1 = Ph) was observed under the same conditions. This is due to the stabilizing effect of the phenyl group on the β,γ position of the side chain double bond.[7] In this case base-catalyzed formation of the less stable isomer *iso*-**1** (R^1 = Ph) must occur under kinetic control to allow formation of the 6-membered ring. By contrast, in aqueous DMF compounds **1** treated with *n*-Bu_4NOAc at 85 °C turned out to be stable.

The intermediacy of *iso*-**1** in the palladium-catalyzed reactions was proved in the case of **1** (R^1 = H). As shown in Table 1 (entries 11 and 12), under anhydrous conditions in THF **1** (R^1 = H) was converted into **2** in 20 hours. After 5 hours **2** (15%) was present together with *iso*-**1** (85%). Apparently, the addition of water caused a decreased medium basicity thus preventing the isomerization process.[8]

Replacing *n*-Bu_4NOAc with other bases such as MgO and Na_2CO_3 in anhydrous DMF, led to 6-membered rings **2** (R^1 = H), deriving from isomerization to *iso*-**1** (less than 20%) to a low extent. Again, their formation could be completely suppressed by water addition.

Interestingly, the water effect was curtailed in the presence of a more active catalyst. With Herrmann palladacycle[9] or $Pd_2(dba)_3$/(*o*-Tol)$_3$P·$CHCl_3$ as catalyst, the reaction of **1** (R^1 = H) in anhydrous DMF led to 7-/8-membered rings with high or complete regioselectivity (entries 16, 17). The substrate ability to undergo base-catalyzed isomerization being unaltered, we argue that **1** (R^1 = H) must undergo palladium-catalyzed annulation at higher rate than isomerization to *iso*-**1**. If performed in aqueous DMF under the same conditions the last two reactions again led to **4**, **4a** and **5**, **5a** with complete regioselectivity and improved yields (90%, 81%).

In summary, we have shown that with $Pd(OAc)_2$/Ph_3P as a catalyst the regiochemistry of the cyclization of **1** can be determined by the presence or absence of water. The α-, β-, and γ-carbon atoms of the 3-butenamide chain of **1** can be selectively involved in the palladium-catalyzed intramolecular carbon-carbon coupling, giving rise to 6-membered rings (isoquinoline) in the absence of water, or seven-membered (2-benzazepine) and 8-membered (2-benzazocine) rings in its presence. These nuclei are related to pharmacologically interesting compounds.[10]

Since the $Pd(OAc)_2$ system in the presence of *n*-Bu_4NOAc is largely used in organic synthesis our results may have implications in all cases where medium basicity affects substrate reactivity.

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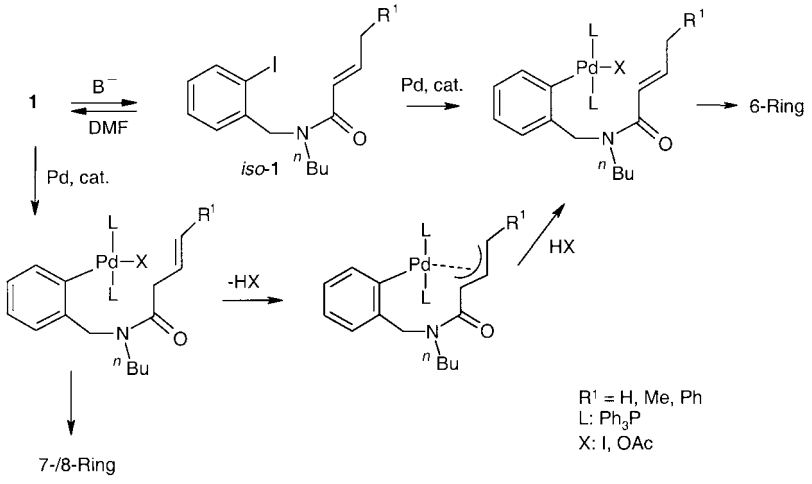

Scheme 3 Proposed isomerization pathways of **1**

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(4) **Palladium-catalyzed Cyclization of 1 in Dry DMF: Synthesis of 1,4-Dihydro-2*H*-isoquinolin-3-ones (3):** *n*-Bu_4NOAc (173 mg, 0.575 mmol) was placed in a Schlenk-type flask and stirred under vacuo at 110 °C for 2 h in order to remove water. After cooling to r.t. **1** (0.23 mmol), $Pd(OAc)_2$ (5.2 mg, 0.023 mmol), Ph_3P (12 mg, 0.046 mmol) and dry and degassed DMF (the content of water was ≤0.005%) (4.6 mL, 0.05 M) were added under nitrogen. The mixture was heated at 85 °C under stirring until the conversion was complete (monitored by TLC). The reaction mixture was cooled, diluted with water (10 mL) and extracted with diethyl ether (3 × 5 mL). After drying (Na_2SO_4) and removal of the solvent the residue was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum ether) leading to (*E*), (*Z*)-**2** (R^1 = H, 1/1, 60% yield), (R^1 = Me, 1/1, 49% yield), (*E*), (*Z*)-**2** and (*E*)-**2a** (R^1 = Ph, 1/1/1, 50% yield), respectively (Table 1, entries 1, 3, 5; the configuration of **2** was determined by NOESY experiments). Due to their instability **2** and **2a**, were submitted to catalytic reduction with 10% Pd/C (25–30% mol) under 1 atm of hydrogen in EtOAc for 24 h. After usual work-up and purification of the crude by flash chromatography on silica gel (EtOAc/petroleum ether) compounds **3** were obtained.
3 (R^1 = H): Oil, yield: 72%; IR (neat): 2961, 2931, 2872, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, 3 H, *J* = 7.53 Hz), 0.87 (t, 3 H, *J* = 7.6 Hz), 1.22–1.34 (m, 2 H), 1.47–1.57 (m, 2 H), 1.71–1.86 (m, 2 H), 3.24–3.34 (m, 1 H), 3.39 (t, 1 H, *J* = 6.86 Hz), 3.55–3.65 (m, 1 H), 4.17 (d, 1 H, *J* = 15.8 Hz), 4.59 (d, 1 H, *J* = 15.8 Hz), 7.05–7.20 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1, 13.8 (Me), 20.1, 27.1, 29.4, 46.9 (CH_2), 49.0 (CH), 50.4 (CH_2), 125.1, 126.4, 127.3, 127.6 (CH), 131.2, 136.6, 171.6 (C_{quat}); Ms (EI): *m/z* (%) = 231(12) [M^+], 202(100), 160(50), 146(25), 132(60), 117(55), 91(20). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N 6.05. Found: C, 78.02; H, 9.14; N, 6.12.
3 (R^1 = Me): Oil, yield 68%; IR(neat): 2959, 2929, 2871, 1647 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 0.76 (t, 3 H, *J* = 7.3 Hz), 0.80 (t, 3 H, *J* = 7.3 Hz), 1.13–1.2 (m, 4 H), 1.40–1.6 (m, 4 H), 3.17–3.20 (m, 1 H), 3.30 (t, 1 H, *J* = 7.0 Hz), 3.43–3.52 (m, 1 H), 4.26 (d, 1 H, *J* = 16.1 Hz), 4.56 (d, 1 H, *J* = 16.1 Hz), 7.10–7.20 (m, 4 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.0 (2 C), 19.8 (2 C), 29.2, 35.2, 45.9, 47.3, 49.5, 125.7, 126.6, 127.4 (2 C), 132.3, 137.1, 170.6; Ms (EI): *m/z* (%) = 245(15) [M^+], 203 (100), 174 (30), 146 (15), 131 (30), 117 (15), 91 (10). Anal Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N 5.71. Found: C, 78.14; H, 9.59; N, 5.78.
3 (R^1 = Ph): Oil, yield: 70%; IR(neat): 2957, 2928, 2860, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, 3 H, *J* = 7.3 Hz), 1.35 (sextet, 2 H, *J* = 7.4 Hz), 1.59 (quintet, 2 H, *J* = 7.5 Hz), 1.96–2.20 (m, 2 H), 2.65 (t, 2 H, *J* = 8.3 Hz), 3.32–3.42 (m, 1 H), 3.60–3.72 (m, 2 H), 4.26 (d, 1 H, *J* = 15.8 Hz), 4.67 (d, 1 H, *J* = 15.8 Hz), 7.14–7.31 (m, 9 H);^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (Me), 20.1, 28.9, 32.9, 35.3, 46.9 (CH_2), 47.5 (CH), 50.4 (CH_2), 125.3, 125.9, 126.5, 127.4, 127.5, 128.3, 128.4 (CH), 131.3, 136.7, 141.4, 171.3 (C_{quat}); MS (EI): *m/z* (%) = 306(75) [M – 1], 214(90), 203(100), 158(25), 91(90). Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.32; H, 8.19; N, 4.61.

(5) **Palladium-catalyzed Cyclization of 1 in Aqueous DMF: Synthesis of 2,3-Dihydro-1*H*-2-benzazepin-3-ones (4a) and 1,4-Dihydro-2*H*-2-benzazocin-3-ones (5a).** In a Schlenk-type flask nBu_4NOAc (173 mg, 0.575 mmol), $Pd(OAc)_2$ (5.2 mg, 0.023 mmol), Ph_3P (12.1 mg, 0.046 mmol), a solution of **1** (0.23 mmol) in degassed DMF (4.2 mL), degassed water (0.42 mL) were added under nitrogen. The mixture was heated at 85 °C under stirring until the conversion was complete (TLC), then worked-up as described in ref.[3] The crude obtained was dissolved in dry DMF (3.0 mL) and added with *t*-BuOK (28 mg, 0.25 mmol). The resulting mixture was heated under stirring at 80 °C for 18 h. After cooling it was poured into water (7 mL) and extracted with ether (3 × 4 mL). The combined organic layer was dried (Na_2SO_4) and evaporated under vacuo. The crude was purified by flash chromatography on silica gel (EtOAc/petroleum ether) to give in order of elution **5a** (R^1 = H, Me) and **4a** (R^1 = H, Me, Ph).
5a (R^1 = H): Mp 41–42 °C (*n*-hexane/EtOAc); IR (nujol): 1737, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, *J* = 7.3 Hz), 1.3 (sextet, 2 H, *J* = 7.4 Hz), 1.49–1.59 (m, 2 H), 3.33–3.40 (m, 4 H), 4.45 (s, 2 H), 5.8 (ddd, 1 H, *J* = 12.6, 6.4, 6.4 Hz), 6.55 (d, 1 H, *J* = 12.6 Hz), 7.16–7.32 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (Me), 20.1, 29.5, 38.9, 45.1, 51.9 (CH_2), 125.7, 127.6, 128.4, 130.1, 131.6, 131.8 (CH), 135.0, 136.5, 168.7 (C_{quat}); MS (EI): *m/z* (%) = 229(60) [M^+], 186(30), 129(100), 115(40). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.48; H, 8.41; N, 6.15.
4a (R^1 = H): Oil; IR (neat): 2931, 2872, 1737, 1636, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, 3 H, *J* = 7.3 Hz), 1.20–1.27 (m, 2 H), 1.47–1.57 (m, 2 H), 2.29 (s, 3 H), 3.44–3.49 (m, 2 H), 3.7–4.5 (br s, 2 H), 6.4 (s, 1 H), 7.25–7.48 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (Me), 19.9 (CH_2), 23.9 (Me), 30.5, 47.1, 51.6 (CH_2), 125.5, 126.9, 127.2, 128.2, 128.8 (CH), 137.1, 137.7, 143.0, 166.4 (C_{quat}); MS (EI): *m/z* (%) = 229(80) [M^+], 187(90), 173(100), 159(60), 129(85), 115(55). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.75; H, 8.15; N, 5.99.
5a (R^1 = Me): Oil; IR(neat): 2958, 2927, 2871, 1728, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, *J* = 7.3 Hz), 1.25–1.37 (m, 2 H), 1.50–1.63 (m, 2 H), 2.06 (s, 3 H), 2.64 (d, 2 H, *J* = 8.0 Hz), 3.49 (pst, 2 H, *J* = 7.49 Hz), 4.16 (s, 2 H), 5.62 (br t, 1 H, *J* = 8.0 Hz), 7.17–7.30 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 20.1, 22.1, 30.3, 39.3, 50.5, 52.4, 119.2, 125.6, 128.0, 128.4, 130.3, 133.8, 140.4, 142.3, 168.4; MS (EI): *m/z* (%) = 243 (15) [M^+], 200 (40), 187 (25), 144 (25), 129 (100), 115 (20); HRMS (EI): Calcd for $C_{16}H_{21}NO$: 243.1623. Found: 243.1654.
4a (R^1 = Me): Mp 52–53 °C (*n*-hexane); IR(nujol): 1733, 1641, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, 3 H, *J* = 7.2 Hz), 1.11 (t, 3 H, *J* = 7.0 Hz), 1.20–1.29 (m, 2 H), 1.45–1.60 (m, 2 H), 2.69–2.73 (br q, 2 H, *J* = 8.0 Hz), 3.46 (pst, 2 H, *J* = 7.3 Hz), 4.0 (br s, 1 H), 4.35 (br s, 1 H), 6.26 (br s, 1 H), 7.27–7.50 (m, 4 H);^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2, 13.7, 19.9, 29.8, 30.5, 46.9, 51.6, 123.9, 126.6, 127.2, 128.1, 128.5, 137.0, 137.6, 148.6, 166.5; MS (EI): *m/z* (%) = 243 (65) [M^+], 201 (72), 187 (100), 173 (45), 144 (30), 128 (43), 115 (20). Anal Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.93; H, 8.41; N, 5.71.

4a (R^1 = Ph): Mp 92–93 °C (*n*-hexane); IR(nujol): 1746, 1636, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.8 (t, 3 H, *J* = 7.3 Hz), 1.16 (sextet, 2 H, *J* = 7.6 Hz), 1.46 (quintet, 2 H, *J* = 7.5 Hz), 3.40 (t, 2 H, *J* = 7.3 Hz), 3.90 (br s, 3 H), 4.25 (br s, 1 H), 6.20 (s, 1 H), 7.10–7.30 (m, 8 H), 7.40–7.45 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (Me), 20.4, 30.9, 43.5, 47.4, 52.1 (CH_2), 126.9, 127.4, 127.7, 128.6, 129.0, 129.2, 129.3 (CH), 137.3, 138.0, 138.8, 146.0, 166.7 (C_{quat}); MS (EI): *m/z* (%) = 305(100) [M^+], 263(87), 249(50), 206(33), 115(25), 91(67) Anal Calcd for $C_{21}H_{23}NO$: C, 82.59; H, 7.59; N, 4.59. Found: C, 82.76; H, 7.46; N, 4.71.

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