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Note

Palladium-catalyzed three-component cyclization: Synthesis of hydroisoindol-1-ones from 2-bromocyclohex-1-enecarbaldehydes, anilines and carbon monoxide

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ABSTRACT

2-Bromocyclohex-1-enecarbaldehydes react with anilines under carbon monoxide pressure in DMF at 60 °C in the presence of a catalytic amount of $PdCl_2(PhCN)_2$ to afford the corresponding hydroisoindol-1-ones in good yields.

1. Introduction

Palladium-catalyzed cascade carbonylation and intramolecular cyclization (carbonylative cyclization) methodology has been recognized as a powerful synthetic tool for lactones and lactams, which plays an important role as an intermediate for the design of pharmaceuticals [1,2]. As part of our ongoing studies toward transition metal-catalyzed carbonylative cyclizations, several lactams could be synthesized via an intramolecular acylpalladation to carbon–nitrogen double bond followed by final substitution with nucleophiles as a key mechanistic step (Scheme 1, route a). For example, it is reported that 2-(2-bromophenyl)-2-oxazolines are carbonylatively cyclized with aliphatic primary alcohols in the presence of a bimetallic palladium–nickel catalyst to give tricyclic isoindol-1-ones [3]. Such a similar palladium-catalyzed carbonylative cyclization was also exemplified by the reaction of 2-bromobenzaldehyde with aminoalcohols and ethylenediamines under carbon monoxide pressure to give tricyclic isoindol-1-ones [4,5]. In connection with this report, 2-bromobenzaldehyde was also found to be carbonylatively cyclized with primary amines under carbon monoxide pressure in DMF in the presence of a palladium catalyst to give isoindol-1-ones which have no substituents at position 3 (Scheme 1, route b) [6]. This protocol led us to extend to the reaction with 2-bromocyclohex-1-enecarbaldehydes, which are readily prepared from cyclohexanones via the bromo analogue of Vilsmeier reaction [7–14]. Herein we describe an expedient synthesis of hydroisoindol-1-ones via such a palladium-catalyzed carbonylative cyclization of 2-bromocyclohex-1-enecarbaldehydes with anilines and carbon monoxide [15].

2. Results and discussion

Based on our recent report on palladium-catalyzed synthesis of isoindol-1-ones from 2-bromobenzaldehyde and primary amines [6], the results of several attempted carbonylative cyclizations of 2-bromocyclohex-1-enecarbaldehyde (**1a**) with aniline (**2a**) are listed in Table 1. When **1a** was generally treated with **2a** in DMF under carbon monoxide pressure in the presence of a catalytic amount of a palladium catalyst, hydroisoindol-1-one **3a** was produced with concomitant formation of 1,2,3,4-tetrahydroacridine (**4**). It is known that β-halovinyl aldehydes are easily cyclized with primary arylamines to give quinolines via N-arylenaminoimine hydrochlorides [16]. The yield and distribution of the mixture of **3a** and **4** was determined from the intensity of a clearly separated signal in ^1H NMR since it was difficult to separate these two products by simple

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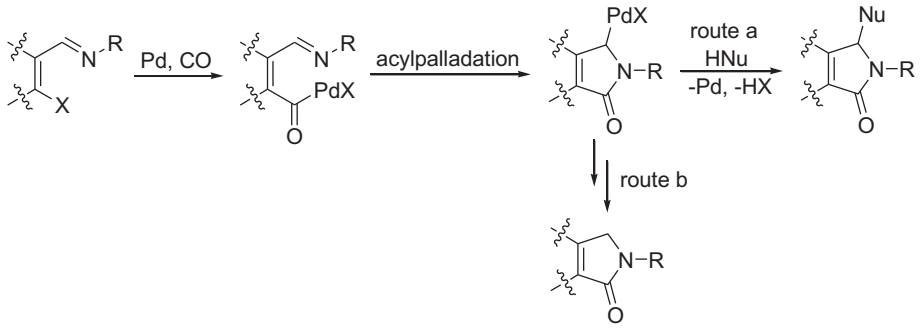


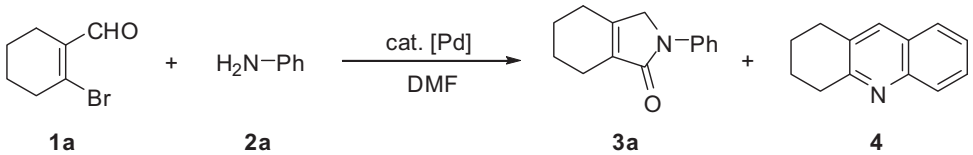
Scheme 1.

elution on TLC without the loss of **4**. The yield of **3a** was formed invariably irrespective of the reaction temperature under $PdCl_2(PhCN)_2$ catalysis, however, higher reaction temperature resulted in a slightly increased yield of **4** (entries 1–3). Further addition of PPh_3 did not give any significant change in the yield of **3a** and product distribution (entry 4). Higher carbon monoxide pressure also did not affect the product yield and distribution (entries 5 and 6). The $PdCl_2$ catalytic system was revealed to be moderately effective for the formation of **3a** (entry 7). The reaction using other solvents such as toluene, dioxane and THF proceeded with complete selectivity of **3a**, but the yield was unsatisfactory (entries 8–10).

Having reaction conditions being established, various six-membered β-bromovinyl aldehydes **1** were subjected to the reaction with primary aromatic amines **2** in order to investigate the reaction scope and several representative results are summarized in Table 2. The reaction of **1a** with anilines (**2b**–**l**) having electron donating and withdrawing substituents proceeds to give the corresponding hydroisoindol-1-ones (**3b**–**l**) in the range of 35–88% yields with predominant selectivity to quinolines. As is the case for the reaction of 2-bromobenzaldehyde with anilines [6], the product yield had relevance to the position of the substituent on the aromatic ring of **2b**–**l** rather than the electronic nature of that. With anilines having *ortho*-substituent, the hydroisoindol-1-one yield was generally higher than that when anilines having *meta*- and *para*-substituents were used. 2-Bromo-5-methylcyclohex-1-ene-carbaldehyde (**1b**) and 2-bromo-5-phenylcyclohex-1-ene-carbaldehyde (**1c**) react similarly with *ortho*-substituted anilines (**2b** and **2e**) to afford the corresponding hydroisoindol-1-ones (**3m**–**o**) in high yields. To test for the effect of the position of formyl group and bromide on cyclic β-bromovinyl aldehydes, **1d** and **1e** were employed. The three-component cyclization readily took place with **1d**, whereas the reaction with **1e** did not proceed toward the desired carbonylative cyclization and gave unidentifiable products on TLC.

The reaction seems to proceed in a similar way as 2-bromobenzaldehyde case [6]. Oxidative addition of the carbon-bromide bond of imine, initially formed by condensation between **1a** and **2a**, to palladium(0) produces a vinylpalladium(II) complex **5** (Scheme 2). This is followed by carbonylation to form intermediate **6** which triggers intramolecular acylpalladation to give cyclized allylpalladium(II) intermediate **7**. Protonation of intermediate **7** by H_2O generated in the initial condensation stage as well as present in solvent gives **3a** [17]. We confirmed that similar treatment of **1a** with **2a** and further addition of D_2O (0.5 mL) under the conditions shown in run 1 of Table 1 afforded ca. 81% deuterated **3a** in 45% yield. Deuterated **3a** was characterized with signal of δ 53.36 (t, $^1J_{C-D}$ = 21.5 Hz) of ^{13}C NMR spectrum and the distribution was

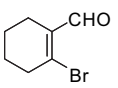
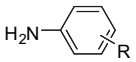
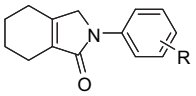
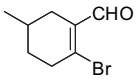
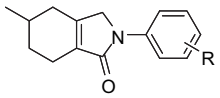
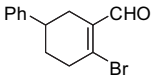
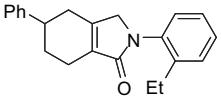
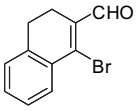
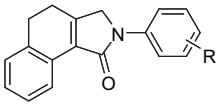
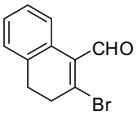
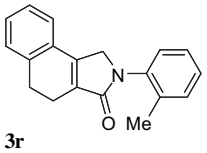
Table 1
Optimization of conditions for the reaction of **1a** with **2a**[a].



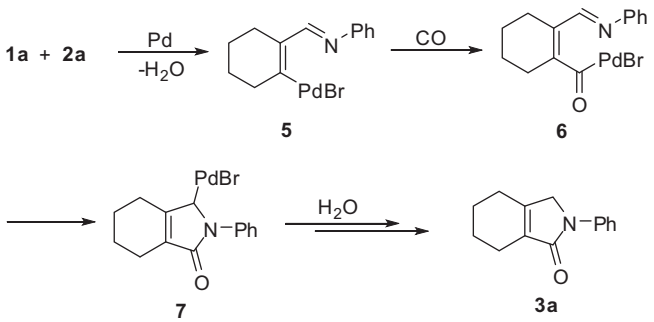
Entry	Palladium catalysts	Solvents	Temp (°C)	CO (atm)	Yield[b] (%)	
					3a	**4**
1	$PdCl_2(PhCN)_2$	DMF	60	10	68 (55)	17
2	$PdCl_2(PhCN)_2$	DMF	100	10	64	26
3	$PdCl_2(PhCN)_2$	DMF	130	10	66	31
4	$PdCl_2(PhCN)_2/2PPh_3$	DMF	100	10	62 (51)	36 (30)
5	$PdCl_2(PhCN)_2$	DMF	100	20	70	23
6	$PdCl_2(PhCN)_2$	DMF	60	20	65	13
7	$PdCl_2$	DMF	60	10	41	22
8	$PdCl_2(PhCN)_2$	Toluene	60	10	(14)	0
9	$PdCl_2(PhCN)_2$	Dioxane	60	10	(30)	0
10	$PdCl_2(PhCN)_2$	THF	60	10	(32)	0

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), palladium catalyst (0.02 mmol), solvent (10 mL), for 10 h.
[b] Determined by ^1H NMR. Isolated yield is shown in parentheses.

Table 2
Palladium-catalyzed synthesis of hydroisoindol-1-ones **3** from **1** and **2**[a].

β-Bromovinyl aldehydes **1**	Anilines **2**	Hydroisoindolin-1-ones **3**	Isolated yield (%)
			
1a	**2a** R = H	**3a**	55
	2b R = 2-Me	**3b**	75
	2c R = 3-Me	**3c**	43
	2d R = 4-Me	**3d**	35
	2e R = 2-Et	**3e**	88
	2f R = 2,3-$(Me)_2$	**3f**	75
	2g R = 2,5-$(Me)_2$	**3g**	78
	2h R = 2-OMe	**3h**	53
	2i R = 4-OMe	**3i**	37
	2j R = 2,5-$(OMe)_2$	**3j**	51
	2k R = 2-Cl	**3k**	81
	2l R = 4-Cl	**3l**	59
			
1b	**2b**	**3m**	83
	2e	**3n**	93
			
1c	**2e**	**3o**	97
			
1d	**2b**	**3p**	72
	2e	**3q**	76
			
1e	**2b**	**3r**	0

[a] Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), $PdCl_2(PhCN)_2$ (0.02 mmol), CO (10 atm), DMF (10 mL), 60 °C, for 10 h.



Scheme 2.

determined from the comparison of the peak area of a clearly separated signal with benzylic signal in ^1H NMR spectrum.

3. Conclusion

We have demonstrated that 2-bromocyclohex-1-enecarbaldehydes are carbonylatively cyclized with various anilines in DMF under carbon monoxide pressure in the presence of a catalytic amount of a palladium catalyst to give the corresponding hydroisoindol-1-ones in good yields. The present reaction is a straightforward methodology for the synthesis of hydroisoindol-1-ones from cyclohexanones. Further study of synthetic applications for heterocycles of this reaction is currently under investigation.

4. Experimental

^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. Melting points were determined on a Standford Research Inc. MPA100 automated melting point apparatus. The isolation of pure products was carried out via thin layer chromatography (silica gel 60 GF_{254}, Merck). β-Bromovinyl aldehydes **1** were synthesized from the corresponding ketones by treatment of PBr_3/DMF/$CHCl_3$ [7]. Commercially available organic and inorganic compounds were used without further purification.

4.1. Typical procedure for palladium-catalyzed carbonylative cyclization of 2-bromocyclohex-1-enecarbaldehydes with anilines

To a 50 mL stainless steel autoclave were added 2-bromocyclohex-1-enecarbaldehyde (**1a**) (0.113 g, 0.6 mmol), aniline (**2a**) (0.047 g, 0.5 mmol), $PdCl_2(PhCN)_2$ (0.008 g, 0.02 mmol) and DMF (10 mL). After the system was flushed and then pressurized with carbon monoxide to 10 atm, the reaction mixture was allowed to react at 60 °C for 10 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate–hexane mixture) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate–hexane mixture) to give 2-phenyl-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-one (**3a**) (0.059 g, 55%). All products prepared by the above procedure were characterized spectroscopically as shown below.

4.1.1. 2-Phenyl-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (*3a*)

Solid, m.p. 115 °C (from hexane); ^{1}H NMR ($CDCl_3$): δ 1.69–1.79 (m, 4H), 2.24–2.31 (m, 4H), 4.16 (s, 2H), 7.05–7.08 (m, 1H), 7.71–7.35 (m, 2H), 7.69–7.71 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 20.28, 21.84, 22.12, 24.24, 53.56, 118.27, 123.40, 129.08, 133.09, 139.85, 149.98, 170.88. Anal. Calc. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.45; H, 7.14; N, 6.52.

4.1.2. 2-(2-Methylphenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (*3b*)

Solid, m.p. 73–75 °C (from hexane–$CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.73–1.83 (m, 4H), 2.23 (s, 1H), 2.28–2.35 (m, 4H), 4.11 (t, J = 2.0 Hz, 2H), 7.12–7.16 (m, 1H), 7.20–7.24 (m, 2H), 7.26–7.29 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 18.45, 20.57, 22.00, 22.24, 24.47, 56.18, 126.74, 127.52, 127.71, 131.18, 132.09, 136.48, 137.54, 150.95, 171.13. Anal. Calc. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 78.88; H, 7.56; N, 6.09.

4.1.3. 2-(3-Methylphenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (*3c*)

Solid, m.p. 131 °C (from hexane–$CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.71–1.82 (m, 4H), 2.26–2.30 (m, 2H), 2.33–2.36 (m, 2H), 2.36 (s, 3H), 4.22 (t, J = 2.3 Hz, 2H), 6.91 (d, J = 7.6 Hz, 1H), 7.24 (t, J = 7.8 Hz, 1H), 7.48–7.50 (m, 1H), 7.58 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.39, 21.88, 21.98, 22.27, 24.38, 53.85, 115.66, 119.32, 124.44, 129.03, 133.33, 139.03, 139.91, 149.84, 170.95. Anal. Calc. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.08; H, 7.50; N, 5.94.

4.1.4. 2-(4-Methylphenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (*3d*)

Solid, m.p. 117 °C (from hexane–$CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.69–1.79 (m, 4H), 2.23–2.27 (m, 2H), 2.29–2.33 (m, 2H), 2.31 (s, 3H), 4.16 (s, 2H), 7.13 (d, J = 8.1 Hz, 2H), 7.56–7.59 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 20.31, 20.90, 21.88, 22.16, 24.26, 53.74, 118.51, 129.61, 133.01, 133.09, 137.36, 149.71, 170.78. Anal. Calc. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 78.90; H, 7.52; N, 6.03.

4.1.5. 2-(2-Ethylphenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (*3e*)

Oil; ^{1}H NMR ($CDCl_3$): δ 1.19 (t, J = 7.6 Hz, 3H), 1.73–1.83 (m, 4H), 2.28–2.34 (m, 4H), 2.58 (q, J = 7.6 Hz, 2H), 4.10 (t, J = 2.0 Hz, 2H), 7.12 (dd, J = 1.2 and 7.8 Hz, 1H), 7.20–7.24 (m, 1H), 7.26–7.33 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.51, 20.60, 22.01, 22.25, 24.39, 24.47, 56.88, 126.76, 128.03, 128.11, 129.22, 132.07, 137.02, 142.46, 150.94, 171.54. Anal. Calc. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.34; H, 7.84; N, 5.81.

4.1.6. 2-(2,3-Dimethylphenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (*3f*)

Solid, m.p. 156.1–157.8 °C (from hexane); ^{1}H NMR ($CDCl_3$): δ 1.75–1.81 (m, 4H), 2.09 (s, 3H), 2.31–2.34 (m, 4H), 2.31 (s, 3H), 4.09 (s, 2H), 6.98–7.01 (m, 1H), 7.12 (d, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.80, 20.64, 20.65, 22.07, 22.31, 24.52, 56.53, 125.29, 126.18, 129.36, 132.16, 135.28, 137.50, 138.38, 150.79, 171.34. Anal. Calc. for $C_{15}H_{17}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.60; H, 8.06; N, 5.82.

4.1.7. 2-(2,5-Dimethylphenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (*3g*)

Oil; ^{1}H NMR ($CDCl_3$): δ 1.74–1.80 (m, 4H), 2.18 (s, 3H), 2.30–2.33 (m, 4H), 2.30 (s, 3H), 4.09 (s, 2H), 6.96 (s, 1H), 7.03 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 17.94, 20.59, 20.92, 22.01, 22.25, 24.47, 56.19, 128.18, 128.56, 130.96, 132.11, 133.19, 136.45, 137.28, 150.83, 171.21. Anal. Calc. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.55; H, 7.85; N, 5.78.

4.1.8. 2-(2-Methoxyphenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (*3h*)

Oil; ^{1}H NMR ($CDCl_3$): δ 1.73–1.81 (m, 4H), 2.29–2.34 (m, 4H), 3.82 (s, 3H), 4.21 (s, 2H), 6.95–7.01 (m, 2H), 7.23–7.27 (m, 1H), 7.35 (dd, J = 1.6 and 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.67, 22.12, 22.37, 24.58, 55.51, 55.83, 112.22, 121.10, 127.41, 128.14, 128.89, 131.99, 151.28, 155.05, 171.66. Anal. Calc. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.94; H, 7.02; N, 5.70.

4.1.9. 2-(4-Methoxyphenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (*3i*)

Solid, m.p. 145 °C (from hexane–$CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.70–1.81 (m, 4H), 2.25–2.29 (m, 2H), 2.31–2.33 (m, 2H), 3.80 (s, 3H), 4.18 (t, J = 2.1 Hz, 2H), 6.87–6.91 (m, 2H), 7.57–7.61 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 20.41, 21.96, 22.25, 24.33, 54.14, 55.64, 114.35, 120.52, 133.11, 133.24, 149.55, 156.00, 170.71. Anal. Calc. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.82; H, 6.95; N, 5.69.

4.1.10. 2-(2,5-Dimethoxyphenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (*3j*)

Solid, m.p. 122.9–124.2 °C (from hexane); ^{1}H NMR ($CDCl_3$): δ 1.74–1.80 (m, 4H), 2.28–2.33 (m, 4H), 3.76 (s, 3H), 3.77 (s, 3H), 4.23 (s, 2H), 6.79 (dd, J = 3.0 and 9.1 Hz, 1H), 6.89 (d, J = 9.1 Hz, 1H), 6.98 (d, J = 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.62, 22.09, 22.33, 24.54, 55.49, 56.00, 56.56, 113.40, 113.47, 114.06, 128.05, 131.90, 149.07, 151.44, 153.85, 171.59. Anal. Calc. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 69.93; H, 6.93; N, 5.06.

4.1.11. 2-(2-Chlorophenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (*3k*)

Solid, m.p. 101.7–102.7 °C (from hexane); ^{1}H NMR ($CDCl_3$): δ 1.75–1.82 (m, 4H), 2.30–2.35 (m, 4H), 4.21 (s, 2H), 7.24–7.36 (m, 3H), 7.46 (dd, J = 1.5 and 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.58, 21.99, 22.24, 24.57, 55.40, 127.79, 128.84, 130.13, 130.61, 131.81, 132.53, 136.45, 151.68, 171.58. Anal. Calc. for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; N, 5.65. Found: C, 67.83; H, 5.71; N, 5.64.

*4.1.12. 2-(4-Chlorophenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (**3l**)*

Solid, m.p. 157.5 °C (from hexane); ^{1}H NMR ($CDCl_3$): δ 1.70–1.81 (m, 4H), 2.23–2.26 (m, 2H), 2.31–2.34 (m, 2H), 4.15 (s, 2H), 7.27–7.30 (m, 2H), 7.64–7.68 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 20.29, 21.84, 22.12, 24.32, 53.54, 119.32, 128.34, 129.09, 133.14, 138.49, 150.22, 170.89. Anal. Calc. for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; N, 5.65. Found: C, 67.88; H, 5.71; N, 5.61.

*4.1.13. 5-Methyl-2-(2-methylphenyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (**3m**)*

Solid, m.p. 121.1–121.9 °C (from hexane); ^{1}H NMR ($CDCl_3$): δ 1.08 (d, J = 6.3 Hz, 3H), 1.30–1.40 (m, 1H), 1.85–2.01 (m, 3H), 2.20–2.29 (m, 1H), 2.23 (s, 3H), 2.40–2.44 (m, 2H), 4.04–4.15 (m, 2H), 7.13–7.28 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 18.50, 20.52, 21.61, 28.80, 30.41, 32.78, 56.03, 126.78, 127.56, 127.75, 131.23, 131.91, 136.53, 137.59, 150.80, 170.98. Anal. Calc. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.45; H, 8.04; N, 5.82.

*4.1.14. 2-(2-Ethylphenyl)-5-methyl-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (**3n**)*

Solid, m.p. 77.7–78.6 °C (from hexane); ^{1}H NMR ($CDCl_3$): δ 1.08 (d, J = 6.3 Hz, 3H), 1.19 (t, J = 7.6 Hz, 3H), 1.30–1.40 (m, 1H), 1.86–1.98 (m, 3H), 2.20–2.29 (m, 1H), 2.40–2.44 (m, 2H), 2.58 (q, J = 7.6 Hz, 2H), 4.03–4.14 (m, 2H), 7.12 (d, J = 7.6 Hz, 1H), 7.23 (dt, J = 1.5 and 7.5 Hz, 1H), 7.26–7.33 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.55, 20.57, 21.64, 24.45, 28.84, 30.45, 32.82, 56.74, 126.82, 128.09, 128.15, 129.29, 131.95, 137.13, 142.52, 150.73, 171.37. Anal. Calc. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.87; H, 8.28; N, 5.55.

*4.1.15. 2-(2-Ethylphenyl)-5-phenyl-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (**3o**)*

Solid, m.p. 110.4–111.2 °C (from hexane); ^{1}H NMR ($CDCl_3$): δ 1.22 (t, J = 7.6 Hz, 3H), 1.82–1.93 (m, 1H), 2.13–2.17 (m, 1H), 2.39–2.43 (m, 1H), 2.47–2.66 (m, 5H), 2.96–3.03 (m, 1H), 4.09–4.23 (m, 2H), 7.14–7.16 (m, 1H), 7.22–7.37 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 14.56, 21.35, 24.46, 29.64, 32.62, 40.40, 56.61, 126.71, 126.84, 127.03, 128.07, 128.23, 128.82, 129.30, 132.13, 136.97, 142.49, 145.76, 150.54, 171.08. Anal. Calc. for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 82.90; H, 7.28; N, 4.36.

*4.1.16. 2-(2-Methylphenyl)-2,3,4,5-tetrahydro-1H-benzo[e] isoindol-1-one (**3p**)*

Solid, m.p. 161.3–162.5 °C (from hexane); ^{1}H NMR ($CDCl_3$): δ 2.27 (s, 3H), 2.69 (t, J = 8.2 Hz, 2H), 3.04 (t, J = 8.2 Hz, 2H), 4.32 (s, 2H), 7.19–7.32 (m, 8H), 8.34 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.51, 23.28, 28.09, 54.95, 123.99, 126.93, 127.16, 127.78, 128.04, 128.11, 129.12, 129.19, 131.33, 134.65, 136.72, 137.31, 151.40, 168.91. Anal. Calc. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.71; H, 6.23; N, 5.39.

*4.1.17. 2-(2-Ethylphenyl)-2,3,4,5-tetrahydro-1H-benzo[e]isoindol-1-one (**3q**)*

Solid, m.p. 143.5–144.1 °C (from hexane); ^{1}H NMR ($CDCl_3$): δ 1.21 (t, J = 7.6 Hz, 3H), 2.61 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 8.2 Hz, 2H), 3.03 (t, J = 8.2 Hz, 2H), 4.29 (s, 2H), 7.17–7.36 (m, 7H), 8.33 (d, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.57, 23.23, 24.49, 28.04, 55.58, 123.94, 126.89, 127.09, 127.75, 128.07, 128.20, 128.35, 129.02, 129.17, 129.32, 134.63, 136.77, 142.64, 151.37, 169.21. Anal. Calc. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.97; H, 6.66; N, 4.66.

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