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An efficient method for the synthesis of 2,3-dihydro-1*H*-isoindoles

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The synthesis of *N*-substituted 2,3-dihydro-1*H*-isoindoles from α,α′-dibromo-*o*-xylene and various primary amines in basic medium under ambient conditions is described. Especially the selection of 1,4-dioxane as solvent and sodium hydroxide as suitable base to maintain the homogeneity of the medium are key steps to promote the reaction efficiently. Primary alkyl amines react faster as compared to their aromatic analogues under the conditions studied. Irrespective of the starting amine used, all the reactions proceed smoothly and provide 2,3-dihydro-1*H*-isoindoles derivatives in excellent yields compared to hitherto known methods.

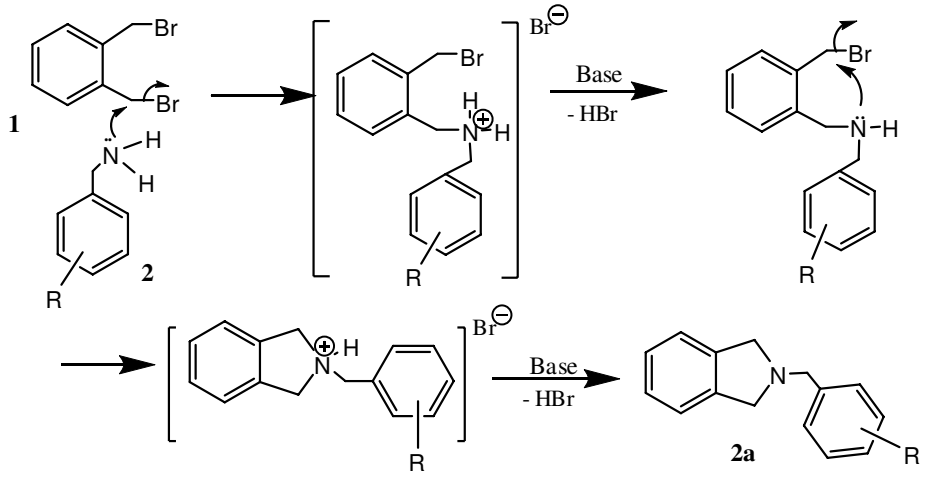
Keywords: α,α′-Dibromo-*o*-xylene, amines, sodium hydroxide, 2,3-dihydro-1*H*-isoindoles

The isoindoline unit is present in numerous synthetic and natural compounds, which exhibit interesting biological properties[1]. Isoindolines has also been shown to elicit a wide array of antagonism receptor properties[2]. Combinatorial chemistry has been extensively applied to medicinal chemistry for the synthesis and optimization of target molecules. Synthesis of heterocycles continues to be an important approach especially for heterocyclic compounds required for multi-step synthesis[3].

A variety of approaches to the synthesis of dihydroisoindole derivative include borane-THF reduction of phthalimide[4], reductive phthalaldehyde by tetracarbonylhydridoferrate[5], multistep metalation-alkylation of formamidine[6], catalytic *N*-hetero-cyclization using a Cp^*Ir complex[7], co-cyclization of nitrogen-containing acetylenes -$NiCl_2(PPh_3)_2$ (Ref. 8), Pictet-Spenger cyclization[9], nickel-catalyzed cyclo-addition[10] and other conventional methods[11,12]. Although the isoindolines are obtained by detosylation of *N*-tosylindoline[13], and also by solid phase synthesis[14], these procedures have one or the other drawbacks which makes them less attractive. Synthesis of 2,3-dihydro-1*H*-isoindole derivatives have also been reported by the use of phase transfer catalysts in combination with the base[15] and in some cases under reflux conditions[16]. K S Reddy *et al*. obtained very low yields with two equivalents of alkylating agent and K_2CO_3 with respect to the amine in ethyl alcohol as solvent[17]. Inspite of the use of phase transfer catalysts[15,16] and two equivalents of alkylating (dibromide) agents, the yields obtained were rather low, which indicates the inefficiency of the process. To meet the requirements of green chemistry in organic synthesis, reactions assisted by microwave irradiation have attracted considerable attention due to their efficient and relatively benign nature[18]. Recently, an efficient method for the synthesis of 2,3-dihydro-1*H*-isoindole derivatives by microwave irradiation has been reported[19]. While these methods are apparently useful for constructing libraries, they need specially designed equipments for large scale preparations.

Results and Discussion

To the best of the knowledge, the direct synthesis of dihydroisoindole derivative in a single step, without any phase transfer catalyst with a short reaction time, technically feasible, economically competitive and under ambient conditions is remarkable. In the present manuscript, is reported an efficient method for the synthesis of dihydroisoindole derivatives under ambient conditions. Initial reaction was carried out with benzyl amine, α,α′-dibromo-*o*-xylene and commercially available sodium hydroxide (1.2 eq.) as base in dioxane as solvent at RT in 30 min (**Scheme I**). As a result, *N*-benzyl-2,3-dihydro-1*H*-isoindole was obtained in 88% isolated yield.



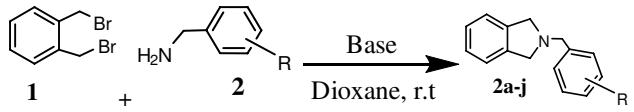
Scheme I — Proposed mechanism for the synthesis of 2,3-dihydro-1*H*-isoindoles

Encouraged by the initial results obtained, a series of benzyl amine derivatives have been reacted with α,α′-dibromo-*o*-xylene under identical conditions to assemble *N*-substituted-2,3-dihydro-1*H*-isoindoles, the results of which are summarized in **Table I**. As can be seen from the **Table I**, all the reactions were completed within 60 min with good to excellent yields. The advantage of the present procedure over the literature results where phase transfer catalysts have been employed for these transformations[15,16] must be noted. In particular O'Brien and Sousa observed the reaction of α,α′-dibromo-*o*-xylene with (*R*)-phenylglycinol needs 19 hr to complete in absence of phase transfer catalyst under optimized conditions[16]. Moreover, these methods are severely limited in scope and restricted to some specific amines.

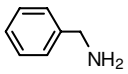
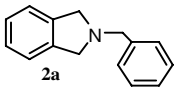
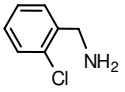
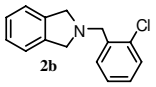
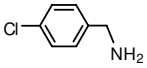
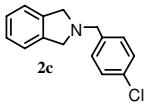
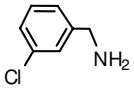
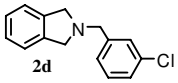
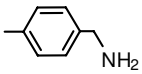
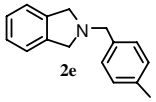
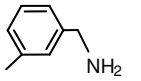
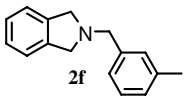
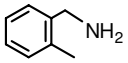
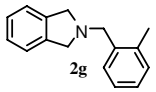
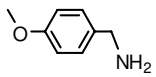
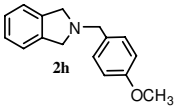
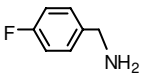
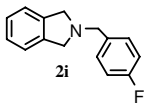
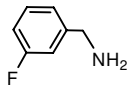
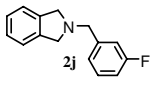
The present protocol provides simple work-up procedures which can be accomplished easily by dispensing the need for heavy metal catalysts, phase transfer catalysts, *etc*. and does not require high energy sources such as microwave irradiations[19]. Hence, major gains could be realized in terms of simplicity and cost effectiveness of the present procedure with reduced reaction time. In order to broaden the scope of present study, the reaction of α,α′-dibromo-*o*-xylene was extended to aniline derivatives and alkyl amines to synthesize various *N*-substituted-2,3-dihydro-1*H*-isoindoles under various key process variables and the results are depicted in **Tables II** and **III** respectively. In order to facilitate the reaction in a shorter period, it was quintessential to use 1.2 equivalents of base in all the reactions studied. The homogeneity of the system in dioxane solvent medium could be another smooth propagating step in the process.

The reaction of aniline derivatives (**Table II**) with α,α′-dibromo-*o*-xylene took longer than with benzyl amines and alkyl amines. This is due to the delocalization of lone pair of electrons on the nitrogen of aniline (**Scheme II**), which are not freely available to attack on the benzylic carbon unlike in the case of benzyl amine and alkyl amines. During the course of the reaction, for complete conversion of anilines to *N*-phenyl-2,3-dihydro-1*H*-isoindoles, double substitution of the nitrogen, the stable intermediate formation will be observed twice (**Schemes I** and **II**), hence apparently it takes longer time. It was further supported by the reaction of 4-nitroaniline, in which, due to the strong electron withdrawing property of nitro group, the availability of lone pair of electrons on the amine nitrogen atom becomes more difficult because of resonance (**Scheme III**). Hence, due to the lack of free availability of lone pair electrons on the nitrogen (of amine), the reaction does not proceed even after 24 hr (entry 4, **Table II**). Further, it can be seen that in the case of *o*-phenylediamine, entry 8, (**Table II**) when two equivalents of α,α′-dibromo-*o*-xylene is used, the yield was moderately low which can be accounted by the steric hindrance of two incoming *ortho* isoindole units. Particularly, in this case the unreacted starting material was not observed. Possibly, the water soluble diamine salt formed with the eliminated HBr during the reaction went into the aqueous phase and could not be isolated. As evident from **Table III**, that *N*-alkyl substituted 2,3-dihydro-1*H*-isoindoles can also be obtained in 70-91% isolated yield under similar reaction conditions. All the reactions proceeded smoothly irrespective of the

Table I — Synthesis of *N*-benzyl substituted 2,3-dihydro-1*H*-isoindoles



1 + **2** → **2a-j**

Entry	Amine **2**	Time (min)	Product	Yield (%)[a]
1		30	 **2a**	88
2		45	 **2b**	79
3		45	 **2c**	75
4		45	 **2d**	74
5		30	 **2e**	69
6		45	 **2f**	68
7		45	 **2g**	89
8		60	 **2h**	70
9		30	 **2i**	62
10		60	 **2j**	90

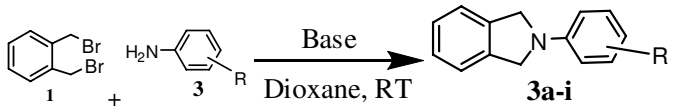
[a]Isolated yields

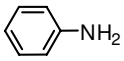
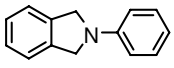
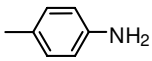
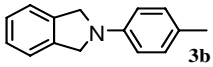
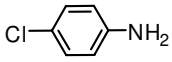
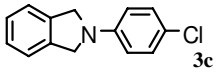
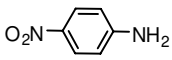
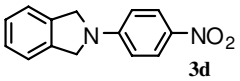
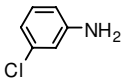
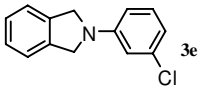
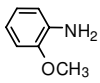
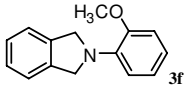
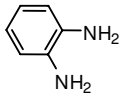
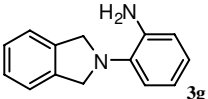
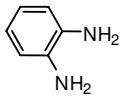
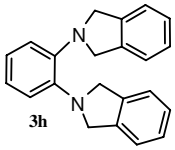
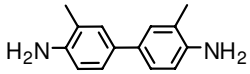
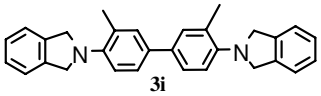
starting amine, and completed within 60 min without any side product formation.

Experimental Section

^{1}H NMR spectra were recorded on Bruker-200 MHz FT-NMR DPX-200 instrument in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard and ^{13}C NMR at 50 MHz. Mass spectra were recorded on Micromass Q-Tof Micro™ ES +ve mode. Melting points were recorded on Veego capillary instrument and are uncorrected. Analytical thin layer chromato-

Table II — Synthesis of *N*-phenyl substituted 2,3-dihydro-1*H*-isoindoles



Entry	Amine **3**	Time (min)	Product	Conversion (%)	Yield (%)[a]
1		12	 **3a**	100	94
2		12	 **3b**	74.5	88
3		12	 **3c**	86.5	90
4		20[b]	 **3d**	--	--
5		12	 **3e**	91	92
6		12	 **3f**	89	87
7		12	 **3g**	67.5	87
8		12	 **3h**	100	34
9		12	 **3i**	100	84[c]

[a]Isolated yields based on the conversion of starting amines;
[b]Reaction did not proceed even after 24 hr; [c]Two equivalents of **1** is used.

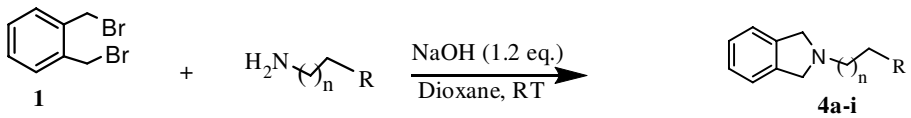
graphy (TLC) was performed on Aluchrosep Silica Gel 60/UV_{254} and visualization under UV light. Purification of the reaction products was carried out by column chromatography using silica gel 100-200 mesh.

General procedure for the synthesis of 2,3-dihydro-1*H*-isoindoles (**2a** is representative) : 0.523g (1.981 mmole) of α,α′-dibromo-*o*-xylene in 5 mL of dioxane and 0.212 g (1.981 mmole) benzyl amine was taken in a 50 mL round bottomed flask. Into it 0.190 g (4.75 mmole) sodium hydroxide was added at RT. The mixture was stirred for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction the solvent was stripped out under reduced pressure and the crude residue obtained was purified by column chromatography over silica gel using ethyl acetate in hexane (2:10) to obtain pure product 0.366 g (1.75 mmole) in 88.3% yield (**2a**) as colorless solid. Spectroscopic data (^{1}H and ^{13}C NMR) of products **2a** (Ref. 7) and **3a** (Ref. 11) are in good agreement with those of authentic samples. This procedure was followed for the synthesis of other 2,3-dihydro-1*H*-isoindoles listed in **Table II** and **Table III**.

Compound characterization data

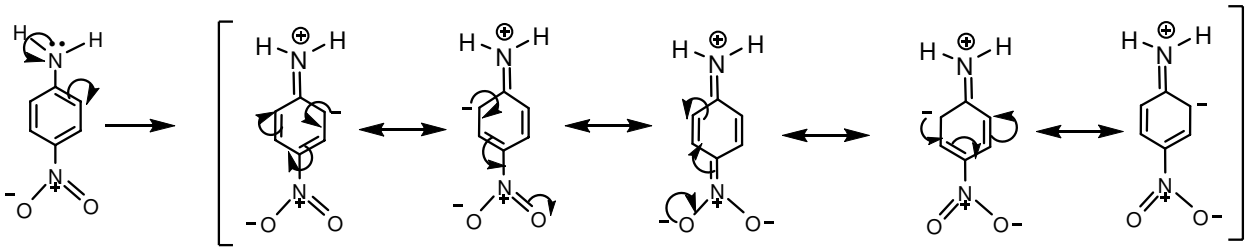
2-(2-Chlorobenzyl)-2,3-dihydro-1*H*-isoindole, **2b**. The title compound is a yellow oil. IR (Nujol): 2934, 2889, 1486, 1469, 1443, 1354, 1147, 1050, 976, 751

Table III — Synthesis of *N*-alkyl substituted 2,3-dihydro-1*H*-isoindoles



Entry	R	n	Time (min)	Product	Yield (%)[a]
1	Ph	1	60	**4a**	74
2	Ph	2	60	**4b**	77
3	Ph	3	60	**4c**	91
4	$-CH_3$	3	60	**4d**	70
5	$-CH_3$	4	60	**4e**	76
6	$-CH_3$	5	60	**4f**	78
7	$-CH_3$	6	60	**4g**	77
8	$-CH_3$	7	60	**4h**	78
9	$-CH_3$	8	60	**4i**	72

[a]Isolated yields based on starting amine.



Scheme III — Resonance structure of 4-nitroaniline

cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.98 (d, 6H, *J* = 5.6), 7.15– 7.56 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 57.33, 59.70, 122.90, 127.31, 128.78, 130.07, 131.17, 134.52, 137.32, 140.79; MS (ESI): *m/z* for $C_{15}H_{14}NCl$ (MH^+): 244.13.

2-(4-Chlorobenzyl)-2,3-dihydro-1*H*-isoindole, **2c**. The title compound is a brown solid; observed m.p. 57-58°C; IR (KBr): 2759, 1488, 1461, 1384, 1149, 1083, 1014, 869, 810, 746 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.85 (d, 6H, *J* =9.4), 7.17 (m, 4H), 7.32 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 59.59, 60.19, 115.09, 122.98, 127.41, 129.18, 130.70, 140.70; MS (ESI): *m/z* for $C_{15}H_{14}NCl$ (MH^+): 244.23.

2-(3-Chlorobenzyl)-2,3-dihydro-1*H*-isoindole, **2d**. The title compound is a yellow oil. IR (Neat): 2776, 1696, 1471, 1431, 1353, 1076, 875, 780, 744 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.86 (s, 2H), 3.91 (s, 4H), 7.17-7.42 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 59.56, 60.26, 115.10, 122.95, 127.42, 127.93, 129.40, 130.27. MS (ESI): *m/z* for $C_{15}H_{14}NCl$ (MH^+): 244.09.

2-(4-Methylbenzyl)-2,3-dihydro-1*H*-isoindole, **2e**. The title compound is a brown solid observed m.p. 52-55°C. IR (KBr): 2770, 1511, 1460, 1377, 1350, 1141, 871, 808, 741 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.85 (s, 2H), 3.90 (s, 4H), 7.15-7.30 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.75, 59.53, 60.63, 115.03, 122.92, 127.27, 129.38, 129.69, 132.91, 136.67, 140.88; MS (ESI): *m/z* for $C_{16}H_{17}N$ (MH^+): 224.09.

2-(3-Methylbenzyl)-2,3-dihydro-1*H*-isoindole, **2f**. The title compound is a brownish-yellow oil. IR (Neat): 2777, 1696, 1466, 1352, 1161, 1139, 1078, 867, 781, 744 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.86 (s, 2H), 3.91 (s, 4H), 7.09-7.23 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.02, 59.59, 60.93, 115.00, 122.94, 126.48, 128.49, 128.88, 130.16, 138.64, 139.62, 140.83; MS (ESI): *m/z* for $C_{16}H_{17}N$ (MH^+): 224.13.

2-(2-Methylbenzyl)-2,3-dihydro-1*H*-isoindole, **2g**. The title compound is a brownish-yellow oil. IR (Neat): 2790, 1694, 1465, 1352, 1137, 873, 744 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.87 (s 2H), 3.92 (s4H), 7.14-7.17 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.72, 58.52, 59.59, 114.98, 122.85, 123.76, 126.30, 127.24, 127.73, 129.94, 130.85, 137.67, 140.80; MS (ESI): *m/z* for $C_{16}H_{17}N$ (MH^+): 224.17.

2-(4-Methoxybenzyl)-2,3-dihydro-1*H*-isoindole, **2h**. The title compound is a brown solid observed m.p. 83-84°C. IR (KBr): 2930, 2792, 2744, 1609, 1510, 1461, 1297, 1244[a] , 1176, 1135, 1077, 1031, 836, 789, 753 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.83 (s, 2H), 3.90 (s, 4H), 6.85 (d, 2H, *J*= 8.6 Hz), 7.17 (m, 4H), 7.29 (d, 2H *J*= 8.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.92, 59.48, 60.25, 114.42, 115.05, 122.97, 127.30, 130.53, 140.87; MS (ESI): *m/z* for $C_{16}H_{17}NO$ (MH^+): 240.11.

2-(4-Fluorobenzyl)-2,3-dihydro-1*H*-isoindole, **2i**. The title compound is a pinkish-brown solid observed m.p. 66-67°C. IR (KBr): 2927, 2886, 2809, 2761, 1602, 1508, 1463, 1348, 1218, 1149, 1078, 870, 824, 747 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.85 (s, 2H), 3.90 (s, 4H), 6.97 (t, 2H *J*= 8.4 Hz), 7.16 (s, 4H), 7.32 (t, 2H *J*= 8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 59.54, 60.14, 115.61, 116.04, 122.99, 127.39, 130.82, 140.78; MS (ESI): *m/z* for $C_{15}H_{14}NF$ (MH^+): 228.17.

2-(3-Fluorobenzyl)-2,3-dihydro-1*H*-isoindole, **2j**. The title compound is a brown oil. IR (Neat): 2788, 1696, 1590, 1486, 1450, 1353, 1256, 877, 785, 746 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.87 (s, 2H), 3.91 (s, 4H), 6.90-7.33 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 59.54, 60.37, 114.40, 114.81, 115.95, 116.38, 122.92, 124.82, 127.39, 130.32, 130.49, 140.57, 166.10; MS (ESI): *m/z* for $C_{15}H_{14}NF$ (MH^+): 228.14.

2-p-Tolyl-2,3-dihydro-1*H*-isoindole, **3b**.The title compound is colorless solid observed m.p. 190-92°C. IR (KBr): 2851, 1620, 1524, 1467, 1375, 1254, 1164, 801, 739 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.27 (S, 3h), 4.60 (S, 4h), 6.57 (D, 2h *J*= 8.2 Hz), 7.08 (d, 2H *J* = 8.4 Hz), 7.30 (m 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.96, 54.64, 112.32, 127.72, 130.54; MS (ESI): *m/z* for $C_{15}H_{15}N$ (MH^+): 210.16.

2-(4-Chlorophenyl)-2,3-dihydro-1*H*-isoindole, **3c**. The title compound is a colorless solid observed m.p. 146-47°C. IR (KBr): 2847, 1606, 1501, 1468, 1376, 1250, 1161, 1094, 804, 743 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.60 (s, 4H), 6.55 (d, 2H *J* = 8.8 Hz), 7.20 (d, 2H *J*=9.0 Hz), 7.31 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 54.58, 113.26, 123.23, 127.95, 129.79, 130.67; MS (ESI): *m/z* for $C_{14}H_{11}NCl$ (MH^+): 230.10.

2-(3-Chlorophenyl)-2,3-dihydro-1*H*-isoindole, **3e**. The title compound is a colorless solid observed m.p. 88-90°C. IR (KBr): 2828, 2360, 1598, 1492, 1465, 1371, 1252, 1164, 1088, 1000, 828, 745, 602 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.46-6.70 (m 3H), 7.11-7.28 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 54.44, 110.52, 112.20, 114.99, 116.78, 123.22, 127.97, 130.05, 130.91, 131.71, 138.01; MS (ESI): *m/z* for $C_{14}H_{12}NCl$ (MH^+): 230.10.

2-(2-Methoxyphenyl)-2,3-dihydro-1*H*-isoindole, **3f**. The title compound is a greenish-black oil. IR (Neat): 2833, 1595, 1504, 1468, 1363, 1331, 1231, 1026, 740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.83, (s, 3H), 4.72 (s, 4H), 6.81-6.92 (m, 4H), 7.23 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.62, 56.75, 113.36, 114.94, 116.19, 120.03, 122.25, 122.74, 127.41, 139.28; MS (ESI): *m/z* for $C_{15}H_{15}NO$ (MH^+): 226.18.

2-(1,3-Dihydro-isoindol-2-yl)-phenylamine, **3g**. The title compound was a light brown solid observed m.p. 99-100°C. IR (KBr): 3454, 3354, 2801, 1603, 1498, 1461, 1295, 1235, 748 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.87 (br s, 2H), 4.44 (s, 4H), 6.77 (t, 2H *J*= 7.8 Hz), 6.94 (t, 1H *J*= 8.4), 7.15-7.25 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 57.09, 114.97, 116.37, 119.42, 121.07, 122.93, 125.02, 127.50, 140.45; MS (ESI): *m/z* for $C_{14}H_{14}N_2$ (MH^+): 211.22.

1,2-Di-(2,3-dihydro-1*H*-isoindole)-benzene (3h). The title compound is a brown solid observed m.p. 133-35°C. IR (KBr): 2798, 1588, 1496, 1455, 1315, 1251, 1173, 1143, 975, 736 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.53 (s, 8H), 6.96 (m, 2H), 7.13-7.17 (m, 2H), 7.24 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.64, 114.93, 118.80, 122.28, 122.94, 127.34, 140.08; MS (ESI): *m/z* for $C_{22}H_{20}N_2$ (MH^+): 313.33.

4,4'-Di-(2,3-dihydro-1*H*-isoindole)-3,3'-dimethyl-biphenyl, **3i**. The title compound is an off white solid, observed m.p. 166-67°C. IR (KBr): 1610, 1496, 1468, 1357, 1316, 749 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.50 (s, 6H), 4.66 (s, 8H), 7.07-7.40 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.40, 57.40, 115.08, 118.19, 122.90, 125.41, 127.72, 130.04, 131.08; MS (ESI): *m/z* for $C_{30}H_{28}N_2$ (MH^+): 417.27.

2-Phenethyl-2,3-dihydro-1*H*-isoindole, **4a**. The title compound is a yellow liquid. IR (Neat): 3027, 2933, 2788, 1694, 1455, 1358, 1147, 871, 744 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.86-3.01 (m, 4H), 3.99 (s, 4H), 7.18-7.29 (m, 9H); ^{13}C NMR (50 MHz,

$CDCl_3$): δ 36.19, 58.52, 59.76, 122.92, 126.76, 127.40, 129.05, 129.32, 140.47; MS (ESI): *m/z* for $C_{16}H_{17}N$ (MH^+): 124.18.

2-(3-Phenylpropyl)-2,3-dihydro-1*H*-isoindole, **4b**. The title compound is a yellow oil. IR (Neat): 2936, 2789, 1694, 1455, 1360, 1146, 744, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.83-1.98 (m, 2H), 2.65-2.75 (q, 4H, *J*= 6.4 & 6.8 Hz), 3.90 (s, 4H), 7.15-7.27 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.90, 34.13, 37.38, 56.16, 59.60, 114.84, 122.80, 126.33, 127.27, 128.98, 140.59, 142.66; MS (ESI): *m/z* for $C_{17}H_{19}N$ (MH^+): 238.21.

2-(4-Phenylbutyl)-2,3-dihydro-1*H*-isoindole, **4c**. The title compound is a yellow oil. IR (Neat): 2934, 2859, 2789, 1693, 1455, 1360, 1145, 867, 744 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.65-1.75 (m, 4H), 2.61-2.75 (m, 4H), 3.90 (s, 4H), 7.16-7.27 (m, 9); ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.01, 29.87, 56.73, 59.70, 115.99, 122.85, 126.31, 127.31, 129.01, 140.60; MS (ESI): *m/z* for $C_{18}H_{21}N$ (MH^+): 252.27.

2-Pentyl-2,3-dihydro-1*H*-isoindole, **4d**. The title compound is a yellow liquid. IR (Neat): 2931, 2872, 2788, 1465, 1357, 1153, 1068, 742 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.9 (t, 3H *J*= 3.4 Hz), 1.34-1.38 (m, 4), 1.56-1.59 (t, 2H *J*= 7.4Hz), 2.66-2.73 (t, 2H *J*= 7.8Hz), 3.92 (s, 4H), 7.17 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.66, 23.26, 29.18, 30.31, 56.98, 59.75, 122.84, 127.28, 140.68; MS (ESI): *m/z* for $C_{13}H_{19}N$ (MH^+): 190.20.

2-Hexyl-2,3-dihydro-1*H*-isoindole, **4e**. The title compound is a yellow liquid. IR (Neat): 2930, 1466, 1071, 743cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, 3H *J*= 3.6 Hz), 1.33-1.58 (m, 8H), 2.66 (t, 2H *J*= 7.0 Hz), 3.91 (s, 4H), 7.16 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.64, 23.21, 27.78, 29.43, 32.43, 56.96, 59.70, 115.00, 122.80, 127.21; MS (ESI): *m/z* for $C_{14}H_{21}N$ (MH^+): 204.25.

2-Heptyl-2,3-dihydro-1*H*-isoindole, **4f**. The title compound is a yellow liquid. IR (Neat): 2928, 2857, 2789, 1467, 1358, 1151, 1072, 741 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, 3H *J*= 6.4 Hz), 1.32-1.62 (m, 10H), 2.65 (t, 2H *J*= 7.6 Hz), 3.91 (s, 4H), 7.16 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.68, 23.25, 28.09, 29.52, 32.44, 56.96, 59.73, 115.02, 122.81, 127.21; MS (ESI): *m/z* for $C_{15}H_{23}N$ (MH^+): 218.28.

2-Octyl-2,3-dihydro-1*H*-isoindole, **4g**. The title compound is a yellow liquid. IR (Neat): 2977, 2752, 1464, 1358, 1151, 741 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, 3H *J*=6.6), 1.28-1.61 (m, 12H), 2.65 (t, 2H *J*= 7.8 Hz), 3.90 (s, 4H), 7.16 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.69, 23.25, 28.11, 29.62, 29.88, 30.21, 32.47, 56.92, 59.76, 122.81, 127.17, 140. 82; MS (ESI): *m/z* for $C_{16}H_{25}N$ (MH^+): 232.22.

2-Nonyl-2,3-dihydro-1*H*-isoindole, **4h**. The title compound is a yellow liquid. IR (Neat): 2927, 2855, 2752, 1467, 1150, 1075, 741 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, 3H *J*= 6.6 Hz), 1.28-1.58 (m, 14H), 2.65 (t, 2H, *J*= 7.6 Hz), 3.90 (s, 4H), 7.16 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.73, 23.29, 28.14, 29.64, 30.22, 30.28, 32.52, 56.95, 59.76, 122.83, 127.21, 140.83; MS (ESI): *m/z* for $C_{17}H_{27}N$ (MH^+): 246.29.

2-Decyl-2,3-dihydro-1*H*-isoindole, **4i**. The title compound is a semisolid at RT (27-30°C). IR (Neat): 2926, 2855, 2788, 1465, 1358, 1150, 741 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, 3H *J*= 6.0 Hz), 1.27-1.58 (m, 16 H), 2.65 (t, 2H *J*= 7.6 Hz), 3.91 (s, 4H), 7.17 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.73, 23.31, 28.16, 29.59, 29.97, 30.28, 32.56, 57.00, 59.78, 122.86, 127.24, 140.78; MS (ESI): *m/z* for $C_{18}H_{29}N$ (MH^+): 260.29.

Conclusions

In summary, a facile and efficient method for the synthesis of isoindolines has been developed *via N*-double alkylation of various primary amines with *o*-dibromoxylene in a single step under ambient conditions. This approach provides regioselective synthesis of isoindoles in excellent yields. The advantages of the process are simple operation, easy work up procedure, and thorough homogeneity of the reaction in dioxane medium. It is further to be noted that the present system eliminates the use of expensive transition metal catalysts, solid supports and phase transfer catalyst. The present protocol is not only cost effective, but also suitable for the bench scale production of the desired products and does not require any specially designed equipment. These are some of the salient features of the present approach.

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