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Facile benzannulation of isocoumarins in the efficient synthesis of diversified 1,3-disubstituted isoquinolines

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Abstract An efficient and facile one-pot synthesis of 1,3-disubstituted isoquinolines **3** was accomplished from 3-substituted isocoumarins **1** through diketones, formed in situ via the Grignard reaction, in the presence of ammonium acetate, montmorillonite K-10 catalyst, and ethanol solvent.

Keywords Annulations · 1,3-disubstituted isoquinolines · Ammonium acetate · MK-10 clay · Grignard reaction · Diketones

Introduction

Isocoumarins have been useful intermediates in the synthesis of a variety of important carbocyclics and heterocyclics [1, 2]. Recently, much attention has been directed towards palladium catalyzed annulations and electrophilic cyclization of alkynes as powerful methods for the construction of various heterocycles, such as isochromenes [3], isoquinolines [4] and benzfurans [5], under mild conditions. The 1,3-disubstituted isoquinolines skeleton forms an integral part of many naturally occurring substances, including pharmaceutically important compounds [6–10], as chiral ligands for the transition metal catalysts [11], and their iridium complexes in organic light-emitting diodes (OLEDs) [12].

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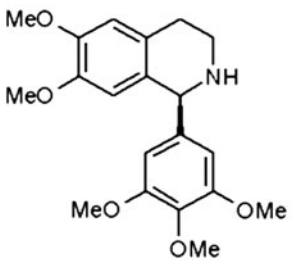
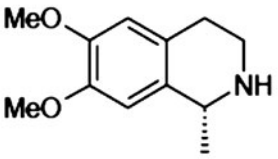
A number of methods have been developed for the synthesis of 1,3-disubstituted isoquinolines including palladium-catalyzed cross-coupling of iodine-mediated electrophilic cyclization of 2-alkynylbenzaldoximes [13], copper-catalyzed tandem synthesis of [1–3] triazolo[5,1-a]isoquinolines [14], irradiation of 1-methoxy-2-azabuta-1, 3-dienes in neutral medium [15], isobenzofuran-nitrile Diels–Alder reaction [16], light-induced iminyl radical cyclization of acyloximes [17], and silver- [18] and gold [19]-catalyzed cyclization of 2-alkynyl benzyl azides. Disubstituted isoquinolines were prepared under mild conditions from allylbenzenes and nitriles using silver triflurom-ethanesulfonate and iodine [20]. The disubstituted isoquinolines are endowed with an extensive range of biological activities [21–23]. Moreover, they display potent thrombin inhibitory activity and antibacterial activity against Gram-positive bacteria [22].

Although the above-mentioned classical methods have been employed in the synthesis of isoquinolines, these approaches have considerable drawbacks, including the use of strong acids and elevated temperatures, many transition metal catalysts, use of trimethyl aluminium in asymmetric synthesis methods and copper catalysts, which are not suitable for sensitive substrates. Recently, we have reported the synthesis of diketones by the Grignard reaction of 3-substituted isocoumarin [24, 25]. As an extension of this study, here we report the intramolecular cyclization of diketones (formed from isocoumarins via the Grignard reaction and without isolating the product from the reaction mixture) using ammonium acetate and Montmorillonite K-10 acidic catalyst.

This provides an efficient economically and environmentally friendly methodology which is in progress in our laboratory for the synthesis of diversified 1,3-disubstituted tetrahydroisoquinolines, TIQ, specifically analogues of (−)-norcriptostiline, (+)-cryptostiline II, alkaloid (−)-salsolidine, laudanozine and (−)-carnegine, and also other isoquinoline system which pave their way to berberine alkaloids.



(-)-Norcriptostiline



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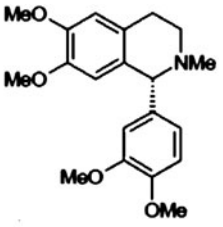

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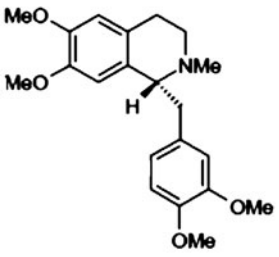

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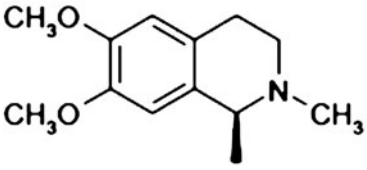
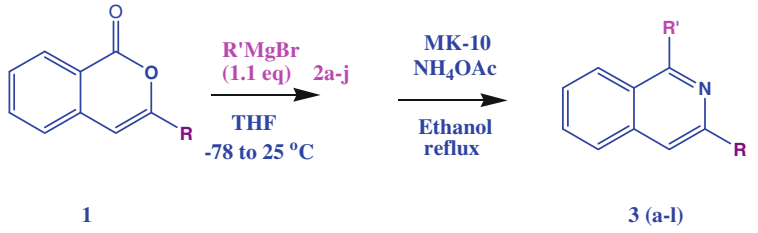


(-)-carnegine

As a continuation of our research interest in isoquinolines and other heterocyclics [24–41], the synthesis of a series of 1,3-disubstituted isoquinolines is reported. The reaction of isocoumarin **1** with various Grignard reagents, **2** in tetrahydrofuran at −30 to 25 °C for 1h (RT) afforded diketones, which without isolating from the reaction mixture, further treated with ammonium acetate and in the presence of Montmorillonite K-10 catalyst, and ethanol solvent at 70 °C afforded 1,3-disubstituted isoquinolines **4** in good yields (Scheme 1).

In our preliminary attempt, the reaction between 3-phenylisocoumarin **1a** and phenyl magnesium bromide afforded the corresponding diketone which, when further reacted with ammonium acetate in the presence of ethanol and Montmorillonite K-10 catalyst under reflux condition, produced the cyclised product in good yields (Scheme 2). In attaining the optimized condition, screening of various catalysts in the presence of ammonium acetate and ethanol solvent was investigated as shown in Table 1. The reaction in the presence of Montmorillonite K-10 catalyst produced the desired product in an excellent yield in comparison to other catalysts.

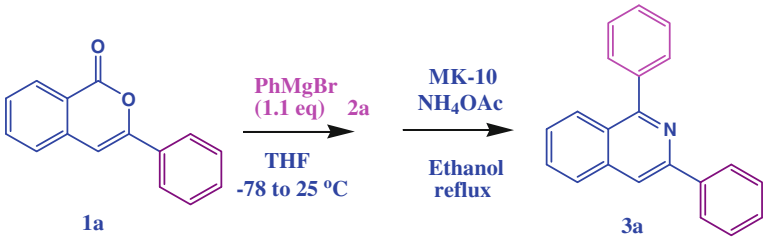
The effect of solvent in the benzannulation reaction was also investigated using the diketones obtained from 3-phenylisocoumarin **1a** and **2a** (Scheme 2; Table 2). Among all the solvents tested, ethanol proved to be excellent at 70 °C (entry 2), while isopropanol, xylene, toluene and 1,4-dioxane were found to be moderately effective in the reaction. With the optimized solvent and catalyst system, the effect of the amount of ammonium acetate in the reaction was explored (Scheme 2;



R= Phenyl, 4-chlorophenyl, 4-methylphenyl

R'= phenyl, methyl, isopropyl, cyclopentyl, cyclohexyl, 3-methoxyphenyl, 2,4-dichlorphenyl,benzyl, biphenyl, 4-pyridyl

Scheme 1 Synthesis of 1,3-disubstituted isoquinolines



Scheme 2 Synthesis of 1,3-diphenylisoquinoline **3a** from 3-phenylisocoumarin **1a**

Table 1 Effect of catalysts in the benzannulation reaction

Entry	Catalyst	Yield[a](%)
1	Nil	No reaction
2	Con. HCl	No reaction
3	MK-10	85
4	Amberlyst	No reaction
5	Acetic acid	No reaction
6	Trifluoroacetic acid	No reaction
7	Perchloric acid	No reaction

Ammonium acetate (5.0 eq), catalyst (10 mol %), ethanol (10 volume), reflux at 70 °C, 12 h

[a] Isolated yields

Table 2 Effect of solvents in the benzannulation reaction

Entry	Solvent	Yield[a] (%)
1	THF	50
2	Ethanol	85
3	Acetonitrile	52
4	1,4-dioxane	67
5	Toluene	68
6	Isopropanol	74
7	Xylene	72

Ammonium acetate (5.0 eq), Montmorillonite K-10 (10 mol %), solvent (10 volume), reflux at 70 °C, 12 h

[a] Isolated yields

Table 3 Optimization of the amount of ammonium acetate in the benzannulation reaction

Entry	Ammonium acetate equivalents	Yield[a] (%)
1	1.0	20
2	1.5	28
3	2.0	35
4	2.5	46
5	3.0	57
6	3.5	63
7	4.0	72
8	4.5	79
9	5.0	85
10	5.5	85
11	6.0	85
12	6.5	85

Montmorillonite K 10 (10 mol %), ethanol (10 volume), reflux at 70 °C, 12 h

[a] Isolated yields

Table 3). The results indicated that increasing amounts of ammonium acetate steadily increased the yield up to 85% with 5 equivalents of ammonium acetate, but beyond that excess ammonia is liberated and further increases do not provide any satisfactory advantages.

With the optimized result to hand, various 1,3-disubstituted isoquinolines were synthesized and the results are reported (Scheme 1; Table 4). The desired products **3a–l** were obtained in high yield and purity and were characterized by different spectral techniques.

The role of montmorillonite K10 in the formation of isoquinolines **3** is well understood as shown below. The first step may involve the Grignard reaction to form the diketone derivatives, which undergo condensation to produce the isoquinolines; the ammonium acetate was used as the source of ammonia. The condensation is promoted by the montmorrillonite K10 catalyst. The imine intermediate, formed in the reaction of diketone and ammonia, was activated by the montmorillonite K10 resulting in enolic intermediate, which later, with the elimination of water and catalyst, produced the corresponding isoquinolines in high yield and purity.

Experimental section

Solvents and reagents were purchased from Sigma Aldrich, India, and used without further purification or preparation. Montmorillonite K-10 catalyst having the surface area of 250 m_2/g was purchased from Sigma-Aldrich. Thin-layered chromatography (TLC) was performed on preparative plates of silica gel (S.D. fine, India). Column chromatography was performed by using silica gel (60–120 mesh). Melting points were taken on Elchem microprocessor-based DT apparatus in open capillary tubes. IR spectra were obtained on a Nucon infrared spectrophotometer using KBr pellets. The NMR spectra were recorded on a Bruker-500 MHz spectrometer including ^{1}H, ^{13}C and LC–MS.

General procedure

A mixture of isocoumarin **1** (2.25 mmol), and THF solvent (10 mL) was cooled to −30 °C using dry ice and acetone. We then added Grignard reagent **2** (1.1 eq) and slowly warmed the reaction to 22–25 °C over a period of 45 min. The reaction was monitored by TLC. After completion of the reaction, the mixture was quenched using aq.NH_4Cl solution and then extracted with DCM (50 mL). The DCM layer was dried over sodium sulphate, filtered in 250-mL single neck RB flask to which was then added ammonium acetate (5.0 eq), MK-10 catalyst (10 mol%) and concentrated solution to 1–2 volume stage. The mixture was heated to reflux in the presence of ethanol solvent at 90 °C for 12 h. The reaction was monitored by TLC. After completion of the reaction, the mixture was filtered off using a funnel and the filtrate concentrated and purified by column chromatography using ethyl acetate/petether as eluent to produce the pure products **3** (Table 4). The compounds were confirmed by ^{1}H NMR, ^{13}C NMR, FTIR and MS techniques.

The analysis data of **3a–j** are given below

3a White solid: mp 165.8 °C; IR (ν cm^{-1}), 3,056, 2,920, 2,850, 1,722, 1,620, 1,566, 1,494, 1,443, 1,384, 1,332, 1,266, 1,138, 1,070, 1,025, 963, 878, 848, 742, 687, 581, 557, 511; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85–7.82 (2H, d, $J = 8.31$), 7.40–7.11 (11H, m), 6.68–6.66 (1H, d, $J = 7.59$), 6.51 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 143.8, 134.4, 133.2, 131.8, 128.6, 128.5, 128.3, 128.28, 128.22, 127.8, 127.7,127.6, 127.2, 126.0, 124.9, 124.0; LC–MS: m/e 282.2,

Table 4 Synthesis of 1,3-disubstituted isoquinolines

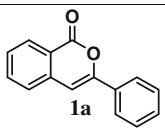
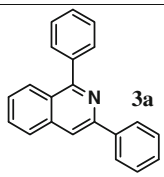
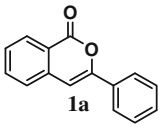
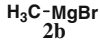
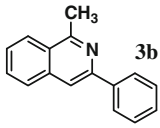
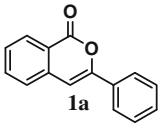
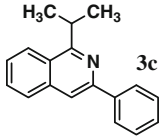
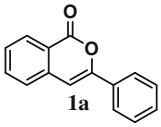
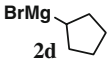
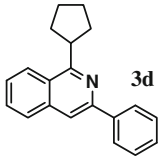
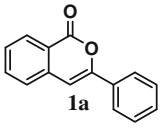
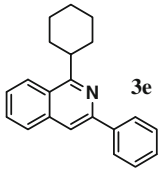
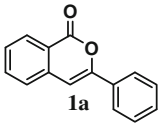
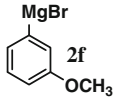
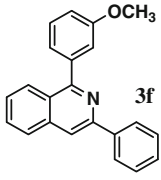
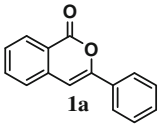
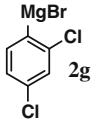
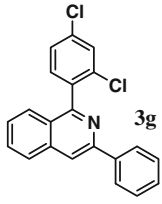
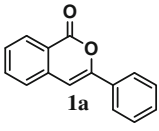
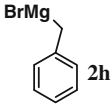
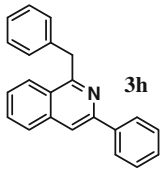
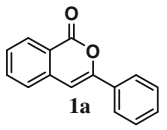
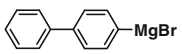
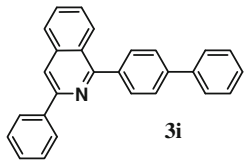
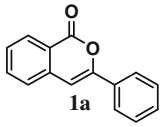
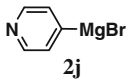
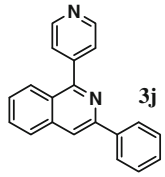
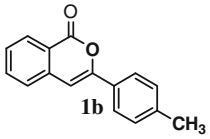
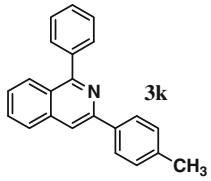
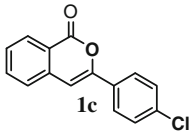
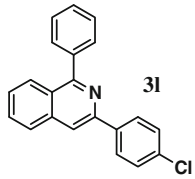
Entry	Isocoumarin, **1**	Grignard reagent, R'MgBr, **2**	Product, **3**	Yield[a] (%)
1				85
2				72
3				77
4				74
5				80
6				84
7				76
8				70

Table 4 continued

Entry	Isocoumarin, **1**	Grignard reagent, R'MgBr, **2**	Product, **3**	Yield[a] (%)
9	 **1a**	 **2i**	 **3i**	87
10	 **1a**	 **2j**	 **3j**	74
11	 **1b**	 **2a**	 **3k**	86
12	 **1c**	 **2a**	 **3l**	89

Grignard reagent **2** (1.1 eq), THF, −30 to 25 °C (1 h), ammonium acetate (5.0 eq), Montmorillonite K-10 (10 mol %), ethanol (10 volume), reffux at 70 °C, 12 h

[a] Isolated yields

$C_{21}H_{15}N$ requires Mol. Wt.: 281.12. Elemental analysis, calculated for $C_{21}H_{15}N$: C, 89.65; H, 5.37; N, 4.98%. Found: C, 89.59; H, 5.31; N, 4.89%.

3b White solid: mp, 147.8 °C, IR (ν cm^{-1}), ν3,053, 3,025, 2,920, 2,853, 1,568, 1,488, 1,444, 1,379, 1,283, 1,232, 1,141, 1,099, 1,073, 1,051, 1,021, 962, 915, 875, 851, 790, 757, 698, 626, 609, 556, 504; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.74 (2H, d, $J = 9.63$), 7.40–7.36 (3H, m), 7.21–7.11 (5H, m), 6.4 (1H, s), 3.05 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 136.2, 135.0, 130.3, 128.5, 128.1, 127.4, 126.6, 124.9, 124.0, 122.3, 100.1, 78.4, 26.9; LC–MS: m/e 220.2, $C_{16}H_{13}N$ requires Mol. Wt.: 219.1. Elemental analysis, calculated for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39%. Found: C, 87.58; H, 5.90; N, 6.32%.

3c White solid, mp, 167.5 °C, IR (ν cm^{-1}), 3,056, 3,023, 2,955, 2,924, 2,867, 2,361, 1,618, 1,600, 1,564, 1,485, 1,465, 1,450, 1,382, 1,366, 1,277, 1,205, 1,076, 1,052, 1,026, 972, 936, 907, 811, 757, 684; ^{1}H NMR (400 MHz, $CDCl_3$)

δ:7.81–7.78 (2H, d, $J = 8.46$), 7.43–7.34 (3H, m), 7.24–7.02 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 134.6, 131.2, 130.1, 128.6, 128.3, 127.7, 125.9, 125.1, 124.8, 123.8, 100.0, 83.5, 31.3, 19.3, 17.9; LC–MS: m/e 248.2, $C_{18}H_{17}N$ requires Mol. Wt.: 247.14. Elemental analysis, calculated for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66%. Found: C, 87.36; H, 6.85; N, 5.59%.

3d White solid, mp, 78.8 °C, IR (ν cm^{-1}), 3,053, 3,017, 2,942, 2,862, 1,619, 1,599, 1,564, 1,490, 1,451, 1,365, 1,298, 1,275, 1,153, 1,048, 1,023, 908, 809, 758, 751, 686, 617; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80–7.78 (2H, d, $J = 6.93$), 7.43–7.35 (3H, m), 7.26–7.06 (4H, m), 6.45 (1H, s), 1.93–1.90 (1H, m), 1.71–1.43 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 134.6, 131.1, 128.6, 128.3, 127.7, 126.0, 125.0, 124.7, 123.7, 100.3, 82.3, 42.3, 29.4, 29.2, 25.3; LC–MS: m/e 273.7, $C_{20}H_{19}N$ requires Mol. Wt.: 273.15. Elemental analysis, calculated for $C_{20}H_{19}N$: C, 87.87; H, 7.01; N, 5.12%. Found: C, 87.84; H, 6.95; N, 5.06%.

3e White solid, mp, 59.7 °C, IR (ν cm^{-1}), 3,058, 2,923, 2,844, 1,968, 1813, 1,618, 1,591, 1,561, 1,496, 1,444, 1,404, 1,372, 1,325, 1,268, 1,196, 1,141, 1,072, 1,028, 991, 917, 884, 849, 800, 770,750, 687, 571; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27–8.24 (2H, d, $J = 8.58$), 8.21 (1H, s), 7.93 (1H, s), 7.88–7.85 (1H, d, $J = 8.01$), 7.67–7.62, (1H, t, $J = 7.86$), 7.58–7.49 (3H, m), 7.43–7.41 (1H, d, $J = 7.14$), 3.60 (1H, m), 2.09–1.84 (7H, m), 1.61–1.44 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 149.3, 140.0, 137.2, 129.4, 128.6, 128.2, 128.0, 126.8,126.4,125.3, 124.7, 114.2, 41.8, 32.6, 26.9, 26.3; LC–MS: m/e 288.2, $C_{21}H_{21}N$ requires Mol. Wt.: 287.17. Elemental analysis, calculated for $C_{21}H_{21}N$: C, 87.76; H, 7.36; N, 4.87%. Found: C, 87.67; H, 7.27; N, 4.78%.

3f White solid, mp, 110.2 °C; IR (ν cm^{-1}), 3,063, 3,032, 2,992, 2,960, 2,918, 2,851, 2,829, 2,361, 1,951, 1,923, 1,662, 1,617,1606, 1,578, 1,559, 1,484, 1,446, 1,431, 1,378, 1,363, 1,337, 1,284, 1,178, 1,244, 1,170, 1,141, 1,086, 1,057, 1,044, 983, 921, 894, 865, 858, 806, 799, 780, 765, 758, 690, 564; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21–8.14 (m, 3H), 8.09 (1H, s), 7.96–7.94 (1H, d, $J = 8.13$), 7.74–7.69 (1H, t, $J = 8.1$), 7.53–7.36 (m, 1H), 7.12–7.10 (1H, d, $J = 8.10$), 3.91 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 159.5, 149.9, 139.1, 137.8, 130.4, 129.2, 128.7, 128.6, 127.7, 127.4, 127.2, 127.1, 125.8, 122.7, 116.2, 115.6, 114.6, 55.4; LC–MS: m/e 312.2, $C_{22}H_{17}NO$ requires Mol. Wt.: 311.13. Elemental analysis, calculated for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50; O, 5.14%. Found: C, 84.79; H, 5.42; N, 4.44%.

3g White solid, mp, 108.4 °C, IR (ν cm^{-1}), 3,058, 3,033, 2,924, 2,361**,** 1954, 1,896, 1,619, 1,588, 1,576, 1,563, 1,545, 1,496, 1,468, 1,451, 1,438, 1,398, 1,370, 1,332, 1,251, 1,207, 1,177, 1,126, 1,072, 1,022, 985, 876, 850, 827,764, 745, 722, 674, 607, 569; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21–8.18 (2H, d, $J = 8.58$), 8.11 (1H, s), 8.07–8,04(1H, d, $J = 8.49$), 7.97–7.93 (2H, m), 7.74–7.69 (1H, t, $J = 7.95$), 7.65 (2H, s), 7.58–7.43 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 150.3, 139.1, 137.8, 132.9, 132.6, 132.0, 130.3, 130.2, 129.4, 128.6, 127.3, 127.0, 126.7, 125.4, 116.2; LC–MS: m/e 350.2, $C_{21}H_{13}C_{l2}N$ requires Mol. Wt.: 349.04. Elemental analysis, calculated for $C_{21}H_{13}C_{l2}N$: C, 72.01; H, 3.74; Cl, 20.24; N, 4.00%. Found: C, 72.13; H, 3.67; N, 3.94%.

3h White solid, mp, 168.4 °C, IR (ν cm^{-1}), 3,052.7, 3,021.8, 2,920.9, 1,628.9, 1,594.4, 1,483.8, 1,443.8, 1,338.6, 1,283.1, 1,230.4, 1,203.4, 1,178.8, 1,155.0, 1,047.7, 1,023.1, 963.3, 923.2, 866.8, 812.3, 750.9, 692.1, 629.0, 557.4, 537.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35–8.25 (1H, m), 7.91–7.84 (1H, m), 7.56–7.52 (3H, m), 7.37–7.31 (3H, m), 7.25–7.23 (2H, m), 7.18 (5H, bs), 5.72 (2H s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 141.2, 139.6, 135.2, 133.5, 131.1, 129.7, 129.1, 127.7, 127.5, 127.4, 126.8, 126.3, 125.4, 123.1, 122.4, 120.9, 29.6; LC–MS: m/e 297.2, $C_{22}H_{17}N$ requires Mol. Wt.: 295.14. Elemental analysis, calculated for $C_{22}H_{17}N$: C, 89.46; H, 5.80; N, 4.74%. Found: C, 89.44; H, 5.75; N, 4.65%.

3i White solid, mp, 189.6 °C, IR (ν cm^{-1}), 3,056, 3,302, 2,921, 2,851, 1,635, 1,597, 1,567, 1,481, 1,451, 1,444, 1,342, 1,303, 1,204, 1,180, 1,157, 1,077, 1,051, 1,025, 964, 924, 815, 776, 752, 709, 693, 631; ^{1}H NMR (400 MHz, DMSO d^6) δ: 8.47 (1H, s), 8.30–8.28 (2H, d, $J = 7.2$), 8.15–8.12 (2H, d, $J = 8.0$), 7.90–7.85 (m 4H), 7.82–7.80 (d, $J = 7.2$, 3H), 7.68–7.64 (t, $J = 7.6$, 1H), 7.56–7.52 (t, $J = 7.6$, 4H), 7.47–7.42 (m, 2 H); ^{13}C NMR (100 MHz, DMSO d^6): δ 159.5, 149.3, 140.9, 140.1, 139.2, 138.8, 138.0, 131.0, 129.5, 129.2, 129.1, 128.2, 127.3, 127.1, 127.0, 125.0, 125.5, 116.0; LC–MS: m/e 358.2, $C_{27}H_{19}N$ requires Mol. Wt.: 357.15. Elemental analysis, calculated for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92%. Found: C, 90.64; H, 5.29; N, 3.83%.

3j White solid, mp, 108.4 °C, IR (ν cm^{-1}), 3,029, 2,918, 2,850, 2,167, 2,027, 1,988, 1,951, 1,588, 1,562, 1,539, 1,492, 1,447, 1,408, 1,379, 1,333, 1,211, 1,176, 1,137, 1,067, 1,026, 977, 881, 856, 828, 761, 680, 643, 621, 594, 564, 516; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83–8.82 (2H, d, $J = 5.60$), 8.21–8.18 (2H, d, $J = 8.40$), 8.14 (1H, s), 8.07–8.05 (1H, d, $J = 8.40$), 7.98–7.96 (1H, d, $J = 8.40$), 7.74–7.71 (3H m), 7.58–7.41 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 150.4, 149.9, 147.3, 139.1, 137.8, 130.4, 128.8, 128.7, 127.7, 127.5, 127.0, 126.5, 125.3, 124.8, 116.6; LC–MS: m/e 283.2, $C_{20}H_{14}N_2$ requires Mol. Wt.: 282.12. Elemental analysis, calculated for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92%. Found: C, 85.11; H, 5.12; N, 9.85%.

3k White solid, mp, 112.6 °C, IR (ν cm^{-1}), 3,051, 2,916, 2,854, 2,729, 2,360, 1,904, 1,872, 1,616, 1,588, 1,561, 1,515, 1,488, 1,441, 1,385, 1,335, 1,308, 1,185, 1,022, 975, 829, 823, 813, 766, 744, 698, 678, 643, 616; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14–8.11(3H, d, $J = 8.16$), 8.06 (1H, s), 7.94–7.91 (1H, d, $J = 8.10$), 7.83–7.81 (2H, d, $J = 7.95$), 7.68 (1H, m), 7.57–7.50 (4H, m), 7.32–7.30 (2H, d, $J = 7.89$), 2.43 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 150.1, 139.8, 138.3, 137.8, 136.7, 130.2, 130.0, 129.4, 128.5, 128.2, 125.5, 127.3, 126,9, 126.7, 125.6, 115.2, 21.28 LC–MS: m/e 296.2, $C_{22}H_{17}N$ requires Mol. Wt.: 294.14. Elemental analysis, calculated for $C_{22}H_{17}N$: C, 89.46; H, 5.80; N, 4.74%. Found: C, 89.37; H, 5.74; N, 4.66%.

3l White solid, mp, 127.4 °C, IR (ν cm^{-1}), 3,052, 2,923, 1,899, 1,728, 1,621, 1,593, 1,560, 1,492, 1,439, 1,413, 1,385, 1,334, 1,210, 1,180, 1,143, 1,099, 1,089, 1,018, 1,008, 976, 881, 858, 826, 806, 769, 743, 701, 677, 632; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19–8.12 (3H, m), 8.06 (1H, s), 7.95–7.92 (1H, d, $J = 8.25$), 7.82–7.79 (2H, dd, $J = 1.77, 7.98$), 7.67–7.73 (1H, t, $J = 8.25$), 7.58–7.45 (6H, m); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 160.5, 148.8, 139.6.138.0, 137.7, 134.5, 130.2, 130.1, 128.8, 128.6, 128.3, 128.2, 127.6, 127.4, 127.1, 125.8, 115.5; LC–MS: m/e 316.0, $C_{21}H_{14}ClN$ requires Mol. Wt.: 315.08. Elemental analysis, calculated for $C_{21}H_{14}ClN$: C, 79.87; H, 4.47; Cl, 11.23; N, 4.44%. Found: C, 79.78; H, 4.39; N, 4.37%.

In short, an efficient and facile benzannulation methodology has been established for the one pot synthesis of diversified 1,3-disubstituted isoquinolines from isocoumarins. The methodology demonstrates an environmentally and ecofriendly technique in achieving biologically active compounds. The methodology may be extended in achieving target isoquinolines such as diversified 1,3-disubstituted tetrahydroisoquinolines, TIQ, specifically for analogues of (−)-norcriptostiline, (+)-cryptostiline II, alkaloid (−)-salsolidine, laudanozine and (−)-carnegine, and also other isoquinoline system which pave their way to berberine alkaloids, active pharmaceutical compounds, which are in progress in our laboratory.

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