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Highly efficient one-pot synthesis of tetrahydropyridines

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ABSTRACT

The combination of aromatic aldehydes, and 1,3-dicarbonyl compounds in the presence of a catalytic amount of poly(*N*,*N*′-dibromo-*N*-ethyl-benzene-1,3-disulfonamide) [PBBS] and *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide [TBBDA] leads to the formation of highly substituted tetrahydropyridines. In this way, a series of pharmacologically interesting substituted piperidine derivatives were obtained in moderate to high yields at room temperature.

1. Introduction

The development of simple synthetic routes for nitrogen-containing heterocyclic systems from ready reagents is an essential task in organic synthesis [1]. Multicomponent reactions (MCRs), involving domino processes, with at least three different substrates reacting in a well-defined manner to form a single compound, have emerged as a powerful tool in organic synthesis [2–5]. These types of reactions have some advantages, including atom economy, good yields, environmentally benign, and mild reaction conditions, which are some of the important features of this protocol [6]. In recent years, extensive research on the synthesis of tetrahydropyridines, has been reported [6–13]. The tetrahydropyridine ring is a structural feature of many alkaloids and drug candidates and there were thousands of piperidine compounds mentioned in clinical and preclinical studies [13–16] (Fig. 1). Compounds containing tetrahydropyridine structural motif exhibit anti-hypertensive [17], antibacterial [11], antimalarial [7], anticonvulsant, and anti-inflammatory activities [12]. Highly substituted tetrahydropyridines were prepared through a combination of 1,3-dicarbonyl compounds, aromatic aldehydes, and amines, using MCRs strategy catalyzed by L-proline/TFA [7], bromo dimethyl sulfonium bromide (BDMS) [6], $InCl_3$ [8], and $ZrOCl_2{\cdot}8H_2O$ [13] in an organic solvent, i.e. ethanol and acetonitrile [11,12]. Due to the importance of the tetrahydropyridine chemistry, a milder, faster and more ecofriendly methods accompanied with higher yields is needed.

2. Experimental

All commercially available chemicals were obtained from Merck and Fluka companies, and used without further purifications unless otherwise stated. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Jeol 90-300 and 400 MHz FT NMR spectrometer using TMS as internal standard and chemical shift are in δ (ppm). Infrared spectra (IR) was recorded on a Perkin Elmer GX FT-IR spectrometer. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. All yields refer to isolated products.

2.1. Typical procedure for the preparation of methyl 1,2,3,6-tetrahydro-2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenyl amino) pyridine-3-carboxylate

A mixture of 4-methoxybenzaldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol), EtOH (5 mL)

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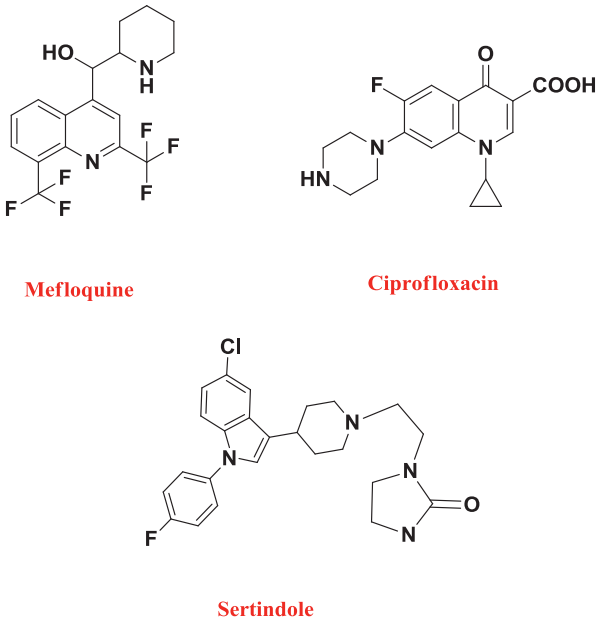


Fig. 1. Compounds containing the tetrahydropyridine structural motif mentioned in clinical and preclinical studies.

and TBBDA (0.08 g, 0.14 mmol) or PBBS (0.1 g) at room temperature was stirred for the appropriate reaction time (Table 3, entry 1). After completion of the reaction, which was monitored by TLC (*n*-hexane/acetone, 13:2), the solid product was collected by filtration (after evaporation of the ethanol, cool methylene dichloride (2 mL) was added, and the catalyst was recovered), washed with ethanol and purified by recrystallization from ethanol.

2.2. Analytical data for selected compounds

Methyl 1,2,3,6-tetrahydro-2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino) pyridine-3-carboxylate (Table 3, **4a)**. White solid. Mp: 182–184 °C. Yield: 91%. IR (KBr, cm^{-1}): 3248 (N–H), 1669 (C=O), 1239 (C–O). ^{1}H-NMR (FT-400 MHz, DMSO-d_6): δ (ppm) 2.71–2.86 (d, *J* = 18.8 Hz, CH_2, 2H), 3.69 (s, OCH_3, 6H), 3.83 (s, OCH_3,3H), 5.26 (s, CH, 1H), 6.21 (s, CH, 1H), 6.41–7.16 (18H, m), 10.14 (s, NH, 1H). ^{13}C-NMR (FT-400 MHz, DMSO-d_6): δ (ppm) 34.0, 51.5, 54.7, 55.4, 55.5, 56.4, 98.4, 112.8, 114.2, 114.2, 116.0, 125.1, 125.8, 127.6, 127.7, 129.2, 129.5, 134.9, 136.2, 138.1, 146.8, 155.2, 158.2, 158.7, 168.0. MS, *m/z*: 520 (M^+), 461, 413, 381, 353, 327, 309, 308, 294, 276, 250, 236, 210, 196, 195, 167, 167, 134, 121, 118, 92, 77, 63, 59, 57, 43, 29, 15, 14.

Methyl 4-(m-tolylamino)-1,2,3,6-tetrahydro-1-m-tolyl-2,6-diptolylpyridine-3-carboxylate (Table 3, **4b)**. White solid. Mp: 135–137 °C. Yield: 81%. IR (KBr, cm^{-1}): 3251 (N–H), 1660 (C=O), 1247 (C–O). ^{1}H-NMR (FT-400 MHz, $CDCl_3$): δ (ppm) 2.31 (s, CH_3, 12H), 2.75 (dd, *J* = 5.6 Hz, *J* = 14.8 Hz, 1H), 2.75 (dd, *J* = 5.2 Hz, *J* = 15.2 Hz, 1H), 3.97 (s, CH_3, 3H), 5.14 (s, CH, 1H), 5.97 (s, CH, 1H), 6.27–7.29 (m, aromatic, 16H), 10.26 (s, NH, 1H). ^{13}C-NMR (FT-400 MHz, $CDCl_3$): δ (ppm) 21.1, 21.2, 22.1, 33.6, 51.0, 54.8, 58.1, 97.7, 110.2, 113.5, 117.0, 123.1, 126.3, 126.6, 126.8, 128.6, 128.7, 128.9, 129.1, 129.4, 135.7, 136.4, 137.8, 138.4, 138.7, 140.1, 141.1, 147.2, 156.6, 168.7. MS, *m/z*: 516 (M^+), 458, 427, 426, 393, 365, 363, 336, 306, 275, 260, 248, 233, 210, 209, 193, 185, 144, 119, 106, 92, 91, 90, 83, 77, 69, 55, 43, 28, 18. Anal. Calcd. for $C_{35}H_{36}N_2O_2$: C, 81.36; H, 7.02; N, 5.42%. Found: C, 81.14; H, 7.04; N, 5.22%.

Methyl 4-(4-methoxyphenylamino)-1,2,3,6-tetrahydro-2,6-bis(3-methoxyphenyl)-1-(4-methoxyphenyl)-pyridine-3-carboxylate (Table 3, **4c)**. Brown solid. Mp: 154–156 °C. Yield: 78%. IR (KBr, cm^{-1}): 3250 (N–H), 1652 (C=O), 1184 (C-O). ^{1}H-NMR (FT-300 MHz, $CDCl_3$): δ (ppm) 2.70–2.90 (m, CH_2, 2H), 3.76 (s, OCH_3, 15H), 5.05 (s, CH, 1H), 5.29 (s, CH, 1H), 6.28–7.22 (m, aromatic, 16H), 10.23 (s, NH, 1H). ^{13}C-NMR (FT-300 MHz, $CDCl_3$): δ (ppm) 33.5, 50.9, 53.5, 55.1, 55.4, 55.6, 55.7, 58.2, 96.7, 110.9, 111.9, 112.7, 113.1, 113.9, 114.0, 114.4, 118.9, 119.2, 128.0, 129.1, 129.6, 130.7, 141.5, 145.1, 146.2, 150.9, 157.2, 157.9, 159.5, 159.9, 168.6. MS, *m/z*: 580 (M^+), 548, 521, 475, 473, 441, 426, 424, 398, 387, 341, 340, 338, 324, 306, 292, 280, 276, 264, 242, 241, 226, 204, 183, 167, 158, 155, 148, 134, 122, 108, 91, 77, 69, 64, 57, 43, 41, 28, 15. Anal. Calcd. For $C_{35}H_{36}N_2O_6$: C, 72.39; H, 6.25; N, 4.82%. Found: C, 74.63; H, 6.44; N, 4.86%.

Ethyl 4-(m-tolylamino)-1,2,3,6-tetrahydro-1-m-tolyl-2,6-dip-tolylpyridine-3-carboxylate (Table 3, **4d)**. White solid. Mp: 160–163 °C. Yield: 74%. IR (KBr, cm^{-1}): 3246 (N–H), 1655 (C=O), 1247 (C–O). ^{1}H-NMR (FT-300 MHz, $CDCl_3$): δ (ppm) 1.49 (t, CH_3, 3H), 2.18 (s, CH_3, 12H), 2.80 (s, CH_2, 2H), 4.36 (m, CH_2, 2H), 5.13 (s, CH, 1H), 5.95 (s, CH, 1H), 6.26-7.24 (m, aromatic, 16H), 10.28 (s, NH, 1H). ^{13}C-NMR (FT-300 MHz, $CDCl_3$): δ (ppm) 14.9, 21.1, 22.1, 33.5, 54.7, 58.1, 59.6, 97.9, 110.2, 113.5, 117.1, 123.0, 126.3, 126.6, 128.67, 128.9, 129.4, 135.6, 136.4, 137.8, 138.4, 138.6, 140.2, 141.2, 147.2, 156.3, 168.3. MS, *m/z*: 530 (M^+), 501, 484, 457, 440, 439, 424, 395, 393, 373, 365, 350, 339, 322, 320, 306, 288, 274, 260, 248, 234, 232, 218, 210, 208, 204, 195, 128, 118, 115, 105, 92, 91, 89, 77, 65, 41, 39, 31, 29, 27. Anal. Calcd. for $C_{36}H_{38}N_2O_2$: C, 81.47; H, 7.22; N, 5.25%. Found: C, 81.11; H, 6.85; N, 3.97%.

Methyl 4-(3-(trifluoromethyl)phenylamino)-1-(3-(trifluoromethyl)phenyl)-1,2,3,6-tetrahydro-2,6-dip-tolylpyridine-3-carboxylate (Table 3, **4e)**. Pink solid. Mp: 153–154 °C. Yield: 76%. IR (KBr, cm^{-1}): 3235 (N–H), 1651 (C=O), 1262 (C–O). ^{1}H-NMR (FT-300 MHz, $CDCl_3$): δ (ppm) 2.36 (s, CH_3, 6H), 2.80 (d, CH_2, *J* = 11.1 Hz, 2H), 3.99 (s, CH_3, 3H), 5.17 (s, CH, H), 6.42–7.38 (m, aromatic, 16H, s, CH, 1H), 10.44 (s, NH, 1H). ^{13}C-NMR (FT-300 MHz, $CDCl_3$): δ (ppm) 21.0, 33.4, 51.3, 55.2, 58.1, 99.0, 109.2, 112.7, 115.9, 122.4, 126.0, 126.4, 129.2, 129.5, 131.3, 136.4, 137.4, 138.5, 155.3, 168.5. MS, *m/z*: 624 (M^+), 605, 593, 565, 535, 533, 503, 501, 473, 464, 434, 432, 430, 416, 409, 404, 362, 360, 346, 328, 314, 302, 288, 285, 272, 264, 262, 231, 218, 212, 204, 186, 172, 161, 146, 145, 142, 118, 115, 105, 91, 77, 65, 59, 51, 39, 29, 15. Anal. Calcd. for $C_{35}H_{30}F_6N_2O_2$: C, 68.96; H, 4.79; N, 2.30%. Found: C, 69.24; H, 4.75; N, 4.5%.

Ethyl 4-(4-methoxyphenylamino)-1,2,3,6-tetrahydro-2,6-bis(3-methoxyphenyl)-1-(4-methoxyphenyl)-pyridine-3-carboxylate (Table 3, **4f)**. Brown solid. Mp: 110–112 °C. Yield: 68%. IR (KBr, cm^{-1}): 3237 (N–H), 1655 (C=O), 1246 (C–O). ^{1}H-NMR (FT-300 MHz, $CDCl_3$): δ (ppm) 1.47 (t, *J* = 6.84 Hz, 3H), 2.70–2.86 (m, CH_2, 2H), 3.76

(s, OCH_3, 12H), 4.33 (m, CH_2, 2H), 5.05 (s, CH, 1H), 6.28–7.21 (m, aromatic,16H, s, CH, 1H), 10.20 (s, NH, 1H). ^{13}C-NMR (FT-300 MHz, $CDCl_3$): δ (ppm) 14.9, 33.5, 55.1, 55.4, 55.6, 58.3, 59.5, 96.9, 111.1, 111.8, 113.0, 114.0, 114.5, 118.9, 119.2, 127.9, 129.0, 129.6, 130.7, 141.5, 145.2, 146.3, 150.9, 157.0, 157.8, 159.6, 159.9, 168.2. MS, *m/z*: 594 (M^+), 550, 548, 521, 489, 487, 472, 443, 441, 398, 379, 356, 354, 352, 338, 324, 308, 306, 292, 280, 276, 266, 263, 242, 241, 226, 220, 183, 167, 154, 134, 122, 108, 92, 77, 64, 51, 39, 29, 27, 15. Anal. Calcd. for $C_{36}H_{38}N_2O_6$: C, 72.71; H, 6.44; N, 4.71%. Found: C, 72.5; H, 6.45; N, 4.62%.

Methyl 4-(4-chlorophenylamino)-1-(4-chlorophenyl)-1,2,3,6-tetrahydro-2,6-bis(3-methoxyphenyl)pyridine-3-carboxylate (Table 3, **4g**). White solid. Mp: 170–172 °C. Yield: 90%. IR (KBr, cm^{-1}): 3250 (N–H), 1651 (C=O), 1257 (C–O). ^{1}H-NMR (FT-90 MHz, $CDCl_3$): δ (ppm) 2.65–2.83 (m, CH_2, 2H), 3.71 (s, CH, 6H), 3.91 (s, CH, 3H), 5.03 (s, CH, 1H), 6.17–7.11 (m, aromatic, 16H, CH, 1H), 10.20 (s, NH, 1H). ^{13}C-NMR (FT-400 MHz, $CDCl_3$): δ (ppm) 33.3, 51.2, 55.1, 55.2, 55.3, 58.2, 98.1, 111.2, 111.9, 112.8, 113.1, 114.0, 118.7, 118.9, 121.3, 127.2, 128.7, 129.0, 129.4, 129.9, 131.5, 136.4, 144.0, 145.1, 145.4, 155.7, 159.7, 160.0, 168.4. MS, *m/z*: 588 (M^+), 558, 530, 487, 485, 481, 465, 463, 452, 449, 434, 430, 428, 395, 373, 347, 344, 342, 328, 310, 296, 286, 284, 280, 270, 268, 248, 246, 244, 233, 216, 204, 201, 177, 151, 138, 113, 111, 102, 92, 77, 75, 59, 51, 39, 15. Anal. Calcd. for $C_{33}H_{30}Cl_2N_2O_4$: C, 67.23; H, 5.13; N, 4.75%. Found: C, 66.78; H, 5.25; N, 4.64%.

Ethyl 4-(4-chlorophenylamino)-1-(4-chlorophenyl)-1,2,3,6-tetrahydro-2,6-bis(3-methoxyphenyl)pyridine-3-carboxylate (Table 3, **4h**). Yellow solid. Mp: 156–158 °C. Yield: 69%. IR (KBr, cm^{-1}): 3235 (N–H), 1647 (C=O), 1248 (C–O). ^{1}H-NMR (FT-90 MHz, $CDCl_3$): δ (ppm) 1.44 (t, *J* = 7.0 Hz, 3H), 2.65–2.92 (m, CH_2, 2H), 3.71 (6H, s), 4.36 (m, CH_2, 2H), 5.04 (s, CH, 1H), 6.18–7.24 (m, aromatic, 16H, s, CH, 1H), 10.23 (s, NH, 1H). ^{13}C-NMR (FT-400 MHz, $CDCl_3$): δ (ppm) 14.8, 33.3, 55.1, 55.3, 58.3, 59.9, 98.4, 111.2, 111.9, 112.8, 112.9, 114.0, 118.7, 118.9, 121.3, 127.1, 128.7, 129.0, 129.3, 129.9, 131.4, 136.5, 144.1, 145.2, 145.4, 155.6, 159.7, 160.0, 168.1. MS, *m/z*: 603 (M^+), 561, 558, 532, 530, 528, 501, 498, 496, 477, 475, 455, 452, 450, 433, 431, 429, 403, 361, 356, 330, 328, 310, 296, 286, 284, 280, 270, 267, 248, 246, 233, 217, 204, 201, 178, 158, 152, 138, 121, 111, 92, 77, 75, 64, 29, 27, 15. Anal. Calcd. for $C_{34}H_{32}C_{12}N_2O_4$: C, 67.66; H, 5.34; N, 4.64%. Found: C, 67.67; H, 5.32; N, 4.53%.

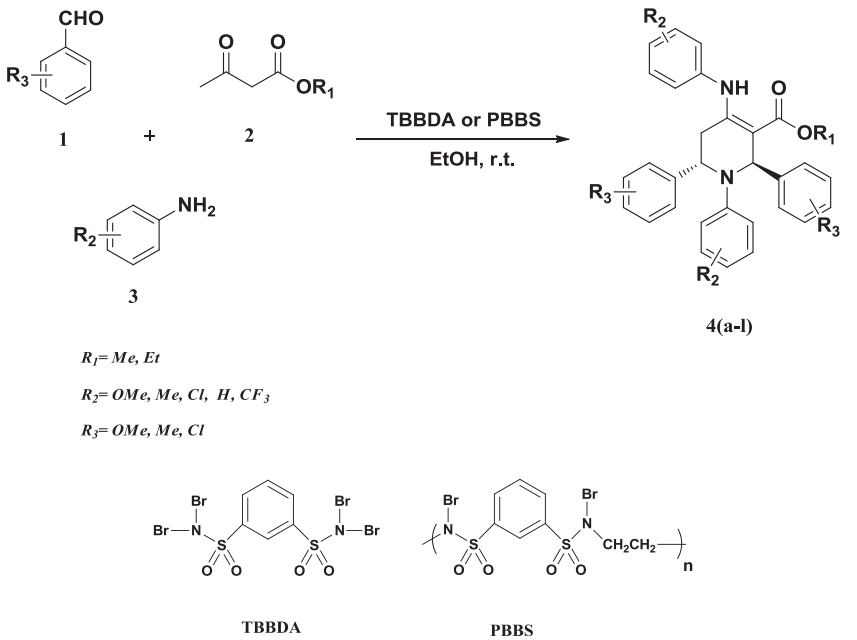
3. Results and discussion

In continuation of our interest in the application of *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide [TBBDA] and poly(*N*,*N*′-dibromo-*N*-ethyl-benzene-1,3-disulfonamide) [PBBS] [18], in organic synthesis [19–32], we report here a convenient method for the preparation of highly substituted tetrahydropyridines from aromatic aldehydes, amines, and 1,3-dicarbonyl compounds at room temperature (Scheme 1).

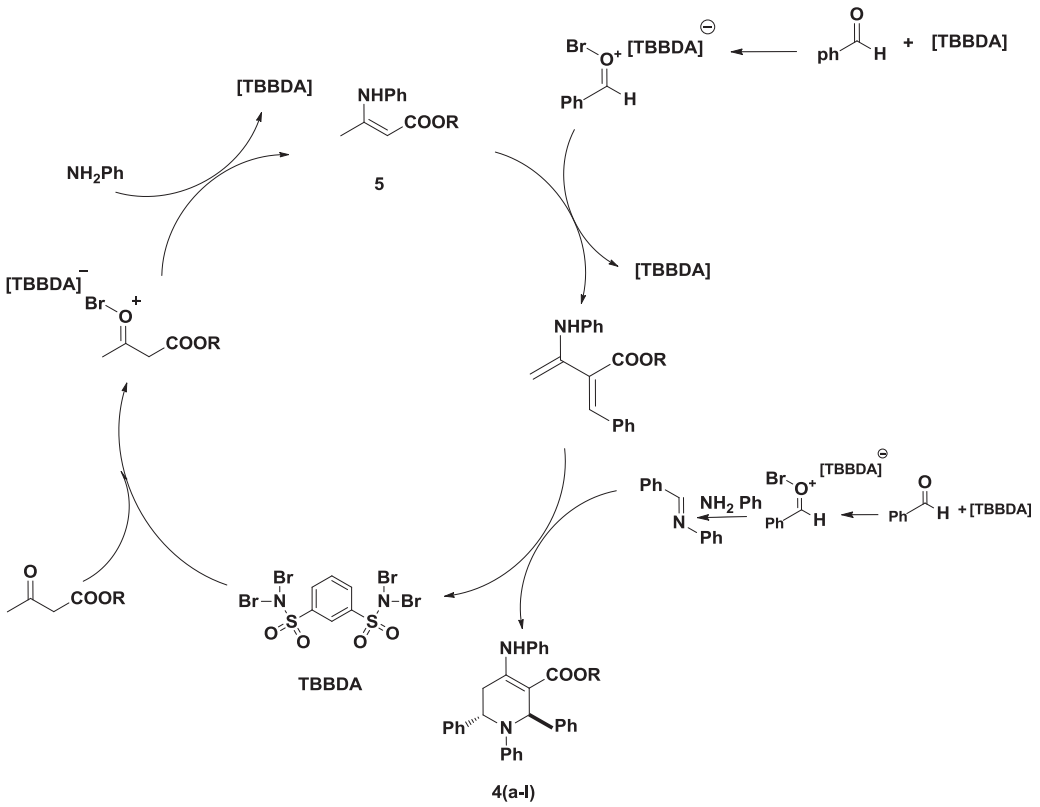
The advantages of PBBS and TBBDA are as follows:

- the preparation of PBBS and TBBDA is easy;
- PBBS and TBBDA are stable under atmospheric conditions for 2 months;
- after completion of the reaction, the catalysts were used many times without decreasing the yield.

Initially, we decided to explore the role of different catalysts in ethanol at room temperature for the synthesis of highly substituted tetrahydropyridines (Table 1) from the reaction of 4-methoxybenzaldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol) and catalyst (0.1 g, 0.18 mmol) used as a model compound. In the



Scheme 1. Convenient method for the preparation of highly substituted tetrahydropyridines.

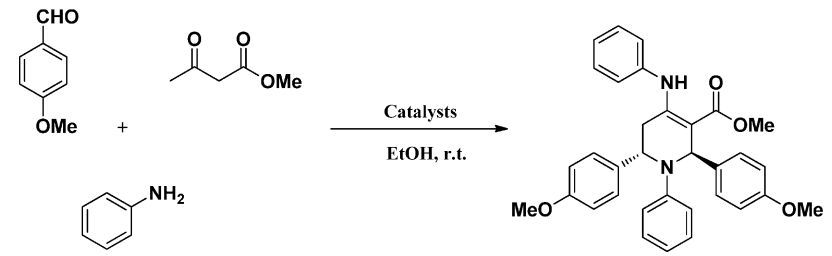


Scheme 2. Suggested mechanism for synthesis of highly substituted tetrahydropyridines.

absence of the catalyst, trace amount of tetrahydropyridine was formed. We found that the reaction was rapid and gave excellent yield of the product when catalyzed by [TBBDA] (8 h, 91%) (Table 1, entry 8).

Then, we decided to study the effect of solvent and reaction conditions for the synthesis of highly substituted tetrahydropyridines (Table 2). The reaction was attempted by different solvents, such as EtOH, CH_3CN, H_2O, EtOH/H_2O. With respect to the solvent system, the best results were achieved using ethanol, used directly without rigorous drying. A satisfactory result was obtained in the presence of 0.1 g (0.18 mmol) of TBBDA (Table 2, entry 9).

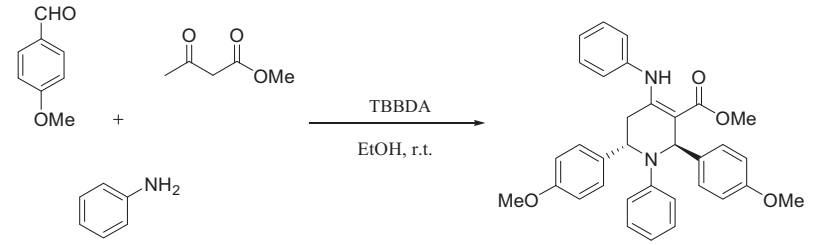
Table 1
Effect of different catalysts on the model reaction of 4-methoxybenzaldehyde, aniline, and methyl acetoacetate[a].



Entry	Catalyst	Reaction time (h)	Yield (%)[b]
1	None	28	Trace
2	$InCl_3$	50	25
3	Silica sulfuric acid	36	10
4	*Ortho*-phosphoric acid	24	5
5	*L*-Proline+TFA	21	72
6	CAN	16	83
7	TBATB	8	80
8	TBBDA	8	91

[a] Experimental conditions: 4-methoxybenzaldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol), and catalyst (0.18 mmol), in EtOH (5 mL) at room temperature.
[b] Isolated yield.

Table 2
Optimization of reaction conditions for the synthesis of highly substituted tetrahydropyridines.



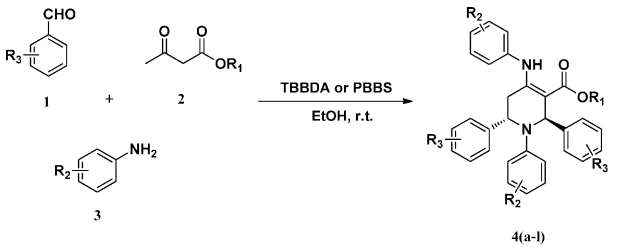
Entry	Solvent/Condition	Catalyst (mmol)	Time (h)	Yield[a] (%)
1	EtOH/rt	No Catalyst	28	Trace
2	CH_3CN/rt	0.09	9	22
3	CH_3CN/rt	0.14	9	43
4	CH_3CN/rt	0.18	9	43
5	H_2O/rt	0.18	10	No reaction
6	EtOH–H_2O/rt	0.18	10	15
7	EtOH/rt	0.09	8	67
8	EtOH/rt	0.14	8	74
9	EtOH/rt	0.18	8	91
10	EtOH/rt	0.18	10	93
11	EtOH/rt	0.18	13	93
12	Neat/reflux	0.14	2	40
13	Neat/reflux	0.14	4	52
14	Neat/reflux	0.18	4	63
15	Neat/reflux	0.18	6	67

rt: room temperature.
[a] Standardization of reaction conditions: 4-methoxybenzaldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol).

To test the generality and versatility of this procedure in the synthesis of tetrahydropyridines, we synthesised a number of tetrahydropyridines from aldehydes, anilines and 1,3-dicarbonyl compounds using [TBBDA] and [PBBS] under optimized conditions (Table 3).

As show in Table 3, various anilines containing either electron-withdrawing or electron-donating substituents successfully react with various benzaldehydes and β-ketoesters, affording good to high yields of products with high purity, at room temperature using TBBDA or PBBS as catalysts. The stereochemistry of products **4(a–l)** was determined as *trans* [6–9]. It is noteworthy that several attempts for the synthesis of tetrahydropyridines from β-naphthylamine and cyclopentylamine using PBBS or TBBDA

Table 3
Synthesis of various highly substituted tetrahydropyridines using *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide [TBBDA] and poly(*N*,*N*′-dibromo-*N*-ethyl-benzene-1,3-disulfonamide) [PBBS] in 5 mL of EtOH, at room temperature.



R_1= Me, Et
R_2= OMe, Me, Cl, H, CF_3
R_3= OMe, Me, Cl

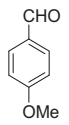
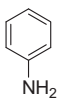
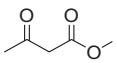
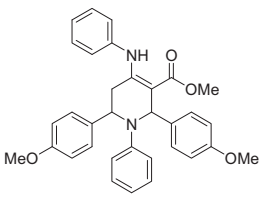
Structure	Aldehydes	Amines	β-ketoesters	Product[a]	TBBDA		PBBS		Reference
					Time (h)	Yield (%)	Time (h)	Yield (%)	
4a					8	91	14	73	[9]

Table 3 (*Continued*)

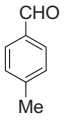
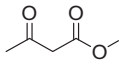
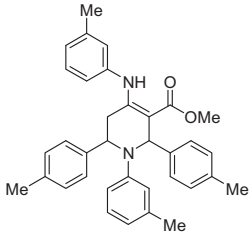
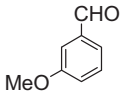
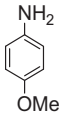
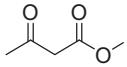
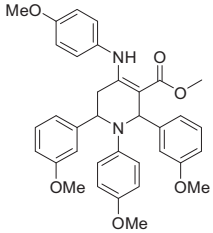
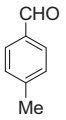
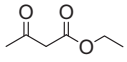
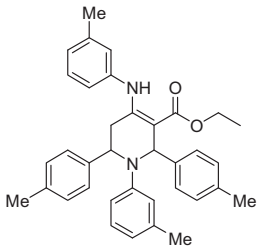
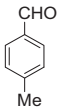
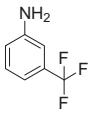
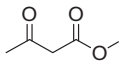
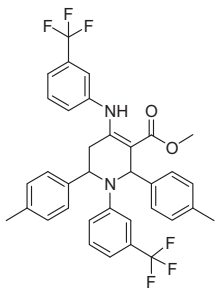
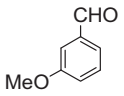
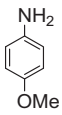
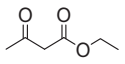
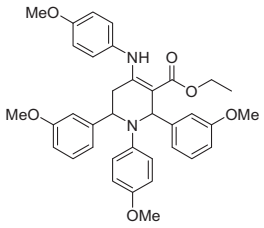
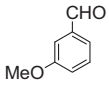
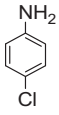
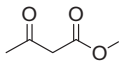
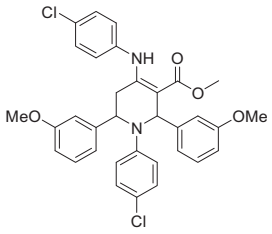
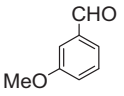
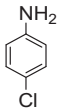
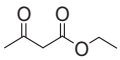
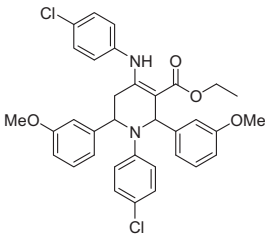
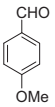
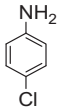
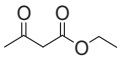
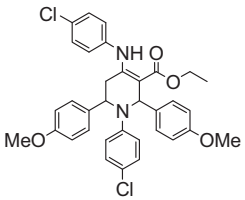
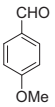
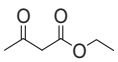
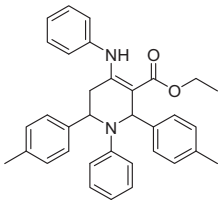
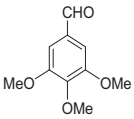
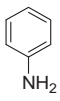
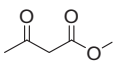
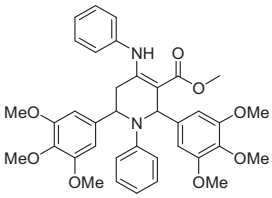
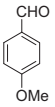
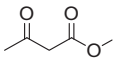
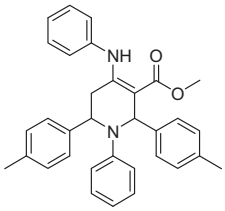
Structure	Aldehydes	Amines	β-ketoesters	Product[a]	TBBDA		PBBS		Reference
					Time (h)	Yield (%)	Time (h)	Yield (%)	
4b					12	81	21	66	–
4c					9	78	14	79	–
4d					13	74	26	67	–
4e					16	76	33	78	–
4f					9	68	15	54	–
4g					7	90	9	81	–

Table 3 (*Continued*)

Structure	Aldehydes	Amines	β-ketoesters	Product[a]	TBBDA		PBBS		Reference
					Time (h)	Yield (%)	Time (h)	Yield (%)	
4h					7	69	11	69	–
4i					8	79	11	70	[10]
4j					8	76	14	66	[9]
4k					20	69	43	65	[9]
4l					7	89	14	78	[9]

[a] Products were characterized from their physical properties, by comparison with authentic samples, and by spectroscopic methods.

under optimized conditions failed, which may be due to the steric hindrance of the bulky naphthyl or cyclopentyl groups.

It is likely that these catalysts release Br^+ in situ, which can act as an electrophilic species [18–29]. Therefore, the mechanism shown in Scheme 2 can be suggested for the reaction [6,8,9]. Initially, TBBDA activated alkyl acetoacetate and then, nucleophilic attack by aniline leads to intermediate **5**. After nucleophilic attack by intermediate **5** on the activated aldehyde, intermolecular cyclization leads to substituted tetrahydropyridines **4(a–l)**.

4. Conclusions

In conclusion, we have developed an efficient procedure for the synthesis of highly substituted tetrahydropyridines using catalytic amount of [TBBDA] and [PBBS] at room temperature. This method offers several advantages such as inexpensive catalysts, easy synthetic procedure, high yields, simple work-up procedure and easy isolation.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.crci.2013.02.015.

References

[1] P. Laszlo, In organic reactions: simplicity and logic, John Wiley, Chichester, New York, 1995.
[2] J. Zhu, H. Bienayme', Multicomponent reactions, 1st ed, WileyVCH, Weinheim, Germany, 2005.
[3] P.A. Tempest, Curr. Opin. Drug. Discov. 8 (2005) 776.
[4] H. Fujioka, K. Murai, O. Kubo, Y. Ohba, Y. Kita, Org. Lett. 9 (2007) 1687.
[5] N.M. Evdokimov, A.S. Kireev, A.A. Yakovenko, M.Y. Antipin, I.V. Magedov, A. Kornienko, J. Org. Chem. 72 (2007) 3443.
[6] A.T. Khan, T. Parvin, L.H. Choudhury, J. Org. Chem. 73 (2008) 8398.
[7] M. Misra, S.K. Pandey, V.P. Pandey, J. Pandey, R. Tripathi, R.P. Tripathi, Bioorg. Med. Chem. 17 (2009) 625.
[8] P.A. Clarke, A.V. Saytsev, A.C. Whitwood, Tetrahedron Lett. 48 (2007) 5209.
[9] H.J. Wang, L.P. Mo, Z.H. Zhang, ACS Comb. Sci. 13 (2011) 181.
[10] G. Brahmachari, S. Das, Tetrahedron Lett. 53 (2012) 1479.
[11] Y. Zhou, V.E. Gregor, B.K. Ayida, G.C. Winters, Z. Sun, D. Murphy, G. Haley, D. Bailey, J.M. Froelich, S. Fish, S.E. Webber, T. Hermann, D. Wall, Bioorg. Med. Chem. Lett. 17 (2007) 1206.
[12] H. Bin, A.M. Crider, J.P. Stables, Eur. J. Med. Chem. 36 (2001) 265.
[13] S. Misra, R. Ghosh, Tetrahedronn Lett. 52 (2011) 2857.
[14] P.S. Watson, B. Jiang, B. Scott, Org. Lett. 2 (2000) 3679.
[15] C. Walsh, Nature 406 (2000) 775.
[16] R.G. Ridley, Nature 415 (2002) 686.
[17] S. Petit, J.P. Nallet, M. Guillard, J. Dreux, R. Chermat, M. Poncelet, C. Bulach, P. Simon, C. Fontaine, M. Barthelmebs, J.L. Imbs, Eur. J. Med. Chem. 26 (1991) 19.
[18] R. Ghorbani-Vaghei, H. Jalili, Synthesis 37 (2005) 1099.
[19] R. Ghorbani-Vaghei, H. Veisi, Synthesis 41 (2009) 945.
[20] R. Ghorbani-Vaghei, S. Akbari-Dadamahaleh, Tetrahedron Lett. 50 (2009) 1055.
[21] R. Ghorbani-Vaghei, A. Khazaei, Tetrahedron Lett. 44 (2003) 7525.
[22] R. Ghorbani-Vaghei, M.A. Zolfigol, M. Chegeny, H. Veisi, Tetrahedron Lett. 47 (2006) 4505.
[23] R. Ghorbani-Vaghei, M. Chegini, H. Veisi, M. Karimi-Tabar, Tetrahedron Lett. 50 (2009) 1861.
[24] R. Ghorbani-Vaghei, R. Karimi-Nami, Z. Toghraei-Semiromi, M. Amiri, M. Ghavidel, Tetrahedron 67 (2011) 1930.
[25] R. Ghorbani-Vaghei, M. Amiri, N. Moshfeghifar, H. Veisi, S. Akbari-Dadamahaleh, J. Iran. Chem. Soc. 6 (2009) 754.
[26] R. Ghorbani-Vaghei, H. Veisi, Mol. Divers. 14 (2010) 249.
[27] R. Ghorbani-Vaghei, H. Veisi, M. Amiri, J. Iran. Chem. Soc. 6 (2009) 761.
[28] R. Ghorbani-Vaghei, H. Veisi, J. Braz. Chem. Soc. 21 (2010) 193.
[29] R. Ghorbani-Vaghei, Z. Toghraei-Semiromi, R. Karimi-Nami, J. Braz. Chem. Soc. 22 (2011) 905.
[30] R. Ghorbani-Vaghei, H. Shahbazi, H. Veisi, Tetrahedron Lett. 53 (2012) 2325.
[31] R. Ghorbani-Vaghei, S. Hajinazari, M. Engashte, J. Iran. Chem. Soc. 9 (2012) 655.
[32] R. Ghorbani-Vaghei, M. Amiri, R. Karimi-Nami, Z. Toghraei-Semiromi, M. Ghavidel, Mol. Divers. (2012), http://dx.doi.org/10.1007/s11030-013-9427-0 [in press].