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Ultrasound-promoted synthesis of novel bipodal and tripodalpiperidin-4-ones and silica chloride mediated conversion to its piperidin-4-ols: Synthesis and structural confinements

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ABSTRACT

The ultrasound-promoted synthesis of novel bipodal and tripodalpiperidin-4-ones was carried out by the reaction of 4-piperidone hydrochloride monohydrate with different alkylating and acylating agents. It was preferably reduced to respective piperidin-4-ols by ultrasonic irradiation using silica chloride, which maintains higher yields by acting as an effective supporting polymer. The sterically hindered phthaloyl derivative of piperidin-4-one was synthesized by ultrasonic irradiation which was difficult by conventional methods.

1. Introduction

Advances in organic chemistry are usually measured by the availability of simple, highly functionalized building blocks that can be used in the synthesis of larger molecules with diverse properties and applications [1]. The synthesis of *N*-substituted-4-piperidones has been a subject of continuing interest due to its importance as a synthetic building block in medicinal chemistry which expands its scope as synthetic intermediates enroute to a considerable number of pharmacological agents [2]. Many CNS agents such as antidepressants, anxiolytics, and antipsychotics possess 4-piperidone pharmacophore [3]. The piperidine ring is a ubiquitous structural feature of many natural alkaloids and drug candidates where piperidones serve as advanced intermediates prior to their conversion to piperidines. The most general approach to the synthesis of *N*-substituted piperidones reported in the literature [4] was adopted by Hosken to synthesize simple 1-(pyridin-2-yl methyl)piperidin-4-one with 50% yield which involves a classical three-step sequence *viz*., *bis*-Michael addition of 2-(aminomethyl)pyridine with ethyl acrylate to generate amino diester followed by Dieckman cyclization and base-catalyzed decarboxylation [5]. In order to synthesize the desired target molecules **1**, **2a–5a**, **8a–10a**, **11–13** by the Hosken method, *bis* and *tris* amines are essential, over which it is cost effective and in some cases it may not be possible and in account large excess of ethyl acrylate in need with a long reaction times for the completion of reaction.

The troublesome *bis*-Michael addition can be avoided by using Kuehne approach to *N*-substituted piperidones by an exchange reaction between 4-oxo-piperidinium iodide and a primary amine [6]. However, shortcomings of this approach are that the exchange reactions often fails to complete and hence not applicable to the systems where quaternary amine salts cannot be formed easily, so it lacks the broad generality; in addition, hindered amines are known to produce cross-coupled side products [7]. Although the methods described above have been beneficial in the specific examples for which they were developed, it may not give a much scope for the direct approach to *bis* and *tris* *N*-substituted piperidones and piperidines. In this context we decided to explore the efficient, simple and fast synthesis of their corresponding heterocycles using ultrasound irradiation.

Ultrasound irradiation, an efficient and innocuous technique for reagent activation in the synthesis of organic compounds, and in particular heterocyclic compounds, has been applied with success, milder reaction condition, and higher yields in comparison to the classical methods [8–10]. Ultrasound-promoted synthesis has attracted much attention during the past few decades. One advantage of using cavitation as an energy source to promote organic reactions includes shorter reaction times [11]. During the

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rarefaction cycle in the cavitation process, the molecules of the liquid are separated, generating bubbles that subsequently collapse in the compression cycle. These rapid and violent implosions generate short-lived regions with temperatures of roughly 5000 °C, pressures of about 1000 atm and heating and cooling rates above 10 billion °C/s. Such localized hot spots can be thought as micro reactors in which the energy of sound is transformed into a useful chemical form [11–13]. This procedure has been considered as a clean and useful protocol in organic synthesis compared with traditional methods, and the procedure is in general, more convenient [11]. The present work describes a direct approach to *N*-substituted bipodal and tripodalpiperidin-4-ones (Schemes 1 and 2) and its reduction to respective piperidin-4-ols using silica chloride as a catalyst under ultrasonic irradiation and all the results were best executed.

2. Results and discussion

The synthesis of bipodal and tripodalpiperidin-4-ones is hitherto unreported in the literature, which involves direct alkylation/acylation of the respective benzyl and benzoyl halides with 4-piperidone under mild basic conditions. Though the initial attempt to synthesize 1,1′-(1,4-phenylene*bis*(methylene))dipiperidin-4-one (**1**) by alkylation of 4-piperidone hydrochloride monohydrate with α,α′-dibromo-*p*-xylene using *N*,*N*-di*iso*-propylethylamine (Hunig's base) was successful, the partitioning of **1** into organic solvents proved to be a significant challenge due to its high aqueous solubility, and the same in case of **2a–5a**. In particular **3a** required highly inert conditions without aqueous workup due to its hygroscopic nature. So the use of Hunig's base was barred in consideration of its aqueous workup and its abject yields.

The same is the case by the use of NaH in dry THF, where the chance for alkylation at α,α′ position to the carbonyl in 4-piperidone is more which lead to undesired side products, which in turn effect the yield of final product and it posses its own limitation due to aqueous workup. The synthesis of **1** was also carried out using K_2CO_3 in benzene under reflux, where it could not give much scope for the satisfactory results [14a,b]. This led us to investigate an efficient approach to synthesize **1** and its derivatives quantitatively. The use of Na_2CO_3 in acetonitrile leads to the formation of **1** and its subsequent derivatives conventionally (Schemes 1 and 2).

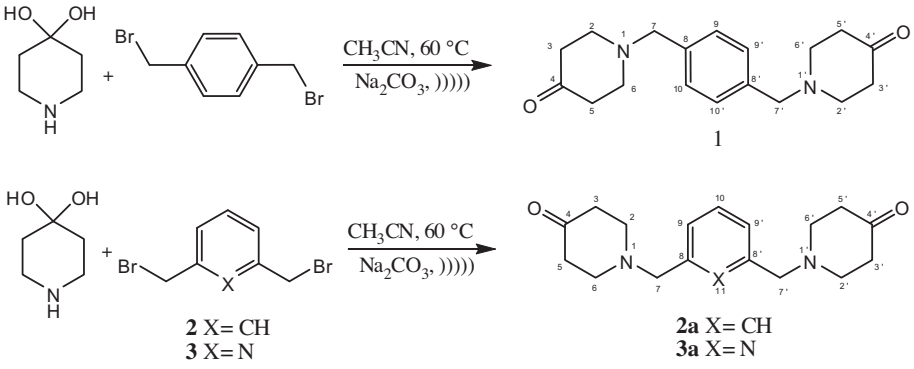
Though Faul et al. [14c] reported the synthesis of simple 1-(pyridin-2-yl-methyl)-piperidin-4-one with 90% yield, the abrupt yields were noticed in case of target molecules **1**, **2a**–**5a** by conventional heating (Table 1). The maximum yield of 64% was noticed in case of bipodal *para* isomer **1**, and the other two *meta* substituted bipodal molecules **2a** and **3a** showed a closely adjusted yields of 14% and 18%, respectively, where as the tripodal molecules **4a** and **5a** showed 20% and 19% yield, respectively. The marked differentiation in yields, and the unsuccessful reaction of 4-piperidone with α,α′-dibromo-*o*-xylene, 1,2,4,5-tetrakis-(bromomethyl)benzene and pentaerythritol tetrabromide to yield the bipodal *ortho* product, and tetrameric products were expected due to high steric hindrance over the molecule.

The yields were greatly increased under sonication (by using E-Chrom ultrasonic horn, 22 kHz frequency) (Table 1) and power ultrasound would be expected to be effective in enhancing this reaction *via* the reduction of the particle size of Na_2CO_3 powder (Fig. 1). This factor was investigated by pre-treating the α,α′-dibromo-*p*-xylene and Na_2CO_3 in acetonitrile under sonication resulting very fine suspension, to that the appropriate proportions of 4-piperidone hydrochloride monohydrate were added and then the reaction was run under conventional conditions. This resulted in about 83% product formation (**1**) in 5 h at 60 °C. Whereas the pre-treated α,α′-dibromo-*p*-xylene and Na_2CO_3 in acetonitrile under sonication was added with appropriate proportions of 4-piperidone hydrochloride monohydrate and then the reaction was run under ultrasonic irradiation which resulted 92% product formation in 20 min at 60 °C. This clearly reveals that even though the pre-treating the base under sonication leads to increase in yield due to its lesser particle size and larger surface area, further increment in the yield in lesser reaction time could be possible by subjecting the reaction under ultrasonic irradiation which allows maximum reactivity of the alkylating agent towards amine. The comparison between the particle sizes of Na_2CO_3 were given in Figs. 1 and 2.

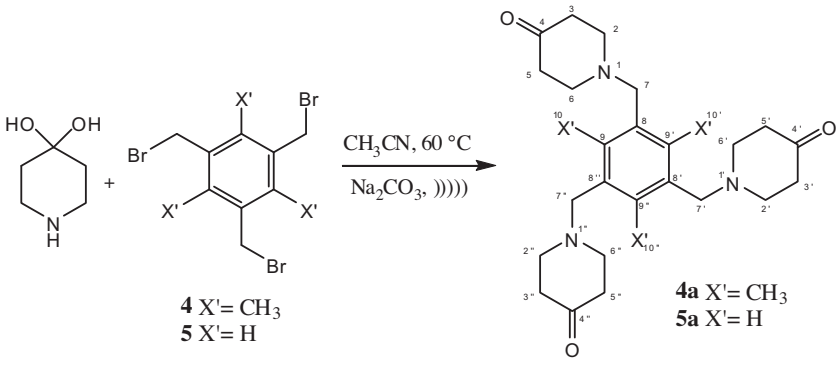
The actual difficulty towards the target molecules lies in its synthesis, where the partitioning of target molecules into organic solvents proved to be a significant challenge after the aqueous workup. So the reaction schemes were designed in such a way by avoiding the solvents and the bases which prefer aqueous workup.

The optimization for the synthesis of 1,1′-(1,4-phenylene*bis*(methylene))dipiperidin-4-one (**1**) were given in Table 2. Though the reaction was successful by the use of DMF and DMSO as solvents, it was not preferred for further optimization of reaction, as these solvents require aqueous workup and hence partitioning of target molecules into organic solvents proved to be a significant challenge. The benzene, THF and acetonitrile were chosen as suitable solvents for the reaction because of their easy workup procedure, where the solid base (Na_2CO_3) left out after the reaction can be filtered off and the excess solvent can be removed under reduced pressure to yield the product.

Average size of Na_2CO_3 particles used in conventional process were found to be 15 μm, where as its average particle size were found to be as 500 nm when it was subjected to ultrasonic irradiation in acetonitrile (Figs. 1 and 2). The size of Na_2CO_3 particles were found to be 800 nm and 1.3 μm when carried the sonication in THF and benzene, respectively. When compared, to the best of our findings, acetonitrile were served as a suitable solvent medium than THF



Scheme 1. Synthesis of *N*-substituted bipodalpiperidin-4-ones, **1**, **2a** and **3a**.



Scheme 2. Synthesis of *N*-substituted tripodalpiperidin-4-ones, **4a**–**5a**.

Table 1
Synthesis of *N*-substituted piperidones using different alkylating/acylating agents and amines by conventional and by ultrasonic irradiation.

Entry	Compound	Alkylating/acylating agent	Amine	Yield (%)[a]	
				Conv, Δ	US,))))
1	**1**	α,α′-Dibromo-*p*-xylene	4-Piperidone	64	92
2	**2a**	α,α′-Dibromo-*m*-xylene	4-Piperidone	14	72
3	–	α,α′-Dibromo-*o*-xylene	4-Piperidone	NR[b]	NR[b]
4	**3a**	2,6-*bis*(Bromomethyl)pyridine	4-Piperidone	18	77
5	**4a**	2,4,6-*tris*(Bromomethyl)mesitylene	4-Piperidone	20	81
6	**5a**	1,3,5-*tris*(Bromomethyl)benzene	4-Piperidone	19	79
7	**8a**	Terephthaloyl chloride	4-Piperidone	13	72
8	**9a**	Isophthaloyl chloride	4-Piperidone	27	86
9	**10a**	Phthaloyl chloride	4-Piperidone	2	37
10	**11**	Terephthaloyl chloride	4-(Hydroxymethyl)piperidine	39	89
11	**12**	Isophthaloyl chloride	4-(Hydroxymethyl)piperidine	NR[b]	NR[b]
12	**13**	Phthaloyl chloride	4-(Hydroxymethyl)piperidine	NR[b]	NR[b]

[a] Isolated yields after purification.
[b] NR = no reaction.

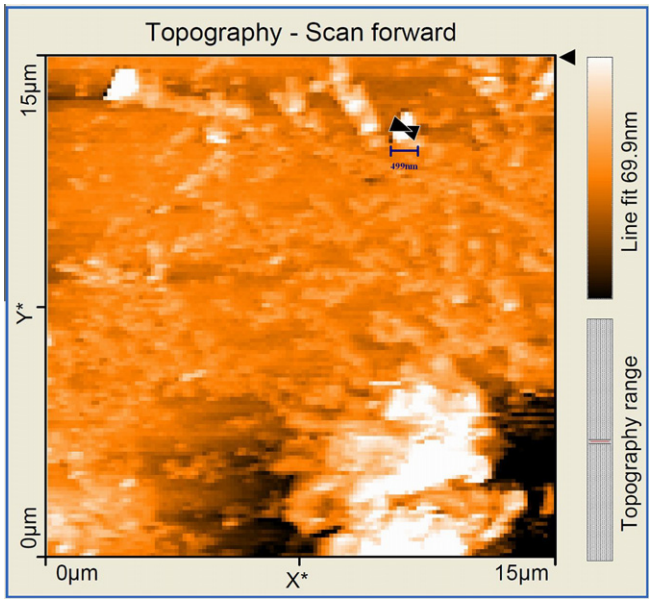


Fig. 1. AFM image of reduced particle size of Na_2CO_3 by ultrasonication; average size of particles is 500 nm.

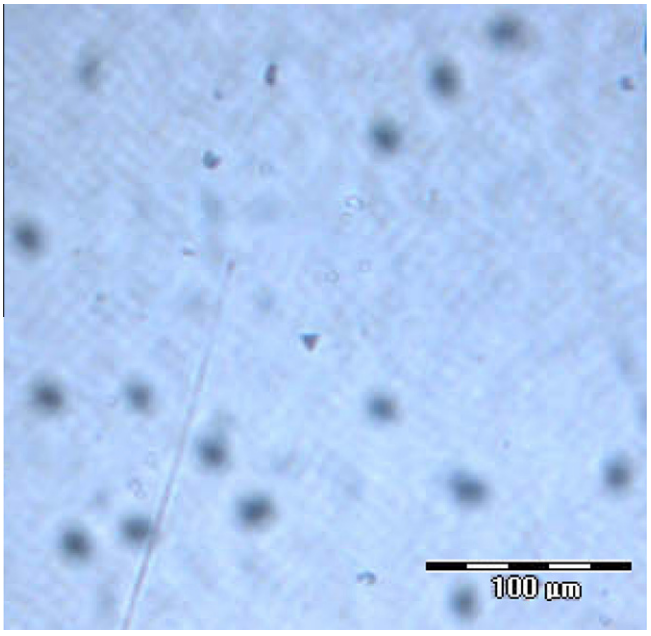


Fig. 2. Optical microscope image of Na_2CO_3 used in conventional process; average size of particles is 15 µm.

and benzene for accelerating the reaction under ultrasonic irradiation allowing maximum reactivity of the alkylating agent towards amine by reducing the particle size of Na_2CO_3.

Control experiments on the *N*-alkylation reaction of 4-piperidones by Faul et al. [14c] reveals that, when alkylating agents (dibromo xylenes) were used, slow generation of a transient carbonation occurs, which is an important feature in obtaining a productive alkylation reaction, so the use of elevated temperatures and stronger base may result faster generation of carbocation and has proclivity to undergo side reactions. If a continuous pulse

Table 2
Optimization for the synthesis of 1,1′-(1,4-phenylene*bis*(methylene))dipiperidin-4-one (**1**).[a]

Entry	Solvent	Time (min)	Yield (%)
1	THF	20	77
2	Acetonitrile	20	92
3	DMF	20	83
4	DMSO	20	75
5	Benzene	20	56

[a] Reaction of 4-piperidone hydrochloride monohydrate (1.05 equiv.) and α,α′-dibromo-*p*-xylene (0.5 equiv.) using Na_2CO_3 (3 equiv.) in different solvents under ultrasonic irradiation.

is given then it will result in the raise in reaction temperature and so a controlled pulsed ultrasound (pulse of 6 s ON and 3 s OFF cycle) was chosen for the reaction. And in the later step, for the productive alkylation, formation of the 4-piperidone free base from 4-piperidone hydrochloride monohydrate is also equally important and the formation of freebase is possible only when the reaction temperature reaches >50 °C. We found that the short pulses are not good enough for the formation of 4-piperidone free base and so a long pulse of 4 min was used at 60 °C.

The reaction was unsuccessful by the use of pyridine, morpholine, KOH/DMF, KOH/DMSO and triethylamine bases. The ORTEP plot of 1,1′,1″-(benzene-1,3,5-triyl*tris*(methylene))tripiperidin-4-one (**5a**) were given in Fig. 3 and its data can be obtained from the Cambridge Crystallographic Data Center (CCDC 769487).

Through results it is evident that the bipodal and tripodalpiperidin-4-ones so obtained (**1**, **2a–5a**) posses high steric hindrance which is responsible for the lowered yields. In order to understand the stereochemistry of the molecule in better, the molecule has to be reduced which could result in splitting of axial and equatorial protons. So, the reduction of a bipodal **1** and tripodal molecule **4a** also was carried under conventional heating by using $NaBH_4$ in methanol (Scheme 3), which resulted compounds **6** and **7** at 61% and 75% of yield, respectively.

In order to maintain higher yields, the reduction of **1** and **4a** were exposed to acoustic cavitation (E-Chrom ultrasonic horn) in the presence of silica chloride [15] which is an effective supporting polymer where the utility of silica chloride in organic synthesis has been well recognized [16]. In view of recent surge in the use of heterogeneous catalysis we have developed a reduction process by ultrasonic irradiation in the presence of silica chloride as an inexpensive, nonvolatile, recyclable, non-explosive, and easy to handle ecofriendly catalyst (Scheme 3). The results of the synthesis and optimization of 1,1′,1″-(2,4,6-trimethylbenzene-1,3,5-triyl)*tris*(methylene)tripiperidin-4-ol (**7**) are summarized in Table 3. As shown in Scheme 3 and Table 3, the effect of ultrasound irradiation in reduction was noticeable and it should be pointed out that in the absence of sonication, the reaction was sluggish. For example, in the absence of ultrasound, the mixture of 1,1′,1″-(2,4,6-trimethylbenzene-1,3,5-triyl)*tris*(methylene)tripiperidin-4-one (**4a**) and silica chloride/$NaBH_4$ was refluxed in an methanolic solution for 7 h which exhibited only 75% of yield.

Exponential increase in yields was not noticed by conventional heating even by the increase in mole ratio of silica chloride, while higher yield of 94% could be achieved after 15 min under ultrasonic irradiation at room temperature in the presence of silica chloride without supplementing any additional heating. Enhanced reaction rates were obtained by ultrasonic irradiation in the presence of silica chloride which showed an excellent yield of 89% and 94% of **6** and **7**, respectively. It may be due to the activation of the surface of silica chloride by the ultrasound irradiation which readily allows the carbonyl group of 4-piperidone to bind and subsequently followed by the borohydride attack which leads to reduction.

Usually the reduction of carbonyl group by the $NaBH_4$ in a conventional way proceeds as described in Fig. 4. In the conventional reduction process, as a part of first step, borohydride will attack the carbonyl carbon in 4-piperidone leaving anionic center on oxygen. The anion will then abstract hydrogen from ethanol leading to the formation of reduction compound piperidin-4-ol. In the absence of catalyst the reaction was sluggish. When the same reaction was carried under ultrasonic irradiation using silica chloride as catalyst, the reaction might have proceeded in another pathway (Fig. 5). The Si–Cl bond in silica chloride is labile and can give rise to Lewis acid centers on silica [17,18]. So ultrasonic process is allowing to displace the Cl very easily by the oxygen of piperidin-4-one by a nucleophilic substitution reaction generating a cationic center on the carbonyl carbon which is a crucial step in the synthesis, that allows nucleophile i.e. borohydride to be easily attacked and leading to reduction. A plausible mechanism is depicted which signifies the role of silica chloride in reduction process by ultrasonic irradiation

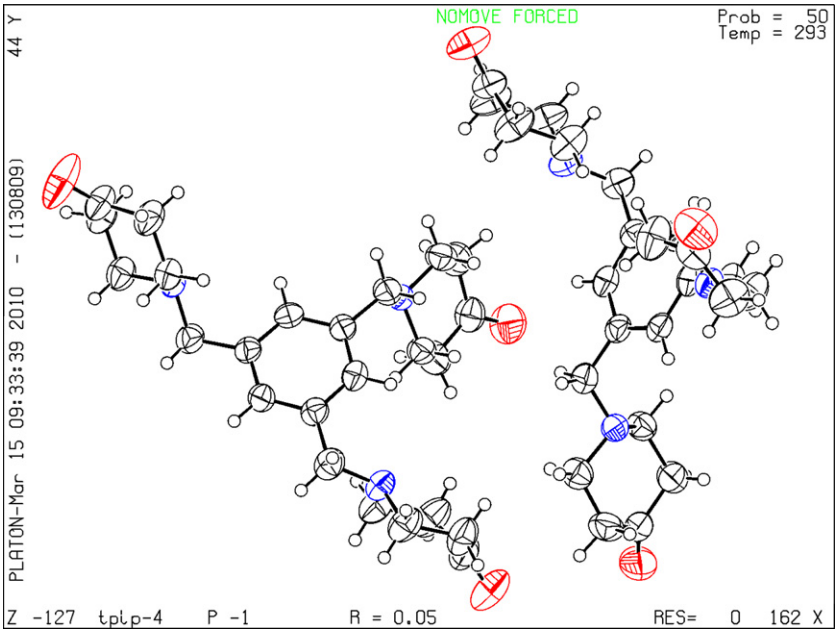
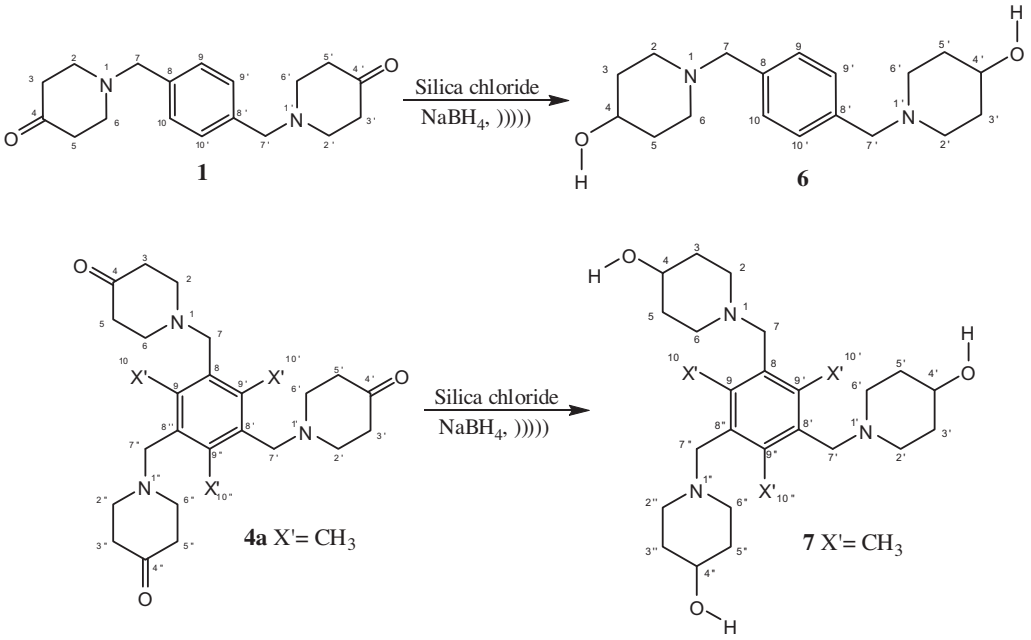


Fig. 3. ORTEP plot of 1,1′,1″-(benzene-1,3,5-triyl*tris*(methylene))tripiperidin-4-one, **5a**.



Scheme 3. Synthesis of *N*-substituted piperidin-4-ols, **6**–**7**.

Table 3
Optimization of 1,1′,1″-(2,4,6-trimethylbenzene-1,3,5-triyl)*tris*(methylene)tripiperidin-4-ol,[a] **7**.

Piperidin-4-one (**4a**) (mmol)	Silica chloride/$NaBH_4$ (mmol)	Time (min)	Yield of **7** (%)[b] by US,)))))
1	1.5/1.5	15	57
1	1.5/3.0	15	79
1	3.0/3.0	15	86
1	4.5/3.3	15	94
1	4.5/6.0	15	94
1	6.0/3.3	15	94
1	4.5/3.3[c]	7 h	75

[a] Reduction of **4a** in the presence of silica chloride/$NaBH_4$ under ultrasonic irradiation at different mole ratios.
[b] Isolated yield after purification.
[c] The reaction was carried out under reflux.

(Fig. 5). The ^1H NMR chemical shift values also clearly shows the axial and equatorial arrangement of protons in tripodalpiperidin-4-ol **7** which represents the reduction.

Compounds **8a–10a** and **11** is the another set of acylated products (Schemes 4 and 5), where its conventional synthesis proved to be experimentally challenging due to high aqueous solubility and its partitioning into organic solvents. In fact, more than five to six extractions of the aqueous layer with CH_2Cl_2 were required to achieve efficient isolation of **8a–10a**. When it was look into the yields, it was significantly low even after tedious workups and it was much diminishing in case of **10a** as the overall yield was 2%. So the synthesis of **8a–10a** and **11** was carried under ultrasonic irradiation, where the increase in yields was noticed under sonication (Table 1).

So the synthesis of **8a–10a** and **11** was carried under ultrasonic irradiation, where the yields were greatly increased under sonication (by using E-Chrom ultrasonic horn, 22 kHz frequency) (Table 1). Sonochemical rate enhancement is a known phenomenon in organic reactions [19] and a plausible reason for this would be that in ultrasonic irradiation, the bubbles formed during the process of cavitation collapse, millions of shock waves, extreme in pressures and temperatures are generated at the implosion sites which facilitate the intermolecular reaction. The available literature clearly reveals that these shock waves can disturb the solvent structure which can influence the reactivity by altering the solvation of reactive species present in the reaction mixture. In our case reactive species may from the phthaloyl chloride since the reaction follows the carbocation mechanism.

The increase in yields of **8a–10a** was also expected due to the same reason, where the ultrasonic irradiation influences the change in reactivity of materials allowing maximum reactivity of phthaloyl chlorides and 4-piperidone by overcoming the steric hindrance. This factor was also investigated by first sonicating the base (TEA) alone in DCM, to that the appropriate proportions of 4-piperidone hydrochloride monohydrate and phthaloyl chloride was added and carried the reaction under conventional heating which could not lead to the formation of product in higher yield. It reveals that sonication of base alone in solvent does not play any role to increase the yields. The same reaction was also carried by altering the order of addition of reactants, where the reactants 4-piperidone hydrochloride monohydrate and phthaloyl chloride

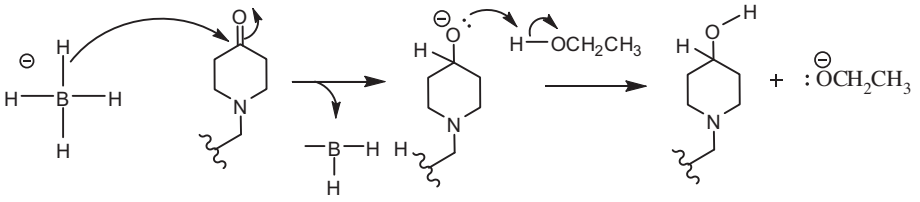


Fig. 4. Plausible mechanism for conventional reduction of carbonyl by the sodiumborohydride.

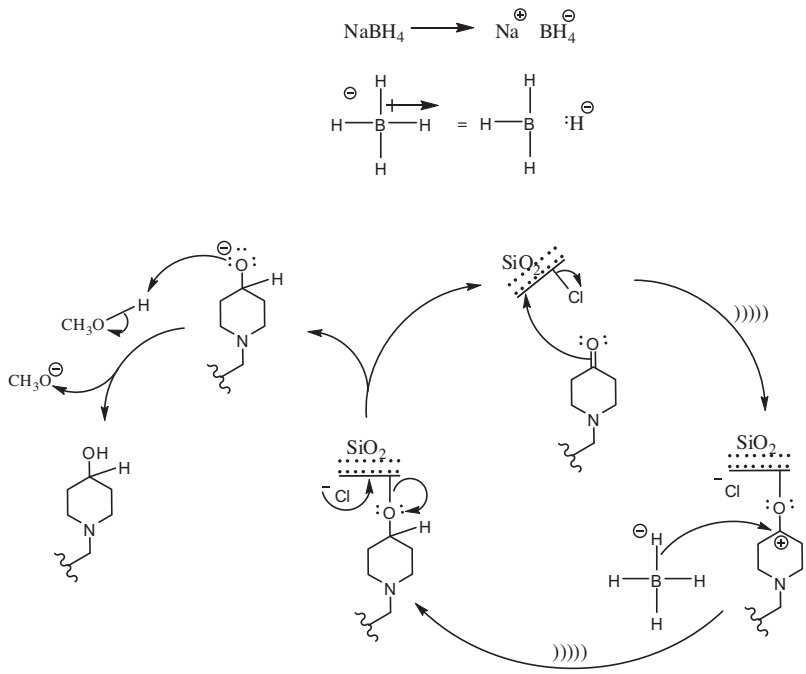
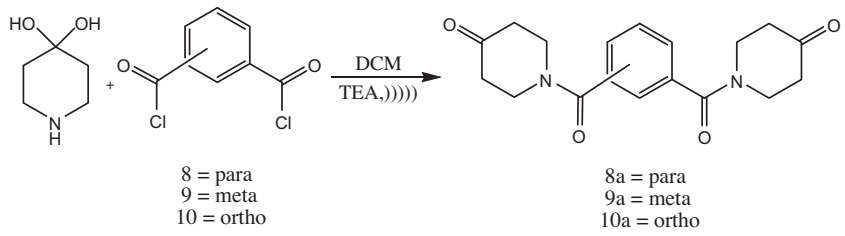
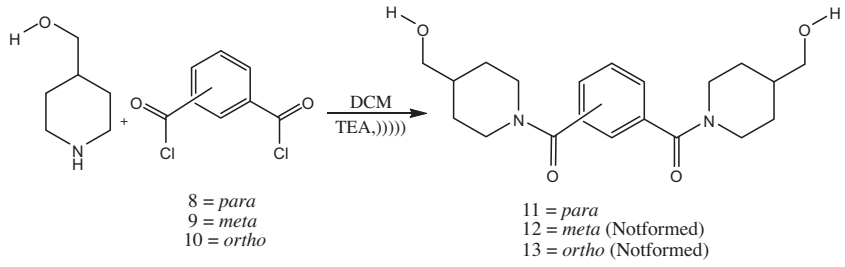


Fig. 5. Plausible mechanism which signifies the role of silica chloride in reduction by ultrasonic irradiation.



Scheme 4. Synthesis of *N*-acylsubstituted bipodalpiperidin-4-ones, **8a**–**10a**.



Scheme 5. Synthesis of *N*-substituted 4-(hydroxymethyl)piperidine, **11**.

was sonicated in presence of solvent, leads to the very fine suspension, to that the TEA was added then the reaction run under conventional conditions which resulted the product in a very high yield. This clearly illustrates that, the sonication influences the reactivity of materials by altering solvation of reactive species.

The structures of compounds **8a–10a** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and by X-ray crystallographic studies. The ^{1}H NMR spectrum of **9a** exhibited broad singlet at δ 2.52 ppm (8 protons at C-3, 3′, 5, 5′), a multiplet at δ 3.77–3.99 ppm (8 protons at C-2, 2′, 6, 6′) and another multiplet at δ 7.55–7.60 ppm (4 protons at C-9, 9′, 10, 11). The two merged triplet's at δ 3.77 ppm and δ 3.99 ppm which looks like a multiplet is due to the contribution of the two possible resonance structures of an amide, where the bond order of the carbonyl C=O bond is reduced, while that of the C–N bond is increased. Also, because of the partial double bond character, the rotation about the C–N axis is slow at room temperature, making the two methyl groups in equivalent on the NMR time scale, giving rise to broadened peak (two merged triplet's) of 4 protons each at δ 3.77 and 3.99 ppm, instead of one signal (triplet) for 8 protons at C-2, 2′, 6, 6′ in the proton NMR spectrum. When it was look into the chemical shift value at δ 2.52 ppm, it appears as a single broad peak without any splitting. This is because of the rotation about the C=N axis which could not show much effect on C-3, 3′, 5, 5′ protons and hence it appeared as a broad singlet at δ 2.52 ppm since both the methylene protons are experiencing almost the same environment.

The principle behind it is the resonance delocalization (Fig. 6) requires that the molecule adopt a planar geometry, and it thus

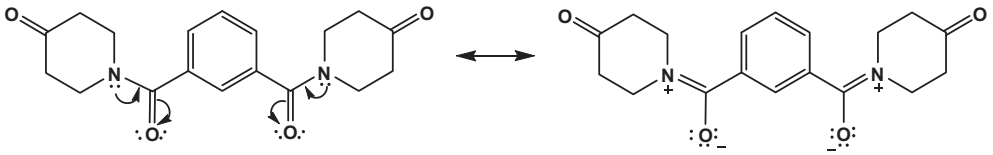


Fig. 6. Resonance delocalization.

interferes with free rotation. If the free rotation is slowed to the point that it takes longer than an NMR transition, the NMR spectrometer sees two different methyl groups, one on the same side of the C=N bond as the carbonyl group and the other on the opposite side. Thus, the groups are in magnetically different environments and have slightly different chemical shifts.

The similar sort of results was seen in case of **11** by the reaction of 4-hydroxymethyl piperidine with terephthaloyl chloride (Scheme 5), but the yields are appreciable when carried the reaction under ultrasonic irradiation. The improved yield would be expected due to the absence of the planarity in the 4-(hydroxymethyl)piperidine, which allows its maximum reactivity towards acylating agent resulting in a non planar bipodal molecule **11** by ultrasonic irradiation. But the yield of its structural isomers **12** and **13** seems to be completely drawn to zero due to high steric hindrance at *meta* and *ortho* positions which restricts the reaction to occur.

3. Experimental

3.1. Chemicals and apparatus

Solvents and reagents were commercially sourced and used without further purification, with the exception of DCM and THF, which were freshly distilled over P_2O_5 and sodium. Melting points were taken on Elchem Microprocessor based DT apparatus in open capillary tubes and corrected with benzoic acid. IR spectra were obtained on an Avatar-330 FTIR spectrophotometer (Thermo Nicolet) using KBr pellets, and only noteworthy absorption levels (reciprocal centimeters) were listed. The NMR spectra were recorded on a Bruker-300 MHz spectrometer using TMS as internal standard (chemical shifts δ in ppm). Mass spectra were recorded on HRMS and LCMS by Agilent 1200 series LC and Micromass zQ spectrometer. Thin-layered chromatography (TLC) was performed on preparative plates of silica gel (s.d.fine). Visualization was made with iodine chamber. Column chromatography was performed using silica gel (60–120 mesh).

3.2. Ultrasound set-up

Ultrasound for sonochemical synthesis is generated with the help of ultrasonic instrument set-up (horn type). The animated representation of the set-up is given in Fig. 7. The specification and details of the experimental set-up are:

Make: E-Chrom Tech Co. Ltd., Taiwan.
Operating frequency: 22 kHz.
Rated output power: 800 W.
Diameter of titanium tip of horn: 1.3×10^{-2} m.
Surface area of ultrasound irradiating face: 1.32×10^{-4} m^2.

3.3. Representative procedure for preparation of N-substituted piperidin-4-ones (1, 2a–5a)

3.3.1. Conventional process

To a suspension of 1.0 equiv. of 4-piperidone hydrochloride monohydrate in 10 volumes of acetonitrile, 3.0 equiv. of Na_2CO_3 and alkylating agent (0.5 equiv. in case of **1**, **2a** and **3a**; 0.333 equiv. in case of **4a** and **5a**) dissolved in acetonitrile was added drop wise with stirring. After the complete addition, the reaction mixture was heated at 60 °C with vigorous stirring for 7 h. The completion of reaction was monitored by TLC. The reaction mixture was then allowed to cool to room temperature and filtered to remove insoluble solids and then the filter cake was washed with acetonitrile. Excess solvents were removed under reduced pressure and the crude products obtained were purified by column chromatography.

3.3.2. Ultrasonic irradiation process

To a suspension of alkylating agent (0.5 equiv. in case of **1**, **2a** and **3a**; 0.333 equiv. in case of **4a** and **5a**) in 10 volumes of acetonitrile, 3.0 equiv. of Na_2CO_3 (depending upon the number of acid equivalents to be neutralized) was added, and subjected to sonication using an ultrasonic horn (by using E-Chrom ultrasonic horn, 22 kHz frequency) at 50% amplitude with a pulse of 6 s ON and 3 s OFF cycle for 5 min. To that, 1.05 equiv. of 4-piperidone hydrochloride monohydrate was added and the reaction mixtures were exposed to acoustic cavitation (E-Chrom ultrasonic horn) at 50% amplitude for 20 min with 5 intervals each for 4 min at 60 °C. The completion of reaction was monitored by TLC, filtered to remove the insoluble solids and then the filter cake was washed with acetonitrile. Excess solvents were removed under reduced pressure and the crude products obtained were purified by column chromatography.

3.4. Spectral data

3.4.1. 1,1′-(1,4-Phenylenebis(methylene))dipiperidin-4-one (*1*)

Purified by column chromatography using a mixture of pet ether and ethyl acetate (3:7). m.p.: 150–152 °C. IR (KBr, cm^{-1}): 2957, 2807, 1713 (–C=O), 1628. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (t, J = 6.0 Hz, 8 protons at H-3, 3′, 5, 5′), 2.76 (t, J = 6.0 Hz, 8 protons at H-2, 2′, 6, 6′), 3.62 (s, 4 protons at H-7, 7′), 7.32 (s, 4 protons at H-9, 9′, 10, 10′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.3 (C-3, 3′, 5, 5′), 52.9 (C-2, 2′, 6, 6′), 61.7 (C-7, 7′), 129.0 (C-9, 9′, 10, 10′), 137.2 (C-8, 8′), 209.3 (C-4, 4′).

3.4.2. 1,1′-(1,3-Phenylenebis(methylene))dipiperidin-4-one (*2a*)

Purified by column chromatography using a mixture of pet ether and ethyl acetate (6:4). Brown viscous liquid. IR (KBr, cm^{-1}): 2959, 2801, 1716 (–C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (t, J = 5.9 Hz, 8 protons at H-3, 3′, 5, 5′), 2.76 (t, J = 6.0 Hz, 8 protons at H-2, 2′, 6, 6′), 3.64 (s, 4 protons at H-7, 7′), 7.29–7.35 (m, 4 protons at H-9, 9′, 10, 11). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.2 (C-3, 3′, 5, 5′), 52.9 (C-2, 2′, 6, 6′), 61.9 (C-7, 7′), 128.0 (C-9, 9′), 128.6 (C-10), 129.4 (C-11), 138.3 (C-8, 8′), 209.2 (C-4, 4′). LCMS: m/z calcd for $C_{18}H_{24}N_2O_2$: 300.18; found 301.2 [M+1], 302.2 [M+2].

3.4.3. 1,1′-(Pyridine-2,6-diylbis(methylene))dipiperidin-4-one (*3a*)

Purified by column chromatography using a mixture of pet ether and ethyl acetate (3:7). m.p.: 94–96 °C. IR (KBr, cm^{-1}): 2950, 2811, 1722 (–C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (t, J = 6.0 Hz, 8 protons at H-3, 3′, 5, 5′), 2.76 (t, J = 6.0 Hz, 8 protons at H-2, 2′, 6, 6′), 3.63 (s, 4 protons at H-7, 7′), 7.29–7.35 (m, 3 protons at H-9, 9′, 10). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.3 (C-3, 3′, 5, 5′),

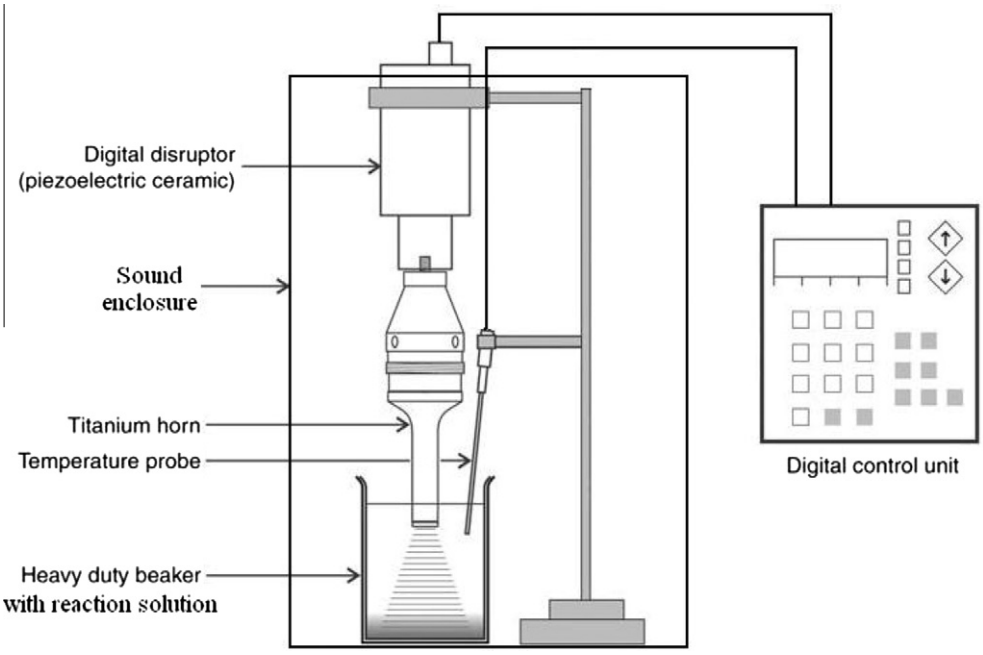


Fig. 7. Schematic of ultrasound horn set-up.

52.9 (C-2, 2′, 6, 6′), 61.3 (C-7, 7′), 121.2 (C-9, 9′), 134.5 (C-10), 155.6 (C-8, 8′), 209.2 (C-4, 4′). LCMS: *m*/*z* calcd for $C_{17}H_{23}N_3O_2$: 301.17; found 302.2 [M+1], 303.2 [M+2].

*3.4.4. 1,1′,1″-(2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene)tripiperidin-4-one (**4a**)*

Purified by column chromatography using a mixture of pet ether and ethyl acetate (8:2). m.p.: 164–166 °C. IR (KBr, cm^{-1}) 2954, 2855, 2793, 1712 (–C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (t, J = 5.7 Hz, 12 protons at H-3, 3′, 3″, 5, 5′, 5″), 2.49 (s, 9 protons at H-10, 10′, 10″), 2.79 (t, J = 5.7 Hz, 12 protons at H-2, 2′, 2″, 6, 6′, 6″), 3.69 (s, 6 protons at H-7, 7′, 7″). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5 (C-10, 10′, 10″), 41.7 (C-3, 3′, 3″, 5, 5′, 5″), 52.4 (C-2, 2′,2″, 6, 6′, 6″), 55.6 (C-7, 7′, 7″), 132.8 (C-9, 9′, 9″), 137.9 (C-8, 8′, 8″), 209.5 (C-4, 4′, 4″). HRMS: *m*/*z* calcd for $C_{27}H_{39}N_3O_3$: 453.2991; found 453.2998 (M^+).

*3.4.5. 1,1′,1″-(Benzene-1,3,5-triyltris(methylene))tripiperidin-4-one (**5a**)*

Purified by column chromatography using a mixture of pet ether and ethyl acetate (5:5). m.p.: 144–146 °C. IR (KBr, cm^{-1}): 2954, 2904, 1712 (–C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (t, J = 5.9 Hz, 12 protons at H-3, 3′, 3″, 5, 5′, 5″), 2.77 (t, J = 6.0 Hz, 12 protons at H-2, 2′, 2″, 6, 6′, 6″), 3.64 (s, 6 protons at H-7, 7′, 7″), 7.27 (s, 3 protons at H-9, 9′, 9″). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.2 (C-3, 3′, 3″, 5, 5′, 5″), 52.9 (C-2, 2′, 2″, 6, 6′, 6″), 61.8 (C-7, 7′, 7″), 128.4 (C-9, 9′, 9″), 138.5 (C-8, 8′, 8″), 209.1 (C-4, 4′, 4″). LCMS: *m*/*z* calcd for $C_{24}H_{33}N_3O_3$: 411.2; found 412.2 [M+1], 413.2 [M+2].

*3.5. Typical procedure for preparation of 1,1′,1″-(2,4,6-trimethylbenzene-1,3,5-triyl)tris (methylene)tripiperidin-4-ol (**7**)*

3.5.1. Conventional reduction

To a solution of 1,1′,1″-(2,4,6-trimethylbenzene-1,3,5-triyl)*tris*(methylene)tripiperidin-4-one (**4a**) (1 mmol) in 20 of methanol was added sodiumborohydride (3.3 mmol) dissolved in minimum amount of water and then refluxed for 7 h. The completion of reaction was monitored by TLC. Then the reaction mixture was allowed to cool to room temperature, to that 5 mL of 6 N NaOH is added and gently heated for 10 min. Excess solvents were removed under reduced pressure and the residue was quenched with ice cold water to give desired **7** as white solid. The crude product were purified by column chromatography and/or crystallization.

3.5.2. Reduction using silica chloride under ultrasonic irradiation

To a solution of 1,1′,1″-(2,4,6-trimethylbenzene-1,3,5-triyl)*tris*(methylene)tripiperidin-4-one (**4a**) (1 mmol) in 20 mL of methanol, sodiumborohydride (3.3 mmol) dissolved in minimum amount of methanol was added. To that silica chloride (4.5 mmol) is added and exposed to ultrasonic irradiation (by using E-Chrom ultrasonic horn, 22 kHz frequency) at 50% amplitude for 15 min. The progress of the reaction was monitored by TLC. The reaction mixture was filtered, and washed with 5 mL methanol. Successively, 5 mL of 6 N NaOH was added and heated gently for 5 min. Excess solvents were removed under reduced pressure and the residue was quenched with ice cold water to give desired **7** as white solid. The crude product were purified by column chromatography and/or crystallization.

3.6. Spectral data

*3.6.1. 1,1′-(1,4-Phenylenebis(methylene))dipiperidin-4-ol (**6**)*

Purified by column chromatography using 100% chloroform. m.p.: 158–160 °C. IR (KBr, cm^{-1}): 3410 (–OH), 2924, 2856. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34–1.41 (m, 4 equatorial protons at H-3, 3′, 5, 5′), 1.67–1.71 (m, 4 axial protons at H-3, 3′, 5, 5′), 1.98–2.02 (t, J = 10 Hz, 4 equatorial protons at H-2, 2′, 6, 6′), 2.62–2.65 (m, 4 axial protons at H-2, 2′, 6, 6′), 3.32 (s, 4 protons at H-7, 7′), 3.44 (m, 2 protons at H-4, 4′), 4.51 (s, 2 -OH), 7.21 (s, 4 arom. protons at H-9, 9′, 10, 10′). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.9 (C-3, 3′), 51.4 (C-2, 2′), 62.4 (C-7, 7′), 66.8 (C-4, 4′), 128.9 (C-9, 9′, 10, 10′), 137.7 (C-8, 8′). LCMS: *m*/*z* calcd for $C_{18}H_{28}N_2O_2$, 304.21; found 305.2 [M+1], 306.2 [M+2].

*3.6.2. 1,1′,1″-(2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene)tripiperidin-4-ol (**7**)*

Purified by column chromatography using 100% chloroform. m.p.: 208–210 °C. IR (KBr, cm^{-1}): 3400 (–OH), 2929, 2852. ^{1}H

NMR (300 MHz, $CDCl_3$): δ 1.42 (q, J = 9.8 Hz, 6 equatorial protons at H-3, 3′, 3″, 5, 5′, 5″), 1.74 (6 axial protons at H-3, 3′, 3″, 5, 5′, 5″), 2.15 (t, J = 9.6 Hz, 6 equatorial protons at H-2, 2′, 2″, 6, 6′, 6″), 2.38 (s, 9 protons at H-10, 10′, 10″), 2.69 (t, J = 9.6 Hz, 6 axial protons at H-2, 2′, 2″, 6, 6′, 6″), 3.48 (s, 6 protons at H-7, 7′, 7″), 3.54 (s, 3 protons at H-4, 4′, 4″), 4.31 (bs, 3 -OH protons at 11, 11′, 11″). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.4 (C-10, 10′, 10″), 35.2 (C-3, 3′, 3″), 51.0 (C-2, 2′, 2″), 56.43 (C-7, 7′, 7″), 67.0 (C-4, 4′, 4″), 133.0 (C-9, 9′, 9″), 137.1 (C-8, 8′, 8″). LCMS: m/z calcd for $C_{27}H_{45}N_3O_3$: 459.35; found 460.4 [M+1], 461.4 [M+2], 462.4 [M+3].

3.7. Representative procedure for preparation of 1,1′-(phenylenebis(carbonyl))dipiperidin-4-ones (**8a–10a**)

3.7.1. Conventional process

To a suspension of 4-piperidone hydrochloride monohydrate (1 mmol) in 20 mL of DCM which was dried over P_2O_5 was added triethylamine (3 mmol), stirred well for 15 min. To that respective phthaloyl dichlorides (0.5 mmol) dissolved in 10 mL of dry DCM were added drop wise with stirring, the stirring was continued for 6–7 h. The progress of the reaction was monitored by TLC. The reaction mixture was washed with 15 mL of 0.5 N HCl and then with 20 mL of water in two parts. The water was extracted 5–6 times with 40 mL of DCM and dried over $MgSO_4$. The extracts was combined with the reaction mixture and the excess solvent was removed under reduced pressure. The crude products obtained were purified by column chromatography.

3.7.2. Ultrasonic irradiation process

To a suspension of 4-piperidone hydrochloride monohydrate (1 mmol) in 20 mL of DCM which was dried over P_2O_5 was added triethylamine (3 mmol), stirred well for 15 min. To that respective phthaloyl dichlorides (0.5 mmol) dissolved in 10 mL of dry DCM were added drop wise with stirring, then the reaction mixtures were exposed to acoustic cavitation (by using E-Chrom ultrasonic horn, 22 kHz frequency) at 50% amplitude for 12 min. The progress of the reaction was monitored by TLC. The reaction mixture was washed with 15 mL of 0.5 N HCl and then with 20 mL of water in two parts. The water was extracted 5–6 times with 40 mL of DCM and dried over $MgSO_4$. The extracts was combined with the reaction mixture and the excess solvent was removed under reduced pressure. The crude products obtained were purified by column chromatography.

3.8. Spectral data

3.8.1. 1,1′-(1,4-Phenylenebis(carbonyl))dipiperidin-4-one (**8a**)

Purified by column chromatography using a mixture of pet ether and ethyl acetate (7:3). m.p.: 228–230 °C. IR (KBr, cm^{-1}): 2923, 1715 (–C=O), 1617 (–N–C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (m, 8 protons at H-3, 3′, 5, 5′), 3.89 (m, 8 protons at H-2, 2′, 6, 6′), 7.56 (s, 4 protons at H-9, 9′, 10, 10′). ^{13}C NMR (125 MHz, $CDCl_3$): δ 41.2 (C-3, 3′, 5, 5′), 46.0 (C-2, 2′, 6, 6′), 127.32 (C-9, 9′, 10, 10′), 137.01 (C-8, 8′), 169.8 (C-7, 7′), 206.0 (C-4, 4′). HRMS: m/z calcd for $C_{18}H_{20}N_2O_4$: 328.1423; found 328.1437 (M^+).

3.8.2. 1,1′-(1,3-Phenylenebis(carbonyl))dipiperidin-4-one (**9a**)

Purified by column chromatography using a mixture of pet ether and ethyl acetate (7:3). m.p.: 142–144 °C. IR (KBr, cm^{-1}): 2924, 1716 (–C=O), 1622 (–N–C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (bs, 8 protons at H-3, 3′, 5, 5′), 3.89 (m, 8 protons at H-2, 2′, 6, 6′), 7.55–7.60 (m, 4 protons at H-9, 9′, 10, 11). ^{13}C NMR (125 MHz, $CDCl_3$): δ 41.0 (C-3, 3′, 5, 5′), 46.0 (C-2, 2′, 6, 6′), 125.7 (C-11), 128.6 (C-9, 9′), 129.1 (C-10), 135.9 (C-8, 8′), 169.8 (C-7, 7′), 206.1 (C-4, 4′). HRMS: m/z calcd for $C_{18}H_{20}N_2O_4$: 328.1423; found 328.1428 (M^+).

3.8.3. 1,1′-(1,2-Phenylenebis(carbonyl))dipiperidin-4-one (**10a**)

Purified by column chromatography using a mixture of pet ether and ethyl acetate (7:3). m.p.: 146–148 °C. IR (KBr, cm^{-1}): 2925, 1716 (–C=O), 1615 (–N–C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (t, J = 6.2, 8 protons at H-3, 3′, 5, 5′), 3.68 (t, J = 5.9, 4 protons at H-2, 2′, 6, 6′), 3.96 (bs, 4 protons at H-2, 2′, 6, 6′), 7.38–7.42 (m, 2 protons at H-9, 9′), 7.45–7.50 (m, 2 protons at H-10, 10′). HRMS: m/z calcd for $C_{18}H_{20}N_2O_4$: 328.1423; found 328.1427 (M^+).

3.9. Typical procedure for preparation of 1,4-phenylenebis((4-(hydroxymethyl)piperidin-1-yl) methanone) (**11**)

To a solution of terephthaloyl dichloride, **8** (2 mmol) in DCM which was dried over P_2O_5 was added triethylamine (2 mmol), stirred well for 15 min. To that 4-hydroxymethyl piperidin (1 mmol) in 10 mL of dry DCM were added drop wise with stirring, then the reaction mixtures were exposed to acoustic cavitation (by using E-Chrom ultrasonic horn, 22 kHz frequency) at 50% amplitude for 12 min. The progress of the reaction was monitored by TLC. Excess solvent was removed and the solid separated out was filtered washed with water and it was recrystallized by using methanol.

3.10. Spectral data

3.10.1. 1,4-Phenylenebis((4-(hydroxymethyl)piperidin-1-yl)methanone) (**11**)

M.p.: 196 °C. IR (KBr, cm^{-1}): 3445 (–OH), 2949, 2896, 1615 (–N–C=O). ^{1}H NMR (500 MHz, CD_3OD): δ 1.21–1.33 (m, 4 equitorial protons at H-3, 3′, 5, 5′), 1.72–1.91 (m, 4 axial protons at H-3, 3′, 5, 5′ and 3H), 2.87–2.92 (t, J = 11.75 Hz, 2H), 3,13–3.18 (t, J = 12 Hz, 2H), 3.46–3.47 (4H, –CH_2–O protons), 3.73–3.75 (d, J = 12 Hz, 2H), 4.57 (s, 1H), 4.66–4.68 (d, J = 12 Hz, 2H), 7.51 (s, 4 arom. protons at H-9, 9′, 10, 10′). ^{13}C NMR (125 MHz, CD_3OD): δ 29.0 (C-3, 3′, 5, 5′), 38.5 (C-4, 4′), 42.0 (C-2, 2′, 6, 6′), 66.0 (C-11, 11′), 126.7 (C-9, 9′, 10, 10′), 137.3 (C-8, 8′), 170.0 (C-7, 7′). LCMS: m/z calcd for $C_{20}H_{28}N_2O_4$: 360.20; found 361.2 [M+1], 362.2 [M+2].

4. Conclusion

In conclusion, we have described the synthesis of novel bipodal and tripodalpiperidin-4-ones by conventional and by ultrasonic irradiation process under mildly basic conditions using powdered Na_2CO_3. The use of ultrasonic irradiation allowed the maximum reactivity of alkylating/acylating agent towards amine leading to the higher yields of product formation in lesser time when compared to the conventional heating. We have also found an efficient procedure for the reduction of bipodal and tripodalpiperidin-4-ones to respective piperidin-4-ols under ultrasonic irradiation using silica chloride/$NaBH_4$. The ultrasonic process is allowing, displacing the chlorine very easily by the oxygen of piperidin-4-one by a nucleophilic substitution reaction generating a cationic center resulting reduction with higher yields. This sonication method provides clean, conversion, greater selectivity and easy workup make this protocol economically attractive.

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