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Sonochemical synthesis of novel pyrano[3,4-e][1,3]oxazines: A green protocol

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ABSTRACT

The atom-efficient and green protocol for formation of pyrano[3,4-e][1,3]oxazines utilizing dimethyl carbonate under ultrasound irradiation in a presence of KF/basic alumina was reported. We provide a novel series of pyrano[3,4-e][1,3]oxazine derivatives interesting for biological screening tests. In general, it was found that ultrasound irradiations enable the reactions to occur which could not be carried out under silent conditions. These remarkable effects appeared in sonicated reactions can be reasonably interpreted in terms of acoustic cavitation phenomenon. Structures of the products were established on analytical and spectral data. This protocol offers several advantages attain many principles of green chemistry including, save energy, atom economy, clean reactions, inexpensive green reagent and use catalysts rather than stoichiometric reagents.

1. Introduction

Green chemistry was introduced in the 1990s with the aim of overcoming health and environmental problems at their source by developing cleaner chemical processes for the chemical industry through the design of innovative and environmentally benign chemical reactions [1,2]. Green organic syntheses must include at least some of the following requirements: avoid waste [2,3], be atom efficient [4], avoid the use and production of toxic and dangerous chemicals, produce compounds that perform better or as well as the existing ones, produce compounds that are biodegradable, avoid auxiliary substances (e.g., solvents) or use eco compatible solvents (water or dense CO_2), reduce energy requirements, use renewable materials and use catalysts rather than stoichiometric reagents [2,5].

Therefore, the introduction of green synthetic methodologies for certain important heterocyclic moieties has attracted a great deal of interest from medicinal chemists, biochemists and pharmacologists as these moieties are lead molecules for designing potential bioactive agents. Among the large variety of heterocyclic moieties, oxazine derivatives are considered to be an important class of heterocyclic compounds, and there have been reports claiming that they have diverse biological activities, such as antimicrobial [6–11], anticoagulant [12,13], anticancer [14,15], fungicidal [16], anti-tubercular [17–21], antimalarial [22], analgesic, anti-inflammatory [23], antidiabetic, hypolipidaemic [24] and antiproliferative [25] activities.

In addition, 1,3-oxazine containing moieties possess a wide synthetic utility as useful intermediates for a variety of functional group interconversions [26–28]. Recently, the 1,3-oxazine ring system has been used for photo induced opening and thermal closing [29]. Furthermore, they can be used as intermediates in the synthesis of *N*-substituted amino alcohols (Betti base) or in the enantioselective synthesis of chiral amines [30].

A great number of synthetic possibilities, realizing the importance of 1,3-oxazine derivatives as intermediates as well as in the synthesis of various drug sources, have been reported, and they were synthesized by a few classical methods using dry methanolic ammonia [31], ammonium acetate [32], $Cu(OAc)_2$-$ZnCl_2$ [33], basic conditions [34], phosgene [35], and triphosogene [36,37]. However, there have only been a few reports of the synthesis of pyrano[3,4-e][1,3]oxazine derivatives by reacting isocyanates with 4-hydroxy-6-methylpyran-2-one [38]. However, most of these reactions require exotic reaction conditions, long reaction times and tedious work-up procedures while having low product yields. Additionally, we cannot overlook the risks of using phosgene, triphosgene and isocyanates in the synthesis of these important heterocyclic systems.

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Therefore, in search of better alternatives, we have attempted to find a convenient and efficient method based on a green approach instead of the previously reported methods for the synthesis of 1,3-oxazine derivatives.

Dimethyl carbonate (DMC) is a versatile compound that represents an attractive ecofriendly alternative to both methyl halides (and dimethyl sulfate) and phosgene for methylation and carbonylation processes, respectively. It is noteworthy that, the reactivity of DMC is tunable; at T ⩽ 90 °C, methoxycarbonylations take place, while at higher reaction temperatures, methylation reactions are observed with a variety of nucleophiles [2].

On the other hand, the ultrasound technique has been proven to be an important tool in the arsenal of "green chemistry" [39]. The use of ultrasound for improving traditional reactions that require longer reaction times, have unsatisfactory yields, use expensive reagents and operate under high temperatures is commonly termed "sonochemistry". "Sonochemistry" is a brand new trend in organic chemistry that shares some aims with green chemistry, including the intention to minimize the environmental impact of chemical synthesis [39,40].

Motivated by the aforementioned findings and in a continuation of our interest in the synthesis of a wide range of heterocyclic systems utilizing different green chemistry tools in our laboratory [41–49], herein we report the synthesis of some novel pyrano [3,4-e][1,3]oxazines utilizing dimethyl carbonate under ultrasound irradiation. This provides a green protocol for obtaining the novel pyrano[3,4-e][1,3]oxazines.

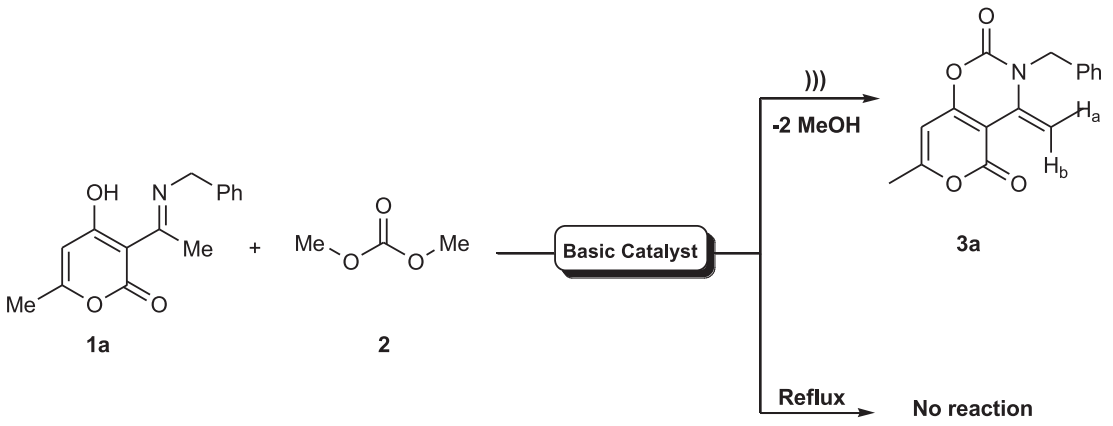
2. Results and discussions

A wide variety of catalysts were scanned in an attempt to prepare novel pyrano[3,4-e][1,3]oxazine derivatives in an ecofriendly way using dimethyl carbonate under ultrasonic irradiation, in which 3-(1-(benzylimino)ethyl)-4-hydroxy-6-methyl-2H-pyran-2-one (**1a**) [50] and dimethyl carbonate (**2**) were allowed to react under ultrasonic irradiation at 70–80 °C as a model reaction, which led to the formation of only one isolable product (as examined by TLC and ^{1}H NMR spectroscopy) (Scheme 1). The reaction times and yields are shown in Table 1.

From Table 1, the results indicate that, under ultrasonic irradiation no product formed in absence of catalyst (entry 1) or in presence of neutral alumina catalyst (entry 3), but the KF/basic alumina catalyst (entry 5) offered the highest yield of the desired product (91%) within a short reaction time (45 min.) under ultrasonic irradiation. The next best catalyst was basic alumina (entry 4), which offered an 82% yield within 60 min. and potassium carbonate (entry 2) afforded low yield (69%) than other active heterogeneous catalysts (entry 4 and 5). To further show the significance of this work, the catalytic activity of KF/basic alumina was compared with the activity of triethylamine (frequently used as a homogeneous catalyst in the literature). The yield of product **3a** was approximately 80%, when we used triethyl amine as a catalyst under the same reaction conditions. This result indicates that KF/basic alumina not only offers a better catalytic activity but is also green in nature [51a]. The reaction product was identified as the 3-benzyl-7-methyl-4-methylene-3,4-dihydropyrano[3,4-e][1,3]oxazine-2,5-dione structure (**3a**) in all cases on the basis of its ^{1}H NMR spectrum. The ^{1}H NMR spectrum of the isolated reaction product revealed, in each case, three singlet signals at δ 2.35, 5.05 and 6.52 ppm due to CH_3, Ph$\underline{CH_2}$ and H_{pyran}, respectively, two doublets at δ 4.58 and 5.73 ppm with coupling constants of approximately 1.6 Hz due to the =$\underline{CH_2}$ and an aromatic multiplet in the region 7.32–7.40 ppm. The absence of any D_2O exchangeable signals indicates the disappearance of the hydroxyl group. Additionally, the ^{13}C NMR of the isolated product shows a distinct signal for the exocyclic methylene group at δ 93.3 ppm, which is in agreement with the structure formed as shown in Scheme 1.

To find the specific effect of ultrasound on this reaction, the above mentioned reaction was carried out under the same conditions in the absence of ultrasound irradiation (silent condition) (Table 1).

It is clear from results cited in Table 1 that, under the silent condition (reflux at 80–90 °C) even after 12 h, no reaction occurs in absence or presence of a catalyst (as indicated by TLC). Therefore, it was found that the ultrasound irradiation enables this reaction to occur, and it could not be carried out under the silent condition. This may be attributed to the fact that ultrasonic irradiation gives the reactants sufficient energy to exceed the energy barrier of the reaction, thus, 3-benzyl-7-methyl-4-methylene-3,4-dihydropyrano[3,4-e][1,3]oxazine-2,5-dione (**3a**) formed. This sufficient energy can be reasonably interpreted in terms of the physical phenomenon called acoustic cavitation (in our case, at solid-liquid interfaces), in which there are two proposed mechanisms for the effect of cavitation near surfaces [51b,52]. The first one is microjet impact and shockwave damage. Along with the shock wave associated with the cavitation collapse, the jet causes localized deformation and surface erosion, which increases the possible reaction area. Therefore, the treated surfaces contain an increased number of dislocations that are widely considered to be the active sites in catalysis. The second mechanism is acoustic streaming, which is the movement of the liquid induced by the sonic wave, and it aids mass transport. Acoustic streaming can be considered to simply be the conversion of sound to kinetic energy and is not a cavitation effect. In our opinion, the first mechanism is more



Scheme 1. Optimization the reaction conditions for the synthesis of pyrano[3,4-e][1,3]oxazine-2,5-dione derivatives.

Table 1
Reaction of **1a** with DMC (**2**) using different heterogeneous catalysts.

Entry	Catalyst	Ultrasonic irradiation		Silent condition	
		Time (min.)	Yield%	Time (h)	Yield%
1	None	180	No reaction	⩾12	No reaction
2	K_2CO_3	60	69	⩾12	
3	Neutral alumina	90	No reaction	⩾12	
4	Basic alumina	60	82	⩾12	
5	KF/basic alumina	45	91	⩾12	

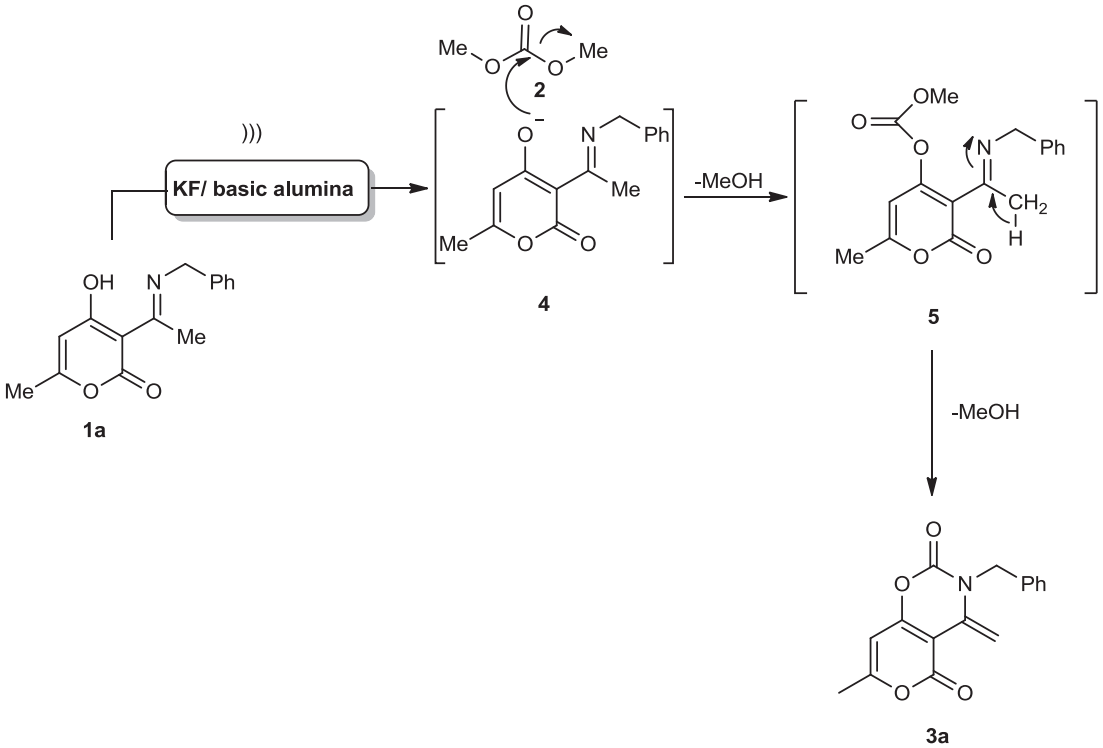
reasonable for the above mentioned reaction, especially because our reaction could not proceed without ultrasonic irradiation (under the silent condition). This means that the reactivity is not only a result of the kinetic energy but that cavitation also has a key role regarding this issue. Therefore, our attention has been directed towards discovering factors influencing cavitation to prove our mechanism choice (first mechanism). The intensity of the cavitations increases depending on the type of solvent and frequency used. The solvent used to perform the sonochemical reaction must be carefully chosen. As a general rule, most applications are performed in water. However, in our reaction we used dimethyl carbonate (DMC). It was found that DMC has almost the same vapor pressure as water at 70–80 °C [53], and cavitation is more difficult with a low vapor pressure liquid. Additionally, DMC also has a low viscosity [54], and cavitation is easier in solvents with low viscosities [51b]. Any particles or motes (solid base catalyst) present in the solvent will act as seeds for cavitation [51b]. The above mentioned facts drove us to select the first mechanism for the observed reactivity.

It is reasonable to propose a mechanism for the formation of 3,4-dihydropyrano[3,4-e][1,3]oxazine-2,5-dione derivative **3a** under the adopted reaction conditions (Scheme 2).

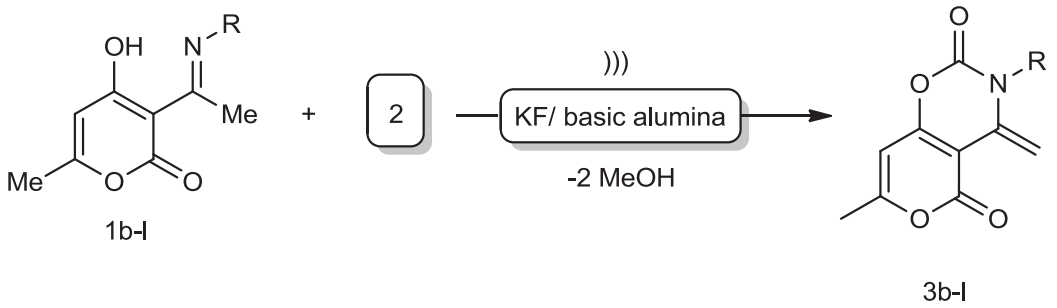
DMC acts primarily as a methoxycarbonylating agent by a B_{AC}^2 (bimolecular base-catalyzed acyl cleavage nucleophilic substitution) mechanism, where the nucleophile **4** attacks the carbonyl carbon of DMC **2** (slow step), giving the non-isolatable intermediate **5** (Trans esterification product). The intermediate rearranged and formed an enamine due to the presence of a basic catalyst (KF/ basic alumina), and then it loses a methanol molecule to give the product **3a**. It is noteworthy that ultrasonic irradiation enhances the proposed slow step.

The scope and generality of this protocol was tested by using various derivatives of 3-(1-(substituted imino)ethyl)-4-hydroxy-6-methyl-2H-pyran-2-one **1b-l** [55,56] as shown in Scheme 3 under the best reaction conditions, and the corresponding pyrano[3,4-e][1,3]oxazines were obtained in excellent yields under ultrasonic protocol (82–92%, Table 2).

The structures of products **3b-l** were confirmed based on their elemental analyses and spectroscopic data. The IR spectra of compounds **3b-l** showed the disappearance of the hydroxyl group absorption bands. Additionally, the IR spectra of compounds **3d-l** showed, in each case, the appearance of a band due to the NH group. The mass spectra of **3l** showed a peak corresponding to a molecular ion at 348, and its ^{1}H NMR spectrum revealed two singlet signals at δ 2.29 and 6.44 ppm due to CH_3 and $H_{pyran,}$ respectively, two doublets at δ 4.85 and 5.61 ppm with coupling constants of approximately 1.2 Hz due to = $\underline{CH_2}$ and a D_2O exchangeable signal at δ 11.05 in addition to the aromatic



Scheme 2. Suggested mechanism for synthesis of pyrano[3,4-e][1,3]oxazine-2,5-dione derivative.



Scheme 3. KF/basic alumina catalyzed synthesis of pyrano[3,4-e][1,3]oxazine-2,5-dione derivatives utilizing DMC under ultrasonic irradiations.

multiplet in the region of δ 7.59–7.86 ppm. Additionally, the ^{13}C NMR of **3l** is in agreement with the structure formed.

On the other hand, to assess the green synthetic procedure for the synthesis of the pyrano[3,4-e][1,3]oxazine derivatives presented above, we conducted the same reaction described above but utilizing triphosgene [bis(trichloromethyl) carbonate (BTC)] instead of DMC. Therefore, the treatment of compound **1a** with triphosgene **6** (0.5 equivalents) in dichloromethane, which was acting as solvent, in the presence of triethylamine (2.5 equivalents) (recommended conditions for reactions with BTC under a nitrogen atmosphere [57]) under ultrasonic irradiation at 60–70 °C as a representative example, afforded a product identical in all respects (mp, mixed mp and spectra) with those of compound **3a** in a 73% yield (Scheme 4) in addition to a mixture of byproducts, such triethylamine hydrochloride, phosogene, carbon tetrachloride, CO_2, ... etc. [58]. Herein, we do not intend to study this reaction depicted in Scheme 4 in detail to identify all of the byproducts obtained, but we take it as example to compare the atom economy between the reactions of Scheme 3 and those in Scheme 4.

It is noteworthy to mention here that, chemists must not only strive to achieve a maximum percent yield, but also design syntheses that maximize the incorporation of the atoms of the reactants into the desired product.

In this context, it is obvious that the reaction mentioned in Scheme 4 has a poorer atom economy than those in Scheme 3, the atom economy being easily calculated by the following Eq. (1) [59]:

$$\textbf{Atom Econmy} = \frac{\text{Mass of atoms of the desired product}}{\text{Mass of atoms of the reactants}} \times 100 \quad (1)$$

Therefore, the reaction representing utilizing DMC (under the best conditions) shows that the atom economy for compound **3a** is 81.66% (as calculated by the Eq. (1)) [*cf.* Supporting information S5].

While the other reaction in Scheme 4 shows an atom economy for compound **3a** of 43.64% (as calculated by the above Eq. (1), triethylamine (TEA) as stoichiometric catalyst share in equation for reaction in Scheme 4) [*cf.* Supporting information S5].

The combination of a reaction with a high atom economy and an easy preparation of the pyrano[3,4-e][1,3]oxazines utilizing DMC as a replacement for triphosgene (although triphosgene is considered the safer substitute for phosgene to certain extent, but it can decompose into phosogene at 85 °C in basic medium [57]) under ultrasonic irradiation is expected to contribute to the development of a novel green protocol for the simple and fast preparation of pyrano[3,4-e][1,3]oxazine derivatives.

3. Conclusion

The green reaction described herein offers a rapid, atom economic and safe alternative to other methods for the formation of 1,3-oxazine derivatives using DMC under ultrasonic irradiation. The reactions proceed under mild conditions and give the products in good yields with high atom economies therefore attaining many principles of green chemistry. Moreover, the present work shows that ultrasound irradiation enables some reactions to occur that could not be carried out under the silent condition, with other advantages of this procedure including a simple separation and purification.

4. Experimental

4.1. General

All organic solvents were purchased from commercial sources and used as received unless otherwise stated. All other chemicals were purchased from Merck, Aldrich or Acros and used without further purification. Thin-layer chromatography (TLC) was performed on precoated Merck 60 GF254 silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile Attenuated Total Reflectance (ATR) sampling accessory on the Nicolet iS10 FT-IR spectrometer.

The NMR spectra were recorded on a Bruker Avance III 400 (9.4 T, 400.13 MHz for ^1H, 100.62 MHz for ^{13}C and 376.25 MHz for ^{19}F) spectrometer with a 5-mm BBFO probe, at 298 K. Chemical shifts (δ in ppm) are given relative to internal solvent, DMSO-d_6 2.50 for ^1H and 39.50 for ^{13}C was used as an external standard. Mass spectra were recorded on a Thermo ISQ Single Quadrupole GC–MS. Elemental analyses were carried out on a EuroVector instrument C, H, N, S analyzer EA3000 Series.

Sonication was performed by Techno-gaz sonicator (with a frequency of 37 kHz and ultrasonic peak max. 320 W).

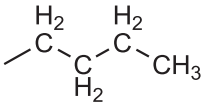
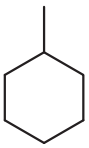
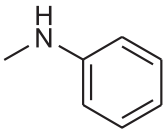
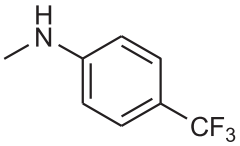
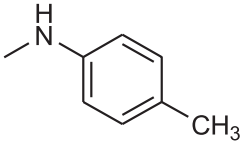
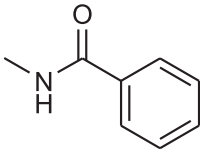
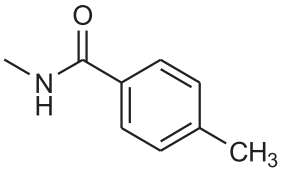
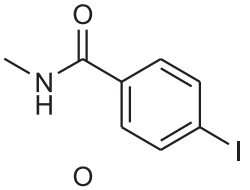
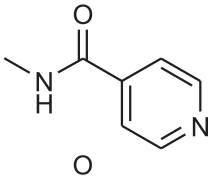
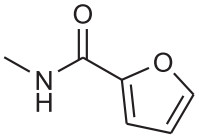
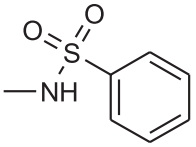
3-(1-(Substiutedimino)ethyl)-4-hydroxy-6-methyl-2H-pyran-2-one (**1a-l**) [50,55,56] [*c.f.* Supporting information S1–S3] and KF/basic alumina [60], were prepared according to the reported literature

4.2. Typical procedure for synthesis of 3,4-dihydropyrano[3,4-e][1,3] oxazine-2,5-dione derivatives 3a-l

4.2.1. Sonicated reactions

In an 100 ml Erlenmeyer flask, a mixture of 3-(1-(substiutedimino)ethyl)-4-hydroxy-6-methyl-2H-pyran-2-one (1 mmol) (**1a-l**) and dimethyl-carbonate (20 ml) (**2**) in the presence of 0.5 g KF/

Table 2
Synthesis of pyrano[3,4-e][1,3]oxazine derivatives under ultrasonic irradiations.

Compound	R	Ultrasonic irradiation	
		Time (min.)	Yield%
3b		45	83
3c		45	89
3d		60	84
3e		45	92
3f		60	86
3g		60	82
3h		60	84
3i		60	88
3j		60	91
3k		60	87
3l		60	85

basic alumina as catalyst subjected to ultrasonic irradiations for appropriate time (*cf.* Tables 1 and 2). All The reactions were kept at 70–80 °C (the temperature inside reaction vessel was 70–75 °C and the reaction flask was put in the mid of sonicator bath to achieve effective cavitations). The sonochemical reactions were continued until the starting material **1a-l** was no longer detectable by TLC. The reaction mixture was filtered (to remove the catalyst) and the filtrate was concentrated in *vacuo* and the residual solid was taken in ethanol then collected by filtration to give the pure product.

The above reaction was studied also for starting material **1a** with DMC (**2**) as model reaction by using various catalysts (i) in presence of 0.5 g of potassium carbonate or basic alumina, these processes were performed on the same scale described above and the progress of the reaction was monitored by TLC, the same product **3a** was formed in each case (*cf.* Table 1) in different percent yield, work up as described above. (ii) The reaction was also performed on the same scale described above without any catalyst under ultrasonic irradiation but no product formed. (iii) in presence of (1 ml) of triethyl amine (TEA), this process was performed on the same scale described above and same product obtained identified as **3a** in 80% yield (*cf.* Table 1). The reaction mixture was concentrated in *vacuo* and the residual solid was taken in ethanol then collected by filtration to give the product recrystallized from hexan/ethylacetate.

4.2.2. Silent reactions

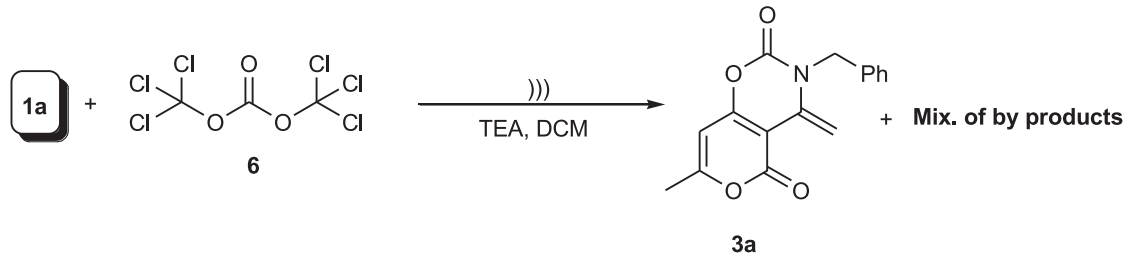
Several attempts were attained to synthesize 3,4-dihydropyr ano[3,4-e][1,3]oxazine-2,5-dione derivative **3a**, in which the reaction was performed on the same scale described above for sonicated reaction. Here the reactant **1a**, DMC (**2**) and catalysts were taken under reflux (at about 80 °C) for time more than 12 h but only the starting material **1a** was detected by TLC and no new product obtained in each case, the reaction did not take place till about 18 h (monitoring reaction by TLC).

4.2.3. Alternative way for synthesis of 3,4-dihydropyrano[3,4-e][1,3] oxazine-2,5-dione derivative 3a under ultrasonic irradiation

Into an oven-dried 100 mL three necked round-bottomed flask, the flask was fitted with a purging valve (inlet & outlet for both left and right neck) through which, at room temperature, air was removed before reaction by purging with a N_2 stream. A reflux condenser was fitted for middle neck (one "nitrogen balloon" connecting to the top end of condenser and wrap the connection with electrical tape to further ensure a tight seal).

First, flush the reaction flask with nitrogen for 5 min by opening one of the side necks of the flask as an outlet for the nitrogen. After 5 min, charge the flask with starting material **1a** (2.00 mmol) dissolved in anhydrous dichloromethane (DCM) (15 mL), and triethylamine (0.70 mL, 5.00 mmol) was then added via syringe, followed by triphosgene (BTC) (297 mg, 1.00 mmol) in one portion. Next, add 10 mL of DCM carefully, washing any BTC on the walls of the inside of the flask so that all of the starting materials is under the surface of the solvent. Continue flushing the flask with nitrogen for 3–4 min and then fit again the purging outlet valve to the side neck. (be sure the nitrogen balloon is still filled), then the reaction subjected to ultrasonic irradiation at 60–70 °C for 60 min., the reaction mixture was poured into separating funnel contain water, and the biphasic mixture was then shaken vigorously. Upon separation of layers, the aqueous layer was re-extracted with dichloromethane (2 × 30 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under vacuum. The resulting crude material was purified by recrystallization from hexanes/ethyl acetate.

The synthesized compounds with their physical data are listed below.



Scheme 4. Synthesis of pyrano[3,4-e][1,3]oxazine-2,5-dione derivative utilizing BTC under ultrasonic irradiations.

4.2.3.1. 3-benzyl-7-methyl-4-methylene-3,4-dihydropyrano[3,4-e][1,3]oxazine-2,5-dione (3a). M.p. = 173–175 °C; IR (KBr): 1719, 1699 (2 CO), 1612 (=CH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.35 (s, 3H, CH_3), 5.05 (s, 2H, Ph$\underline{CH_2}$), 4.58 (d, 1H, J = 1.6 Hz, H_a), 5.73 (d, 1H, J = 1.6 Hz, H_b), 6.52 (s, 1H, H_{pyran}), 7.32–7.40 (m, 5H, ArH); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ: 20.0, 48.5, 93.3, 96.3, 98.6, 127.7, 128.1, 129.4, 133.4, 135.7, 146.3, 159.3, 160.6, 165.3. MS (*m*/*z*): 283 (M^+). (Found: C, 68.11; H, 4.51; N, 4.79; $C_{16}H_{13}NO_4$ requires C, 67.84; H, 4.63; N, 4.94.)

4.2.3.2. 3-butyl-7-methyl-4-methylene-3,4-dihydropyrano[3,4-e][1,3]oxazine-2,5-dione (3b). M.p. = 100–102 °C; IR (KBr): 1723, 1701 (2 CO), 1616 (=CH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 0.98 (t, 3H, CH_3), 1.56 (m, 2H, CH_2), 1.93 (quintet, 2H, CH_2), 2.71(s, 3H, CH_3), 3.88 (t, 2H, CH_2), 4.52 (d, 1H, J = 0.62 Hz, H_a), 4.99 (d, 1H, J = 0.62 Hz, H_b), 6.48 (s, 1H, H_{pyran}); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ: 12.9, 18.2, 19.5, 28.7, 48.5, 92.1, 96.0, 100.3, 144.2, 151.8, 156.1, 159.8, 163.3. MS (*m*/*z*): 249 (M^+). (Found: C, 62.88; H, 5.96; N, 5.49; $C_{13}H_{15}NO_4$ requires C, 62.64; H, 6.07; N, 5.62.)

4.2.3.3. 3-cyclohexyl-7-methyl-4-methylene-3,4-dihydropyrano[3,4-e][1,3]oxazine-2,5-dione (3c). M.p. = 126–128 °C; IR (KBr): 1723,1701 (2 CO), 1622 (=CH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.12–1.13 (m, 1H), 1.35–0.39 (m, 2H), 1.61–1.62 (m,1H), 1.71–1.77 (m, 4H), 2.16–2.21 (m, 2H), 2.27 (s, 3H, CH_3), 3.82 (m, 1H), 4.92 (d, 1H, J = 0.84 Hz, H_a), 5.73 (d, 1H, J = 1 Hz, H_b), 6.38 (s, 1H, H_{pyran}); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ: 20.0, 25.4, 25.9, 28.4, 59.2, 94.1, 97.2, 98.4, 134.4, 144.3, 159.4, 160.6, 165.2. MS (*m*/*z*): 275 (M^+). (Found: C, 65.69; H, 6.11; N, 4.95; $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22; N, 5.09.)

4.2.3.4. 7-methyl-4-methylene-3-(phenylamino)-3,4-dihydropyrano[3,4-e][1,3]oxazine-2,5-dione (3d). M.p. = 202–204 °C; IR (KBr): 3331 (NH), 1721, 1705 (2 CO), 1614 (=CH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 4.96 (d, 1H, J = 0.42 Hz, H_a), 5.69 (d, 1H, J = 0.42 Hz, H_b), 6.52 (s, 1H, H_{pyran}), 6.84–6.88 (m, 3H, ArH), 7.23–7.27 (m, 2H, ArH), 8.76 (s, 1H, NH, D_2O excheangable); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ: 20.0, 91.6, 96.3, 98.7, 112.8, 120.4, 129.5, 134.6, 145.6, 145.9, 159.4, 160.2, 165.3. MS (*m*/*z*): 284 (M^+). (Found: C, 63.66; H, 4.14; N, 9.68; $C_{15}H_{12}N_2O_4$ requires C, 63.38; H, 4.25; N, 9.85.)

4.2.3.5. 7-methyl-4-methylene-3-((4-(trifluoromethyl)phenyl)amino)-3,4-dihydropyrano[3,4-e][1,3]oxazine-2,5-dione (3e). M.p. = 191–193 °C; IR (KBr): 3316 (NH), 1728, 1706 (2 CO), 1611 (=CH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.33 (s, 3H, CH_3), 4.82 (d, 1H, J = 0.62 Hz, H_a), 5.62 (d, 1H, J = 0.62 Hz, H_b), 6.53 (s, 1H, H_{pyran}), 6.99 (d, 2H, J = *8.2*Hz, ArH), 7.53 (d, 2H, J = *8.2* Hz, ArH), 9.39 (s, 1H, NH, D_2O excheangable); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ: 20.0, 91.3, 96.3, 98.7, 112.5, 120.5, 126.9, 134.3, 145.5, 149.4, 159.3, 160.3, 165.5. ^{19}F NMR (DMSO-d_6): δ -62.67;. MS (*m*/*z*): 352 (M^+). (Found: C, 54.77; H, 3.03; N, 7.85; $C_{16}H_{11}F_3N_2O_4$ requires C, 54.55; H, 3.15; N, 7.95.)

4.2.3.6. 7-methyl-4-methylene-3-(p-tolylamino)-3,4-dihydropyrano[3,4-e][1,3]oxazine-2,5-dione (3f). M.p. = 221–223 °C; IR (KBr): 3321 (NH), 1729, 1701 (2 CO), 1611 (=CH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 4.89 (d, 1H, J = 0.82 Hz, H_a), 5.63 (d, 1H, J = 0.82 Hz, H_b), 6.47 (s, 1H, H_{pyran}), 6.92 (d, 2H, J = 7.4 Hz, ArH), 7.14 (d, 2H, J = 7.4 Hz, ArH), 9.27 (s, 1H, NH, D_2O excheangable); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ:19.9, 20.2, 92.0, 97.5, 98.9, 112.2, 127.4, 132.6, 141.9, 145.2, 152.0, 159.5, 163.9, 164.1. MS (*m*/*z*): 298 (M^+). (Found: C, 64.73; H, 4.60; N, 9.21; $C_{16}H_{14}N_2O_4$ requires C, 64.42; H, 4.73; N, 9.39.)

4.2.3.7. N-(7-methyl-4-methylene-2,5-dioxopyrano[3,4-e][1,3]oxazin-3(2H,4H,5H)-yl)benzamide (3g). M.p. = 198–200 °C; IR (KBr): 3337 (NH), 1726, 1713, 1703 (3 CO), 1612 (=CH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.66 (s, 3H, CH_3), 4.71 (d, 1H, J = 0.8 Hz, H_a), 5.36 (d, 1H, J = 0.8 Hz, H_b), 6.43 (s, 1H, H_{pyran}), 7.39–7.88 (m, 5H, ArH), 9.49 (s, 1H, NH, D_2O excheangable); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ:20.0, 91.3, 93.5, 98.6, 112.6, 125.2, 129.5, 142.0, 144.3, 149.8, 154.9, 159.8, 162.9, 167.0. MS (*m*/*z*): 312 (M^+). (Found: C, 61.81; H, 3.87; N, 8.83; $C_{16}H_{12}N_2O_5$ requires C, 61.54; H, 3.87; N, 8.97.)

4.2.3.8. 4-methyl-N-(7-methyl-4-methylene-2,5-dioxopyrano[3,4-e][1,3]oxazin-3(2H,4H,5H)-yl)benzamide (3h). M.p. = 226–228 °C; IR (KBr): 3322 (NH), 1731, 1715, 1702 (3 CO), 1618 (=CH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 4.87 (d, 1H, J = 0.90 Hz, H_a), 5.24 (d, 1H, J = 0.88 Hz, H_b), 6.37 (s, 1H, H_{pyran}), 7.48 (d, 2H, J = *8* Hz, ArH), 7.64 (d, 2H, J = *8* Hz, ArH), 9.78 (s, 1H, NH, D_2O excheangable); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ:19.9, 20.4, 92.4, 95.6, 99.0, 126.8, 129.4, 141.0, 143.6, 149.9, 155.1, 162.9, 163.0, 167.1. MS (*m*/*z*): 326 (M^+). (Found: C, 62.81; H, 4.21; N, 8.44; $C_{17}H_{14}N_2O_5$ requires C, 62.57; H, 4.32; N, 8.59.)

4.2.3.9. 4-iodo-N-(7-methyl-4-methylene-2,5-dioxopyrano[3,4-e][1,3]oxazin-3(2H,4H,5H)-yl)benzamide (3i). M.p. = 252–254 °C; IR (KBr): 3317 (NH), 1728, 1712, 1701 (3 CO), 1611 (=CH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.52 (s, 3H, CH_3), 4.47 (d, 1H, J = 0.8 Hz, H_a), 5.39 (d, 1H, J = 0.8 Hz, H_b), 6.27 (s, 1H, H_{pyran}), 7.78 (d, 2H, J = *8* Hz, ArH), 7.97 (d, 2H, J = *8* Hz, ArH), 9.98 (s, 1H, NH, D_2O excheangable); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ: 20.0, 91.0, 95.3, 99.7, 102.3, 129.1, 132.5, 136.0, 146.1, 150.6, 157.4, 162.7, 165.1. MS (*m*/*z*): 437 (M^+). (Found: C, 44.12; H, 2.43; N, 6.26; $C_{16}H_{11}IN_2O_5$ requires C, 43.86; H, 2.53; N, 6.39.)

4.2.3.10. N-(7-methyl-4-methylene-2,5-dioxopyrano[3,4-e][1,3]oxazin-3(2H,4H,5H)-yl)isonicotinamide (3j). M.p. = 228–230 °C; IR (KBr): 3349 (NH), 1731, 1714, 1708 (3 CO), 1621 (=CH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.89 (s, 3H, CH_3), 4.85 (d, 1H, J = 0.6 Hz, H_a), 5.61 (d, 1H, J = 0.6 Hz, H_b), 6.34 (s, 1H, H_{pyran}), 8.22 (d, 2H, J = 5.90 Hz, 3,5-$H_{Pyridine}$), 8.45 (d, 2H, J = 5.90 Hz, 2,6-$H_{Pyridine}$), 10.03 (s, 1H, NH, D_2O excheangable); ^{13}C NMR

(100.62 MHz, DMSO-d_6) δ: 20.2, 93.0, 96.2, 98.6, 119.5, 141.5, 143.6, 148.0, 150.5, 157.0, 161.7, 163.0, 167.8. MS (*m*/*z*): 313 (M^+). (Found: C, 57.78; H, 3.41; N, 13.27; $C_{15}H_{11}N_3O_5$ requires C, 57.51; H, 3.54; N, 13.41)

4.2.3.11. N-(7-methyl-4-methylene-2,5-dioxopyrano[3,4-e][1,3]oxazin-3(2H,4H,5H)-yl)furan-2-carboxamide (3k). M.p. = 175–178 °C; IR (KBr): 3315 (NH), 1723, 1717, 1703 (3 CO), 1616 (=CH_2) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.33 (s, 3H, CH_3), 4.81(d, 1H, J = 0.8 Hz, H_a), 5.61 (d, 1H, J = 0.8 Hz, H_b), 6.36 (s, 1H, H_{pyran}), 7.21 (d, J = 2.4 Hz, 1H, H_{Furan}), 7.46 (d, J = 1.2 Hz, 1H, H_{Furan}), 7.63 (dd, J = 2.4, 1.2 Hz, 1H, H_{Furan}), 9.62 (s, 1H, NH, D_2O excheangable); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ: 20.1, 92.1, 94.9, 98.2, 113.4, 118.3, 142.9, 144.5, 148.8, 156.8, 158.0, 163.6, 163.7. MS (*m*/*z*): 302 (M^+). (Found: C, 55.92; H, 3.20; N, 9.11; $C_{14}H_{10}N_2O_6$ requires C, 55.63; H, 3.33; N, 9.27.)

4.2.3.12. N-(7-methyl-4-methylene-2,5-dioxopyrano[3,4-e][1,3]oxazin-3(2H,4H,5H)-yl)benzenesulfonamide (3l). M.p. = 211–213 °C; IR (KBr): 3324 (NH), 1714, 1701 (2 CO), 1613 (=CH_2), 1149, 1284 (SO_2) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.29 (s, 3H, CH_3), 4.85 (d, 1H, J = 0.6 Hz, H_a), 5.61 (d, 1H, J = 0.6 Hz, H_b), 6.43 (s, 1H, H_{pyran}), 7.59–7.86 (m, 5H, ArH), 11.05 (s, 1H, NH, D_2O excheangable); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ:20.06, 93.2, 96.3, 984, 127.8, 129.7, 134.0, 134.7, 140.2, 145.2, 159.0, 159.6, 165.7. MS (*m*/*z*): 348 (M^+). (Found: C, 52.03; H, 3.36; N, 7.90; S, 9.14. $C_{15}H_{12}N_2O_6S$ requires C, 51.72; H, 3.47; N, 8.04; S, 9.21.)

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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.ultsonch.2016.12.015.

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