Heterocyclic Letters
Vol. 14| No.1|109-119|Nov-Jan|2024
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF N-SUBSTITUTED AZEPINES *VIA* CU(II)-CATALYZED IONIC LIQUID OXIDATIVE CYCLIZATION OF DIMETHYL 2-(ARYLAMINO) MALEATE ION WITH 2,5- DIMETHOXYTETRAHYDROFUR AN UNDER MICROWAVE IRRADIATON

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Abstract : The ionic liquid of Lewis acid [n-Bu_4P][$CuBr_3$], was found to be an efficient and reusable catalyst for three component synthesis of fully N-substituted azepines from the reaction of 2,5-dimethoxytetrahydrofuran, anilines and dimethyl acetylenedicarboxylate (DMAD). One benefit of the MW/IL approach is that it can be used as a tool to accelerate organic conversions. simple workup procedure, clear reaction profile and high yield in short reaction time (3-5mints).

Key-words:oxidative cyclization, ionic liquid[IL],microwave irradiation,Amines, Dimethyl/diethyl acetylenedicarboxylate, 2,5-dimethoxytetrahydrofuran.

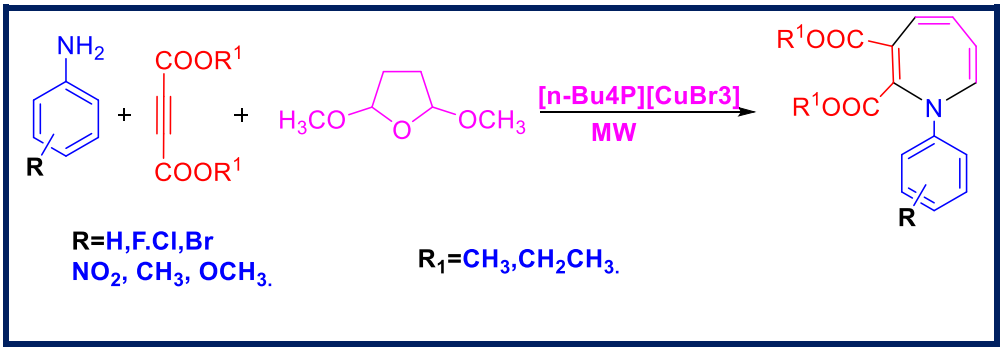
Introduction :

Azepines are important class of heterocyclic compounds found in many biologically active molecules. Azepines and it derivatives shows varied biological activities, such as serotonin antagonistic, anticonvulsive, antiemetic, anti-inflammatory,spasmolytic and antihistaminic. They have also been widely used in anti-HIV drug theraphy[I], antimalarial drug theraphy[II], in treatment for stomach disorders[III], hypertension (glaucoma)[IV,V], anti-arrhythmia[VI],other pharmaceutical applications[VII], fungicidal activity[VIII],and anticonvulsant[IX].

Azepines exhibit a broad range of biological activities and are also present in several biologically active natural products such as Silvaticamide and Clavizepine. Usually these can be prepared by the incorporation of nitrenes accomplished by the thermolysis of azides, cyclization of diene conjugated nitrile ylides, synthesized by the base catalyzed dehalogenation of the analogous of imidoyl chlorides, and [4+2] cycloaddition reactions[X]. Intramolecular aza-Wittig reaction has been one of the suitable methods for the synthesis of azepines. F. D. Toste et al., developed Au(III)-catalyzed synthesis of *N*-arylazepines via inter molecular process of forming ringsbetween propargyl ester and *N*-phenylimine[XI]. P. A. Wender et al., synthesized *N*-substituted azepines by transition metal-catalyzed aza [5+2] cycloaddition strategy, involving various imines[XII]. Raghu et al., reported the preparation of *N*-substituted azepines derivatives via tandem Michael addition–cyclization using PEG-400 as a recyclable

medium without additional organic solvent[XIII]. Ramesh et al., developed β-Cyclodextrin catalyzed synthesis of *N*-substituted azepines *via* Tandem Michael Addition and Cyclization[XIV]. While various procedure have been developed for the synthesis of N-substituted azepine derivatives, many of the methods possess disadvantage such as insensitive reaction conditions, unsatisfactory yields, tedious experimental procedures and long reaction times. In view of these inadequacy, there is a need to develop eco-friendly synthetic protocol for the synthesis of N- substituted azepines by replacing toxic or carcinogenic organic solvents with Cu (II) using a catalyst in the context of green chemical methodologies.

In recent years, researchers have applied MW heating be use in the presence of an IL, a faster reaction rate was achieved, to shorten reaction times, avoid side products, increase yields and simplify reaction procedures for Microwave-assisted organic synthesis (MAOS). Temperature ILs as catalysts or growing media in for environmentally friendly and economically attractive processes have found many applications New materials[XV,XVI], inorganic synthesis[XVII] ,materials science[XVIII], electrochemistry[XIX], and separation technology[XX],Biotechnology[XXI]Chemical engineering [XXII–XXV]. Due to the wide range of applications of ionic liquids in academic and industrial fields, great development in the structure and property of ionic liquids has been made over the last two decades. In this scope,Fraga-Dubreuil and Bazureau combined MW dielectric heating and task-specific ILs as synthetic equivalent ofIL-phase matrices for the efficient one-pot three-component synthesis of a small library of 4-thiazolidinones[XXVI].Hu et al. synthesis of MW-assisted liquid-phase Gewald synthesis of 2-aminothiophenes [XXVII].Sun et al developed aerobic oxidation of phenol[XXVIII] and 2,3,6-triethylphenol[XXIX] to their corresponding quinones in the presence of[bmim][$CuCl_3$]. Comparison of the results obtained using this catalytic system with some of those reported in the literature using different oxidizing agents or copper(II) salts shows that the reaction is more selective and environmentally friendly using [bmim][$CuCl_3$].Also the reaction in the presence of catalytic amount of this ionic liquid leads to higher yields and shorter reaction times. In continuation of our interest towards the development of environmentally friendly methods for heterocyclic synthesis [XXX] herein, we report a novel and efficient procedure for the synthesis of azepine by simple cyclization–oxidation of Dimethyl 2-(Arylamino) maleate ion with 2,5-dimethoxytetrahydrofuran in the presence of copper(II) ionic liquid,[n-Bu4P][CuBr3], as a reusable catalyst **(Scheme 1)**.



Scheme I. Synthesis of N-substituted azepines *via* oxidative cyclization of Dimethyl 2- (Aryl amino) maleate ion with 2,5-dimethoxytetrahydrofuran

The structure of compounds **1-18**were distinguished by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopy, as well as elemental analysis. IR spectra of compounds **1-18**highlighted signal of ester carbonyl groups at 1724-1780 cm^{-1}.

Results and discussion

In order to achieve the optimized reaction conditions, the reaction of aniline, 2,5-dimethoxytetrahydrofuran and DMAD was chosen as a model (Table 1). Initially, the model

reaction wascarried out in the absence of the catalyst. As shown in Table 1,the reaction was not successful even after prolonged reaction times. Then, the reaction was carried out in the presence of 25 mol% $CuBr_2$ and the corresponding product was obtained in 37% yield after 5 min (Table 1, entry 3). In order to liquefy thereaction mixture for well stirring, we used [n-Bu_4P][$CuBr_3$] IL as a catalyst. The results showed that the reaction was carried out efficiently and the desired product was obtained in 87% yield(Table 1, entry 12). Several other Lewis acid ionic liquids such as [bmim][$FeCl_4$], [bmim][$ZnCl_3$], [bmim][$CuCl_3$], [bmim][$CuBr_3$] and [bmim][$InCl_4$] were also tested for this reaction (Table 1,entries 7–11), showing lower yields of the product. Finally, the reaction of aniline(1 mmol), 2,5-dimethoxytetrahydrofuran (1 mmol) and DMAD (1.2 mmol) in the presence of [n-Bu_4P][CuBr3] (0.25 mmol) under microwave irradiation was chosen as the optimized reaction conditions.

Table 1 Optimization of the reaction conditions using different IL catalyst[a]

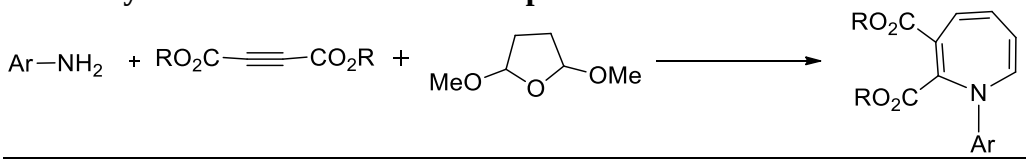
Entry	Catalyst	Time (min)	Yield[b]
1	No Catalyst	10	30
2	$CuBr_2$	5	35
3	CuO	5	37
4	$CuCl_2$	5	34
5	$Cu(OTf)_2$	6	45
6	$Cu(OAc)_2.H_2O$	4	42
7	[bmim][$FeCl_4$]	5	50
8	[bmim][$ZnCl_3$]	6	38
9	[bmim][$CuCl_3$]	4	62
10	[bmim][$CuBr_3$]	5	65
11	[bmim][$InCl_4$]	6	59
12	**[n-Bu_4P][$CuBr_3$]**	**3**	**94**
13	[IsoBu_4P][$CuBr_3$]	5	72

[a]aniline(1 mmol), 2,5-dimethoxytetrahydrofuran (1 mmol) and DMAD (1.2 mmol) in the presence of various IL's (0.25 mmol) under microwave irradiation

[b] Isolated yield.

To survey the scope and generality of this method, a wide range of anilines and 2,5-dimethoxytetrahydrofuran andDimethyl/diethyl acetylenedicarboxylate were used under the optimized reaction conditions (Table 2). Substitution on the aromatic ring played a crucial role in governing the product yield as it can be seen from Table 2. Electron-donating groups on aniline gave good yields (Table 2, entry4,11) while electron-withdrawing groups on aniline gave lower yields, (Table 2, entry 2, 6, 13, 16) in comparison with aniline (Table 2, entry 8,10). To the best of our knowledge this is the first report using copper based ionic liquids in the synthesis of N-substituted azepine.

Table 2Synthesis of N-Substituted Azepine Derivatives



Entry	Amines	R	Product	Time (Min)	Yield (%)
1	4-bromoaniline	Me	$C_{16}H_{14}BrNO_4$	3	92
2	4-nitroaniline	Me	$C_{16}H_{14}N_2O_6$	5	84
3	4-chloroaniline	Me	$C_{16}H_{14}ClNO_4$	3	89
4	4-methoxyaniline	Me	$C_{17}H_{17}NO_5$	3	94
5	4-fluoroaniline	Me	$C_{16}H_{14}FNO_4$	4	88
6	3-nitroaniline	Me	$C_{16}H_{14}N_2O_6$	5	85
7	naphthalen-1-amine	Me	$C_{20}H_{17}NO_4$	4	89
8	aniline	Me	$C_{16}H_{15}NO_4$	3	90
9	pyridin-2-amine	Me	$C_{15}H_{14}N_2O$	4	87
10	aniline	Et	$C_{18}H_{19}NO_4$	3	89
11	4-methoxyaniline	Et	$C_{19}H_{21}NO_5$	3	94
12	naphthalen-1-amine	Et	$C_{22}H_{21}NO_4$	4	89
13	3-nitroaniline	Et	$C_{18}H_{18}N_2O_6$	5	85
14	4-chloroaniline	Et	$C_{18}H_{18}ClNO_4$	3	89
15	4-fluoroaniline	Et	$C_{18}H_{18}FNO_4$	4	88
16	4-nitroaniline	Et	$C_{18}H_{18}N_2O_6$	5	84
17	pyridin-2-amine	Et	$C_{17}H_{18}N_2O_4$	4	87
18	4-bromoaniline	Et	$C_{18}H_{18}BrNO_4$	3	92

[a]aniline(1 mmol), 2,5-dimethoxytetrahydrofuran (1 mmol) and DMAD (1.2 mmol) in the presence of [n-Bu_4P][CuBr3] (0.25 mmol) under microwave irradiation
[b] Isolated yield.

Reusability and recyclability of a catalyst is of practical importance in minimizing the amount of waste. In this context, we investigated the reusability of this ionic liquid in the model reaction. After completion of the reaction, water (30 ml) was added and the organic materials were filtered. Then, the water was evaporated, the catalyst was dried at 80^0C under reduced pressure for 2 h and reused. The catalyst could be recycled five times with slight loss of its activity (Fig. 2).

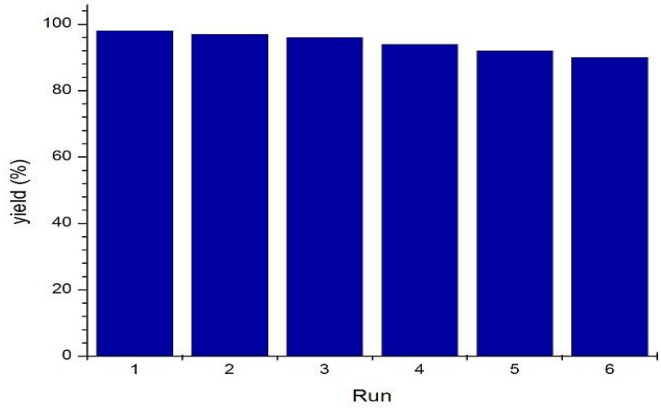
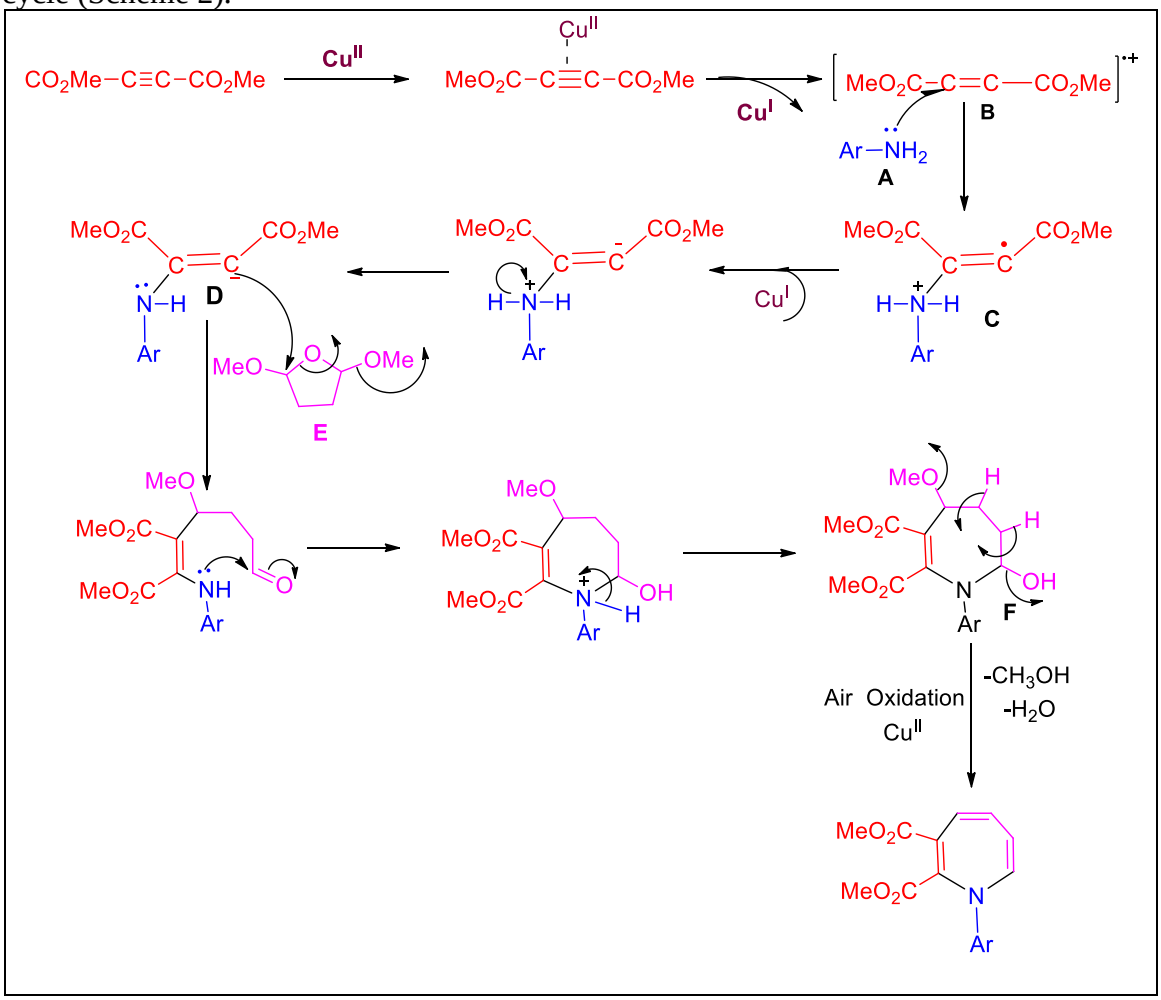


Fig. 2 Reusability of the catalyst for synthesis of N-substituted azepine

A plausible mechanism for this multi-component reaction is illustrated in Scheme 2. Complexation of Cu(II) with the triple bond of DMAD 3 and subsequent transfer of an electron from DMAD to Cu(II) results in a radical cation intermediate B and Cu(I) species.[28] Nucleophilic attack of anilineA on radical cation B provides C. One-electron transfer from Cu(I) to C gives D which react with2,5-dimethoxytetrahydrofuran gives dimethyl 2-(aryl amino)-3-(1-methoxy-4-oxobutyl)maleate E which in turn converts to 1-argio-2-hydroxy-5-methoxy-6,7-bis(methoxycarbonyl)-2,3,4,5-tetrahydro-1H-azepin-1-ium F by intramolecular nucleophilic attack. The intermediate F in the presence of Cu(II) catalyst affords the corresponding N-substituted azepenes 4 and releases the Cu(II) species for thenext catalytic cycle (Scheme 2).



Scheme-2 Proposed mechanism for the oxidative cyclizationof Dimethyl 2-(Arylamino) maleate ion with 2,5-dimethoxytetrahydrofuran

Experimental

All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with a 400 or 500 MHz spectrometer for ^{1}H NMR, 50, 100 or 125 MHz for ^{13}C NMR spectroscopy. Chemical shifts are reported relative to the residual signals of tetramethylsilane in $CDCl_3$ or deuterated solvent $CDCl_3$/[D6]DMSO for ^{1}H and ^{13}C NMR spectroscopy. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m). HRMS were recorded by using QTof mass spectrometer. Column chromatography was performed with silica gel (100–200 mesh) as the stationary phase. All reactions were monitored by using TLC. The purity and characterization of compounds were further established by using HRMS.

General procedure for Synthesis of N-substituted azepines via oxidative cyclization of Dimethyl 2-(arylamino) maleate ion with 2,5-dimethoxytetrahydrofuran

A mixture of DMAD (1.2 mmol) and [n-Bu_4P][$CuBr_3$](0.25 mmol) was added to aniline(1 mmol) and 2,5-dimethoxytetrahydrofuran (1 mmol) was exposed to MW irradiation at 200 W intermittently at 30 Seconds for the appropriate time (Table 2).The progress of the reaction was monitored by TLC (eluent:n-hexane–ethyl acetate, 9 : 1). After completion of the reaction, the mixture was cooled to room temperature and water was added (30 ml). The mixture was filtered and the crude product was purified by recrystallization from EtOH to afford the pure product. If necessary, the product was purified by silica gel column chromatography (eluent: n-hexane–ethyl acetate: 12/1).

Spectral data of representative compounds

Dimethyl 1-(4-bromophenyl)-1*H*-azepine-2, 3-dicarboxylate(Table 2, Entry -1):pale yellow oil.IR spectrum, ν, cm^{-1}:2921, 2852, 1724(C=O), 1641, 1584, 1456, 1320, 1283, 1191,770.^{1}H NMR spectrum, δ, ppm (J, Hz):(400 MHz, $CDCl_3$) δ_H 13.22 (1H, d, *J* = 13.5, ArH), 7.95 (1H, d, *J* = 13.5, ArH), 7.51 (1H, d, *J* = 9.0, ArH), 7.25-7.12 (2H, m, ArH), 6.72 (1H, d, *J* = 4.5, ArH), 6.53 (1H,d, *J* = 9.0, ArH), 6.44 (1H, d, *J* = 4.5, ArH), 3.97-3.69 (6H, m,-OCH_3,-OCH_3).^{13}C NMR spectrum, δ, ppm: 164.2, 145.7, 132.6, 131.2, 120.3, 119.1, 116.5, 52.2, 51.8,29.5.Mass spectrum, m/z: 364.2010$[M+H]^+$. Found, %: C 52.74; H 3.85; N 3.85.$C_{16}H_{14}NO_4Br$. Calculated, %:C 52.77; H 3.87,N 3.85.

Dimethyl 1-(4-nitrophenyl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2 Entry -2) light yellow oil, R_f (8%EtOAc /n-Hexane).IR spectrum, ν, cm^{-1}:3344, 2854, 1730(C=O), 1657, 1511, 1449, 1374, 1286, 1223, 1184, 1098, 834.^{1}H NMR spectrum, δ, ppm (J, Hz):13.17 (1H,d, 1H, *J* = 12.0,ArH), 8.1 (1H, d, *J* = 13.5, ArH), 7.21 (2H, t, *J* = 12.0, ArH), 6.93 (2H, d, *J* = 9.0, ArH), 6.71 (1H, d, *J* = 4.5,ArH), 6.46 (1H, d, *J* = 4.5, ArH), 3.85 (6H, d, *J* = 3.7,-OCH_3, -OCH_3).^{13}C NMR spectrum, δ, ppm: 149.2, 141.3, 138.3, 133.4, 130.4,129.6, 126.8, 125.1, 120.1, 117.9, 113.2, 110.1, 96.1, 29.7.Mass spectrum, m/z: 331.1062$[M+H]^+$.Found, %:C 58.14; H 4.24; N 8.42; O 29.02.$C_{16}H_{14}N_2O_6$.Calculated, %:C 58.18; H 4.27; N 8.48; O 29.06.

Dimethyl 1-(4-chlorophenyl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -3) pale yellow oil, R_f (8%EtOAc/n-Hexane).IR spectrum, ν, cm^{-1}:2923, 2852, 1736(C=O),1643, 1591, 1441, 1322, 1193, 1092, 1015.^{1}H NMR spectrum, δ, ppm (J, Hz):13.19 (1H, d, *J* = 12.8, ArH), 7.92 (1H, d, *J* = 13.5, ArH), 7.31 (2H, d, *J* = 8.3, ArH), 7.16 (2H, d, *J* = 9.0, ArH), 6.71 (1H, d, *J* = 4.5, ArH), 6.42 (1H, d, *J* = 4.5, ArH), 3.81 (6H, d, *J* = 9.0, -OCH_3, -OCH_3).^{13}C NMR spectrum, δ, ppm: 168.2, 167.7, 145.8, 138.2, 137.5, 131.4, 129.5, 120.2, 118.8, 118.1, 51.9, 29.6.Mass spectrum, m/z:320.2523$[M+H]^+$.Found, %: C 60.06; H 4.39; Cl 11.04; N 4.34; O 19.98.$C_{16}H_{14}NO_4Cl$.Calculated, %:C 60.10; H 4.41; Cl 11.09; N 4.38; O 20.01

Dimethyl 1-(4-methoxyphenyl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -4) pale yellow oil, R_f (7% EtOAc /n-Hexane). IR spectrum, ν, cm^{-1}:3428, 2923, 1762(C=O), 1715, 1637, 1513, 1438, 1328, 1247, 1189, 1138, 1095, 1026.^{1}H NMR spectrum, δ, ppm (J, Hz):13.28 (1H, d,*J* = 13.5,ArH),7.96 (1H,d, *J* = 13.5, ArH), 7.24 (2H,t, *J* = 15.1, ArH), 6.94 (2H,d, *J* = 9.0, ArH), 6.73 (1H, d, *J* = 4.5, ArH), 6.44 (1H, d, *J* = 4.5, ArH), 3.84 (6H, d,*J* = 3.7,-OCH_3,-OCH_3), 3.83 (s, 3H,-OCH_3).^{13}C NMR spectrum, δ, ppm: 147.2,132.0, 130.2, 119.5, 119.1, 117.9, 115.1, 55.6, 52.1, 51.9, 29.7.Mass spectrum, m/z:316.1128$[M+H]^+$.Found, %: C 64.69; H 5.41; N 4.38; O 25.34.$C_{17}H_{17}NO_5$.Calculated, %:C 64.75; H 5.43; N 4.44; O 25.37.

Dimethyl 1-(4-fluorophenyl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -5) light yellow oil, R_f (8%EtOAc/n-Hexane).IR spectrum, ν, cm^{-1}:3449, 2951, 1723(C=O), 1642, 1512, 1482, 1441, 1320, 1285, 1234, 1191, 1138, 1096, 1049, 798.^{1}H NMR spectrum, δ, ppm (J, Hz):7.90 (2H,d, *J* = 13.5,ArH), 7.16-7.02 (4H,m, ArH), 6.69 (1H,d, *J* = 4.3,ArH), 6.41

(1H,d, *J* = 4.3,ArH), 3.82 (6H,d, *J* = 10.7, -OCH_3,-OCH_3).^{13}C NMR spectrum, δ, ppm: 168.7, 167.5, 162.1, 158.6, 148.3, 143.3, 136.2, 120.1, 119.2, 118.1, 116.5, 112.6,52.3, 51.9, 29.2. Mass spectrum, m/z:304.0910$[M+H]^+$.Found, %: C 63.32; H 4.58; F 6.22; N 4.52; O 21.08.$C_{16}H_{14}NO_4F$. Calculated, %:C 63.36; H 4.65; F 6.26; N 4.62; O 21.10.

Dimethyl 1-(3-nitrophenyl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -6) light yellow oil, R_f (7%EtOAc /n-Hexane).IR spectrum, ν, cm^{-1}:3384, 2874, 1780(C=O), 1677, 1469, 1274, 1214, 1194, 1058, 774.^{1}H NMR spectrum, δ, ppm (J, Hz):13.23 (1H, d,*J* = 12.0, ArH), 7.89 (1H, d, *J* = 13.5,ArH), 7.21 (2H, t, *J* = 12.0,ArH), 6.91 (2H,d, *J* = 9.0,ArH), 6.73 (1H,d, *J* = 4.5 ArH), 6.46 (1H,d, *J* = 4.5,ArH), 3.86 (6H, d,*J* = 3.7,-OCH_3,-OCH_3).^{13}C NMR spectrum, δ, ppm:148.8, 141.1, 137.8, 134.1, 130.2, 125.8, 124.4, 120.1, 117.1, 110.3, 95.8, 22.9. Mass spectrum, m/z:331.2954$[M+H]^+$.Found, %: C 58.12; H 4.25; N 8.46; O 29.04.$C_{16}H_{14}N_2O_6$.Calculated, %:C 58.18; H 4.27; N 8.48; O 29.06

Dimethyl 1-(napthalen-1-yl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -7) light yellow oil, R_f (7%EtOAc /n-Hexane).IR spectrum, ν, cm^{-1}:3835, 3420, 2928, 2865, 1780(C=O), 1677, 1254, 1053.^{1}H NMR spectrum, δ, ppm (J, Hz):13.61 (1H,d, *J* = 12.8,ArH), 8.25 (1H,d, *J* = 7.5,ArH), 8.07 (1H, d, *J* = 12.8,ArH), 7.81 (1H,d, *J* = 7.5,ArH), 7.67-7.32 (5H,m, *J* = 4.5,ArH), 6.68 (1H, d,*J* = 4.5,ArH), 6.40 (1H,d, *J* = 4.5,ArH), 3.88 (3Hs, -OCH_3), 3.85 (3H,s,-OCH_3).^{13}C NMR spectrum, δ, ppm: 168.1, 148.4, 135.7, 134.3, 131.2, 128.5, 127.4, 126.8, 126.7, 125.4, 121.2, 120.7, 119.3, 113.8, 96.3, 52.2, 51.8, 32.8.Mass spectrum, m/z:336.1265$[M+H]^+$.Found, %: C 71.58; H 5.08; N 4.16; O 19.04.$C_{20}H_{17}NO_4$.Calculated, %:C 71.63; H 5.11; N 4.18; O 19.08.

Dimethyl 1-phenyl-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry-8) yellow oil, R_f (6.5%EtOAc/n-Hexane). IR spectrum, ν, cm^{-1}:3832, 3418, 2924, 2856, 1730(C=O), 1647, 1217, 770.^{1}H NMR spectrum, δ, ppm (J, Hz):13.29 (1H, d, *J* = 12.8, ArH), 8.05 (1H, d, *J* = 13.5, ArH), 7.39 (2H, t, *J* = 15.8, ArH), 7.33-7.22 (2H, m, ArH), 6.95 (1H, s, ArH), 6.74 (1H, d, *J* = 4.5, ArH), 6.42 (1H, d, *J* = 4.5, ArH), 3.85-3.69 (6H, m,-OCH_3,-OCH_3).^{13}C NMR spectrum, δ, ppm:165.8, 150.3, 149.6, 148.1, 139.8, 137.2, 95.6, 71.6, 52.4, 32.8, 28.8..Mass spectrum, m/z:286.1026$[M+H]^+$.Found, %: C 67.32; H 5.25; N 4.86; O 22.40. $C_{16}H_{15}NO_4$. Calculated, %:C 67.36; H 5.30; N 4.91; O 22.43.

Dimethyl 1-(pyridine-2-yl)-1H-azepine-2, 3-dicarboxylate:(Table 2, Entry -9) pale brown low melting solid, R_f (40%EtOAc /n-Hexane).IR spectrum, ν, cm^{-1}:3384, 2874, 1780(C=O), 1679, 1469, 1274, 1058, 774 cm^{-1} ; ^{1}H NMR spectrum, δ, ppm (J, Hz):9.05 (1H, d, *J* = 7.2, ArH), 7.84-7.34 (3H, m, ArH), 7.21 (1H, s, ArH), 7.17 (2H, t, *J* = 7.2, ArH), 7.10 (1H, s, ArH), 3.98 (6H, s, ,-OCH_3,-OCH_3).^{13}C NMR spectrum, δ, ppm: 136.3, 127.4, 115.9, 105.8, 96.1, 53.1.Mass spectrum, m/z:287.6278$[M+H]^+$.Found, %: C 62.93; H 4.93; N 9.79; O 22.35.$C_{15}H_{14}N_2O_4$.Calculated, %:C 62.90; H 4.92; N 9.76; O 22.31.

Diethyl 1-phenyl-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -10) yellow oil; R_f (7%EtOAc/n-Hexane); IR spectrum, ν, cm^{-1}:3449, 2923, 2852, 1720(C=O), 1638, 1591, 1451, 1321, 1189, 1140.^{1}H NMR spectrum, δ, ppm (J, Hz):13.28 (1H, d, *J* = 13.2, ArH), 8.19 (1H, d, *J* = 13.4, ArH), 7.24-7.11 (5H, m, ArH), 6.68 (1H, d, *J* = 4.5, ArH), 6.34 (1H, d, *J* = 4.3, ArH), 4.31-4.23 (4H, m,-OCH_2,-OCH_2), 1.38-1.23 (6H, m,-CH_3,-CH_3).^{13}C NMR spectrum, δ, ppm: 146.1, 131.1, 129.7, 125.4, 120.1, 117.5, 96.0, 60.9, 60.4, 29.5, 22.5, 14.2.Mass spectrum, m/z:314.3452$[M+H]^+$.Found, %: C 68.96; H 6.08; N 4.44; O 20.38.$C_{18}H_{19}NO_4$.Calculated, %:C 69.00; H 6.11; N 4.47; O 20.42.

Diethyl 1-(4-methoxyphenyl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -11) pale yellow oil, R_f (6.5%EtOAc/n-Hexane).IR spectrum, ν, cm^{-1}:2924, 2851, 1718(C=O), 1638, 1515, 1480, 1328, 1250, 1190, 1140, 1093, 1029.^{1}H NMR spectrum, δ, ppm (J, Hz):13.29 (1H, d, *J* = 13.4, ArH), 7.86 (1H, d, *J* = 13.5, ArH), 7.14 (2H, d, *J* = 8.8, ArH), 6.81 (2H, d, *J* = 8.8, ArH), 6.63 (1H, d, *J* = 4.1, ArH), 6.36 (d, 1H, *J* = 4.3, ArH), 4.30-4.21 (4H, m, -OCH_2,-OCH_2),

3.88 (3H, s,-OCH_3), 1.26-1.20 (6H, m,-CH_3,-CH_3).^{13}C NMR spectrum, δ, ppm: 160.5, 146.8, 130.5, 119.3, 119.2, 115.1, 60.9, 60.7, 55.6, 30.7. 14.Mass spectrum, m/z:344.1592[M+H]$^+$.Found, %: C 66.43; H 6.13; N 4.06; O 23.24.$C_{19}H_{21}NO_5$.Calculated, %:C 66.46; H 6.16; N 4.08; O 23.30.

Diethyl 1-(napthalen-1-yl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -12) yellow oil, R_f (6%EtOAc/n-Hexane).IR spectrum, ν, cm^{-1}:3446, 3044, 2929, 2853, 1724(C=O), 1633, 1594, 1446, 1329, 1191, 1088.^{1}H NMR spectrum, δ, ppm (J, Hz):13.65 (1H, d, *J* = 12.8, ArH), 8.24 (d, 1H, *J* = 8.3, ArH), 8.05 (1H, d, *J* = 12.8, ArH), 7.82-7.23 (6H, m, ArH), 6.68 (1H, d, *J* = 4.5,ArH), 6.38 (1H, d, *J* = 4.5,ArH), 4.38-4.19 (4H, m, -OCH_2,-OCH_2), 1.41-1.26 (6H, m,-CH_3,-CH_3).^{13}C NMR spectrum, δ, ppm: 167.4, 147.8, 138.5, 130.1, 128.4,127.2, 126.4, 126.2, 121.4, 120.3, 119.2, 118.8, 113.4, 96.2, 76.8, 60.6, 60.4, 29.5, 18.9, 14.2.Mass spectrum, m/z:364.7512[M+H]$^+$.Found, %: C 72.68; H 5.78; N 3.80; O 17.58.$C_{22}H_{21}NO_4$.Calculated, %:C 72.71; H 5.82; N 3.85; O 17.61.

Diethyl 1-(3-nitrophenyl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -13) yellow oil, R_f (7%EtOAc/n-Hexane).IR spectrum, ν, cm^{-1}: 3434, 3044, 2853,1738(C=O), 1633, 1564, 1088.^{1}H NMR spectrum, δ, ppm (J, Hz):13.29 (1H, d, *J* = 12.2, ArH), 8.12-7.96 (2H, m,ArH), 7.58-7.20 (2H, m, ArH), 6.88 (1H, d, *J* = 8.1, ArH), 6.73 (1H, d, *J* = 4.5, ArH), 6.37 (1H, d, *J* = 4.5, ArH), 4.34-4.23 (4H, m,-OCH_2,-OCH_2),1.38-1.23 (6H, m,-CH_3,-CH_3).^{13}C NMR spectrum, δ, ppm: 147.3, 143.8, 131.7,131.1, 129.7, 122.8, 120.1, 119.4, 112.8, 96.1, 61.4, 60.8, 29.3, 14.3.Mass spectrum, m/z: 359.6241[M+H]$^+$.Found, %: C 60.26; H 5.02; N 7.80; O 26.74.$C_{18}H_{18}N_2O_6$. Calculated, %: C 60.33; H 5.06; N 7.82; O 26.79.

Diethyl 1-(4-chlorophenyl)-1*H*-azepine-2, 3-dicarboxylate: (Table 2, Entry -14) yellow oil, R_f (6.5%EtOAc /n-Hexane).IR spectrum, ν, cm^{-1}:3249, 2973, 2858, 1729(C=O), 1641, 1574, 1484, 1324, 1144, 1119, 1091.^{1}H NMR spectrum, δ, ppm (J, Hz):13.29 (1H, d, *J* = 12.2, ArH), 7.85 (2H, d, *J* = 13.0, ArH), 7.35-7.17 (2H, m, ArH), 6.69 (2H, s, ArH), 6.44 (1H, s, ArH), 4.35-4.24 (4H, m,-OCH_2,-OCH_2), 1.38-1.24 (6H, m,-CH_3,-CH_3).^{13}C-NMR (75MHz, $CDCl_3$, TMS) δ= 145.4, 131.1, 129.8, 120.4, 118.5, 96.0, 60.8, 60.6, 29.6, 14.1.Mass spectrum, m/z:348.0526[M+H]$^+$.Found, %: C 62.16; H 5.22; Cl 10.19; N 4.03; O 18.40.$C_{18}H_{18}NO_4Cl$.Calculated, %:C 62.16; H 5.22; Cl 10.19; N 4.03; O 18.40.

Diethyl 1-(4-fluorophenyl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -15) pale yellow oil, R_f (6.5%EtOAc/n-Hexane).IR spectrum, ν, cm^{-1}:3539, 2952, 1730(C=O), 1658, 1539, 1431, 1291, 1209, 1058.^{1}H NMR spectrum, δ, ppm (J, Hz):13.29 (1H, d, *J* =12.4, ArH), 7.88 (2H, d, *J* = 13.0, ArH), 7.21-7.06 (3H, m, ArH), 6.64 (1H, s, ArH), 6.35 (1H, s, ArH), 4.33-4.22 (4H m, ,-OCH_2,-OCH_2), 1.38-1.26 (6H, m, -CH_3,-CH_3).^{13}C NMR spectrum, δ, ppm:165.6, 158.3, 154.8, 150.6, 139.8, 138.7, 136.4, 136.1, 115.5, 96.3, 80.2, 33.9.Mass spectrum, m/z:332.8235[M+H]$^+$.Found, %: C 65.20; H 5.44; F 5.70; N 4.19; O 19.26.$C_{18}H_{18}NO_4F$.Calculated, %:C 65.25; H 5.48; F 5.73; N 4.23; O 19.31.

Diethyl 1-(4-nitrophenyl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -16) yellow oil, R_f (7%EtOAc/n-Hexane).IR spectrum, ν, cm^{-1}:3433, 3094, 2921, 2851, 1713(C=O), 1630, 1522, 1465, 1349, 1312, 1138, 1092, 1024, 732.^{1}H NMR spectrum, δ, ppm (J, Hz):13.28 (1H, d, *J* = 12.2, ArH), 8.06-7.95 (2H, m, ArH), 7.58-7.22 (2H, d, ArH), 6.88 (1H, d, *J* = 8.1, ArH), 6.75 (d, 1H, *J* = 4.5 ArH), 6.39 (1H, d, *J* = 4.5, ArH), 4.34-4.26 (4H, m, -OCH_2,-OCH_2), 1.41-1.24 (6H, m, -CH_3,-CH_3).^{13}C NMR spectrum, δ, ppm: 147.2, 144.3, 132.1,130.5, 129.8, 123.2, 120.1, 119.2, 113.1, 96.2, 61.2,60.8, 29.6, 14.2.Mass spectrum, m/z:359.4826[M+H]$^+$.Found, %: C 60.30; H 5.02; N 7.79; O 26.73.$C_{18}H_{18}N_2O_6$. Calculated, %: C 60.33; H 5.06; N 7.82; O 26.79.

Diethyl 1-(pyridine-2-yl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -17) pale brown low melting solid, R_f (40%EtOAc/n-Hexane).IR spectrum, ν, cm^{-1}:3434, 2853, 1742(C=O),1633, 1564, 1088.^{1}H NMR spectrum, δ, ppm (J, Hz):9.08 (1H, d, *J* = 6.3, ArH),

7.86 (2H, d, *J* = 8.2, ArH), 7.82-7.76 (2H, m, ArH), 7.21 (2H, d, *J* = 7.2, ArH), 7.13 (1H, s, ArH), 4.48-4.46 (4H, m, -OCH_2,-OCH_2), 1.46 (t, 6H, *J* = 14.5, -CH_3,-CH_3).^{13}C NMR spectrum, δ, ppm: 164.1, 157.8, 136.2, 127.5, 116.1, 105.9, 96.1, 62.1, 14.2.Mass spectrum, m/z:315.0284$[M+H]^+$.Found, %: C 64.93; H 5.74; N 8.89; O 20.32.$C_{17}H_{18}N_2O_4$. Calculated, %:%: C 64.96; H 5.77; N 8.91; O 20.36.

Diethyl 1-(4-bromophenyl)-1*H*-azepine-2, 3-dicarboxylate:(Table 2, Entry -18) pale yellow oil, R_f (7%EtOAc/n-Hexane).IR spectrum, ν, cm^{-1}:3444, 2973, 2872, 1730(C=O), 1642, 1574, 1454, 1331, 1143, 1038, 774.^{1}H NMR spectrum, δ, ppm (J, Hz):13.24 (1H, d, *J* = 13.0, ArH), 7.84 (2H, d, *J* = 13.2, ArH), 7.47 (2H, d, *J* = 8.3,ArH), 7.10 (d, 1H, *J* = 8.49,ArH), 6.63 (1H, d, *J* = 4.3, ArH), 6.35 (1H, d, *J* = 4.3, ArH), 4.31-4.21 (4H, m, -OCH_2,-OCH_2), 1.40-1.23 (m, 6H, -CH_3,-CH_3).^{13}C NMR spectrum, δ, ppm:145.1, 138.1, 132.9, 131.3, 120.8, 118.6, 96.2, 60.7, 60.4, 29.9, 14.3.Mass spectrum, m/z:392.5862$[M+H]^+$.Found, %: C 55.08; H 4.61; Br 20.34; N 3.55; O 16.28. $C_{18}H_{18}NO_4Br$.Calculated, %:C 55.12; H 4.63; Br 20.37; N 3.57; O 16.32.

Conclusion

In conclusion, we have demonstrated an efficient, novel, eco-friendly synthesis of N-substituted Azepines, using Lewis acidic ionic liquid [n-Bu4P][CuBr3] as a reusable catalyst. Short reaction times,simple operation, high yields of products, a green procedure andavoiding toxic organic solvents and reagents are noteworthy advantages of the current method.

Acknowledgements

The authors would like to thankful The Head Department of Chemistry, Osmania University for providing research facilities and One of the author (Ashok K) thanks to the council of scientific and industrial research (CSIR) New Delhi, India for providing financial support. Finally the authors wish to express their gratitude to CFRD, OU for providing NMR and mass facilities.

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Received on August 22, 2023.