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THE SYNTHESIS OF CYTOTOXIC 2-SUBSTITUTED, 4-HALOGENATED, 5, 6-DIHYDRO-2H- PYRAN COMPOUNS BY USING IONIC LIQUID CHLOROALUMINATE

Gnaneswar Duggheni* and V. Harikrishna

Holy Mary Institute of Technology & Science, Bogaram, Keesara, Telangana, India.

ABSTRACT

Enviro-economics has become the spotlighted theme for the development of new processes for livening products or new products. The fact is that recently ascertained room temperature ionic liquids are emerging as a set of green solvents, mainly as replacement for unadventurous organic solvents, have shown great promise as an attractive alternative to predictable solvents.

Keywords: **C**hloroaluminate Ionic Liquid, Deferent Aldehydes and Aryl or Alkyl Coupling, Prins Cylizetion, Regioselective.

INTRODUCTION

Environmental protection laws demands to minimize the amount of toxic waste arise from chemical processes have incited the development of innovative and environmentally friendly chemical technologies [1], [2], [3], [5]. As result, especially those are volatile and difficult to handle. Ionic liquids those based on the 1-*n*-alkyl-3-methylimidazolium cation, they are thermally strong, easy to handle, non-volatile, recyclable, non-explosive, and in addition they are well-suited with various organic compounds. The unique property is that they have effectively no vapor pressure, which makes them most excellent replacements for volatile organic solvents. A pleasant feature of ionic liquids is the properties of cation optimize yields by changing anions. These ionic liquids show improvement in reaction rates and selectivity, compared to molecular organic solvents. The use of room temperature ionic liquids has led to significant advances in the development of clean chemical processes in organic synthesis targeted to avoid or minimize the use of toxic or waste generating reagents; they can make an important contribution to green chemistry [6,7].

In recent years, $AlCl_3$ has evolved as a versatile Lewis acid for a variety of organic transformations, such as the Diels-Alder reacton, Mukaiyama-aldol reactions, Mannich reaction, Michael additions, Prins cyclization, glycosylation reactions and Sakurai allylation reactions under mild conditions [8], [9]. They play an important role in the multi-step synthesis of complex natural products; hence there is always a demand for selective reagents. Compared to conventional Lewis acids, In view of the emerging importance of ionic liquids as novel reaction media, we wish to report a mild and highly efficient method for the using a catalytic amount of trichloride in ionic liquids. The treatment of the reactions proceeded efficiently at ambient temperature with high chemo selectivity. The reaction conditions are mild enough not to induce isomerization of multiple bonds during of allylic and propargylic systems and are selective for the reaction proceeds smoothly at ambient temperature with high chemoseletivity [10-20].

Enhanced reaction rates, improved yields and high functional group compatibility are the features are there in these ionic liquids. Another advantage of the use of ionic liquids as a novel reaction medium as well as promoters for this transformation is that these ionic solvents can be easily removed after completion of the reaction and can be reused in subsequent reactions. As the

Corresponding Author: - **Gnaneswar Duggheni** Email: dughani.eswar5@gmail.com

products were weakly soluble in the ionic phase, they were easily separated by simple extraction with ether. The rest of the viscous ionic liquid was thoroughly washed with ether and dried at 80°C under reduced pressure and recycled in five runs without any loss of activity. The products obtained were of the same purity

As in the first run and no decrease in yields was obtained in runs carried out using recycled ionic liquid. For example, the treatment of ([bmim] $AlCl_4$) afforded 92%, 91%, 91% and 90% yield over five cycles. Another advantage of this method thus, the present method is mild enough to abide a wide range of functional groups present in the substrate. Finally, the catalytic performance of various quaternary ammonium salts was studied for this conversion. The dihydropyrans was not successful when n-tetra butyl ammiounm chloride (n-Bu^4 NCl) or 1-n-butyl-3-methylimivazolium chloride ([bmim] Cl) was used as the reaction media. Similar results were obtained even in the n-Bu_4 NCl-$InCl_3$ or ([bmim] Cl)-$InCl_3$ catalytic systems. This indicates that the cation and anion play an important role as the solvent in this transformation. Furthermore the recovery and reuse of ([bmim] $AlCl_4$) is especially simple in ionic liquids compared to organic solvents.

In summary, this paper describes a method for the conversion of aldehydes and homopropargylic alcohols to produce dihydropyrans using a catalytic amount of using 1-n-Butyl-3-methylimidazolium chloroaluminate [bmim] Cl·$AlCl_3$(N = 0.56-0.67) in ionic liquids that operates under mild conditions, The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction, media is expected to contribute to the development of a green strategy for the chemistry. Furthermore the 1-butyl-3-methylimdazonum tetrafluoroborate ([bmim] BF4) ionic liquids as promoter for this transformation avoid the use of toxic or corrosive and moisture-sensitive reagents.

GENERAL

General procedure and material

To a mixture of benzaldehyde (212 mg, 2 mmol) and 3-butyn-1-ol (140 mg, 2 mmol) was added 1-n-Butyl-3-methylimidazolium chloroaluminate (1mL) at room temperature. The mixture was stirred for 5 min. and the reaction mass was quenched with ice cold water and extracted with diethyl ether (3-10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and purified by column chromatography on silica gel (Merck, 60-120 mesh, ethyl acetate/hexane, (1.0-9.0) to afford pure dihydropyran. The products were characterized by IR, NMR and mass spectroscopy. All the products **3a-m** was prepared by the same procedure.

Ionic liquids were prepared as described previously [8]. IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS asinternal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

1. 4-chloro-6-phenyl-3, 6-dihydro-2*H*-pyran 3a: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.25-7.35 (m, 5H), 5.92-5.95 (m, 1H), 5.09-5.14 (m, 1H), 3.99-4.09 (m, 1H), 3.77-3.87 (m, 1H), 2.56-2.69 (m, 1H), 2.28-2.38 (m, 1H). LCMS 217 (M+Na). IR (neat) ν cm^{-1}: 2922, 1730, 1637, 1603, 1060, 763, 697. Anal Calcd for $C_{11}H_{11}$ ClO (194.7): C, 67.87; H, 5.70. . Found: C, 67.91; H, 5.76.

2. 6-benzyl-4-chloro-3, 6-dihydro-2H-pyran 3b: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.20-7.40 (m, 5H), 5.72 (m, 1H), 4.31-4.40(m, 1H),4.05-4.15 (m, 1H), 3.65-3.75(m, 1H), 2.86(dd, , *J*=6.04 and 6.79 Hz, 1H), 2.68(dd,*J*=6.79 and 7.55 Hz, 1H), 2.54-2.64(m, 1H), 2.11-2.21(m, 1H)

3. 4-chloro-6-(2-furyl)-5-methyl-3, 6-dihydro-2*H*-pyran 3c: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 3.02 Hz, 1H), 6.35 (dd, *J* = 1.51 Hz, 1H), 6.27 (d, *J* = 3.02 Hz, 1H), 5.05-5.08 (s, 1H), 3.83-3.93 (m, 1H), 3.72-3.81 (m, 1H), 2.57-2.70 (m, 1H), 2.31-2.41 (m, 1H), 1.72-1.75 (s, 3H). EIMS: *m/z*: 198 (35) M^+, 182 (15), 167 (40), 163 (20), 149 (25), 121 (25), 107 (35), 91 (77), 65 (45), 43 (100). IR (neat) ν cm^{-1}: 2923, 1092, 758. Anal. Calcd for $C_{10}H_{11}ClO_2$ (198): C, 60.46; H, 5.58. Found: C, 60.49, H, 5.61.

4. 4-chloro-6-isobutyl-3, 6-dihydro-2*H*-pyran 3d: ^{1}H NMR (200 MHz, $CDCl_3$) δ:5.70 (s,1H),4.07-4.14(m,1H), 3.95-4.05 (m,1H), 3.59-3.69(m,1H), 2.47-2.59(m,1H), 2.08-2.18(m, 1H),1.73-1.89(m,1H),1.46-1.56(m,1H)1.16-1.19(m,1H),0.87-1.00(d, *J* = 2.66 Hz, 6H). LCMS 197 (M+Na). IR (neat) ν cm^{-1}: 2926,2852, 1068, 760 . Anal. Calcd for $C_9H_{15}ClO$ (174.7): C, 61.89; H, 8.66. Found : C, 61.90; H, 8.67.

5. 4-chloro-6-isopropyl-3, 6-dihydro-2*H*-pyran 3e: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.62 (s,1 H), 4.10-4.20(m, 1H), 3.50-3.70(m, 2H), 2.40-2.50(m, 2H), 1.84-1.94(m, 1H),0.86-1.00(m, 7H). LCMS 193 (M+Na). IR (neat) ν cm^{-1}: 2926, 2855, 1066, 759. . Anal. Calcd for $C_8H_{13}ClO$ (160.5): C, 59.81; H, 8.61. Found: C, 59.83; H, 8.63.

6. 4-chloro-6-isopropyl-5-methyl-3, 6-dihydro-2*H*-pyran 3f: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.11 (d, *J* = 6.79 Hz, 1H),3.59- 3.67 (m, 1H), 3.45-3.55 (m, 1H), 2.32-2.39 (m, 2H), 1.83-1.93(m, 1H), 1.76(t, *J* = 2.26 Hz, 3H), 0.90 (d, *J* = 6.79 Hz, 6H). LCMS 197 (M+Na). IR (neat) ν cm^{-1}: 2958, 2854, 1068, 759. Anal. calcd for $C_9H_{15}ClO$ (174.7): C, 61.89; H, 8.66. Found: C, 62.02; H, 8.69.

7. 4-chloro-6-cyclohexyl-3, 6-dihydro-2*H*-pyran 3g: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.75(s, 1H), 4.01(dd, J = 4.04Hz, 1H), 3.82-3.88(m, 1H), 3.58-3.68 (m, 1H), 2.43-2.63 (m,1H), 2.05-2.15(m,1H), 1.60-1.90(m,5H),1.34-1.52(m,1H),0.96-1.33(m,5H). LCMS 223 (M+Na). IR (neat) ν cm^{-1}: 2958, 2850, 1458, 1067, 759. Anal. Calcd for $C_{11}H_{17}ClO$ (200.7): C, 65.83; H, 8.54. Found:C, 65.87;

H, 8.60.

LCMS 231 (M+Na). IR (neat) ν cm^{-1}: 2922, 1730, 1659, 1603, 1060. Anal. Calcd for $C_{12}H_{13}ClO$ (208.1): C, 69.07; H, 6.28. Found: C, 69.09; H, 6.30.

8. 4-chloro-1-oxaspiro[5.5]undec-4-ene 3h: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.72 (s, 1H), 3.79 (t, *J* = 5.2 Hz, 2H), 2.27-2.34 (m, 2H), 1.18-1.74 (m, 10H). EIMS: *m/z*: 186 (10) M^+, 151 (10), 144 (100), 130 (15), 100 (10), 79 (15), 39 (20). IR (neat) ν cm^{-1}: 2921, 2852, 1630, 1080, 759. .Anal. calcd for $C_{10}H_{15}ClO$ (186.7): C, 64.34; H, 8.10. Found: C, 64.43; H, 8.17.

9. 4-chloro-5-methyl-1-oxaspiro [5.5] undec-4-ene 3i: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.74-3.84(m, 2H), 2.66-2.76(m, 2H), 2.19(t, *J* = 2.34 and1.56 Hz, 3H), 1.53-1.82(m, 12H).). LCMS 223 (M+Na). IR (neat) ν cm^{-1}: 2921, 2852, 1630, 1080, 759 .Anal. calcd for $C_{11}H_{17}ClO$ (200.7): C, 65.83; H, 8.54. Found: C, 65.85; H, 8.58.

10. 4-chloro-2-phenyl-1-oxaspiro [5.5] undec-4-ene 3j: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.29-7.40 (m, 5H), 5.78-5.87 (s, 1H), 4.97 (t, *J* = 6.78 7.63 Hz, 1H), 2.91-3.01 (m, 2H), 1.21-1.81 (m, 10H). EIMS: *m/z*: 262 (10) M^+, 227 (10), 164 (15), 141 (15), 125 (100), 89 (15), 77 (15), 63 (20), 51 (25), 39 (25). IR (neat) ν cm^{-1}: 2927, 1065, 758. Anal. Calcd for C16H19ClO (262.8): C, 73.13; H, 7.29 Found: C, 73.15; H, 7.32.

11. 4-chloro-2-ethyl-1-oxaspiro [5.5]undec-4-ene 3k: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.70 (d, *J* = 1.88 Hz, 1H), 3.55-3.65 (m, 1H), 2.16-2.30 (m, 2H), 0.92-1.66 (m, 15H). EIMS: *m/z*: 214 (10) M^+, 179 (80), 121 (100), 93 (60), 79 (85), 41 (90). IR (neat) ν cm^{-1}: 2925, 2854, 1099, 761. Anal. Calcd for $C_{12}H_{19}ClO$ (214.7): C, 67.12; H, 8.92. Found: C, 67.15; H, 8.97.

12. **4-chloro-1-oxaspiro[5.11]heptadec-4-ene 3l:** ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.79-5.81 (t, *J* = 1.51 Hz, 1H), 3.77-3.82 (t, *J* = 5.28 Hz, 2H), 2.28-2.34 (dt, 2H), 1.24-1.48 (m, 22H). EIMS: *m/z*: 271(45) M^+, 236 (100), 179 (10), 130 (75), 96 (15), 68 (20), 56 (65), 42 (85). IR (neat) ν cm^{-1}: 2925, 2854, 1099, 761. Anal. Calcd for $C_{16}H_{27}ClO$ (270.8): C, 70.95; H, 10.05. Found: C, 71.01; H, 10.08.

13. **4-chloro-2-ethyl-1-oxaspiro[5.11]heptadec-4-ene 3m:** ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.64-5.70 (m, 1H), 3.99-4.10 (m, 1H), 2.34-2.44 (m, 2H), 0.74-1.72 (m, 27H). EIMS: *m/z*: 298 (10) M^+, 263 (70), 183 (10), 172 (45), 99 (20), 72 (25), 56 (90), 42 (100). IR (neat) ν cm^{-1}: 2930, 2859, 1127, 721. Anal. Calcd for $C_{18}H_{31}ClO$ (298.9): C, 72.33; H, 10.45. Found: C, 72.37; H, 10.48.

14. 9-chloro-7-ethyl-6-oxaspiro[4.5]dec-9-ene 3n: ^{1}H NMR (200 MHz, $CDCl_3$) δ:5.71(d,*J* = 1.51 Hz, 1H), 3.98-4.07(m, 1H),3.45-3.58(m, 2H), 2.17-2.27(m,2H), 1.77-1.89(m,2H), 1.47-1.70(m, 11H) . LCMS 223 (M+Na)..IR (neat) ν cm^{-1}: 2931, 2859, 1710, 1648, 1450, 1216, 757. Anal. Calcd for $C_{11}H_{17}ClO$ (200.7): C, 65.83; H, 8.54. Found: C, 65.85; H, 8.57.

15. 9-chloro-6-oxaspiro[4.5]dec-9-ene 3o: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.69 (s, 1H), 3.77 (t, *J* = 5.2 and 6.0 Hz, 2H), 2.39 (t, *J* = 4.5 Hz, 1H), 2.30-2.34 (m, 1H), 1.45-1.85 (m, 10H). EIMS: *m/z*: 172 (100) M^+, 137 (85), 109 (20), 81 (15), 67 (30), 53 (10). IR (neat) ν cm^{-1}:2930, 2857,1216, 1066, 759. Anal. calcd for $C_9H_{13}ClO$ (172.7): C, 62.61; H, 7.59. Found: C, 62.72; H, 7.67.

16. 4-chloro-6,6-diethyl-3,6-dihydro-2*H*-pyran 3p: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.68 (s, 1H), 3.80 (t, *J* = 5.3 and 6.0 Hz, 2H), 2.27-2.32 (m, 2H), 1.54 (q, *J* = 6.8 and 7.5 Hz, 4H), 0.85 (t, *J* = 7.5 and 7.6 Hz, 6H). LCMS 197 (M+Na). IR (neat) ν cm^{-1}: 2927, 2855, 1460, 1080, 749. Anal. calcd for $C_9H_{15}ClO$ (174): C, 61.89; H, 8.66. Found: C, 61.92; H, 8.72.

17. 4-chloro-2,6,6-triethyl-3, 6-dihydro-2*H*-pyran 3q: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.69-5.73 (s, 1H), 4.06-4.16 (m, 1H), 2.15 (d, *J* = 3.02 Hz, 2H), 0.92-1.33 (m, 15H). EIMS: *m/z*: 202 (10) M^+, 173 (20), 167 (40), 137 (20), 79 (15), 43 (100). IR (neat) ν cm^{-1}: 2927, 2854, 1066, 742. Anal. Calcd for C11H19ClO (202.7): C, 65.17; H, 9.45 .Found: C, 65.58; H, 9.59.

18. 4-chloro-6,6-dimethyl-3,6-dihydro-2*H*-pyran 3r: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.70-5.72 (m, 1H), 3.80-3.84 (m, 2H), 2.28-2.34 (m, 2H), 1.24 (s, 6H). EIMS: *m/z*: 146 (100) M^+, 96 (10), 79 (20), 65 (10), 51 (15). IR (neat) ν cm^{-1}: 2920, 2854, 1064, 750. Anal. calcd for $C_7H_{11}ClO$ (146.6): C, 57.34; H, 7.56. Found: C, 57.38; H, 7.63.

RESULT AND DISCUSSION

In view of our previous work we extended auxiliary the emerging importance of the use of Ionic liquids as cost-effective and environmentally benign catalysts [21]. We herein describe a simple and efficient protocol for the cyclization reactions of aldehydes and homopropargylic alcohols to produce dihydropyrans using 1-n-Butyl-3-methylimidazolium chloroaluminate [bmim]Cl·$AlCl_3$(N = 0.56-0.67) ionic liquid under mild reaction conditions (Scheme 1).

For instance treatment of benzaldehyde with 3-butyn-1-ol in [bmim]Cl·$AlCl_3$ionic liquid afforded dihydropyran in 91% yield. The reaction is very clean and complete within 5 min. at room temperature. In a similar manner, various aldehydes and ketones underwent smooth cyclization reaction with homopropargylic alcohols to give the corresponding dihydropyran derivatives in high yields. In all cases, the reactions proceeded readily at room temperature with high efficiency. The reaction worked well both with aromatic, aliphatic aldehydes and ketones[22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33]. When symmetrical ketones like cyclohexanone and 3-pentanone reacted with **2c** and **2d** the formation of single product was observed. But when applied to aldehydes the formation of a mixture of the isomers were observed by TLC and ^{1}HNMR spectrum. This is due to the formation of the diastereomers in the later case (Scheme 2). The mechanism for the formation of dihydropyrans can be explained by the attack of homopropargylic alcohol and cyclised to the dihydropyran

carbenium ion which is further attacked by the chloride nucleophile to form the 4-Chloro dihydropran derivative (Scheme 2, scheme 3).

The preliminary screening identified derivatives **3a** and **3b** as the more active compounds. From the biological data, the presence of the chlorovinyl in the six-membered heterocyclic ring seems to play an essential role. According to this rationale, we decided to explore the activity of this class of compounds through modifications on the alkyl side chain (Table 1, Table-2) [30], [31], [32], [33]. We have described a green protocol for the preparation of dihydropyran derivatives through cyclization reaction of aldehydes/ketones with homopropargylic alcohols using 1-n-Butyl-3-methylimidazolium chloroaluminate ionic liquidsystem. It is based on the small differences reported for the diverse natural derivatives aplysiapyranoids A-D. On the other hand, modifications on the heterocyclic ring by addition of diverse substituents might lead to new products with better activity profiles. While the compounds reported herein are racemic, we think it is unlikely that enantiomerically pure derivatives would improve the activity profile considerably.

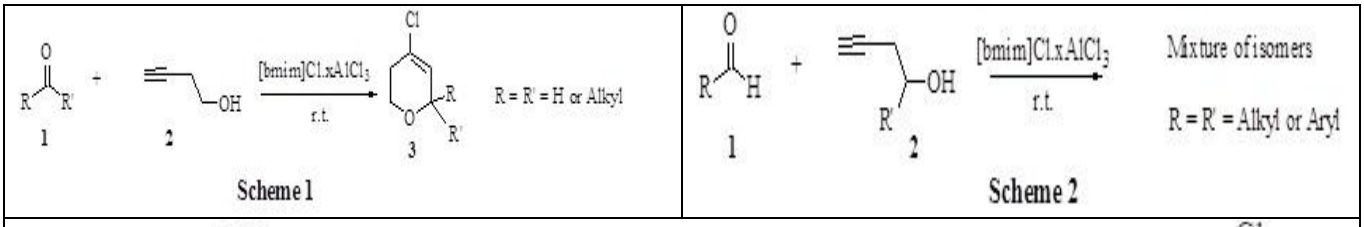
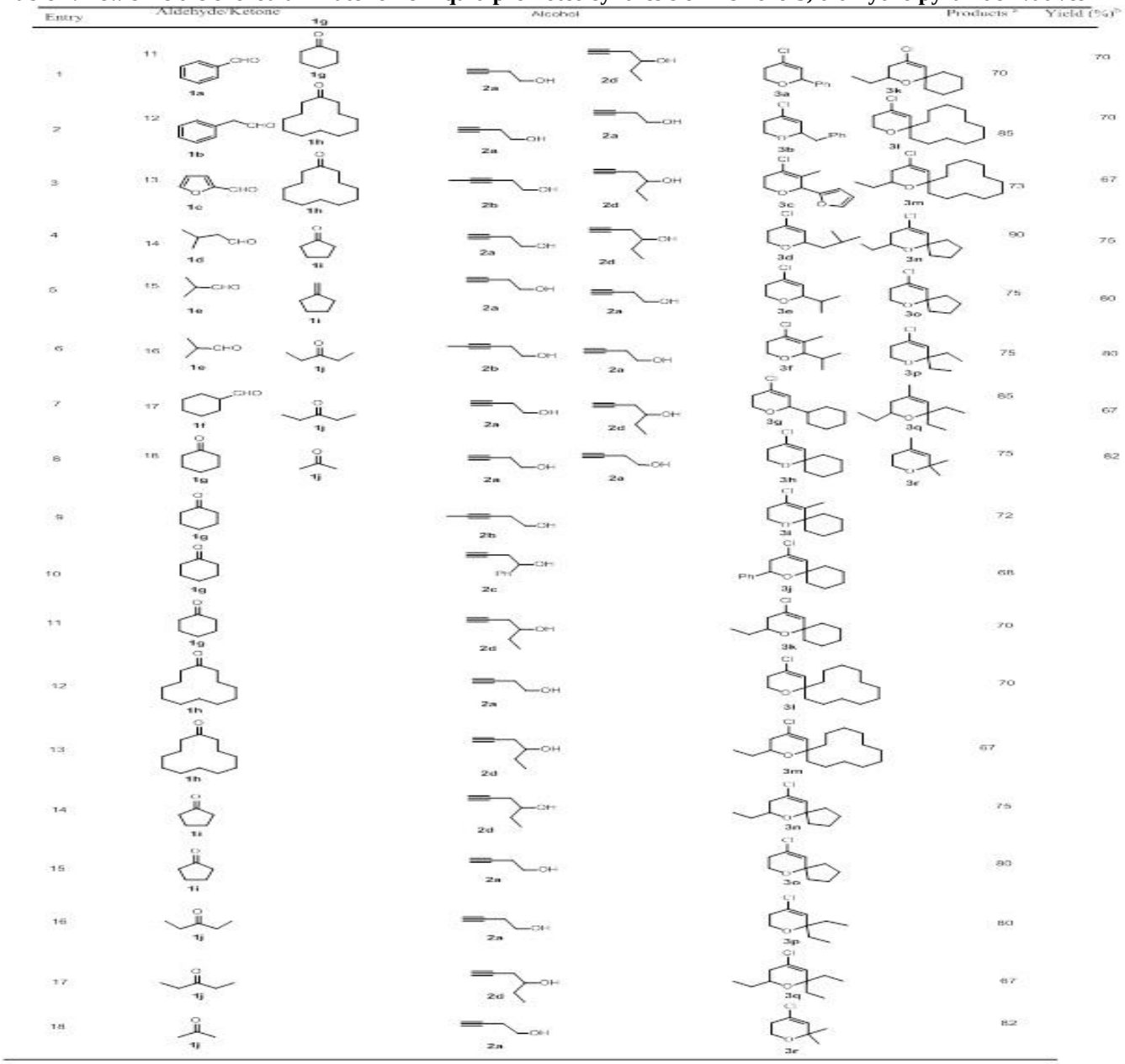


Table 1. Lewis Acidic choroaluminate Ionic Liquid promoted synthesis of 4-chloro-5, 6-dihydro pyran derivatives

Entry	Aldehyde/Ketone	Alcohol	Products [a]	Yield (%)[b]
1	1a	2a	3a	70
2	1b	2a	3b	85
3	1c	2b	3c	73
4	1d	2a	3d	90
5	1e	2a	3e	75
6	1e	2b	3f	75
7	1f	2a	3g	85
8	1g	2a	3h	75
9	1g	2b	3i	72
10		2c	3j	68

Table 1. Lewis Acidic choroaluminate Ionic Liquid promoted synthesis of 4-chloro-5, 6-dihydro pyran derivatives



a: All the products were characterized by ^{1}H NMR and mass spectroscopy.
b: Isolated yields after column chromatography.

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