INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN:2320-2831

IJPAR |Vol.5 | Issue 1 | Jan- Mar -2016

Journal Home page: www.ijpar.com

Research article *Open Access*

Novel and efficient cytotoxic 2-alkyl, 4-chloro-5,6-dihydro-2h-pyran derivatives of aplysiapyranoids a-d,an anti solod tumer of human cells.

Dr. V. Harikrishna,* Prof. Dr. Gnaneswar Duggheni

Division of Organic Chemistry-I, Discovery Laboratory, Indian Institute of Chemical Technology, Hyderabad-500007, India.

***Corresponding Author: Dr. V. Harikrishna**

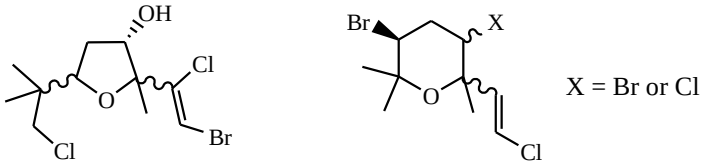
ABSTRACT

Cytotoxic 2-alkyl, 4- chloro-5, 6- dihydro-2H-pyran derivatives were first synthesized in single step method by using recyclable catalytic chloroaluminate immobilized in ionic liquids the reaction of aldehydes and ketones with homopropargylic alcohols using chloroaluminate ionic liquids generated the dihyropyran derivatives in good yields and with high stereoselectivity.

Keywords: Coupling of Alkynes to Aldehydes, Regioselective and Efficient, Cyclization is promoted by the Ionic Liquid

INTRODUCTION

The chloro vinyl group in the moiety is responsible for the activity exerted by diverse marine natural products such as aplysiapyranoids A-D [1] and furoplocamioids A-C[2], are halogenated monoter-penes oxacyclic skeletons . aplysiapyranoids A-D have shown modest in Viro cytotoxicity against diverse solid tumor cell lines with IC_{50} values in the range of 60 –300 µm. Aplysiapyranoids D was the most active compound of series against moser cells[1] (human colon cancer) with an IC_{50} values in the range of 46 µm. As proof of this principle, Jose M. Padron et al. Synthesize linear oxacyclic derivatives of chloro vinyl group like 2-alkyl functioned -4-chloro-5,6-dihydro-2H-brains for further chemical modifications and biological studies. According to their biological studies, In preliminary vitro screening tests against human solid tumor cells **3a** and **3b** oxacyclic derivatives able to induce anti-proliferative effects on the ovarian(A 2780) and lung cancer cell lines(SW 1573), with GI_{50} values in range 20-58 µm. The selectivity of both cell lines to these drugs is similar. These findings suggest clearly that, the presence of the chloro vinyl group with an aliphatic chain, proved to be essential for the anti-tumor effect. So, we synthesize diverse aliphatic chain analogues containing 2-alkyl –4-chloro-2H-pyrans, which might improves activity for the anti-tumor effect.



Furoplocamioids (A-C) **Aplysiapyranoids (A-D)**

Figure 1

Many natural products like Swinholides [3], Laulimalides, [4] Ambruticins [5] and Jerangolids [6] contains dihydropyran skeleton [7] and Substituted dihydropyrans are the key intermediates for the synthesis of many natural products. Moreover, the Olefin function is having synthetic value for further functionalisation in obtaining polysubstituted tetrahydropyrans [8]. Particularly with our approach based on that a series of functionalized 4-chloro-5,6-dihydro-2H-pyrans were synthesized by means of a Prins type cyclization is promoted by the ionic liquid. The coupling of alkynes to aldehydes is an important transformation in organic synthesis [9]. The direct synthesis of dihydropyrans by the coupling of alkynes to aldehydes provides a useful synthetic method for the synthesis of dihydropyrans. Overall, this process builds up a ring in a regioselective and efficient manner. Although other methods were reported [10], Consequent methods that successfully minimize the use of toxic and volatile organic solvents are the focus of much attention. In this respect, ionic liquids are attracting growing interest as alternative reaction media for various chemical and biotransformations[11].In particular, choloroaluminate ionic liquids are having Lewis acidity, which can be varied over a wide range, and their intrinsic ability to solvate a variety of substances. These ionic liquids are easily prepared from $AlCl_3$and 1-butyl-3-methylimidazolium chloride. These chloroaluminate ionic liquids have the advantage of being liquid at room temperature over a considerable composition range of apparent mole fraction of $AlCl_3$ (N = 0.30-0.67) and also have negligible vapor pressures, making them useful alternatives to conventional molecular organic solvents for various synthetically useful transformations [12]. Furthermore, chloroaluminate ionic liquids play dual roles both as Lewis acid catalyst and as solvent [13].

EXPERIMENTAL

General procedure for the preparation of dihydropyrans

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 vacuo 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, NULTMR and mass spectroscopy.

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 the Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

4-chloro-6-cyclohexyl-3, 6-dihydro-2*H*-pyran 3a

^{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) (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.

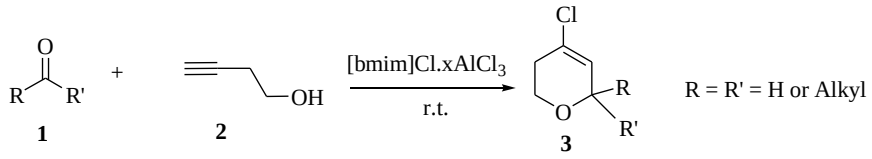
6-benzyl-4-chloro-3, 6-dihydro-2H-pyran 3b

^{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) LCMS 231 (M+Na). IR (neat) (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.

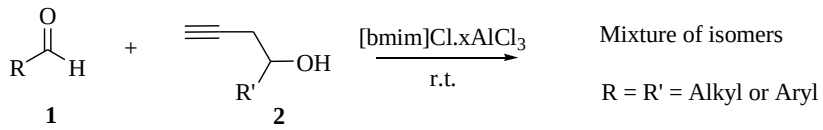
RESLTS AND DISCUSSION

In view of the emerging importance of the use of Ionic liquids as cost-effective and environmentally benign catalysts, 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] $Cl{\cdot}AlCl_3$ (N = 0.56-0.67) ionic liquid under mild reaction conditions (Scheme 1).



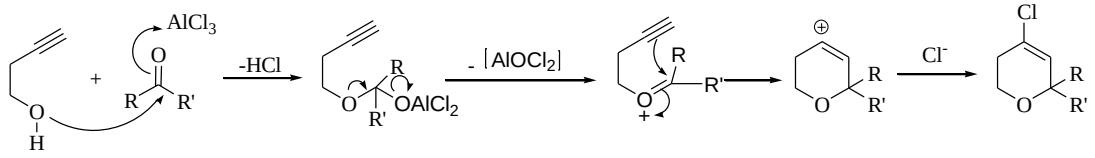
Scheme 1

For instance treatment of benzaldehyde with 3-butyn-1-ol in [bmim] $Cl{\cdot}AlCl_3$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.. 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 latter case (Scheme 2).



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 3).



Scheme 3

The preliminary screening identified derivatives **3a** and **3b** as the most 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) [14].

Table 1. Preliminary in vitro screening against human solid tumor cells.

Compound	R	GI_{50}[µm] [a]	
		A2780 [b]	SW1573 [c]
3a	*c*Hex	20(± 2.6)	26(± 3.6)
3b	Bn	36(± 13)	58(± 18)

Values are means of at least three experiments,

- Human solid tumor -cells A2780 (ovarian cancer),
- SW1573 (non-small cell lung cancer (NSCLC).

ACKNOWLEGEMENTS

Dr.V.H.K and Prof Dr. D.G. thanks CSIR, New Delhi for the award of fellowships.

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