Synthesis of Nitrogen-Substituted Pyran-2-ones*via* Radical Cyclisation Approach

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Abstract

Four new4-*N*-substituted pyran-2-ones (*δ*-lactones) were successfully synthesised from their corresponding cyanoalcohols *via* two reaction steps; (i) acylation and (ii) radical cyclisation. Four cyanobromoesters that were produced from acylation were treated with tris(trimethylsilyl)silane (TTMSH) and azobisisobutyronitrile (AIBN) in toluene to obtain 5-hydro-4-imino-3,6-dimethylpyran-2-one (**4a**), 4-amino-5-hydro-3,6,6-trimethylpyran-2-one (**4b**),3,5-dihydro-4-imino-6-methylpyran-2-one (**4c**), and 3,5-Dihydro-4-imino-6,6-dimethylpyran-2-one (**4d**).

Keywords:pyran-2-one, 3-ene-lactones, radical cyclisation, TTMSH, AIBN, 6-*exo-dig*

1. Introduction

Radical cyclisation is a method that is widely used for the carbon-carbon bond formation with carbon-centered radicals is the most preferred intermediates. This method has a dominant role in the development of novel methodology where, the reaction will be more selective and predictable. Moreover, radical chemistry has greater functional group tolerance where it will only attack the desired functional group.

A number of radical cyclisation studies towards heterocycles were published involving the cyclisation of lactams [1-6], lactones[3,7-10], polycyclics [11-15], pyrroles [16-21], azoles [22-24] and indoles [25-29].Usually this radical cyclisation was performed in organic solvent such as benzene and toluene but the used of water also reported [30-32]. Radical cyclisation are typically generated by hydrogen donors or their derivatives such astin hydride [33-35], silane hydride [36-38], germanium hydride [39], gallium hydride [40], organoborane [10,41], hypophosphorous acid[42-44]with the presence of radical initiators (*e.g.* peroxides, boranes or azo).

Tributyltinhydride (Bu_3SnH) is known for its major role in most radical cyclisation approaches and often gives products in high yield. However, this reducing agent is also known to be difficult to handle and is toxic. In contrast, tris(trimethylsilyl)silane ($(Me_3Si)_3SiH$) is also known for its effectiveness and lowers the formation of unwanted reduction products. Among the radical initiators present in the market, azo-based initiators are relatively inexpensive, safer to useand greater thermal stability.

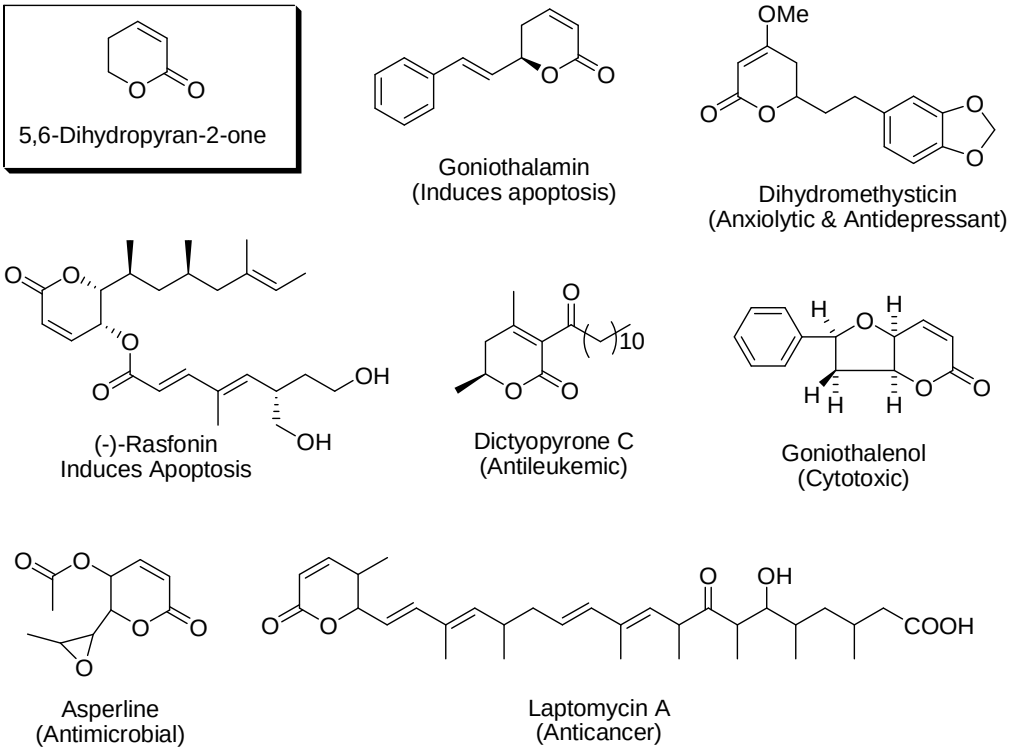


Figure 1:Bioactive compounds containing 5,6-dihydropyran-2-ones

5,6-Dihydropyran-2-one (δ-lactone)is an important class of oxygen-containing six-membered heterocycliccompound and can be found in many important bioactive natural products. This 3-ene-lactone is a common precursor for the synthesis, and possesses key structural units that are of interest and have potential in pharmaceuticals or drug discovery (**Figure 1**) [45-51].The complexity of structures, together with their known bioactivities have made the synthesis of substituted pyran-2-ones are worthwhile. Many studies have been reported in developing new approach towards the synthesis of lactones such as radical cyclisation onto alkenes or alkynes. Therefore, the aim of this study is to investigate the possibility of cyclisation onto nitriles using radical chemistry.

It was proposed that δ-lactone could be produced from the 4-imino or 4-amino lactones which in turn can be prepared from the precursors' cyanobromoesters*via* radical cyclisation approach. Further retrosynthetic disconnection of the precursors lead to the commercially available cyanoalcohols and 2-bromoacyl chlorides (**Figure 2**).

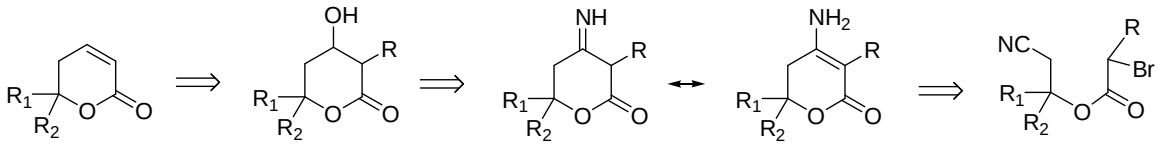
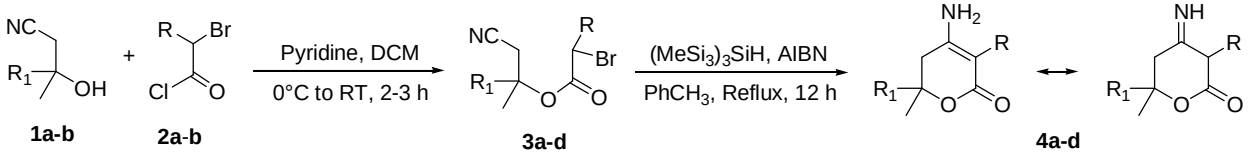


Figure 2:Retrosynthetic analysis of δ-lactones

2. Materials and Methods

2.1 General

All experiments were carried out under nitrogen atmosphere. Reactions were monitored by TLC (Merck, silica gel 60 F_{254}) then visualised under UV (UVGL-58) and $KMnO_4$ solution. The column chromatography was performed by using Merck silica gel 60 (230-400 mesh ASTM). The NMR spectra were obtained from JOEL JMTC-500/54/SS (500 MHz for ^1H and 125 MHz for ^{13}C) and NM-SCM40J/SS (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometers in $CDCl_3$, CH_3OD, $(CD_3)_2SO$ or $(CD_3)_2CO$ as solvent. The coupling constants were recorded in Hz and the chemical shifts (δ) were recorded in ppm relative to TMS signal. The signals were described in terms of chemical shift with appropriate abbreviations for multiplicities as s (singlet), d (doublet), t (triplet) and m (multiplet). IR spectra were obtained from a Perkin-Elmer FT-IR Model Spectrum 100 series using UATR techniques and the adsorption bands were measured inrange 280 to 4000 cm^{-1}. MS spectra were recorded on Shimadzu QP5050A series or QP2010PLUS. The melting points were recorded on Leica Galen III Serial No. 1109xz.



1a $R_1 = H$ **3a** $R_1 = H, R_2 = CH_3$ **4a** $R_1 = H, R_2 = CH_3$

1b $R_1 = CH_3$ **3b** $R_1 = CH_3, R = CH_3$ **4b** $R_1 = CH_3, R = CH_3$

2a $R = CH_3$ **3c** $R_1 = H, R = H$ **4c** $R_1 = H, R = H$

2b $R = H$ **3d** $R_1 = CH_3, R = H$ **4d** $R_1 = CH_3, R = H$

Scheme 1: General acylation and radical cyclisation reactions

2.2 General Procedure for Acylation of Cyanoalcohols

Acyl chlorides**2**(1.2 eq.) in anhydrous CH_2Cl_2 (8 mL) was added dropwise into a stirred solution of cyanoalcohols **1** (1.0 eq.) and pyridine (1.0 eq.) in anhydrous CH_2Cl_2 (20 mL) at 0°C. The reaction mixture was allowed to warm to RT and was stirred continuously for 2-3 h. EtOAc (10 mL) was added to the reaction mixture and stirred for an additional 10-15 mins. The organic layer was washed successively with water (3 x 15 mL), saturated $NaHCO_3$ (3 x 15 mL) and brine (3 x 15 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo* to give the crude product which was then chromatographed on silica gel (EtOAc-Hexane, 3:7) to yield cyanobromoesters**3**.

2.3 General Procedure for Radical Cyclisation of Cyanobromoesters

Cyanobromoesters**3** (1.0 eq.) was dissolved in degassed toluene (67 mL) and stirred under nitrogen atmosphere. A solution of TTMSH (1.1 eq.) and AIBN (0.1 eq.) in degassed toluene (16.7 mL) was added dropwise *via* mechanical syringe into the stirred solution over 12 hours under reflux condition. The mixture was allowed to cool to RT before the solvent was removed under *vacuo* to

give crude product which was then chromatographed on silica gel (EtOAc-Hexane, 1:9) to yield *δ*-lactones **4**.

2.3.1 5-Hydro-4-imino-3,6-dimethylpyran-2-one (4a)

Orange solid (0.13 g, 53%); mp 107°C; ν_{max} (UATR) 3383, 2940, 1725, 1462, 1030 cm^{-1}; δ_H (500 MHz, $CDCl_3$)5.11 (1H, br. s, N*H*), 3.48 (1H, q, *J* 7.5 Hz, C*H*CH_3),3.01-2.90 (1H, m, OC*H*CH_3), 2.21 (6H, d, *J* 7.5 Hz, 2(CHC*H*$_3$)),1.64 and 1.62 (2H, s, C*H*$_2$CH); δ_C (125 MHz, $CDCl_3$) 207.4, 191.9, 134.5, 53.4, 31.1, 19.1; *m/z* (EI) 127 ([M^+], $C_6H_9O_2N$ requires 127).

2.3.2 4-Amino-5-hydro-3,6,6-trimethylpyran-2-one (4b)

Yellow solid (0.08 g, 60%); mp 210°C; ν_{max} (UATR) 3367, 2924, 1626, 1462, 1172 cm^{-1}; δ_H (500 MHz, $(CD_3)_2CO$) 3.27 (2H, br. s, N*H*$_2$), 1.67 (3H, s, C=CC*H*$_3$), 1.40 (6H, s, (C*H*$_3$)$_2$CO, 1.01 (1H, s, C*H*$_2$CNH$_2$) 0.99 (1H, s, C*H*$_2$CNH$_2$); δ_C (125 MHz, $(CD_3)_2CO$) 170.7, 162.5, 115.0, 54.2, 42.1, 24.6, 12.6; *m/z* (EI) 155 ([M^+], $C_8H_{13}NO_2$ requires 155).

2.3.3 3,5-Dihydro-4-imino-6-methylpyran-2-one (4c)

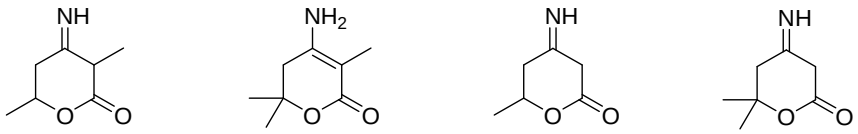
Sticky white solid (0.12 g, 55%); ν_{max} (UATR) 3743, 2924, 1741, 1460, 966 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.80 (1H, s, N*H*), 1.59 (2H, s, C*H*$_2$CNH), 1.25 (2H, d,*J* 29.2 Hz, C*H*$_2$CO), 0.89-0.76 (1H, m, OC*H*CH_3), 1.80 (3H, d, *J* 14.9 Hz, OCHC*H*$_3$); δ_C (125 MHz, $CDCl_3$) 192.8, 182.6, 119.8, 29.6, 25.5, 22.8; *m/z* (EI) 127 ([M^+], $C_6H_9NO_2$ requires 127).

2.3.4 3,5-Dihydro-4-imino-6,6-dimethylpyran-2-one (4d)

White solid (0.13 g, 40%); mp 230°C; ν_{max} (UATR) 3376, 3206, 2502, 1645, 1211 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.11 (1H, br. s, N*H*), 1.88 (6H, s, C(C*H*$_3$)$_2$), 1.44 (2H, s, C*H*$_2$CNH), 1.07 (1H, d,*J* 6.9 Hz, C*H*$_2$CO); δ_C (125 MHz, $CDCl_3$) 179.6, 177.7, 35.4, 24.1, 23.0, 18.6; *m/z* (EI) 141 ([M^+], $C_7H_{11}NO_2$ requires 141).

3. Results and Discussion

The synthetic strategies were started with the preparation of the cyanobromoesters **3** using different cyanoalcohols and acyl chlorides *via* simple and standard acylation protocol. These reactions were performed in pyridine/CH_2Cl_2 for 2-3 hoursand managed to produce esters **3a**-**3d** in good yields. All esters were then treated under radical mediated approach in the next step to produce lactones.



4a (53%) **4b** (41%) **4c** (55%) **4d** (40%)

Figure 3:*N*-substituted *δ*-lactones obtained from radical cyclisation reactions

The reactionwas performed using cyanobromoesters**3**(1.0 eq.), $(Me_3Si)_3SiH$ (1.1 eq.) and AIBN (0.1 eq.) in degassed toluene. The effect of the addition time was studied by varying the time from 1, 2, 4 and 6 hours. Unfortunately, the desired product **4** was not produced at these short addition times. Changing to very slow dropwise addition of $(Me_3Si)_3SiH$ and AIBN over 12 hours then allowed for the successful production of lactones**4a**, **4b**, **4c**and **4d** in good yields.

6-Methylpyran-2-ones **4a** and **4c** were produced in higher yields (53% and 55%) compared to 6,6-dimethylpyran-2-ones **4b** and **4d**(41% and 40%).Increase the number of alkyl on position C-6 also increased the yield of lactones. However, no significant effects were observed with the addition of alkyl at position C-3. As comparison, lactone **4a** was obtained in 53% yield whereas lactone **4c**was obtained in 55% yield.Similar results were observed for lactones **4b** and **4d**. These results showed that these *δ*-lactones can be prepared using radical cyclisation approach and the structures confirmed that all *N*-substituted lactones were obtained either in forms of 4-amino or 4-imino through 6-*exo*-*dig* mechanism. It was believed that 6-membered ring lactonesare easy to form due to the proximity of C≡N and radical carbon ($C^{\bullet}$) during the reaction that conducted under diluted conditions and slow addition of silane. The chain length together with the flexibility of ester bond allowed the C≡N moiety to be closer to $C^{\bullet}$ and therefore increased the cyclisation rate. Acyclic reduction product was not observed for all radical cyclisation reaction.

4. Conclusion

A general radical cyclisation approach has been developed for the synthesis of 4-*N*-substituted pyran-2-ones. Four new amino- or imino-substituted*δ*-lactones have been successfully synthesised starting from commercially available cyanoalcohols and bromoacyl chlorides through 6-*exo*-*dig* type of cyclisation.

5. Acknowledgement

This research was funded by the Fundamental Research Grant Scheme (FRGS vot. No.: 5523918). We also thank Prof. Dr. Mohd Aspollah Hj. Md. Sukari for the financial support, Mr. Zainal Abidin Kassim for recording the MS and Mrs. Rusnani Amirudin for IR spectra.

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