Tetrahedron Letters 54 (2013) 874–877

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Construction of novel steroidal isoxazolidinone derivatives under Vilsmeier–Haack conditions

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ARTICLE INFO

Article history:
Received 11 September 2012
Revised 22 November 2012
Accepted 24 November 2012
Available online 1 December 2012

Keywords:
6-Hydroxyiminocholestane
Isoxazolidinone
Vilsmeier reagent
Steroid

ABSTRACT

A novel expeditious and convenient synthesis of 5α-cholestano-[5,6-*c*]-isoxazolidin-5′-ones based on the reaction of 5α-6-hydroxyiminocholestanes with Vilsmeier–Haack reagent (DMF/$POCl_3$) is described. The systems presented here, are novel scaffolds and have not been described before. Structural assignment of newly synthesized compounds was performed by IR, ^1H NMR, ^{13}C NMR, 2D ^1H–^1H COSY, MS and analytical data.

Isoxazolidinones are well-established building blocks in synthetic organic chemistry. One of the reasons the isoxazolidinones, particularly 5-isoxazolidinones, are of considerable interest to organic chemists is that they are good precursors to unnatural β-amino acids: these are, indeed, unmasked forms of 5-isoxazolidinones. These structures exhibit a wide range of biological activities.[1,2] These type of compounds are an important class of heterocyclic structures, that can be applied in drug and pharmaceutical fields. These compounds have attracted scientific interest because of their potential cytotoxic, pro-apoptotic and antimicrobial capabilities.[3] Furthermore, they can be used for the preparation of nucleoside analogues.[4] Nucleoside analogues have emerged in recent years as highly promising candidates for the development of new efficient drugs against cancer and viral infections, particularly that of the HIV.[5] Moreover, Parnafungins, natural products containing an isoxazolidinone ring, have been isolated from *Fusarium larvarum* and have been shown to be potent inhibitors of the fungal polyadenosine polymerase.[6] Because of the importance of these scaffolds in synthetic organic chemistry and their usefulness as pharmacological molecules, much attention has been focused on their synthesis.

Synthetic routes to them are numerous, including the enantioselective conjugate addition of hydroxylamines to pyrazolidinone acrylamides,[7] propenoates,[8] crotonic acid esters[9] and α,β-unsaturated-δ-lactones.[10] The 1,3-dipolar cycloaddition of nitrones with ynolates to give isoxazolidinones has been developed quite recently.[11] Significant effort continues to be directed into the development of efficient methodologies to new isoxazolidinone-based structures.

The Vilsmeier–Haack reagent (halomethyleniminium salt) formed from the interaction of dialkyl formamide such as DMF with $POCl_3$ has attracted the attention of synthetic organic chemists since its discovery in 1927.[12] It is one of the most commonly used reagents for the introduction of an aldehydic (CHO) group into electron rich aromatic systems.[13] However, the scope of the Vilsmeier reagent is not confined to the aromatic formylation reaction alone. A wide variety of alkene[14] derivatives, carbonyl[15] compounds, activated methyl and methylene[16] groups exhibit reactivity towards the Vilsmeier reagent. In addition to the carbon nucleophiles, some oxygen[17] and nitrogen[18] nucleophiles are also reactive towards Vilsmeier reagent. Numerous transformations of the iminium salts into products other than aldehydes have been achieved[19,20] and these transformations enhance the scope and versatility of the Vilsmeier–Haack reaction. Following our interest on the synthesis of new steroidal derivatives[21] we herein report a prompt and novel strategy for the synthesis of 5α-cholestano-[5,6-*c*]-isoxazolidin-5′-ones (**7–9**) based on the reaction of 5α-6-hydroxyiminocholestanes (**4–6**) with Vilsmeier reagent. Interestingly, the reaction proceeded smoothly and the desired steroidal 5′-isoxazolidinone derivatives (**7–9**) were obtained in good yield (80–87%). With the best of our knowledge there are no reports, however, describing the synthesis of steroidal 5′-isoxazolidinones via Vilsmeier–Haack reaction.

The 5α-6-hydroxyiminocholestanes[22] (**4–6**) employed for the present investigation, were conveniently obtained from the corre-

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http://dx.doi.org/10.1016/j.tetlet.2012.11.105

sponding steroidal ketones[23] (**1–3**) by the known literature method. Treatment of compounds (**4–6**) with DMF/$POCl_3$ at room temperature furnished corresponding steroidal isoxazolidinone derivatives (**7–9**) (Scheme 1). To search for optimum reaction conditions and establish a reproducible procedure, the temperature of reaction was increased. Reaction time was interestingly reduced when it was carried out at 60–65 °C (Table 1). Moreover, to examine the solvent effects, we applied the same conditions with solvents of different polarity. DMF with medium polarity was found to be the best solvent among acetonitrile, chloroform, dichloromethane and toluene in terms of yield and rate (Table 2). With acetonitrile (most polar) and toluene (least polar) even at refluxing temperature did not improve rate and yield significantly. With solvents other than DMF poor yield of products was observed (<40%). Thus most appropriate conditions for this important conversion were found to be (a) 60–65 °C temperature and (b) solvent: DMF. Detailed experimental procedure and spectral data (Figs. S1–S15) can be found in Supplementary data.

Elucidation of the proposed structures (**7–9**) was based on their correct elemental analyses and compatible IR, ^{1}H NMR, ^{13}C NMR, 2D ^{1}H–^{1}H COSY and MS spectral data. The mass spectrum of compound **7** displayed the molecular ion [$M^{+\cdot}$] peak at *m/z* 487. The IR absorption showed peaks at 3310 cm^{-1} for stretching of the N–H group and at 1759 cm^{-1} for stretching of the C=O group. The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **7** featured a signal as singlet at δ 8.70 integrating for one hydrogen, which is the characteristic signal of the N–H proton, while another downfield signal as doublet of doublets at δ 3.22 (J = 4.24, 13.52 Hz) was assigned to the C-6 methine proton. The ^{13}C NMR spectra (100 MHz, $CDCl_3$) showed distinct signals. Resonance at δ 167.26 was diagnostic signals for the carbonyl carbon of heterocyclic ring. Based on these spectral data, the formation of isoxazolidinone ring attached to steroidal skeleton was confirmed. However, the position of the ring was still undecided, and this was determined with the help of 2D-NMR experiments.

The signal at δ 8.70 in the ^{1}H NMR spectrum of compound **7** was unambiguously assigned to the spin system containing the N–H function. It did not show any cross peak with any of the protons in the 2D spectrum, clearly suggesting that there are no adjacent protons which are coupled to N–H proton. The signal at δ 4.67 was assigned to H-3α, which further showed cross-peaks at δ 1.66, 1.57 (H-2β, H-2α) and at δ 2.00, 1.88 (H-4β, H-4α). Neither H_2-4 proton showed any cross peaks, indicating that there is an interruption at C-5. Thus N–H is attached to this carbon. A doublet of doublet at δ 3.20–3.25 was attributed to H-6 which showed cross peaks with the signals at δ 1.59 and 1.40 due to H-7β and H-7α. All these data clearly suggest the fusion of heterocyclic moiety to the 5, 6 position of steroid. The other compounds **8** and **9** were characterized in the same way.

Table 1
Effect of temperature on rate of reaction

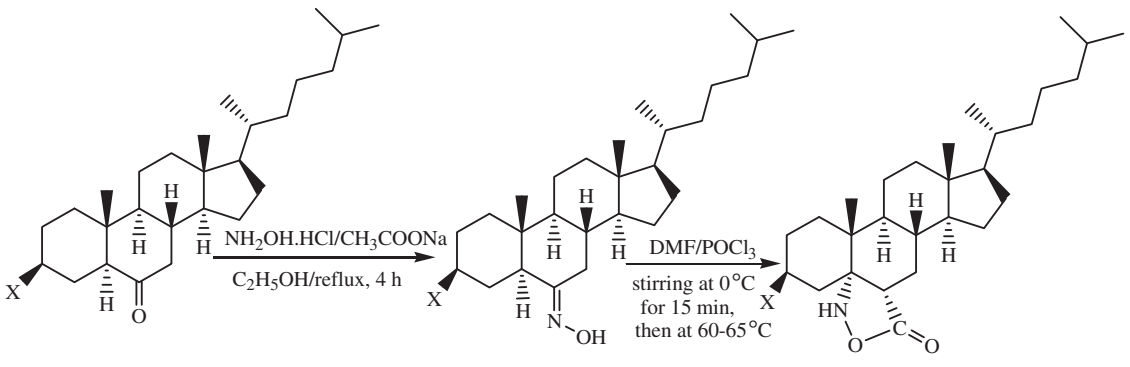
Compound	Time (h): rt	Time (min): 60–65 °C
7	6	50
8	4	45
9	3	30

Table 2
Effect of solvent on rate and yield of reaction at 60–65 °C temperature

Compound	Solvent	Time (h)	Yield (%)
7	CH3CN	16	22
	DMF	50 (min)	87
	CHCl3	12	35
	CH2Cl2	14	30
	C7H8	20	25
8	CH3CN	12	20
	DMF	45 (min)	84
	CHCl3	11	32
	CH2Cl2	10	26
	C7H8	17	20
9	CH3CN	10	18
	DMF	30 (min)	84
	CHCl3	9	30
	CH2Cl2	8	24
	C7H8	16	18

Mechanistically, we assume that aminooxymethylene-dimethyl-ammonium derivative of cholestane is formed from cholesteryl oxime and chloromethyleniminium intermediate (formed in situ from DMF/$POCl_3$) followed by intramolecular cyclization to form a four membered spiro intermediate which undergoes 1,2-hydride shift and simultaneous intramolecular rearrangement to give corresponding products (**7–9**) as depicted in Scheme 2.

The stereochemistry at C-6 can be established on the basis of the mechanism as well as on the coupling constant (J) value of C_6-proton. The proposed reaction mechanism gives rise to a *chiral* centre at C_6 with C_6–CO bond being equatorially (α) oriented,



1-3 **4-6** **7-9**

OAc	(**1**)	OAc	(**4**)	OAc	(**7**)
Cl	(**2**)	Cl	(**5**)	Cl	(**8**)
H	(**3**)	H	(**6**)	H	(**9**)

Scheme 1. Synthesis of steroidal isoxazolidinone derivatives.