Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis and biological evaluation of new nucleosides derived from trifluoromethoxy-4-quinolones

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ARTICLE INFO

Article history:
Received 2 June 2015
Accepted 10 July 2015
Available online xxxx

Keywords:
Trifluoromethoxy-quinolone
Enolethers
Vorbrüggen reaction
Gammaherpesvirus
Gould–Jacobs reaction

ABSTRACT

The synthesis of new nucleoside derivatives from 6- and 7-trifluoromethoxy-4-quinolones is described. The present synthesis is a combination of the Gould–Jacobs reaction for the preparation of 4-quinolones and a modified Vorbrüggen reaction for the construction of nucleoside derivatives. The target compounds were tested against murine gammaherpesvirus MHV-68 type.

Introduction

Fluoroquinolones are recognized as antibacterial agents[1] but also, recently, their anticancer and antiviral[2] activities have been evidenced.[3] Nalidixic acid was the first quinolone used for the treatment of urinary tract infections (Fig. 1). This compound was effective only against Gram-negative bacteria. However, the introduction of a cyclopropyl substituent at the *N*-atom of the pyridinone ring or the presence of a fluorine atom at the quinolone moiety has allowed the preparation of new and more active derivatives such as ciprofloxacine (Fig. 1). Ciprofloxacine belongs to the generally used fluoroquinolone drugs, and according to FDA it could be also an efficient anthrax agent.[4] Natural and synthetic nucleoside analogues are very potent chemotherapeutics employed in the treatment of infections caused by viruses, mainly against HIV infection.[5]

Besides, fluorine introduction has attracted growing interest in pharmaceutical industry as it may advantageously alter the lipophilicity (and thus membrane permeability) of organic compounds. The combination of these important facts (antibacterial activity of fluoroquinolones and antiviral activity of nucleosides) inspired us to prepare novel nucleoside derivatives based on trifluoromethoxy-4-quinolones. These nucleosides consist of a 4-quinolone skeleton bearing a trifluoromethoxy group (as a nucleobase), which is bound to D-ribose via a modified Vorbrüggen reaction. Such a synthetic approach towards nucleosides usually employs trimethylsilyl triflate (TMSOTf) as Lewis acid catalyst in combination with silylated bases.[6] The silylation process of the novel quinolones is the key step in the synthesis of nucleosides. Another analogues of trifluoromethoxyquinolone were prepared by coupling trifluoromethoxyquinolone-3-carboxylic acids with adamantylamine, due to the recognized influence on the antiviral activity of this amine. In the presented Letter, the synthetic route for the preparation of new trifluoromethoxyquinolone derivatives, their innovative structural modifications and biological properties is described.

Results and discussion

Synthesis

The synthesis of the target compounds started with nucleophilic vinylic substitution[7] of the alkoxy group of activated enolethers **3a–h** with commercially available 3-trifluoromethoxyaniline (**1**) or 4-trifluoromethoxyaniline (**2**) to give enamines **4** to **5a–h** in good

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http://dx.doi.org/10.1016/j.tetlet.2015.07.031
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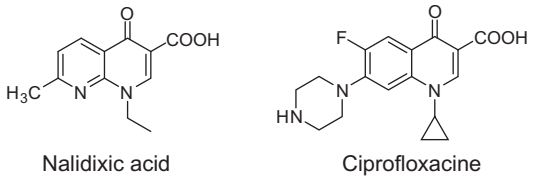


Figure 1. Structures of biologically active 4-quinolones.

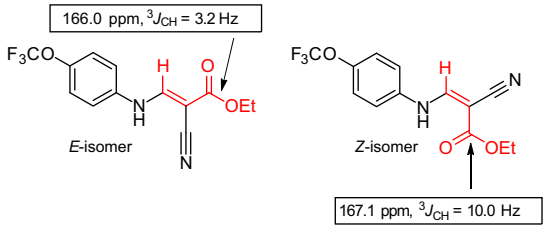


Figure 2. Coupling constants from ^{13}C NMR coupled spectra for *E*-/*Z*-isomers of compound **4f**.

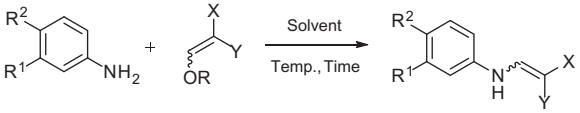
yields (Table 1). The substitution was conducted under reflux (120 °C) within 2–120 min. However, compounds **4–5d** were formed readily at room temperature and reflux conditions were thus not required (Table 1, entries 4 and 12). If necessary, methanol (Table 1, entries 3, 5, 7 and 11) or ethanol (Table 1, entries 8 and 16) were used as solvents. Enamines (Table 1, entries 1–4 and 9–12) bearing two equal substituents (X and Y) on the double bond can exist as one geometrical isomer, while enamines (Table 1, entries 5–7 and 13–15) with two different substituents (X and Y) exist as a mixture of two geometrical isomers. These isomers cannot be separated because the isomerization occurs readily in a solution, mainly if the solvent used is basic.[8] Therefore, the isomeric ratio was determined by NMR spectroscopy. The determination of *E*-/*Z*-isomers for enamines **4** to **5e–g** was accomplished by the coupled ^{13}C NMR technique. The values of coupling constants ($^3J_{CH}$) between the olefinic hydrogen and the carbon atom of the carbonyl group (acetyl or ester) enabled us to assign the geometrical isomers. The values of trans coupling constants $^3J_{CH}$ were in the range of 8.0–10.0 Hz while the corresponding values of cis coupling constants $^3J_{CH}$ were in the range of 3.0–5.0 Hz (Fig. 2).[9] The ratio of *E*-/*Z*-isomers of compounds **4e–g** and **5e–g** was determined on the basis of peak integration in their ^1H NMR spectra.

In all cases of prepared compounds **4e–g** and **5e–g** (Table 1, entries 5–7 and 13–15), the *E*-isomer was observed as the major product. In the case of compounds **4e** and **5e** (Table 1, entries 5 and 13) it can be explained by strong hydrogen bonding between the amino hydrogen and the oxygen of the acetyl group.[8a] The *E*-isomer prevails also because the hydrogen bond between the amino hydrogen and the carbonyl oxygen of the ester group is weaker than the hydrogen bond between the amino hydrogen and oxygen of the acetyl group.[8a] This interaction also stabilized the antiperiplanar conformation of —NH—CH= group. This arrangement was also confirmed by the coupling constant in the ^1H NMR spectra ($^3J_{NH-CH}$ = 12–14 Hz). For enamines **4f** and **5f** (Table 1, entries 6 and 14), having a cyano or ethylester group in vinylic position, and for enamines **4g** and **5g** (Table 1, entries 7 and 15), having a cyano or acetyl group in vinylic position, also *E*-isomers were observed as the major products. In this case steric hindrance plays an important role.

Next, the thermal cyclization of enamines **4–5a,b,f** under Gould–Jacobs conditions smoothly afforded the fluorinated quinolones **6** to **7a–c** in good yields (Scheme 1). In the case of enamines **5**, two regioisomers could potentially be formed, nonetheless only 7-substituted quinolones **7** were isolated. Carboxylic acids **8** and **9** were obtained by alkaline hydrolysis of ethyl esters **6a** and **7a** in good yields.

Several structural modifications of the trifluoromethoxyquinolones **6a** and **7a** were carried out to increase both their biological activity and their solubility (Scheme 2). First, ethylation of trifluoromethoxyquinolone ethyl esters **6a** and **7a** with ethyl iodide in DMF in the presence of K_2CO_3 provided derivatives **10** and **11** in 63% and 80% yields, respectively. Next, acid hydrolysis

Table 1
Nucleophilic vinylic substitution between enolethers **3a–h** and trifluoromethoxyanilines **1** and **2**



1 (R^1=H, R^2=OCF_3)
2 (R^1=OCF_3, R^2=H)
3a-h
4a-h (R^1=H, R^2=OCF_3)
5a-h (R^1=OCF_3, R^2=H)

(a) R = Et, X = Y = COOEt, (b) R = Me, X = Y = COOMe, (c) R = Et, X = Y = CN, (d) R = Et, X = Y = $COCH_3$, (e) R = Et, X = $COCH_3$, Y = COOEt, (f) R = Et, X = CN, Y = COOEt, (g) R = Et, X = CN, Y = $COCH_3$, (h) R = Me, X = Y = $COOC(CH_3)_2OCO$.

Entry	Aniline	Enolether	Solvent	Temp (°C)	Time (min)	Product	Yield[a] (%)	*E*:*Z* ratio[b]
1	**1**	**3a**	—	120	60	**4a**	66	—
2	**1**	**3b**	—	120	60	**4b**	83	—
3	**1**	**3c**	Ethanol	120	60	**4c**	98	—
4	**1**	**3d**	—	rt	2	**4d**	81	—
5	**1**	**3e**	Ethanol	120	60	**4e**	98	83:17
6	**1**	**3f**	—	120	15	**4f**	88	67:33
7	**1**	**3g**	Ethanol	120	45	**4g**	98	59:41
8	**1**	**3h**	Methanol	120	60	**4h**	87	—
9	**2**	**3a**	—	120	120	**5a**	70	—
10	**2**	**3b**	—	120	60	**5b**	75	—
11	**2**	**3c**	Ethanol	120	60	**5c**	67	—
12	**2**	**3d**	—	rt	2	**5d**	70	—
13	**2**	**3e**	—	120	60	**5e**	99	83:17
14	**2**	**3f**	—	120	60	**5f**	96	67:33
15	**2**	**3g**	—	120	45	**5g**	66	63:37
16	**2**	**3h**	Methanol	120	60	**5h**	57	—

[a] Isolated total yield.
[b] Isomer ratio of products in a solution of deuterated solvent.