Tetrahedron Letters 50 (2009) 1625–1628

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Improved modular synthesis of thieno[3,2-*b*]pyrroles and thieno[2,3-*b*]pyrroles

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ARTICLE INFO

Article history:
Received 18 December 2008
Accepted 20 January 2009
Available online 23 January 2009

ABSTRACT

A convenient modular synthesis for the construction of densely functionalized thieno[3,2-*b*]pyrroles, allosteric inhibitors of the Hepatitis C virus NS5B polymerase, is described. The route allows the introduction of substituents in positions 4, 5, and 6 of the thienopyrrole scaffold and can also be applied to the regioisomeric thieno[2,3-*b*]pyrrole core.

The Hepatitis C virus (HCV) is the principal etiological agent of chronic hepatitis C infection, affecting 170 million people worldwide.[1] If untreated, more than 60% of these individuals will develop chronic liver disease that leads to chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. The current therapy, pegylated α-interferon (IFN) alone or in combination with ribavirin, is poorly tolerated. Additionally, it is of limited efficacy in patients infected with HCV genotype 1, which accounts for about 70% of the infections in the western world. Thus, new treatment regimens are needed. The NS5B RNA-dependent RNA polymerase plays a central role in virus replication and is considered an attractive target for drug discovery efforts. In recent years, several non-nucleoside inhibitors (NNIs) that bind to different areas of the enzyme have been disclosed.[2]

Indole-*N*-acetamides have been identified by us and others as potent allosteric inhibitors of HCV polymerase.[3] Essential features for binding of the indole scaffold to NS5B are the cyclohexyl group at C-3, the carboxylic acid at C-6, and an aryl group at C-2.The acetamide moiety was found to confer cell-based activity.[3a]

Parallel to the work in the indole series, the replacement of the indole core system with bioisosteric structures was explored. In this context, thieno[3,2-*b*]pyrroles were identified as equipotent inhibitors of HCV polymerase (Fig. 1).[4] In scheme 1, the synthetic pathway to **2** is reported. Starting from thiophene **3**, intermediate **4** was prepared according to a published procedure.[5]

The cyclohexyl moiety was introduced by condensation with cyclohexanone[6] followed by reduction with triethylsilane[7] to give **6**. Alkylation of the indole nitrogen and basic hydrolysis of the methyl ester furnished compound **2**. SAR studies around the thieno[3,2-*b*]pyrrole structure were then initiated to improve potency and physicochemical properties. We knew from the work around the indole series that substitution at C-2 and N-1 is crucial for cell-based activity.[3a] Since our approach to prepare **2** introduces the aryl substituent early on, it was not deemed suitable for the rapid exploration of SAR. Other synthetic routes to build up the thienopyrrole system are known, but are generally characterized by low yields and difficult access to the starting materials.[8] To advance our studies, we postulated a different synthetic route that is shown in scheme 2. Here, the aryl residue is introduced near the end by Pd-mediated cross-coupling performed on key intermediate **8**, which is prepared by manipulation of **9**. We reasoned that intermediate **9** should be accessible from thiophene **10** via a palladium-catalyzed ring-closure with concomitant installation of the cyclohexyl group, chemistry which has been widely applied for the construction of indoles.[9]

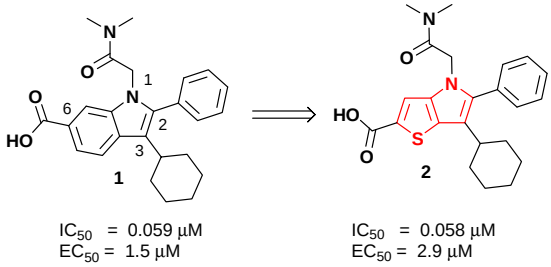
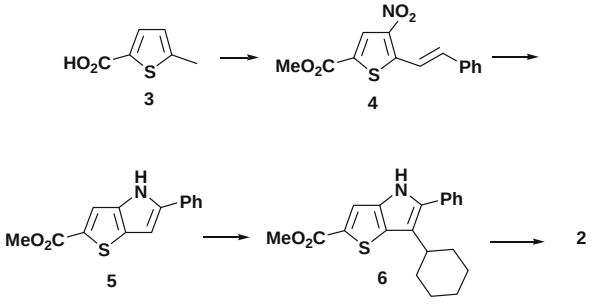


Figure 1.



Scheme 1. Classical approach to **2**.[4]

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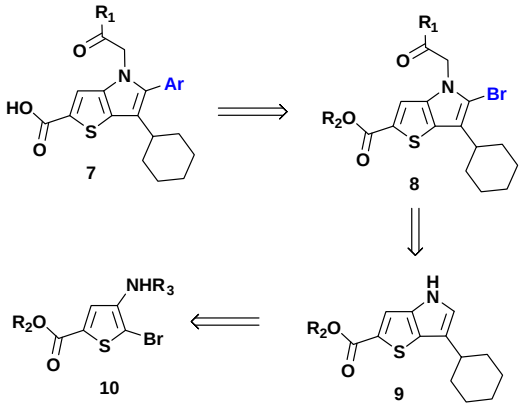
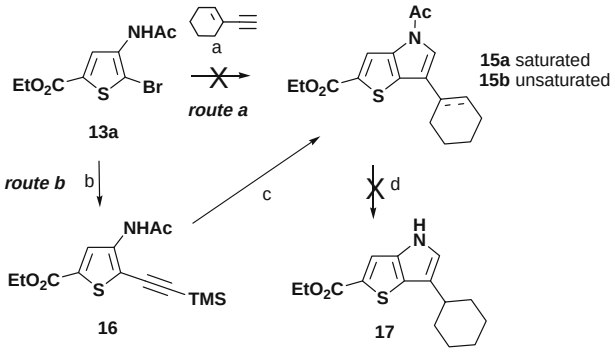
doi:10.1016/j.tetlet.2009.01.109



Scheme 2. Retrosynthetic analysis.

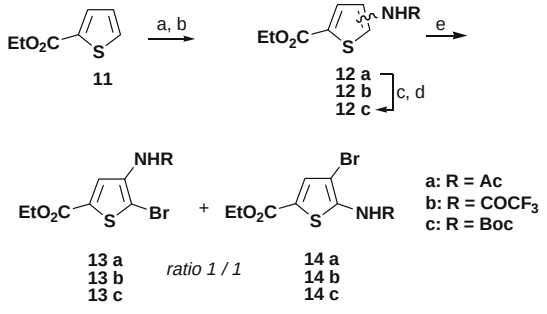


Scheme 4. Reagents and conditions: (a) LiCl or nBu$_4$NCl, Na_2CO_3 or KOAc, Pd(AcO)$_2$ or $Pd_2(dba)_3$, DMF, 100 °C; (b) Me_3SiCCH, CuI, $PdCl_2(PPh_3)_2$, TEA, THF, rt, 80%; (c) 1-cyclohexenyl triflate, Cs_2CO_3, $Pd(PPh_3)_4$, MeCN, rt, 80%; (d) TFA, Et_3SiH then HCl (3 N), reflux.

To put this idea into practice, commercial ethyl thiophene-2-carboxylate was nitrated giving a 1:1 mixture of the two regioisomers, ethyl 4-nitrothiophene-2-carboxylate and ethyl 5-nitrothiophene-2-carboxylate. The mixture was reduced with Fe in Ac_2O/AcOH[10] to generate the acetylated amino derivatives **12a**. This one-pot method of reduction–protection was preferred since it avoided substantial degradation of the aminothiophene. Decomposition also occurred when the nitro-intermediate was reduced by hydrogenation over Pd/C. After bromination, the mixture of the two regioisomers could be conveniently separated by flash chromatography on silica gel (Scheme 3). We submitted regioisomer **13a** first to the classical one-pot Pd-catalyzed heteroannulation[11] of internal alkynes (Scheme 4, route a), using either cyclohexyl- or cyclohexenyl acetylene. Although this approach has been reported to work extremely well in the synthesis of functionalized indole systems, in our case at best only traces of **15a** or **b** were observed. Instead, it was possible to obtain **15b** by a stepwise process via the Sonogashira coupling of trimethylsilylacetylene followed by Pd-catalyzed cyclization of **16** in the presence of cyclohexenyl triflate (Scheme 4, route b).[12]

Despite numerous attempts further elaboration of **15b** was unsuccessful. The reduction of the double bond in the cyclohexenyl ring using palladium under hydrogen atmosphere or the TFA/triethylsilane[7] system failed or led to unidentified side products. Removal of the acetyl group in both basic and acidic conditions gave no reaction or led to decomposition under more forcing conditions. Bromination gave the product contaminated with various side products, probably due to the presence of the double bond.

To overcome these problems, we further remodeled the synthetic pathway. The acetyl substituent was exchanged for protecting groups, which can be cleaved under milder conditions. The trifluoroacetyl intermediate **12b** was prepared similar to **12a** (Fe in TFAA/TFA) and **12c** was prepared from **12a** in a two-step procedure (Scheme 3). After bromination and separation of the regioisomers compounds **13b,c** were submitted to the Sonogashira coupling to give **20b,c** (Scheme 5).

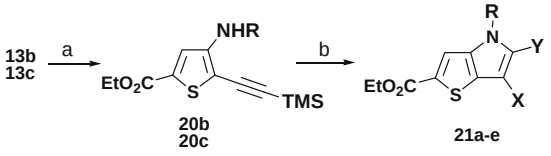


Scheme 3. Reagents and conditions: (a) HNO_3, H_2SO_4, −10 °C, 96%; (b) Fe, Ac_2O, AcOH, 80 °C (77% for **12a**); Fe, TFAA, TFA (52% for **12b**); (c) BOC_2O, TEA, DCM; (d) Hydrazine, EtOH, 96% over two steps; (e) NBS, DCM, rt, 80%.

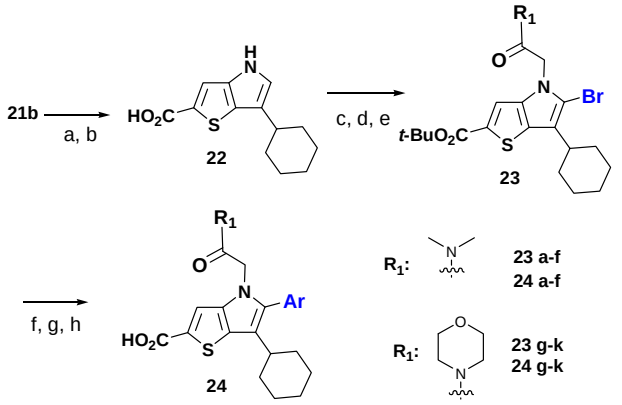
Different conditions for the cyclization to the pyrrole ring were screened,[9] including Pd(II) and Cu(I)-catalyzed methods, as well as base and TBAF-mediated cyclizations. As the results in Table 1 show, most of the conditions did not give the desired product **21**, with the exceptions of the palladium-catalyzed cyclization in the presence of cyclohexenyl triflate, and the TBAF-catalyzed cyclization. When the palladium-catalyzed cyclization procedure was applied to indole synthesis, it furnished exclusively the silylated product. In our case with **20b** the main product was **21d**, but also the desilylated product was isolated. On the contrary, in the Boc-protected case **20c** only the desilylated product was recovered. Considering the yields better results were obtained in the Boc-protected case (compare entries 7 and 8), where on a small scale **21e** was obtained in 64% yield. Unfortunately, the yield dropped to around 15% on multigram scale. This led us to prefer the TBAF-mediated route, which gave the best results in terms of yield and ease of purification when the cyclization was performed under microwave irradiation, leading directly to the deprotected thienopyrrole **21b** (R = X = Y = H).

Next, the cyclohexyl moiety was introduced under basic conditions, and the double bond was reduced by hydrogenation over $Pd(OH)_2$ at high pressure (Scheme 6). These conditions caused also the hydrolysis of the ethyl ester. This drawback turned out to be useful since we could install a t-butyl ester,[13] which allowed for a more convenient deprotection to obtain the final compounds. In the case of the methyl ester, we had observed cleavage of the acetamide moiety in some cases. Bromination and alkylation finally gave the desired intermediate **23**. This was used to introduce diversity via palladium-catalyzed cross-coupling reaction. A variety of boronic acids were tested with good results as reported in Table 2.

As a further extension of this work, we were interested if this chemistry would also be applicable to the regioisomeric thieno[2,3-*b*]pyrrole (Scheme 7). Having in hand intermediate **14c**,



Scheme 5. Reagents and conditions: (a) Me_3SiCCH, CuI, $PdCl_2(PPh_3)_2$, TEA, THF, 50 °C, 89%; (b) see Table 1.



Scheme 6. Reagents and conditions: (a) cyclohexanone, NaOEt/EtOH, reflux, then water; (b) H_2, $P = 45$ psi, $Pd(OH)_2$, MeOH/AcOEt, 45% over two steps; (c) 2-*t*Bu-1,3-diisopropylisourea, THF, reflux; (d) NBS, DCM, 0 °C, 40% over two steps; (e) $ClCH_2CON(Me)_2$, NaH, DMF, rt, 92%; (f) $ArB(OH)_2$, $PdCl_2(dppf)_2$, Na_2CO_3, DME, 80 °C; (g) DCM/TFA, rt; (h) RP-HPLC.

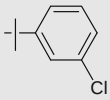
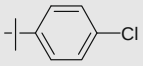
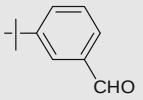
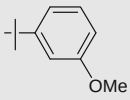
we performed the Sonogashira coupling to introduce the phenylacetylene group. The 3-bromo isomer **14c** was less reactive than the corresponding isomer **13c** and as a matter of fact that did not react under the conditions applied to isomer **13c**. Switching to $Pd(PhCN)_2Cl_2/P(t\text{-}Bu)_3$, with the electron-rich, sterically demanding phosphine, developed by Fu,[14] allowed the reaction to take place. In contrast to the reaction of arylbromides, which undergo the Sonogashira coupling at room temperature, we had to reflux the reaction to achieve complete conversion in high yield. The cyclization to the pyrrole was carried out through Pd-catalyzed heteroannulation of internal alkynes in acceptable yield. Further elaborations gave compound **28**.

In summary, we have developed a suitable synthesis of thieno[3,2-*b*]pyrroles, which allowed us to further extend our SAR studies. This method is highly flexible and allows the investigation of positions 4, 5, and 6 of the thienopyrrole nucleus, and might also be used for the construction of combinatorial libraries around this core. We could also show that the same chemistry can be applied to the thieno[2,3-*b*]pyrrole scaffold.

Supplementary data

Supplementary data contains experimental details of the synthesis and characterization of compounds. Supplementary data

Table 2

24	Ar	Y[a] (%)
a		10
b		60
c		30
d		40
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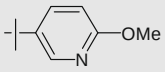
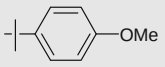
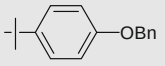
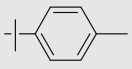
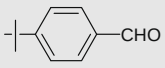
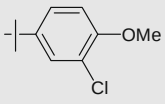
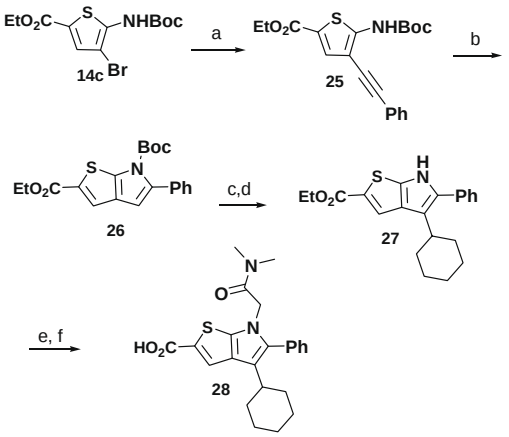
f		66
g		20
h		10
i		20
j		53
k		10

[a] Yield calculated from compounds **23** to **24** in a three steps sequence.

Table 1

Entry	20	21	R	X	Y	Conditions yield
1	**b**	**a**	$COCF_3$	H	H	CuI, DMF, 100 °C;[9b] 0%
2	**b**	**b**	H	H	H	KO*t*Bu, *t*BuOH, reflux;[9c] 0%
3	**b**	**b**	H	H	H	NaOEt, EtOH, reflux;[9c] 0%
4	**b**	**b**	H	H	H	$n\text{Bu}_4\text{F}$, THF, 120 °C;[9d] 78%
5	**b**	**c**	$COCF_3$	H	TMS	$Pd_2(dba)_3$, K_2CO_3, DMSO, 40 °C;[12] 0%
6	**b**	**c**	$COCF_3$	H	TMS	Pd $(PPh_3)_4$, K_2CO_3, THF, reflux;[12] 0%
7	**b**	**d**	$COCF_3$		TMS[a]	Cyclohexenyl triflate, $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, rt;[11] 30%
8	**c**	**e**	Boc		H	Cyclohexenyl triflate, $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, rt;[11] 64%
9	**c**	**b**	H	H	H	$n\text{Bu}_4\text{F}$, THF, 120 °C;[9d] 70%

[a] 10% of desilylated product was recovered.



Scheme 7. Reagents and conditions: (a) Me_3SiCCH, CuI, $PdCl_2(PhCN)_2$, P(*t*Bu)$_3$, DIPEA, dioxane, rt, 96%; (b) K_2CO_3, $Pd_2(dba)_3$, P(*t*Bu)$_3$, THF, 80 °C, 66%; (c) cyclohexanone, H_3PO_4, AcOH, Ac_2O, 80 °C; (d) Et_3SiH, TFA, rt, 58% over two steps; (e) NaOH, THF/MeOH, reflux, 54%; (f) $ClCH_2CON(Me)_2$, NaH, DMF, rt, then RP-HPLC, 27%.

associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.109.

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