Tetrahedron Letters xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

A highly facile approach to the synthesis of novel 2-(3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-N-phenylacetamides

Mikhail S. Novikov [a], Denis A. Babkov [a], Maria P. Paramonova [a], Alexander O. Chizhov [b], Anastasia L. Khandazhinskaya [c], Katherine L. Seley-Radtke [d,*]

[a] Department of Pharmaceutical & Toxicological Chemistry, Volgograd State Medical University, PavshikhBortsov Sq., 1, Volgograd 400131, Russia
[b] Zelinsky Institute of Organic Chemistry, Russian Academy of Science, Leninsky pr., 47, Moscow 119991, Russia
[c] Engelhardt Institute of Molecular Biology, Russian Academy of Science, Vavilov Str., 32, Moscow 119991, Russia
[d] Department of Chemistry & Biochemistry, University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250, USA

ARTICLE INFO

Article history:
Received 5 November 2012
Revised 17 November 2012
Accepted 21 November 2012
Available online xxxx

Keywords:
Heterocycles
NNRTI
Heteroaromatic
Pyrimidines

ABSTRACT

A series of heterocyclic compounds were designed as potential nonnucleoside HIV reverse transcriptase inhibitors. Although the compounds ultimately proved inactive against HIV, during the course of the synthesis, a new and highly facile method to realize N-phenylacetamides was developed. Notably, the new route avoids the intractable workups and byproducts previously reported procedures have been associated with, thereby making this approach highly attractive to adaptation with other heterocyclics.

© 2012 Elsevier Ltd. All rights reserved.

As a part of our ongoing efforts to synthesize aryl and heteroaromatic nonnucleoside HIV reverse transcriptase inhibitors (NNRTIs), we sought to construct a new series of N-3 phenylacetamides for use in alkylating various uracils. The amide unit is one of the most important and widely occurring functional groups; it is present in many natural products and is a key feature of many important drugs. Among the more notable examples of amide-containing compounds, those found in conjunction with N-heterocycles exhibit diverse and marked pharmacological activities. In particular, the HIV-1 NNRTIs,[1] dihydrofolate reductase (DHFR) inhibitors,[2] and histone deacetylase (HDAC) inhibitors stand out.[3] It is not surprising therefore that there are numerous papers in which amide bond formation has been described.[4] Despite the plethora of available routes, most are plagued with problems, in particular, low yields and difficult workups. As a result, a new and more facile route was sought.

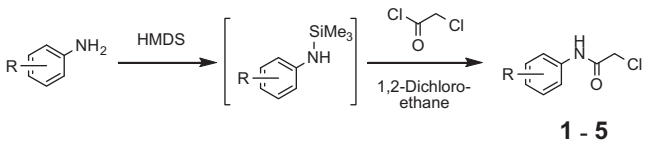
A preliminary search of the literature revealed several known methods for the formation of 2-chloroacetanilides. The most commonly used methodology involves condensation of chloroacetyl chloride with various anilines in aprotic solvents (e.g. ether, dioxane, chloroform, dichloromethane, ethyl acetate, or DMF) in the presence of anhydrous K_2CO_3,[5] triethylamine[6] or pyridine[7] as the base. Another variant utilizes methylethylketone and $CaCO_3$[8] while other references describe condensation promoted by triethylamine in acetic acid.[9] Examples of aniline acylation in acetate buffer[10] and aqueous K_2CO_3[11] are also known, while another approach proposes the synthesis of 2-chloroacetanilides in base-free conditions. In the latter case, the reaction takes place in nonpolar solvent[12] or in a mixed solvent system.[13] Although there are many options available, it is important to note that most of these methods suffer from numerous side reactions arising from either N-quaternization of the organic base or hydrolysis, which lead to low yields and tedious work-up procedures.

It has however, been shown that amide bond formation could be achieved by the cleavage of the silicon–nitrogen bonds in TMS-protected alkylamines and anilines by acid halides.[14] The absence of a base renders the silyl method very attractive for the synthesis of 2-chloroacetanilides, as this serves to bypass the problems with side reactions such as quaternization and hydrolysis that are common with the aforementioned routes. Surprisingly, there was no information in the literature for the preparation of 2-chloroacetanilides that utilized the silyl methodology. As a result, we have now employed this approach to synthesize a series of 2-chloroacetanilides, as shown in Scheme 1, which were then used for the synthesis of the desired NNRTIs.

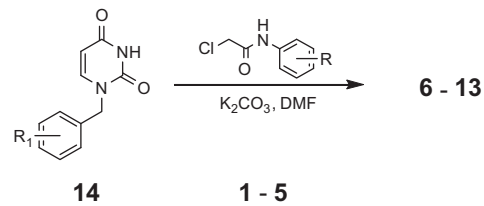
As shown in Scheme 1, the starting anilines were converted into *N*-trimethylsilyl derivatives by refluxing in excess HMDS to form the N-silylated intermediates, followed by treatment with chloroacetyl chloride in anhydrous 1,2-dichloroethane to produce target

* Corresponding author. Tel.: +1 410 455 8684 (O); fax: +1 410 455 2608.
E-mail address: kseley@umbc.edu (K.L. Seley-Radtke).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.11.090

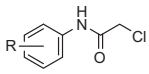


Scheme 1. Proposed pathway to 2-chloroacetanilides.



Scheme 2. Synthesis of target uracil derivatives.

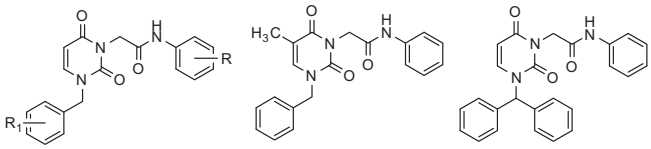
Table 1
Physical properties of 2-chloroacetanilides



Compd	R	R_f[a]	Yield (%)	Mp (°C)
1	H	0.70	82	135–136.5
2	2-Me	0.60	86	111.5–113
3	4-Me	0.67	87	163–165
4	3,4-Me_2	0.71	97	110–112
5	3,5-Me_2	0.73	98	143–145

[a] Ethyl acetate/hexane 1:1.

Table 2
Physical properties of 2-(1-benzyluracil-3-yl)-N-phenylacetamides



Compd	R_1	R	R_f[a]	Yield (%)	Mp (°C)
6	H	H	0.57	96	212–213
7	2,5-Me_2	H	0.65	90	175–176.5
8	3,5-Me_2	H	0.61	84	248–250
9	4-^{t}Bu	H	0.63	90	219–220
10	H	2-Me	0.48	84	201–202
11	H	4-Me	0.59	83	221–222
12	H	3,4-Me_2	0.56	78	222.5–224
13	H	3,5-Me_2	0.64	87	214–215
15	—	—	0.71	90	197.5–198.5
16	—	—	0.78	96	125–127

[a] Ethyl acetate/1,2-dichloroethane 1:1.

amides **1**–**5** in 82–98% yield (Table 1).[15] Notably, this occurred without any of the tar-like by-products typically observed with these reactions.

The target 2-(1-benzyluracil-3-yl)-N-phenylacetamides **6**–**13** were then obtained in excellent to almost quantitative yields (78–96%, see Table 2) by alkylation of 1-benzyluracils[16] **14** with the appropriate 2-chloroacetanilides **1**–**5** in the presence of a 1.5-fold molar excess of K_2CO_3 in DMF as shown in Scheme 2.[17]

In an analogous fashion, N-phenylacetamides **15** and **16** were synthesized starting with 1-benzylthymine[18] and 1-(benzhydryl)uracil,[19] respectively. It should be noted that all the compounds were obtained without suffering the intractable workups or side products the typical procedures have been associated with, thereby making this approach highly attractive to adaptation with other heterocyclic compounds.

Compounds **6**–**13**, **15,** and **16** were evaluated as inhibitors against a large set of DNA and RNA viruses. Disappointingly, none of them proved to be active against any of the strains tested including HIV-1, HIV-2, HSV-1, HSV-2, HCMV, VZV, Vaccinia virus, Parainfluenza-3 virus, Reovirus-1, Sindbis virus, Vesicular stomatitis virus, Respiratory syncytial virus, Coxsackie virus B4 or Feline Corona Virus.[20,21]

In summary, while the target NNRTIs synthesized proved inactive, a facile and high-yielding route to N-phenylacetamides was developed, which should prove useful for many synthetic applications employing heterocyclic amides.

Acknowledgments

This work was supported by the Russian Foundation for Basic Research (Grant 10-04-0056a). The authors would like to thank Professor Jan Balzarini of the Rega Institute for antiviral evaluation of synthesized compounds.

Supplementary data

Supplementary data (specific experimental details for each of the target compounds including ^{1}H and ^{13}C NMR data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.090.

References and notes

1. (a) De La Rosa, M.; Kim, H. W.; Gunic, E.; Jenket, C.; Boyle, U.; Koh, Y.-H.; Korboukh, I.; Allan, M.; Zhang, W.; Chen, H.; Xu, W.; Nilar, S.; Yao, N.; Hamatake, R.; Lang, S. A.; Hong, Z.; Zhang, Z.; Girardet, J.-L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4444–4449; (b) Gagnon, A.; Amad, M. H.; Bonneau, P. R.; Coulombe, R.; DeRoy, P. L.; Doyon, L.; Duan, J.; Garneau, M.; Guse, I.; Jakalian, A.; Jolicoeur, E.; Landry, S.; Malenfant, E.; Simoneau, B.; Yoakim, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4437–4441; (c) Yu, M.; Liu, X.; Li, Z.; Liu, S.; Pannecouque, C.; Clercq, E. D. *Bioorg. Med. Chem. Lett.* **2009**, *17*, 7749–7754.
2. Al-Omary, F. A. M.; Abou-Zeid, L. A.; Nagi, M. N.; Habib, E.-S. E.; Abdel-Aziz, A. A.-M.; El-Azab, A. S.; Abdel-Hamide, S. G.; Al-Omar, M. A.; Al-Obaid, A. M.; El-Subbagh, H. I. *Bioorg. Med. Chem.* **2010**, *18*, 2849–2863.
3. (a) Zhang, Y.; Fang, H.; Feng, J.; Jia, Y.; Wang, X.; Xu, W. *J. Med. Chem.* **2011**, *54*, 5532–5539; (b) Wang, H.; Yu, N.; Chen, D.; Lee, K. C. L.; Lye, P. L.; Chang, J. W. W.; Deng, W.; Ng, M. C. Y.; Lu, T.; Khoo, M. L.; Poulsen, A.; Sangthongpitag, K.; Wu, X.; Hu, C.; Goh, K. C.; Wang, X.; Fang, L.; Goh, K. L.; Khng, H. H.; Goh, S. K.; Yeo, P.; Liu, X.; Bonday, Z.; Wood, J. M.; Dymock, B. W.; Kantharaj, E.; Sun, E. T. *J. Med. Chem.* **2011**, *54*, 4694–4720.
4. Bailey, P. D.; Mills, T. J.; Pettecrew, R.; Price, R. A. *In Comprehensive Organic Functional Group Transformations II*; Elsevier: Vol. null, 2005. pp 201–294.
5. (a) Sauter, F.; Stanetty, P. *Monatsh. Chem.* **1975**, *106*, 1111–1116; (b) Vejdělek, Z.; Holubek, J.; Bartošová, M.; Protiva, M. *Collect. Czech. Chem. Commun.* **1982**, *47*, 3297–3305; (c) Vejdělek, Z.; Bartošová, M.; Protiva, M. *Collect. Czech. Chem. Commun.* **1983**, *48*, 156–162; (d) Effland, R. C.; Helsley, G. C.; Tegeler, J. J. *J. Heterocycl. Chem.* **1982**, *19*, 537–539.
6. (a) Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 3683–3686; (b) Szmuszkovicz, J.; Chidester, C. G.; Laurian, L. G.; Scahill, T. A. *J. Org. Chem.* **1986**, *51*, 5001–5002; (c) Kizuka, H.; Hanson, R. N. *J. Med. Chem.* **1987**, *30*, 722–726; (d) Wolfbeis, O. S.; Marhold, H. *Monatsh. Chem.* **1983**, *114*, 599–604.
7. Reddy, P. S. N.; Nagaraju, C. *Synth. Commun.* **1991**, *21*, 173–181.
8. Perez, M.; Ayerbe, N.; Fourrier, C.; Sigogneau, I.; Pauwels, P.; Palmier, C.; John, G.; Valentin, J.; Halazy, S. *Eur. J. Med. Chem.* **1997**, *32*, 129–134.
9. (a) Deak, G.; Doda, M.; Gyorgy, L.; Hazai, L.; Sterk, L. *J. Med. Chem.* **1977**, *20*, 1384–1388; (b) Gall-Istok, K.; Sterk, L.; Toth, G.; Deak, G. *J. Heterocycl. Chem.* **1984**, *21*, 1045–1048.
10. (a) Löfgren, N.; Tegnér, C.; Bonnichsen, R.; Virtanen, A. I. *Acta Chem. Scand.* **1955**, *9*, 493–496; (b) Byrnes, E. W.; McMaster, P. D.; Smith, E. R.; Blair, M. R.;

Boyes, R. N.; Duce, B. R.; Feldman, H. S.; Kronberg, G. H.; Takman, B. H.; Tenthorey, P. A. *J. Med. Chem.* **1979**, *22*, 1171–1176.

11. Kim, S.-C.; Kwon, B.-M. *Synthesis* **1982**, *1982*, 795–796.
12. (a) Meth-Cohn, O.; Rhouati, S.; Tarnowski, B.; Robinson, A. *Perkin Trans. 1* **1981**, 1537–1543; (b) Neumeyer, J. L.; Perianayagam, C.; Ruchirawat, S.; Feldman, H. S.; Takman, B. H.; Tenthorey, P. A. *J. Med. Chem.* **1977**, *20*, 894–898; (c) Hromatka, O.; Knollmüller, M.; Foroutan-Rad, M. *Monatsh. Chem.* **1974**, *105*, 1057–1066; (d) Lin, W. O.; Souza Coutinho, E. *Monatsh. Chem.* **1983**, *114*, 1231–1235.
13. Martelli, S.; Dzieduszycka, M.; Stefanska, B.; Bontemps-Gracz, M.; Borowski, E. *J. Med. Chem.* **1988**, *31*, 1956–1959.
14. (a) Bowser, J. R.; Williams, P. J.; Kurz, K. *J. Org. Chem.* **1983**, *48*, 4111–4113; (b) Taddei, M.; Tempesti, F. *Synth. Commun.* **1985**, *15*, 1019–1024; (c) Oishi, Y.; Kakimoto, M.; Imai, Y. *Macromolecules* **1987**, *20*, 703–704; (d) Lozano, A. E.; de Abajo, J.; de la Campa, J. G. *Macromolecules* **1997**, *30*, 2507–2508; (e) Rajeswari, S.; Jones, R. J.; Cava, M. P. *Tetrahedron Lett.* **1987**, *28*, 5099–5102.
15. *General method for synthesis of 2-chloro-N-phenylacetamides* ***1–5***. A mixture of 16.50 mmol of aniline, 20 mL of HMDS and NH_4Cl (250 mg) was refluxed for 10 h until a homogeneous solution was obtained. Excess of HMDS was removed under reduced pressure, and the residual clear oil dissolved in 40 mL of anhydrous 1,2-dichloroethane. A solution of chloroacetyl chloride (1.4 ml, 17.60 mmol) in 1,2-dichloroethane (10 mL) was added dropwise with stirring at 0 °C. The reaction mixture was stirred overnight at rt and then evaporated to 1/3 volume. Hexane (30 mL) was added and the mixture was kept overnight in a refrigerator. The resulting precipitate was filtered and recrystallized from EtOAc/hexane.
16. Kundu, N. G.; Sikdar, S.; Hertzberg, R. P.; Schmitz, S. A.; Khatri, S. G. *Perkin Trans. 1* **1985**, 1295–1300.
17. *General method for the synthesis of 2-(3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-N-phenylacetamides* ***6–13***, ***15*** *and* ***16***. A suspension of 7.72 mmol of 1-benzyluracil[16] **14**, 1-benzylthymine[18] or 1-(diphenylmethyl)uracil[19] and K_2CO_3 (1.6 g, 11.58 mmol) in 15 mL of DMF was stirred at 80 °C for 1 h then cooled to rt. After addition of 2-chloroacetanilide **1–5** (7.66 mmol), the reaction mixture was stirred for 2 h, chilled overnight, filtered and the solvent removed under reduced pressure. The residue was treated with 50 mL of water, and the resulting precipitate filtered and recrystallized from a mixture of acetone-^{i}PrOH-DMF.
18. Lopez, F. J.; Arias, L.; Chan, R.; Clarke, D. E.; Elworthy, T. R.; Ford, A. P. D. W.; Guzman, A.; Jaime-Figueroa, S.; Jasper, J. R.; Morgans, D. J.; Padilla, F.; Perez-Medrano, A.; Quintero, C.; Romero, M.; Sandoval, L.; Smith, S. A.; Williams, T. J.; Blue, D. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1873–1878.
19. Wu, F.; Buhendwa, M. G.; Weaver, D. F. *J. Org. Chem.* **2004**, *69*, 9307–9309.
20. *The methodology of the anti-HIV assays in MT-4 cell cultures was as follows*: Virus stocks were titrated in MT-4 cells and expressed as the 50% cell culture infective dose ($CCID_{50}$). MT-4 cells were suspended in culture medium at 1×10^5 cells/ml and infected with HIV at a multiplicity of infection of 0.02. Immediately after viral infection, 100 μl of the cell suspension was placed in each well of a flat-bottomed microtiter tray containing various concentrations of the test compounds. After 4 days of incubation at 37°C, the number of viable cells was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method. The selection and characterization of mutant virus strains have been performed previously.
21. *The compounds were evaluated against the following viruses*: Herpes simplex virus type 1 (HSV-1) strain KOS, thymidine kinase-deficient (TK^-) HSV-1 KOS strain resistant to ACV (ACV^r), herpes simplex virus type 2 (HSV-2) strains Lyons and G, varicella-zoster virus (VZV) strain Oka, TK^- VZV strain 07−1, human cytomegalovirus (HCMV) strains AD-169 and Davis, vaccinia virus Lederle strain, respiratory syncytial virus (RSV) strain Long, vesicular stomatitis virus (VSV), Coxsackie B4, Parainfluenza 3, Influenza virus A (subtypes H1N1, H3N2), influenza virus B, Reovirus-1, Sindbis and Punta Toro. The antiviral assays were based on the inhibition of virus-induced cytopathicity or plaque formation in human embryonic lung (HEL) fibroblasts, African green monkey cells (Vero), human epithelial cells (HeLa) or Madin-Darby canine kidney cells (MDCK). Confluent cell cultures in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures) or with 20 plaque forming units (PFU) (VZV) in the presence of varying concentrations of the test compounds. Viral cytopathicity or plaque formation was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. Antiviral activity was expressed as the EC_{50} or compound concentration required to reduce virus-induced cytopathogenicity or viral plaque formation by 50%.