Synthesis and transformations of pyrrolo[1,2-*a*][1,3,5]-triazines

Jonas Verhoeven, B. Narendraprasad Reddy, Lieven Meerpoel, Jan Willem Thuring, Guido Verniest

PII: S0040-4039(18)31318-2
DOI: https://doi.org/10.1016/j.tetlet.2018.11.002
Reference: TETL 50387

To appear in: *Tetrahedron Letters*

Received Date: 5 October 2018
Revised Date: 1 November 2018
Accepted Date: 2 November 2018

Please cite this article as: Verhoeven, J., Reddy, B.N., Meerpoel, L., Thuring, J.W., Verniest, G., Synthesis and transformations of pyrrolo[1,2-*a*][1,3,5]-triazines, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.11.002

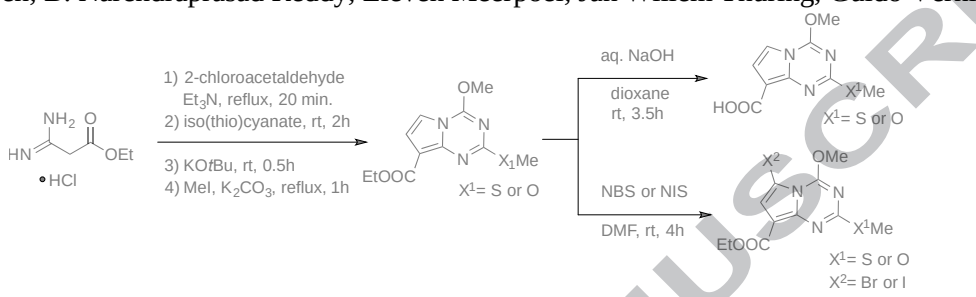
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Synthesis and transformations of pyrrolo[1,2-*a*][1,3,5]-triazines

Leave this area blank for abstract info.

Jonas Verhoeven, B. Narendraprasad Reddy, Lieven Meerpoel, Jan Willem Thuring, Guido Verniest



Tetrahedron Letters
journal homepage: www.elsevier.com

Synthesis and transformations of pyrrolo[1,2-*a*][1,3,5]-triazines

Jonas Verhoeven[a], B. Narendraprasad Reddy[a], Lieven Meerpoel[b], Jan Willem Thuring[b], Guido Verniest[a,b]

[a] *Research Group of Organic Chemistry, Department of Chemistry and Department of Bioengineering Sciences, Faculty of Sciences and Bioengineering Sciences Vrije Universiteit Brussel, Pleinlaan 2, 1050 Brussels, Belgium*
[b] *Janssen Research & Development, Turnhoutseweg 30, B-2340 Beerse, Belgium*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

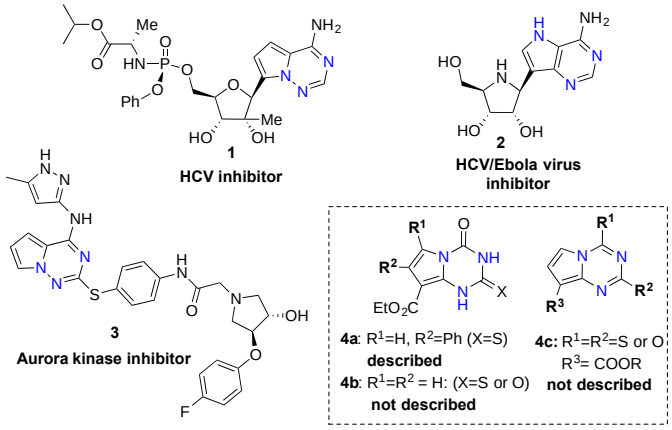
Keywords:
Pyrrolotriazines
Bromination
Cyclocondensation
Aminopyrrole
Nucleoside analogues

ABSTRACT

Pyrrolotriazines and related fused azaheterocycles have high potential for the synthesis of bioactive compounds, especially as a purine base isoster in carbon linked nucleosides. Although many structurally related compounds have already been synthesized and used in medicinal chemistry, pyrrolo[1,3,5]triazines have barely been described. The present work describes the synthesis of such heterocycles via condensation of 2-amino-3-ethoxycarbonylpyrrole with ethoxycarbonyliso(thio)cyanate. In a brief reactivity study of the obtained fused pyrroles, O- and S-alkylation, ester hydrolysis as well as regioselective bromination at the 6-position was demonstrated.

1. Introduction

Pyrrolotriazine templates are commonly used in medicinal chemistry to synthesize various biologically active molecules.[1-3] As examples in the field of antiviral carbon linked nucleoside analogues (C-nucleosides), the well described pyrrolo[1,2,4]triazine heterocyclic moiety has been used as nucleobase replacement in the development of the anti-HCV compound **1**[4], whereas the pyrrolo[2,3]pyrimidine scaffold is the nucleobase analogue in the broad spectrum antiviral compound BCX4430 **2**[5] (Scheme 1). Also in biologically active small molecules with kinase activity, various pyrrolotriazine building blocks are frequently implemented, for example in the potent pan-Aurora kinase inhibitor **3**.[6] The pyrrolo[1,3,5]triazine scaffold (Scheme **1**, type **4**) however, is far less described in the literature. Few examples are reported in which pyrrolo[1,3,5]triazines (type **4**) are synthesized from the condensation of 2-aminopyrroles with iso(thio)cyanates followed by intramolecular cyclization.[7-9] Alternatively, their synthesis has been described via photolytic transformations of pyridazino[l,2-*b*]phthalazine-6,11-dione[10] or 1,2,4-triazolo[1,2-a]pyridazine-l,3-dione.[11] Also, treatment of 2,5-diaryl-3,3,4,4-tetracyanopyrrolidines with diazomethane[12] and [3+2]-cycloaddition chemistry using 1,3,5-triazines and 3,3-dimethoxycyclopropene[13] has yielded heterocyclic structures of type **4**. A large variety of phenyl substituted pyrrolotriazines (type **4a**) has been disclosed in a patent published in 2000.[14] In all prepared examples, a phenyl group (R^2=Ph) is attached to the pyrrole ring, decreasing its usefulness as a versatile, low molecular weight building block. The synthesis of the corresponding pyrrolotriazine in which R^2=H (**4b**) has not been described despite its potential as novel building block in medicinal chemistry.

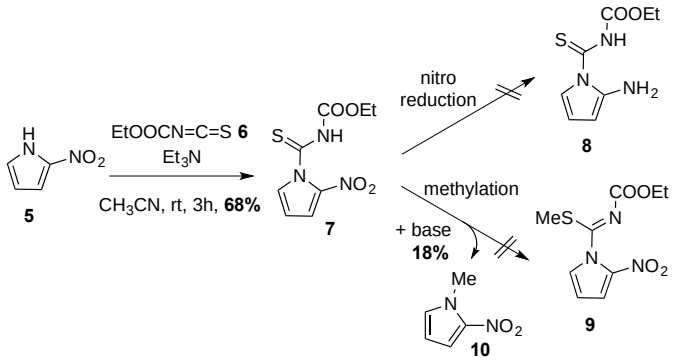


Scheme 1. Examples of biological relevant scaffolds containing a pyrrolotriazine motif and previously described pyrrolo[1,3,5]triazine **4a**.

2. Results and discussion

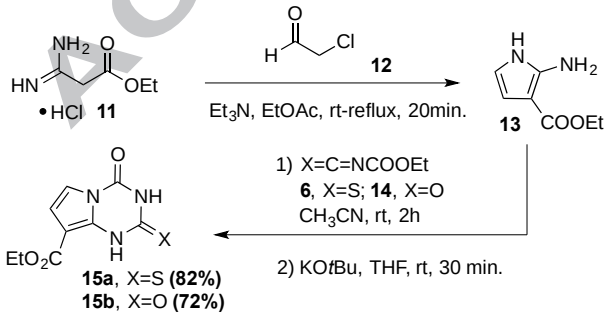
In a first attempt to provide entry to pyrrolotriazines **4b-c**, 2-nitropyrrole **5** was treated with isothiocyanate **6** in the presence of triethylamine, affording the condensation product **7** (Scheme **2**). In a following step, a cyclization was planned by reduction of the nitro group and *in situ* attack of the formed N-atom to the carbamate carbonyl group.[15] Unfortunately, various attempts to reduce the nitro group in **7** to obtain 2-aminopyrrole **8** using $SnCl_2$/HCl, Fe or Zn/HOAc, or hydrogenation over Pd/C were

not successful. As we suspected that the thiocarbonyl functionality could interfere with the reduction reaction, the S-methylated precursor **9** was deemed to be a better substrate. However, the synthesis of **9** proved to be unsuccessful as the presence of base resulted in the deprotonation of the nitrogen followed by expulsion of the nitropyrrole, which was subsequently methylated (**10**) by the present MeI (Scheme 2).



Scheme 2. Condensation of 2-nitropyrrole **5** with isothiocyanate **6** and unsuccessful attempts to reduce and methylate pyrrole **7**.

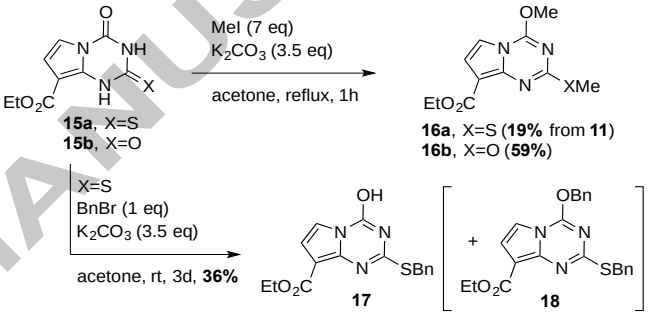
Because of the observed difficulties in this strategy, and because of the known instability of 2-aminopyrroles when the pyrrole is devoid of aromatic or electron withdrawing substituents, attempts were shifted towards the use of a pyrrolo carboxylate **13** as substrate. This 2-amino-3-ethoxycarbonylpyrrole **13** was synthesized via a Hantzsch type synthesis by base catalysed condensation of amidine ester **11** and freshly distilled chloro acetaldehyde **12** (Scheme 3).[16-17] The desired aminopyrrole **13** was obtained smoothly after a short reaction time and could be stored for two weeks at -20°C without significant degradation. Substrate **13** was subsequently used without purification in a condensation reaction with isothiocyanate **6** (X=S) or isocyanate **14** (X=O) which readily proceeds at room temperature resulting in full conversion of the starting material after two hours. A slow degradation of the condensation products from step 2 (Scheme **3**) was observed upon prolonged storage (0.5- 2 weeks) at 4°C which resulted in a reduced reaction quality of the subsequent step. Therefore, the intermediates were directly treated with KO*t*Bu to promote intramolecular cyclization, affording desired pyrrolo triazines **15a** and **15b** after acidic work-up. The use of DBU to promote cyclization was also successful, however compound **15a** was obtained as a DBU-salt in low yield and an additional acid-base extraction was required to obtain the neutral compound **15a**.



Scheme 3. Synthesis of pyrrolo[1,3,5]triazine scaffolds **15a** and **15b** from amidine ester **11**.

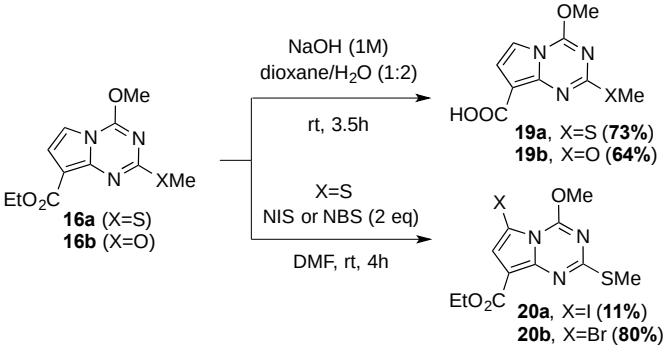
Purification via either normal phase silica gel- or reversed phase chromatography of all intermediates as well as the cyclized products **15a** and **15b** showed to be inefficient resulting in poor recovery at different reaction scales mainly due to poor solubility of **15a,b** in organic solvents such as Et_2O, EtOAc, etc. Attempted crystallization of **15a** and **15b** was unsuccessful and consequently, isolated yields were calculated after further modification (protection) of the pyrrolotriazine scaffold structure **15a** and **15b**.

Pyrrolotriazines **15a** and **15b** could be efficiently bis-methylated using standard protection conditions with MeI and K_2CO_3 to afford the less polar products **16a** and **16b**, which were easily purified via normal phase silica gel chromatography, or via recrystallization from diethyl ether (Scheme **4**). Overall isolated yields showed to be reproducible on 5-30 g reaction scales ranging from 19-23% (4 steps) for the synthesis of **16a**. Selective sulphur or oxygen monomethylation could not be achieved by using stoichiometric amounts of methyl iodide. However, when equimolar amounts of benzyl bromide were used, a 3:1 ratio of **17** and **18** was obtained, respectively (Scheme 4). The resulting monobenzylated building block **17** can potentially be used for orthogonal modifications at the triazine ring.



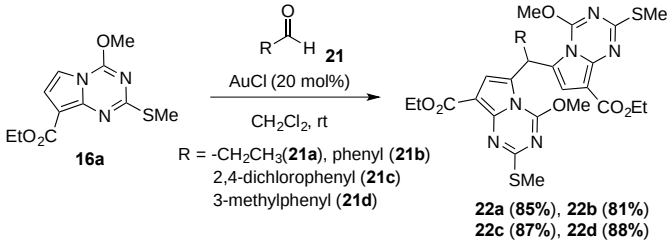
Scheme 4. Bismethylation and monobenzylation of pyrrolo[1,3,5]triazine **15a** and **15b**.

Treatment of intermediates **16a** and **16b** with aqueous NaOH in dioxane afforded the corresponding carboxylic acids (**19a** and **19b**), which could be isolated in moderate to good yield when the pH was carefully controlled to neutral conditions during work up. Bismethylated pyrrolotriazine **16a** was reacted with *N*-iodosuccinimide and *N*-bromosuccinimide affording **20a** and **20b**, respectively, both as single products (Scheme **5**). Whereas a clean NMR conversion was obtained, compound **20a** was isolated in rather low yield after silica gel chromatography. This is believed to be a result of the instability of **20a** during the purification and therefore, the halogenated pyrrolotriazines **20a** and **20b** are used preferably as such. The halogen atoms in compounds **20a** and **20b** can be regarded as handles for a potential further derivatization of the pyrrole ring.



Scheme 5. Saponification and halogenation of pyrrolo[1,3,5]triazine **16a** and **16b**.

Further evaluation of the reactivity of the pyrrole ring revealed that when **16a** was treated with aldehydes **21a-d** in the presence of gold(I)chloride, dimeric structures were obtained (Scheme 6). This addition was found to proceed smoothly with a three-fold excess of various aromatic and aliphatic aldehydes at room temperature in dichloromethane or acetonitrile, affording **22a-d** in high isolated yields after normal phase silica gel chromatography. Indium(I)chloride also showed to effectively afford the dimeric product **22b**, however in lower (10%) yield in comparison to the use of gold(I)chloride as Lewis acid.



Scheme 6. Gold(I)chloride catalyzed coupling of pyrrolo[1,3,5]triazine **16a**.

3. Conclusion

In summary, a scalable and reproducible protocol for the synthesis of pyrrolotriazines **15a** and **15b** has been described starting from ethyl 3-amino-3-iminopropanoate **11**. The novel protected pyrrolotriazines **16a** and **16b** carry different anchor points for orthogonal functionalization of the central scaffold structure. An unexpected gold(I)chloride mediated double addition to aldehydes was found to efficiently yield dimeric pyrrolotriazine structures **22a-d**.

Acknowledgments

The authors acknowledge the Vrije Universiteit Brussel (ZAP-starting grant) for financial support.

References and notes

1. Song, Y.; Zhan, P.; Zhang, Q.; Liu, X. *Curr. Pharm. Des.* **2013**, *19*, 1528.
2. Hunt, J. T.; Mitt, T.; Borzilleri, R.; Gullo-Brown, J.; Fargnoli, J.; Fink, B.; Han, W.-C.; Mortillo, S.; Vite, G.; Wautlet, B.; Wong, T.; Yu, C.; Zheng, X.; Bhide, R. *J. Med. Chem.* **2004**, *47*, 4054.
3. Li, Q.; Lescrinier, E.; Groaz, E.; Persoons, L.; Daelemans, D.; Herdewijn, P.; De Jonghe, S. *Chem. Med. Chem.* **2017**, *13*, 97.
4. Tyndall, E. M.; Draffan, A. G.; Frey, B.; Pool, B.; Halim, R.; Jahangiri, S.; Bond, S.; Wirth, V.; Luttick, A.; Tilmanis, D.; Thomas, J.; Porter, K.; Tucker, S. P. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 869.
5. Taylor, R.; Kotian, P.; Warren, T.; Panchal, R.; Bavari, S.; Julander, J.; Dobo, S.; Rose, A.; El-Kattan, Y.; Taubenheim, B.; Babu, Y.; Sheridan, W. P. *J. Infect. Public Health.* **2016**, *9*, 220.
6. Abraham, S.; Hadd, M. J.; Tran, L.; Vickers, T.; Sindac, J.; Milanov, Z. V.; Holladay, M. W.; Bhagwat, S. S.; Hua, H.; Ford Pulido, J. M.; Cramer, M. D.; Gitnick, D.; James, J.; Dao, A.; Belli, B.; Armstrong, R. C.; Treiber, D. K.; Liu, G. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5296
7. Breslin, H. J.; Chatterjee, S.; Diebold, J. L.; Dorsey, B. D.; Dunn, D.; Gingrich, D. E.; Hostetler, G. A.; Hudkins, R. L.; Hunter, R.; Josef, K.; Lisko, J.; Mesaros, E. F.; Milkiewicz, K. L.; Ott, G. R.; Sundar, B. G.; Theroff, J. P.; Thieu, T. Tripathy, R.; Underiner, T. L.; Weinberg, L.; Wells, G. J.; Zificsak, C. A. Cephalon, Inc. **2010**, 2010071885.
8. Haddach, M.; Dyck, B. P.; Huang, C. Q.; Nelson, J.; Guo, Z.; McCarthy, J. R. Neurocrine Biosciences, Inc. **2000**, 2000027850.
9. Wamhoff, H.; Wehling, B. *Chem. Ber.* **1976**, *109*, 2983.
10. Sheradsky, T.; Moshenberg, R. *J. Org. Chem.* **1985**, *50*, 5604.
11. Sheradsky, T.; Moshenberg, R. *J. Org. Chem.* **1984**, *49*, 587.
12. Lyshchikov, A. N.; Nasakin, O. E.; Lukin, P. M.; Zolotoi, A. B.; Prokhorov, A. I. *Chem. Heterocycl. Compd.* **1998**, *34*, 712.
13. Rischke, M.; Seitz, G.; Frenzen, G. *Chem. Ber.* **1993**, *126*, 2317.
14. Yanaghira, N.; Mitamura, Y.; Kawagishi, T. Jpn. Kokai Tokkyo Koho. **2000**, 2000319279.
15. *(a)* Charton, J.; Girault-Mizzi, S.; Debreu-Fontaine, M.; Foufelle, F.; Hainault, I.; Bizot-Espiard, J.; Caignard, D.; Sergheraert, D. *Bioorg. Med. Chem.* **2006**, *14*, 4490. *(b)* Pogorelic, I.; Filipan-Litvic, M.; Merkas, S.; Ljubic, G.; Cepanec, I.; Litvic, M. *J. Mol. Catal. A-Chem.* **2007**, *274*, 202. *(c)* Fu, L.; Gribble, G. W. *Tetrahedron Lett.* **2007**, *48*, 9155. *(d*) Gamble, A. B.; Garner, J. A.; Gordon, C.; O'Conner, S. M. J.; Keller, P. A. *Synth. Comm.* **2007**, *37*, 2777.
16. Toja, E.; Tarzia, G.; Ferrari, P.; Tuan, G. *J. Heterocycl. Chem.* **1986**, *23*, 1555.
17. Gangjee, A. Kurup, S.; Ihnat, M. A.; Thorpe, J. E.; Shenoy, S. S. *Bioorg. Med. Chem.* **2010**, *18*, 3575.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/……..

Highlights

* Pyrrolotriazines are isosteres of nucleobases used to synthesize C-nucleosides
* Pyrrolo[1,3,5]triazines are not well described
* A scalable synthesis of 6-carboxylated [1,3,5]pyrrolotriazines was developed
* A regioselective halogenation of pyrrolotriazines was demonstrated