Cyanoguanidine as a versatile, eco-friendly and inexpensive reagent for the synthesis of 2-aminobenzoxazoles and 2-guanidinobenzoxazoles

Oleksandr Grytsai, Tetiana Druzhenko, Luc Demange, Cyril Ronco, Rachid Benhida

PII: S0040-4039(18)30350-2
DOI: https://doi.org/10.1016/j.tetlet.2018.03.036
Reference: TETL 49805

To appear in: *Tetrahedron Letters*

Received Date: 8 February 2018
Revised Date: 7 March 2018
Accepted Date: 15 March 2018

Please cite this article as: Grytsai, O., Druzhenko, T., Demange, L., Ronco, C., Benhida, R., Cyanoguanidine as a versatile, eco-friendly and inexpensive reagent for the synthesis of 2-aminobenzoxazoles and 2-guanidinobenzoxazoles, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.03.036

Cyanoguanidine as a versatile, eco-friendly and inexpensive reagent for the synthesis of 2-aminobenzoxazoles and 2-guanidinobenzoxazoles

Oleksandr Grytsai,[#a] Tetiana Druzhenko,[#a] Luc Demange,[a,b] Cyril Ronco*[a] and Rachid Benhida*[a,c]

[a]Institut de Chimie de Nice UMR7272, Université Côte d'Azur, CNRS, Nice, France.

[b]Département de Chimie, Université Paris Descartes, Sorbonne Paris Cité, UFR des Sciences Pharmaceutiques, 4 avenue de l'Observatoire & UFR Biomédicale des Saints Pères, 45 rue des Saints Pères, Paris, France.

[c]Mohammed VI Polytechnic University, UM6P, Ben Guerir, Morocco.

* Corresponding authors:

E-mail addresses: cyril.ronco@unice.fr (C. Ronco); rachid.benhida@unice.fr (R. Benhida)

Phone numbers: 0033 492076517 (C. Ronco); 0033 492076143 (C. Ronco);

Abstract

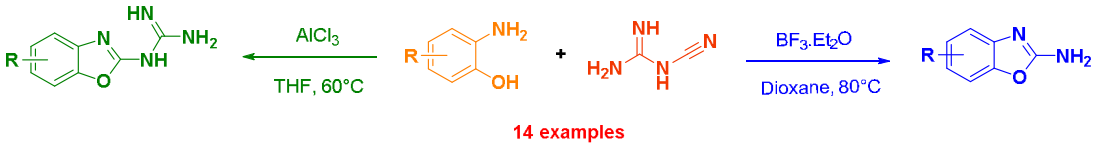
An effective, easy-to-handle, safe and inexpensive protocol is reported for the synthesis of 2-aminobenzoxazoles under Lewis acid activation, utilising cyanoguanidine as the cyanating reagent. An optimized procedure for the synthesis of 2-guanidinobenzoxazole and novel derivatives is also described.

1. Introduction

2-Aminobenzoxazoles are heterocyclic compounds, which play important roles in medicine, biology and material science. This scaffold has been used for the design of hepatitis C virus (HCV) ligands,[1] antimicrobial,[2] anti-inflammatory[3,4] and anti-cancer agents,[5,6] as well as for the marketed anti-insomnia drug suvorexant.[7] In addition, their photophysical properties have been exploited for the preparation of fluorescent dyes.[8] Several methods have been already reported for the synthesis of 2-aminobenzoxazoles**.** Historically, the conventional route consists of coupling 2-aminophenol derivatives with cyanogen bromide.[9] However, this approach suffers from the high toxicity of cyanogen bromide, whose production and use might be strongly restricted in the future because of increasing safety regulations. Therefore, other synthetic methodologies have been recently explored, based on reagents such as di(imidazole1-yl)methanimine,[10] *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide,[11] isothiocyanates followed by cyclodesulfurization[12] and carbon disulfide at reflux.[13] However all these reagents require preliminary preparation steps, such as the use of cyanogen bromide with imidazole for the preparation of di(imidazole1-yl)methanimine, or are limited by similar safety restrictions, such as the highly explosive and toxic carbon disulfide.[14] Therefore, despite this apparent variety of reagents to access 2-aminobenzoxazoles, there is still a need for an efficient, straightforward and safe method to produce these highly important heterocycles.

2. Results and Discussion

To the best of our knowledge, the synthesis of heterocycles using cyanoguanidine as a cyanating agent has not been reported. Thus, in continuation of our studies directed towards the development of new and eco-friendly synthetic methodologies of bioactive molecules,[15] we report herein an effective, easy-to-handle, safe and inexpensive protocol for the synthesis of 2-aminobenzoxazoles (Scheme 1).

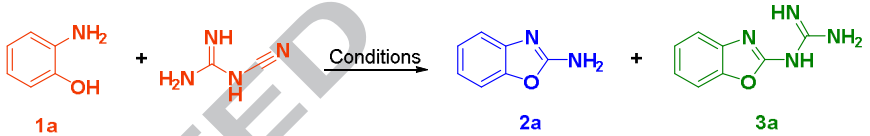


Scheme 1. Selective synthesis of either 2-aminobenzoxazoles or 2-guanidinobenzoxazoles from *o*-aminophenols.

Cyanoguanidine is a non-toxic, readily available and inexpensive chemical.[16] This reagent has been described for the synthesis of 2-guanidinobenzoxazole.[17] From a mechanistic point of view, the cyano group can be activated by Lewis or Brønsted acids to facilitate nucleophilic attack of the aniline group. Subsequent ring closure and aromatization *via* ammonia condensation affords the 2-guanidinobenzoxazoles. We hypothesized that, under defined hydrolysis conditions, the amidine group of the guanidine can be cleaved to yield the corresponding 2-aminobenzoxazoles, along with a stable urea molecule. By adapting the reaction conditions, we aimed to perform these two reaction steps in one-pot, with selective hydrolysis of 2-guanidinobenzoxazole over cyanoguanidine.

We started our study by the survey of various reaction conditions, *i.e.* Lewis or Brønsted acids, mode of activation (classical heating *versus* microwave activation), using the cyclocondensation of 2-aminophenol **1a** with cyanoguanidine as a model reaction (Table 1).

Table 1. Survey of the reaction conditions



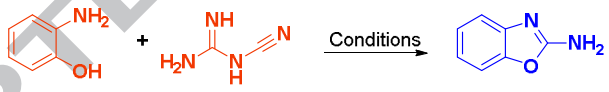
Entry	Reactant	Solvent	Time (h)	T (°C)	Results (%)
1	*p*-TSA	1,4-Dioxane	16	65	n.r.[a]
2	$SnCl_2$	1,4-Dioxane	16	65	Traces of **3a**
3	$Ti(OiPr)_4$	1,4-Dioxane	16	65	n.r.[a]
4	$BF_3{\cdot}Et_2O$	1,4-Dioxane	16	65	100%[b] (**2a**), (58%)[c]
5	$AlCl_3$	1,4-Dioxane	16	65	95%[b] (**3a**), (57%)[c]
6	$FeCl_3$	1,4-Dioxane	16	65	90%[b] (mixture of **2a**/**3a**, 50/50)
7	$Yb(OTf)_3$	H_2O	48	100	60%[b] (mixture of **2a**/**3a**, 30/70)

8	$Sc(OTf)_3$	H_2O	48	100	25%[b] (mixture of **2a/3a**, 80/20)
9	None	H_2O	16	100	n.r.[a]
10	None	H_2O	1	140 (MW)	Traces of **2a**
11	$Sc(OTf)_3$	H_2O	1	140 (MW)	10%[b] (mixture of **2a/3a**, 80/20)
12	None	10% aq. NaOH	1	140 (MW)	n.r.[a]

Reagents and conditions: 2-aminophenol (1.0 mmol), cyanoguanidine (1.3 mmol), reactant (1.0 mmol), solvent (5.0 mL). MW: microwave irradiation. [a]n.r.: no reaction. [b] Conversion based on LCMS analyses. [c]Isolated yield.

Depending on the applied conditions, very different behaviour in terms of reactivity and selectivity were observed. For example, Brønsted acid and base, as well as mild Lewis acids such as $SnCl_2$, $Ti(OiPr)_4$, $Yb(OTf)_3$ and $Sc(OTf)_3$ led to no or poor conversion, with various ratios of **2a/3a** being formed (Table 1, entries 1-3 and 7-8). Conversely, the use of strong Lewis acids provided interesting results. First, **2a** could be obtained by a one-pot procedure through formation of the heterocycle and subsequent cleavage of the amidine using boron trifluoride (Entry 4). The desired product was isolated in 58% yield after purification by silica gel chromatography. Second, treatment with aluminum chloride selectively led to the intermediate guanidine **3a** in 57% yield after work-up and purification (Entry 5). These encouraging results prompted us to select these two reagents for further optimization of each reaction

Table 2. Optimization of the reaction conditions for the synthesis of 2-aminobenzoxazole **2a**



1a 2a

Entry	Reactant (equiv.)	Solvent	T (°C)	Results
1	$BF_3{\cdot}Et_2O$ (1)	1,4-Dioxane	65	100%[a] (**2a**), 58%[b]
2	$BF_3{\cdot}Et_2O$ (1)	Methanol	65	Partial conversion, mixture of **2a** and **3a**
3	$BF_3{\cdot}Et_2O$ (1)	DMF	65	100%[a] (**2a** in mixture with by-products)
4	$BF_3{\cdot}Et_2O$ (1)	*n*-BuOH	65	100%[a] (**2a** in mixture with by-products)
5	$BF_3{\cdot}Et_2O$ (1)	$ClCH_2CH_2Cl$	65	100%[a] (**2a** in mixture with by-products)

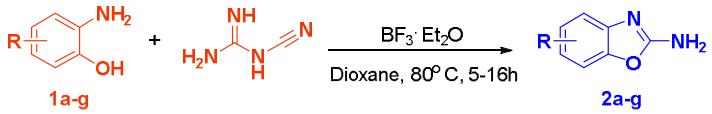
6	$BF_3{\cdot}Et_2O$ (1)	THF	65	100%[a] (**2a** in mixture with by-products)
7	$BF_3{\cdot}Et_2O$ (1)	DME	65	100%[a] (**2a** in mixture with by-products)
8	$BF_3{\cdot}Et_2O$ (0.1)	1,4-Dioxane	65	10%[a] of **2a**, 90%[b] of **1a**
9	$BF_3{\cdot}Et_2O$ (2)	1,4-Dioxane	65	100%[a] (**2a** in mixture with by-products)
10	$BF_3{\cdot}Et_2O$ (1)	1,4-Dioxane	80	100%[a] (**2a**), 90%[b]
11	$BF_3{\cdot}Et_2O$ (1)	1,4-Dioxane	90	100%[a] (**2a**), 37%[b]

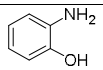
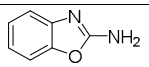
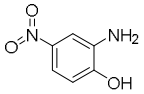
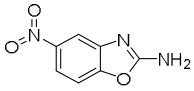
Reagents and conditions: 2-aminophenol (1.0 mmol), cyanoguanidine (1.3 mmol), reactant (1.0 mmol), solvent (5.0 mL). [a] Conversion after 16 h, based on LCMS analyses. [b] Isolated yield.

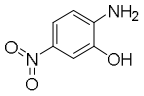
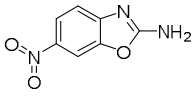
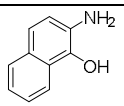
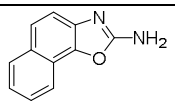
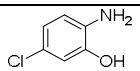
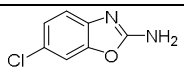
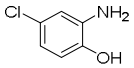
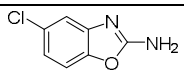
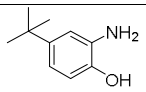
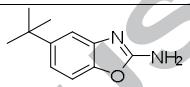
Replacement of 1,4-dioxane by other solvents resulted in the formation of varying amounts of side-products (Table 2, entries 1-7). Furthermore, the stoichiometric role of the Lewis acid was demonstrated (Entry 8), as 10 mol% $BF_3{\cdot}Et_2O$ loading provided only 10% conversion. Conversely, the use of excess (2 equiv.) induced the formation of side-products (Entry 9). Finally, we evaluated the temperature effects, and after a careful screening, 80 °C was determined to be optimal, providing the desired product in 90% isolated yield. Increasing the temperature to 90 °C resulted in significant amounts of non-identified side-products and an isolated yield of only 37%.

The optimized procedure (*i.e.* $BF_3{\cdot}Et_2O$ in dioxane at 80 °C) was then applied to a selection of commercially available substituted *o*-aminophenols (**1a-g**, Table 3) in order to explore the reaction scope. We successfully obtained the expected 2-aminobenzoxazoles **2d-g** with good yields. However, it is worth noting that yields were slightly decreased when using 2-amino-4-nitrophenol (**2b**, 55%) or 3-amino-4-nitrophenol (**2c**, 48%), due to the lower reactivity of nitro derivatives.

Table 3. Substrate scope for the synthesis of 2-aminobenzoxazoles (**2a-g**)

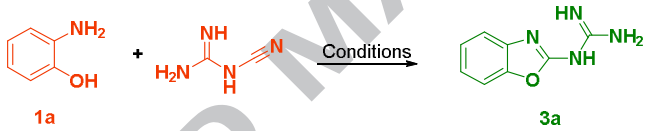


Entry	Substrate	Product	Isolated Yield (%)
1	 **1a**	 **2a**	90
2	 **1b**	 **2b**	55

3	 **1c**	 **2c**	48
4	 **1d**	 **2d**	73
5	 **1e**	 **2e**	83
6	 **1f**	 **2f**	75
7	 **1g**	 **2g**	74

Reagents and conditions: **1a-g** (1 mmol), cyanoguanidine (1.3 mmol), $BF_3{\cdot}Et_2O$ (1.0 mmol), dioxane (5 mL), 80 °C.

Table 4. Optimization of the reaction conditions for the synthesis of 2-guanidinobenzoxazole **3a**



1a **3a**

Entry	Reactant (equiv)	Solvent	Time (h)	T (°C)	Isolated Yield (%)
1	$AlCl_3$ (1)	1,4-Dioxane	16	65	57%
2	$AlCl_3$ (1)	THF	16	65	57%
3	$AlCl_3$ (1)	MeOH	16	65	n.r.[a]
4	$AlCl_3$ (1)	THF	96	60	69%
5	$AlCl_3$ (2)	THF	60	60	70%
6	$Al(OTf)_3$ (1)	THF	96	60	68%
7 [b]	H_2SO_4	EtOH/H_2O, 1/1	2	90	27%
8 [c]	HCl	EtOH/H_2O, 4/1	6	90	19%

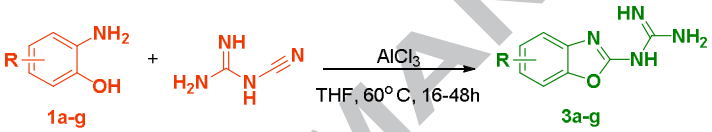
Reagents and conditions: 2-aminophenol (1.0 mmol), cyanoguanidine (1.3 mmol), reactant (1.0 mmol), solvent (5.0 mL). [a] n.r.: no reaction. [b] Following reference[17] procedure on a 5 mmol scale. [c] Following reference[18] procedure on a 5 mmol scale.

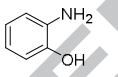
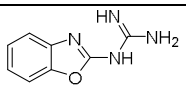
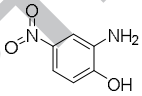
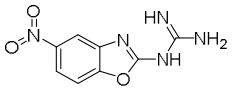
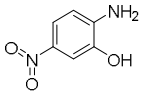
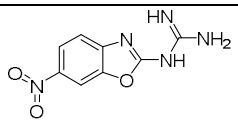
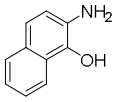
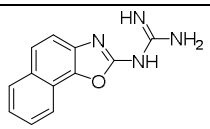
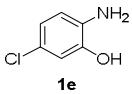
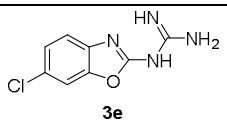
Although a large-scale protocol (1 mol scale) for the synthesis of unsubstituted 2-guanidinobenzoxazole has been already described,[17] no efficient, reproducible and generalizable procedure affording substituted 2-guanidinobenzoxazoles on a millimolar scale with high yields has been disclosed. The synthesis of the 2-

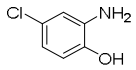
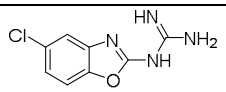
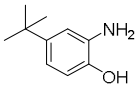
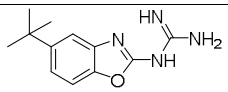
aminobenzoxazole ring is challenging because the strong acidic conditions required for the formation of this heterocycle, simultaneously promote its reopening (e.g. through hydrolysis). Therefore, we decided to carry out the reactions in dry solvents, 1,4-dioxane or THF (Table 4, entries 1-3), which resulted in a significant yield improvement compared to the aqueous conditions protocols depicted in the literature (Entries 7, 8). The yields were further enhanced by slightly decreasing the temperature to 60 °C, despite a slower reaction time (Entry 4). It is notable that the kinetics could be partially restored by using 2 equivalents of aluminum salt (Entry 5), leading to the expected product in 70% isolated yield. Lastly, since the use of $Al(OTf)_3$ yielded **3a** in similar yields (Entry 6), we selected $AlCl_3$ as the Lewis acid for economic reasons.

We next explored the scope of this reaction by applying the optimized procedure (*i.e.* $AlCl_3$ in THF at 60 °C) to a selection of commercially available substituted *o*-aminophenols (**1a-g**, Table 5) to afford the expected 2-guanidinobenzoxazoles **3a-g** in good yields (45-70%). To further investigate our methodology, we tested this procedure on a 50-100 mmol scale for compounds **3a**, **3b**, **3c**, **3e** and **3f**. Consistent and reproducible yields were obtained for these five compounds delivering multi-gram amounts of the desired products.

Table 5. Substrate scope for the synthesis of 2-guanidinobenzoxazoles (**3a-g**)



Entry	Substrate	Product	Isolated Yield (%)
1	 1a	 3a	70
2	 1b	 3b	61
3	 1c	 3c	54
4	 1d	 3d	45
5	 1e	 3e	52

6	 **1f**	 **3f**	58
7	 **1g**	 **3g**	52

Reagents and conditions: **1a-g** (1 mmol), **8** (1.3 mmol), $AlCl_3$ (2.0 mmol), THF (5 mL), 60 ^oC

3. Conclusion

In summary, we have successfully developed a facile, eco-friendly and efficient synthesis of 2-aminobenzoxazoles from 2-aminophenols using inexpensive commercially available cyanoguanidine as a cyanating reagent. Moreover, we report an unprecedented Lewis Acid catalyzed procedure for the synthesis of 2-guanidinobenzoxazoles. This allowed the syntheses of novel 2-guanidinobenzoxazole derivatives, which were not accessible using the procedures currently available in the literature. We believe that the simplicity and versatility of our approach, will offer an effective alternative for the preparation of these scaffolds, which are relevant for biological purposes.

4. Acknowledgements

The authors are grateful for the financial support from CNRS, Université Côte d'Azur and Ministry of Higher Research and Education for the PhD grant to O.G., the Research fund from the Canceropôle PACA, ANR and INCA.

Supplementary data

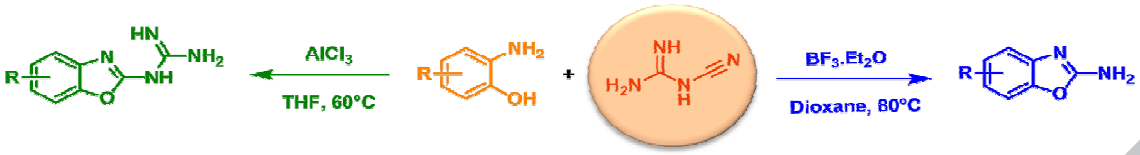
Supplementary data associated with this article can be found, in the online version, at https://doi.org/.

#: Equal contribution, *: co-first authors.

References

1. Rynearson KD, Charrette B, Gabriel C, Moreno J, Boerneke MA, Dibrov SM, Hermann T. *Bioorg. Med. Chem. Lett.* 2014;24:3521-3525.
2. Raj I, Shrivastava M.. *Heterocycl. Lett.* 2017;7:701-704.
3. Rao CN, Kalyani B, Priyanka KB, Dayaka, G.. *Indo Am. J. Pharm. Res.* 2015;5:2368-2373.
4. Lavanya A, Parlapalli A, Ciddi M, Sarangapani M. *Int. J. Pharm. Sci. Res.* 2015;6:212-218.
5. Ortega JA, Arencibia JM, La Sala G, Borgogno M, Bauer I, Bono L, Braccia C, Armirotti A, Girotto S, Ganesan A, De Vivo M.. *J. Med. Chem.* 2017;60:5800-5815.
6. An Y, Lee E, Yu Y, Yun J, Lee MY, Kang JS, Kim WY, Jeon R. *Bioorg. Med. Chem. Lett.* 2016;26:3067-3072.
7. Bennett T, Bray D, Neville MW.. *Pharmacy and Therapeutics* 2014;39:264.
8. Desai TR, Desai KR.. *Asian J. Chem.* 1997;9:677-680.
9. Nagano, T.; Itoh, M.; Matsumura, K.: Preparation of certain derivatives of benzoxazole. *J. Am. Chem. Soc.*1953, *75*, 2770-2771.
10. Wu YQ, Limburg DC, Wilkinson DE, Hamilton GS. *Journal of heterocyclic chemistry* 2003;40:191-193.
11. Kasthuri M, Babu HS, Kumar KS, Sudhakar C, Kumar PN. *Synlett* 2015;26:897-900.

(12. Tian Z, Plata DJ, Wittenberger SJ, Bhatia AV. *Tetrahedron letters* 2005;46:8341-8343.
(13. Guntreddi T, Allam BK, Singh KN. *RSC Advances* 2013;3:9875-9880.
(14. Ferris JP, Huang CH, Hagan Jr W J. *Nucleosides & nucleotides* 1989;8:407-414.
15. (a) Millet A, Plaisant M, Ronco C, Cerezo M, Abbe P, Jaune E, Cavazza E, Rocchi S, Benhida R. *J. Med Chem* 2016;59:8276-8292;
(b) Ronco C, Millet A, Plaisant M, Abbe P, Hamouda-Tekaya N, Rocchi S, Benhida R *Bioorg. Med. Chem. Lett.*2017;27:2192-2196;
(c) Marzag H, Robert G, Dufies M, Bougrin K, Auberger P, Benhida R. *Ultrasonics sonochemistry* 2015;22: 15-21;
(d) Barthes N, Karpenko I, Dziuba D, Spadafora M, Auffret J, Demchenko A, Mély Y, Benhida R, Michel B, Burger A. *RSC Advances* 2015;5:33536-33545;
(e) Driowya M, Saber A, Marzag H, Demange L, Benhida R, Bougrin K. *Molecules* 2016;21:492.
16. Prices for cyanoguanidine in 2018: 4.27$/100g by Arctom Chemicals; bulk : 630$/60kg by APAC Pharmaceutical
17. Smith G, Kane J, Mason C *J. Am. Chem. Soc.*1929;51:2522-2527.
18. Dolzhenko A V, Chui WK, Dolzhenko, AV. *Synthesis* 2006;4:597-602.



Highlights

- Under specific Lewis acid activation, cyanoguanidine acts as cyanating agent
- Cyanoguanidine/BF_3 allows safe and eco-friendly synthesis of 2-aminobenzoxazoles
- $AlCl_3$ activation broadens and optimizes the synthesis of 2-guanidinobenzoxazoles