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Efficient propylphosphonic anhydride (®T3P) mediated synthesis of benzothiazoles, benzoxazoles and benzimidazoles

Xiaoan Wen [a,b,c,†], Jamal El Bakali [b,c,†], Rebecca Deprez-Poulain [b,c,*], Benoit Deprez [b,c,*]

[a] Center for Drug Discovery, China Pharmaceutical University, Nanjing 210009, China
[b] Biostructures and Drug Discovery, INSERM U761, Institut Pasteur de Lille, Université Lille Nord de France, Lille F-59006, France
[c] PRIM, Lille F-59000, France

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ABSTRACT

Propylphosphonic anhydride (®T3P) promotes cyclization of *o*-aminobenzenethiol, *o*-aminophenol, and *o*-phenylenediamine with carboxylic acids under microwave irradiation. The one-pot procedure is efficient and allows short reaction times, easy workup, and good yields. Thus, we describe here a method for quick preparation of benzothiazoles, benzoxazoles and benzimidazoles.

1,3-Benzazoles include three scaffolds: benzothiazole, benzoxazole and benzimidazole that are considered as privileged structures in the medicinal chemistry field.[1] Drugs displaying a benzimidazole ring include proton-pump inhibitors (omeprazole), AT1 receptor antagonists (candesartan, telmisartan), direct thrombin inhibitor dabigatran, and H1 receptor antagonist mizolastin (Fig. 1). Less frequent benzoxazole and benzothiazole rings are found for example in the NSAID flunoxaprofen or inhibitors of CETP,[2] and in sodium-channel blocker riluzole or antitumor agents,[3] respectively (Fig. 1). Besides, benzoxazoles and benzimidazoles are of interest in material science.[4]

The most commonly used synthetic method to access 1,3-benzazoles consists in the condensation of either *o*-aminobenzenethiol, *o*-aminophenol, or *o*-phenylenediamine with substituted aldehydes,[5] nitriles,[6] acyl chlorides,[7] or carboxylic acids.[8] These methods often require long reaction times and strong conditions. A recent example describes the synthesis of benzimidazoles and benzothiazoles from alcohol.[9] No benzoxazole is described using this method. The use of aldehydes or alcohols requires oxidative steps which may affect the economy of synthesis.[10] Also, a larger diverse set of carboxylic acids is available from commercial sources as compared to aldehydes and alcohols.[11] This prompted us to focus on carboxylic acids as reagents for this isohypsic heterocyclization.

®T3P (propylphosphonic anhydride, Fig. 2)[12] is a powerful water scavenger and coupling reagent, usually used for amide synthesis. It was for example, recently used for the large scale preparation of denagliptin, a dipeptidyl peptidase IV inhibitor.[13] Because of the low toxicity, high safety, and ease of handling of this reagent, it has in the recent years been used for many other applications,[14] like Fischer indolization[15] or production of acyl azides.[16]

Herein, we report an eco-friendly, one-pot T3P-mediated, synthesis of 2-substituted 1,3-benzazoles from carboxylic acids, relevant for the synthesis of benzothiazoles, benzoxazoles, and benzimidazoles.

2-(4-Chlorophenyl)benzothiazole (**3a**) was selected as a prototype compound to optimize the reaction conditions (Table 1) from *o*-aminobenzenethiol (**1**) and *p*-chlorobenzoic acid (**2a**). We first conducted the reaction of **1** (1 equiv) and **2a** (1 equiv) in the presence of T3P (1 equiv) and DIPEA (1.5 equiv) under classical heating at different temperatures (Table 1, entries 1–3). As expected, T3P can mediate the reactions. Even at room temperature, the conversion rate after 3 h reached 42%, which increased to 80% under reflux conditions. With the aim to reduce reaction time, we then carried the reaction under microwave irradiation. The conversion of reactants was complete after 10 min at 100 °C (entry 6) and **3a** was isolated with a 96% yield. Effects of T3P amounts were further investigated. As can be seen from Table 1 (entries 6–8), increasing

* Corresponding authors. Tel.: +33 320 964 947; fax: +33 320 964 709.
E-mail addresses: rebecca.deprez@univ-lille2.fr (R. Deprez-Poulain), benoit.deprez@univ-lille2.fr (B. Deprez).
URLs: http://www.deprezlab.fr, http://www.drugdiscoverylille.org (B. Deprez).
† These authors contributed equally to this work.

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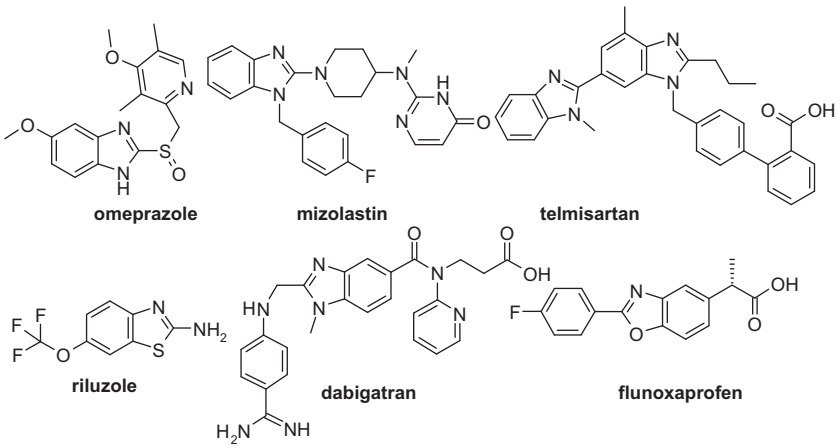


Figure 1. Examples of 1,3-benzazoles drugs.

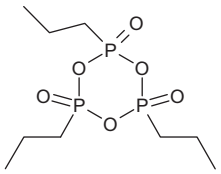
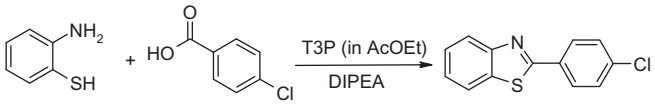


Figure 2. Structure of propylphosphonic anhydride (®T3P).

Table 1
Optimization of conditions for synthesis of **3a**



1 **2a** **3a**

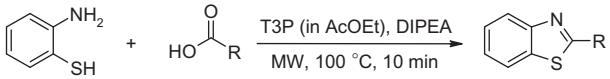
Entry	T3P	Temp (°C)	Time	Conversion rate[a] (%)
Classical heating				
1	1 equiv	20	3 h	42
2	1 equiv	50	3 h	69
3	1 equiv	Reflux	3 h	80
Microwave irradiation				
4	1 equiv	80	10 min	73
5	1 equiv	100	5 min	82
6	1 equiv	100	10 min	100[b]
7	2 equiv	100	10 min	100
8	0.5 equiv	100	10 min	70
9	0	100	10 min	0
10	1 equiv[c]	100	10 min	62

[a] Determined by LC–MS at 215 nm.
[b] Isolated in 96% yield.
[c] No DIPEA.

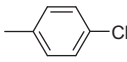
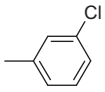
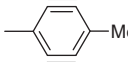
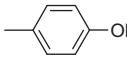
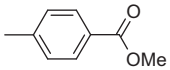
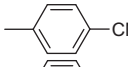
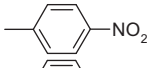
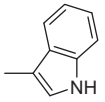
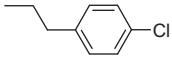
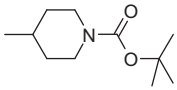
T3P amount to 2 equiv was not necessary, while decreasing it to 0.5 equiv remarkably lowered the conversion rate. Eventually, without T3P (entry 9), no conversion was observed, confirming the importance of T3P in the reaction. In addition, DIPEA is necessary to achieve quick and complete conversion (entry 10 vs entry 6).

The optimized conditions (MW, 100 °C, 10 min, DIPEA) were then used to explore the scope of the reaction. As shown in Table 2, a variety of functions including electron withdrawing/donating groups, acidic/basic sensitive groups, and diverse heterocycles were compatible with this T3P mediated method (**3a–h**, **3j–o**). The exception was nitro group, which gave **3i** using adapted

Table 2
Scope of the benzothiazoles synthesis

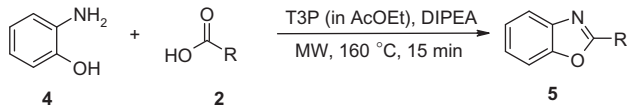


1 **2** **3**

Product	R	Yield (%)
3a		96
3b		90
3c		88
3d		91
3e		84
3f		78
3g		96
3h		95
3i		93[a]
3j		86
3k		91
3l		83
3m		81
3n		90
3o		97

[a] The reaction was conducted without DIPEA and the irradiation time adjusted to 15 min.

Table 3
Scope of the benzoxazoles synthesis



4 2 5

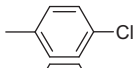
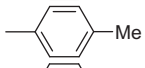
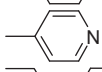
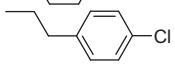
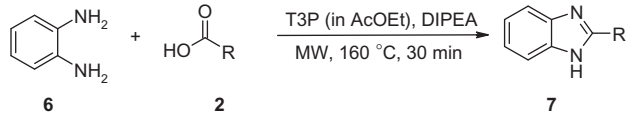
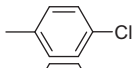
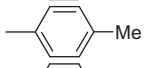
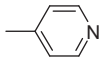
Product	R	Yield (%)
5a		95
5b		76
5c		73
5d		93
5e		91

Table 4
Scope of the benzimidazoles synthesis



6 2 7

Product	R	Yield (%)
7a		77
7b		77
7c		80
7d		62
7e		93
7g		90

conditions. Thus, all of the examined substrates provided the respective benzothiazoles in good to excellent yields.

The above procedure (MW, 100 °C, 10 min) was expanded to the synthesis of benzoxazoles from *o*-aminophenol (**4**). However, very poor conversion to cyclic compound (**5a**) was observed using *p*-chlorobenzoic acid. Therefore stronger reaction conditions were assayed. Microwave irradiation for 15 min at 160 °C allowed a clean and almost complete conversion of reagents. All of the five carboxylic acids used (Table 3) gave the corresponding benzoxazoles in good to excellent yields (73–95%).

The reaction at 100 °C between *o*-phenylenediamine (**6**) and *p*-chlorobenzoic acid gave a main product with a *m*/*z* corresponding to undesired diamide **8** (Fig. 3) and only traces of expected benzimidazole (**7a**). As for the benzoxazoles synthesis, increasing the temperature (160 °C) gave good reaction profiles. The benzimidazole (**7a**) vs diamide (**8**) ratio was found to be time-dependent. Irradiation for 30 min gave the best results[17] and allowed the synthesis of benzimidazoles **7a–f** in 62–93% yield (Table 4).

In conclusion, an efficient method[18] for quick preparation of benzothiazoles, benzoxazoles, and benzimidazoles has been developed through T3P-mediated microwave reactions of *o*-aminobenzenethiol, *o*-aminophenol, and *o*-phenylenediamine with diverse carboxylic acids. The method is environmentally friendly and the work-up easy allowing final products in good to excellent yields. It is especially suitable in medicinal chemistry to rapidly enlarge compound library for biological evaluation.

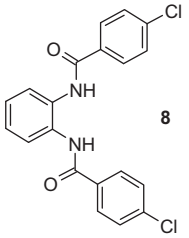


Figure 3. Structure of diamide **8**.

Acknowledgments

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Supplementary data

Supplementary data (synthesis procedures, characterization of compounds comparison of commercial sets of acids, aldehydes and alcohols, putative mechanisms) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.007.

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11. Search performed in ACS SYMYX™ database in December 2011. See Supplementary data for details.

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17. Irradiation for 15 min gave more than 30% diamide, whereas irradiation for 40 min led to a new byproduct with a mass corresponding to 2-(4-chlorophenyl)-*N*-ethylbenzimidazole.
18. *General procedure for synthesis of benzothiazoles, benzoxazoles and benzimidazoles*: A mixture of *o*-aminobenzenethiol (1 mmol), carboxylic acid (1 mmol), *N*,*N*-diisopropylethylamine (1.5 mmol) and propylphosphonic anhydride (1 mmol, 50% w/w in AcOEt) was irradiated for 10 min under microwave (max. setting power: 150 W and max. setting pressure: 17 bar) at 100 °C in a sealed tube. The reaction mixture was then diluted with H_2O, followed by alkalinization with a saturated aqueous $NaHCO_3$ solution. The precipitate was collected by filtration and washed thoroughly with H_2O to afford the respective benzothiazole. If necessary, simple recrystallization was carried out in $EtOH/H_2O$. For synthesis of benzoxazoles and benzimidazoles, *o*-aminophenol and *o*-phenylenediamine were used, respectively instead of *o*-aminobenzenethiol and the microwave irradiation was performed at 160 °C, respectively for 15 min and 30 min.