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

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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

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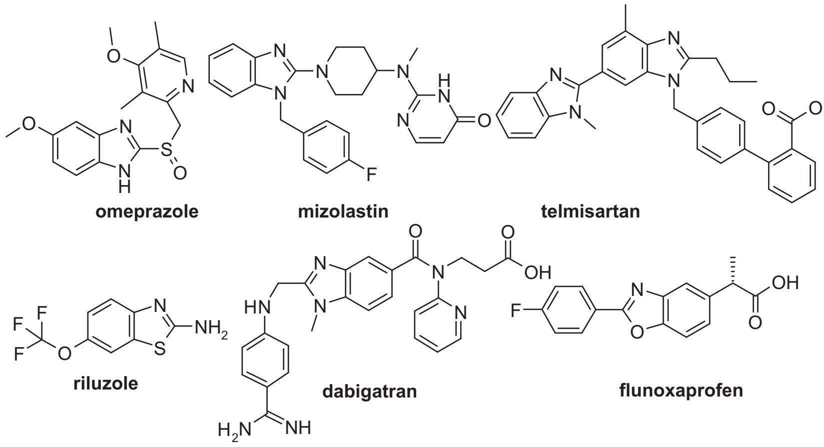


Figure 1. Examples of 1,3-benzazoles drugs.

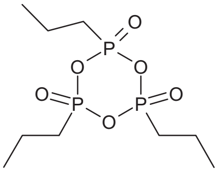
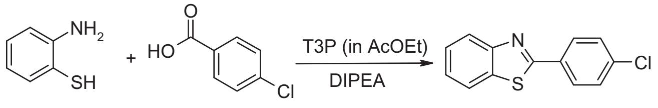


Figure 2. Structure of propylphosphonic anhydride (®T3P).

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

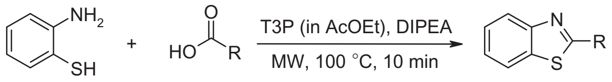


1 **2a** **3a**

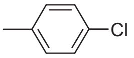
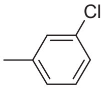
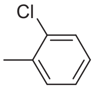
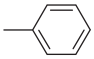
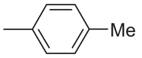
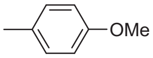
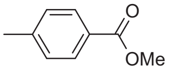
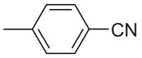
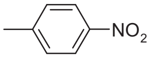
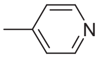
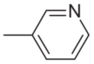
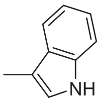
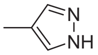
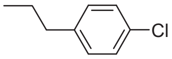
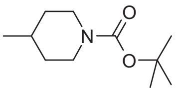
Entry	T3P	Temp (°C)	Time	Conversion rate[a] (%)
Classical heating				
1	1 equiv	20	3 h	42
2	1 equiv	50	3 h	69
3	1 equiv	Reflux	3 h	80
Microwave irradiation				
4	1 equiv	80	10 min	73
5	1 equiv	100	5 min	82
6	1 equiv	100	10 min	100[b]
7	2 equiv	100	10 min	100
8	0.5 equiv	100	10 min	70
9	0	100	10 min	0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

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

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.

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