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Facile Construction of an Amino-1,3-Oxazine Scaffold using Burgess Reagent Under Mild Conditions

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ABSTRACT

The development of a cyclization reaction to access amino-1,3-oxazines under mild conditions is described. The synthesis was achieved using dehydrating reagents, such as phosphorus pentoxide and Burgess reagent. In particular, the cyclization with Burgess reagent proceeded under mild conditions and tolerated potentially labile functional groups, such as the acetoxy group, and therefore can be used to synthesize β-secretase (BACE1) inhibitors with a variety of amino-1,3-oxazine warheads.

Accumulation of Aβ peptides is a hallmark and causal factor of Alzheimer's disease (AD) [1]. β-Secretase (BACE1) is a key enzyme responsible for producing Aβ peptides. Inhibition of BACE1 has therefore emerged as a potential disease-modifying treatment of AD [2]. Although amidine-based compounds were identified as potent BACE1 inhibitors, their high basicity caused high P-gp efflux and hERG inhibitory activity [3a,b]. Our research program identified amino-1,3-oxazine derivatives, such as compounds **2**–**5**, as potent BACE1 inhibitors with reduced P-gp efflux and hERG activity [4]. During the course of this research, the incorporation of a double bond in dihydro-1,3-oxaine **1** led to 1,3-oxazine **2** with a pK_a value lowered by 2.1 units, which translated into an improved profile (Fig. 1) [4]. Herein, we disclose the detailed investigations that led to the efficient synthesis of the amino-1,3-oxazine scaffold using Burgess reagent.

Our effort began with the synthesis of 6-methyl-1,3-oxazine **3**, according to literature procedures (Scheme 1) [6]. Although the yield was quite low, the method afforded key intermediate **7** *via* the cyclization of thiourea **6**. Compound **7** was then successfully converted into compound **3** in 19% yield over 2 steps [5]. To access the non-substituted oxazine **2**, we next sought to prepare the corresponding aldehyde analogue of **6**. Unfortunately, the synthesis failed, as it prompted cyclization to the thiazine ring and not the oxazine ring. We therefore avoided use of the thiourea intermediate; instead, urea intermediates were employed. To obtain the amino-1,3-oxazine scaffold *via* the urea intermediate, we explored reaction conditions using urea **8**. Various acidic conditions were investigated, and selected examples are shown in Table 1. Treatment with acetic acid under reflux conditions did not afford the product (Entry 1). Addition of a dehydrating agent, phosphorus pentoxide (P_2O_5), successfully led to cyclization providing 1,3-oxazine **9** in 26% yield along with the formation of side product **12** (Entry 2) [7]. Interestingly, increasing the amount of P_2O_5 improved the yield to 54%. Further exploration of dehydrating reagents identified Burgess reagent, a mild and selective dehydrating agent for secondary and tertiary alcohols, as the optimal one, which afforded oxazine **9** in 83% yield (Entry 5) [8a,b]. Finally, the cyclization reaction proceeded with high yield at room temperature (Entry 6).

Having identified the optimal reaction conditions, we returned our attention to the synthesis of non-substituted 1,3-oxazine **2**. The urea containing an aldehyde moiety (**10a**) was subjected to the cyclization reaction to give non-substituted oxazine **11a** in 13% yield. Addition of pyridinium *p*-toluene sulfonate (PPTS) slightly improved the yield to 27%. To further reduce the basicity of **2** and **3**, oxazines with a fluorine, such as **4** and **5**, were designed, and the corresponding urea intermediates **10b** and **10c** [4] were subjected to the reaction using Burgess reagent and PPTS to afford the cyclization products **11b** and **11c** in 41% and 62% yield, respectively (Scheme 2).

The proposed reaction mechanism of the 1,3-oxazine cyclization using Burgess reagent is depicted in Scheme 3. The first step is acid-catalyzed cyclization of the ketone group with urea **A** to form intermediate **C**. Both Burgess reagent and phosphorus pentoxide could generate a small amount of acid *via* decomposition

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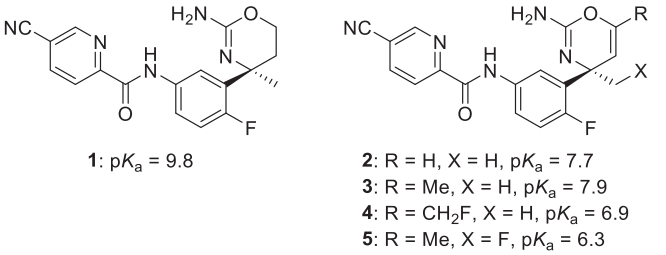


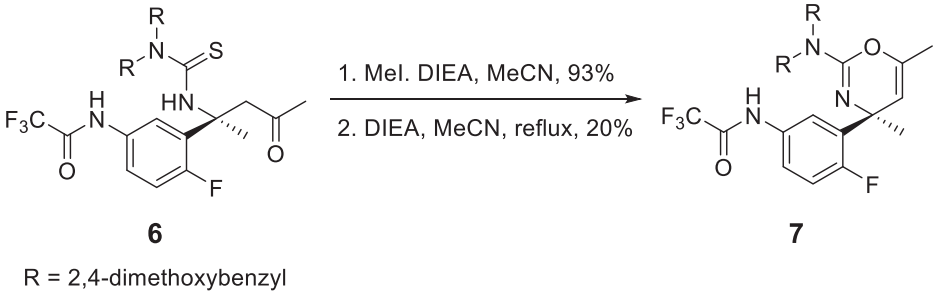
Fig. 1. Previously reported amino dihydro-1,3-oxazine **1** and amino-1,3-oxazines **2**, **3**, **4** and **5**.

of the reagents. This mechanism is supported by the findings that intermediate **12** was obtained under the conditions of entry 2 in Table 1 and an improved yield was observed when PPTS was added. Finally, intermediate **C** can react with Burgess reagent to afford intermediate **D** followed by *syn* elimination to the desired 1,3-oxazine **E**.

In conclusion, a facile synthesis of amino-1,3-oxazine derivatives was achieved *via* the cyclization of urea derivatives using Burgess reagent under mild conditions. The reaction conditions tolerated reactive functional groups, such as acetoxy and fluorine groups, which provides an opportunity to synthesize a variety of analogues [9]. The amino-1,3-oxazines demonstrated preferable basicity that can retain potency and reduce P-gp efflux and hERG activity. The method described can help develop amino-1,3-oxazines with improved profiles for the treatment of AD.

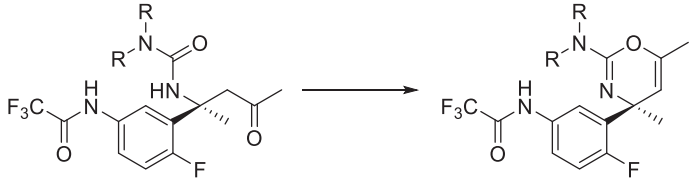
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



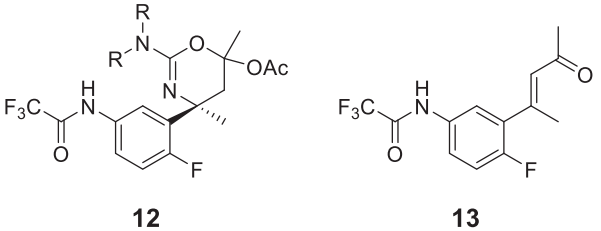
Scheme 1. Synthesis of amino-1,3-oxazine **7** from thiourea intermediate **6** [5].

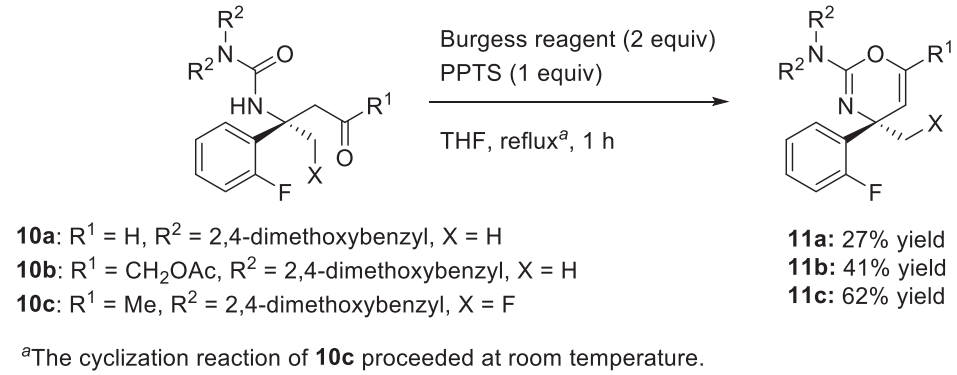
Table 1
Optimization of the reaction conditions using various dehydration reagents.



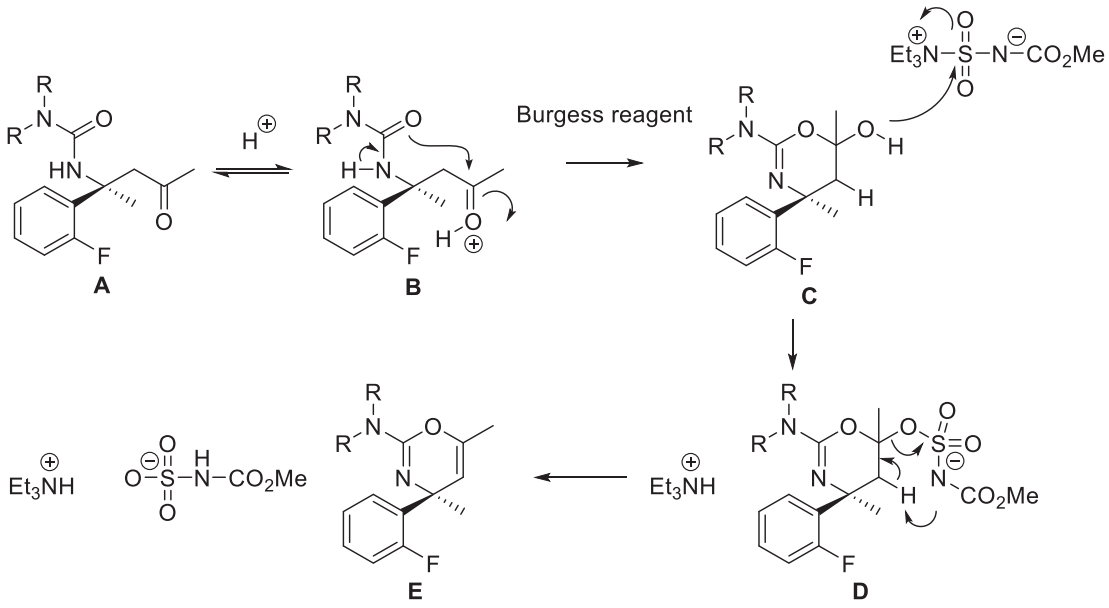
Entry	Reagent (equiv)	Solvent	Temp	Yield **9** (%)
1	–	AcOH	120	ND[a]
2	P_2O_5 (15)	AcOH	120	26[b]
3	P_2O_5 (15)	MeCN	70	54
4	P_2O_5 (2)	MeCN	70	ND[c]
5	Burgess reagent (2)	THF	80	83
6	Burgess reagent (2)	THF	rt	88

[a]**9** was not detected by LC/MS. [b]**12** was obtained in 24% yield. [c]The urea group was eliminated to give **13**.





Scheme 2. Synthesis of amino-1,3-oxzines **11a-c** using Burgess reagent.



Scheme 3. Plausible mechanism for the cyclization of urea **A** using Burgess reagent.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152684.

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