Synthesis of pyrrolo[2,1-f][1,2,4]triazin-4(3H)-ones: Rearrangement of pyrrolo[1,2-d][1,3,4]oxadiazines and regioselective intramolecular cyclization of 1,2-bis-carbamoyl-substituted 1H-pyrroles

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Abstract
Pyrrolo[2,1-f][1,2,4]triazin-4(3H)-ones 12 have been easily prepared via nucleophile-induced rearrangement of pyrrolooxadiazines 11 and regioselective intramolecular cyclization of 1,2-bis-carbamoyl-substituted 1H-pyrroles 10. In this work, we demonstrated that the described synthetic approaches can be considered to be more facile and practical than previously reported procedures.

Introduction
Pyrrolo[2,1-f][1,2,4]triazin-4(3H)-ones have been considered to be biologically active compounds. For example, these nitrogen-containing heterocycles have shown intriguing activities as tankyrase inhibitors 1 [1,2], stearoyl CoA desaturase inhibitors 2 [3], Eg5 inhibitors 3 [4,5], melanin-concentrating hormone receptor (MCH)-R1 antagonists 4 [6], and CRF1 receptor antagonists 5 [7,8] (Figure 1). Notably, many patent applications have described pyrrolotriazinones as phosphoinositide 3-kinase (PI3K) inhibitors 6 [9-12]. These skeletons are the key intermediates for the synthesis of pyrrolo[2,1-f][1,2,4]triazines, which have been shown to have outstanding biological activities [13-17]. Consequently, many research groups have developed synthetic approaches; two main synthetic routes involve N-imine intermediates and could be considered for the preparation of pyrrolotriazinones (Figure 2). Based on the reported cyclization methods, however, the reactions require high temperatures and long reaction times (generally overnight) to obtain the desired products [1-12]. For exam-
ple, these cyclization methods involve procedures such as microwave-assisted heating with NaOMe [1] and H$_2$N-Ar [6] at 150–160 °C, refluxing with HC(OEt)$_3$ [3] and xylene [4,5,8], stirring at 100 °C in the presence of either NaOH or KOH [4,9], and heating with POCl$_3$ [11] (Figure 2). It is reasonable to consider that these harsh conditions are required because it is difficult to form the $N$-imine structure and to subsequently perform intramolecular cyclization (Figure 2).

In our efforts to discover drugs that are PI3K inhibitors, a Hutchison Medipharma patent caught our attention. They reported that pyrrolotriazinones showed excellent inhibitory activities against PI3K enzymes [9]. However, their synthetic method to prepare the target molecule 9 demonstrated a limited scope, and involved high temperature, long reaction time, and low yield (approach A, Scheme 1). Another synthetic approach, reported by researchers at Infinity Pharmaceuticals Inc., has been used to obtain triazinone 12a' via rearrangement of oxadiazines 11a' (approach B, Scheme 1) [10].

However, in our investigation of the reported rearrangement reaction, the desired product 12a' was not accessed (approach B, Scheme 1). For the procedure using silica-gel column chromatography to afford triazinone 12a' from the free amine-containing oxadiazine 11a' [10], compound 11a' was not present after the boc-deprotection reaction because of its instability in the acidic conditions.

Based on the literature and the attempts reported herein, it should be highlighted that limitations exist for the preparation of the desired compounds 12. Due to these difficulties, we have investigated the synthesis of pyrrolotriazinones 12 by using a...
more convenient and facile approach than those that have been previously reported in the literature [9-12].

Results and Discussion

Our studies started with the synthesis of aminopyrrolocarbamate 10. The preparation of compound 10, which is illustrated in Scheme 2, involved chlorination of 3-chloro-1H-pyrrole-2-carboxylic acid (13) using the Vilsmeier reagent [9], followed by further amination to produce 1H-pyrrole-2-carboxamide 14 in good to excellent yield [9]. A reaction mixture of 14 with NaOH, NH₄Cl, and NaClO led to the formation of the N-aminopyrrole 15 [11]. The addition of the NH₂⁺ to the nitrogen of pyrrole 14 by using the NaOH/NH₄Cl/NaClO system [11] can be considered as a more practical method than others, such as those that use NH₂Cl and HOSA [19]. In contrast to other substituents, 2-fluorophenyl and 4-cyanophenyl groups caused low yields (15b: 15%, 15f: 31%). The N-aminopyroles 15 were then reacted with EDC·HCl and Boc-

![Scheme 1: Synthesis of pyrrolotriazinones 9 and 12 [9,10,18].](image1)

![Scheme 2: Synthesis of aminopyrrolocarbamate 10.](image2)
L-alanine in THF to give the desired aminopyrrolocarbamate 10 in good to excellent yield [9].

To synthesize the desired pyrrolotriazinones 12 regioselectively we initially considered the work of Mazurkiewicz [20,21]. He reported that a mixture of 4H-3,1-benzoxazines (O-imidoylation products) and 4-quinoxalolones (N-imidoylation products) could be obtained after heating N-acylanthranilamide in CH2Cl2 under reflux with PPh3Br2 in the absence of triethylamine. In his research, it was proved that HCl or HBr influenced the rearrangement of benzoazines to quinoxalones. Importantly, triethylamine was considered to be an HBr captor [20,21].

With regard to Mazurkiewicz’s work, the effect of Et3N on intramolecular cyclization was explored, and the acid-assisted rearrangement was also evaluated.

As shown in Table 1, although all of the obtained yields were influenced by the amount of Et3N, the attempt to synthesize compound 12a directly by optimizing the amount of base was not successful. For example, no reaction was observed in the absence Et3N (entry 1, Table 1). When excess amounts of base were used, compounds 11a and 12a were only obtained in low yields (40% combined yield, entry 3, Table 1). Alternatively, when 2.5 equivalents of Et3N were used, the two regioisomers 11a and 12a were obtained in an excellent overall yield of 87% (entry 2, Table 1). In addition, the ratio of 11a to 12a was not significantly affected by reaction times and temperatures (entries 4–6, Table 1).

Although initial attempts to synthesize pyrrolotriazinone 12a regioselectively were not successful, it should be highlighted that the regioisomers oxadiazine 11a and triazinone 12a could be easily prepared under very mild conditions (0 °C for 5 min), whereas only the oxadiazine 11a had been obtained in other reported procedures [10,12].

The acid-promoted rearrangement of oxadiazine 11 to triazinone 12 was also examined. However, the trial reaction was not successful because compound 11 did not tolerate acidic conditions.

Because of this result, the rearrangement reaction of pyrroloxadiazine 11a to pyrrolotriazinone 12a was explored (Table 2). For nucleophile-induced cyclization, pyrrolidine, Li(Me3AlSPh) [22], NaSMe, and NaOMe were assessed. Attempting the Mazurciewicz–Ganesan procedure [23], using pyrrolidine as a nucleophile, was not successful (entry 1, Table 2). In the cases of Li[Me3AlSPh], NaSMe, and NaOMe, the triazinone 12a was readily obtained after the nucleophlic-addition/ring-closure reaction (entries 2–5, Table 2). For example, similar to benzoxazine [22], treatment of 11a and 11d with lithium trimethyl(phenylsulfido)aluminate Li(Me3AlSPh) provided the desired pyrrolotriazinone, 12a and 12d, in excellent yields and with retention of enantiomeric excesses (ee) (entries 2 and 3, Table 2). Interestingly, the rearrangement of oxadiazine 11a with sodium thiomethoxide led to the desired compound 12a (92% yield, entry 4, Table 2), and retention of ee was observed. With sodium methoxide, the ee was not retained, but the desired product 12a was obtained in excellent yield.

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**Table 1:** The studies on various reaction conditions.

| Entry | Et3N (equiv) | Reaction conditions | Yield [%] \(11a (12a)\) |
|-------|-------------|---------------------|--------------------------|
| 1     | None        | 0 °C, 1 h → rt, 0.5 h | \(b \sim b\)          |
| 2     | 2.5         | 0 °C, 5 min          | 53 (34)                  |
| 3     | 10          | 0 °C, 5 min          | 11 (29)                  |
| 4     | 5           | 0 °C, 5 min          | 68 (22)                  |
| 5     | 5           | 0 °C, 1 h → rt, 6 h  | 63 (20)                  |
| 6     | 5           | reflux, 10 min       | 59 (16)                  |

\(^a\)After column chromatography, \(^b\)not obtained.
Table 2: Rearrangement of pyrrolooxadiazine 11 to pyrrolotriazinone 12.

| Entry | R  | Substrate/Product | Rearrangement conditions          | Yield [%]a | ee [%]b |
|-------|----|-------------------|-----------------------------------|------------|--------|
| 1     | Ph | 11a/12a           | 1. pyrrolidine, rt, 18 h          | –c         | –d     |
| 2     | Ph | 11a/12a           | Li(Me_3AlSPh), THF, rt, 20 h      | 90         | 99     |
| 3     | 4-F-Ph | 11d/12d | Li(Me_3AlSPh), THF, rt, 20 h      | 69         | 99     |
| 4     | Ph | 11a/12a           | NaSMe, THF, DMF, rt, 0.5 h        | 92         | 99     |
| 5     | Ph | 11a/12a           | NaOMe, THF, DMF, rt, 3 h          | 85         | 88     |

aAfter column chromatography; bthe enantiomeric excess (ee) was determined after the amide coupling reaction of boc-deprotected 12 with moscher’s acid; cnot obtained; danot determined.

Table 3: Investigation of regioselectivity.

| Entry | R               | X_2 | Products | Yield [%]a 11 (12) |
|-------|-----------------|-----|----------|-------------------|
| 1     | phenyl          | Cl  | 11a (12a) | 10 (87)          |
| 2     | phenyl          | Br  | 11a (12a) | 63 (18)          |
| 3     | phenyl          | I   | 11a (12a) | 81 (13)          |
| 4     | 3-fluorophenyl  | Cl  | 11c (12c) | 11 (72)          |
| 5     | 4-fluorophenyl  | Cl  | 11d (12d) | 15 (81)          |
| 6     | 4-methoxyphenyl | Cl  | 11e (12e) | 20 (78)          |
| 7     | 4-cyanophenyl   | Cl  | 11f (12f) | 43 (41)          |
| 8     | 2-fluorophenyl  | Br  | 11b (12b) | 16 (29)          |
| 9     | 3-fluorophenyl  | Br  | 11c (12c) | 25 (68)          |
| 10    | 4-fluorophenyl  | Br  | 11d (12d) | 41 (19)          |
| 11    | 4-methoxyphenyl | Br  | 11e (12e) | 70 (10)          |
| 12    | 4-cyanophenyl   | Br  | 11f (12f) | –b (–b)          |
| 13    | 4-methoxybenzyl | Br  | (12g)     | –b (60)          |
| 14    | cyclopropyl     | Br  | (12h)     | –b (66)          |

aAfter column chromatography; bnot obtained.

(12). Notably, it has proven that sulfur-based reagents such as Li(Me_3AlSPh) and NaSMe are efficient for the nucleophile-induced cyclization. Next, the effect of different halogens on the regioselectivity of the cyclization of 10 was investigated (Table 3). In general, the mixture of oxadiazines 11 and triazinones 12 was obtained in
45–98% overall yield. The results show that the regioselectivity is highly dependent on the halogen used. In particular, when PPh₃Cl₂ was used, triazinones 12a (N-imidoylation product) were more easily obtained than oxadiazines 11 (entries 1 and 4–6, Table 3). In the case of bromine, the O-imidoylation products 11a were preferred over the N-imidoylation products 12, whereas for substrates with 2- and 3-fluorophenyl groups different results were obtained (entries 2 and 8–11, Table 3). Based on the literature results [9-12,22-25] and the reactions that are reported herein, the O-imidoylation product 11a is more accessible than the N-imidoylation product 12 when PPh₃Br₂/I₂-Et₃N/DIPEA systems are applied (entries 2, 3, 10 and 11, Table 3).

Interestingly, in the case of the 4-cyanophenyl group, it appeared that the different reaction patterns might be a result of the reagents PPh₃Br₂ and PPh₃Cl₂ (entries 7 and 12, Table 3). For alkyl substituents (4-methoxybenzyl and cyclopropyl, entries 13 and 14, Table 3), triazinones 12g and 12h were selectively prepared in over 60% yield. Based on these results, it is possible to consider that due to the presence of electron-donating groups, such as alkyl substituents, only the N-imidoylation products 12g, and 12h were formed.

It is possible to propose a reaction mechanism after considering our studies and the literature results (Figure 3) [20-28]. For example, it is not reasonable to consider Mazurkiewicz’s acid-promoted rearrangement [20,21], because oxadiazine is not stable under acidic conditions. In the case of the rearrangement of 11a to 12a, the mechanism of the nucleophile-induced cyclization is proposed after considering Hart’s research on the synthesis of fumiquinazolines [22]. It was shown that the nucleophilicity of the N-acylnitrenium ion was increased when the oxygen ion was stabilized by counter ions such as lithium and sodium. For the intramolecular cyclization step, it was shown that the regioselectivity depends on the halogen source (Br/Cl) and neighboring groups of the N-acylnitrenium ions (electron-withdrawing aryl and -donating alkyl substituents). This is highlighted by the observation that the N-imidoylation product (triazinone) 12a was preferentially obtained when a chlorine-halogen source and electron-donating alkyl groups were used. While further studies are required, we suggest the intermediates are N-acylnitrenium ions [26] and halogen-imine structures (the Vilsmeier type) [27,28].

Because oxadiazines 11a and triazinones 12a are non-crystalline, their exact structures were assigned by NMR spectroscopy (¹H and ¹³C). With the literature results alone [9-12] the identity of the regioisomers could not be accurately confirmed; therefore, the NMR studies were required. As shown in Table 4, different NOEs were observed for compounds 11a and 12a.

Upon examination of the ¹H NMR spectra of oxadiazines 11a and triazinones 12a, different peak patterns of the NH protons

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**Figure 3:** Probable mechanism for the synthesis of triazinone 12a.
were observed (11 – NH: 4.8 ppm, 12 – NH: 5.1 ppm, see Supporting Information File 1).

Through $^{13}$C NMR and IR analysis the presence of two regioisomers could be confirmed by the peaks of specific functional groups (Figure 4).

According to the NMR and IR data, compounds 11 and 12 are believed to have pyrrolooxadiazine and pyrrolotriazinone structures, respectively. Notably, this is the first report in which the exact structures of these regioisomers have been determined.

**Conclusion**

In summary, to develop straightforward methods for the synthesis of pyrrolo[2,1-f][1,2,4]triazin-4(3H)-ones, intramolecular cyclization and rearrangement reactions were investigated. Notably, we found that triazinones 12 can be readily accessed under very mild conditions (0 °C, 5 min). The regioselectivity was influenced by the identities of halogen sources of triphenylphosphorane and the N-functional groups. For the rearrangement reaction, it was demonstrated that triazinone 12a was easily obtained when counter ions of oxygen such as lithium and sodium were used. Finally, we predict that these methods could be useful for the preparation of biologically active pyrrolotriazinones and -triazines.

**Supporting Information**

**Supporting Information File 1**
Experimental and analytical data. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-168-S1.pdf]

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