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First synthesis of pyrrolothiadiazinones. An alternative core ring for xanthine based structures

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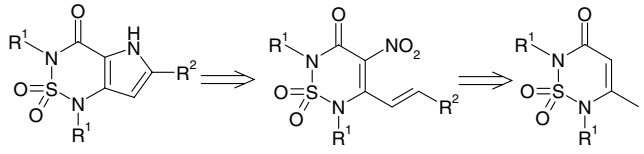
Abstract—The first synthesis of pyrrolothiadiazine core ring bearing substituents at positions 1, 3 and 6 is described, using a straightforward synthesis from diversely substituted 5-methylthiadiazines. These structures are of interest not only because they can be considered as useful building blocks but also because they can potentially be used as alternative core rings for biologically important molecules bearing xanthine as a central core.

The xanthine ring is an ubiquitous central core present in many biologically important small molecules. Xanthine based structures are present in drugs such as theophylline as well as, for instance, many phosphodiesterase inhibitors,[1] adenosine receptor antagonists,[2] calcitonin inducing agents[3] or DNA intercalating agents.[4]

In the course of our work to identify novel adenosine receptor antagonists, we became very interested in compounds bearing pyrrolothiadiazinone (**1**) as a central core (Scheme 1).

Even though imidazo and pyrazolo thiadiazines (**2–3**) are known,[5] to our knowledge there are no precedents for the synthesis of pyrrolothiadiazines (**1**) (Fig. 1).

Herein, we report the first synthesis of substituted 2,2-dioxo-2,3-dihydro-1*H*-2λ⁶-pyrrolo[3,2-*c*][1,2,6] thiadiazin-4-ones (also called 1,5-dihydropyrrolo[3,2-*c*][1,2,6] thiadiazin-4(3*H*)-one 2,2-dioxide) following a convenient and straightforward approach depicted in Scheme 1.



Scheme 1. Retrosynthetic analysis.

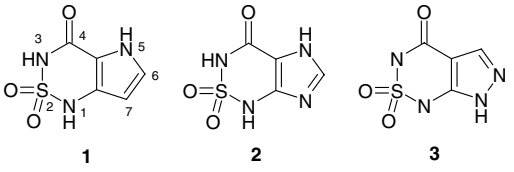
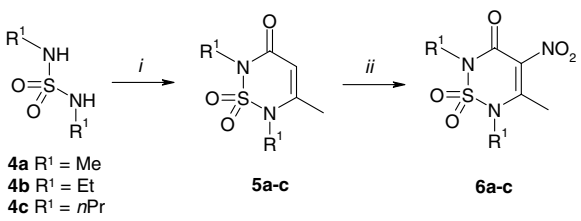


Figure 1. Structure of thiadiazine condensed core rings **1**–**3**.

First we attempted the synthesis of the thiadiazines **5a**–**c** by treating *N*,*N*′-sulfonyl dialkylamines **4a**–**c**[6] with diketene in NaOH[7] or using diketene in the presence of mercuric cyanide[8] and the desired products were obtained in very poor yields. We also tried a known method to prepare 5-methyl uracil using urea and acetic anhydride under reflux.[9] In this case, we recovered exclusively the diacylated sulfamide. Finally, thiadiazines **5a**–**c** were synthesized smoothly by treatment of the corresponding sulfamides **4a**–**c** with diketene in glacial acetic acid (Scheme 2 and Table 1).



Scheme 2. Reagents and conditions: (i) diketene, acetic acid, reflux, 3 h and (ii) HNO_3–H_2SO_4, −30 °C, 30 min.

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Table 1. Yields for condensation products with diketene **5** and nitration products **6**

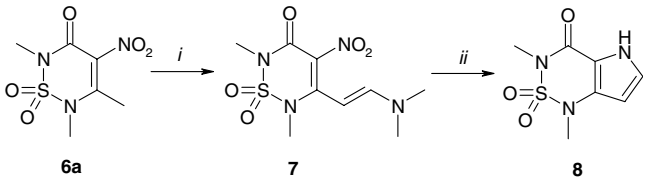
Entry	Product[a]	R^1	Yield[b] (%)
1	**5a**	Me	40
2	**5b**	Et	67
3	**5c**	*n*-Pr	73
4	**6a**	Me	60
5	**6b**	Et	68
6	**6c**	*n*-Pr	90

[a] All products were characterized by NMR and MS.
[b] Pure isolated yield (two steps). No chromatography was required.

Further 5-nitration of thiadiazines **5a–c** in a mixture of sulfuric and nitric acid[10] produced nitrothiadiazines **6a–c** in good yields (Table 1).

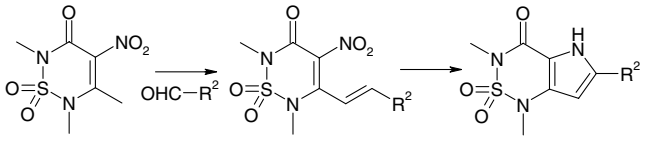
We then targeted the synthesis of pyrrolothiadiazine **8** by reaction of 1,3,5-trimethylthiadiazinone **6a** with dimethylformamide diethyl acetal in DMF to give the dimethylaminomethylene derivative (**7**) (Scheme 3). Reductive cyclization using sodium dithionite provided compound **8** in good yield.[11,12]

We next turned our attention towards functionalization of position 6 of the pyrrolothiadiazine core ring (Scheme 4). Condensation of thiadiazines **6a–c** with benzaldehyde proceeded smoothly in the presence of piperidine at room temperature to give the benzylidene intermediates **9a–c** in excellent yields. In this step, we found that addition of molecular sieves improved the yield and decreased the reaction time to 4 h (without molecular sieves the reaction takes more than 24 h for completion).[13] In order to avoid the use of piperidine (that in some cases was difficult to remove from the reaction products) we explored the use of an immobilized secondary amine such as polymer supported piperidine. When the reaction of **6a** with benzaldehyde (1 equiv) was performed using piperidine-4-carboxylic acid polyamine



Scheme 3. Reagents and conditions: (i) DMF–diethyl acetal (1.5 equiv), DMF, rt, 1 h, 93% and (ii) $Na_2S_2O_4$ (4 equiv), THF–H_2O (1:1), reflux, 2 h, 72%.

Table 2. Global yields for condensation products of thiadiazine **6a** with aldehydes followed by reductive cyclization



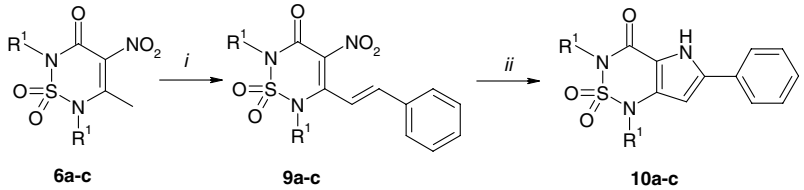
Entry	R^2	Product[a]	Yield[b] (%)
1	4-F–C_6H_5	**11**	62
2	3-F–C_6H_5	**12**	85
3	2,4-DiF–C_6H_5	**13**	40
4	4-Cl–C_6H_5	**14**	52
5	4-Br–C_6H_5	**15**	38
6	4-CF_3–C_6H_5	**16**	40
7	4-CF_3O–C_6H_5	**17**	42
8	2-MeO–C_6H_5	**18**	45
9	2-Thienyl	**19**	22
10	4-Bromo-2-thienyl	**20**	22
11	5-Bromo-2-thienyl	**21**	28
12	3-Methyl-2-thienyl	**22**	20
13	3-Thienyl	**23**	30
14	2-Pyridyl	**24**	25

[a] All products were characterized by NMR and MS.
[b] Pure isolated yield (2 steps).

resin (Novabiochem, 1.34 mmol basic NH/g, 1 equiv) in ethanol, the reaction product **9a** was isolated simply by filtration and evaporation of the solvent in a 58% yield.

Compounds **10a–c** were prepared by reductive ring closure of **9a–c** with sodium dithionite in formic acid. When the cyclization reaction of **9a** was performed in neat triethylphosphite, product **10a** could not be isolated.[14]

We then applied the same condensation–cyclization protocol for the synthesis of several substituted pyrrolothiadiazines using 1,3,5-trimethylthiadiazine **6a** and the corresponding aldehydes. As depicted in Table 2, when diversely substituted benzaldehydes were used (entries 1–8) the corresponding cyclization products were isolated in acceptable yields (Table 2). However, when heterocyclic aldehydes such as thienyl (entries 9-13) or pyridyl (entry 14) were used, the global yields were much lower basically due to poor yields in the cyclization step. When 2-furaldehyde was used, although the condensation product could be isolated, the cyclization reaction failed to provide the desired compound.



Scheme 4. Reagents and conditions: (i) benzaldehyde, piperidine, EtOH, 3 = C5 molecular sieves, rt, 4 h, 70–90% and (ii) $Na_2S_2O_4$ (4 equiv), HCOOH, reflux, 3 h, 50–70%.

In conclusion, we have described the first synthesis of the pyrrolothiadiazinone core ring from diversely substituted 5-methylthiadiazinones using a straightforward methodology. Furthermore, we have expanded this synthetic approach to the synthesis of substituted derivatives at position 6. These structures can be considered as useful and original building blocks for further derivatization and also can potentially be used as alternative core rings for biologically important molecules bearing xanthine as a central core.

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11. Procedure for the preparation of compound **8**: (i) To a solution of compound **6a** (1 g, 4.25 mmol) in dimethylformamide (2 mL) at room temperature was added dimethylformamide diethylacetal (1.1 mL, 6.4 mmol). The resulting deep red solution was stirred at room temperature for 1 h. The solvent was then removed in vacuo and **7** (1.12 g, 91%) was isolated as a brown solid after treating the residue with diethylether and filtration of the precipitate ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58 (d, $J = 8$ Hz, 1H); 5.84 (d, $J = 8$ Hz, 1H); 3.33 (s, 3H); 3.31 (s, 3H); 3.12 (s, 3H); 3.06 (s, 3H). (ii) To a solution of **7** (0.5 g, 1.7 mmol) in a mixture of tetrahydrofuran and water (8 mL, 1:1) was added sodium dithionite (1.4 g, 6.9 mmol) and the resulting solution was refluxed for 2 h. The mixture was cooled to room temperature and ethyl acetate and water were added, the layers separated, the organic layer washed with a saturated solution of sodium bicarbonate and brine, dried over sodium sulfate, filtered and evaporated in vaccuo. Compound **8** (0.31 g, 84%) was isolated as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.80 (br s, 1H); 7.02 (m, 1H); 6.13 (m, 1H); 3.39 (s, 3H); 3.36 (s, 3H).
12. When the reductive ring closure was performed using hydrogen and palladium on carbon, 6-dimethylaminopyrrolo thiadiazine was isolated almost exclusively.
13. Procedure for the preparation of **10a**: (i) To a solution of **6a** (3 g, 15 mmol) and piperidine (1.4 mL, 15.6 mmol) in ethanol (70 mL) at room temperature, were added benzaldehyde (1.58 mL, 15.6 mmol) and 3 = C5 molecular sieves (6 g). The mixture was stirred under reflux for 4 h. After cooling, the reaction mixture was filtered, evaporated and the residue was treated with a mixture of diethyl ether and dichloromethane. Compound **9a** was isolated by filtration of the corresponding precipitate as a yellow solid (3.5 g, 80%) ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.41 (m, 5H); 7.06 (d, $J = 8$ Hz, 1H); 6.64 (d, $J = 8$ Hz, 1H); 3.50 (s, 3H); 3.44 (s, 3H). (ii) To a solution of compound **9a** (2.6 g, 9.1 mmol) in formic acid (80 mL) was added sodium dithionite (9.3 g, 45 mmol) and the mixture was refluxed overnight. After cooling, the reaction mixture was poured into water and the precipitate formed was filtered, washed with water, diethylether, a mixture of dichloromethane–methanol (9:1) and dried to provide compound **10a** as a white solid (1.54 g, 66%) ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.61 (br s, 1H); 7.82 (m, 2H); 7.41 (m, 3H); 6.83 (s, 1H); 3.35 (s, 3H); 3.37 (s, 3H).
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