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Annulations of α-Carbamoyl Ketene Dithioacetals with Dicarboxylic Acid Dichlorides: Synthesis of Functionalized Pyrrolidinetriones and Piperidinetriones

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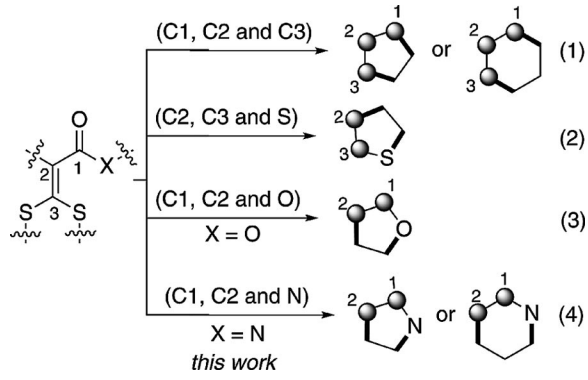
An annulation strategy based on ketene dithioacetals is described. Under very mild conditions, a number of pyrrolidinetriones **2** and piperidinetriones **3** have been synthesized by the cycloaddition reaction of α-carbamoyl ketene dithioacetals **1** with di-carboxylic acid dichlorides in good to excellent yields. Further application of this protocol is highlighted by the synthesis of a set of fused pyrimidine derivatives **4/5** from **2/3** and amidines.

Introduction

Rapid assembly of acyclic molecules provides an efficient method for the construction of cyclic compounds. Ketene dithioacetals are important organic intermediates.[1,2] Although the cyclization strategies based on them, including [3 + 2],[3] [3 + 1 + 1],[4] [3 + 3],[5] [4 + 2],[6] [5 + 1][7] and [7 + 1][8] annulation reactions, have been well documented and become powerful tools for the synthesis of a wide variety of carbo- and heterocyclic compounds,[1] new types of cyclization processes are still sought after in this field.

Among [3 + *n*] annulation reactions, ketene dithioacetals have been extensively used as 3-carbon (C1, C2 and C3) 1,3-bielectrophilic fragments for constructing five- and six-membered cyclic compounds (Scheme 1, Part 1)[3b–3d,3g,3h,5] Alternatively, Rao and co-workers described a cyclization reaction with ketene dithioacetals as 1,3-binucleophilic (C2 and S atom) components (Scheme 1, Part 2).[3f] Recently, α-cinnamoyl ketene dithioacetals were also reported as 1,3-binucleophilic reagents (C1 and carbonyl oxygen) in a tandem three-component [3 + 2] cycloaddition reaction under basic conditions (Scheme 1, Part 3).[9] During our continuous interest in developing a synthetic strategy based on ketene dithioacetals,[2] we designed a new [3 + *n*] cyclization mode, in which the C2 and N atoms of α-carbamoyl ketene dithioacetals **1** act as 1,3-binucleophilic centers (Scheme 1, Part 4). Herein, we report these [3 + 2] and [3 + 3] annulation reactions of α-carbamoyl ketene dithioacetals **1** with dicarboxylic acid dichlorides leading efficiently to pyrrolidine-2,3,5-triones **2** and piperidine-2,4,6-triones **3**. Furthermore, fused pyrimidine derivatives,[10] including 6*H*-pyrrolo[3,4-*d*]pyrimidine-5,7-diones **4** and pyrido[4,3-*d*]pyrimidine-5,7(6*H*,8*H*)-diones **5** were prepared through facile condensation reactions of **2/3** with amidines in high to excellent yields.



Scheme 1. [3 + *n*] Cyclization reaction strategies based on ketene dithioacetals.

Results and Discussion

We first examined the reaction of 3,3-bis(ethylthio)-*N*-phenylacrylamide (**1f**) with oxalyl dichloride under the same conditions as the previous report[9] [in tetrahydrofuran (THF), at room temperature, Et_3N as base; Table 1, Entry 1]. To our delight, 4-[bis(ethylthio)methylene]-1-phenylpyrrolidine-2,3,5-trione (**2f**) was obtained after 1 h in 98% yield. The structure of **2f** was successfully confirmed by NMR and MS spectroscopy, and further in a single-crystal X-ray diffraction study (Figure 1).[11] The annulation reaction rate appears to be temperature dependent and **2f** was isolated in 89% yield after 18 h at 0 °C

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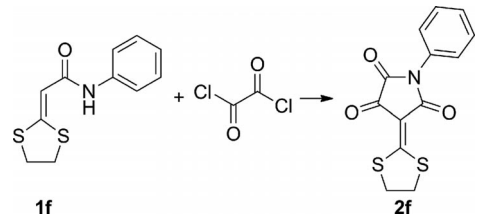
(Table 1, Entry 2). Notably, α-carbamoyl ketene dithioacetal (**1f**) proved to be reactive enough to react with oxalyl dichloride leading to **2f** in excellent yield even in the absence of Et_3N under identical conditions (Table 1, Entry 3). Other solvents proved to be less efficient than THF for the reaction and no reaction occurred in dimethylformamide (DMF; Table 1, Entries 4–6).

Table 1. Optimization of the [3 + 2] cyclization reaction of **1f** with oxalyl dichloride.[a]



Entry	Base [equiv.]	Solvent	*T* [°C]	Time [h]	**2f** Yield [%][b]
1	Et_3N (2.0)	THF	room temp.	1	98
2	Et_3N (2.0)	THF	0	18	89
3	–	THF	room temp.	1	97
4	–	CH_2Cl_2	room temp.	2	93
5	–	toluene	room temp.	9	92
6	–	DMF	room temp.	10	n.r.

[a] The reactions were carried out with **1f** (0.5 mmol) and oxalyl dichloride (0.6 mmol). [b] Isolated yield.

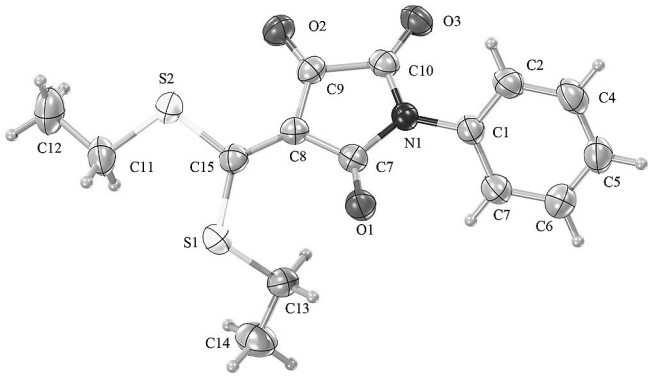
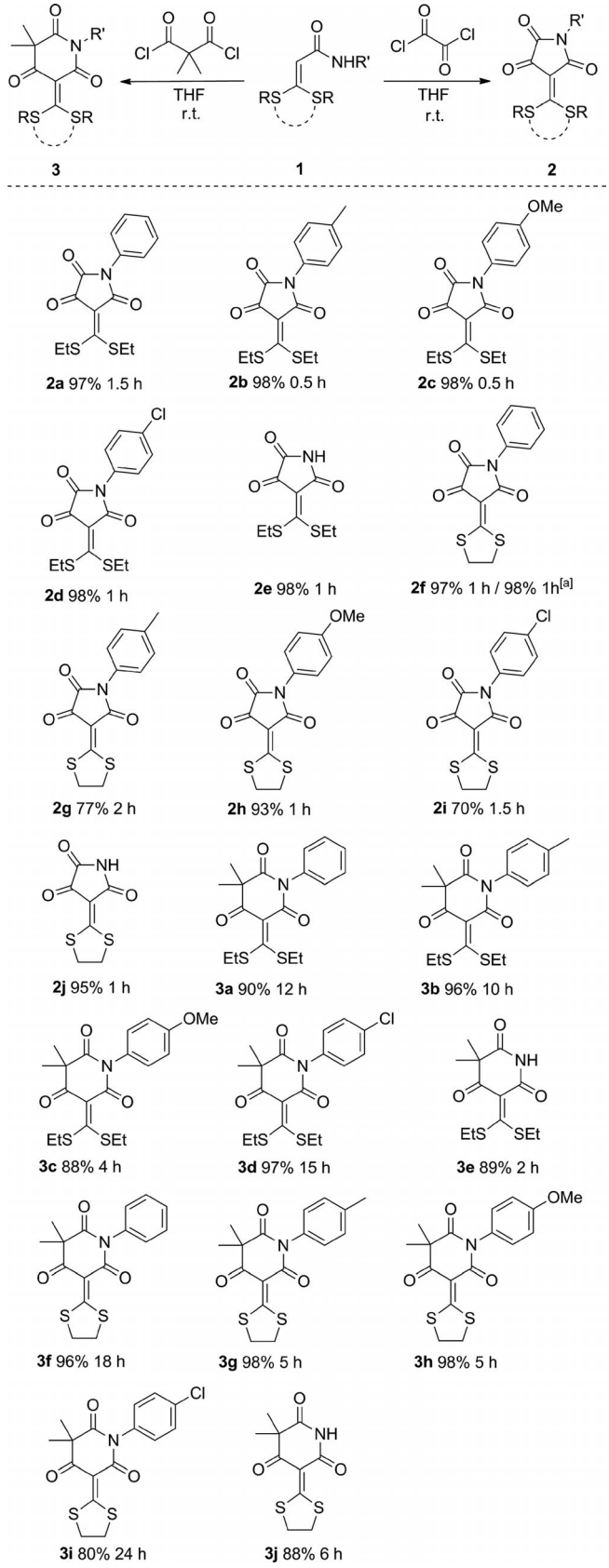


Figure 1. ORTEP diagram of **2f**.

The above process indicates a simple and efficient route to pyrrolidine-2,3,5-trione derivatives, which are of importance in biological and pharmaceutical compounds,[12] starting from readily available acyclic precursors under very mild conditions. Thus, we set out to explore the scope of α-carbamoyl ketene dithioacetals **1** through the [3 + 2] cyclization reaction. As shown in Scheme 2, both acyclic and cyclic ketene dialkylthioacetals tested afforded products **2** in good to excellent yields. α-Carbamoyl ketene dithioacetals with N-protecting groups containing either an electron-donating or electron-withdrawing aryl group successfully provided pyrrolidine-2,3,5-triones **2a**–**2d** and **2f**–**2i** in good to excellent yields. In addition, the mild conditions were also compatible with substrates **1e** and **1j** with free NH_2. Compounds **2e** and **2j** were isolated in 98% and 95% yields, respectively. Next, we selected malonyl dichloride, phthaloyl

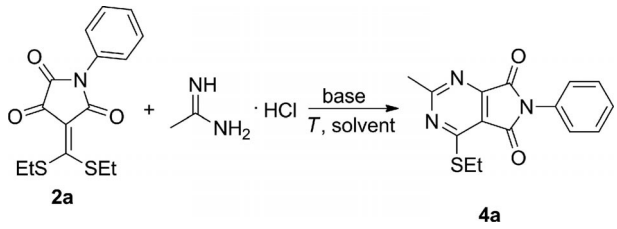


Scheme 2. Cyclization of α-carbamoyl ketene dithioacetals **1** with acid dichlorides. *Reaction conditions:* **1** (0.5 mmol), dicarboxylic acid dichloride (0.6 mmol), THF (1 mL), room temperature. Isolated yield. [a] Et_3N (1.2 mmol) was used.

dichloride and maleoyl dichloride for the annulation reaction. However, complex mixtures were often obtained and no desired product was isolated under identical reaction conditions. All attempts to optimize the reaction failed. Next, we turned our investigation to non-enolizable diacid dichlorides. Pleasingly, 2,2-dimethylmalonyl dichloride proved to be compatible with this protocol. As described in Scheme 2, a variety of α-carbamoyl ketene dithioacetals **1** reacted well with 2,2-dimethylmalonyl dichloride to give corresponding piperidine-2,4,6-triones **3**[13] in 88–98% yields, although longer reaction times were often required.

Pyrrolidine-2,3,5-triones **2** and piperidine-2,4,6-triones **3** possess the structural characters of ketene dithioacetals that may provide synthetic potential in the construction of fused heterocycles. In connection with previous reports,[14] we attempted to identify the condensation reactions of **2/3** with amidines. Initially, we chose pyrrolidinetrione **2a** with an acyclic dithioacetal functional as the model substrate, and various bases were tested in different solvents at different temperatures (Table 2). The reaction afforded desired product **4a** in 37% yield when NaOH was used as base in THF at room temperature (Table 2, Entry 2). Screening of various bases revealed that the yield of **4a** could be improved to 67% yield by using NaH (Table 2, Entry 5). Switching the solvent from THF to DMF identified DMF as the optimum solvent. Pleasingly, it was found that increasing the reaction temperature resulted in an improved yield (Table 2, Entry 6). We settled on 90 °C as the optimal temperature and the yield of **4a** reached 98% when 2.0 equiv. NaH was used (Table 2, Entry 8).

Table 2. Optimization of the [3 + 3] cyclization reaction of **2a** with acetamidine hydrochloride.[a]

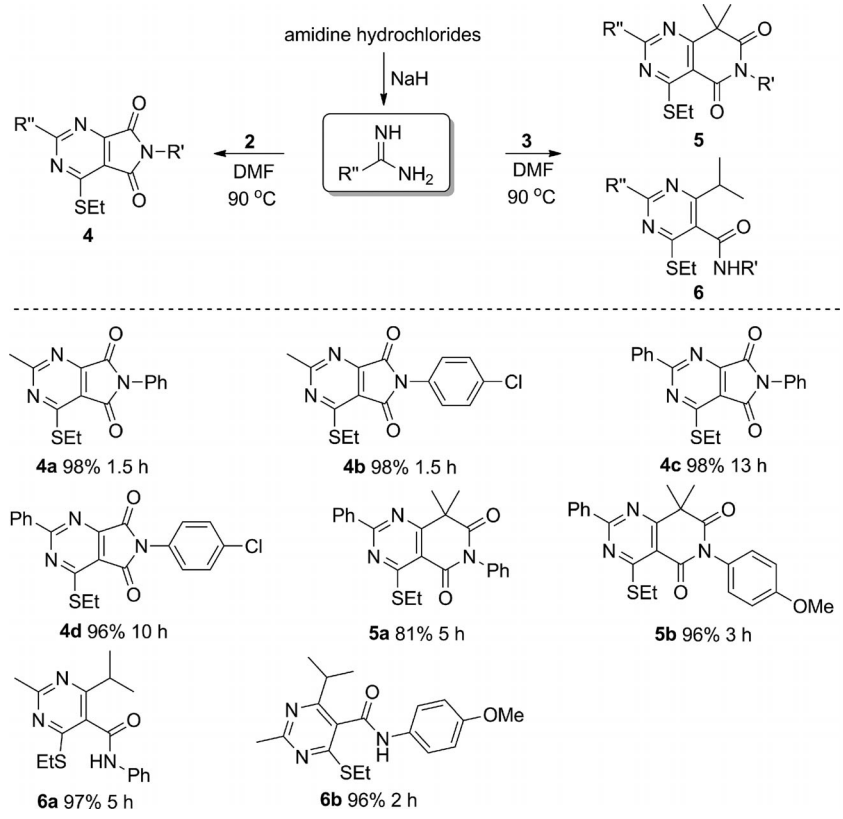


2a **4a**

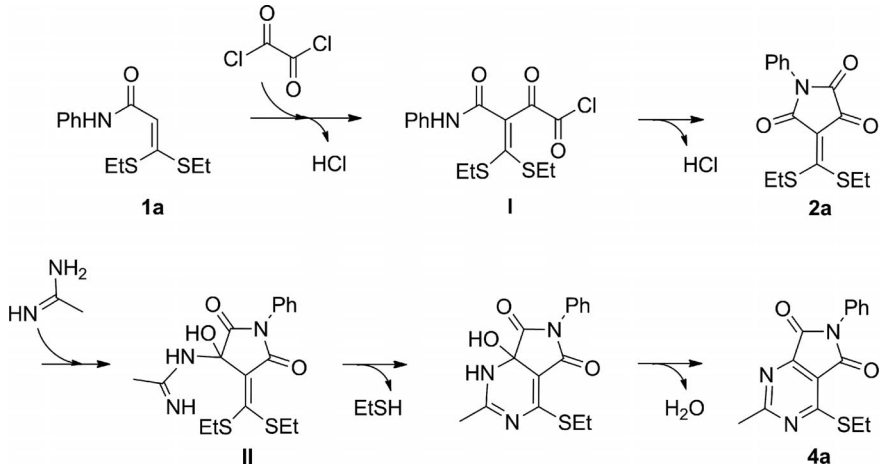
Entry	Base [equiv.]	Solvent	*T* [°C]	**4a** Yield [%][b]
1	Na_2CO_3 (1.2)	THF	room temp.	n.r.
2	NaOH (1.2)	THF	room temp.	37
3	*t*BuOK (1.2)	THF	room temp.	14
4	EtONa (1.2)	THF	room temp.	40
5	NaH (1.2)	THF	room temp.	67
6	NaH (1.2)	DMF	50	81
7	NaH (2.0)	DMF	50	82
8	NaH (2.0)	DMF	90	98

[a] The reactions were carried out with **2f** (0.5 mmol), acetamidine hydrochloride (0.6 mmol). [b] Isolated yield.

Under the optimized conditions, the reactions between pyrrolidine-2,3,5-triones **2a**/**2d** and acetamidine hydrochloride or benzamidine hydrochloride were carried out



Scheme 3. Condensation reactions of **2** and **3** with amidines. *Reaction conditions:* **2/3** (0.5 mmol), amidine hydrochloride (0.6 mmol), NaH (1.0 mmol), DMF (1 mL), 90 °C. Isolated yield.



Scheme 4. Proposed mechanism for the synthesis of **2** and **4** (by using **1a** as example).

(Scheme 3). The reaction proceeded smoothly and corresponding 6*H*-pyrrolo[3,4-*d*]pyrimidine-5,7-diones **4** were formed in excellent yields in all cases. Notably, purification of **4** only required recrystallization in diethyl ether that demonstrates the simplicity of the annulation strategy. When piperidinetriones **3a** and **3c** were tested in the condensation reaction with amidines under identical conditions, desired pyrido[4,3-*d*]pyrimidine-5,7(6*H*,8*H*)-diones **5** could be obtained with benzamidine as substrates. Similarly, acetamidine gave pyrimidine-5-carboxamides **6** as the sole products, which resulted from the hydrolyzation of piperidinetrione and subsequent decarboxylation, in good to excellent yields (Scheme 3).

On the basis of the above experimental results and our previous report,[9] we proposed a mechanism for the annulation reaction of **1a** with oxalyl dichloride and condensation reaction of **2a** with acetamidine, as depicted in Scheme 4. It was clear that α-acylation intermediate **I** was first formed and then intramolecular cyclization afforded **2a**. In the condensation of **2a** with acetamidine, intermediate **II** was firstly formed through nucleophilic attacked the ketyl of **2a** with acetamidine, followed by an intramolecular addition-elimination and dehydration reaction to afford **4a**.

Conclusions

In summary, new annulations of α-carbamoyl ketene dithioacetals with dicarboxylic acid dichlorides have been described to provide a simple and general method for the synthesis of functionalized pyrrolidinetriones and piperidinetriones. The utilization of this annulation strategy is highlighted by efficient synthesis of 6*H*-pyrrolo[3,4-*d*]-pyrimidine-5,7-diones, and pyrido[4,3-*d*]pyrimidine-5,7-(6*H*,8*H*)-diones.

Experimental Section

General Procedure for the Preparation of 2 (2a as example): To a well-stirred solution of 3,3-bis(ethylthio)-*N*-phenylacrylamide **1a** (134 mg, 0.5 mmol) in anhydrous THF (1 mL), oxalyl dichloride (0.057 mL, 0.6 mmol) in 1 mL of anhydrous THF was added dropwise over 10 min. After the reaction mixture was stirred at room temperature for 1.5 h, **1a** was consumed as indicated by TLC. The reaction was quenched with iced water (10 mL) and then saturated $NaHCO_3$ (25 mL) was added before extraction with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to provide the crude product, which was purified by flash chromatography (silica gel; eluent, petroleum ether/ethyl acetate: 16:1, v/v) to give **2a** (156 mg, 97%) as a yellow crystalline solid.

4-[Bis(ethylthio)methylene]-1-phenylpyrrolidine-2,3,5-trione (2a): 157 mg, 97%, R_f = 0.4 (petroleum ether/ethyl acetate, 4:1), yellow crystalline solid, m.p. 149–150 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 (t, J = 7.5 Hz, 6 H), 3.30 (q, J = 7.5 Hz, 4 H), 7.40 (q, J = 7.5 Hz, 3 H), 7.48 (t, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.5 (2 C), 31.7, 34.2, 110.9, 126.0 (2 C), 128.3, 128.8 (2 C), 130.8, 160.5, 165.3, 174.1, 186.3 ppm. HRMS (ESI-TOF): calcd. for $C_{15}H_{16}NO_3S_2$ [M + H$^+$] 322.0566; found 322.0562.

General Procedure for the Preparation of 3: The procedure for the synthesis of **3** is the same as for **2**.

5-[Bis(ethylthio)methylene]-3,3-dimethyl-1-phenylpiperidine-2,4,6-trione (3a): 163 mg, 90%, R_f = 0.3 (petroleum ether/ethyl acetate, 5:1), yellow solid, m.p. 125–126 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.5 Hz, 6 H), 1.58 (s, 6 H), 3.07 (q, J = 7.5 Hz, 4 H), 7.14 (d, J = 8.0 Hz, 2 H), 7.41 (d, J = 7.5 Hz, 1 H), 7.47 (t, J = 7.5, 8.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.1 (2 C), 24.3 (2 C), 33.1 (2 C), 52.5, 113.9, 128.4 (2 C), 128.8, 129.1 (2 C), 135.8, 162.6, 174.6, 190.3, 190.4 ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}NO_3S_2$ [M + H$^+$] 364.1036; found 364.1045.

General Procedure for the Preparation of 4 (4a as example): To a well-stirred solution of acetamidine hydrochloride (56.7 mg, 0.6 mmol) in anhydrous DMF (1 mL), sodium hydride (24 mg, 1.0 mmol) was added. After stirring at room temperature for 5 min, 4-[bis(ethylthio)methylene]-1-phenylpyrrolidine-2,3,5-trione **2a** (160 mg, 0.5 mmol) was added. Then, the reaction mixture was stirred at 90 °C for 1.5 h. After **2a** was consumed as indicated by TLC, the reaction mixture was quenched with iced water (50 mL) whilst stirring and the precipitate was collected by filtration, washed with water (3 × 50 mL) and recrystallized from diethyl ether to give 4-(ethylthio)-2-methyl-6-phenyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-5,7-dione (**4a**, 147 mg, 98%) as a white crystalline solid.

4-(Ethylthio)-2-methyl-6-phenyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-5,7-dione (4a): 147 mg, 98%, R_f = 0.3 (petroleum ether/ethyl acetate, 2:1), white crystalline solid, m.p. 161–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.45 (t, J = 7.0 Hz, 3 H), 2.89 (s, 3 H), 3.38 (q, J = 7.0 Hz, 2 H), 7.40–7.43 (m, 3 H), 7.49–7.52 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 23.6, 26.8, 116.8, 126.4 (2 C), 128.5, 129.2 (2 C), 130.8, 158.2, 164.5, 164.8, 168.9, 173.6 ppm. HRMS (ESI-TOF): calcd. for $C_{15}H_{14}N_3O_2S$ [M + H$^+$] 300.0801; found 300.0810.

General Procedure for the Preparation of 5 and 6: The procedure for the synthesis of **5** and **6** is the same as for **4**.

4-(Ethylthio)-8,8-dimethyl-2,6-diphenylpyrido[4,3-*d*]pyrimidine-5,7-(6*H*,8*H*)-dione (5a): 163 mg, 81%, R_f = 0.3 (petroleum ether/ethyl acetate, 3:2), white crystalline solid, m.p. 207–208 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (t, J = 7.0 Hz, 3 H), 1.84 (s, 6 H), 3.36 (q, J = 7.0 Hz, 2 H), 7.21 (d, J = 7.0 Hz, 2 H), 7.44 (t, J = 7.0 Hz, 1 H), 7.49–7.59 (m, 5 H), 8.59–8.61 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.5, 24.9, 27.3 (2 C), 46.9, 112.1, 128.5 (2 C), 128.69 (2 C), 128.7, 129.2 (2 C), 129.3 (2 C), 132.1, 134.6, 136.6, 163.1, 163.9, 171.1, 174.6, 175.6 ppm. HRMS (ESI-TOF): calcd. for $C_{23}H_{22}N_3O_2S$ [M + H$^+$] 404.1427; found 404.1435.

4-(Ethylthio)-6-isopropyl-2-methyl-*N*-phenylpyrimidine-5-carboxamide (6a): 153 mg, 97%, R_f = 0.4 (petroleum ether/ethyl acetate, 4:1), white solid, m.p. 130–131 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (d, J = 6.5 Hz, 6 H), 1.35 (t, J = 7.0 Hz, 3 H), 2.65 (s, 3 H), 3.12–3.17 (m, 1 H), 3.22 (q, J = 7.0 Hz, 2 H), 7.19 (t, J = 7.0, 8.0 Hz, 1 H), 7.38 (t, J = 8.0 Hz, 2 H), 7.51 (s, 1 H), 7.61 (d, J = 7.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.26, 21.82 (2 C), 24.09, 26.23, 32.89, 120.11 (2 C), 124.10, 125.09, 129.14 (2 C), 137.29, 164.43, 166.13, 167.34, 170.02 ppm. HRMS (ESI-TOF): calcd. for $C_{17}H_{22}N_3OS$ [M + H$^+$] 316.1478; found 316.1470.

Supporting Information (see footnote on the first page of this article): Characterization data for **2b**–**2j**, **3b**–**3j**, **4b**–**4d**, **5b** and **6b**, crystallographic data for **2f** and copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **2**, **3**, **4**, **5** and **6**.

Acknowledgments

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[11] Crystallographic data for **2f** is available as Supporting Information or as CCDC-947174. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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