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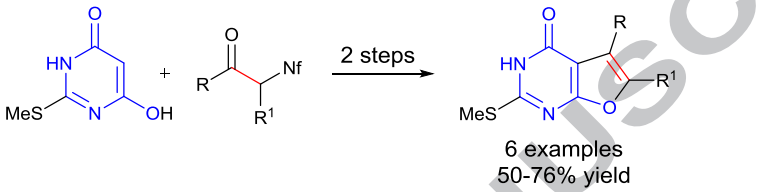

R = Ph, 4-BrPh, 4-PhPh, 4-OMePh, *tert*-butyl; R^1 = Ph or H; Nf = Br or OMs

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Synthesis of 5-substituted and 5,6-disubstituted furo[2,3-*d*]pyrimidines from 2-methylthio-4,6-pyrimidindione and bifunctional electrophiles

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ABSTRACT

A two-step protocol for the synthesis of 5-substituted or 5,6-disubstituted furo[2,3-*d*]pyrimidines using bifunctional electrophiles and a pyrimidine derivative was developed. The first step is *O*-alkylation of 2-methylthiopyrimidin-4,6-dione utilizing bifunctional electrophiles which are readily available from the corresponding ketones *via* bromination or oxidative mesylation procedures. The reaction furnishes 6-(2-oxoethoxy)pyrimidine derivatives in moderate yields, and the di-*O*-alkylated product, while still unavoidable under the proposed conditions, is easily removed upon recrystallization of the target compound. The second step is intramolecular cyclization of the mono *O*-alkylated pyrimidines on silica gel to give the target furo[2,3-*d*]pyrimidines in moderate to good yields.

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1. Introduction

Designing/expanding methods for the formation of various heterocyclic scaffolds is crucial for the advancement of medicinal chemistry and materials sciences alike. Pyrimidine based heterocycles are found amongst various biologically active compounds as well as amongst compounds with promising photophysical properties - furo[2,3-*d*]pyrimidine is one such heterocycle. For the most part furo[2,3-*d*]pyrimidines have been synthesized and investigated as potential inhibitors of folic acid cycle enzymes,[1] multireceptor tyrosine kinase inhibitors,[1c] and glycogen synthase kinase-3 inhibitors.[2] There are also indications that this heterocyclic motif can be employed to construct oligoarylenes with potential applications in optoelectronic devices.[3]

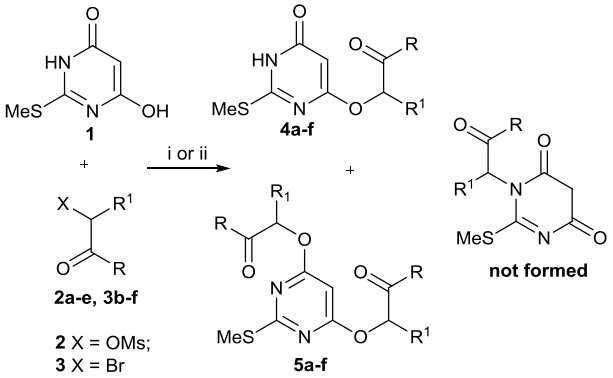
The construction of the furo[2,3-*d*]pyrimidine moiety can be achieved *via* annulation of the pyrimidine or furan ring onto an existing heterocycle. In the latter case, good candidates for developing the furan ring are pyrimidines bearing an oxygen atom at the 4th or 6th position. There are several general strategies for construction of the furo[2,3-*d*]pyrimidine skeleton involving pyrimidinones. One is applying the Sonogashira coupling reaction for the synthesis of 5-alkynylpyrimidinones and subsequent annulation to form the target furo[2,3-*d*]pyrimidines.[4,5] While this approach can be effectively applied to the synthesis of various 6- and with an external electrophile 5,6-disubstituted furo[2,3-*d*]pyrimidines,[5c] dialkynyl substrates and alkynyl substrates bearing halogens are often outside of the reaction scope for this protocol due to the competing bicoupling and polycoupling of such alkynes, respectively.[6] Also in some cases Glaser-Elington homocoupling is a problem in the Sonogashira reaction[7] and in the annulation reaction[4] as well.

Another approach to 5-arylfuro[2,3-*d*]pyrimidines proposed by Dauzonne and Adam-Launay[8] utilizes the reaction of pyrimidin-4,6-dione with (*Z*)-(2-chloro-2-nitroethenyl)benzenes as bifunctional electrophiles. While this protocol gives 5-arylfuro[2,3-*d*]pyrimidines in moderate to good yields, it is limited to 5-substituted furo[2,3-*d*]pyrimidines. Also the bifunctional electrophiles used in this reaction are commercially unavailable, but can be synthesized *via* a two-step protocol from the corresponding benzaldehyde and nitromethane.[9] A similar strategy for synthesis of the furo[2,3-*d*]pyrimidine scaffold was proposed by Li and Zhang[10] using (*E*)-(2-nitroprop-1-en-1-yl)arenes as bifunctional electrophiles. While the yields were excellent (79-95%), this protocol was limited to furo[2,3-*d*]pyrimidines with methyl or ethyl groups at the 6th position.

Other, more common, bifunctional electrophiles can be utilized for the synthesis of 5-substituted furo[2,3-*d*]pyrimidines. Earlier our group reported[11] that selected 2,6-disubstituted pyrimidin-4-ones readily react with ethyl bromopyruvate to furnish furo[2,3-*d*]pyrimidine derivatives. Unfortunately, the analogous reaction of 2-methylthiopyrimidin-4,6-dione with less reactive α-bromo carbonyl moiety possessing compounds did not give the target furo[2,3-*d*]pyrimidines.

2. Results and Discussion

We present herein a two-step protocol for the synthesis of 5-substituted or 5,6-disubstituted furo[2,3-*d*]pyrimidines from 2-methylthiopyrimidin-4,6-dione and bifunctional electrophiles bearing an oxo group and a bromo or mesyl nucleofuge. Bifunctional electrophiles can be readily prepared from the corresponding methylketones by bromination[12] or oxidative mesylation,[13] while for benzoin only the latter option is viable. While the *O*-alkylation of 2-methylthiopyrimidin-4,6-dione with either bromo or mesyl nucleofuge containing electrophiles gave similar yields of target compound **4b** using NaH, more varied yields were obtained with other bases. A survey of the reaction conditions was performed in the presence of potassium *tert*-butoxide, triethylamine, DBU, DIPEA, sodium hydride and potassium fluoride. While performing the reactions with all these bases resulted in the formation of the target 2-methylthio-6-(2-oxo-1,2-diphenylethoxy)pyrimidin-4-one **4a** or 2-methylthio-6-(2-oxo-2-phenylethoxy)pyrimidin-4-one **4b**, the best yields in neat DMF were obtained when sodium hydride (32% for **4a** and 15% for **4b**) or potassium fluoride (38% for **4a** and 14% for **4b**) was applied. Due to the low solubility of the pyrimidinone salt formed upon addition of sodium hydride or potassium fluoride in DMF, water was added prior to addition of the alkylating agent. This procedure gave mono *O*-alkylated products **4a** and **4b** in 62% and 63% yield, respectively. The main drawback of this reaction is the formation of di-*O*-alkylated side-products (15–29% isolated yield for compounds **5a-f**). Due to the apparent difference in solubility of the mono *O*-alkylated products (**4a-f**) and the undesired di-*O*-alkylated pyrimidines (**5a-f**) in benzene and 1,2-dichloroethane, a simple recrystallization procedure was utilised to separate these compounds. Additionally, no *N*-alkylation products were formed under these conditions. Dolakova and co-workers[14a] reported the alkylation of 2-substituted-4,6-dihydroxypyrimidines afforded a mixture of *N*,*O*- and di-*O*-alkylated products using chloro derivatives as alkylating agents. In this case the authors also reported poor solubility of the sodium salts of pyrimidinone in DMF which was circumvented by using DMSO as a solvent. The reported literature yields for the mono-*O*-alkylation of pyrimidin-2,4-dione reached up to 43%,[14,15] while our procedure gave mono *O*-alkylated pyrimidinones **4a-f** in moderate yields (47–63%, see Table 1).

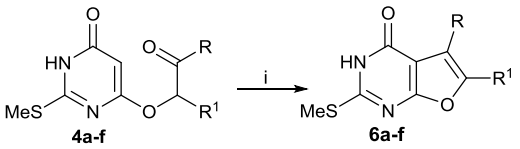


a) R = R^1 = Ph; **b**) R = Ph, R^1 = H; **c**) R= 4-BrPh, R^1= H;
d) R = 4-PhPh, R^1 = H; **e**) R = 4-OMePh, R^1 = H; **f**) R= *tert*-butyl, R^1= H.

Scheme 1. Reagents and conditions: (i) (a) NaH or KF, DMF, 1 h, r.t.; (b) H_2O, 2-substituted or 1,2-diphenyl-2-oxo methanesulfonate **2a-e**, -10-0 °C to r.t.; (ii) (a) NaH or KF, DMF, 1 h, r.t.; (b) H_2O, 1-substituted 2-bromo-1-ethanone **3b-f**, -10-0 °C to r.t.

The second step of the proposed protocol is an electrophilic intramolecular cyclization reaction of 6-(2-oxoethoxy)pyrimidin-4-one derivatives to the corresponding furo[2,3-*d*]pyrimidines. The aryl- or *tert*-butyloxo group containing electrophiles are less reactive (the latter is about 2 times less reactive than the former) towards the pyrimidine 5th position in the intramolecular electrophilic reaction compared to the previously reported pyruvate moiety;[11] thus harsh conditions were required. High boiling point solvents (DMF, HMPA, diglyme, NMP, nitrobenzene) with and without acidic catalysis (PTSA) were

applied with no positive results, while adding $ZnCl_2$ gave the target furopyrimidines in negligible amounts. Cyclization without solvent upon melting gave the target furo[2,3-*d*]pyrimidines in low yields (15–25%) due to decomposition of the starting material. When the reactions were carried out on silica gel at elevated temperature (230–240 °C) furo[2,3-*d*]pyrimidines **6a-f** were obtained in moderate to good (50–76%) yields.



a) R = R^1 = Ph; **b**) R = Ph, R^1 = H; **c**) R = 4-BrPh, R^1 = H;
d) R = 4-PhPh, R^1 = H; **e**) R = 4-MeOPh, R^1 = H; **f**) R = *tert*-butyl, R^1 = H.

Scheme 2. Reagents and conditions: (i) Silica gel, 230-240 °C (Wood's metal bath temperature).

The structural assignments of compounds **6a-f** were based on spectroscopic data. The ^{1}H NMR spectra of compounds **4a-f** show a singlet peak for the proton at the pyrimidine 5th position (5.59–5.55 ppm). Conversely, furo[2,3-*d*]pyrimidines **6a-f** lack this singlet, and the ^{1}H NMR spectra show a singlet peak for the proton at the furo[2,3-*d*]pyrimidine 6th position (8.22–8.04 ppm). Other ^{1}H NMR spectroscopic data were also consistent with the expected structures.

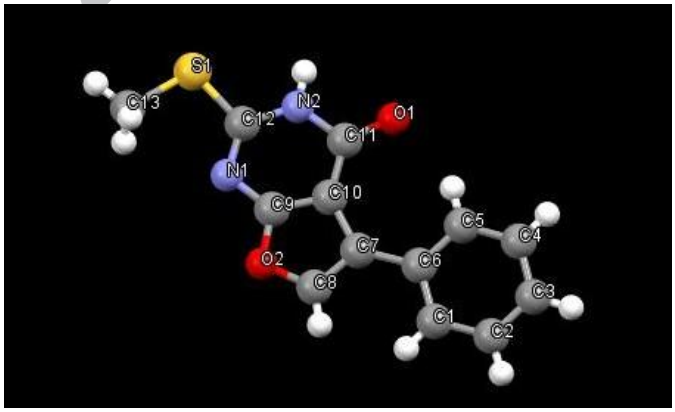
Table 1. *O*-Alkylation yields for the reaction of 2-methylthiopyrimidin-4,6-dione using NaH as a base and the yields of furo[2,3-*d*]pyrimidines.

Entry	R, R^1	Yield (%) **4**[a, b]	Yield (%) **5**[a, b]	Yield (%) **6**[a]	Cyclization reaction time (min)
1	Ph, Ph	**4a** (62)[b]	**5a** (15)[b]	**6a** (76)	70
2	Ph, H	**4b** (63)	**5b** (26)	**6b** (64)	55
3	4-Br-C_6H_4, H	**4c** (47)	**5c** (29)	**6c** (51)	60
4	4-Ph-C_6H_4, H	**4d** (48)	**5d** (29)	**6d** (54)	45
5	4-OMe-C_6H_4, H	**4e** (53)	**5e** (27)	**6e** (50)	65
6	*tert*-butyl, H	**4f** (58)	**5f** (23)	**6f** (65)	130

[a] isolated yields; [b] methanesulfonate was used as a bifunctional electrophile.

Due to lactam-lactim tautomerism the ^{13}C NMR spectra of *O*-alkylated pyrimidines **4a-f** lack peaks corresponding to the 4th and 6th pyrimidine carbons when recorded in DMSO-d_6. Recording the spectra in $CDCl_3$ (**4a** and **4f**) or Py-d_5 (**4b-e**) allowed all carbon peaks to be recorded, presumably due to a change in tautomerism.

This two-step synthetic protocol relies on selective *O*-alkylation. *N*-Alkylation and C^5-alkylation pathways were also



considered, but were excluded based on spectroscopic data. The OCH_2 ^{1}H and ^{13}C NMR shifts for compounds **4b-f** are 5.7-5.2 ppm and 68.4-66.6 ppm, respectively, while the same methylene signals of the *N*-alkylation and C^5-alkylation products would be found upfield. Subsequent intramolecular cyclization of compounds **4a-f** gives the target furo[2,3-*d*]pyrimidines **6a-f**; this was proven beyond doubt by X-ray crystallography of compound **6b** (Fig. 1).[18]

Figure 1. Crystal structure of compound **6b**.

3. Conclusion

In conclusion, an effective two-step protocol for the formation of 5-substituted furo[2,3-*d*]pyrimidine derivatives has been developed. The reactions proceed in moderate-to-good yields, and silica gel appears to be a good choice for preventing intermolecular interactions (thus the formation of side products and decomposition) for high temperature intramolecular reactions, when compared to the typical high boiling solvents or performing the reaction upon compound melting.

Acknowledgments

This work is a part of ongoing program "Synthesis and functionalization of fused pyrimidine heterocycles, study on heterocyclization reactions" (2015-2020). We would like to thank Dr. Audrius Bucinskas for X-ray crystal structure measurements and analysis.

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16. **General procedure for the synthesis of 2-methylthiopyrimidin-4(3*H*)-ones 4**. To a solution of 2-methylthiopyrimidin-4,6-dione (0.17 g, 1.07 mmol) in DMF (4 mL) sodium hydride 60% dispersion in oil (38 mg, 1.6 mmol) or potassium fluoride (57 mg, 0.97 mmol) was added and the mixture stirred for 1 h at room temperature. Then, H_2O (approximately 1.5 mL) was added to the reaction mixture until the pyrimidone salt completely dissolved. The reaction mixture was cooled to -10 °C and the corresponding methanesulfonate or 2-bromo-1-arylethanone (0.97 mmol) was added. The reaction mixture was left to reach r.t. and stirred for approximately 48 h (TLC monitoring of the alkylating agent). Water was added to the reaction mixture and the formed precipitate was filtered off, washed with water and recrystallized to give the target compound.
17. **General procedure for the synthesis of 2-methylthiofuro[2,3-*d*]pyrimidin-4(3*H*)-ones 6**. A mixture of the corresponding *O*-alkylated pyrimidone (1.1 mmol), silica gel (10 times the starting material in grams) and $CHCl_3$ (25 mL) was stirred for 0.5 h at room temperature. After solvent evaporation under reduced pressure, the flask with silica gel and starting material was placed in a Wood's metal bath preheated to 230-240 °C. The silica gel inside the flask was stirred until completion of cyclization reaction (approximately 1 h, TLC monitoring). The target product was isolated by eluting the reaction content through a layer of fresh silica gel (1-2 cm) using $CHCl_3$-EtOAc (9:1). The solvents were evaporated under reduced pressure and the residue recrystallized to afford the target furo[2,3-*d*]pyrimidines.
18. X-ray data (CCDC No. 1900559) can be obtained free of charge from the Cambridge Crystallographic Data Center.

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Highlights:

5-substituted furo[2,3-*d*]pyrimidines from pyrimidines and bifunctional electrophiles

Silica gel is a “solvent” of choice for intramolecular reactions at high temperature

Lactam-lactim tautomerism can be source of unaccounted carbons in ^{13}C NMR spectra