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# Mild and Catalyst-Free Microwave-Assisted Synthesis of 4,6-Disubstituted 2-Methylthiopyrimidines – Exploiting Tetrazole as an Efficient Leaving Group

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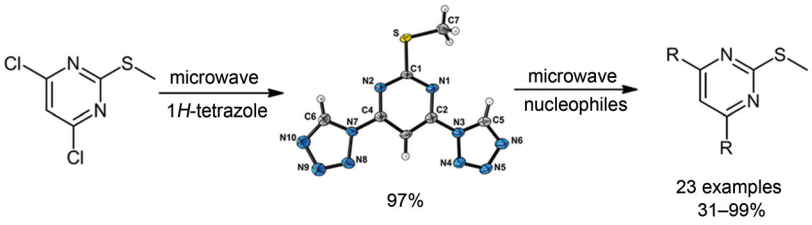


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**Abstract** Typically, 4,6-disubstituted 2-thiomethylpyrimidines are synthesized starting from 4,6-dichloro-2-thiomethylpyrimidine or an amino-substituted precursor. However, these reactions take several hours up to days and require multiple steps. Herein, we report a novel, easy, and quick-to-prepare synthetic intermediate, namely 2-(methylthio)-4,6-di(1*H*-tetrazol-1-yl)pyrimidine, for the synthesis of these interesting target compounds. The intermediate can be transformed within minutes into desired substituted pyrimidines under mild conditions with moderate to excellent yields. The reaction can be conducted in an automated microwave system, at room temperature or by conventional heating. Furthermore, we demonstrate the robustness of the method in a one-pot procedure.

**Keywords** tetrazole, pyrimidine, combinatorial chemistry, medicinal chemistry, nucleophilic aromatic substitution

Tetrazole moieties have drawn increasing attention by medicinal chemists as they can be exploited for the generation of bioactive small molecules.[1] In addition to their desirable physicochemical properties, these azoles display reasonable metabolic stability and can serve as bioisosteric replacements of carboxylic acids.[2] The family of 4,6-disubstituted pyrimidines and tetrazolyl-substituted pyrimidines is a prominent class of chemical scaffolds for the design of kynurenine-3-monooxygenase inhibitors,[3,4] c-Kit modulators,[5] herbicides,[6] Bmi-1 inhibitors,[7] kinase inhibitors,[8–10] cell protective agents,[11] antibacterials,[12–14] inhibitors of $NF_{\kappa}B$ DNA binding,[15] and corticotropin releasing hormone type 1 antagonists.[16] One well-reported step for the synthesis of these interesting target compounds proceeds via $S_NAr$ reaction conditions employing 4,6-dichloro-2-methylthiopyrimidine as a commercially available starting material. These conditions generally require reaction times between several hours and days to couple different nucleophiles to the 4- and 6-position of pyrimidine.[8,10,11,15–17] Interestingly, to directly decorate the pyrimidine core with a tetrazole substituent a novel method can be employed, which has recently been published by us.[18] Unfortunately, the developed protocol using different conditions failed to introduce a tetrazole moiety into the 6-chloro-*N*,*N*-dimethyl-2-(methylthio)pyrimidin-4-amine scaffold (see Table 1 in Supporting Information). We hypothesized that the electron-donating properties of the dimethylamine substituent in the 6-position drastically reduced the leaving-group properties of the chloro substituent at the 4-position. Consequently, we tried to synthesize 4-chloro-2-(methylthio)-6-(1*H*-tetrazol-1-yl)pyrimidine, but to our surprise the major product was compound **1**, substituted with two tetrazoles. NMR analysis revealed both tetrazoles to be attached in the same regioselectivity to the 2-thiomethylpyrimidine core. However, an unambiguous clarification of the structure was achieved by X-ray crystallography. The structure coordinates of compound **1** revealed that the tetrazole substituents were linked via N1 of the tetrazole scaffold (viz. N3 and N7 in Figure 1) to the 4- and 6-position of 2-thiomethylpyrimidine (C4 and C2 in Figure 1).

Moreover, when applying four equivalents of tetrazole instead of one, the reaction can be completed with almost quantitative yield (97%) within 10 minutes at 60 °C under microwave irradiation.[19] With regard to product yield, we could not determine any differences between thermal heating and microwave conditions (Table 1).

As microwave irradiation ensures a homogeneous and fast energy input, we consider this procedure the method-of-choice for facile and rapid generation of intermediate **1** (Scheme 1).

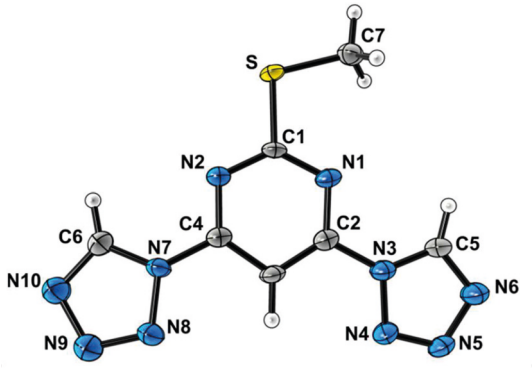
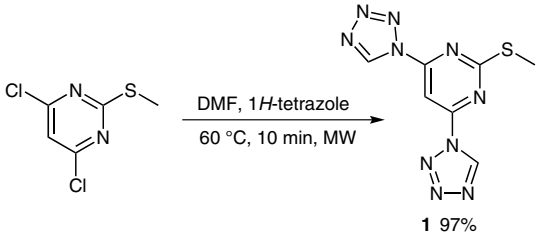



**Figure 1** X-ray crystal structure of **1** revealing the regiochemistry of attached tetrazol-1-yl substituents; blue = nitrogen, grey = carbon, yellow = sulfur, white = hydrogen

**Table 1** Conditions Used To Obtain 2-(Methylthio)-4,6-di(1*H*-tetrazol-1-yl)pyrimidine (**1**)[a]

| Method | Conditions | Yield (%) |
|---|---|---|
| Heating | DMF, 60 °C, $Et_3N$, 1*H*-tetrazole, 10 min | 95 |
| Microwave | DMF, 60 °C, $Et_3N$, 1*H*-tetrazole, 10 min | 97 |

[a] Conditions: 1 equiv of 4,6-dichloro-2-methylthiopyrimidine and 4 equiv of 1*H*-tetrazole were employed.

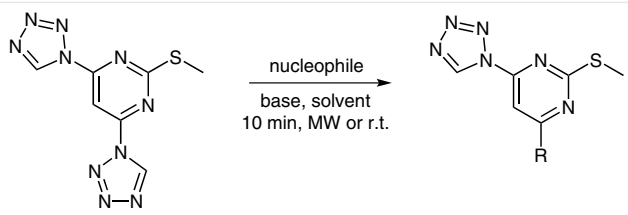



**Scheme 1** Reaction conditions to obtain compound **1**

Moreover, to investigate the applicability of our novel synthetic route for automated combinatorial synthesis we performed all reactions in an automated microwave system (Tables 2 and 3).

Inspired by a previously observed side reaction, we tested whether compound **1** could be an appropriate precursor for the synthesis of further 4,6-disubstituted target compounds. Indeed, di-tetrazolyl intermediate **1** could be successfully transformed into compound **2** under microwave irradiation by usage of one equivalent dimethylamine. In addition to the clean conversion, the reaction only needs 10 minutes for completion and, hence, is much faster than traditional approaches.[8,10,11,15–17] Moreover, due to its acidity,[20] the cleaved tetrazole can be directly removed from the reaction mixture by simple aqueous workup, making it a convenient leaving group. Thus, this method may be easily implemented in automated combinatorial chemistry approaches.

To test the scope of the reaction, we used different nitrogen-, oxygen-, and sulfur-containing nucleophiles (Scheme 2). For instance, alkyl (**2**, **3**), saturated and unsaturated heterocyclic amines (**6**–**9**), benzylamine (**5**), and unsubstituted amine (**4**) were successfully attached to the pyrimidine core yielding the substituted pyrimidines in moderate to excellent yields (Table 2) within minutes. Preliminary tests with aromatic amines, such as aniline, showed no conversion and are not suitable to be used in this reaction.




**Scheme 2** Generic reaction scheme for the generation of 6-substituted 4-(1*H*-tetrazol-1-yl)-2-thiomethylpyrimidines

The subset of oxygen-containing nucleophiles consisted of methanol, sodium hydroxide, sodium ethoxide, and phenol. With no exception, all hydroxyderivatives readily reacted with **1** to achieve the corresponding 6-substituted 4-(1*H*-tetrazol-1-yl)-2-thiomethylpyrimidines (**10**–**13**, Table 2). Notably, the methoxy group can be conveniently attached at room temperature under treatment with potassium carbonate in a methanol–THF mixture. 4-Hydroxypyrimidine is known to be a very weak acid ($pK_a$ = 8.59).[21] Thus, we were curious whether **10** also shows acidic character and conducted titration experiments to determine its $pK_a$. Indeed, **10** showed a $pK_a$ of 3.17 ± 0.05 which is about five orders of magnitude lower than the unsubstituted 4-hydroxypyrimidine. A plausible explanation for the increase in acidity could be the electron-withdrawing properties of the tetrazole and thiomethyl substituent with respective Hammett constants of $\sigma_{meta}^{tetrazole} = 0.52$ and $\sigma_{meta}^{thiomethyl} = 0.15$.[22]

To study the reactivity of **1** towards thiols, we used alkylmercaptans, benzylmercaptan, and thiophenols as reactants. All sulfur-containing nucleophiles were successfully introduced into the 2-thiomethylpyrimidine core in good to excellent yields (**13**–**19**, Table 2).

Notably, these results show that **1** is also able to react with sterically hindered (**15**, **20**), electron-poor (**18**), and electron-rich (**19**) nucleophiles demonstrating that the procedure can be used in automated robotic systems for one-pot combinatorial approaches. Furthermore, this protocol is a convenient approach for the synthesis of 6-substituted 4-(1*H*-tetrazol-1-yl)-2-thiomethylpyrimidines which we

**Table 2** Microwave-Assisted Synthesis of 6-Substituted 4-(1*H*-tetrazol-1-yl)-2-thiomethylpyrimidines **2**–**20**[a]

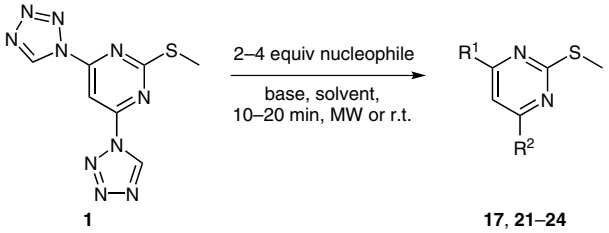
| Nucleophile | Product | R | Method | Yield (%) |
|---|---|---|---|---|
| dimethylamine | **2** | $NMe_2$ | DMF, $Et_3N$, 60 °C | 66 |
| methylamine | **3** | NHMe | DMF, $Et_3N$, 60 °C | 53 |
| ammonia[b] | **4** | $NH_2$ | DMF, $Et_3N$, 60 °C | 60 |
| benzylamine | **5** | NHBn | DMF, $Et_3N$, 60 °C | 80 |
| pyrrolidine | **6** | pyrrolidin-1-yl | DMF, $Et_3N$, 60 °C | 88 |
| morpholine | **7** | morpholin-1-yl | DMF, $Et_3N$, 60 °C | 95 |
| piperidine | **8** | piperidin-1-yl | DMF, $Et_3N$, 60 °C | 94 |
| imidazole | **9** | imidazol-1-yl | DMF, $Et_3N$, 60 °C | 63 |
| sodium hydroxide | **10** | OH | THF, $H_2O$, 60 °C | 70 |
| methanol (excess) | **11** | OMe | THF, $K_2CO_3$, r.t. | 85 |
| sodium ethoxide | **12** | OEt | EtOH, r.t. | 88 |
| phenol | **13** | OPh | DMF, $Et_3N$, 60 °C | 68 |
| ethylmercaptan | **14** | SEt | DMF, $K_2CO_3$, r.t. | 83 |
| *tert*-butylmercaptan | **15** | S*t*-Bu | DMF, $K_2CO_3$, r.t. | 82 |
| benzylthiol | **16** | SBn | DMF, $K_2CO_3$, r.t. | 79 |
| thiophenol | **17** | SPh | DMF, $K_2CO_3$, r.t. | 96 |
| 4-chlorothiophenol | **18** | S(4-$ClC_6H_4$) | DMF, $K_2CO_3$, r.t. | 99 |
| 4-methoxythiophenol | **19** | S(4-$MeOC_6H_4$) | DMF, $K_2CO_3$, r.t. | 84 |
| 2-methylthiophenol | **20** | S(2-$MeC_6H_4$) | DMF, $K_2CO_3$, r.t. | 85 |

[a] Except noted otherwise, a 1:1 stoichiometry of reactant and compound **1** was used. Reactions were carried out under microwave irradiation for 10 min.
[b] As a 7 N solution in MeOH.

could not obtain using a substituted chloro-substituted precursor (compare Table 1 and Table 1 in Supporting Information).

To investigate whether both tetrazole substituents can also be replaced in one pot, we used thiophenol, imidazole, and sodium methanolate as representative reactants (Scheme 3,Table 3).

In all three cases, the corresponding 4,6-homo-disubstituted 2-thiomethylpyrimidine compounds (**21**–**23**) were obtained within 10–20 minutes in near quantitative yields (except **24**, vide supra) which underlines the good leaving-




**Scheme 3** Reaction conditions of the one-pot procedure to replace both tetrazole substituents in **1** to obtain 4,6-homo- or 4,6-hetero-disubstituted 2-thiomethylpyrimidines

**Table 3** Microwave-Assisted One-Pot Synthesis of 4,6-Disubstituted 2-Thiomethylpyrimidines **17** and **21**–**24**[a]

| Nucleophile (equiv) | Product | $R^1$ | $R^2$ | Method | Yield (%) |
|---|---|---|---|---|---|
| thiophenol (1) | **17**[b] | 1*H*-tetrazol-1-yl | SPh | DMF, $Et_3N$, 20 min, 60 °C to r.t., 'one-pot' | 83 |
| methanolate (3) | **21** | MeO | MeO | MeOH, 60 °C | 96 |
| thiophenol (2) | **22** | SPh | SPh | DMF, $K_2CO_3$, 10 min, r.t. | 95 |
| imidazole (4) | **23** | imidazol-1-yl | imidazol-1-yl | DMF, $Et_3N$, 20 min, 80–100 °C | 99 |
| benzylamine (1) + thiophenol (1) | **24** | NBn | SPh | DMF, $Et_3N$, $K_2CO_3$, 20 min, 60–120 °C | 31 |

[a] Compound **1** was used as a starting material unless otherwise noted. In all reactions 1 equiv of starting material was treated with the equivalents of nucleophile indicated in brackets.
[b] For compound **17**, 4,6-dichloro-2-thiomethylpyrimidine was employed as starting material.

group properties of the tetrazolyl group (Scheme 3 and Table 3).

To study the robustness and broaden its applicability for combinatorial chemistry and with regard to the good overall yields we investigated if the reaction could also be used as a one-pot sequence to introduce two different substituents using intermediate **1** as starting material. Consequently, we used one equivalent of benzylamine and after 10 minutes of reaction time, we added one equivalent of thiophenol to replace the remaining tetrazole substituent from in situ prepared **5**. The hetero-4,6-disubstituted product **24** was successfully obtained in this one-pot, two-step reaction (Scheme 3 and Table 3).

To demonstrate the applicability for library synthesis and with respect to the excellent yield of **1**, we speculated whether the method could be also exploited for another one-pot procedure which directly starts from the commercially available chlorinated starting material. The idea was to charge the reaction with a nucleophile after **1** was formed in situ and apply 10 additional minutes of microwave irradiation to yield the final product. For this reaction, we chose thiophenol as a model reactant, and as expected, the two-step one-pot sequence showed complete conversion within 20 minutes, and **17** was isolated in high yield (Table 3). These model reactions clearly demonstrate the good leaving-group characteristics of the tetrazole group (fast to replace by nucleophiles and easy to remove from the reaction mixture) for $S_NAr$ reactions at 2-thiomethylpyrimidine cores. By this means, homo- and hetero-disubstituted compounds were easily prepared.

In this study, we have discovered a novel synthetic intermediate **1** for the rapid synthesis of 4,6-disubstituted 2-thiomethylpyrimidines which accepts a broad range of nucleophiles under microwave irradiation. Next to the wide scope of nucleophilic additions, precursor **1** is accessible via the same route in excellent yields and short time, therefore enabling one-pot generation of this ditetrazole intermediate and subsequent coupling of nucleophiles. A further advantage of our protocol is that the reactions can be carried out without the need of highly demanding experimental setups (no inert gas, no reactive reagents, no catalysts) in automated systems, thus making it an ideal candidate for chemical library synthesis of biologically relevant scaffolds. As the 2-position of the pyrimidines synthesized is substituted with thiomethyl moiety, all of the herein displayed compounds can be easily further modified towards the sulfone by simple oxidation using established general methods (i.e., oxone,[23], MCPBA,[24] or hydrogen peroxide[25]). In a subsequent reaction these 2-methylsulfones might then be reacted with various nucleophiles (i.e., amino,[26] thio,[27] and hydroxyl[28] derivatives) allowing access to an even broader chemical diversity.[29]

## Acknowledgment

We thank Michael Hoffmann for recording HRMS spectra and Volker Huch for the determination of the X-ray crystal structure of compound **1**. Many thanks go to Nadja Klippel for synthetic support.

## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560577.

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(19) **Experimental Procedure for the Synthesis of 2-(Methylthio)-4,6-di(1*H*-tetrazol-1-yl)pyrimidine (1)**
4,6-Dichloro-2-methylthiopyrimidine (195 mg, 1 equiv, 1.0 mmol) and 1*H*-tetrazole (280 mg, 4 equiv, 4.0 mmol) was dissolved in anhydrous DMF (3 mL). To the orange solution $Et_3N$ (580 µL,4 equiv, 4.0 mmol) was given, and the mixture was stirred in a capped vial for 10 min in a CEM Discover SP microwave at 60 °C and 50 W power. The reaction mixture was poured into $H_2O$, filtered, and washed with $H_2O$ to yield an off-white solid (yield: 255 mg, 0.97 mmol, 97%); mp 193 ± 3 °C (decomp.). UV-Vis (MeOH): 221, 236, 269, 320 nm. FT-IR: 3168, 3138, 3098, 2161, 1704, 1597, 1563, 1539, 1466, 1446, 1432, 1416, 1403, 1330, 1316, 1307, 1284, 1248, 1189, 1170, 1101, 1092, 1073, 1004, 990, 951, 937, 881, 846, 824, 791, 758, 710, 681, 659 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 10.51 (s, 2 H), 8.24 (s, 1 H), 2.77 (s, 3 H) ppm. $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 174.1, 154.9, 142.5, 142.4, 95.8, 14.2 ppm. ESI-MS: *m/z* = 235.1 $[M + H - N_2]^+$, 207.1 $[M + H - 2N_2]^+$. HRMS: *m/z* calcd: 263.05704; found: 263.05688 $[M + H]^+$. CCDC 1052351 contains the supplementary crystallographic data for this paper. 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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(29) Caution: High-nitrogen-content compounds are known to be unstable. Although we experienced no difficulties in handling these compounds, all experiments were performed on a small scale (0.4–1.0 mmol) and with best safety precautions (e.g., gloves, protective eyewear, shield).