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# Facile and efficient synthesis of 5, 7-disubstituted thiazolo [5,4-*d*] pyrimidine-4, 6 (5*H*, 7*H*)-diones

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**Abstract**

A facile and efficient approach was developed to access 5, 7-disubstitued thiazolo[5,4-*d*]pyrimidine-4, 6(5*H*, 7*H*)-diones through condensation of *N*-substituted 5-amino-4-carbethoxythiazole with structurally diverse isocyanates in the presence of sodium hydride. The easy availability of substrates and tolerance of structural diversity in this reaction make it attractive to be used for construction of libraries in drug discovery process.



*Keywords:* Thiazolo[5,4-*d*]pyrimidine-4; 6(5*H*; 7*H*)-dione; Isocyanate; Isothiocyanate; Sodium hydride

Thiazolo[5,4-*d*] pyrimidine-4, 6(5*H*, 7*H*)-diones are of great medicinal interest since it can be considered as a bioisostere of adenine, guanine and xanthine which are the important physiological active molecules. By now, only a few examples have been reported on the preparation and properties of thiazolo[5,4-*d*] pyrimidine-4, 6(5*H*, 7*H*)-dione derivatives. It has been demonstrated that thiazolo[5,4-*d*] pyrimidines can act as antagonists of the vanilloid-1 receptor for the treatment of pain [1] and inhibitors of PI3K for the treatment of cancer [2]. Several methods of preparation of thiazolo[5,4-*d*]pyrimidine-4,6(5*H*, 7*H*)-diones have been developed starting either from uracil [3,4], or from 4, 5-disubstituted thiazole derivatives [5,6]. To our best knowledge, only the synthesis of 5,7-dimethyl thiazolo[5,4-*d*]pyrimidine-4, 6(5*H*, 7*H*)-dione was reported from 1,3-dimethyl uracil [7–9]. However, no examples have been presented about the synthesis of other 5,7-disubstituted thiazolo[5,4-*d*]pyrimidine-4, 6(5*H*, 7*H*)-dione analogs. Herein, we wish to present an efficient and concise approach for construction of 5,7-disubstituted thiazolo [5,4-*d*]pyrimidine-4, 6(5*H*, 7*H*)-dione derivatives using ethyl 5-aminothiazole-4-carboxylate as starting materials in details.

The synthetic strategy of 5,7-disubstituted thiazolo[5,4-*d*] pyrimidine-4, 6(5*H*, 7*H*)-dione derivatives was shown in Scheme 1. Starting from ethyl 5-aminothiazole-4-carboxylate **1**, which was prepared from ethyl 2-cyano-2-(hydroxyimino)acetate in three steps according to the literature method [10–13], the reductive amination reaction was successfully performed with different aldehydes or ketones in the presence of trifluoroacetic acid and sodium triacetoxyborohydride, thus providing the *N*-alkylated intermediates **2** in good yields. Upon treatment of 1.0

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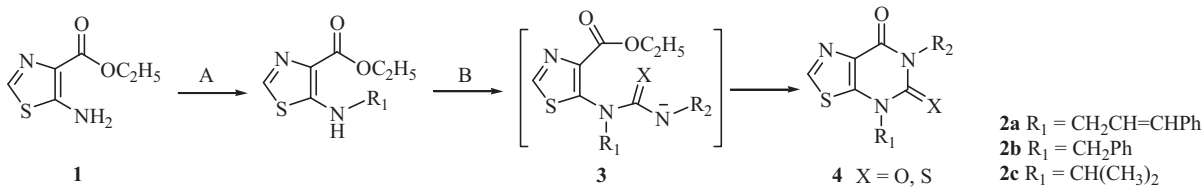



Scheme 1. Reagents and conditions: (A) $R_1CHO$, $NaBH(OAc)_3$, TFA, THF; (B) $R_2NCO$ or $R_2NCS$, NaH, THF.

equivalent of *N*-substituted 4-amino-5-carbethoxythiazoles **2** with 3.0 equivalents of NaH for 30 min, followed by reacted with 2.0 equivalents of isocyanates or isothiocyanates, the final products thiazolo[5,4-*d*]pyrimidine-4, 6(5*H*, 7*H*)-diones (**4a**–**4k, 4n**–**4r**) or thiazolo[5,4-*d*]pyrimidine-4(5*H*)-one-6(7*H*)-thione (**4l** and **4m**) were obtained within 1 h in moderate to excellent yields (49–96%) as shown in Table 1.

Table 1
Condensation of *N*-substituted 5-amino-4-carbethoxythiazoles **2** with various isocyanates or isothiocyanates.[a]

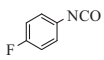
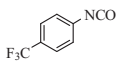
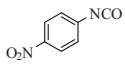
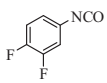
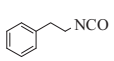
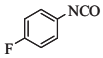
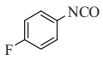
| Entry | Compound | $R_1$ | $R_2NCO/R_2NCS$ | Time (min) | Yield (%)[b] | Mp (°C) |
|---|---|---|---|---|---|---|
| 1 | **4a** | $CH_2CH{=}CHPh$ |  | 10 | 73 | 186–187 |
| 2 | **4b** | $CH_2CH{=}CHPh$ |  | 50 | 85 | 112–113 |
| 3 | **4c** | $CH_2CH{=}CHPh$ |  | 10 | 83 | 96–97 |
| 4 | **4d** | $CH_2CH{=}CHPh$ |  | 10 | 78 | 182–183 |
| 5 | **4e** | $CH_2CH{=}CHPh$ |  | 10 | 62 | 208–209 |
| 6 | **4f** | $CH_2CH{=}CHPh$ |  | 40 | 60 | 108–109 |
| 7 | **4g** | $CH_2CH{=}CHPh$ |  | 6 | 69 | 108–109 |
| 8 | **4h** | $CH_2CH{=}CHPh$ |  | 40 | 71 | 114–115 |
| 9 | **4i** | $CH_2CHCHPh$ |  | 40 | 77 | 108–109 |
| 10 | **4j** | $CH_2CH{=}CHPh$ |  | 10 | 76 | 147–148 |
| 11 | **4k** | $CH_2CH{=}CHPh$ |  | 15 | 83 | 185–186 |
| 12 | **4l** | $CH_2CHCHPh$ |  | 6 | 63 | 115–116 |
| 13 | **4m** | $CH_2CH{=}CHPh$ |  | 15 | 49 | 246–247 |

Table 1 (*Continued*)

| Entry | Compound | $R_1$ | $R_2NCO/R_2NCS$ | Time (min) | Yield (%)[b] | Mp (°C) |
|---|---|---|---|---|---|---|
| 14 | **4n** | $CH_2CH{=}CHPh$ |  | 15 | 68 | 232–233 |
| 15 | **4o** | $CH_2Ph$ |  | 5 | 70 | 221–222 |
| 16 | **4p** | $CH_2Ph$ |  | 50 | 62 | 235–236 |
| 17 | **4q** | $CH(CH_3)_2$ |  | 10 | 96 | 103–104 |
| 18 | **4r** | $CH(CH_3)_2$ |  | 10 | 65 | 105–106 |

[a] All reactions were carried out in THF at room temperature in the presence of NaH.
[b] Isolated yields after silica gel column chromatography.

It was suggested that in the presence of NaH, compound **2** was condensed with isocyanates or isothiocyanates to generate the urea anion **3**, which was ready for the nucleophilic attack at the ethyloxycarbonyl group on the thiazole ring, giving rise to the target compounds (**4a**–**4r**) after aqueous workup. It has been demonstrated that the use of NaH was necessary to initiate the reaction due to the weak nucleophilicity of nitrogen on thiazole fragment. In the absence of NaH, the same reaction did not take place at all.

In order to extend the scope of this reaction, a number of aldehydes, isocyanates and isothiocyanates were utilized. Initially, cinnamaldehyde was chosen for the introduction of $R_1$ substituent using the determined reductive amination based on the purpose of our ongoing drug discovery project. The resulting intermediate **2a** was subjected to reaction with electron-poor (entries **1**–**6**) or electron-rich (entries **7**–**9**) aromatic isocyanates or alkyl isocyanates (entries **10**–**11**) providing the corresponding thiazolo[5,4-*d*]pyrimidine-4, 6(5*H*, 7*H*)-diones (**4a**–**4k**) in moderate to high yields (60–85%). While isothiocyanates (entries **12**–**13**) were condensed with compound **2a** to produce the corresponding thiazolo[5,4-*d*]pyrimidine-4(5*H*)-one-6(7*H*)-thiones (**4l** and **4m**) in somewhat low yields (63% and 49%) in comparison with those of compounds **4h** and **4g** mainly due to the lower electrophilicity of isothiocyanates. In addition to the cinnamaldehyde, benzaldehyde and acetone were employed to broaden $R_1$ substituent. The benzyl and isopropyl substituted compounds **2b** and **2c** underwent condensation with isocyanates smoothly and afforded the corresponding products **4n**–**4r** in yields from 62% to 96%.

In summary, a concise and efficient protocol was developed for the synthesis of 5,7-disubstitued thiazolo[5,4-*d*] pyrimidine-4, 6(5*H*, 7*H*)-diones or 5,7-disubstitued thiazolo[5,4-*d*]pyrimidine-4(5*H*)-one-6(7*H*)-thiones. This approach was well tolerated to structurally diverse substrates such as aldehydes, ketones, aromatic isocyanates, alkyl isocyanates and isothiocyanates. Therefore, it could be used to construct a library of thiazolo[5,4-*d*]pyrimidine-4, 6(5*H*, 7*H*)-diones featuring a great deal of structural diversity. Further exploration of this method to our drug discovery program is in progress.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2012.04.007.

## References

[1] B. Tracy, B.R. Elizabeth, WO 2006100520 A1, 2006-09-28.
[2] C. Georgettem, G. Janetl, WO 2009042607 A1, 2009-04-02.
[3] S.J. Childress, R.L. McKee, J. Am. Chem. Soc. 73 (1951) 3862.
[4] C.L. Schmidt, L.B. Townsend, J. Org. Chem. 40 (1975) 2476.
[5] M. Sekiya, Y. Osaki, Chem. Pharm. Bull. 13 (1965) 1319.
[6] L.C. Seok, L.T. Hee, WO 2010027236 A2, 2010-03-11.
[7] K. Senga, M. Ichiba, H. Kanazawa, J. Heterocycl. Chem. 19 (1982) 77.
[8] T. Itoh, Y. Tomii, T. Naitoh, Chem. Pharm. Bull. 37 (1989) 2197.
[9] K. Senga, J. Sato, S. Nishigaki, Chem. Pharm. Bull. 3 (1978) 765.
[10] B. Bernd, C. Simonam, US 2006160857 A1, 2006-07-20.
[11] J.B. Holtwick, B. Golankiewicz, B.N. Holmes, J. Org. Chem. 44 (1979) 3835.
[12] P.P. Kung, J.J. Meng, WO 2008059368 A2, 2008-05-22.
[13] The synthetic procedure and structure identification about compounds **2a**–**2c** and **4a**–**4r** are available in supporting information. All synthesized products were characterized by $^{1}$H NMR and ESI-HRMS. For example, compound **4h**: light yellow solid; $^{1}$H NMR (400 MHz, Acetone-$d_6$): $\delta$ 8.74 (s, 1H), 7.48 (d, 2H, $J$ = 7.6 Hz), 7.32–7.40 (m, 3H), 7.27 (t, 2H, $J$ = 7.2 Hz), 7.15 (d, 2H, $J$ = 7.2 Hz), 6.88 (d, 1H, $J$ = 16.0 Hz), 6.35–6.40 (dt, 1H, $J_1$ = 16.0 Hz, $J_2$ = 6.0 Hz), 4.87 (d, 2H, $J$ = 6.0 Hz), 2.38 (s, 3H); $^{13}$C NMR (100 MHz, Acetone-$d_6$): $\delta$ 157.57, 151.72, 151.25, 146.08, 139.43, 137.33, 137.01, 135.45, 131.82, 130.33, 129.69, 129.48, 128.92, 127.38, 126.84, 122.27, 52.37, 21.16; HRMS (ESI): calcd. for $C_{21}H_{18}N_3O_2S$ [M+1] 376.1114, found 376.1099.