http://dx.doi.org/10.5012/bkcs.2013.34.12.3677

Novel Tri- and Tetra-substituted Pyrimido[4,5-*d*]pyridazines: Regiospecific Synthesis Catalyzed by Silica Supported Yttrium Trinitrate

Bahador Karami,* Sedigheh Akrami, and Saeed Khodabakhshi

*Department of Chemistry, Yasouj University, Yasouj, Iran, Zip Code: 75918-74831. *E-mail: karami@mail.yu.ac.ir*
Received June 13, 2013, Accepted September 20, 2013

Novel tri- and tetra-substituted pyrimido[4,5-*d*]pyridazines-2(1*H*,3*H*,7*H*)-ones have been synthesized *via* the regiospecific condensation reaction of hydrazine derivatives with 5-acetyl-4-aryloyl-6-methyl-3,4-dihydropyrimidinones in the presence of SiO_2-$Y(NO_3)_3$ as a green and recyclable catalyst under solvent-free conditions. All products were obtained in high yields and short reaction time. Employing this method is in accord with green chemistry principles.

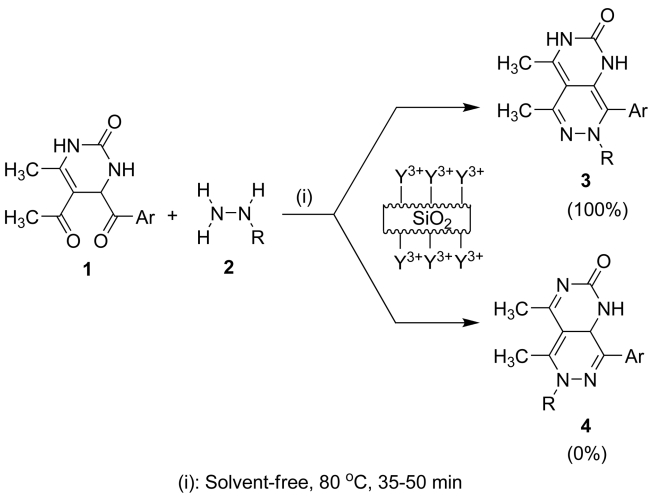
Key Words : Pyrimido[4,5-*d*]pyridazines, Silica supported yttrium trinitrate, Hydrazine, Solvent-free

Introduction

Pyrimidines and pyridazines have been known for chemists[1,2] and functionalized pyrimidopyridazines are known in the recent years to attract much attention due to their importance in biological and pharmaceutical research.[3-5] Several reports on synthesis and biological evaluation of pyrimido[4,5-*d*]pyridazine-8(7*H*)-ones are available in the literature.[6-8]

Activation of carbonyls towards attack by nitrogen nucleophiles such as amines, amides, and ureas is an important C-N bond-forming reaction.[9-11] In this direction, some workers synthesized a number of heterocyclic compounds, but, to the best of our knowledge, no reaction of 5-acetyl-4-aryloyl-6-methyl-3,4-dihydropyrimidinones with hydrazine derivatives has been previously reported. In view of the above observations and as a continuation of our ongoing programs directed to the synthesis of heterocyclic compounds[12-14] and catalyzed organic reactions,[15-17] we report herein, the synthesis of some new tri- and tetra-substituted pyrimido[4,5-*d*]pyridazines-2(1*H*,3*H*,7*H*)-ones **3** by using 5-acetyl-4-aryloyl-6-methyl-3,4-dihydropyrimidinones **1** and various hydrazines **2** as starting materials in the presence of immobilized yttrium trinitrate on silica gel as a safe and recyclable catalyst under solvent-free conditions (Scheme 1).

These reactions are regiospecific, therefore, gave only compounds **3** rather than compounds **4**.

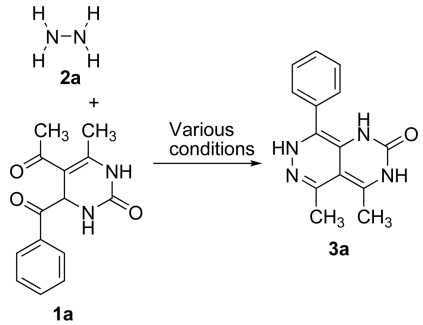


Scheme 1. Regiospecific synthesis of tri- and tetra-substituted pyrimido[4,5-*d*]pyridazines-2(1*H*,3*H*,7*H*)-ones.

Results and Discussion

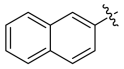
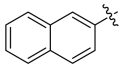
In order to optimize the reaction conditions for the synthesis of compounds **3**, the reaction of 5-acetyl-4-benzoyl-6-methyl-3,4-dihydropyrimidinone **1a** with hydrazine **2a** was selected as a model (Scheme 2). We found that in the absence of the catalyst, the reaction did not complete, even for a long reaction time at high temperature. Through screening, we found that this reaction was completed with SiO_2-$Y(NO_3)_3$ (0.05 g) under solvent-free conditions at 80 ºC.

To test the generality of the reaction, this thermal and solvent-free procedure was employed for similar substrates in the presence of SiO_2-$Y(NO_3)_3$. The results have been shown in Table 1. In regard of thin layer chromatography experiments during the reaction progresses, we found that only one regioisomer has been formed. The regiospecificity of these reactions was also proved by NMR spectroscopy. For example, the ^{1}H NMR (DMSO, 400 MHz) spectrum of



Scheme 2. Optimization of the reaction conditions in the synthesis of compound **3a**.

Table 1. Synthesis of tri- and tetra-substituted pyrimido[4,5-*d*]pyridazines using SiO_2-Y(III) under solvent-free conditions

Product	Ar	R	Yield[a] (%)	Time (min)	mp (°C)
3a	C_6H_5	H	85	45	308-310
3b	C_6H_5	C_6H_5	85	45	313-315
3c	C_6H_5	2,4-$(NO_2)_2$-C_6H_3	80	40	313-315
3d	4-Cl-C_6H_4	H	85	45	220-222
3e	4-Cl-C_6H_4	C_6H_5	85	35	215-217
3f	4-Cl-C_6H_4	2,4-$(NO_2)_2$-C_6H_3	85	35	224-226
3g	4-NO_2-C_6H_4	H	85	45	258-260
3h	4-NO_2-C_6H_4	C_6H_5	85	45	275-277
3i	4-Br-C_6H_4	C_6H_5	85	35	212-214
3j		H	80	50	290-292
3k		C_6H_5	80	45	215-217

[a]Refers to isolated yields.

3b exhibited two sharp singlets identified as two methyl protons (δ 2.05, 2.08). The multiplets (δ 7.15-7.55) corresponding to the protons of the two phenyl groups. The protons of NH groups also appeared as two distinct signals at δ 10.23 and δ 10.64. The proton decoupled ^{13}C NMR spectrum of **3b** showed 16 distinct resonances in agreement with the proposed structure. The disappearance of the signal for methine hydrogen can prove that the compounds **4** have not been formed.

The nature of R and Ar groups showed no significant effect on the yield or reaction rate. Minimizing catalyst loss and avoidance of organic solvents during chemical reactions requires a fundamental understanding of green chemistry factors. These concepts provide direction for improvements in organic synthesis and finishing of environmental and economic concerns. The advantages of solvent-free procedures include cost savings, reduced energy consumption, decreased reaction time, and a considerable reduction in reactor size and, therefore, capital investment. These attributes have inspired a substantial research effort directed toward the development of solvent-free reactions.[18-20] Supported catalysts are interesting alternatives for the common metallic Lewis acids since the immobilization of metal on an inert solid matrix minimizes the explosion hazard, allows the design of continuous flow processes, and simplifies both the isolation of the reaction products and reagents.[21-24] A practical test of the recyclability of the catalyst was also examined for the model reaction. In this process, the catalyst was recycled and reused for three cycles during which a little appreciable loss was observed in the catalytic activities.

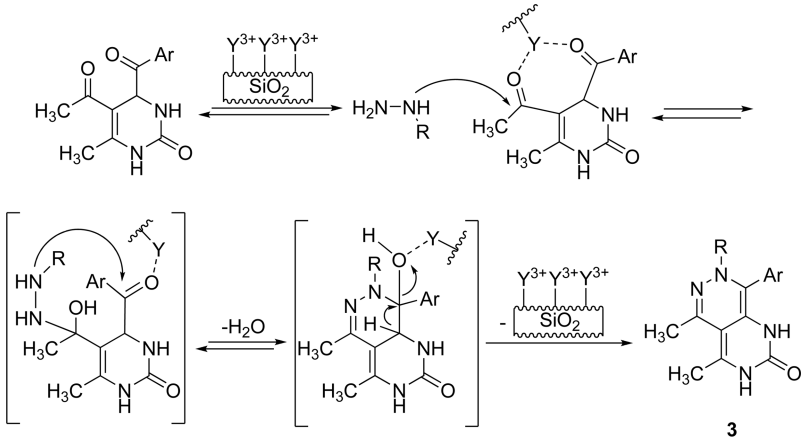
On the basis of the general mechanistic pathway for the formation of tri- and tetra-substituted pyrimido[4,5-*d*]pyridazines **3**, the yttrium (III) firstly acts as an efficient Lewis acid and activates the d-dicarbonyl through chelation, thus, the energy of the transition state decreases and the rate of the nucleophilic displacement increases. After nuclephilic attack of the hydrazine to the activated carbonyls and dehydration, the final products **3** would be formed.

Experimental

General. Chemicals were purchased from Merck and Aldrich. Dihydropyrimidinones **1** were prepared according to previous report.[9] The reactions were monitored by TLC (silica gel 60 F_{254}, hexane/EtOAc). IR spectra were recorded on a FT-IR JASCO-680 and the NMR spectra were obtained on a Bruker-Instrument DPX-400 MHz Avance III model. The varioEl CHNS Isfahan Industrial University was used for elemental analysis.

Preparation of Catalyst. The grafted silica gel (4 g) was stirred with yttrium nitrate hexahydrate (0.766 g, 0.2 mmol) in $CHCl_3$ (10 mL) which was heated under reflux conditions for 2 h. The mixture was then filtered, washed thoroughly with chloroform (3 × 10 mL), and the obtained catalyst was dried.

Preparation of Pyrimido[4,5-*d*]pyridazines 3. A mixture of **1** (1 mmol), **2** (1 mmol) and SiO_2-Y$(NO_3)_3$ (0.05 g) was stirred and heated at 80 °C in a preheated oil bath for an appropriate time (Table 1). After completion of the reaction as indicated by TLC (EtOAc/hexane, 1:4), the reaction mixture was dissolved in hot EtOH and catalyst was separated



Scheme 3. Suggested mechanism for the formation of tri- and tetra-substituted pyrimido[4,5-*d*]pyridazines **3**.

by filtration. The solvent was removed under vacuum and the products **3** were purified by recrystallization in EtOH.

4,5-Dimethyl-8-phenylpyrimido[4,5-*d*]pyridazin-2(1*H*, 3*H*,7*H*)-one (3a): Pale yellow solid, IR (KBr): 3300-3500, 3030-3075, 2995, 2990, 2890, 1690, 1650, 1490, 1100 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.41 (s, 1H), 10.64 (s, 1H), 10.19 (s, 1H), 7.14 (dd, 1H, J = 8.4, 4.4 Hz), 7.24 (d, 4H, J = 4 Hz), 1.97 (s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 154.88, 147.17, 138.58, 131.11, 128.90, 126.43, 124.62, 118.57, 111.71, 107.34, 12.80, 10.19; Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.25; H, 4.89; N, 23.56.

4,5-Dimethyl-7,8-diphenylpyrimido[4,5-*d*]pyridazin-2(1*H*,3*H*,7*H*)-one (3b): Light yellow solid, IR (KBr): 3300-3500, 3030-3075, 2995, 2990, 2890, 1690, 1650, 1490, 1100 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.64 (s, 1H), 10.23 (s, 1H), 7.55-7.50 (m, 4H), 7.43-7.36 (m, 1H), 7.31-7.27 (m, 4H), 7.18-7.15 (m, 1H), 2.08 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 154.72, 148.09, 139.75, 138.80, 130.90, 129.72, 129.05, 129.05, 127.85, 126.69, 124.81, 124.56, 119.31, 110.78, 110.76, 12.72, 11.97; Anal. Calcd. for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 71.98; H, 5.23; N, 17.90.

8-(4-Chlorophenyl)-7-(2,4-dinitrophenyl)-5-methylpyrimido[4,5-*d*]pyridazin-2(1*H*,3*H*,7*H*)-one (3f): Light yellow solid, IR (KBr): 3420, 1689, 1545, 1504, 1382, 1345 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.66 (s, 1H), 10.17 (s, 1H), 7.91-7.84 (m 3H), 7.41-7.35 (m, 4H), 1.94 (s, 6H) cm^{-1}; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 154.04, 147.44, 144.50, 136.78, 136.32, 136.10, 133.00, 132.61, 129.21, 127.57, 124.29, 124.18, 115.20, 109.51, 12.21, 11.43 cm^{-1}; Anal. Calcd. for $C_{19}H_{13}ClN_6O_5$: C, 51.77; H, 2.97; N, 19.07. Found: C, 51.91; H, 2.90; N, 18.98.

4,5-Dimethyl-8-(4-nitrophenyl)-7-phenylpyrimido[4,5-*d*]pyridazin-2(1*H*,3*H*,7*H*)-one (3h): Orange solid, IR (KBr): 3462, 1686, 1593, 1512, 1330 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.92 (d, 1H, J = 1.6 Hz), 10.63 (d, 1H, J = 1.6 Hz), 8.17 (d, 2H, J = 8.8 Hz), 7.57-7.50 (m, 6H), 7.46-7.42 (m, 1H), 2.10, 2.09 (two s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 154.04, 147.44, 14.50, 139.10, 138.61, 136.78, 129.20, 127.57, 124.59, 127.19, 117.31, 115.22, 109.50, 121.22, 11.46; Anal. Calcd. for $C_{20}H_{17}N_5O_3$: C, 63.99; H, 4.56; N, 18.66. Found: C, 64.10; H, 4.45; N, 18.61.

8-(4-Bromophenyl)-4,5-dimethyl-7-phenylpyrimido[4,5-*d*]pyridazin-2(1*H*,3*H*,7*H*)-one (3i): Pale orange solid, IR (KBr): 3415, 1689, 1504, 1382 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.64 (d, 1H, J = 2 Hz), 10.18 (s, 1H), 7.84-7.70 (m, 5H), 7.47-7.44 (m, 3H), 7.26-7.24 (m, 1H), 1.97 (s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 193.23, 154.21, 133.01, 131.21, 128.23, 127.68, 127.44, 126.46, 125.53, 122.76, 122.10, 117.98, 112.03, 106.89, 72.23, 60.20; Anal. Calcd. for $C_{20}H_{17}BrN_4O$: C, 58.69; H, 4.19; N, 13.69. Found: C, 58.89; H, 4.02; N, 13.63.

4,5-Dimethyl-8-(naphthalen-2-yl)pyrimido[4,5-*d*]pyridazin-2(1*H*,3*H*,7*H*)-one (3j): Yellow solid, IR (KBr): 3400, 330, 1690, 1505, 1384 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.65 (d, 1H, J = 1.6 Hz), 10.29 (s, 1H, J = 1.6 Hz), 7.53-7.48 (m, 6H), 7.44-7.40 (m, 1H), 2.06, 2.05 (two s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 154.08, 147.48, 139.18, 138.28, 131.50, 129.60, 129.20, 127.41, 126.16, 124.12, 118.92, 117.73, 111.27, 109.89; Anal. Calcd. for $C_{18}H_{16}N_4O$. Found: C, 71.04; H, 5.30; N, 18.41. Found: C, 71.25; H, 5.15; N, 18.33.

Conclusion

In summary, a novel method was developed for the regiospecific synthesis of novel tri- and tetra-substituted pyrimido[4,5-*d*]pyridazines *via* a solvent-free reaction of hydrazine derivatives and 5-acetyl-4-aryloyl-6-methyl-3,4-dihydropyrimidinones under silica supported yttrium (III) catalyzed conditions. The important factors such as the use of a small amount of an environmentally friendly catalyst and avoidance of organic solvents are in accord with green chemistry principles which in this work have been fully considered. It is worthwhile to note that the presence of transformable functionalities in the products makes them potentially valuable for further synthetic manipulations.

Acknowledgments. This work was supported by Yasouj University and we are grateful. And the publication cost of this paper was supported by the Korean Chemical Society.

References

1. Singh, K.; Arora, D.; Singh, K.; Singh, S. *Mini. Rev. Med. Chem.* **2009**, *9*, 95.
2. Dawood, K. M.; Kandeel, Z. E.; Farag, A. M. *Heteroatom Chem.* **1999**, *10*, 417.
3. Giovannoni, M. P.; Vergelli, C.; Cilibrizzi, A.; Crocetti, L.; Biancalani, C.; Graziano, A.; Piaz, V. D.; Loza, M. I.; Cadavid, M. I.; Diaz, J. L.; Gavalda, A. *Bioorg. Med. Chem. Lett.* **2010**, *18*, 7890.
4. Feixas, J.; Giovannoni, M. P.; Vergelli, C.; Gavaldà, A.; Cesari, N.; Graziano, A.; Dal Piaz, V. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2381.
5. Stanovnik, B.; Tisler, M. *Tetrahedron Lett.* **1968**, *9*, 33.
6. Distefano, L.; Castle, R. N. *J. Heterocycl. Chem.* **1968**, *5*, 845.
7. Turbiak, A. J.; Kampf, J. W.; Showalter, H. D. H. *Tetrahedron Lett.* **2010**, *51*, 1326.
8. Rosa, F. A.; Machado, P.; Fiss, G. F.; Vargas, P. S.; Fernandes, T. S.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. *Synthesis* **2008**, 3639.
9. Karami, B.; Haghighijou, Z.; Farahi, M.; Khodabakhshi, S. *Phosphorus Sulfur Silicon Relat. Elem.* **2012**, *187*, 754.
10. Karami, B.; Khodabakhshi, S.; Nikrooz, M. *Polycyclic. Aromat. Compd.* **2011**, *31*, 97.
11. Karami, B.; Khodabakhshi, S.; Hashemi, F. *Tetrahedron Lett.* **2013**, *54*, 3583.
12. Karami, B.; Khodabakhshi, S.; Eskandari, K. *Tetrahedron Lett.* **2012**, *53*, 1445.
13. Karami, B.; Eskandari, K.; Khodabakhshi, S. *Arkivoc* **2012**, *(ix)*, 76.
14. Karami, B.; Farahi, M.; Khodabakhshi, S. *Helv. Chim. Acta* **2012**, *95*, 455.
15. Karami, B.; Hoseini, S. J.; Eskandari, K.; Ghasemi, A.; Nasrabadi, H. *Catal. Sci. Technol.* **2012**, *2*, 331.
16. Karami, B.; Ghashghaee, V.; Khodabakhshi, S. *Catal. Commun.* **2012**, *20*, 71.
17. Karami, B.; Khodabakhshi, S.; Safikhani, N.; Arami, A. *Bull. Korean Chem. Soc.* **2012**, *33*, 754.

18. Jeon, S.-J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416.
19. Karami, B.; Khodabakhshi, S.; Vahabinia, H. R. *Heterocyles* **2013**, *87*, 399.
20. Khodabakhshi, S.; Karami, B. *Catal. Sci. Technol.* **2012**, *2*, 1940.
21. Mello, R.; Alcalde-Aragoneìs, A.; Gonzalez Nunez, M. E.; Asensio, G. *J. Org. Chem.* **2012**, *77*, 6409.
22. Khalafi-Nezhad, A.; Panahi, F. *Green. Chem.* **2011**, *13*, 2408.
23. Pourmousavi, S. A.; Kazemi, S. S. *Monatsh. Chem.* **2012**, *143*, 917.
24. (a) Karami, B.; Montazerozohori, M.; Karimipour, G. R.; Habibi, M. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 1431. (b) Karami, B.; Montazerozohori, M.; Habibi, M. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 1125.