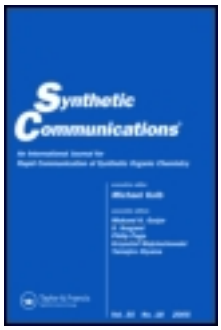


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

One-Pot Synthesis of Novel 2-(Thiazol-2-yl)-4,5-dihydropyridazin-3(2H)-one Derivatives Catalyzed by Activated KSF

Nosrat O. Mahmoodi [a], Niloufar Safari [a] & Bahman Sharifzadeh [a]

[a] Department of Chemistry, Faculty of Sciences, University of Guilan, Iran

Accepted author version posted online: 27 Aug 2013.

To cite this article: Synthetic Communications (2013): One-Pot Synthesis of Novel 2-(Thiazol-2-yl)-4,5-dihydropyridazin-3(2H)-one Derivatives Catalyzed by Activated KSF, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, DOI: 10.1080/00397911.2013.801077

To link to this article: http://dx.doi.org/10.1080/00397911.2013.801077

One-pot synthesis of novel 2-(thiazol-2-yl)-4,5-dihydropyridazin-3(2*H*)-one derivatives catalyzed by activated KSF

Nosrat O. Mahmoodi[1], Niloufar Safari[1], Bahman Sharifzadeh[1]

[1]Department of Chemistry, Faculty of Sciences, University of Guilan, Iran

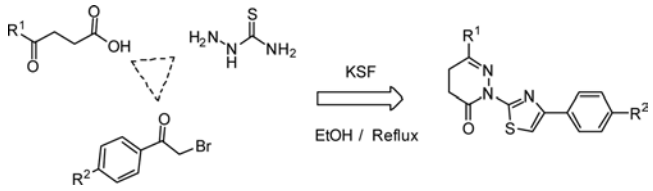
, E-mail: mahmoodi@guilan.ac.ir

Abstract

A series of 2-(thiazol-2-yl)-4,5-dihydropyridazin-3(2H)-one derivatives were synthesized by one-pot multicomponent cyclocondensation of ketoacid, thiosemicarbazide and phenacyl bromide using catalytical amount of KSF in EtOH under reflux. The straightforward synthesis, presence of two important class of heterocyclic rings in individual molecule, easy work-up of the products, rapid reaction, mild conditions and providing the title compounds in good to high yields are notable features of this protocol. [Supplementary materials are available for this article. Go to the publisher's online

edition of *Synthetic Communications*® for the following free supplemental resource(s):

Full experimental and spectral details.]



KEYWORDS: 2-(Thiazol-2-yl)-4,5-dihydropyridazin-3(2H)-one, Pyridazinone,

Thiazole, Regioselective, KSF, Multicomponent

INTRODUCTION

Properties of pyridazinone derivatives have been extensively studied and many of them display important pharmacological properties, including antihypertensive, antidepressant, antibacterial, anti HIV and anticancer [1-5]. Recently some drugs containing pyridazinone derivatives like levosimendan, [6] azanrinone, [7] emorfazone, [8] primobendan, [9]

minaprine, [10] indolidan [11] and bemoradan [12] is employing widely in the medical market.

One of the other most important moieties are thiazole derivatives that have effective function in treatment of allergies, [13] hypertension, [14] inflammation, [15] schizophrenia, [16] bacterial, [17] HIV infections [18] and hypnotics [19].

Literature survey shows that one pot synthesized of compounds with two rings containing thiazole and pyridazinone has not yet been reported. Recently, we report the synthesis of pyridazinone derivatives in the presence of montmorillonite KSF and via one pot multicomponent reaction [20] and have been announced new methods for synthesis of novel heterocyclic ring as pioneer in drug compounds [21-26].

RESULTS AND DISCUSSION

In this protocol, we explain an efficient method for the regioselective synthesis of new thiazolyl-pyridazinone derivatives **4a**–**l** via a one-pot three-component reaction. Using an equimolar mixture of ketoacid **1**, thiosemicarbazide **2** and phenacyl bromide **3** in anhydrous EtOH in the presence of catalytic amounts of activated KSF leads to **4**.

Intermolecular preparation of thiohydrazone was achieved via nucleophilic attack of thiosemicarbazide **2** to activated ketoacid by KSF and subsequently addition of phenacyl bromide **3** led to **4**.

Here, we used montmorillonite KSF as a catalyst due to its environmental compatibility, reusability, simple preparation, no toxicity, non corrosiveness, low cost and ease of isolation [27–30]. High catalytic activity and excellent chemo- and regioselectivity remained essentially the same even after third reuse of the catalyst. After more than three cycles the yield of product 7–11% was decreased.

This type of reactions is of exacting significance in combinatorial chemistry because it allows the production of infinite array of molecules in an efficient mode.

All of the compounds described in Scheme 1 were characterized by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR) and elemental analysis. The IR spectra of 2-(thiazol-2-yl)-4,5-dihydropyridazin-3(*2H*)-one **4a-l** reveals the presence of thiocarboxamide amino stretching vibration bands at 3482–3123 cm^{-1}, absorption bands in the 1509–1610 cm^{-1} region corresponding to endocyclic C=N stretching bands, and peaks in the regions 1355–1365 cm^{-1} and 1055–1096 cm^{-1} indicate the presence of C–S and C–N groups.

The ^{1}H NMR spectra of 2-(thiazol-2-yl)-4,5-dihydropyridazin-3(*2H*)-one **4a-l** showed a sharp singlet at 7-7.30 ppm due to the thiazole ring proton. The vicinal protons of the adjacent carbon atom in the dihydropyridazinone ring of compounds **4a-l** appear in the regions of 1.90-4.2 and 2.45-3.05 ppm with J = 8.4 Hz. Protons belonging to the aromatic ring were observed within the expected chemical shift regions along with their integral values.

The ^{13}C NMR spectra of 2-(thiazol-2-yl)-4,5-dihydropyridazin-3(*2H*)-one **4a-l** showed signals at 172.11-173.09 and 107.31-107.91 ppm assigned ordonnance to C_2 and C_5 of thiazol ring. Also C_3 (C=O) and C_6 (C=N) of pyridazinone ring appeared in the region of 167.11- 168.12 and 146.03-147.12 ppm. The signals due to the aromatic and aliphatic carbon groups resonate at their usual positions (see the Section on Experimental and Supporting Information).

CONCLUSION

In conclusion we have verified a convenient simple, efficient and versatile one-pot three-component protocol for the chemo- and regioselective synthesis of novel derivatives of functionalized 2-(thiazol-2-yl)-4,5-dihydropyridazin-3(*2H*)-one by the reaction of keto acid, thiosemicarbazide and phenacyl bromide in the presence of active-KSF catalyst in moderate to high yields and short reaction time. The simplicity, high atom economy, effortless carrying out, easy workup, and good yields, together with the use an environmentally friendly procedure, are features of this procedure.

EXPERIMENTAL

General Procedure For The Synthesis Of 2-(Thiazol-2-Yl)-4,5-Dihydropyridazin-3(2h)-One

To a 100 ml round bottom flask equipped with condenser and magnetic stir bar were added absolute EtOH (20 mL), ketoacid (10 mmol), 0.2 g activated KSF and thiosemicarbazide (10 mmol). The reaction mixture was refluxed for required reaction time (about 7 hours). The progress of reaction was monitored by TLC (EtOAc:petroleum

ether 2:1). After completion of the reaction, phenacyl bromide (10 mmol) was added and refluxed for required reaction time (about 2 hours). The progress of the reaction was monitored by TLC (EtOAc: petroleum ether 1:2). The catalyst was removed by filtration. The reaction solution was cooled to r.t. The product was isolated by filtration and purified by washing with EtOH.

2-(4-(4-Hydroxyphenyl)Thiazol-2-Yl)-6-(*P*-Tolyl)-4,5-Dihydropyridazin-3(*2H*)-One (*4a*)

Yield 78%; mp 243-245 °C; yellow; IR (KBr, υmax, cm^{-1}): 3350, 3080, 2980, 1667, 1587, 1560, 1500, 1300, 1260, 1187; ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): δ 2.39 (s, 3H), 2.62 (t, 2H, J = 8.4 Hz), 3.03 (t, 2H, J = 8.4 Hz), 5.48 (s, 1H), 6.81-6.83 (d, 2H, J = 7.6 Hz), 7.16 (s, 1H), 7.27-7.29 (d, 2H, J = 8.0 Hz), 7.49-7.51 (d, 2H, J = 7.6 Hz), 7.74-7.76 (d, 2H, J = 8.0 Hz); ^{13}C-NMR (100 MHz, DMSO-d_6, ppm): δ 21.42, 24.45, 32.56, 107.66, 117.25, 125.81, 126.92, 128.23, 129.36, 132.86, 139.21, 146.56, 150.41, 157.23, 167.72, 172.91. Anal. calcd. for $C_{20}H_{17}N_3O_2S$: C, 66.10; H, 4.72; N, 11.56, Found: C, 66.08; H, 4.73; N, 11.54%.

6-(2,4-Dimethylphenyl)-2-(4-(4-Hydroxyphenyl)Thiazol-2-Yl)-4,5-Dihydropyridazin-3(*2H*)-One (*4b*)

Yield 75%; mp 231-232 °C; yellow; IR (KBr, υmax, cm^{-1}): 3350, 3075, 2925, 1665, 1587, 1560, 1500, 1300, 1260, 1187; ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): δ 2.38 (s, 3H), 2.43 (s, 3H), 2.63 (t, 2H, J = 8.4 Hz), 3.03 (t, 2H, J = 8.4 Hz), 5.36 (s, 1H), 6.80-6.82 (d, 2H, J = 7.6 Hz), 7.07 (s, 1H), 7.10-7.12 (d, 1H, J = 8.0Hz), 7.17 (s, 1H), 7.49-

7.51 (d, 2H, J = 7.6 Hz), 7.62-7.64 (d, 1H, J = 8.0 Hz). ^{13}C-NMR (100 MHz, DMSO-d_6, ppm): δ 19.52, 21.63, 26.91, 33.11, 107.91, 117.31, 122.02, 122.91, 124.04, 126.42, 128.36, 129.24, 135.31, 136.21, 146.12, 150.88, 157.41, 168.12, 173.08. Anal. calcd. for $C_{21}H_{19}N_3O_2S$: C, 66.82; H, 5.07; N, 11.13, Found: C, 66.80; H, 5.09; N, 11.12%.

Full experimental detail, ^{1}H and ^{13}C NMR spectra, can be found via the "Supplementary Content" section of this article's webpage.

ACKNOWLEDGMENTS

The authors are grateful to the Research Council of University of Guilan for the financial support of this research work.

REFERENCES

1. Siddiqui, A. A.; Mishra, R.; Shaharyar, M. Synthesis, characterization and antihypertensive activity of pyridazinone derivatives. *Eur J Med Chem* **2010,** *45*, 2283-2290.

2. Coelho, A.; Sotelo, E.; Ravina, E. Pyridazine derivatives. Part 33: Sonogashira approaches in the synthesis of 5-substituted-6-phenyl-3(2*H*)-pyridazinones. *Tetrahedron* **2003**, *59*, 2477-2484.

3. Longo, J. G.; Laguna, M. D. L. R.; Verde, I.; Castro, M. E.; Orallo, F.; Fontenla, J. A.; Calleja, J. M.; Ravina, E.; Teran, C. Pyridazine derivatives. XI: Antihypertensive activity of 3-hydrazinocycloheptyl[1,2-c]pyridazine and its hydrazone derivatives. *J. Pharm. Sci.* **1993**, *82*, 286-290.

4. Livermone, D. G. H.; Bethell, R. C.; Cammack, N.; Hancock, A. P.; Hann, M. M.; Green, D. V. S.; Lamont, R. B.; Noble, S. A.; Orr, D. C. Synthesis and anti-HIV-1 activity of a series of imidazo[1,5-b]pyridazines. *J. Med. Chem.* **1993**, *36*, 3784-3794.

5. Malinka, W.; Redzicka, A.; Lozach, O. New derivatives of pyrrolo[3,4-d]pyridazinone and their anticancer effects. *II Farmaco* **2004**, *59*, 457-462.

6. Figgitt, D. P.; Gillies, P. S.; Goa, K. L. levosimendan. *Drugs* **2001**, *61*, 613-627.

7. Combs, D. W.; Rampulla, M. S.; Bell, S. C.; Klaubert, D. H.; Tobia, A. J.; Falotico, R.; Haertlein, B.; Weiss, C. L.; Moore, J. B. J. 6-Benzoxazinylpyridazin-3-ones: Potent, long-acting positive inotrope and peripheral vasodilator agents. *J. Med. Chem.* **1990**, *22*, 380-386.

8. Siddiqui, A. A. S. M.; Ashok, Wani. Synthesis and antiinflammatory activity of 6-(substitutedaryl)-2,3,4,5-tetrahydro-3-thiopyridazinones. *Ind. J. Heterocycl. Chem.* **2004**, *13*, 257-260.

9. Archan, S.; Toller, W. Perioperative use of levosimendan: Best practice in operative settings. *Curr. Opin. Anesthesiol.* **2008**, *21*, 78-84.

10. Contreras, J. M.; Rival, Y. M.; Chayer, S.; Bourguignon, J. J.; Wermuth, C. G. Aminopyridazines as acetylcholinesterase inhibitors. *J. Med. Chem.* **1999**, *42*, 730-741.

11. Abouzid, K.; Hakeem, M. A.; Khalil, O.; Maklad, Y. Pyridazinone derivatives: Design, synthesis, and in vitro vasorelaxant activity. *Bioorg. Med. Chem.* **2008**, *16*, 382-389.

12. Robertson, D. W.; Jones, N. D.; Krushinski, J. H.; Pollock, G. D.; Swartzendruber, J. K.; Hayes, J. S. Molecular structure of the dihydropyridazinone cardiotonic 1,3-dihydro-3,3-dimethyl-5-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-2*H*-

indol-2-one, a potent inhibitor of cyclic AMP phosphodiesterase. *J. Med. Chem.* **1987**, *30*, 623-627.

13. Hargrave, K. D.; Hess, F. K.; Oliver, J. T. *N*-(4-substituted-thiazolyl)oxamic acid derivatives, new series of potent, orally active antiallergy agents. *J. Med. Chem.* **1983**, *26*, 1158-1163.

14. Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor Jr. D. G.; Connolly, C. J. C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. Structure-activity relationships of a series of 2-amino-4-thiazole containing renin inhibitors. *J Med Chem.* **1992**, *35*, 2562-2572.

15. Sharma, R. N.; Xavier, F. P.; Vasu, K. K.; Chaturvedi, S. C.; Pancholi, S. S. Synthesis of 4-Benzyl-1,3-thiazole derivatives as potential anti-inflammatory agents: An analogue-based drug design approach. *J. Enz. Inhib. Med. Chem.* **2009**, *24*, 890-897.

16. Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzner, L. T.; Pugsley, T. A. 4-(1,2,5,6-Tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamines: A novel class of compounds with central dopamine agonist properties. *J. Med. Chem.* **1990**, *33*, 311-317.

17. Tsuji, K.; Ishikawa, H. Synthesis and anti-pseudomonal activity of new 2-isocephems with a dihydroxypyridone moiety at C-7. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1601-1606.

18. Bell, F. W.; Cantrell, A. S.; Hogberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kinnick, M. D.; Lind, P.; Morin, J.r. J. M.; Noreen, R.; Oberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.;

Vrang, L.; West, S. J.; Zhang, H.; Zhou, X. X. Phenethylthiazolethiourea (PETT) compounds, a new class of HIV-1 reverse transcriptase inhibitors. Synthesis and basic structure-activity relationship Studies of PETT analogs. *J. Med. Chem.* **1995**, *38*, 4929-4936.

19. Ergenc, N.; Capan, G.; Gunay, N. S.; Ozkirimli, S.; Gungor, M.; Ozbey, S.; Kendi, E. Synthesis and hypnotic activity of new 4-thiazolidinone and 2-thioxo- 4,5-imidazolidinedione derivatives. *Arch. Pharm. Med. Chem.* **1999**, *332*, 343-347.

20. Zare, L.; Mahmoodi, N. O.; Yahyazadeh, A.; Mamaghani, M.; Tabatabaeian, K. An efficient chemo- and regioselective three-component synthesis of pyridazinones and phthalazinones using activated KSF. *Chin. Chem. Lett.*, **2010**, *21*, 538-541.

21. Mahmoodi, N. O.; Rineh, A.; Abdollahi, M.; Foroumadi, A.; Sorkhi, M.; Shafiee, A. Synthesis, analgesic and anti-inflammatory activity of 4-(2-phenoxyphenyl)semicarbazones. *Arch. Pharm.* **2007**, *340*, 409-415.

22. Mahmoodi, N. O.; Khodaee, Z. One-pot diastereoselective synthesis of new racemic and achiral spirohydantoins. *Mendeleev Commun.* **2004**, *14*, 304-306.

23. Mahmoodi, N. O.; Emadi, S. One-pot synthesis of phenytoin analogs. *Russ. J. Org. Chem.* **2004**, *40*, 377-382.

24. Mahmoodi, N. O. Synthesis of competitive inhibitors of phospholipase A2 (PLA2). *Phosphorus Sulfur Silicon Relat. Elem.* **2002**, *177*, 2887-2893.

25. Mahmoodi, N. O.; Sharifzadeh, B., Mamaghani, M.; Tabatabaeian, K.; Salimi Chirani, A.; Nikokar, I. Facile regioselective synthesis of novel bioactive thiazolyl-pyrazoline derivatives via a three-component reaction and their antimicrobial activity. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 548-551.

26. Zare, L.; Mahmoodi, N. O.; Yahyazadeh, A.; Mamaghani, M. Convenient ultrasound-promoted regioselective synthesis of fused 6-amino-3-methyl-4-aryl-1*H*-pyrazolo[3,4-b]pyridine-5-carbonitrile. *Synth. Communin.* **2011,** *41*, 2323-2330.

27. Ballini, R.; Fiorini, D.; Gil, V. M.; Palmieri, A. Michael addition of α-nitro ketones to conjugated enones under solventless conditions using silica. *Green Chem.* **2003**, *5*, 475-476.

28. Rani, R. V.; Srinivas, N.; Kishan, R. M.; Kulkarni, S. J.; Raghavan, K. V. Zeolite-catalyzed cyclocondensation reaction for the selective synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. *Green Chem.* **2001**, *3*, 305-306.

29. Bigi, F.; Zambonin, E. Reaction of aromatic amines and ethyl acetoacetate promoted by zeolite HSZ-360. Phosgene-free synthesis of symmetric diphenylureas. *Chem. Commun.* **1998**, *4*, 513-514.

30. Krstic, L. J.; Sukdolak, S.; Solujic, S. An efficient synthesis of warfarin acetals on montmorillonite clay K-10 with microwaves. *J. Serb. Chem. Soc.* **2002**, *67*, 325-329.

Scheme 1. One-pot synthesis of 2-(thiazol-2-yl)-4,5-dihydropyridazin-3(*2H*)-one. 4a: R^1 = 4-MeC_6H_4, R^2 = OH; 4b: R^1 = 2,4-$(Me)_2C_6H_4$, R^2 = OH; 4c: R^1 = 4-ClC_6H_4 , R^2 = OH; 4d: R^1 = 4-BrC_6H_4 , R^2 = OH; 4e: R^1 = Me, R^2 = OH; 4f: R^1 = 4-MeC_6H_4 , R^2 = OMe; 4g: R^1 = 2,4-$(Me)_2C_6H_4$, R^2 = OMe; 4h: R^1 = 4-ClC_6H_4 , R^2 = OMe; 4i: R^1 = 4-BrC_6H_4 , R^2 = OMe; 4l: R^1 = Me, R^2 = OMe