Tetrahedron Letters 53 (2012) 5619–5623

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

T3P®-DMSO mediated one pot cascade protocol for the synthesis of 4-thiazolidinones from alcohols

Kothanahally S. Sharath Kumar, Toreshettahally R. Swaroop, Kachigere B. Harsha, Kereyagalahally H. Narasimhamurthy, Kanchugarakoppal S. Rangappa *

Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India

ARTICLE INFO

Article history:
Received 16 June 2012
Revised 2 August 2012
Accepted 4 August 2012
Available online 14 August 2012

Keywords:
Propylphosphonic anhydride (T3P®)
Cascade
4-Thiazolidinones
Thioglycolic acid (or mercaptoacetic acid)

ABSTRACT

Propylphosphonic anhydride (T3P®)-DMSO mediated oxidation of alcohols to carbonyl compounds and their subsequent cyclization with aryl/hetero aryl amines and thioglycolic acid to afford 4-thiazolidinones has been reported. Synthesis of 4-thiazolidinones directly from alcohols has been carried out for the first time. Mild reaction conditions, wide functional group tolerance, ease of work-up, and good yields are the noteworthy features of this protocol.

4-Thiazolidinone represents an important class of heterocyclic compounds in the view of its broad biological activities.[1–9] Because of its diverse pharmacological activities, several synthetic efforts have been made to construct this ring. Most commonly employed method is one-pot cyclocondensation of aldehydes, amines, and mercaptoacetic acid.[10] Many catalysts[11–16] have been reported in literature to accelerate the cyclocondensation and, in addition, solid phase,[17] micro wave heating,[18] and polymer supported[19] systems have also been developed.

However, the above mentioned methods advocate prolonged heating, Dean-Stark removal of water, and tedious work-up procedure. Hence, a protocol which circumvents these demerits attracts a lot of attention of chemists. To the best of our knowledge, synthesis of 4-thiazolidinones directly from alcohols has not been reported, probably due to lack of reagent that oxidizes alcohol to carbonyl compounds and mediates subsequent in-situ cyclocondensation of carbonyl compounds with amines and mercaptoacetic acid.

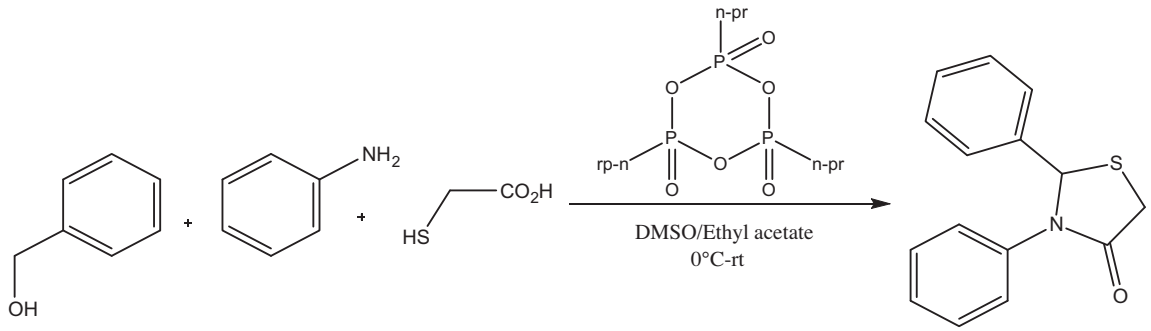
On the other hand, several synthetic applications of T3P® have been reported in the literature.[20] Also, DMSO has been found to be a good oxidizing agent in the presence of electrophilic reagents.[21a] For instance, it oxidizes alcohols to carbonyl compounds in the presence of polyphosphoric acid[21b] and T3P®.[21c,d]

Recently, we have reported an one pot tandem approach for the synthesis of benzimidazoles and benzothiazoles from alcohols using DMSO-propylphosphonic anhydride (T3P®) media[22] as an oxidizing as well as cyclodehydrating agent. In continuation of our work toward the development of new synthetic methodologies toward biologically important heterocyclic compounds, we report herein an efficient T3P®-DMSO mediated one pot three-component synthesis of 4-thiazolidinones directly from various alcohols.[23] This process involves oxidation, condensation followed by cyclization under mild reaction conditions.

Initially, we selected the reaction between benzyl alcohol(**1a**), aniline(**2a**) and thioglycolic acid(**3**) in the presence of T3P® (50% solution in ethyl acetate) in ethyl acetate and DMSO solvent mixture in the ratio 2:1 as a media of choice (Scheme 1). Thus, the reaction between **1a**, **2a,** and **3** in the presence of T3P® (1 equiv) gave the required product **4a** in 15% yield after 10 h (Table 1 entry 1). We observed that increase in the quantity of T3P® in the reaction would enhance yield up to 92% in 5 h (Table 1 entry 2 and 3). Further increase in the quantity of T3P® in the reaction does not affect the reaction time and yield (Table 1 entry 4). Later, we diverted our interest to explore the effect of various solvents on the reaction with solvent: DMSO ratio being 2:1 as a choice. Thus, the reaction was screened in various solvents – toluene, benzene, dichloromethane, chloroform, acetonitrile, dioxane and THF gave decreased yield of **4a** (Table 1, entries 5–11). At this stage, we converged our interest to study the effect of temperature on the EtOAc: DMSO mediated reaction. Thus, increase in temperature

* Corresponding author. Tel.: +91 821 2419661; fax: +91 821 2500846.
E-mail addresses: rangappaks@chemistry.uni-mysore.ac.in, rangappaks@gmail.com (K.S. Rangappa).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.08.020



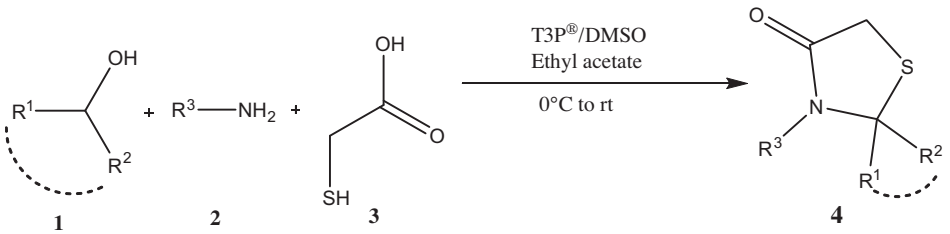
1a 2a 3 4a

Scheme 1. Synthesis of 2,3-diphenylthiazolidin-4-one (**4a**).

Table 1
T3P®-DMSO mediated synthesis of **4a** under different reaction conditions

Sl. No.	Solvent[a]	T3P® (equiv)[b]	Time (h)	Temperature (°C)	Yield[c] (%) of **4a**
1	EtOAc	1.0	10	0–25	15
2	EtOAc	2.0	5	0–25	86
3	**EtOAc**	**2.5**	**5**	**0–25**	**92**
4	EtOAc	3.5	5	0–25	91
5	Toluene	2.5	5	0–25	72
6	Benzene	2.5	5	0–25	60
7	CH_2Cl_2	2.5	5	0–25	40
8	$CHCl_3$	2.5	5	0–25	45
9	CH_3CN	2.5	5	0–25	52
10	Dioxane	2.5	5	0–25	50
11	THF	2.5	5	0–25	25
12	EtOAc	2.5	4.5	50	90
13	EtOAc	2.5	4	60	90
14	EtOAc	2.5	3	65	88
15	EtOAc	2.5	2	70	87

[a] Solvent and DMSO were taken in 2:1 volume ratio.
[b] T3P® (50% solution in EtOAc) was used to carry out the reactions.
[c] Isolated yield.



1 2 3 4

Scheme 2. Synthesis of 4-thiazolidinones (**4**).

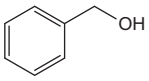
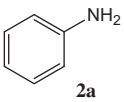
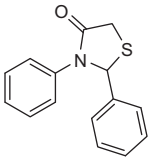
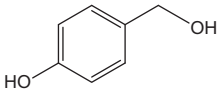
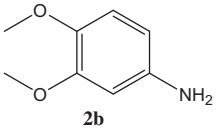
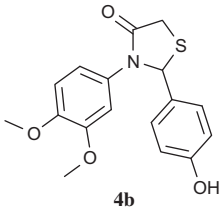
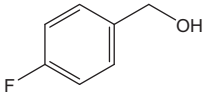
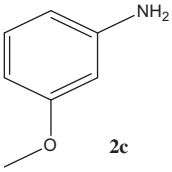
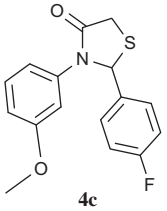
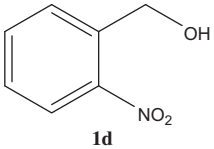
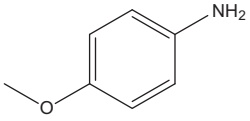
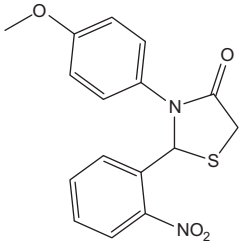
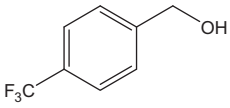
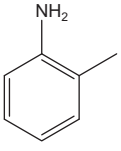
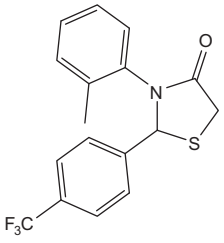
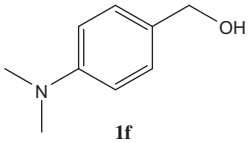
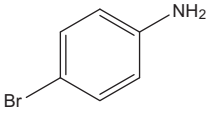
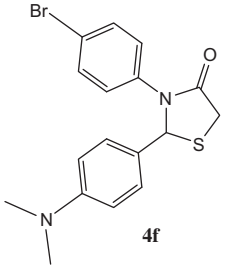
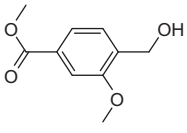
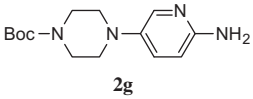
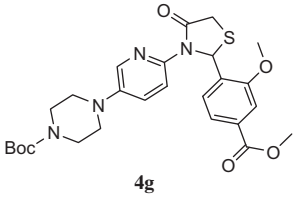
of the reaction resulted in gradual decrease in reaction time with very slight decrease in yield of **4a** (Table 1, entry 12–15) as summarized in Table 1.

With the optimized reaction condition in hand, we next explored the generality of the protocol by reacting various aryl/heteroaryl primary alcohols with aryl/heteroaryl amines and thioglycolic acid as shown in Scheme 2. Thus, primary alcohols and amines bearing various electron donating and electron withdrawing substituents underwent reaction smoothly to give respective 4-thiazolidinones in high yields (Table 2, entries 1–11). It should be noted that many functional groups such as hydroxyl, nitro, ester, methoxy, and Boc remain unaffected throughout the reaction. Interestingly, secondary alcohols (**1k**, **1l**, & **1m**) also underwent smooth oxidation followed by cyclization to afford respective 4-thiazolidinones in high yields (Table 2, entry 12–14).

The possible mechanism involves the reaction of DMSO with T3P® followed by substitution reaction of alcohol and results in the cleavage of phosphoester bond to form intermediate **5**. Elimination of dimethyl sulfide gives carbonyl compound **6** which undergoes condensation and cyclization with amine and mercaptoacetic acid to afford thiazolidinone **4** as shown in Scheme 3.

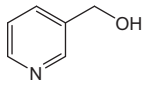
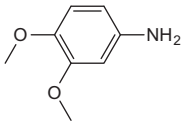
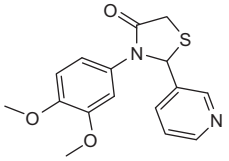
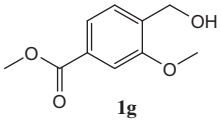
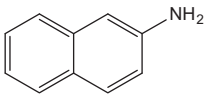
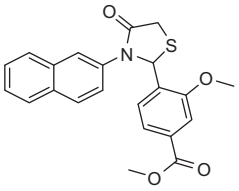
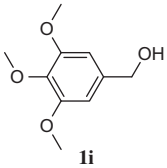
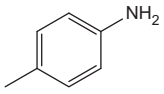
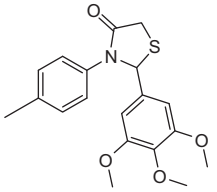
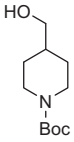
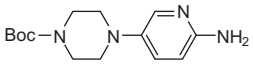
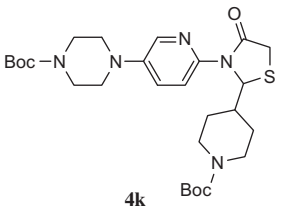
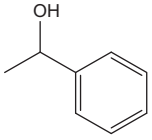
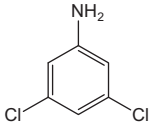
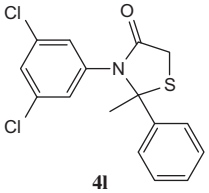
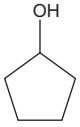
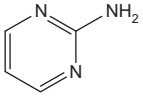
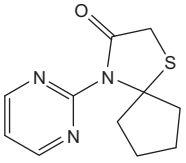
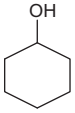
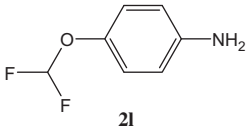
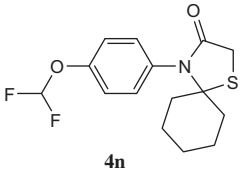
In conclusion, we have demonstrated an excellent, mild, and high yielding protocol for the synthesis of 4-thiazolidinones starting

Table 2

Entry[a]	1	2	4	Time (h)	Yield[b,c] (%)
1	 **1a**	 **2a**	 **4a**	5	92[24]
2	 **1b**	 **2b**	 **4b**	4.5	93
3	 **1c**	 **2c**	 **4c**	4	90
4	 **1d**	 **2d**	 **4d**	4.5	94
5	 **1e**	 **2e**	 **4e**	4	95
6	 **1f**	 **2f**	 **4f**	5	88
7	 **1g**	 **2g**	 **4g**	4.5	89

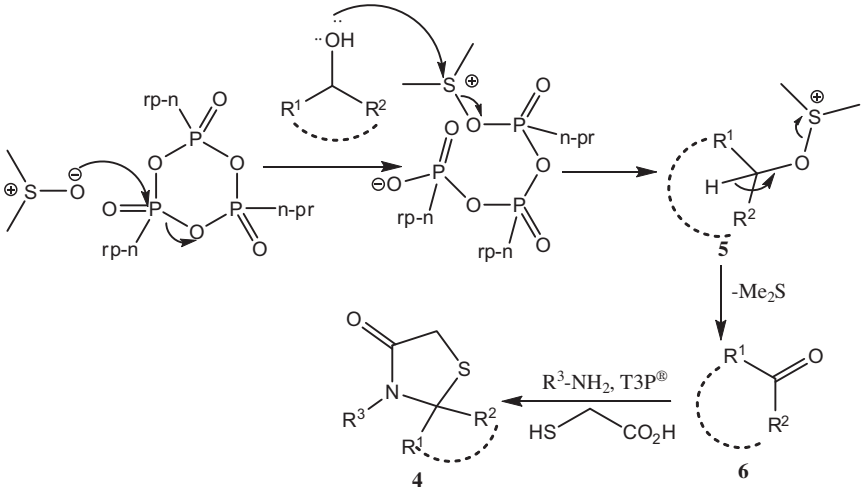
(*continued on next page*)

Table 2 (*continued*)

Entry[a]	1	2	4	Time (h)	Yield[b,c] (%)
8	 **1h**	 **2b**	 **4h**	4	90
9	 **1g**	 **2h**	 **4i**	4	94
10	 **1i**	 **2i**	 **4j**	3	95[25]
11	 **1j**	 **2g**	 **4k**	4	90
12	 **1k**	 **2j**	 **4l**	5	89
13	 **1l**	 **2k**	 **4m**	4	96
14	 **1m**	 **2l**	 **4n**	3.5	97

[a] T3P® (2.5 equiv), Alcohol (1.1 equiv), Amine (1.0 equiv) and Thioglycolic acid (1.0 equiv).
[b] Isolated yield.
[c] Literature reported compounds.

directly from a variety of primary and secondary alcohols, aryl/hetero aryl amines, and thioglycolic acid. The main advantages of this procedure are one pot operation, short reaction time, mild reaction condition, broad functional group tolerance, ease of product purification, and excellent yield. Further synthetic applications of T3P® are currently underway in our laboratory.



Scheme 3. Possible mechanism of the T3P®-DMSO mediated 4-thiazolidinone synthesis.

Acknowledgments

The authors are grateful to the DST-IFCPAR Project, Govt. of India for financial support to K.S.R. for the project vide NO. IFC/4303-1/2010-11 Dated 22-12-2010.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.020.

References and notes

1. Desai, K. G.; Desai, K. R. *J. Sulfur Chemistry* **2006**, *27*, 315–328.
2. (a) Barreca, M. L.; Balzsarini, J.; Chimirri, A.; De Clercq, E.; De Luca, L.; Höltje, H. D.; Höltje, M.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Rao, A.; Zapalla, M. *J. Med. Chem.* **2002**, *45*, 5410–5413; (b) Rao, A.; Balzarini, J.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zapallà, M. *Antivir. Res.* **2004**, *63*, 79–84; (c) Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Bioorg. Med. Chem.* **2007**, *15*, 3134–3142.
3. (a) Archana; Srivastava, V. K.; Kumar, A. *Eur. J. Med. Chem.* **2002**, *37*, 873–882; (b) Dwivedi, C.; Gupta, S. S.; Parmar, S. S. *J. Med. Chem.* **1972**, *15*, 553–554.
4. Hongyu, Z.; Wu, S.; Zhai, S.; Liu, A.; Sun, Y.; Li, R.; Zhang, Y.; Ekins, S.; Swaan, P. W.; Fang, B.; Zhangand, B.; Yan, B. *J. Med. Chem.* **2008**, *51*, 1242–1251.
5. Diurno, M. V.; Mazzoni, O.; Calignano, P. E.; Giorodano, F.; Bolognese, A. *J. Med. Chem.* **1992**, *35*, 2910–2912.
6. Solomon, V. R.; Haq, W.; Srivastava, K.; Puri, S. K.; Katti, S. B. *J. Med. Chem.* **2007**, *50*, 394–398.
7. Jackson, C. M.; Blass, B.; Coburn, K.; Djandjighian, L.; Fadayel, G.; Fluxe, A. J.; Hodson, S. J.; Janusz, J. M.; Murawsky, M.; Ridgeway, J. M.; White, R. E.; Wu, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 282–284.
8. Kucukguzel, G. C.; Shchullek, J. R.; Kaocatepe, A.; De Clercq, E.; Sahinv, F.; Gulluce, M. *Eur. J. Med. Chem.* **2006**, *41*, 353–359.
9. Look, G. C.; Schullek, J. R.; Homes, C. P.; Chinn, J. P.; Gordon, E. M.; Gallop, M. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 707–712.
10. Homes, C. P.; Chinn, J. P.; Look, C. G.; Gordon, E. M.; Gallop, M. A. *J. Org. Chem.* **1995**, *60*, 7328–7333.
11. Srivastava, S. K.; Srivastava, S. L. *J. Ind. Chem. Soc.* **2002**, *77*, 104.
12. Kumar, R. C.; Kumar, D. *J. Ind. Chem. Soc.* **2002**, *77*, 492.
13. Rawal, R. K.; Srivastava, T.; Haq, W.; Katti, S. B. *J. Chem. Res.* **2004**, *5*, 368–369.
14. Srivastava, T.; Haq, W.; Katti, S. B. *Tetrahedron* **2002**, *58*, 7619–7624.
15. (a) Yadav, A. K.; Kumar, M.; Yadav, T.; Jain, R. *Tetrahedron Lett.* **2009**, *50*, 5031–5034; (b) Zhang, X.; Li, X.; Li, D.; Qu, G.; Wang, J.; Loiseau, P. M.; Fan, X. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6280–6283.
16. Kanagarajana, V.; Thanusua, J.; Gopalakrishnana, M. *Green Chem. Lett. Rev.* **2009**, *2*, 161–167.
17. Holmes, C. P. WO 96/ 00148, 1996.
18. Gududuru, V.; Nguyen, V.; Dalton, J. T.; Miller, D. D. *Synlett* **2004**, 2357–2358.
19. Stephanie, E.; Justus, A.; Hodges, J. C.; Wilson, M. W. *Biotech. Bioeng.* **2000**, *61*, 17–22.
20. (a) Meudt, A.; Scherer, S.; Nerdinger, S. PCT Int. Appl. WO 2005070879, 2005; Chem. Abstr. 2005, 143, 172649.; (b) Meudt, A.; Scherer, S.; Böhm, C. PCT Int. Appl. WO 2005123632, 2005; Chem. Abstr. 2005, 144, 69544.;; (c) Burkhart, F.; Hoffmann, M.; Kessler, H. *Angew. Chem. Int. Ed.* **1997**, *36*, 1191; (d) Wedel, M.; Walter, A.; Montforts, F.-P. *Eur. J. Org. Chem.* **2001**, 1681; Augustine, J. K.; Sharmila, v. v.; Alagarsamy, N. P.; Radhakrishnan, A. *Tetrahedron* **2009**, *65*, 9989–9996.
21. (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165; (b) Sato, T.; Takatsu, A.; Saito, Y.; Tohyama, T.; Hata, K. *Bull. Chem. Soc. Japan* **1968**, *41*, 221; (c) Meudt, A.; Scherer, S.; Böhm, C. PCT Int. Appl. WO 2005102978, 2005.; (d) Chem. Abstr. 2005, 143, 440908.
22. Raghavendra, G. M.; Ramesha, A. B.; Revanna, C. N.; Nandeesh, K. N.; Mantelingu, k.; Rangappa, K. S. *Tetrahedron Lett.* **2011**, *52*, 5571–5574.
23. *General procedure for one pot synthesis of 4-thiazolidinones* ***(4)****:* To a solution of alcohol (1.1 mmol) in a mixture of solvents EtOAc: DMSO (4 ml: 2 ml), was added T3P® (2.5 mmol, 50% solution in ethyl acetate) at 0 °C, and the resulting mixture was stirred at room temperature for 1–2 h under nitrogen atmosphere. The reaction was monitored by TLC, amine (1.0 mmol) and thioglycolic acid (1.0 mmol) were added once and stirred further for 1–3 h at room temperature. After completion of the reaction, the mixture was diluted with water (20 ml) and neutralized by adding 10% $NaHCO_3$ solution. The product was extracted with ethyl acetate (10 ml × 2) and the combined organic layers were washed with water followed by brine solution. The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford a crude product which was purified by column chromatography using hexane: ethyl acetate mixture (8:2) as an eluent.
24. Dinesh, L.; Dhanaji, J.; Rahul, W.; Ramrao, M. *Synth. Commun.* **2010**, *40*, 2397–2401.
25. Zuhal, T.; Cigdem, Y.; Feray, A.; Emine, B.; Nuket, O. *Molecules* **2007**, *12*, 2151–2159.