



An efficient synthetic route for quinazolinyl 4-thiazolidinones

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ARTICLE INFO

Article history:

Received 19 May 2009

Revised 15 June 2009

Accepted 17 June 2009

Available online 21 June 2009

Keywords:

4-Thiazolidinones

Quinazolin-4-(3H)-one

Silica chloride

Solvent-free condition

ABSTRACT

An efficient solvent-free cyclocondensation route for condensing mercaptoacetic acid with quinazolinyl-substituted azomethines has been developed using silica chloride as a catalyst for obtaining heteryl-substituted 4-thiazolidinones. The route is found to be rapid, relatively economical, and eco-friendly. The precursors, quinazolinyl azomethines have been obtained in multisteps starting from quinazolinone.

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1. Introduction

4-thiazolidinones and their derivatives are an important class of compounds in organic and medicinal chemistry. The 4-thiazolidinone ring system is a core structure in various synthetic pharmaceutical agents, displaying a broad spectrum of biological activities¹ such as *anti-tubercular*,² *anti-convulsant*,³ *anti-cancer*,⁴ *anti-fungal*,⁵ *anti-inflammatory*, and *analgesic*.⁶

Quinazolinones are gaining importance as medicinal agents.⁷ Quinazolinone and its derivatives have been found to possess a wide spectrum of biological activities such as *anti-tubercular*, *anti-convulsant*, *anti-cancer*, *anti-diabetic*, *anti-hypertensive*, and *anti-inflammatory*.⁸ The combination of quinazolin-4-(3H)-ones and 4-thiazolidinones in a molecular framework has shown remarkable *anti-microbial* and *anti-inflammatory* activities.^{9,10}

Literature survey reveals that several synthetic protocols have been developed for the synthesis of 4-thiazolidinones. The most commonly employed method¹¹ allows cyclocondensation of azomethines (Schiff's base) with mercaptoacetic acid. The media used are volatile organic solvents such as toluene, benzene, 1,4-dioxane, and THF. Attempts have also been made to accelerate the cyclocondensation by simultaneous removal of reaction water azeotropically or by using dehydrating agents such as anhydrous ZnCl₂,¹² sodium sulfate,¹³ and DCC.¹⁴ The use of Hunig's base,¹⁵ ionic liquid,¹⁶ KSF Montmorillonite,¹⁷ and DMF in ZnCl₂,¹⁸ etc. has also been reported to expedite the cyclocondensation of the azomethines and mercaptoacetic acid. It is observed that the reported methods used for the cyclocondensation are having one or other kind of drawbacks. The

media used are found to be carcinogenic and hazardous. The reaction conditions require prolonged heating, tedious work-up, and costly dehydrating agents. Therefore it was thought worthwhile to develop a new rapid method for the cyclocondensation.

Silica chloride is gaining importance as a heterogeneous catalyst and is used in various organic transformations. It has also been used as a dehydrating agent.¹⁹ Some cyclocondensations yielding dihydropyrimidinone,²⁰ 2-amino thiazoles,²¹ 6-methyl-3-propynylthio-1,2,4-triazin-5(2H)-one,²² pyranoquinolines, or furanoquinolines²³ are catalyzed by silica chloride. The use of silica chloride to expedite oxidation of alcohol,²⁴ esterification and transesterification,²⁵ transdithioacetalization of acetals,²⁶ deprotection of oximes/hydrazones/semicarbazones,²⁷ synthesis of nitriles and amides,²⁸ synthesis of sulfoxide,²⁹ synthesis of bis-indolylmethanes,³⁰ etc. has been well explored.

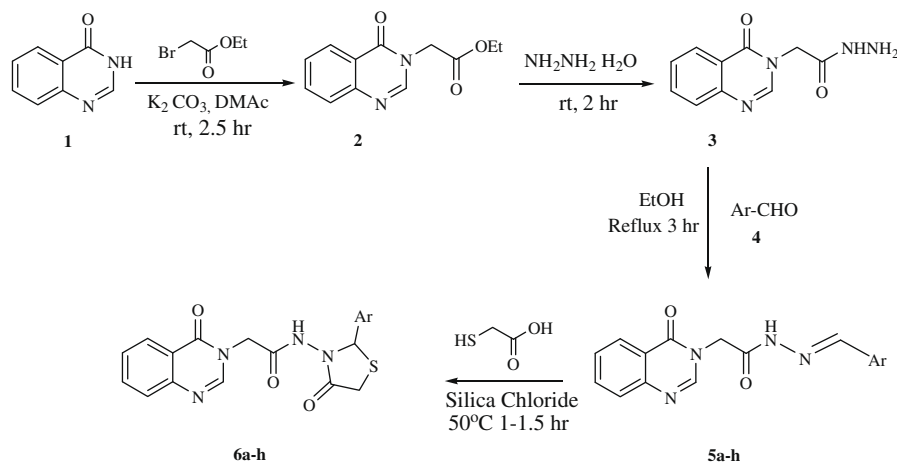
Considering the significance of the silica chloride and in continuation of our earlier interest in providing new and convenient synthetic protocols for the construction of bioactive heterocycles³¹ herein, we report a rapid, efficient method for the cyclocondensation of quinazolinyl azomethines and mercaptoacetic acid to yield 4-thiazolidinones using silica chloride as a heterogeneous catalyst under solvent-free condition (Scheme 1).

2. Results and discussion

In the present work, the synthesis of 4-thiazolidinones (**6**) bearing quinazolinone moiety has been carried using quinazolin-4-(3H)-one (**1**). Quinazolin-4-(3H)-one on N-alkylation with ethylbromoacetate in the presence of K₂CO₃ in *N,N*-dimethylacetamide at room temperature gave ethyl-2-(4-oxoquinazolin-3-(4H)-yl)acetate (**2**) in a quantitative yield (95%). There is a possibility of

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Scheme 1. Synthesis of 3-quinazolinyl-substituted acetamido-4-thiazolidinones.

O-alkylation of enolic-OH. It was confirmed by ^{13}C NMR that the N-alkylation takes place at the ring nitrogen. Ethyl 2-(4-oxoquinazolin-3(4H)-yl) acetate (**2**) on further neat condensation with hydrazine hydrate at room temperature yielded 2-(4-oxoquinazolin-3(4H)-yl) acetohydrazide (**3**). The acetohydrazide (**3**) condensation with the various aromatic aldehydes (**4**) gave the respective quinazolinyl-substituted azomethines (**5**) in high yields.

Various attempts were made to cyclocondense the azomethines (**5**) and mercaptoacetic acid using the literature procedures. It was noticed that none of the approach was convenient to obtain the desired 4-thiazolidinones (**6**) at least in moderate yields. Considering the synthetic utilities of silica chloride as a condensing catalyst and a dehydrating agent here it was therefore thought worthwhile to incorporate silica chloride to carry out cyclocondensation of azomethines and mercaptoacetic acid for obtaining the 4-thiazolidinones (**6a–h**) (Table 1).

To optimize the reaction conditions, several alternatives were attempted. The condensation was carried by using equimolar amount of the azomethines, mercaptoacetic acid, and 25 mmol % of silica chloride in refluxed toluene/acetonitrile. The reaction was monitored by thin layer chromatography (TLC) and was found to reach completion in 4 h giving 75–80% yields of the 4-thiazolidinones. It was observed in another attempt that when the cyclocondensation was carried under neat condition using the same mole proportions of the reactants and silica chloride the cyclocondensation was completed within an hour at 50 °C and gave 88–93% yields of the 4-thiazolidinones. This was found to be the better alternative for obtaining 4-thiazolidinones as the time required for the completion of the reaction had been reduced and it does not require an organic medium.

The expedition rate can be accounted for the electrophilic behavior of silica chloride which might be helping to enhance the nucleophilic character of mercapto of mercaptoacetic acid

and also may be working as a dehydrating agent to remove the water formed in the reaction. Hence it is claimed that the developed route for the cyclocondensation is high yielding and needs simple reaction parameters.

3. Experimental

3.1. Preparation of silica chloride

Silica chloride was prepared by following the literature procedure.²¹ A suspension of silica gel (20 mL) in CH_2Cl_2 (50 mL) was added dropwise to SOCl_2 (20 mL) at room temperature. Evolution of a copious amount of HCl and SO_2 gas was observed. After stirring the reaction mass for 1 h, the solvent was removed under reduced pressure. The silica chloride obtained was dried and stored in a desiccator.

3.2. Synthesis of ethyl 2-(4-oxoquinazolin-3(4H)-yl) acetate from quinazolin-4-(3H)-one (**2**)

Quinazolin-4-(3H)-one **1** (0.01 mol), potassium carbonate (0.02 mol), and ethyl bromoacetate were dissolved in *N,N*-dimethylacetamide (DMAc) (20 mL) and the reaction solution was stirred for 2.5 h. After completion of the reaction, the reaction mixture was poured on crushed ice and acidified with hydrochloric acid. The thus-obtained solid was filtered, washed with water, and crystallized from aqueous ethanol. Yield: 95%, mp: 67 °C.

3.3. Synthesis of 2-(4-oxoquinazolin-3(4H)-yl) acetohydrazide from ethyl 2-(4-oxoquinazolin-3(4H)-yl) acetate (**3**)

Ethyl 2-(4-oxoquinazolin-3(4H)-yl) acetate **2** (0.01 mol) and excess hydrazine hydrate were mixed thoroughly and stirred at room temperature for 2 h under solvent-free condition. The reaction was monitored by TLC. After completion of the reaction, the reaction mass was poured on crushed ice and the solid formed was filtered, washed with water, and crystallized from DMF.

Yield: 89%, mp: 225 °C.

3.4. Synthesis of *N'*-(4-methoxybenzylidene)-2-(4-oxoquinazolin-3(4H)-yl) acetohydrazide (**5b**)

2-(4-Oxoquinazolin-3(4H)-yl) acetohydrazide **3** (0.01 mol) and 4-methoxy benzaldehyde **4b** (0.01 mol) were dissolved in ethanol (10 mL) and the solution was refluxed for three and half hour. After completion of the reaction ethanol was removed under reduced

Table 1
Physical data of the quinazolinyl 4-thiazolidinones

Entry	Ar	4-Thiazolidinones	Time (h)	Yield ^a (%)	Mp (°C)
1	H	6a	1	91	185–187
2	4-OMe	6b	1	93	140–143
3	4-Me	6c	1	89	245–247
4	4-F	6d	1.15	90	213–215
5	4-NO ₂	6e	1.25	89	233–235
6	4-Cl	6f	1	88	220–223
7	2,3-Cl	6g	1.50	89	155–157
8	3,4-OMe	6h	1	89	218–220

^a Isolated yields.

pressure. The residue was obtained and added to ice-cold water. The solid that was obtained was filtered, washed with water, and crystallized from ethanol–DMF.

Yield: 90%, mp: 230–231 °C.

3.5. Synthesis of *N*-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-(4-oxoquinazolin-3-(4*H*)-yl) acetamide (6b quinazolinyl 4-thiazolidinone)

A mixture of *N*-(4-methoxybenzylidene)-2-(4-oxoquinazolin-3-(4*H*)-yl) acetohydrazide **5b** (0.1 mol), mercaptoacetic acid (0.15 mol), and silica chloride (0.025 mol) was heated at 50 °C under solvent-free condition for 1 h. The progress of the reaction was monitored by TLC using hexane–ethyl acetate (7:3). After the completion of the reaction, the reaction mixture was extracted with ethyl acetate and organic layer was washed with 5% sodium bicarbonate solution and brine. Organic layer was separated and dried over anhydrous sodium sulfate. From the organic extract the solvent was removed under reduced pressure and the residual crude solid, thiazolidinone was crystallized from ethanol.

Yield: 93%, mp: 140–143 °C.

All the synthesized compounds were characterized by IR, ¹H NMR, and mass spectroscopic techniques.³²

4. Conclusion

The use of silica chloride to accelerate the rate of the cyclocondensation of azomethines and mercaptoacetic acid to obtain 4-thiazolidinones under solvent-free condition has been reported for the first time. The developed synthetic route is simple, eco-friendly, and high yielding.

Acknowledgment

The authors are thankful to Professor D. B. Ingle for his invaluable discussions and guidance.

References and notes

- Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. *J. Med. Chem.* **1994**, *37*, 3977.
- Bhat, A. R.; Shetty, S. J. *Ind. Pharm. Sci.* **1987**, *194*.
- Ragah, F. A.; Eid, N. M.; El-Tawab, H. A. *Pharmazie* **1997**, *52*, 926.
- Vigorita, M. G.; Ottana, R.; Monforte, F.; Maccari, R.; Trovato, A.; Monforte, M. T.; Taviano, M. F. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2791.
- Bhatt, J. J.; Shah, B. R.; Shah, H. P.; Trivedi, P. B.; Undavia, N. K.; Desai, N. C. *Indian J. Chem., Sect. B* **1994**, *33*, 184.
- Capan, G.; Ulusoy, N.; Ergenc, N.; Kiraz, M. *Monatsh. Chem.* **1999**, *130*, 1399.
- Maskey, P. R.; Shaaban, M.; Grun-Wollny, I.; Laatsch, H. J. *Nat. Prod.* **2004**, *67*, 1131. and references cited therein.
- Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 659. and references cited therein.
- Patel, N. B.; Patel, V. N. *Iranian J. Pharma. Res.* **2007**, *6*, 251.
- Kumar, A.; Rajput, C. S.; Bhati, S. K. *Bioorg. Med. Chem.* **2007**, *15*, 3089.
- Holmes, C. P.; Chinn, J. P.; Look, G. C.; Gordon, E. M.; Gallop, M. A. *J. Org. Chem.* **1995**, *60*, 7328.
- Srivastava, S. K.; Srivastava, S. L.; Srivastava, S. D. *J. Ind. Chem. Soc.* **2000**, *77*, 104.
- Sharma, R. C.; Kumar, D. J. *J. Ind. Chem. Soc.* **2000**, *77*, 492.
- Srivastava, T.; Haq, W.; Katti, S. B. *Tetrahedron* **2002**, *58*, 7619.
- Gududuru, V.; Nguyen, V.; Dalton, J. T.; Miller, D. D. *Synlett* **2004**, 2357.
- Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron* **2003**, *59*, 6121.
- Dandia, A.; Singh, R.; Khaturia, S.; Merienne, C.; Georges, M.; Loupy, A. *Bioorg. Med. Chem.* **2006**, *14*, 2409.
- Patel, K. H.; Mehta, A. G. *E-J. Chem.* **2006**, *3*, 103.
- Firouzabadi, H.; Iranpoor, N.; Karimi, B.; Hazarkhani, H. *Synth. Commun.* **2003**, *33*, 3653.
- Karade, H.; Sathe, M.; Kaushik, M. P. *Molecules* **2007**, *12*, 1341.
- Karade, H.; Sathe, M.; Kaushik, M. P. *Cat. Commun.* **2007**, *8*, 741.
- Hervani, M. M.; Zadmard, R.; Ghassemzadeh, M.; Tajbaksh, M.; Riahiar, N. *Phosphorus, Sulfur Silicon* **2001**, *17*, 687.
- Das, B.; Reddy, M. R.; Holla, H.; Ramu, R.; Vekateswarlu, K.; Rao, Y. K. *J. Chem. Res. (S)* **2005**, 793.
- Shirini, F.; Zolfigol, M. A.; Khaleghi, M. *Phosphorus, Sulfur Silicon* **2003**, *178*, 2107.
- Srinivas, K. V. N. S.; Mahender, I.; Das, B. *Synthesis* **2003**, 2479.
- Firouzabadi, H.; Iranpoor, N.; Karimi, B.; Hazarkhani, H. *Synlett* **2000**, 263.
- Shirini, F.; Zolfigol, M. A.; Khaleghi, M.; Mohammadpour-Baltork, I. *Synth. Commun.* **2003**, *33*, 1839.
- Srinivas, K. V. N. S.; Mahender, I.; Das, B. *Chem. Lett.* **2003**, *32*, 738.
- Mohanazadeh, F.; Momeni, A. J. *Sci. I.R. Iran* **1996**, *7*, 261.
- Hasaninejad, A.; Zare, A.; Sharghi, H.; Shekouhy, M.; Khalifeh, R.; Beni, A. S.; Zare, A. R. M. *Can. J. Chem.* **2007**, *85*, 416.
- (a) Pratap, U. R.; Mali, J. R.; Jawale, D. V.; Mane, R. A. *Tetrahedron Lett.* **2009**, *50*, 1352; (b) Mahalle, S. R.; Netankar, P. D.; Bondge, S. P.; Mane, R. A. *Green Chem. Lett. Rev.* **2008**, *2*, 103.
- Spectral data for selected compounds: compound **2**: IR (KBr, cm⁻¹): 1736, 1611. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{ppm} 3.02 (t, 3H), 4.22 (q, 2H), 4.74 (s, 2H), 7.58 (d, 1H, *J* = 8 Hz), 7.77 (m, 2H), 7.80 (s, 1H), 8.29 (d, 1H, *J* = 8 Hz). ¹³C NMR (400 MHz, DMSO-*d*₆): 14.68, 47.92, 62.00, 121.94, 126.69, 128.01, 135.36, 148.61, 160.81, 168.62. Mass: *m/z* 233 (M⁺). Compound **3**: IR (KBr, cm⁻¹): 3153, 3051, 1683, 1607. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{ppm} 4.27 (s, 2H), 4.58 (s, 2H), 7.52 (t, 1H, *J* = 8 Hz), 7.67 (d, 1H, *J* = 8 Hz), 7.80 (t, 1H, *J* = 8 Hz), 8.10 (d, 1H, *J* = 8 Hz), 8.21 (s, 1H), 9.40 (s, 1H). Mass: *m/z* 219 (M⁺). Compound **5b**: IR (KBr, cm⁻¹): 3294, 1682, 1607. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{ppm} 3.80 (s, 3H), 5.21 (s, 2H), 7.04 (d, 2H, *J* = 8 Hz), 7.5–7.8 (m, 4H), 8.1 (s, 1H), 8.2 (d, 2H, *J* = 8 Hz), 8.40 (s, 1H), 11.68 (s, 1H). Mass: *m/z* 337 (M⁺). Compound **6a**: IR (KBr, cm⁻¹): 3423, 1573 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{ppm} 3.68 (s, 2H), 4.70 (s, 2H), 5.73 (s, 1H), 7.37–7.44 (m, 5H, Ar), 7.53 (t, 1H, *J* = 8 Hz), 7.67 (d, 1H, *J* = 8 Hz), 7.81 (t, 1H, *J* = 8 Hz), 8.25 (s, 1H), 8.11 (d, 1H, *J* = 8 Hz), 10.65 (s, 1H). Mass: *m/z* 381 (M⁺). Compound **6b**: IR (KBr, cm⁻¹): 3188, 1678, 1608, 1519. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{ppm} 3.70 (s, 2H), 4.68 (s, 2H), 5.69 (s, 1H), 6.94 (d, 2H, *J* = 8 Hz), 7.31 (d, 2H, *J* = 8 Hz), 7.55 (t, 1H, *J* = 8 Hz), 7.67 (d, 1H, *J* = 8 Hz), 7.82 (t, 1H, *J* = 8 Hz), 8.11 (d, 1H, *J* = 8 Hz), 8.25 (s, 1H), 10.58 (s, 1H). Mass: *m/z* 411 (M⁺). Compound **6c**: IR (KBr, cm⁻¹): 3344, 1735, 1676, 1611. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{ppm} 2.28 (s, 3H), 3.70 (s, 2H), 4.57 (s, 2H), 5.85 (s, 1H), 7.15 (d, 2H, *J* = 8 Hz), 7.25 (d, 2H, *J* = 8 Hz), 7.52 (t, 1H, *J* = 8 Hz), 7.65 (d, 1H, *J* = 8 Hz), 7.81 (t, 1H, *J* = 8 Hz), 8.09 (d, 1H, *J* = 8 Hz), 8.20 (s, 1H). Mass: *m/z* 395 (M⁺). Compound **6d**: IR (KBr, cm⁻¹): 3221, 1681, 1611, 1511. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{ppm} 3.71 (s, 2H), 4.69 (s, 2H), 5.77 (s, 1H), 7.27 (t, 1H, *J* = 8 Hz), 7.56 (d, 1H, *J* = 8 Hz), 7.71 (d, 1H, *J* = 8 Hz), 7.82 (d, 2H, *J* = 8 Hz), 7.86 (t, 1H, *J* = 8 Hz), 8.15 (d, 2H, *J* = 8 Hz), 8.27 (s, 1H), 10.67 (s, 1H). Mass: *m/z* 399 (M⁺).