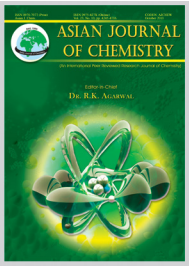
Asian Journal of Chemistry; Vol. 24, No. 11 (2012), 5242-5244

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



An Efficient Synthetic Route for Synthesis of Thiazolidine-4-ones Derivatives

KHALIL PORSHAMSIAN*, NASER MONTAZERI, MASUOD MOHAMMADI-ZEYDI and FARZANEH FOTOKKIANI

Department of Chemistry, Tonekabon Branch, Islamic Azad University Tonekabon, P.O. Box 46841-61167, Iran

*Corresponding author: E-mail: kshams49@gmail.com; kh_pourshamsian@toniau.ac.ir

(*Received*: 14 October 2011; *Accepted*: 15 June 2012) AJC-11606

Reaction of substituted thioureas with α-haloesters in toluene at reflux conditions lead to novel thiazolidine-4-ones derivatives in good yields and comparatively in short times. All structures of the newly synthesized compounds were elucidated by elemental analysis and spectral data.

Key Words: Thiazolidine-4-one, α-Haloesters, High substituted thiourea.

INTRODUCTION

Thiazolidine-4-ones are important building blocks in pharmaceutical agent and biologically active products[1]. Several substituted thiazolidinones have been found to possess hypnotic, anesthetic, sedative, anticonvulsant and microbiological activities[2-4]. Some thiazolidine derivatives show interesting anti-HIV or anticancer activities and can inhibit cell division[5-9]. In view of the various physiological activities of thiazolidinones, many thiazolidinone derivatives have been prepared and several new methods for the preparation of substituted thiazolidine-4-one have been reported[10-11]. However, these methods have several drawbacks, *e.g.*, the need for a high reaction temperature and long reaction time. The development of mild and efficient methods is still desired. We present here an expedient, mild and efficient method to give (2Z)-3-(2-methylphenyl)-2-[(4-chlorobenzoyl)imino]-1,3-thiazolidine-4-one and other same derivatives in good yields and in short times.

EXPERIMENTAL

Compounds **1** (substituted thioureas) and **2** were obtained from E. Merck and used without further purification. Melting points were recorded on an Electrothermal-9100 apparatus. IR spectra were recorded on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 AVANCE instrument; in $CDCl_3$ at 400.13 and 100 MHz, respect to d in ppm and J in Hz. EI-MS (70 ev): Finnigan-MAT-8430 mass spectrometer, in m/z elemental analyses (C, H, N)were performed with a Heraeus CHN-O-rapid analyzer.

Typical procedure for the preparation of compounds 3: To a stirred solution of **1** (2 mmol) in 10 mL of toluene was added dropwise a mixture of **2** (2 mmol) in 2 mL toluene at room temperature over 10 min. Then the mixture was heated under reflux conditions. The progress of reaction was monitored by TLC. After completion of reaction over 4 h, the mixture was cooled and the solvent evaporated by rotatory evaporator. The residue was filtered and recrystallized from EtOH to afford the pure title compounds.

Physical and spectroscopic data of isolated products

(2Z)-3-(2-Methylphenyl)-2-[(4-chlorobenzoyl)imino]-1,3-thiazolidine-4-one (3a): Yellow crystals, yield: (65 %), m.p. 169-171 ºC. IR (KBr, ν_{max} cm^{-1}): 3079 (arom. CH Str.); 2936 (aliph C-H str.) 1729, 1649 (C=O str.); 1593 (C=N str.). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.21(3H, s, CH_3); 4.05(2H, s, CH_2); 7.19(H, d, *J* = 1.2 Hz, CH); 7.34(2H, d, *J* = 4.8 Hz, 2CH); 7.38 -7.48(3H, m, 3CH); 7.88(2H, d, *J* = 4.8 Hz, 2CH). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 17.6 (CH_3); 33.2 (CH_2); 127.1 (CH); 128.0 (CH); 128.6 (2CH); 129.9 (CH); 131.1 (CH); 131.4(2CH); 133.4 (C); 133.9 (C); 135.6 (C); 139.5 (C); 172.0(C=N); 172.3 (C=O); 176.4 (C=O). MS m/z: 344[M^+], 346 [M^++2]; Anal. calcd. for $C_{17}H_{13}N_2O_2SCl$: C, 59.20; H, 3.70; N, 8.10; Found: C, 58.82; H, 3.64; N, 8.68.

(2Z)-3-(4-Ethylphenyl)-2-[(4-methylbenzoyl)imino]-1,3- thiazolidine-4-one (3b): White crystals, yield: (69 %), m.p.: 217-219 ºC. IR (KBr, ν_{max} cm^{-1}): 3048 (arom. CH str.); 2974 (aliph. C-H str.) 1730, 1645 (C=O str.); 1609 (C=N str.). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.34(3H, t, *J* = 7.6 Hz, CH_3); 2.39(3H, s, CH_3); 2.79(2H, q, *J* = 7.6 Hz, CH_2); 4.0(2H, s, CH_2), 7.19(2H, d, *J* = 8.0 Hz, 2CH); 7.28(2H, d, *J* = 6.4 Hz, 2CH); 7.40(2H, d, *J* = 4.8 Hz, 2CH); 7.92(2H, d, *J* = 4.8 Hz, 2CH). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.2 (CH_3); 21.7

(CH_3); 28.6 (CH_2); 33.2 (CH_2); 127.5 (2CH); 128.6 (2CH); 129.0 (2CH); 130.1(2CH); 132.2 (C); 132.4 (C); 143.9 (C); 145.3 (C); 171.6(C=N); 172.6 (C=O); 177.3 (C=O). MS m/z: 338[M^+]; Anal. calcd. for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 3.30; N, 8.20; Found: C, 57.88; H, 3.44; N, 8.98.

(2Z)-3-(4-ethylchlorophenyl)-2-[(4-chlorobenzoyl) imino]-1,3-thiazolidine-4-e(3c): White crystals, yield: (70 %), m.p.: 219-221 ºC. IR (KBr, ν_{max} cm^{-1}): 1740, 1630 (C=O str.); 1593 (C=N str.). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.34(3H, t, *J* = 7.6 Hz, CH_3); 2.79(2H, q, *J* = 7.6 Hz, CH_2); 4.02(2H, s, CH_2), 7.27 (2H, d, *J* = 8.4 Hz, 2CH); 7.34(2H, d, *J* = 4.8 Hz, 2CH); 7.39(2H, d, *J* = 8.4 Hz, 2CH); 7.96(2H, d, *J* = 4.8 Hz, 2CH). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.2 (CH_3); 28.6 (CH_2); 33.2 (CH_2); 127.4 (2CH); 128.6 (2CH); 128.7 (2CH); 131.4(2CH); 132.1 (C); 133.5 (C); 139.5 (C); 145.5 (C); 172.4(C=N); 172.9 (C=O); 176.4 (C=O). MS m/z: 358 [M^+]; Anal. calcd. for $C_{18}H_{15}N_2O_2SCl$: C, 60.20; H, 4.10; N,7.80; Found: C, 59.92; H, 4.24; N, 8.01.

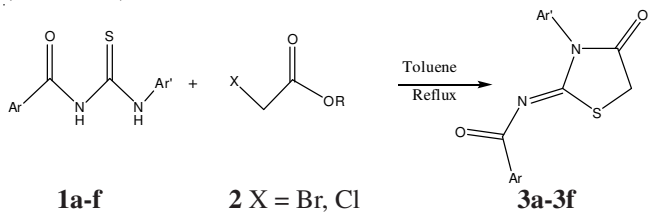
(2Z)-3-(2-Methylphenyl)-2-[4-methylbenzoyl)imino]-1,3-thiazolidine-4-one(3d): Yellow crystals, yield: (73 %), m.p. 171-173 ºC. IR (KBr, ν_{max} cm^{-1}): 1750, 1640 (C=O str.); 1593 (C=N str.). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.21 (3H, s, CH_3); 2.37 (3H, s, CH_3); 4.03(2H, s, CH_2); 7.16(2H, d, *J* = 8.0 Hz, 2CH); 7.21(H, d, *J* = 7.6 Hz, CH); 7.37-7.45(3H, m, 3CH); 7.85(2H, d, *J* = 8.0 Hz, 2CH). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 17.6 (CH_3); 21.7 (CH_3); 33.2 (CH_2); 127.0 (CH); 128.1 (2CH); 129.7 (CH); 130.1 (2CH); 131.1 (CH); 132.4 (C); 134.1 (C); 135.7 (C); 144.0 (C); 171.2(C=N); 172.2 (C=O); 177.3 (C=O). MS m/z: 324[M^+], 326 [M^++2]; Anal. calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.60; H, 4.90; N, 8.60; Found: C, 66.12; H, 4.54; N, 8.88.

(2Z)-3-(4-methylphenyl)-2-[4-methylbenzoyl)imino]-1,3-thiazolidine-4-one(3e): Yellow crystals, yield: (75 %), m.p. 232-224 ºC. IR (KBr, ν_{max} cm^{-1}): 1740, 1640 (C=O str.); 1593 (C=N str.). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.38 (3H, s, CH_3); 2.47(3H, s, CH_3); 3.99(2H, s, CH_2); 7.19(2H, d, *J* = 8.0 Hz, 2CH); 7.24(2H, d, *J* = 4.8 Hz, 2CH); 7.37(2H, d, *J* = 8.0 Hz, 2CH); 7.91(2H, d, *J* = 8.0 Hz, 2CH). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 21.3(CH_3); 21.7 (CH_3); 33.2 (CH_2); 127.4 (2CH); 129.0 (2CH); 129.9 (2CH); 130.1(2CH); 132.1 (C); 132.4 (C); 139.2 (C); 144.0 (C); 171.7(C=N); 172.6 (C=O); 177.3 (C=O). MS m/z: 324[M^+]; Anal. calcd for $C_{18}H_{16}N_2O_2S$: C, 66.60; H, 4.90; N, 8.60; Found: C, 66.12; H, 4.68; N, 8.98.

(2Z)-3-(4-Methylphenyl)-2-[4-chlorobenzoyl)imino]-1,3-thiazolidine-4-one(3f): Yellow crystals, yield: (78 %), m.p. 191-193 ºC. IR (KBr, ν_{max} cm^{-1}): 1740, 1640 (C=O str.); 1593 (C=N str.). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.48 (3H, s, CH_3); 4.0(2H, s, CH_2); 7.22(2H, d, *J* = 4.8 Hz, 2CH); 7.35(2H, d, *J* = 4.8 Hz, 2CH); 7.37(2H, d, *J* = 2.0 Hz, 2CH); 7.95(2H, d, *J* = 4.8 Hz, 2CH). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 21.3(CH_3); 33.2 (CH_2); 127.3 (2CH); 128.6 (2CH); 129.9 (2CH); 131.4(2CH); 131.9 (C); 133.5 (C); 139.4 (C); 139.5 (C); 172.5(C=N); 172.9 (C=O); 176.4 (C=O). MS m/z: 344[M^+], 346 [M^++2]; Anal. calcd. for $C_{17}H_{13}N_2O_2SCl$: C, 59.20; H, 3.70; N, 8.10; Found: C, 59.22; H, 3.76; N, 9.01.

RESULTS AND DISCUSSION

In our continuous guest aimed toward developing biologically active heterocyclic synthesis via acetylenic esters-based reactions involving CH-, NH- or OH-acid compounds [12,13]. Herein we wish to explain an expedient method for construction of some novel 2-imino-thiazolidine-4-one derivatives (**3**) from one-pot reaction between N-aryl-N'-acylthioureas (**1a**) and α-haloesters (**2**) in good yields (**Scheme-I**). The results are summarized in Table-1.



1a-f **2** X = Br, Cl **3a-3f**

Scheme-I: Synthesis of thiazolidine-4-ones derivatives

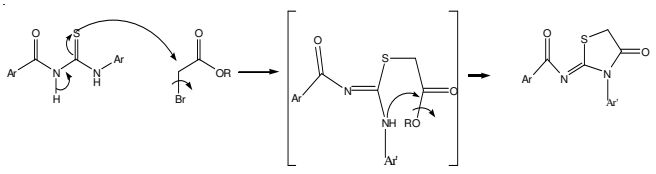
TABLE-1
REACTION PARAMETERS AND YIELDS
FOR THE SYNTHESIS OF **3a-f**

Compound	R	R´	m.p. (ºC)	Yield[a] (%)
3a	*p*-Cl	*o*-Me	169 – 171	65
3b	*p*-Me	*p*-Et	217 – 219	69
3c	*p*-Cl	*p*-Et	219 – 221	70
3d	*p*-Me	*o*-Me	171 – 173	73
3e	*p*-Me	*p*-Me	222 – 224	75
3f	*p*-Cl	*p*-Me	191 – 193	78

[a]Isolated yields.
Reactions were performed using 2 mmol thiourea and α-haloester

High substituted thioureas (**1a-f**) and α-haloesters undergo a smooth reaction in dry toluene at reflux conditions to produce (2Z)-3-aryl-2-aroylimino-1,3-thiazolidine-4-one (**3a-f**) in reasonable yield (**Scheme-I**). The structures of compounds were deduced from their elemental analyses and their IR, ^{1}H and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. The ^{1}H NMR spectrum, of **3a** in $CDCl_3$ showed a singlet for methyl group at δ = 2.21 ppm, methylene at δ = 4.05 ppm along with multiplets δ = 7.19-7.88 ppm for the aromatic protons. The ^{13}C NMR spectra of **3a** showed 15 signals in agreement whit the proposed structure. Partial assignments of these resonances are given in the experimental section. The ^{1}H and ^{13}C NMR spectra of **3b-3f** are similar to those for **3a**, except for the ester and aryl moieties, which exhibit characteristic signals at appropriate chemical shift.

On the basis of well established chemistry of electrophilic esters[10] it is reasonable to assume that compounds **3** results from the initial nucleophilic substitution of the sulfur atom of **1** to the α-haloester and facile exit of chlorine or bromine atom the subsequent conversion of the to **3**. Then the ester group of intermediate **3** is attacked by the amino moiety to yield **3** by elimination of ROH. The proposed mechanism is given in **Scheme-II**.



Scheme-II: Proposed mechanism for the reaction

ACKNOWLEDGEMENTS

Financial support by the Research Council of Islamic Azad University, Tonekabon Branch, is gratefully acknowledged.

REFERENCES

1. G.R. Newkome and A. Nayak, *Adv. Heterocycl. Chem.*, **25**, 83 (1979).
2. S.J. Shah, S.R. Shah and N.C. Desai, *J. Indian Chem. Soc*., **61**, 648 (1984).
3. M.P. Dave, J.M. Patel and N.L. Langalia, *J. Indian Chem. Soc*., **61**, 891 (1984).
4. R.J. Boyce, G.C. Mulqueen and G. Pattenden, *Tetrahedron Lett*., **35**, 5705 (1994).
5. P. Wipf and P.C. Fritch, *Tetrahedron Lett*., **35**, 5397 (1994).
6. J.Y. Lai, J. Yu, B. Mekonnen and J.R. Falck, *Tetrahedron Lett*., **37**, 7167 (1996).
7. M.H. Shih and F.Y. Ke, *Bioorg. Med. Chem*., **12**, 4633 (2004).
8. A. Rao, A. Carbone, A. Chimirri, E.D. Clercq, A.M. Monforte, P. Monforte, C. Pannecouque and M. Zappalà, *IL Farmaco,* **57**, 747 (2002).
9. R. Lakhan and R.L. Singh, *J. Agric. Food Chem*., **39**, 580 (1991).
10. I. Yavari, M. Sabbaghan, K. Pourshamsian, M. Bagheri, S. Ali-Asgari and Z. Hossaini, *Mol. Divers*, **11**, 81 (2007).
11. I. Yavari, K. Porshamsian, M. Bagheri and S. Ali- Asgari, *J. Sulfur Chem.*, **28**, 269 (2007).
12. Kh. Pourshamsian, N. Montazeri, K. Rad-Moghadam and S. Ali-Asgari, *J. Heterocycl. Chem.,* **47**, 1439 (2010).