Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

Synthesis of imidazo[2,1-b]thiazoles through the reaction of thiohydantoins and α-bromoketones

Mohammad M. Ghanbari [a], Issa Yavari [b] & Abedin Emadi [c]

[a] Chemistry Department, Sarvestan Branch, Islamic Azad University, Sarvestan, Iran

[b] Chemistry Department, Science and Research Branch, Islamic Azad University, Tehran, Iran

[c] Chemistry Department, Marvdasht Payam Noor University, Marvdasht, Iran

Published online: 19 Apr 2013.

To cite this article: Mohammad M. Ghanbari , Issa Yavari & Abedin Emadi , Journal of Sulfur Chemistry (2013): Synthesis of imidazo[2,1-b]thiazoles through the reaction of thiohydantoins and α-bromoketones, Journal of Sulfur Chemistry, DOI: 10.1080/17415993.2013.789516

To link to this article: http://dx.doi.org/10.1080/17415993.2013.789516

Journal of Sulfur Chemistry, 2013
http://dx.doi.org/10.1080/17415993.2013.789516

Taylor & Francis
Taylor & Francis Group

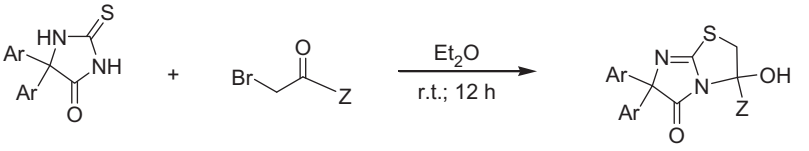
Synthesis of imidazo[2,1-b]thiazoles through the reaction of thiohydantoins and α-bromoketones

Mohammad M. Ghanbari[a]*, Issa Yavari[b] and Abedin Emadi[c]

[a]*Chemistry Department, Sarvestan Branch, Islamic Azad University, Sarvestan, Iran;*
[b]*Chemistry Department, Science and Research Branch, Islamic Azad University, Tehran, Iran;*
[c]*Chemistry Department, Marvdasht Payam Noor University, Marvdasht, Iran*

(*Received 13 February 2013; final version received 21 March 2013*)

Imidazo-fused heterocycles are used as anticancer agents. In this study, some novel imidazo[2,1-b]thiazoles were synthesized from thiohydantoins and α-bromoketones in good yields. This method has the advantages of simple operation, high yields, and mild reaction conditions and uses less toxic and low-cost chemical reagents.



74–97%

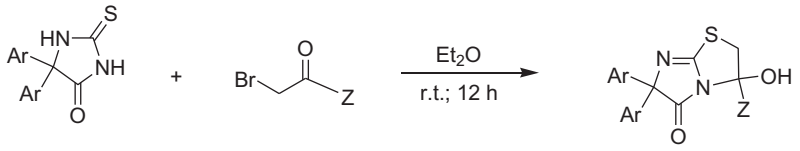
Z=CO_2Et,4-MeO-C_6H_5,4-Br-C_6H_5
Ar=Ph,4-Me-C_6H_5,4-Cl-C_6H_5,4-Br-C_6H_5,4-MeO-C_6H_5

Keywords: imidazo[2,1-b]thiazole; thiohydantoin; α-bromoketones; anticancer; thioxoimidazolidin

1. Introduction

The search for anticancer drugs led to the discovery of several imidazo-fused heterocycles having anticancer activity (*1–5*). Imidazo[2,1-b][1,3,4]thiadiazole, imidazo[2,1-b][1,3]-thiazoles, and diazepinone-fused derivatives occupy a prominent place in medicinal chemistry because of their significant properties as therapeutics (*6*). As part of our current studies on the development of new routes in heterocyclic synthesis (*7–9*), we now report an efficient one-pot synthesis of imidazo[2,1-b]thiazoles **4** (Scheme 1).

*Corresponding author. Email: m.mehdi.ghanbari@gmail.com



1	Ar
a	C_6H_5
b	4-Me-C_6H_5
c	4-Cl-C_6H_5

2	Z
a	CO_2Et
b	4-MeO-C_6H_5
c	4-Br-C_6H_5

3	Ar	Z
a	C_6H_5	CO_2Et
b	4-Me-C_6H_5	CO_2Et
c	4-Cl-C_6H_5	CO_2Et
d	C_6H_5	4-MeO-C_6H_5
e	C_6H_5	4-Br-C_6H_5
f	4-Me-C_6H_5	4-MeO-C_6H_5
g	4-Me-C_6H_5	4-Br-C_6H_5

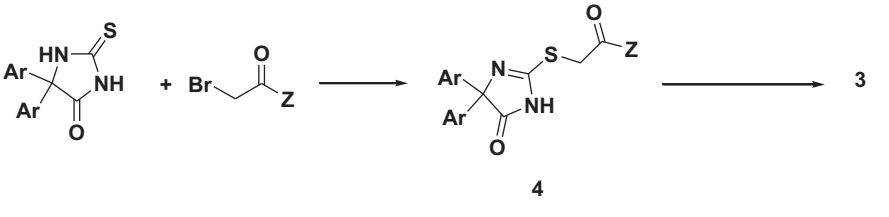
Scheme 1. The one-pot synthesis of imidazo[2,1-b]thiazole **3**.

2. Results and discussion

The reaction shown in Scheme 1 proceeded spontaneously in diethyl ether and was completed after a few hours. The ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of **3**. The structures of compounds **3a**–**3g** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}CNMR spectra. The mass spectra of these compounds displayed molecular and fragmentation ion peaks at appropriate *m*/*z* values.

The ^{1}H NMR spectrum of **3a** exhibited five sharp singlets readily recognized as arising from a methyl group ($\delta = 1.25$ ppm), a methylene group ($\delta = 3.65$ and 4.15 ppm), and CH_2O ($\delta = 4.25$–4.49 ppm) protons, along with a multiplet for the aromatic ($\delta = 7.24$–7.52 ppm) protons. The ^{1}H and ^{13}C NMR spectra of **3b**–**3g** are similar to those of **3a** except for the alkoxy and aromatic moieties, which exhibited characteristic signals with appropriate chemical shifts. The structural assignments of compounds **3a**–**3g** made on the basis of their NMR spectra were supported by their IR spectra. Of special interest are the alcohol absorption bands, observed in all of the compounds **3**, at approximately 3440 cm^{-1}.

A plausible mechanism for the formation of imidazo[2,1-b]thiazoles **3a**–**3g** is shown in Scheme 2. The reaction proceeds by addition of the thiohydantoins to the α-bromoketones to produce intermediate **4**. Finally, the negatively charged ion collapses by attack at the carbonyl group to produce **3** (Scheme 2). The absence of a strong ketone carbonyl signal at about 190 ppm in all the compounds and the presence of a peak at about 90 ppm indicative of a C–OH carbon in ^{13}C-NMR indicate conversion of the intermediate **4** to the imidazo[2,1-b] thiazole **3**.



Scheme 2. Proposed mechanism for the formation of imidazo[2,1-b]thiazole **3**.

3. Conclusions

The reaction between thiohydantoins and α-bromoketones provides a simple one-pot synthesis of imidazo[2,1-b]thiazoles of potential synthetic and pharmaceutical interest. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

4. Experimental

4.1. *General*

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHNO-Rapid analyzer. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance instrument with $CDCl_3$ as the solvent at 300.1 and 75.1 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Isocyanides and dialkyl acetylenedicaboxylates were obtained from Fluka and were used without further purification. 5,5-Diaryl-2-thioxoimidazolidin-4-ones **1** were prepared by known methods (*10*, *11*).

4.2. *Typical procedure for the preparation of ethyl-2,3,5,6-tetrahydro-2-hydroxy-5-oxo-6, 6-diphenylimidazo[2,1-b]thiazole-2-carboxylate (3a)*

A solution of 0.390 g **2a** (2 mmol) in 3 ml of ether was added dropwise to a stirred solution of 0.537 g of **1a** (2 mmol) in 3 ml of ether at room temperature over a period of 10 min. The reaction mixture was left to stand for 12 h and the resulting product was filtered off and washed with cold diethyl ether.

4.2.1. *Ethyl-2,3,5,6-tetrahydro-3-hydroxy-5-oxo-6,6-diphenylimidazo[2,1-b]thiazole-3-carboxylate (**3a**)*

White powder; mp: 202–203°C; yield: 0.73 g (95%); IR (KBr) (ν_{max}/cm^{-1}): 3442 (OH), 1750 (C9O), 1448 (C9C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (3 H, t, $^3J_{HH} = 7.1$, Me), 3.65 (1 H, d, $^2J_{HH} = 11.7$, CH), 4.15 (1 H, d, $^2J_{HH} = 11.7$, CH), 4.25–4.49 (2 H, m, ABX_3 system, $J_{AX} = 7.1$, $J_{BX} = 7.1$, $J_{AB} = 10.6$ Hz, CH_2O), 4.99 (1 H, br s, OH), 7.24–7.52 (10 H, m, 2 C_6H_5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.3$ (Me), 45.7 (CH_2), 64.7 (CH_2), 83.2 (C), 87.4 (C), 127.2 (2 CH), 127.4 (2 CH), 127.5 (2 CH), 128.4 (2 CH), 128.9 (CH), 129.2 (CH), 139.6 (C), 140.2 (C), 166.9 (C9O), 168.2 (C9O), 176.0 [NC(S)N] ppm. Anal. Calcd (%) for $C_{20}H_{18}N_2O_4S$ (382.43): C, 62.81; H, 4.74; N, 7.33; S, 8.38. Found: C, 62.60; H, 4.82; N, 7.16; S, 8.57; EI-MS: *m*/*z*(%), 382 (M^+, 15), 364 (78), 337 (75), 266 (20), 166 (100), 77 (26), 59 (14), 45 (84).

4.2.2. *Ethyl-2,3,5,6-tetrahydro-3-hydroxy-5-oxo-6,6-dip-tolylimidazo[2,1-b]thiazole-3-carboxylate (**3b**)*

White powder; mp: 148–150°C; yield: 0.70 g (85%); IR (KBr) (ν_{max}/cm^{-1}): 3440 (OH), 1750 (C9O), 1447 (C9C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.22$ (3 H, t, $^3J_{HH} = 7.1$, Me), 2.29 (3 H, S, Me), 2.36 (3 H, S, Me), 3.64 (1 H, d, $^2J_{HH} = 11.7$, CH), 4.14 (1 H, d, $^2J_{HH} = 11.7$, CH), 4.25–4.38 (2 H, m, ABX_3 system, $J_{AX} = 7.1$, $J_{BX} = 7.1$, $J_{AB} = 10.6$ Hz, CH_2O), 4.98 (1 H, br s, OH),

7.12–7.35 (8 H, m, 2 C_6H_4) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.3$ (Me), 21.5 (Me), 21.6 (Me), 50.3 (CH_2), 65.2 (CH_2), 82.6 (C), 87.1 (C), 126.9 (2 CH), 127.0 (2 CH), 127.7 (2 CH), 130.4 (2 CH), 130.5 (C), 132.4 (C), 140.3 (C), 140.4 (C), 165.8 (C9O), 167.6 (C9O), 176.8 [NC(S)N] ppm. Anal. Calcd (%) for $C_{22}H_{22}N_2O_4S$ (410.49): C, 64.37; H, 5.40; N, 6.82; S, 7.81. Found: C, 64.50; H, 5.52; N, 6.70; S, 8.01.

4.2.3. *Ethyl-6,6-bis(4-chlorophenyl)-2,3,5,6-tetrahydro-3-hydroxy-5-oxoimidazo[2,1-b] thiazole-3-carboxylate (**3c**, $C_{20}H_{16}C_{l2}N_2O_4S$)*

White powder; mp: 208–210°C; yield: 0.68 g (75%); IR (KBr) (ν_{max}/cm^{-1}): 3440 (OH), 1751 (C9O), 1448 (C9C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (3 H, t, $^3J_{HH} = 7.1$, Me), 3.69 (1 H, d, $^2J_{HH} = 11.7$, CH), 4.17 (1 H, d, $^2J_{HH} = 11.7$, CH), 4.26–4.52 (2 H, m, ABX_3 system, $J_{AX} = 7.1$, $J_{BX} = 7.1$, $J_{AB} = 10.5$ Hz, CH_2O), 4.97 (1 H, br s, OH), 7.24–7.45 (8 H, m, 2 C_6H_4) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.5$ (Me), 50.6 (CH_2), 65.4 (CH_2), 82.5 (C), 87.1 (C), 129.3 (2CH), 129.5 (2CH), 129.8 (2CH), 129.9 (2CH), 131.5 (C), 131.6 (C), 138.4 (C), 138.5 (C), 165.8 (C9O), 167.8 (C9O), 176.9 [NC(S)N] ppm.

4.2.4. *2,3-Dihydro-3-hydroxy-3-(4-methoxyphenyl)-6,6-diphenylimidazo [2,1-b]thiazol-5(6H)-one (**3d**, $C_{24}H_{20}N_2O_3S$)*

White powder; mp: 232–234°C; yield: 0.89 g (97%); IR (KBr) (ν_{max}/cm^{-1}): 3442 (OH), 1750 (C9O), 1448 (C9C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.92$ (3 H, S, MeO), 3.96 (1 H, br s, OH), 4.72 (1 H, d, $^2J_{HH} = 14.5$, CH), 4.39 (1 H, d, $^2J_{HH} = 14.5$, CH), 7.04–8.31 (14 H, m, 2 C_6H_5, C_6H_4) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 47.7$ (CH_2), 54.7 (Me), 64.7 (CH_2), 83.0 (C), 87.4 (C), 114.4 (C), 127.4 (2 CH), 127.5 (2 CH), 127.8 (CH), 127.9 (CH), 128.8 (2 CH), 128.9 (2 CH), 129.0 (2 CH), 129.1 (2 CH), 131.5 (C), 139.1 (C), 139.2 (C), 166.9 (C9O), 176.1 [NC(S)N] ppm. Anal. Calcd (%) for $C_{24}H_{20}N_2O_3S$ (416.49): C, 69.21; H, 4.84; N, 6.73; S, 7.70. Found: C, 69.30; H, 4.72; N, 6.58; S, 7.81.

4.2.5. *3-(4-Bromophenyl)-2,3-dihydro-3-hydroxy-6,6-diphenylimidazo[2,1-b]thiazol-5(6H)-one (**3e**, $C_{23}H_{17}BrN_2O_2S$)*

White powder; mp: 225–227°C; yield: 0.70 g (75%); IR (KBr) (ν_{max}/cm^{-1}): 3441 (OH), 1750 (C9O), 1452 (C9C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.37$ (1 H, d, $^2J_{HH} = 14.8$, CH), 4.75 (1 H, d, $^2J_{HH} = 14.8$, CH), 4.99 (1 H, br s, OH), 7.24–8.10 (14 H, m, 2 C_6H_5, C_6H_4) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.2$ (CH_2), 83.2 (C), 87.4 (C), 127.3 (2 CH), 127.5 (2 CH), 127.8 (CH), 127.9 (CH), 128.3 (C), 128.8 (2 CH), 128.9 (2 CH), 130.7 (2 CH), 132.3 (2 CH), 131.5 (C), 141.0 (C), 141.1 (C), 166.9 (C9O), 176.2 [NC(S)N] ppm.

4.2.6. *4-Methoxyphenyl 2,3,5,6-tetrahydro-3-hydroxy-5-oxo-6,6-dip-tolylimidazo [2,1-b]thiazole-3-carboxylate (**3f**, $C_{26}H_{24}N_2O_3S$)*

White powder; mp: 194–196°C; yield: 0.66 g (74%); IR (KBr) (ν_{max}/cm^{-1}): 3442 (OH), 1750 (C9O), 1450 (C9C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.29$ (3 H, S, Me), 2.36 (3 H, S, Me), 3.92 (3 H, S, MeO), 3.96 (1 H, br s, OH), 4.72 (1 H, d, $^2J_{HH} = 14.5$, CH), 4.39 (1 H, d, $^2J_{HH} = 14.5$, CH), 7.00–8.31 (14 H, m, 3 C_6H_4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.5$ (Me), 21.6 (Me), 54.8 (Me), 47.7 (CH_2), 83.2 (C), 87.4 (C), 114.4 (C), 126.9 (2 CH), 127.0 (2 CH), 127.7 (2 CH), 128.7 (2 CH), 128.9 (2 CH), 130.4 (2 CH), 130.5 (C), 131.5 (C), 132.4 (C), 140.3 (C), 140.4 (C), 166.9 (C9O), 176.0 [NC(S)N] ppm.

4.2.7. *4-Bromophenyl 2,3,5,6-tetrahydro-3-hydroxy-5-oxo-6,6-dip-tolylimidazo [2,1-b]thiazole-3-carboxylate (**3g**, $C_{25}H_{21}BrN_2O_2S$)*

White powder; mp: 180–182°C; yield: 0.76 g (77%); IR (KBr) (ν_{max}/cm^{-1}): 3441 (OH), 1750 (C9O), 1452 (C9C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.29$ (3 H, S, Me), 2.36 (3 H, S, Me), 4.37 (1 H, d, $^2J_{HH} = 14.8$, CH), 4.75 (1 H, d, $^2J_{HH} = 14.8$, CH), 4.99 (1 H, br s, OH), 7.12–8.10 (14 H, m, 2 C_6H_4) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.5$ (Me), 21.6 (Me), 52.2 (CH_2), 83.0 (C), 87.4 (C), 126.9 (2 CH), 127.0 (2 CH), 127.7 (2 CH), 128.3 (C), 128.5 (2 CH), 128.7 (2 CH), 130.5 (2 CH), 131.5 (C), 131.7 (C), 132.3 (C), 141.0 (C), 141.1 (C), 166.7 (C9O), 176.0 [NC(S)N] ppm.

References

(1) Andreani, A.; Rambaldi, M.; Andreani, F.; Bossa, R.; Galatulas, I. *Eur. J. Med. Chem.* **1988,** *23,* 385–389.
(2) Chern, J.; Liaw, Y.; Chen, C.; Rong, J.; Huang, C. *Heterocycles* **1993,** *36,* 1091–1103.
(3) Andreani, A.; Rambaldi, M.; Leoni, A.; Locatelli, A.; Bossa, R. *J. Med. Chem.* **1996,** *39,* 2852–2855.
(4) Terzioglu, N.; Gursoy, A. *Eur. J. Med. Chem.* **2003,** *38,* 781–786.
(5) Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Giorgi, G.; Salvini, L.; Garaliene, V. *Anti-Cancer Drug Des.* **2001,** *16,* 167–174.
(6) Kolavi, G.; Hegde, V.; Khazi, I.A. *Tetrahedron Lett*. **2006,** *47,* 2811–2814.
(7) Blackshire, R.B.; Sharpe, C.J. *J. Chem. Soc. C*. **1971,** 3602–3605.
(8) Ghanbari, M.M. *Monatsh Chem.* **2011,** *142,* 749–752.
(9) Yavari, I.; Ghanbari, M.M.; Azizian, J.; Sheikholeslami, F. *J. Chem. Res.* **2011,** *5,* 87–88.
(10) Ghanbari, M.M.; Mahdavinia, G.H.; Safari, J.; Naeimi, H.; Zare, M. *Synth. Commun.* **2011,** *16,* 2414–2420.
(11) Safari, J.; Naeimi, H.; Ghanbari, M.M.; Sabzi-Fini, O. *Russ. J. Org. Chem.* **2009,** *45,* 477–479.