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# The Effect Of Different Kinds Of Catalyst On Synthesis Of Some New Imidazo[2,1-b]Thiazoles Through The Reaction Of Thiohydantoins And A-Bromoketones

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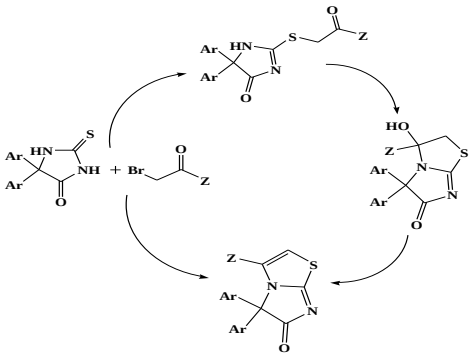
**Abstract:** Some novel imidazo[2,1-b]thiazoles were synthesized from thiohydantoins and α-bromoketones in good yields and two methods. These methods has the advantages of simple operation, high yields, mild reaction conditions, and uses less toxic and low cost chemical reagents.



**Keywords:** Thiohydantoin; Imidazo[2,1-b]thiazole; α-Bromoketones; Anticancer; Acetic acid.

## 1 Introduction

The imidazo[2,1-b]thiazole derivatives are important *N*-bridge heterocyclic compounds scaffolds are known to exhibit broad spectrum of various biological and medicinal activities such as antibacterial, antiparasitic, antifungal, antiviral, anthelmintic, antitumor, cardiotonic, chemopreventive, and antioxidant anti-inflammatory and antihypertensive properties [1-6]. 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 **5** in good yield by two methods (Scheme 1).

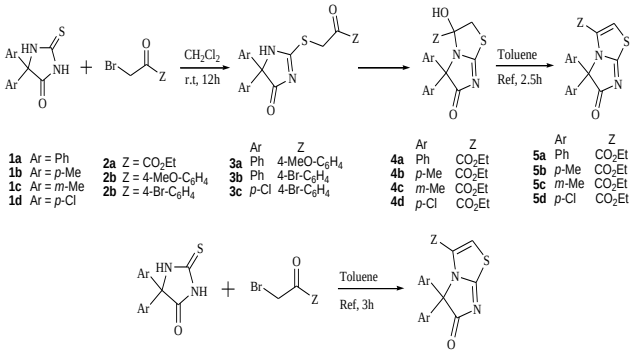
## 2 Results and Discussion

The reaction shown in Scheme 1 proceeded spontaneously in solvent and the present catalyst, was completed after a few hours. The $^{1}$H and $^{13}$C NMR spectra of the crude products clearly indicated the formation of **5**. The structures of compounds **5a–5d** 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 **5a** exhibited four sharp picks readily recognized as arising from a methyl group ($\delta$ = 1.24 ppm), a $CH_2O$ ($\delta$ = 4.23 ppm) and CH group ($\delta$ = 6.53 ppm) protons, along with a multiplet for the aromatic ($\delta$ = 7.01–7.76 ppm) protons. The $^{1}$H and $^{13}$C NMR spectra of **5b–5d** are similar to those of **5a** except for the aromatic moieties, which exhibited characteristic signals with appropriate chemical shifts. The structural assignments of compounds **5a–5d** made on the basis of their NMR spectra were supported by their IR spectra.

Of special interest the alcohol absorption bands didn't observed in all of the compounds **5**, at approximately 3440 $cm^{-1}$. In this study we reported an efficient synthetic procedure for the preparation of imidazo[2,1-b]thiazoles **5** in the presence of acetic acid as a catalyst. To choose the best catalyst among various common acidic catalyst (Table 2), the results showed that AcOH has the best yield in the shortest reaction time, so that it was selected as catalyst for subsequent experiments.

The absence of a strong ketone carbonyl signals 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 **3** to the imidazo[2,1-b]thiazole **4**. Finally, one water will be eliminate and produce imidazo[2,1-b]thiazoles **5** in 50-98% yields (see Scheme 1 and Table 1).




**Schem 1.** The one-pot and two-steps synthesis of imidazo[2,1-b]thiazole-3-carboxylate **5**.

**Table 1.** The two-steps and one-pot synthesis of Imidazo[2,1-b]thiazoles **5**

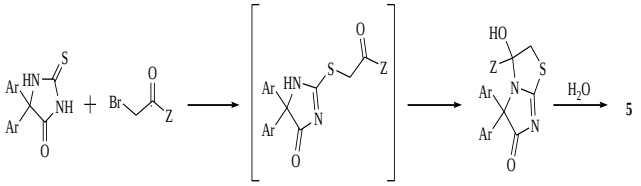
| Entry | Ar | Z | Product | Yield (%) Two-steps | Yield (%) One-pot |
|---|---|---|---|---|---|
| 1 | Ph | $CO_2Et$ | **5a** | 98 | 95 |
| 2 | *p*-Me | $CO_2Et$ | **5b** | 90 | 80 |
| 3 | *m*-Me | $CO_2Et$ | **5c** | 80 | 60 |
| 4 | *p*-Cl | $CO_2Et$ | **5d** | 75 | 50 |

**Table2.** The effect of catalyst on the Imidazo[2,1-b]thiazoles **5** synthesis

| Catalyst | Time (h) | Yield (%) |
|---|---|---|
| **AcOH** | **3** | **95** |
| $AlCl_3$ | 6 | 50 |
| *p*-TSA | 6 | 50 |
| $H_3BO_3$ | 3 | 35 |

For confirming of this mechanism we used two types of α-bromoketones. When the ethyl bromopyruvate (ethyl-3-bromo-2-oxopropanoate) was used the reaction goes to the final product **5** but when was used 2-bromo-1-arylethanone the reaction was stopped until intermediate **3** in 74-88% yields (Scheme 1). No other products than **3** could be detected.

A plausible mechanism for the formation of imidazo[2,1-b]thiazoles **5a–5d** is shown in Scheme 2. The reaction proceeds by addition of the thiohydantoins and α-bromoketones to produce intermediate **3**. Then the negatively charged ion collapses by attack at the carbonyl group to produce **4** (Scheme 2).




**Scheme 2**. Proposed mechanism for the formation of imidazo[2,1-b]thiazole **5**.

## 3 Conclusions

The reaction between 2-thiohydantoins and α-bromopyrovate (ethyl-3-bromo-2-oxopropanoate) provides an efficient synthesis of imidazo[2,1-b]thiazoles of potential synthetic and pharmaceutical interest. However, in the other reaction the ring did not close. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used with acetic acid as a catalyst.

## 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 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 dialkylacetylenedicaboxylates, 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 Synthesis of ethyl 2,3,5,6-tetrahydro-3-hydroxy-6-oxo-5,5-diphenylimidazo[2,1-b]thiazole-3-carboxylate (4a)*

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

### *4.3 Typical Procedure for the Synthesis of 2-(2-(4-methoxyphenyl)-2-oxoethylthio)-5,5-diphenyl-1H-imidazol-4(5H)-one (3a)*

A solution of 2-bromo-1-(4-methoxyphenyl)ethanone **2b** (0.458 g, 2 mmol) in 3 mL of dichloromethane was added drop wise to a stirred solution of **1a** (0.537 g, 2 mmol) in 3 mL of dichloromethane at room temperature over a period of 10 min. The reaction mixture walls left to stand for 12 h, and the resulting product was filtered off and washed with cold diethyl ether.

### *4.4 Typical Procedure for the Synthesis of ethyl 5,6-dihydro-6-oxo-5,5-diphenylimidazo [2,1-b] thiazole-3-carboxylate (5a)*

#### *4.4.1 Two-steps method*

The compound **4a** (0.765 g, 2 mmol) refluxed in 2 mL toluene in the presence of acetic acid (10 mol %) for 2.5 h. After cooling the residue was purified by column chromatography ($SiO_2$; hexane/EtOAc 3:1) to give the title compounds.

#### *4.4.2 One-step method*

A mixture of ethyl bromopyruvate **2a** (0.390 g, 2 mmol), **1a** (0.537 g, 2 mmol) and AcOH catalyst (10 mol %) in 4 mL toluene was refluxed for 3h. The reaction mixture was allowed to cool and was purified by column chromatography ($SiO_2$; hexane/EtOAc 3:1) to give the title compounds.

## 5 Spectra data of intermediate 3

### *5.1 2-(2-(4-methoxyphenyl)-2-oxoethylthio)-5,5-diphenyl-1H-imidazol-4(5H)-one (3a)*

White powder; mp: 172-174°C; yield: 0.73 g (88%); IR (KBr) ($\nu_{max}/cm^{-1}$): 1774 (C=O), 1725 (C=O), 1452 (C=C); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 3.94 (3 H, s, MeO), 4.70 (2 H, s, $CH_2$), 7.04-8.31 (14 H, m, 2 $C_6H_5$, $C_6H_4$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 45.6 ($CH_2$), 54.8 (Me), 83.2 (C), 114.4 (C), 127.3 (4 CH), 127.9 (2 CH), 128.9 (4 CH), 129.0 (2 CH), 129.1 (2 CH), 131.5 (C), 139.1 (2 C), 178.2 (C=O), 183.0 [NC(S)N], 192.3 (C=O) 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, 4.92; N, 6.63; S, 7.77.

### *5.2 2-(2-(4-bromophenyl)-2-oxoethylthio)-5,5-diphenyl-1H-imidazol-4(5H)-one (3b)*

White powder; mp: 162-164°C; yield: 0.78 g (84%); IR (KBr) ($\nu_{max}/cm^{-1}$): 1774 (C=O), 1724 (C=O), 1450 (C=C); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 4.88 (2 H, s, $CH_2$), 7.24-8.11 (14 H, m, 2 $C_6H_5$, $C_6H_4$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 37.6 ($CH_2$), 78.2 (C), 127.3 (4 CH), 127.9 (2 CH), 128.3 (C), 128.5 (4 CH), 130.7 (2 CH), 132.3 (2 CH), 131.5 (C), 141.1 (2 C), 178.2 (C=O), 182.3 [NC(S)N], 192.5 (C=O) ppm.

### *5.3 2-(2-(4-bromophenyl)-2-oxoethylthio)-5,5-bis(4-chlorophenyl)-1H-imidazol-4(5H)-one (3c)*

White powder; mp: 181-183°C; yield: 0.83 g (78%); IR (KBr) ($\nu_{max}/cm^{-1}$): 1774 (C=O), 1724 (C=O), 1450 (C=C); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 4.76 (2 H, s, $CH_2$), 7.24-7.94 (12 H, m, 3 $C_6H_4$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 35.6 ($CH_2$), 78.0 (C), 129.3 (4 CH), 129.9 (2 C), 128.3 (C), 128.5 (4 CH), 130.7 (2 CH), 132.3 (2 CH), 131.5 (C), 138.4 (2 C), 178.2 (C=O), 182.3 [NC(S)N], 192.5 (C=O) ppm.

## 6 Spectra data of imidazo[2,1-b]thiazole-3-carboxylate (5)

### *6.1 Ethyl 5,6-dihydro-6-oxo-5,5-diphenylimidazo [2,1-b]thiazole-3-carboxylate (5a)*

White powder; IR (KBr) ($\nu_{max}/cm^{-1}$): 1750 (C=O), 1448 (C=C); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.24 (3 H, t, $^3J_{HH}$ = 6.8, Me), 4.23 (2 H, q, $^3J$ = 6.8 Hz, $CH_2O$), 6.53 (1 H, s, CH), 7.01-7.76 (10 H, m, 2 $C_6H_5$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 14.3 (Me), 64.7 ($CH_2$), 83.2 (C), 114.8 (CH), 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), 145.4 (C), 166.9 (C=O), 168.2 (C=O), 176.0 [NC(S)N] ppm; Anal. Calcd (%) for $C_{20}H_{16}N_2O_3S$ (364.42): C, 65.92; H, 4.43; N, 7.69; S, 8.80. Found: C, 65.81; H, 4.52; N, 7.76; S, 8.77;

### *6.2 Ethyl 5,6-dihydro-6-oxo-5,5-di-p-tolylimidazo [2,1-b]thiazole-3-carboxylate (5b)*

White powder; IR (KBr) ($\nu_{max}/cm^{-1}$): 1750 (C=O), 1447 (C=C); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.33 (3 H, t, $^3J_{HH}$ = 7.1, Me), 2.41 (6 H, s, 2 Me), 4.17 (2 H, q, $^3J_{HH}$ = 7.1 Hz, $CH_2O$), 6.60 (1 H, s, CH), 7.22-7.60 (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), 65.2 ($CH_2$), 82.6 (C), 114.9 (CH), 126.9 (2 CH), 127.0 (2 CH), 127.7 (2 CH), 130.4 (2 CH), 130.5 (C), 132.4 (C), 139.3 (C), 139.4 (C), 145.5 (C), 165.8 (C=O), 167.6 (C=O), 176.8 [NC(S)N] ppm; Anal. Calcd (%) for $C_{22}H_{20}N_2O_3S$ (392.47): C, 67.33; H, 5.14; N, 7.14; S, 8.17. Found: C, 67.50; H, 5.12; N, 7.20; S, 8.21.

### *6.3 Ethyl 5,6-dihydro-6-oxo-5,5-di-m-tolylimidazo [2,1-b]thiazole-3-carboxylate (5c)*

White powder; IR (KBr) ($\nu_{max}/cm^{-1}$): 1750 (C=O), 1447 (C=C); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.33 (3 H, t, $^3J_{HH}$ = 7.1, Me), 2.31 (6 H, s, 2 Me), 4.17 (2 H, q, $^3J_{HH}$ = 7.1 Hz, $CH_2O$), 6.62 (1 H, s, CH), 7.22-7.60 (8 H, m, 2 $C_6H_4$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 14.3 (Me), 21.8 (Me), 21.9 (Me), 65.2 ($CH_2$), 82.6 (C), 114.9 (CH), 126.8 (2 CH), 127.1 (2 CH), 127.8 (2 CH), 130.4 (2 CH), 131.5 (C), 132.9

(C), 140.3 (C), 140.5 (C), 145.4 (C), 165.8 (C=O), 167.6 (C=O), 176.8 [NC(S)N] ppm.

### *6.4 Ethyl 5,5-bis(4-chlorophenyl)-5,6-dihydro-6-oxoimidazo [2,1-b]thiazole-3-carboxylate (5d)*

White powder; IR (KBr) ($\nu_{max}/cm^{-1}$): 1751 (C=O), 1448 (C=C); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.29 (3 H, t, $^3J_{HH}$ = 7.1, Me), 4.38 (2 H, q, $^3J_{HH}$ = 7.1 Hz, $CH_2O$), 6.68 (1 H, s, CH), 7.24-7.45 (8 H, m, 2 $C_6H_4$) ppm;$^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 14.5 (Me), 65.4 ($CH_2$), 82.5 (C), 114.8 (CH), 129.3 (2 CH), 129.5 (2 CH), 129.8 (2 CH), 129.9 (2 CH), 131.5 (C), 131.6 (C), 138.4 (C), 138.5 (C), 145.4 (C), 165.8 (C=O), 167.8 (C=O), 176.9 [NC(S)N] ppm. Anal. Calcd (%) for $C_{20}H_{14}N_2O_3S$ (433.31): C, 55.44; H, 3.26; N, 6.47; S, 7.40 Found: C, 55.50; H, 3.30; N, 6.40; S, 7.35.

## References


[1] S. Garima, A. A. Ranjana; *Journal of Sulfur Chemistry*. **2015**, 36, 170-177.

[2] B. Thirupaiah, R. R. Vedula; *Indian Journal of Chemistry*. **2015**, 54B, 811-814.

[3] A. R. Ali, E. R. El-Bendary, M. A. Ghaly, I. A. Shehata; *European Journal of Medicinal Chemistry*. **2014**, 75, 492-500.

[4] M. Barazandehtehrani, S. Emami, M. Asadi, M. Saeedi, M. R. Mirzahekmati, S. M. Ebrahimi, M. Mahdavi, H. Nadri, A. R. Moradi, F. Homayounimoghadam, S. Farzipour, M. Vosooghi, A. R. Foroumadi, A. Shafiee; *European Journal of Medicinal Chemistry*. **2014**, 87, 759-764.

[5] M. Mahdavi, M. Asadi, M. Saeedi, M. Ebrahimi, M. A. Rasouli, P. R. Ranjbar, A. R. Foroumadi, A. Shafiee; *Synthesis*. **2012**, 44, 3649–3654.

[6] N. S. Shetty, R. S. Koti, R. S. Lamani, N. P. Badiger, I. M. Khazi; *Journal of Sulfur Chemistry*. **2008**, 29, 539-547.

[7] R. B. Blackshire, C. J. Sharpe; *J. Chem. Soc. C*. **1971**, 3602–3605.

[8] M. M. Ghanbari; *Monatsh Chem*. **2011**, 142, 749–752.

[9] M. M. Ghanbari, I. Yavari, A. Emadi; *Journal of Sulfur Chemistry*. **2014**, 35, 57-61.

[10] M. M. Ghanbari, G. H. Mahdavinia, J. Safari, H. Naeimi. M. Zare; *Synth. Commun*. **2011**, 16, 2414–2420.

[11] J.Safari, H. Naeimi, M. M. Ghanbari, O. Sabzi-Fini; *Russ. J. Org. Chem*. **2009**, 45, 477-479.