Research article

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Preparation of imidazo[2,1-b]thiazole-3-carboxylate by the condensation of thiohydantoins and ethylbromopyruvate

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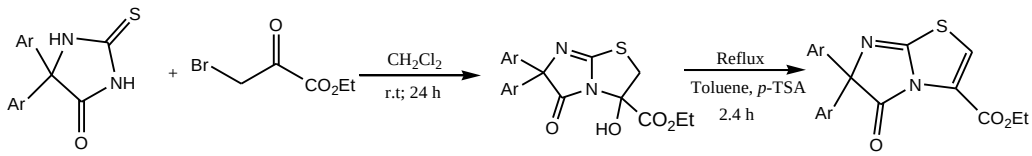
Abstract- Imidazo[2,1-b]thiazoles are obtaind in excellent yields from the addition reaction between thiohydantoin and ethylbromopyruvate. These imidazo[2,1-b]thiazoles in the presence of p-TSA in boiling toluene refluxed for 2.5 hours led to imidazo[2,1-b]thiazole-3-carboxylates in elimination reactions.

Keywords: Imidazo[2,1-b]thiazole; Thiohydantoin; Ethylbromopyruvate; Anticancer; Thioxoimidazolidin.

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 synthesis of imidazo[2,1-b]thiazole-3-carboxylate **4** (see Scheme 1).



1 2 3 4

1	Ar
a	C_6H_5
b	p-Tolyl

3	Ar
a	C_6H_5
b	p-Tolyl

4	Ar
a	C_6H_5
b	p-Tolyl

Scheme 1. Synthesis of imidazo[2,1-b]thiazole-3-carboxylate .

Experimental

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. 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].

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 ethylbromopyruvate (2mmol) in 3 mL of dichloromethane was added dropwise to a stirred solution of 0.537 g of **1a** (2 mmol) in 3 mL of dichloromethane at room

temperature over a period of 10 min. The reaction mixture walls left to stand for 24 h, and the resulting product was filtered off and washed with cold diethyl ether.

Finally the compound **3a** refluxed in 2 mL toluene in the presence of 10% p-TSA for 2.5 h. After cooling the residue was purified by column chromatography (SiO_2; hexane/EtOAc 3:1) to afford the title compounds.

Results and discussion

A simple and efficient approach for the synthesis of imidazo[2,1-b]thiazole-3-carboxylate. The reaction proceeds by addition of the thiohydantoins to the ethylbromopyruvate to produce **3**. Finally, in elimination reaction on **3** affords product **4**. The reaction shown in Scheme 1 proceeded spontaneously in dichloromethane, and was completed after 24 hours. The ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of **3**. The structures of compounds **3a–3b** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectra.

Conclusions

The reaction between thiohydantoins and ethylbromopyruvate provides a simple 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.

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 (C=O), 1448 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (3 H, t, $^{3}J_{HH}$ = 7.1, Me), 3.65 (1 H, d,

$^{2}J_{HH}$ = 11.7, CH), 4.15 (1 H, d, $^{2}J_{HH}$ = 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, $CDCl_3$): δ = 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 (C=O), 168.2 (C=O), 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).

Ethyl-5,6-dihydro-3-hydroxy-5-oxo-6,6-diphenylimidazo[2,1-b]thiazole-3-carboxylate (4a)

White powder; mp: 233.5-234.5°C; yield: 0.78 g (95%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (3 H, t, Me), 4.20 (2 H, q, CH_2O), 6.84-7.54 (10 H, m, 2 C_6H_5) ppm.

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