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Short Note

Diethyl 4-(6-Chloroimidazo[2,1-*b*]thiazol-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate and Ethyl 4-(6-Chloroimidazo[2,1-*b*]thiazol-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

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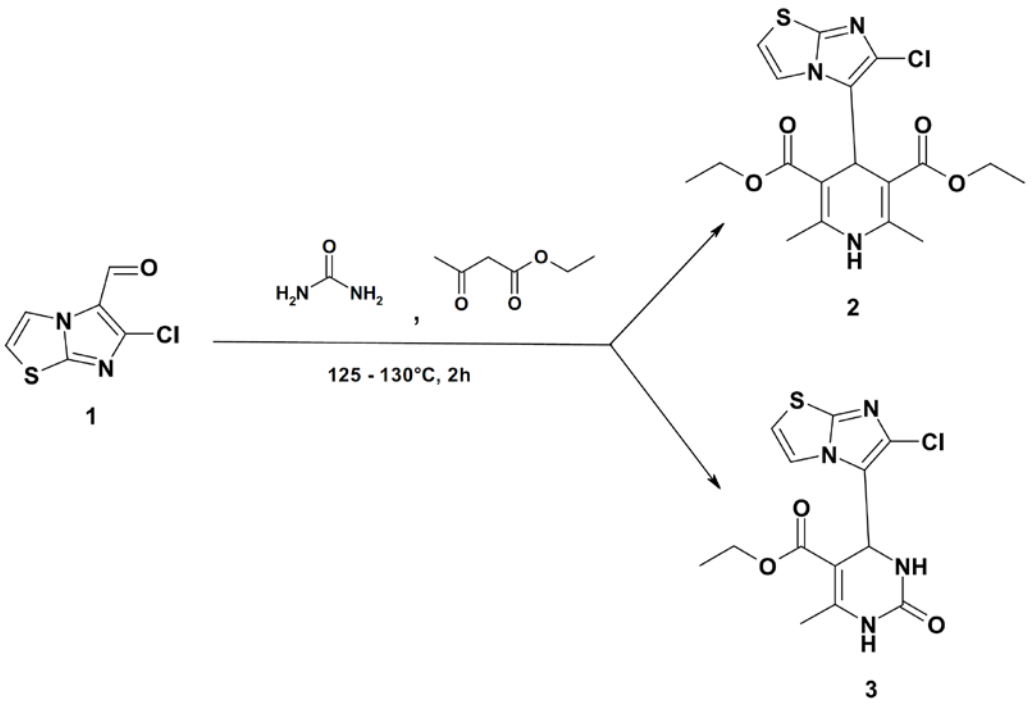
Abstract: Diethyl 4-(6-chloroimidazo[2,1-*b*]thiazol-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate and ethyl 4-(6-chloroimidazo[2,1-*b*]thiazol-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate were obtained simultaneously by the Biginelli reaction using a green protocol and curtailing reaction time.

Keywords: 3,4-dihydropyrimidin-2(1*H*)-ones; 1,4-dihydropyridines; imidazo[2,1-*b*]thiazole

Molecular scaffolds such as 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs), synthesized the first time by Biginelli reaction [1], fascinated both biologists and medicinal chemists for their polyhedral pharmacological worth and the synthetic challenge to improve reaction conditions and yields. DHPMs motifs appropriately decorated, as far as 1,4-dihydropyridines (1,4-DHPs), play a role in a large range of activities: antitumor [2], antihypertensive [3], antitubercular [4]. Interestingly, the imidazo[2,1-*b*]thiazole is a well-known system able to endow 1,4-DHPs specific activities such as the cardiovascular [5] one. Moreover, 3,4-DHPMs bearing an imidazo[2,1-b]thiazole system are still unknown in literature and they could show new and interesting activities. For these reasons, we focused our study on the synthesis of a library of 3,4-DHPMs and 1,4-DHPs bearing an imidazo[2,1-*b*]thiazole system, using a Biginelli reaction protocol [6]. This procedure is green, fast, cheap to apply and assures the simultaneous production of both 1,4-DHPs and 3,4-DHPMs by means of a *one-pot* system. The present paper reports the synthesis of compounds **2** and **3** (see Scheme 1).

The aldehyde **1** was synthesized by Vilsmeier formylation of the imidazo[2,1-*b*]thiazole scaffold as previously described [7], then compound **1** was submitted to the Biginelli cyclocondensation, applying a method reported by Ranu *et al.* [6] (Scheme 1) and modified to be suitable for the imidazo[2,1-*b*]thiazole moiety.

Scheme 1. Synthesis of the title compounds **2** and **3**.



Experimental

General

The melting points are uncorrected. TLC analysis were performed on Bakerflex plates (silica gel IB2-F). Kieselgel 60 (VWR, Milan, Italy) was used for flash chromatography. The IR spectra were recorded in nujol on a Nicolet Avatar 320 E.S.P.; ν_{max} are expressed in cm^{-1}. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 on a Varian MR 400 MHz (ATB PFG probe); the chemical shifts (referenced to solvent signal) are expressed in ppm (δ) and *J* in Hz (abbreviations: th = thiazole, py = pyridine, pym = pyrimidinone). Urea and ethyl acetoacetate were purchased from Sigma Aldrich and were used as delivered without further purification, whereas aldehyde **1** was prepared according to the literature [7].

Diethyl 4-(6-Chloroimidazo[2,1-b]thiazol-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**2**)*, Ethyl 4-(6-Chloroimidazo[2,1-b]thiazol-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate* (**3**)

Aldehyde **1** (2 g, 0.01 mol) was mixed homogeneously with ethyl acetoacetate (1.4 mL, 0.01 mol) and urea (0.96 g, 0.01 mol). The mixture was stirred at 125–130 °C for two hours according to a TLC test, the eluent was a mixture of dichloromethane/ethanol 9:1. Afterwards, the mixture was allowed to

cool at room temperature. The black fused solid obtained was grinded to get a powder, added to hot water (30 mL) and filtered off by suction. The washed powder was then purified by flash chromatography eluting with a gradient of acetone/petroleum ether from 0:1 to 6:4, v/v. After separation, a yellow solid and an orange powder were obtained, corresponding to analytically pure samples of compounds **2** (yield 15%) and **3** (yield 45%) respectively.

Data for Compound **2**

M.p.: 165 °C.

IR (nujol, cm^{-1}): 1653, 1458, 1377, 1272, 1160.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 0.97 (6H, t, $COOCH_2CH_3$, J = 7.2), 2.25 (6H, s, CH_3), 3.91 (4H, m, $COOCH_2CH_3$), 5.20 (1H, s, py), 7.32 (1H, d, th, J = 4.8), 7.77 (1H, d, th, J = 4.8), 9.04 (1H, s, NH).

^{13}C-NMR (400 MHz, DMSO-d_6) δ (ppm): 14.99, 18.87, 31.47, 60.03, 98.22, 113.09, 120.88, 129.20, 131.08, 144.87, 147.02, 167.53.

Anal. Calculated for $C_{18}H_{20}ClN_3O_4S$ (MW 409.89): 52.74 (C), 4.92 (H), 10.25 (N). Found: 52.75 (C), 4.92 (H), 10.24 (N).

Data for Compound **3**

M.p.: 195 °C.

IR (nujol, cm^{-1}): 1694, 1555, 1375, 1283, 1021.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 0.95 (3H, t, $COOCH_2CH_3$, J = 7.0), 2.26 (3H, s, CH_3), 3.90 (2H, m, $COOCH_2CH_3$), 5.70 (1H, d, pym, J = 2), 7.41 (1H, d, th, J = 4.2), 7.71 (1H, s, NH), 7.77 (1H, d, th, J = 4.2), 9.43 (1H, s, NH).

^{13}C-NMR (400 MHz, DMSO-d_6) δ (ppm): 14.87, 18.61, 46.81, 60.14, 95.07, 114.52, 120.14, 125.63, 130.60, 146.18, 150.13, 151.94, 165.84.

Anal. Calculated for $C_{13}H_{13}ClN_4O_3S$ (MW 340.79): 45.82 (C), 3.85 (H), 16.44 (N). Found: 45.84 (C), 3.84 (H), 16.45 (N).

Acknowledgements

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