A New synthesis of functionalized imidazo[2,1-b][1,3]thiazines with thiohydantoins, isocyanides and dialkyl acetylenedicarboxylates

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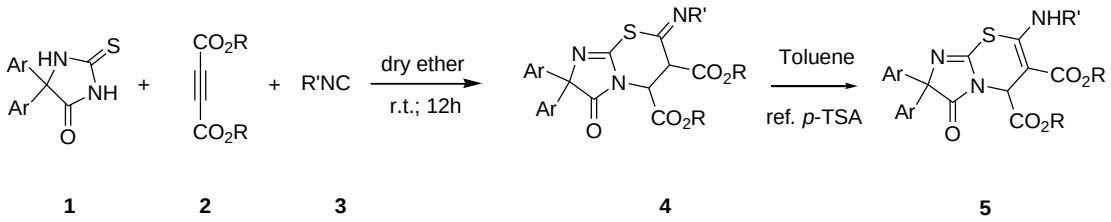
Abstract- The reaction of stoichiometric amounts of dialkyl acetylenedicarboxylates with alkyl isocyanides and 5,5-diaryl thiohydantoins in toluene and catalytic amount of *p*-TSA afforded imidazo[2,1-b][1,3]thiazines in good overall yields.

Keywords: Thiohydantoin, Imidazo[2,1-b][1,3]thiazine, Isocyanide, Acetylenedicarboxylate, Zwitterionic.

Introduction

1,3-thiazines possess strong analgesic and muscle relaxing properties. They have also stimulation of the entire sympathetic system, hypothermic activities and other pharmaceuticals [1-2]. Investigations in another laboratory have shown that the zwitterionic intermediate generated by the reaction of nucleophilic carbenes such as isocyanides and dimethyl acetylenedicarboxylate (DMAD) underwent facile addition to aldehydes and quinines to afford highly functionalized novel aminofurans and iminolactones in good yields [3]. As part of our current studies on the development of new routes in heterocyclic synthesis [4-5], we report the results of our studies involving the reaction of the zwitterionic intermediates derived from alkyl isocyanides **3** and acetylenic esters **2** with 5,5-diaryl-2-thioxoimidazolidin-4-one **1**, which constitutes a synthesis of dialkyl 7-(alkylimino)-3,5,6,7-tetrahydro-3-oxo-2,2-diaryyl-2H-imidazo[2,1-b][1,3]thiazine-5,6-dicarboxylate **4** in 80-91% yields. Then, this compound **4** undergo a smooth reaction in boiling toluene in the presence of catalytic amount of p-TSA to produce **5** (see Scheme and Table 1).



1 **2** **3** **4** **5**

Scheme 1. Synthesis of Imidazo[2,1-b][1,3]thiazines.

Experimental

General

Acetylenic esters and isocyanides were obtained from Fluka and were used without further purification. 5,5-diarylthiohydantoin was prepared by known methods [8-9]. Melting points (uncorrected) were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, N and S were performed using a Heraeus CHN-O-Rapid analyzer. The experimental data were in good agreement with the calculated values. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were measured with a Bruker DRX-300 Avance and Avance II-500 spectrometer. IR spectra were recorded on a Shimadzu IR-460 spectrometer.

Typical Procedure for the Preparation of Dimethyl 7-(cyclohexylimino)-3,5,6,7-tetrahydro-3-oxo-2,2-diphenyl-2H- imidazo[2,1-b][1,3]thiazine-5,6-dicarboxylate (exemplified by 4):

To a magnetically stirred solution of 0.536 g **1** (2 mmol) and 0.284 g **2** (2 mmol) in 5 cm^3 ether was added dropwise a solution of 0.218 g **3** (2mmol) in 2 cm^3 ether at 5°C over 10min. After 12 h stirring at room temperature, the product was filtered and washed with cold ether to give **4.**

Typical Procedure for the Preparation of dimethyl 7-(cyclohexylamino)-3-5-dihydro-3-oxo-2,2-diphenyl-2H-imidazo[2,1-b][1,3]thiazine-5,6-dicarboxylate (exemplified by 5):

A solution of 1.2 mmol of **4** in toluene (20 mL) in the presence of catalytic amount of p-TSA was refluxed for 17 h. The solvent was removed under reduced pressure, and the yellowish oil was separated by silica column chromatography (Merck 230–400 mesh) using hexane/AcOEt as eluent to afford pure imidazoles **5**.

Results and discussion

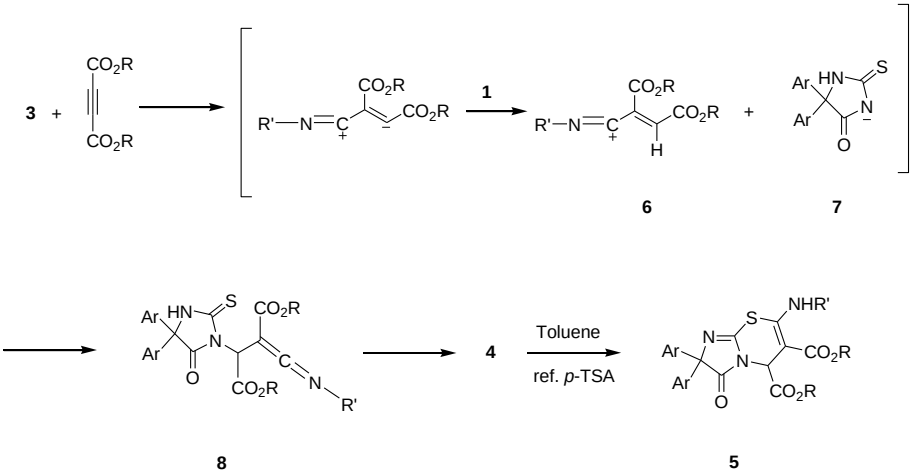
The reaction of 5,5-diaryl-2-thioxoimidazolidin-4-one **1** with dialkyl acetylenedicarboxylates **2** in the presence of isocyanides proceeded at room temperature in dry diethyl ether, and was complete about 12 hours. ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the

formation of stable dialkyl 7-(alkylimino)-3,5,6,7-tetrahydro-3-oxo-2,2-diaryl-2H-imidazo[2,1-b][1,3]thiazine-5,6-dicarboxylate **4**. No other products other than **4** could be detected. Finally, the reaction of compounds **4** in boiling toluene in the presence of p-TSA produced **5.** The structures of compounds **5a–5e** were deduced from their elemental analyses and ^{1}H NMR spectra.

Table 1. Synthesis of Imidazo[2,1-b][1,3]thiazines

Entry	Ar	R	R'	Product	Yield %
1	Ph	Me	Cy	**5a**	91
2	*p*-Tolyl	Me	Cy	**5b**	98
3	Ph	Me	^{t}Bu	**5c**	50
4	Ph	Et	1,1,3,3-tetramethylbutyl	**5d**	47
5	Ph	Me	1,1,3,3-tetramethylbutyl	**5e**	85

Although we have not yet established the mechanism of formation of **4** in an experimental manner, a plausible rationalization for the formation of functionalized imidazo[2,1-b][1,3] thiazines **5a-5e** is shown in Scheme 2. Presumably, the zwitterionic intermediate [6-7], formed from **2** and **3**, is protonated by the NH acidic compound **1**. Then, the positively charged ion **6** undergo intramolecular reaction with compounds **7** to produce the ketenimines **8**; which apparently isomerise under the reaction conditions employed to produce the final products **4** in excellent yields Scheme 2. The absence of the strong ketenimine absorption bands at about 2050 cm^{-1} in the IR spectra of compounds **4**, excludes the conjugate addition of the anion **7** to the intermediate **6**. Finally, a hydrogen shift from **6** affords product **5.**



Scheme 2. Proposed mechanism.

Conclusions

In conclusion, we have developed a simple and efficient method for the synthesis of functionalized dimethyl 7-(cyclohexylamine)-3-5-dihydro-3-oxo-2,2-diphenyl-2H-imidazo[2,1-b][1,3]thiazine-5,6-dicarboxylate. The present method carries the advantage that not only is the reaction performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.

Dimethyl7-(cyclohexylimino)-3,5,6,7-tetrahydro-3-oxo-2,2-diphenyl-2H-imidazo[2,1-b][1,3]thiazine-5,6-dicarboxylate (4a)

White powder; mp: 188-190°C; yield: 0.92 g (91%); IR (KBr) (ν_{max}/cm^{-1}): 1741 and 1735 (C=O), 1447 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (2 H, m, CH_2), 1.08 (4 H, m, 2 CH_2), 1.44 (2 H, m, CH_2), 1.55 (2 H, m, CH_2), 3.09 (1 H, m, CH), 3.58 (3 H, s, MeO), 3.87 (3 H, s, MeO), 4.51 (1 H, d, $^3J_{HH}$ = 3.0 Hz, CH), 4.59 (1 H, d, $^3J_{HH}$ = 3.0 Hz, CH), 7.22-7.58 (10 H, m, 2 C_6H_5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6 (CH_2), 23.7 (CH_2), 25.4 (CH_2), 32.7 (CH_2), 33.1 (CH_2), 42.1 (CH), 44.5 (CH), 53.2 (MeO), 53.6 (MeO), 57.1 (CH), 77.2 (C), 127.5 (2 CH), 127.6 (2 CH), 127.8 (CH), 128.0 (CH), 128.2 (2 CH), 129.9 (2 CH), 136.3 (C), 137.9 (C), 138.7 (C), 166.2 (OC=O), 169.2 (OC=O), 178.5 (C=O), 186.3 [NC(S)N] ppm; MS (EI, 70 eV): m/z (%) = 520 (M^+, 15), 322 (75), 263 (78), 225 (30), 192 (40), 166 (100), 77 (28), 59 (12); Anal. Calcd (%) for $C_{28}H_{29}N_3O_5S$ (519.61): C, 64.72; H, 5.63; N, 8.09; S, 6.17. Found: C, 64.83; H, 5.71; N, 7.94; S, 6.08.

Diethyl7-(cyclohexylimino)-3,5,6,7-tetrahydro-3-oxo-2,2-diphenyl-2H-imidazo[2,1-b][1,3]thiazine-5,6-dicarboxylate (5b)

White powder; yield: 1.01 g (98%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.02 (2 H, m, CH_2), 1.17 (4 H, m, 2 CH_2), 1.50 (4 H, m, 2 CH_2), 3.12 (1 H, m, CH), 3.62 (3 H, s, MeO), 3.72 (3 H, s, MeO), 5.48 (1 H, s, CH), 7.00-7.38 (10 H, m, 2 C_6H_5), 9.16 (1 H, d, NH) ppm.

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