Short Note



# Rel-(2R, 3S)-2-((Diphenylmethylene)amino)-5-Oxo-5-Phenyl-3-(Thiophen-2-Yl)pentanenitrile

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# *rel*-(2*R*,3*S*)-2-((Diphenylmethylene)amino)-5-oxo-5-phenyl-3-(thiophen-2-yl)pentanenitrile

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**Abstract:** The reaction of 2-((diphenylmethylene)amino)acetonitrile with (*E*)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one was performed by using 33% NaOH in $CH_3CN$ for 30 min at 0°C. The main product - *rel*-(2*R*,3*S*)-2-((diphenylmethylene)amino)-5-oxo-5-phenyl-3-(thiophen-2-yl)pentanenitrile was isolated and characterized by IR, $^1H$ NMR, $^{13}C$ NMR and high-resolution mass spectrometry (HRMS).

**Keywords:** 2-((diphenylmethylene)amino)acetonitrile; Michael addition; non-proteinogenic aminoacids

## 1. Introduction

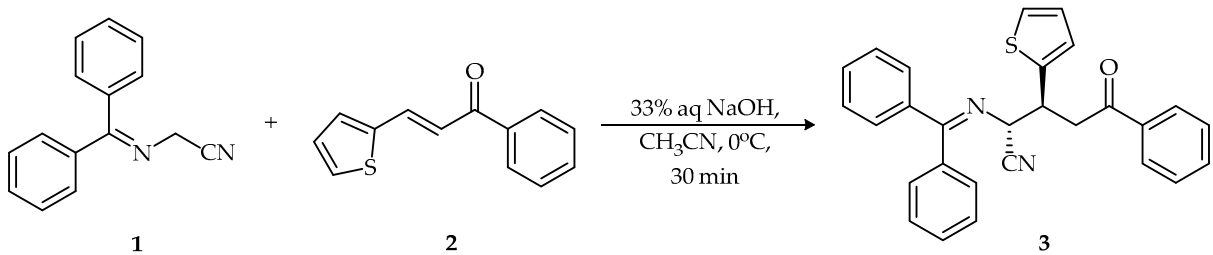
Non-proteinogenic $\alpha$-amino acids play an important role in biological systems, which determines the importance of developing synthetic routes for their synthesis [1]. Imines of glycine esters and aminoacetonitrile are useful building blocks for the synthesis of nonproteinogenic $\alpha$-amino acids and their derivatives [2-4]. O'Donnell Schiff bases have been used for the synthesis of unnatural $\alpha$-amino acids by alkylation reactions [5-9], aldol reactions [10-12] and Michael additions [13-20].

In our previous work we reported the reaction of 2-((diphenylmethylene)amino)acetonitrile and several arylmethyleneacetophenones in aqueous conditions. The substituted 2-amino-5-oxonitriles obtained were converted to 3,5-diaryl-3,4-dihydro-2*H*-pyrrole-2-carbonitriles [15].

The aim of present work is the reaction of 2-((diphenylmethylene)amino)acetonitrile with chalcone, containing heterocyclic ring for synthesis of *rel*-(2*R*,3*S*)-2-((diphenylmethylene)amino)-5-oxo-5-phenyl-3-(thiophen-2-yl)pentanenitrile.

## 2. Results and Discussion

The synthesis of *rel*-(2*R*,3*S*)-2-((diphenylmethylene)amino)-5-oxo-5-phenyl-3-(thiophen-2-yl)pentanenitrile (**3**) was performed by the Michael reaction of 2-((diphenylmethylene)amino)acetonitrile (**1**) and (*E*)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (**2**) under the conditions previously described by us (33% NaOH in $CH_3CN$ at 0°C) [15] for 30 min (Scheme 1).




**1** **2** **3**

**Scheme 1.** Synthesis of *rel*-(2*R*,3*S*)-2-((diphenylmethylene)amino)-5-oxo-5-phenyl-3-(thiophen-2-yl)pentanenitrile (**3**).

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The reaction proceeds with high diastereoselectivity and the diastereoisomeric ratio 95:5 ($^1$H NMR) was observed for the crude product **3**. The major diastereoisomer was isolated with 83% yield after the recrystallization of crude crystalline product from ethyl acetate-methanol. The structure of compound **3** was confirmed by IR and $^1$H NMR, $^{13}$C NMR and HRMS. A *rel*-(2*R*,3*S*)-configuration for the major diastereoisomer of oxonitrile **3** was assigned based on a comparison between the proton NMR spectra of this compound and the proton NMR spectra of oxonitriles, previously reported by us [15].

## 3. Materials and Methods

### *3.1. General*

All starting chemicals were purchased from Acros Organics and Fisher Scientific GmbH. The nitrile Schiff base **1** [5] and chalcones **2** [21] were prepared according to literature procedures. Reaction and purity of the final compound was monitored by thin-layer chromatography (TLC) on silica gel aluminium plates Kieselgel 60 $F_{254}$ (Merck), using petroleum ether/acetone (6:1 *v*/*v*) as eluent. Melting points were determined on a Boetius micromelting point apparatus and were uncorrected. Infrared spectrum (FT-IR) was acquired on a Nicolet 6700 FT-IR Thermo Scientific infrared spectrophotometer. NMR spectra were recorded in $CDCl_3$, on a Bruker Avance III HD 500, operating at 500.13 MHz for $^1$H and at 125.76 MHz for $^{13}$C. Chemical shifts ($\delta$) are reported in parts per million (ppm) and were referenced to the tetramethylsilane (TMS) as an internal standard. Coupling constants (*J*) were measured in hertz (Hz). High-resolution mass spectra (HRMS) was obtained with Q Exactive hybrid quadrupole-Orbitrap mass spectrometer (Thetmo Scientific Co, USA) equipped with TurboFlow® LC system, heated electrospray model HESI II on IonMax® (Thetmo Scientific Co, USA).

### *3.2. Synthesis of rel-(2R,3S)-2-((Diphenylmethylene)amino)-5-oxo-5-phenyl-3-(thiophen-2-yl)pentanenitrile*

Cooled to 0°C aqueous sodium hydroxide (33% NaOH, 0.75 mL) was added to a cooled (0°C) solution of 2-((diphenylmethylene)amino)acetonitrile (0.55 g, 2.5 mmol) and (*E*)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (0.54 g, 2.5 mmol) in 1.25 mL $CH_3CN$. The reaction mixture was stirred for 30 min at 0°C. Water (50 mL) was added and the crystalline product **3** was filtered, washed with water to neutral and dried. The crude product was recrystallized from ethyl acetate-methanol. Yield: 83% (0.90 g)

White crystals, m.p.: 154-156°C (ethyl acetate-methanol). IR (KBr): 2235 ($\nu$CN), 1690 ($\nu$C=O), 1623 ($\nu$C=N), 1595, 1578, 1489, 1446 ($\nu$C=C), 764, 695 ($\gamma$C-H) cm$^{-1}$. $^1$H NMR (500.13 MHz, $CDCl_3$) $\delta$ (ppm): 3.76, 3.87 (2dd, 2H, $^2J$ = 17.6 Hz, $^3J$ = 8.9 Hz, $^3J$ = 4.6 Hz, $CH_2CO$), 4.32-4.35 (m, 1H, $CHC_4H_3S$), 4.55 (d, 1H, $^3J$ = 4.4 Hz, CHCN), 6.90 (dd, 1H, $^3J$ = 5.0 Hz, $^3J$ = 3.6 Hz, aromatic), 6.93-6.95 (m, 3H, aromatics), 7.14-7.15 (m, 1H, aromatic), 7.36-7.39 (m, 2H, aromatics), 7.42-7.48 (m, 6H, aromatics), 7.55-7.59 (m, 1H, aromatic), 7.67-7.69 (m, 2H, aromatics), 7.96-7.98 (m, 2H, aromatics). $^{13}$C NMR (125.76 MHz, $CDCl_3$) $\delta$ (ppm): 40.59, 41.19, 57.98, 118.18, 124.73, 126.07, 126.72, 127.13, 128.14, 128.27, 128.67, 128.92, 129.24, 129.31, 131.41, 133.35, 135.01, 136.68, 138.30, 141.95, 174.84, 196.91. HRMS (ESI): calculated for $C_{28}H_{22}N_2OS$ $[M+H]^+$ *m*/*z* 435.1526, found 435.1545.

**Supplementary Materials:** Figure S1: FT-IR spectrum of compound **3**; Figure S2: $^1$H NMR spectrum of compound **3**; Figure S3: $^{13}$C NMR spectrum of compound **3**; Figure S4: HRMS of compound **3**; Figure S5: HRMS/ESI-$MS^2$ spectrum of compound **3**; Figure S6: HRMS/ESI-$MS^2$: proposed structure of the fragment ions of compound **3.**

**Author Contributions:** Conceptualization, D.N.T. and V.M.M.; methodology, V.M.M.; writing—original draft preparation, D.N.T. and V.M.M.; writing—review and editing, D.N.T. and V.M.M. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest:** The authors declare no conflicts of interest.

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