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A facile one-pot synthesis of functionalized thiazines in water

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Abstract

An efficient synthesis of thiazines from the three component reactions between dialkyl acetylenedicarboxylates, arylisothiocyanates and *N*-nucleophiles at room temperature in water as the solvent is described.

Keywords: One-pot reactions; Thiazines; Arylisothiocyanates; Dialkyl acetylenedicarboxylates

1. Introduction

Water is the best solvent and reagent for biochemical conversions. In the past, water was not used as a solvent for synthetic organic chemistry due to the poor solubility and, in some cases, the instability of organic reagents in aqueous solutions. Now, it has been distinguished that chemical reactions in mixed aqueous solutions or two-phase systems often give better results than in organic solvents and often the insolubility of the final products facilitates their isolation [1,2]. The isoquinoline skeleton is found in a large number of naturally occurring and synthetic biologically active heterocyclic compounds [3–7]. These compounds also exhibit sedative [8], antidepressant [9,10], antitumour and antimicrobial activity [11–13]. Herein, we present our results of a novel discovery involving synthesis of thiazine derivatives, using commercially available starting materials in excellent yields. Thus, the reaction of arylisothiocyanates **1** and activated acetylenic esters **2** in the presence of isoquinoline **3** in water produced thiazine derivatives **4** in good yields (Scheme 1).

2. Experimental

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N

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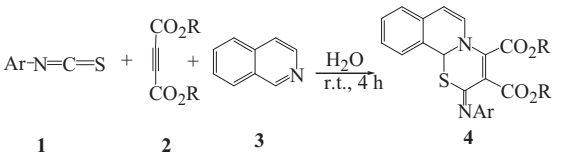


1 2 3 4

1, 2, 4	R	Ar	Yield % of 4
a	Me	Phenyl	85
b	Me	4-nitrophenyl	94
c	Me	4-bromophenyl	92
d	Me	3-bromophenyl	92
e	Et	Phenyl	90
f	Et	4-nitrophenyl	89
g	Et	4-bromophenyl	87
h	Et	3-bromophenyl	87

Scheme 1.

were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H, and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H, and ^{13}C, spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 as external standard.

2.1. General procedure for preparation of compounds *4a–h* and *8a–d*

To a magnetically stirred solution of arylisothiocyanate **1** and dialkyl acetylenedicarboxylates **2** (2 mmol) in water was added isoquinoline **3** or quinoline **7** (2 mmol) slowly and the reaction mixture stirred for 4 h at room temperature. After completion of the reaction as indicated by TLC (ethyl acetate/n-hexane), the reaction mixture was purified by column chromatography to afford pure title compounds.

2.1.1. Dimethyl 2-(phenylimino)-2H,11bH-[1,3]thiazino-[2,3-a]isoquinoline-3,4-dicarboxylate (*4a*)

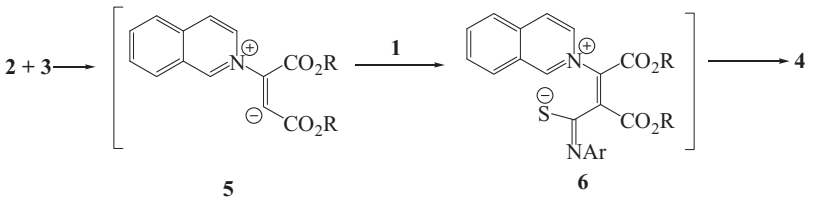
Yellow powder, mp 135–137 °C, yield 85%, IR (KBr) (ν_{max}/cm^{-1}): 1725, 1720, 1685, 1587, 1432 and 1129. ^{1}H NMR: δ 3.65 (s, 3 H, MeO), 3.82 (s, 3 H, MeO), 7.25 (s, 1 H, CH), 7.54 (d, 1 H, ^{3}J = 7.6 Hz, CH), 7.53 (t, 2 H, ^{3}J = 7.2, 2 CH), 7.61 (t, 1 H, ^{3}J = 7.2, CH), 7.69 (t, 1 H, ^{3}J = 7.2 Hz, CH), 7.73 (t, 1 H, ^{3}J = 7.2 Hz, CH), 7.93 (d, 1 H, ^{3}J = 7.5 Hz, CH), 8.02 (d, 2 H, ^{3}J = 7.3, 2 CH), 8.69 (d, 1 H, ^{3}J = 7.5 Hz, CH), 9.31 (d, 1 H, ^{3}J = 7.6 Hz, CH). ^{13}C NMR: δ 52.5 (MeO), 53.0 (MeO), 65.2 (CH), 103.4 (CH), 112.4 (C), 120.3 (2 CH), 122.3 (CH), 123.6 (CH), 125.4 (CH), 125.7 (CH), 128.7 (2 CH), 129.0 (CH), 138.2 (C), 133.5 (C), 139.7 (C), 140.1 (C), 148.7 (C–N), 157.4 (C=N), 160.7 (C=O), 161.5 (C=O). Anal. Calcd. for $C_{22}H_{18}N_2O_4S$ (406.45): C, 65.01; H, 4.46; N, 6.89 found: C, 64.95; H, 4.38; N, 6.75.

2.1.2. Dimethyl 2-(4-nitrophenylimino)-2H,11bH-[1,3]thiazino-[2,3-a]isoquinoline-3,4-dicarboxylate (*4b*)

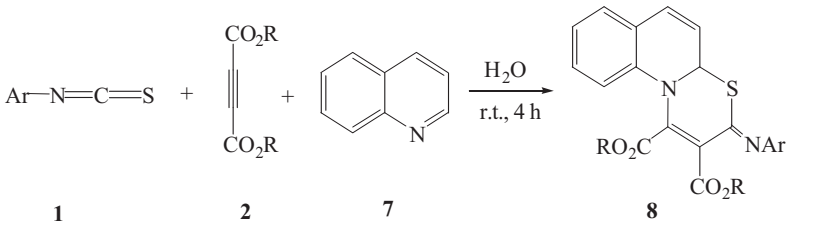
Pale yellow crystals, mp 153–155 °C, yield 94%. IR (KBr) (ν_{max}/cm^{-1}): 1745, 1732, 1658, 1587, 1489, 1365, 1258 and 1157. ^{1}H NMR: δ 3.81 (s, 3 H, MeO), 3.92 (s, 3 H, MeO), 6.98 (d, 2 H, ^{3}J = 7.6, 2 CH), 7.28 (s, 1 H, CH), 7.49 (d, 1 H, ^{3}J = 7.6 Hz, CH), 7.65 (t, 1 H, ^{3}J = 7.3 Hz, CH), 7.68 (t, 1 H, ^{3}J = 7.3 Hz, CH), 7.88 (d, 1 H, ^{3}J = 7.5 Hz, CH), 8.28 (d, 2 H, ^{3}J = 7.5, 2 CH), 8.65 (d, 1 H, ^{3}J = 7.5 Hz, CH), 9.27 (d, 1 H, ^{3}J = 7.6 Hz, CH). ^{13}C NMR: δ 53.2 (MeO), 53.8 (MeO), 65.4 (CH), 103.8 (CH), 111.4 (C), 120.0 (2 CH), 123.5 (CH), 126.1 (2 CH), 127.2 (CH), 127.8 (CH), 128.5 (CH), 130.8 (CH), 139.6 (C), 141.6 (C), 146.8 (C), 154.2 (C), 154.9 (C–N), 156.2 (C=N), 160.7 (C=O), 166.5 (C=O). Anal. Calcd. for $C_{22}H_{17}N_3O_6S$ (451.45): C, 58.53; H, 3.80; N, 9.31 found: C, 58.48; H, 3.75; N, 9.28.

2.1.3. Dimethyl 2-(4-bromophenylimino)-2H,11bH-[1,3]thiazino-[2,3-a]isoquinoline-3,4-dicarboxylate (*4c*)

Orange crystals, mp 165–167 °C, yield 92%. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1715, 1658, 1424. 1310, 1258 and 1100. ^{1}H NMR: δ 3.81 (s, 3 H, MeO), 3.91 (s, 3 H, MeO), 6.76 (d, 2 H, ^{3}J = 7.8, 2 CH), 7.19 (d, 1 H, ^{3}J = 7.7 Hz, CH), 7.32 (s, 1 H, CH), 7.51 (d, 2 H, ^{3}J = 8.0, 2 CH), 7.54 (t, 1 H, ^{3}J = 7.4 Hz, CH), 7.59 (t, 1 H, ^{3}J = 7.4 Hz, CH), 7.70 (d, 1 H, ^{3}J = 7.5 Hz, CH), 8.44 (d, 1 H, ^{3}J = 7.5 Hz, CH), 9.23 (d, 1 H, ^{3}J = 7.7 Hz, CH). ^{13}C NMR: δ 52.6 (MeO), 53.2 (MeO),



Scheme 2.



1, 2, 7	R	Ar	Yield % of 8
a	Me	Phenyl	75
b	Me	4-nitrophenyl	78
c	Et	Phenyl	80
d	Et	4-nitrophenyl	78

Scheme 3.

64.3 (CH), 103.5 (CH), 112.0 (C), 121.2 (2 CH), 124.3 (CH), 126.7 (2 CH), 127.8 (CH), 128.2 (CH), 128.9 (CH), 131.2 (CH), 139.5 (C), 142.6 (C), 145.8 (C), 153.8 (C), 155.4 (C–N), 158.9 (C=N), 161.7 (C=O), 164.5 (C=O).

The data of compounds **4d–h** and **8a–d** are available in the supporting information.

3. Results and discussion

As indicated in Scheme 1, arylisothiocyanates **1**, activated acetylenes **2**, and isoquinoline **3** undergo a smooth 1:1:1 addition reaction in water at room temperature to produced thiazins **4** in 85–94% yields (Scheme 1). The data obtained from elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectra confirmed all of the proposed products. The ^{1}H NMR spectrum of **4b** exhibited two sharp singlet signals recognized as arising from methoxy groups δ_H = 3.81, 3.92 ppm. Two doublets at 6.98 (^{3}J = 7.6 Hz), 8.28 (^{3}J = 7.5 Hz) is attributed to arylisothiocyanate moiety protons. The ^{1}H decoupled ^{13}C NMR spectrum of **4b** showed 23 distinct signals, which were in agreement with the proposed structure. Although we have not established the mechanism of our reaction in an experimental manner, a possible explanation is proposed in Scheme 2. It is conceivable that, the reaction involves the initial formation of a 1,3-dipolar intermediate **5** between isoquinoline and the acetylenic compounds, which reacts with the arylisothiocyanate to produce **6**. Cyclization of zwitterionic intermediate **6** leads to the **4**.

Under similar conditions, the reaction of arylisothiocyanates **1**, activated actylenic compounds **2** with quinoline **7** produced thiazine derivatives **8** in good yields (Scheme 3).

In summary, we reported an efficient method for the synthesis of thiazine derivatives. The advantages of our work are as follows: (1) the reaction is performed in water as the solvent. (2) The simplicity of the present procedure makes it an interesting alternative to the complex multistep approaches.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2012.06.033.

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