

Synthesis of functionalized thiazins *via* multicomponent reaction of isothiocyanates and activated acetylenes in the presence of isoquinoline

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Abstract: An efficient synthesis of thiazine derivatives *via* one-pot reactions between acetylenic esters, arylisothiocyanates and isoquinoline is described.

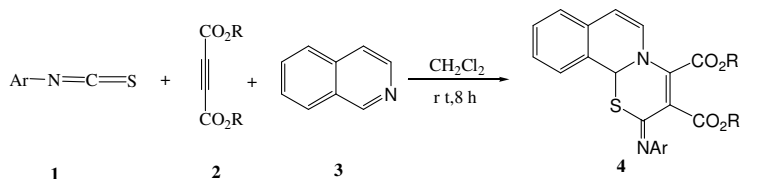
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Introduction

The isoquinoline skeleton is found in a large number of naturally occurring and synthetic biologically active heterocyclic compounds [1]. In particular, 1,2-dihydroisoquinoline derivatives act as delivery systems that transport drugs through the otherwise highly impermeable blood–brain barrier [2]. These compounds also exhibit sedative [3], antidepressant [4], antitumor, and antimicrobial activities [5]. For the functionalization of quinoline, isoquinoline and related aromatic amines, the Reissert reaction has remained one of the most powerful tools [6]. This reaction can be considered as a multi-component reaction, where adducts are formed from an azine, an acyl chloride, and sodium cyanide via an *N*-acyliminium intermediate. Multi-component reactions (MCRs), due to their productivity, simple procedures, convergence,

and facile execution, are one of the best tools in combinatorial chemistry [7]. Therefore, the design of novel MCRs has attracted great attention from research groups working in areas such as drug discovery, organic synthesis and materials science. As a result, the number of new MCRs has grown rapidly [8].

In this paper, as part of our ongoing studies on the multicomponent area [9-11], we present herein 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**, activated esters **2** with isoquinoline **3**, in dichloromethane as the solvent, produced thiazine derivatives **4** in good yields (Scheme 1).



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

Scheme 1.

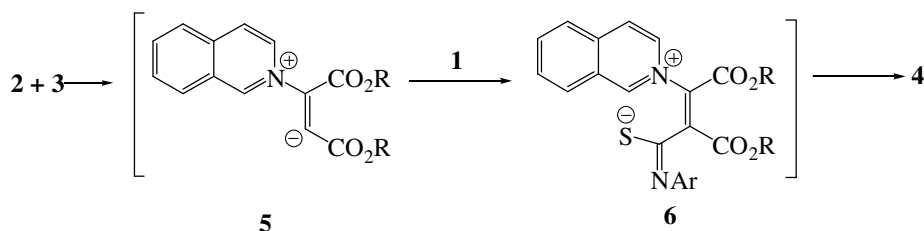
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As indicated in Scheme 1, arylisothiocyanates **1**, activated acetylenes **2**, and isoquinoline **3** undergo a smooth 1:1:1 addition reaction in dichloromethane at room temperature to produce thiazines **4** in 85–94% yields (Scheme 1).

The data obtained from elemental analysis, IR, ^1H NMR, ^{13}C NMR, and mass spectra confirmed all of the proposed products. The mass spectrum of **4b** displayed a molecular ion peak at m/z 451 and more important, an ion peak at m/z 297 indicated that aryl group has been lost and thus the presence of this group on the structure was confirmed. Absorption bands at 1745 and 1732 cm^{-1} are due to the two carbonyl groups. The ^1H NMR spectrum of **4b** exhibited two sharp singlet signals recognized as arising from methoxy groups

($\delta_{\text{H}} = 3.81, 3.92\text{ ppm}$). Two doublets at 6.98 (2 H, d, $^3J = 7.6\text{ Hz}$, 2 CH), 8.28 (2 H, d, $^3J = 7.5\text{ Hz}$, 2 CH) is attributed to aryl protons. The ^1H decoupled ^{13}C NMR spectrum of **4b** showed 23 distinct signals, which were in agreement with the proposed structure. Partial assignment of these resonances for compounds **4** is given in experimental section.

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 either **6**. Cyclization of zwitterionic intermediate **6** leads to the **4**.



Scheme 2.

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 under neutral and more important in water as a solvent. (2) No catalyst is required for this reaction. (3) The simplicity of the present procedure makes it an interesting alternative to the complex multistep approaches.

Experimental

All chemicals were obtained from *Fluka* and were used without further purification. Mp: Electrothermal-9100 apparatus. IR spectra: *Shimadzu IR-460* spectrometer. ^1H and ^{13}C NMR spectra: *Bruker DRX-500 Avance* instrument; in CDCl_3 at 500.1 and 125.7 MHz, respectively; δ in parts per million, J in hertz. EIMS (70 eV): *Finnigan-MAT-8430* mass spectrometer, in m/z . Elemental analyses (C, H, N) were performed with a *Heraeus CHN-O-Rapid* analyzer.

General procedure

To a magnetically stirred solution of arylisothiocyanate **1** and dialkyl acetylenedicarboxylates **2** (2 mmol) in CH_2Cl_2 was added isoquinoline **3** (2 mmol) slowly and

the reaction stirred for 8 h at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane, 5:1), the reaction mixture was purified by column chromatography to afford pure title compounds.

Compound 4a: Yellow powder, mp $135\text{--}137^\circ\text{C}$, yield 85%. IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 1725, 1720, 1685, 1587, 1432 and 1129 cm^{-1} . ^1H -NMR: δ 3.65 (3 H, s, MeO), 3.82 (3 H, s, MeO), 7.25 (1 H, s, CH), 7.54 (1 H, d, $^3J = 7.6\text{ Hz}$, CH), 7.53 (2 H, t, $^3J = 7.2$, 2 CH), 7.61 (1 H, t, $^3J = 7.2$, CH), 7.69 (1 H, t, $^3J = 7.2\text{ Hz}$, CH), 7.73 (1 H, t, $^3J = 7.2\text{ Hz}$, CH), 7.93 (1 H, d, $^3J = 7.5\text{ Hz}$, CH), 8.02 (2 H, d, $^3J = 7.3$, 2 CH), 8.69 (1 H, d, $^3J = 7.5\text{ Hz}$, CH), 9.31 (1 H, d, $^3J = 7.6\text{ Hz}$, CH) ppm. ^{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) ppm. Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{NO}_4\text{S}$ (406.45): C, 65.01; H, 4.46; N, 6.89 found: C, 64.95; H, 4.38; N, 6.75.

Compound 4b: Pale yellow crystals, mp $153\text{--}155^\circ\text{C}$, yield 94%. IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 1745, 1732, 1658,

1587, 1489, 1365, 1258 and 1157 cm^{-1} . $^1\text{H-NMR}$: δ 3.81 (3 H, s, MeO), 3.92 (3 H, s, MeO), 6.98 (2 H, d, $^3J = 7.6$, 2 CH), 7.28 (1 H, s, CH), 7.49 (1 H, d, $^3J = 7.6$ Hz, CH), 7.65 (1 H, t, $^3J = 7.3$ Hz, CH), 7.68 (1 H, t, $^3J = 7.3$ Hz, CH), 7.88 (1 H, d, $^3J = 7.5$ Hz, CH), 8.28 (2 H, d, $^3J = 7.5$, 2 CH), 8.65 (1 H, d, $^3J = 7.5$ Hz, CH), 9.27 (1 H, d, $^3J = 7.6$ Hz, CH) ppm. $^{13}\text{C-NMR}$: 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 $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_6\text{S}$ (451.45): C, 58.53; H, 3.80; N, 9.31 found: C, 58.48; H, 3.75; N, 9.28.

Compound **4c**: Orange crystals, mp 165-167°C, yield 92%. IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 1725, 1715, 1658, 1424, 1310, 1258 and 1100 cm^{-1} . $^1\text{H-NMR}$: δ 3.81 (3 H, s, MeO), 3.91 (3 H, s, MeO), 6.76 (2 H, d, $^3J = 7.8$, 2 CH), 7.19 (1 H, d, $^3J = 7.7$ Hz, CH), 7.32 (1 H, s, CH), 7.51 (2 H, d, $^3J = 8.0$, 2 CH), 7.54 (1 H, t, $^3J = 7.4$ Hz, CH), 7.59 (1 H, t, $^3J = 7.4$ Hz, CH), 7.70 (1 H, d, $^3J = 7.5$ Hz, CH), 8.44 (1 H, d, $^3J = 7.5$ Hz, CH), 9.23 (1 H, d, $^3J = 7.7$ Hz, CH) ppm. $^{13}\text{C-NMR}$: δ 52.6 (MeO), 53.2 (MeO), 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).

Compound **4d**: White powder, yield: (92%); m.p. 169-171°C. IR(KBr)($\nu_{\text{max}}/\text{cm}^{-1}$): 1723, 1714, 1699, 1523, 1489, 1358 and 1124 cm^{-1} . $^1\text{H-NMR}$: δ 3.81 (3 H, s, MeO), 3.91 (3 H, s, MeO), 6.81 (1 H, t, $^3J = 7.8$, CH), 7.09 (1 H, d, $^3J = 7.8$ Hz, CH), 7.25 (1 H, d, $^3J = 7.8$ Hz, CH), 7.34 (1 H, s, CH), 7.50 (1 H, d, $^3J = 7.7$ Hz, CH), 7.71 (1 H, d, $^3J = 7.2$ Hz, CH), 7.73 (1 H, t, $^3J = 7.2$ Hz, CH), 7.93 (1 H, t, $^3J = 7.5$ Hz, CH), 8.55 (1 H, d, $^3J = 7.5$ Hz, CH), 9.21 (1 H, d, $^3J = 7.7$ Hz, CH) ppm. $^{13}\text{C-NMR}$: δ 53.2 (MeO), 53.7 (MeO), 62.7 (CH), 105.2 (CH), 112.5 (C), 121.8 (2 CH), 125.0 (CH), 126.8 (2 CH), 128.2 (CH), 128.7 (CH), 129.2 (CH), 131.8 (CH), 138.6 (C), 142.5 (C), 145.8 (C), 154.0 (C), 155.6 (C-N), 157.5 (C=N), 161.5 (C=O), 163.4 (C=O).

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