Iranian Journal of Organic Chemistry Vol. 5, No. 4 (2013) 1153-1155

Synthesis of 1-aryl-2-(3-aryl-2*H*-1,4-benzothiazin-2-yliden)-1-ethanones

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Received: September 2013; Revised: September 2013; Accepted: October 2013

Abstract: The reaction of 2-aminothiophenols with dibenzoylacetylenes leads to 1-aryl-2-(3-aryl-2*H*-1,4-benzothiazin-2-yliden)-1-ethanones in 92-96% yields.

Keywords: 1,4-benzothiazin, 2-aminothiophenols, dibenzoylacetylene.

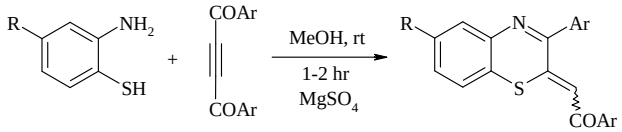
Introduction

The effort to prepare large numbers of diverse, novel and biologically active small molecules for drug discovery and development has caused an unprecedented growth in both combinatorial chemistry and organic synthesis [1-3].

1,4-Benzothiazin is a heterocyclic scaffold frequently used in drug design. For example, Sesamodil, an 2-aryl-4-methyl 1,4-Benzothiazin compound has been clinically used as an antihypertensive and antiarrhythmic agent [4]. Compounds based on the BZTZN motif were also reported as histamine H1 antagonist [5], anticonvulsant/antifungal agents [6], sodium glucose co-transported inhibitors [7], Ca^{2+}-activated potassium channel opener [8], phosphodiesterase inhibitors [9], 5-HT_3 antagonists [10], and Na^+/H^+ exchange inhibitors [11]. Several efficient routes to 4*H*-1,3-benzothiazin-2-amine derivatives have been published [12-17].

Major synthetic methods documented in the literature include: (i) SNAr reaction of 2-halonitrobenzene with 2-mercaptoacetate followed by reductive cyclization [18], and (ii) multi-component condensation of 2-chlorothiophenol, chloroacetyl chloride, and primary aliphatic amines via Smile rearrangement [19]. Recently, Cu or Pd-catalyzed coupling of *N*-(2-haloaryl)-2-haloacetamide with thioacetic acid was reported to produce BZTZNs [20]. These existing methods suffer a number of drawbacks such as limited availability of diverse starting materials or lengthy synthesis of requisite starting materials, multi-step reaction sequences, harsh reaction conditions, narrow reaction scopes, and in many cases, low yields.

In the course of our research program on the facile synthesis of heterocycles in mild conditions [21-23], Herein we report a novel one-step synthesis of 1,4-Benzothiazin derivatives (**3**) from 2-amino 1-benzenthiol (**1**) and dibenzoylacetylene (**2**) in the presence of $MgSO_4$ as drying agent (Scheme **1**).



1	R
a	H
b	Cl

2	Ar
a	Ph
b	4-Me-Ph

3	R	Ar
a	H	Ph
b	H	4-Me-Ph
c	Cl	Ph

Scheme 1: Synthesis of 1, 4-Benzothiazin derivatives.

Results and discussion

The structures of compounds **3a-3c** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR. For example, the ^{1}H NMR spectrum of **3a**

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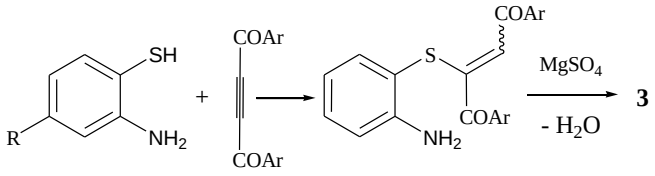
exhibited a singlet (δ = 6.90) identified as vinyl proton. The protons of the aromatic moieties appear as a multiplet. The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed 18 distinct resonances which further confirmed the proposed structure. The IR spectrum of **3a** displayed characteristic ketone and aromatic bands. The ^{1}H NMR and ^{13}C NMR spectra of **3b**–**3c** were similar to those for **3a** except for the aromatic moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.

A possible mechanism for the formation of **3** is shown in Scheme **2**. Although there is no experimental verification of this. The first step maybe involves the addition of thiol group [24] of **1** to the acetylenic compound **2** and formation of 1:1 adducts **4**. Then the carbonyl group of the closer benzoyl moiety is coupled by the amino group to produce **3.**



1 **2** **4**

Scheme 2: Proposed mechanism for the formation of products.

Conclusion

In summary, we have reported the synthesis of some novel 1,4-Benzothiazin derivatives from a cheap and easily available starting material. The reaction procedure is mild, work-up procedure is simple and the products were isolated by filtration and washing with cooled water and methanol. Further, the reaction protocol can be utilized for the synthesis of many other heterocyclic compounds of importance.

Experimental

General procedure:

All compounds were obtained from Fluka or Merck and were used without further purification. Dibenzoylacetylene (DBA) was prepared according to the literature procedure [25]. M.p.: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H-, ^{13}C- NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500, 125 MHz, respectively; δ in ppm. Elemental analyses (C, H, N, S) were performed with a Heraeus CHNS-O-Rapid analyzer.

Typical procedure for preparation of **3a**:

To a stirred solution of **1** (2 mmol) in 3 mL dry MeOH was added (2 mmol) dibenzoylacetylene and $MgSO_4$ (1mmol) at rt. The reaction mixture was then stirred for 1 hr. The precipitate was filtered off and washed with cooled water and methanol to get pure product **3a**.

*1-phenyl-2-(3- phenyl -2H-1,4-benzothiazin-2-yliden)-1-ethanone (**3a**):*

Pale yellow powder, mp 80–82 °C, 0.324 g, yield 95%. IR (KBr) (ν_{max}/cm^{-1}): 1720, 1530, 1278, 751. MS, m/z (%): 341 (M^+, 4), 264 (70), 236 (50), 105 (100), 77 (57). Anal. Calcd for $C_{22}H_{15}NOS$ (341.42): C, 77.39; H, 4.43; N, 4.10; S, 9.39%. Found: C, 77.25; H, 4.45; N, 4.18; S, 9.49%. ^{1}H NMR: δ 6.90 (1 H, s, CH), 7.13 (1 H, t, $^{3}J_{=}$ 6.78, CH), 7.31 (1 H, t, $^{3}J_{=}$ 6.95, CH), 7.38-7.42 (5 H, m, 5 CH), 7.45-7.49 (5 H, m, 5 CH), 7.77 (2 H, t, $^{3}J_{=}$ 7.08, 2 CH) ppm. ^{13}C NMR: δ 117.9 (CH), 125.5 (CH), 127.6 (CH), 127.8 (2 CH), 128.4 (C), 128.6 (2 CH), 128.7 (2 CH), 128.8 (2 CH), 129.0 (CH), 129.7 (CH), 131.4 (CH), 132.4 (CH), 138.2 (C), 139.2 (C),139.6 (C), 142.4 (C), 157.6 (C), 188.5 (C=O) ppm.

*1-(4-metylphenyl)-2-[3-(4-metylphenyl) -2H-1,4-benzothiazin-2-yliden]-1-ethanone (**3b**):*

Pale yellow powder, mp 86–88 °C, 0.339 g, yield 92%. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1540, 1275, 753. MS, m/z (%): 369 (M^+, 2), 278 (49), 250 (55), 119 (100), 91 (65). Anal. Calcd for $C_{24}H_{19}NOS$ (369.48): C, 78.02; H, 5.18; N, 3.79; S, 8.68%. Found: C, 78.25; H, 5.35; N, 3.90; S, 8.79%. ^{1}H NMR: δ 2.25 (3 H, s, CH_3), 2.45 (3 H, s, CH_3), 6.85 (1 H, s, CH), 7.13 (1 H, t, $^{3}J_{=}$ 6.80, CH), 7.31 (1 H, t, $^{3}J_{=}$ 6.7, CH), 7.33-7.37 (3 H, m, 3 CH), 7.39- 7.44 (3 H, m, 3 CH), 7.65 (2 H, t, $^{3}J_{=}$ 7.09, 2 CH), 7.74 (2 H, t, $^{3}J_{=}$ 7.1, 2 CH) ppm. ^{13}C NMR: δ 21.3, (CH_3), 23.8 (CH_3), 117.5 (CH), 125.9 (CH), 126.8 (CH), 127.5 (2 CH), 128.4 (C), 128.6 (2 CH), 128.1 (2 CH), 128.3 (2 CH), 129.2 (CH), 129.5 (CH), 136.9 (C), 137.4 (C), 138.2 (C), 139.1 (C), 139.7 (C), 142.3 (C), 155.6 (C), 189.3 (C=O) ppm.

*2-(6-chloro-3-phenyl -2H-1,4-benzothiazin-2-yliden)-1-phenyl-1-ethanone (**3c**):*

Pale yellow powder, mp 90–92 °C, 0.60g, yield 96%. IR (KBr) (ν_{max}/cm^{-1}): 1727, 1529, 1278, 765, 753. MS, m/z (%): 375 (M^+, 7), 298 (40), 270 (49), 269 (37), 105 (100), 77 (31). Anal. Calcd for $C_{22}H_{14}ClNOS$ (375.87): C, 70.30; H, 3.75; N, 3.73; S, 8.53%. Found: C, 70.45; H, 3.92; N, 3.84; S, 8.49%. ^{1}H NMR: δ 6.79 (1 H, s, CH), 7.19 (1 H, t, $^{3}J_{=}$ 6.35, CH), 7.32-7.36 (5 H, m, 5 CH), 7.405-7.44 (5 H, m, 54 CH), 7.54 (1 H, s, CH), 7.77 (2 H, t, $^{3}J_{=}$ 7.08, 2 CH) ppm. ^{13}C NMR: δ 118.8

(CH), 125.1 (CH), 127.4 (CH), 127.9 (2 CH), 128.4 (C), 128.7 (2 CH), 128.9 (2 CH), 128.8 (2 CH), 129.3 (CH), 129.7 (CH), 131.4 (CH), 132.4 (C), 138.2 (C), 139.2 (C),139.7 (C), 142.2 (C), 157.3 (C), 189.2 (C=O) ppm.

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