Arabian Journal of Chemistry (2014) **xxx**, xxx–xxx

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Novel synthesis of biologically active indolo [3,2-C] isoquinoline derivatives

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Received 6 December 2013; accepted 14 July 2014

KEYWORDS

Indole-2-carboxylates;
Thiones;
Indolo [3,2-C] isoquinolin-2′-yl sulfanyl methylene benzimidazole

Abstract Indole-2-carboxylates are refluxed with hydrazine hydrate to form 5-substituted-3-phenylindole-2-carboxyhydrazides. These are again converted to corresponding indole-2-carboxyazides. Azides are further converted into carbamates and finally these carbamates are cyclized to form the respective substituted 6H, 11H-indolo [3,2-C] isoquinolin-2-ones (**1a**–**c**). These (**1a**–**c**) were reacted with phosphorus pentasulfide in refluxing pyridine to yield the respective thiones (**2a**–**c**). These thiones (**2a**–**c**) on reaction with chloroacetic acid and sodium acetate in acetic acid under refluxing temperature for 5 h yielded isoquinoline-thioacetic acids (**3a**–**c**). Compounds (**3a**–**c**) on reaction with orthopheneylene diamine dihydrochloride in ethylene glycol at refluxing temperature yielded substituted indolo [3,2-C] isoquinolin-2′-yl sulfanyl methylene benzimidazoles (**4a**–**c**).

1. Introduction

1.1. Synthesis of substituted indolo [3,2-C] isoquinolene-2′-4′-sulfanyl methylene benzimidazole

Winters et al. (1979a,b) have reported the synthesis of indolo [2,3-C] isoquinoline derivatives from 3-phenyl-2-carbamate derivatives of amino indole by thermal cyclization. These compounds have exhibited bactericidal and better fungicidal activities against *Staphylococcus aureus* and *Trichophyton mentagrophytes*. The patent (Ishizumi and Katsube, 1979; Ishizumi and Katsube, 1980a) reported in 1980 describes the tuberculostatic properties of indolo [2,3-C] isoquinolines. Ishizumi and Katsube, (1978a,b) have reported the synthesis of chloro-substituted compounds of the above type with their anticarcinogenic activities. The same workers have also synthesized several compounds of indolo [2,3-C] isoquinoline series, which are substituted with alkoxy, nitro, alkyl, alkenyl and cycloalkyl groups to assess their antitumor activities (Ishizumi and Katsube, 1978c, 1980b).

During the synthesis of indolo [2,3-C] isoquinoline (3,4-Benz-α-carbolines) from the corresponding 3-phenyl indole-2-carboxyazides and 3-phenyl indole-2-carboxycarbamates, the final product was found to be contaminated with a lot of impurities. The starting azides could not be purified due to their instability. Then it was thought to modify the method to get better yields. The azides so obtained were refluxed with anhydrous ethanol to get the corresponding 5-ethyl 3-phenyl-indole-2-carbamates. These carbamates were purified by

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Peer review under responsibility of King Saud University.

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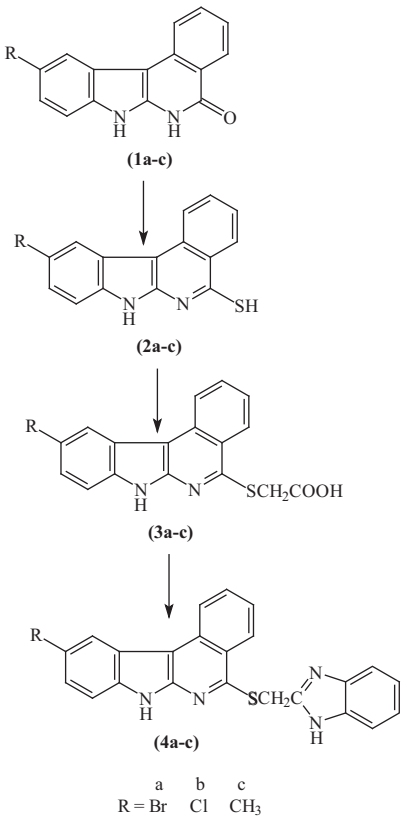
http://dx.doi.org/10.1016/j.arabjc.2014.07.009



Scheme 1 Synthetic Route

repeated crystallization. The purified carbonates were relaxed in diphenyl ether to effect the thermal ring closure to yield 5,6-dihydro-7H-indolo [2,3-C] isoquinolin-5-one.

In continuation of this work, they have also synthesized substituted 6H, 11H-indolo [3,2-C] isoquinolin-5-ones, ethyl [substituted 6H, 11H-indolo [3,2-C] isoquinolin-5-one-6yl] acetates and 5′-[substituted 6H, 11H-indolo [3,2-C] isoquinolin-5-one-6-yl] methyl-1′,3′,4′-oxadiazole-2′-thiones and tested them for antihistaminic, oxytocic, antibacterial and antifungal activities (Saundane et al., 2005a,b; Saundane and Veeresha Sharma, 2004).

In view of the above reports, for the development of good antibacterial and antifungal molecules, the synthesis of indolo isoquinolines linked to other heterocycles has been undertaken, and synthesis of these new molecules is thus described in this study.

2. Results and discussions

The starting materials substituted 6H, 11H-indolo [3,2-C] isoquinolin-2-ones (**1a**–**c**) were prepared as per the literature procedure. These (**1a**–**c**) were reacted with phosphorus pentasulfide in refluxing pyridine to yield the respective thiones (Raghunath, 1993) (**2a**–**c**). These thiones (**2a**–**c**) on reaction with chloroacetic acid and sodium acetate in acetic acid under refluxing temperature for 5 h yielded isoquinoline-thioacetic acids (**3a**–**c**). The IR spectrum of **3c** exhibited absorption peaks at 3281 cm^{-1} for NH function, and 1653 cm^{-1} for C═O functions. ^1H NMR of **3c** exhibited a singlet at 11.5 δ for the H of carboxylic acid, the singlet at 8.7 δ for proton of

Table 1 Characterization data of (**3a**–**c**) and (**4a**–**c**) compounds.

Compd.	M.P. (°C)	Yield (%)	Molecular formula	Found (calc.)			IR (cm^{-1})	NMR (ppm)
				C	H	N		
3a	265	55	$C_{17}H_{11}N_2O_2SBr$	52.68 (52.71)	2.66 (2.84)	7.20 (7.23)	3279 indole NH, 2880 –CH functions, 1660 C═O	
3b	280	58	$C_{17}H_{11}N_2O_2SCl$	59.62 (59.64)	3.20 (3.21)	8.18 (8.18)	3310 indole NH, 2930 –CH functions, 1690 C═O	
3c	260	56	$C_{18}H_{14}N_2O_2S$	67.00 (67.08)	4.32 (4.34)	8.67 (8.69)	3281 indole NH, 2865 –CH function, 1653 C═O	11.5 –COOH-Proton, 8.7 indole proton, 4.4 –CH_2 protons, 7.0–7.5 (Ar-H)
4a	286	60	$C_{23}H_{15}N_4SBr$	60.11 (60.13)	3.24 (3.26)	12.20 (12.20)	3330, 3250 NH/NH, 1670 C═N	
4b	293	62	$C_{23}H_{15}N_4SCl$	66.63 (66.66)	3.60 (3.62)	13.50 (13.52)	3350, 3277 NH/NH, 1657 C═N	12.5 indole –H, 11.5 benzimidazole –H, 4.3 –CH_2 –H, 7.2–8.3 (Ar-H)
4c	280	64	$C_{24}H_{18}N_4S$	73.06 (73.09)	4.55 (4.56)	14.20 (14.21)	3375, 3280 NH/NH, 1667 (C═N)	

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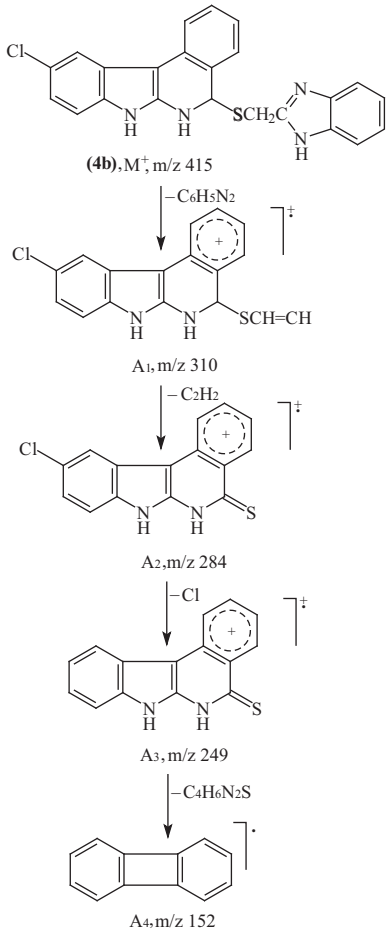
indole NH. The singlet at 4.4 δ accounts for two protons of the CH_2 group. A sharp singlet was noticed at 2.40 δ for the proton of the CH_3 group. The aromatic cluster in the region of 7.00–7.5 δ was noticed to support the formation of **3c** from **2c**. Compounds (**3a**–**c**) on reaction with orthopheneylene diamine dihydrochloride in ethylene glycol at refluxing temperature yielded substituted indolo [3,2-C] isoquinolin-2′-yl sulfanyl methylene benzimidazoles (**4a**–**c**). The IR spectrum of **4b** exhibited peaks at 3350, 3277 cm^{-1} for NH/NH, and 1657 cm^{-1} for the C═N functional group present in **4b**. The ^1H NMR spectrum of **4b** displayed an absorption peak at 12.5 δ accounting for single proton probably due to H of indole NH. Another singlet at down field at 11.5 δ is accountable for benzimidazole NH. The methylene protons at 4.3 δ, for two protons of CH_2 group. The aromatic cluster was found from 7.2 to 8.3 δ. The mass spectrum of **4b** displayed a molecular ion peak at m/z 413 which corresponds to the molecular weight of compound **4a**. Further it looses $C_6H_4N_2$ and exhibited a peak at m/z 309. With the loss of C_2H_5 it gave a peak at m/z 284. The chloride ion cluster has disappeared to display a peak at m/z 247. Then it fragmented to give peak at m/z 154, which supports the formation of **4c** from **3c**. All the compounds (**4a**–**c**) exhibited same spectral data as mentioned above (see Scheme 1 and Table 1).



3. Experimental

*3.1. Synthesis of substituted 6H, 11H-indolo [3,2-C] isoquinolin-2-one (**1a**–**c**)*

A solution of substituted-3-phenyl/indole-2-carbamate (0.01 mol) in dry diphenyl ether (10 ml) was heated under reflux for 1–2 h. The solid that separated on cooling was filtered, washed with diphenyl ether (2 ml) and then with petroleum ether, dried and crystallized from suitable solvent.

*3.2. Synthesis of substituted 6H, 11H-indolo [3,2-C] isoquinolin-thiones (**2a**–**c**)*

A mixture of (**1a**–**c**) (0.005 mol) and phosphorus pentasulfide (0.005 mol) in dry pyridine (10 ml) was refluxed for 4 h. The resulting mixture was cooled and decomposed in ice-cold water (100 ml) the crude product was separated out, filtered, washed with cold water, dried and crystallized.

*3.3. Synthesis of 6H, 11H-indolo [3,2-C] isoquinolin-2-thioacetic acid (**3a**–**c**)*

A mixture of (**2a**–**c**) (0.01 mol), an appropriate alkylating agent ($ClCH_2COOH$) (0.03 mol) and sodium acetate (3 g) in acetic acid was refluxed for 5 h and then the solution was evaporated. The residue was washed with little water and crystallized.

*3.4. Synthesis of 6H, 11H-indolo[3,2-C]isoquinolin-2′-yl sulfanyl methyl]benzimidazole (**4a**–**c**)*

A mixture of (**3a**–**c**) (0.01 mile) and ortho phenylenediamine dihydrochloride (0.01 mile) in ethylene glycol (20 ml) was refluxed for 5 h. The reaction mixture was cooled to room temperature and poured into water (100 ml). The solid obtained was filtered, resuspended with sodium bicarbonate filtered, washed, dried and recrystallized.

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.arabjc.2014.07.009.

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