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Synthesis of Some Derivatives of Benzophenothiazinone Of Pharmaceutical Interests Via Nickel Catalysed Grignard Couplings

E.A. Onoabedje[1], B.E. Ezema[1*], C.G. Ezema[2], D.I. Ugwu[1]

1* Department of Pure & Industrial Chemistry, University of Nigeria, Nsukka

1. Department of Pure & Industrial Chemistry, University of Nigeria, Nsukka

2. National Centre For Energy Research and Development, University of Nigeria, Nsukka

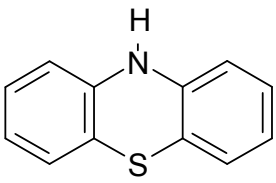
Email: eberechy2007@yahoo.com

Abstract

Some derivatives of 6-chlorobenzo[a]phenothiazin-5-one were synthesized via nickel catalyzed Grignard couplings. The parent compound 6-chlorobenzo[a]phenothiazin-5-one was prepared by refluxing a mixture of 2-aminobenzenethiol and 2,3-dichloro-1,4-napthoquinone in anhydrous potassium acetate in benzene/ethanol to obtain a deep orange crystalline powder in an excellent yield after work-up. The structures of new prepared derivatives were determined by elemental analysis and spectroscopic methods (nmr, ir and ms).

INTRODUCTION

Interest in phenothiazine [**1**] has remained unabated because of its versatile utilities; chiefly as drugs[1-3], and as pesticidal agents[4], antioxidants in grease and fuels[5-7], dyes and pigments[8] among others.



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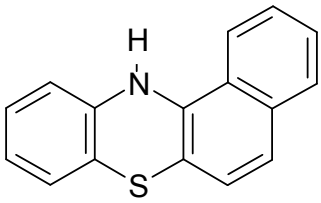

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As one of the most useful heterocyclic rings that are known so far; extensive structural modifications on this parent compound (phenothiazine) is in progress in an attempt to improve on its pharmacological activities. Presently all the four monoaza, ten diaza, three triaza and even tetraaza of linear phenothiazine have been reported[9,10]. Although benzo[a]phenothiazine **[2]**, the prototype of nonlinear phenothiazines was reported by Kym nearly a century ago its chemistry has remained poorly develop compare to that of phenothiazine discovered a few year later[11-13]. Only a few reports are available in literature on the synthesis of benzophenothiazine and its derivatives in spite of the fact that these compounds are used as potential carcinogenic agents, anthelminitics, as antioxidants, stabilizers and in photography[14]. In view of the promising interest for this class of compounds in pharmacology, we therefore describe a simple and inexpensive synthesis of some derivatives of 6-chlorobenzo[a]phenothiazin-5-one by nickel catalyzed Grignard coupling.

EXPERIMENTAL

General

Melting points were determined by open tube capillary method and are uncorrected. UV-visible spectra were recorded on Cecil Ultra-Violet spectrophotometer in ethanol using 1 cm quartz cells. Absorption maxima are given in nanometers (nm) and figure in parenthesis are the log ε values. Infrared spectra were obtained on Magna-IR system 750 spectrophotometer using nujol mull and absorptions are giving in wave numbers (cm^{-1}). Proton Nuclear Magnetic Resonance was recorded on Varian NMR Mercury-200 MHz spectrometer and chemical shifts reported in δ scale relative to TMS as internal standard and mass spectra on a shimazu LKB-9000 spectrometer. Elemental analyses were obtained using Heraeus CHN-O Rapid Analyzer. Analytical samples were obtained by column chromatography on aluminium oxide 90 (Merk, 70-230 Mesh ASTM) employing benzene- acetone (3:1). All physical data of compounds described are presented in Table 1.

6-Chlorobenzo[a]phenothiazin-5-one (5)

To a stirred solution of 2,3-dichloro-1,4-naphthoquinone (**4)** (2.35 g, 10 mmol) and anhydrous potassium acetate (1.5 g) in 80 ml benzene was added drop by drop an alcoholic solution of 2-aminobenzenthiol (**3)** (1.25 g, 10 mmol) and the entire mixture was stirred for 30 min at room temperature. Then after the reaction mixture was reflux for 5 h. At the end of the refluxing period the solvent was removed in vacuum and the resulting slurry poured into crushed ice (100 g) and stirred. The resulting precipitate was collected, washed with distilled water and air-dried. It was then recrystallized from ethanol-benzene to give compound **(5)** (0.92 g, yield 74 %). M.p. 211-212 ^{o}C

General Procedure for the Synthesis of 6-substituted derivatives of benzo[a]phenothiazine compound

6-Butylbenzo[a]phenothiazin-5-one (7a)

To a mixture of compound **(5)** (1.49 g; 5.0 mmol), [$NiCl_2$(dppe)] (50 mg; 0.092 mmol), and anhydrous THF (10 ml) in an ice-bath was added a dropwise THF solution of butylmagnesium bromide (7.6 mmol) under N_2 atm while stirring. The resulting blackish homogenous mixture was stirred at room temperature for 6 h .The crude product was made alkaline by adding 10% NaOH solution and extracted with benzene and ether. The organic layer was dried and evaporated to give crystalline crude product. Recrystallization from benzene-ethanol afforded compound (**7a)** (0.98 g, 66 %). Uv-visible spectrum (nm): 215(4.68), 251(3.95), 270(3.25), 345(1.34), 401(4.64). Infrared spectrum (cm^{-1}): 3090 (Ar-H), 1637 (C=O), 2987, 2928 (R-H), 810, 760. Mass spectrum m/z: 319(M^+, 100), ^{1}H-NMR δ: 0.8 (t, CH_3); 1.22(m, CH_2); 1.9(t, CH_2); 7.2-8.2(m, 8H of aromatic rings), ^{13}C-NMR ppm; 173.0 (C=O), 120.4-160.3 (15C of all the rings), 28.3-14.0 (4C of butyl group).

The other derivatives (7**b-e**) were prepared using the same protocol as for **7a**.

6-Methylenephenylbenzo[a]phenothiazin-5-one (7b)

Uv-visible spectrum (nm): 217(4.81), 244(4.05), 261 (3.39), 315 (1.25); 456 (4.81). Infrared spectrum (cm^{-1}): 3050 (Ar-H), 1647(C=O), 2896 (R-H), 1610, 1578, 830, 724. Mass spectrum m/z: 353 (M^+, 100). ^{1}H-NMR δ: 2.4 (s, CH_2), 7.6-8.4 (m, 13H of aromatic rings), ^{13}C-NMR ppm; 173.0 (C=O), 120.4-160.3 (21C of the rings), 29.6 (CH_2).

6-Methylenethiophenylbenzo[a]phenothiazin-5-one (7a)

Uv-visible spectrum (nm): 214(3.19), 252 (4.17), 350 (1.24), 461 (4.31). Infrared spectrum (cm^{-1}): 3010 (Ar-H), 1630 (C=O), 1540, 845, 750. Mass spectrum m/z: 345(M^+, 100). ^{1}H-NMR signals at δ 3.4 (s, CH_2), 6.8-8.2 (m, 11H), ^{13}C-NMR signals at ppm; 173.0 (C=O), 120.4-160.3 (19C of the rings), 22.4(CH_2).

6-Phenylbenzo[a]phenothiazin-5-one (7d)

Uv-visible spectrum (nm): 214(3.69), 225(3.71), 249(4.01), 373(1.62), 410 (3.69). Infrared spectrum (cm^{-1}): 3035(Ar-H), 1638(C=O), 1545, 1468, 880, 730. Mass spectrum m/z: 339(M^+, 100). ^{1}H-NMR exhibited signals at δ 7.2-8.2(m, 13 of aromatic rings), ^{13}C-NMR showed signals at ppm; 173.0 (C=O), 120.4-160.3 (21C of the rings),

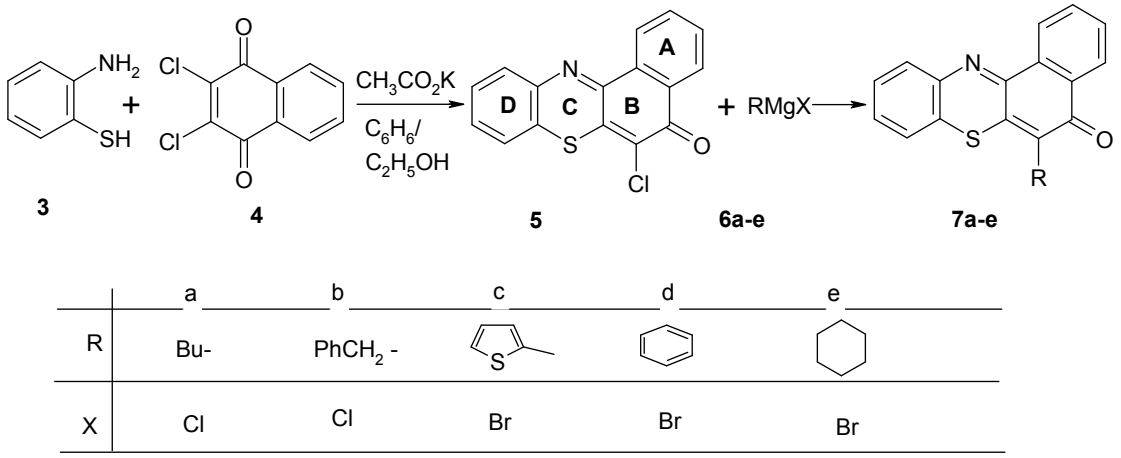
6-Cyclohexylphenothaizin-5-one (7e)

Uv-visible spectrum (nm): 220(4.23), 245(4.27), 272(3.11),354(1.92), 420(2.03). Infrared spectrum (cm^{-1}): 3030(Ar-H), 2987, 2898(R-H), 1634(C=O), 1605, 1589, 1525, 1498, 765, 710. Mass spectrum m/z: 345(M^+, 100). ^{1}H-NMR signals δ: 1.4-2.2 (m, 6H), 7.4-7.8(m, 8H of aromatic). ^{13}C-NMR showed signals at ppm; 173.0 (C=O), 120.4-160.3 (15C of rings A, B, C, D), 23.4-27.2 (6C of cyclohexyl ring).

The physical and micro analytical data of compounds 5 & 7a-e are contain in Tables 1

RESULTS AND DISCUSSION

The parent compound 6-chlorobenzo[a]phenothiazin-5-one **(5)** was prepared by heating a mixture of 2-aminobenzenethiol (**3)** and 2,3-dichloro-1,4-napthoquinone (**4)** under reflux in anhydrous potassium acetate in benzene/ethanol for 5 h to obtain a deep-orange crystalline powder in an excellent yield after work-up, melting at 211-212^{o}C. Elemental analyses are consistent with the molecular formula $C_{16}H_8ONSCl$. The Uv- visible bands were observed at 241 nm(log ε 3.37) , 250 nm (log ε 4.25) , 270 nm (log ε 2.84) & 433 (log ε 4.22); IR spectrum showed a strong absorption band at 1643 (C=O), H^1-NMR spectrum exhibited signals at δ 6.8-7.7 (m, 8H) and ^{13}C-NMR showed signal at ppm: 173.0 assigned to (C=O), 120.1-160-3 for other carbons in the rings.

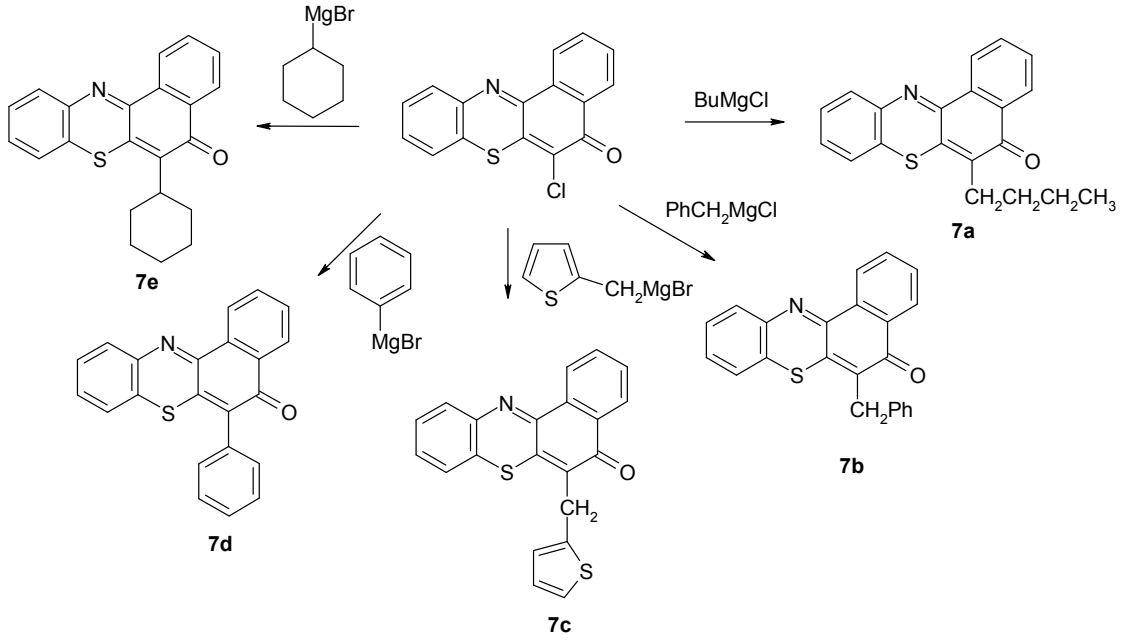


	a	b	c	d	e
R	Bu-	$PhCH_2$ -	S		
X	Cl	Cl	Br	Br	Br

Scheme 1

To a mixture of 6-chlorobenzo[a]phenothiazin-5-one (**5)**, catalyst and THF solvent in a reaction flask was added drop wise a Grignard solution of THF within 30 min and the whole solution were stirred at room temperature for 6 to 12 h. Dichloro[1,3-bis(diphenyl phosphino) propane],($NiCl_2$(dppp)), was used as catalyst because it has been found to be one of the most effective catalysts for Grignard coupling.[15,16] Although analogous palladium complexes were also employed as effective catalyst precursors[17] for Grignard coupling, their high costs give them disadvantage over nickel complexes. The reaction is generally exothermic and as the reaction warms to ambient temperature there is usually colour change of the reaction mixture from yellow to dark brown. The resulting mixture was made alkaline by adding 10% NaOH solution and then later extracted with various solvents to obtain the desire products in good yields after recrystallization. The structures of the derivatives **7a-e** were supported by elemental and spectral data.

The IR spectrum of all the derivatives exhibited strong characteristic band for C=O group. ^{1}H-NMR and ^{13}C-NMR spectrum gave further evidence by providing the following signals for the derivatives: ^{1}H-NMR spectrum of **7a** showed signals at δ 0.8 (t, CH_3); 1.22(m, CH_2); 1.9(t, CH_2); 7.2-8.2(m, 8H of aromatic rings), ^{13}C-NMR spectrum showed signals at ppm; 173.0 (C=O), 120.4-160.3 (15C of all the rings), 28.3-14.0 (4C of butyl group). ^{1}H-NMR spectrum of **7b** gave signals at δ 2.4 (s, CH_2), 7.6-8.4(m, 13H of aromatic rings), ^{13}C-NMR spectrum showed signals at ppm; 173.0 (C=O), 120.4-160.3 (21C of the rings), 29.6 (CH_2). ^{1}H-NMR of **7c** gave signals at δ 3.4 (s, CH_2), 6.8-8.2 (m, 11H), ^{13}C-NMR spectrum showed signals at ppm; 173.0 (C=O), 120.4-160.3 (19C of the rings), 22.4(CH_2). ^{1}H-NMR spectrum of **7d** exhibited signals at δ 7.2-8.2(m, 13 of aromatic rings), ^{13}C-NMR spectrum showed signals at ppm; 173.0 (C=O), 120.4-160.3 (21C of the rings), whereas ^{1}H-NMR of **7e** gave signals at δ 1.4-2.2 (m, 6H), 7.4-7.8(m, 8H of aromatic). ^{13}C-NMR spectrum showed signals at ppm; 173.0 (C=O), 120.4-160.3 (15C of rings A, B, C, D), 23.4-27.2 (6C of cyclohexyl ring).

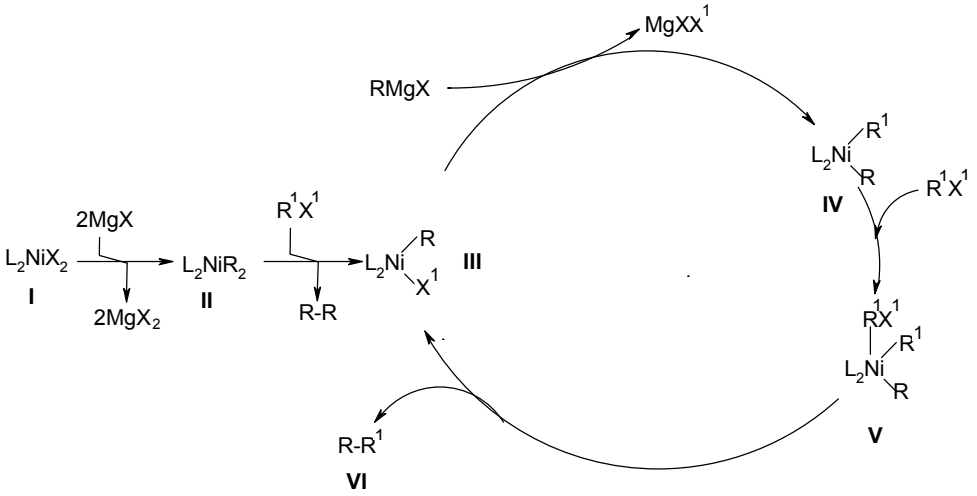


Scheme 2

Table 1: Physical Data for Compounds **5** & **7a-e**.

Entry	R	Reflux Time (hr)	Recrystallisation solvent	Yield (%)	M.p (^{o}C)	Molecular Formula	Elemental Analysis(%); Calcd/(Found)				
							C	H	N	S	Cl
5	-Cl	5	ethanol/water	74	211-212	$C_{16}H_8ONS$	64.54 (63.87)	2.69 (2.71)	4.71 (4.91)	10.76 (10.83)	11.93 (11.88)
7a	Bu-	6	Benzene/ethanol	66	245-246	$C_{20}H_{17}ONS$	75.24 (75.32)	5.33 (5.31)	4.39 (4.34)	10.03 (9.98)	-
7b	$PhCH_2$-	12	Acetone/ethanol	60	>300	$C_{23}H_{15}ONS$	78.19 (78.13)	4.25 (4.27)	3.97 (3.83)	9.07 (10.11)	-
7c	C_4H_3S-	10	Benzene/ethanol	67	250-251	$C_{20}H_{11}ONS_2$	69.57 (69.91)	3.19 (3.21)	4.06 (4.10)	18.55 (18.47)	-
7d	C_6H_5-	12	Acetone/water	68	>300	$C_{22}H_{13}ONS$	77.88 (77.75)	3.83 (4.11)	3.51 (3.55)	9.44 (9.37)	-
7e	C_6H_{11}-	6	Benzene/acetone	58	269-270	$C_{22}H_{19}ONS$	76.52 (76.61)	5.51 (5.43)	4.06 (4.13)	9.28 (9.22)	-

The probable mechanisms [17] of these reactions are as follows:



The dihalodiphosphate **I** reacts with the Grignard reagent to form the intermediate diorganonickel complex **II** which is converted to haloorganonickel complex **III** by an organic halide with concomitant formation of isommerized (undesired) product, R-R. Reaction of **III** with the Grignard reagent forms a new diorgano complex **IV** which

generates cross-coupling product **VI** by its reaction with organic halide via pentaco-ordinate intermediate **V** and eventually the original complex **III** is regenerate to complete the catalytic cycle.

CONCLUSION

We have shown that nickel catalyzed Grignard coupling offer excellent route in the preparation of alkyl and aryl derivatives of benzophenothiazines. This study has open up window for further synthesis of other derivatives. Further study needed to be conducted on these new compounds to ascertain their medicinal potentials.

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