Synthesis and Study of Dimethyl-2-(11-isoindolo [1,2-b] benzothiazolyl) but-2-ene-4-diate and Related Compounds

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Abstract

Dimethyl-2-(11-iso[1,2-b] benzothiazolyl) but-2-ene-4-diate (5) was synthesized from the reaction of isoindole [1,2-b] benzothiazole (3) with dimethyl acetylene dicarboxylate (4).

Also the products from the reaction of a phthalaldehyde with appropriate substituted amines and 2-mercaptoethanol in the presence of dimethyl acetylene dicarboxylate (4) was carried out. A quantum and molecular mechanic theories were applied to prove electrophilic attack to obtain a substitution product with extended conjugation rather than Diels-Alder adduct.

The structure of all compounds were identified by physical, chemical and spectroscopic data.

الخلاصة

ثنائي مثيل (11-ايزواندول [1,2-b] بنزوثايزولال) بت-2-ين-4-دايوت (5) حضر من خلال تفاعل الايزواندول [1,2-b] ثايزول (3) مع ثنائي مثيل استلين ثنائي الكاربوكسيل (4). كذلك ناتج تفاعل الفثالديهايد مع مشتقات امينية مختارة و 2-ثايوإيثانول بوجود ثنائي مثيل ثنائي الكاربوكسيل (4) تم الحصول عليه. نظرية الكم وميكانيكية الجزيئة طبقت لاثبات ان الايزواندول اكثر تعرضا للهجوم الالكتروفيلي للحصول على ناتج معوض مع اواصر مزدوجة متعاقبة متعددة وليس ناتج ديلز-الدر. تم تشخيص المركبات المحضرة بواسطة الطرق الفيزيائية والكيميائية اضافة الى الطرق الطيفية المتوافرة.

Introduction

The chemistry of the simplest aromatic dialdehyde (1,2,1,3 and 1,4 benzodicarboxy-aldehyde) is remarkable except for the ease with which the ortho isomer (reffered as o-phthalaldehyde) undergo cyclization. This characteristic has been widely used in the synthesis of carboxylic and heterocyclic compounds via base catalysed condensation(1,2) and benzoin condensation(3) or by the reaction with amino acid derivatives(4). Also was used to prepare a number of fascinating natural-artificial bioactive compounds such as staurosporin, indoprofin and DN 2327(5-7).

o-Phthalaldehyde was first reported by Thiele and Winter(8) to react with amines to give color material. Roth(9) showed that

(O.P.T) in the presence of strong agent such as 2-mercaptoethanol or sodium borohydrate produce highly fluorescent compounds with most amino acids. The reaction of 2-mercaptoethanol has been reported by Simons and Johnson(10). They show that the fluorescent product is alkyl thio-2-alkyl isoindole. We herin reported that molecule containing amine and thiol groups such as aminothiophenol could play the part of amine and mercaptan together to produce a more stable isoindole.

Experimental

Uncorrected melting point were determined using GalkenKamp melting point apparatus. I.R spectra were recorded by using Py-Unicam SP 1100 spectrophotometer as KBr disc. U.V visible spectra were performed on double beam Shimadzu U.V-160 (U.V. visible) spectrophotometer. Reactions progress were monitored by the T.L.C technique. Column chromatography was carried out on silica (60-120 mesh). Theoretical physical calculation and three dimentional (3D) configuration were pointed out using (ChemOffice) program, Version 7 MOPAC method.

Synthesis of isoindolo [1,2-b] benzothiazole (3)

Phthalaldehyde (1.3 gm, 0.01 mole) and
2-aminothiophenol (1.25 gm, 0.01 mole) in benzene (50 ml) were stirred for 2 hrs at room temperature. The resulting yellow precipitate was filtered and crystallized from chloroform-petroleum ether (40-60°C) to give isoindolo-[1,2-b]-benzothiazole (3) (1.4 gm, 65%), m.p. = 202-205 °C (Lit.(11) = 204-207 °C). I.R. (KBr disc) □$_{max}$ 3030, 1120, 810 cm^{-1}, □$_{max}$ (EtOH) 345, 320, 250.

Synthesis of dimethyl-2-(11-isoindolo [1,2-b] benzothiazolyl) but-2-ene-4-dioate (5)

Isoindolo [1,2-b] benzothiazole (3) (2.2 gm, 0.01 mole) in benzene was stirred for 1hr at room temperature. A solution of dimethyl acetylene dicarboxylate (1.42 gm, 0.01 mole) in benzene (20 ml) was added and stirring continued for 3hrs. The resulting red solution was evaporated to give a red black precipitate, which was redissolved in chloroform and then saturated solution of sodium bisulphate (75 ml) added. The reaction mixture was stirred at room temperature for 2hrs, and the mixture extracted with chloroform (2 x 30 ml). The combined extracts were washed with water (50 ml), dried over anhydrous sodium sulphate, filtered and evaporated to give a black-red residue which was chromatographed on silica column (100 gm) (5-90% ethyl acetate-petroleum ether (40-60°C) as eluant). This gave a red precipitate which crystallized from chloroform-petroleum ether (40-60°C) to give dimethyl-2-(11-isoindolo [1,2-b] benzothiazolyl) but-2-ene-4-dioate (0.72 gm, 19.7%), m.p 143-145 °C. I.R. (KBr disc) □$_{max}$ 3050, 1740, 1625, 1330, 1250, 915 cm^{-1}, □$_{max}$ (EtOH) 490, 402, 365, 252.

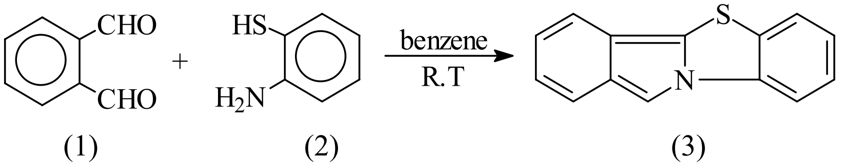
Synthesis of isoindole from reaction of phthaladehyde with amino pyridine and mercaptoethanol in the presence of dimethyl acetylene dicarboxylate (13).

Appropriate substituted amino pyridine (0.01 mol) in chloroform (20 ml) was added to a solution of phthaladehyde (1.3 gm, 0.01 mole) and mercaptoethanol (0.01 mole) dissolved in chloroform (50 ml) and stirred for 20 mins at room temperature.

A solution of dimethyl acetylene dicarboxylate (1.4 gm, 0.01 mole) in chloroform (20 ml) was added and stirred for 3 hrs. The resulting solution was evaporated to give a red-black precipitate, which then was redissolved in chloroform and saturated solution of sodium bisulphate (75 ml) was added. The reaction mixture was stirred at room temperature for 2 hrs, and the mixture was extracted with chloroform (2 x 50 ml). The combined extracts were washed with water, dried over anhydrous sodium sulphate. Filtration and concentrated to give a red-black which on crystallization from ether-petroleum ether (40-60 °C) gave the product. Physical properties and spectral data are listed in Table (I).

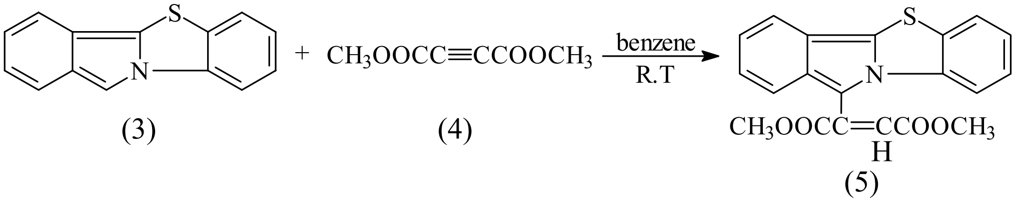
Results and Discussion

When 2-aminothiophenol (2) was added to phthalaldehyde (1) in equivalent amounts in benzene, there was a yellow precipitate, and it found to be fluorescent (Scheme I).



Scheme I

The structure of the yellow product was shown to be isoindolo [1,2-b] benzothiazole (3) from the spectral data and chemical reaction. The presence of the benzothiazole (3) was inferred from the formation of adduct with dimethtyl acetylene dicarboxylate (4) to give a red-black 1:1 adduct (5), a substitution product with extended conjugation (Scheme II).

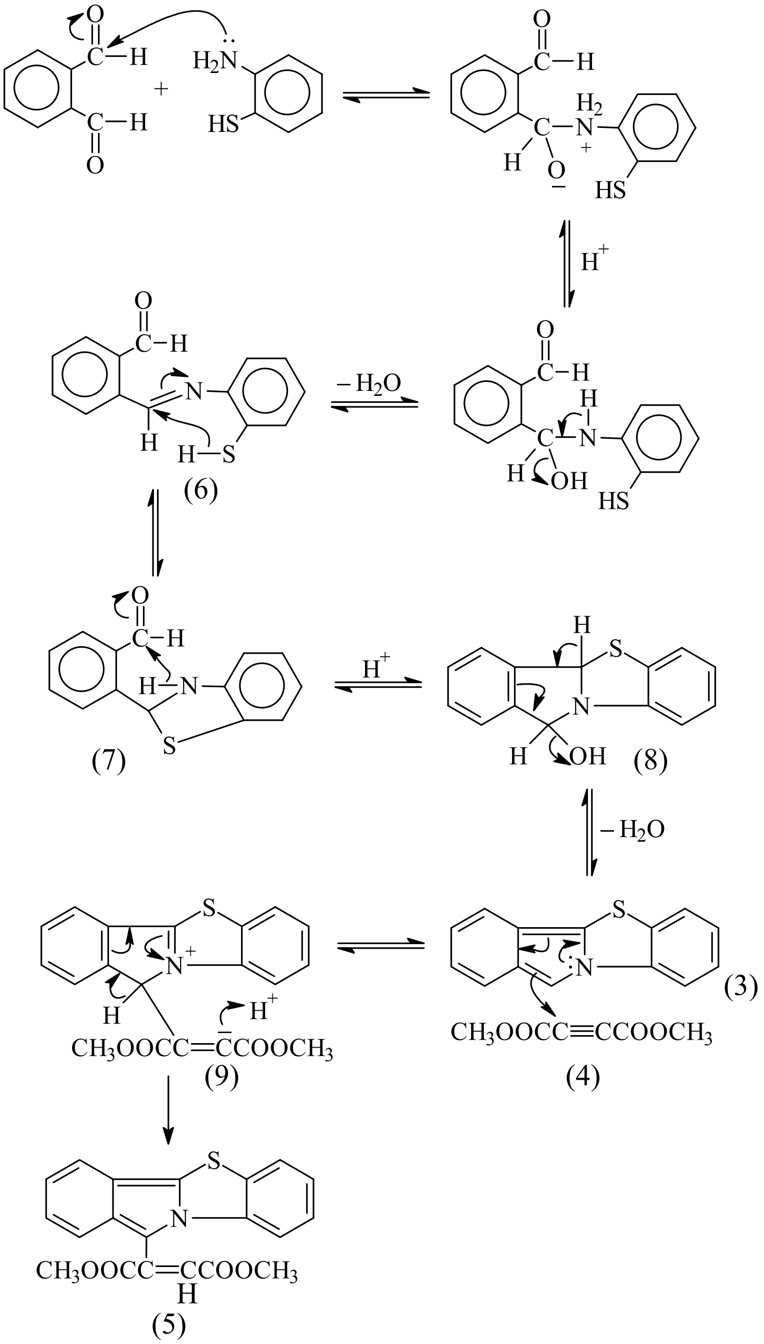


Scheme (II)

The i.r. spectra of the product (5) showed absorption band at (1740 cm^{-1}) due to C=O group and $\square_{max}$ 495 nm.

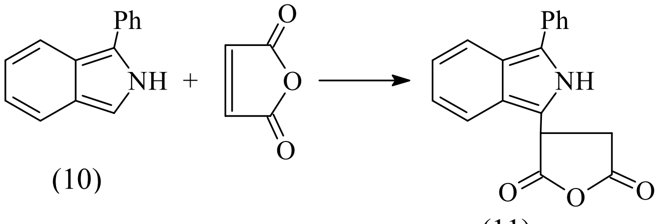
The mechanism of the reaction can be suggested as follow:

The reaction would probably proceed initially attack on the phthalaldehyde (Scheme III). Dehydration to give imine (6). Nucleophilic attack of imine (6) by the thio group gives the benzothiazoline (7). Trans-annular dehydration of (8) gives the isoindole (3). The adduct (5) can be formed by the attack of isoindole (3) at an acetylenic carbon of ester (4) to give zwitterion (9) which lead to adduct (5).



Scheme (III)

In certain cases where a Diels-Alder addition might have been anticipated, substitution of isoindole is apparently preferred. For example, 1-phenyl isoindole (10) with maleic anhydride gives the succinnic anhydride derivative (11)⁽¹²⁾. In this respect the chemistry of isoindole resembles that of pyrrole(13). 1,2,3-Trisubstituted isoindole do not react with phenyl isocyanate(14).



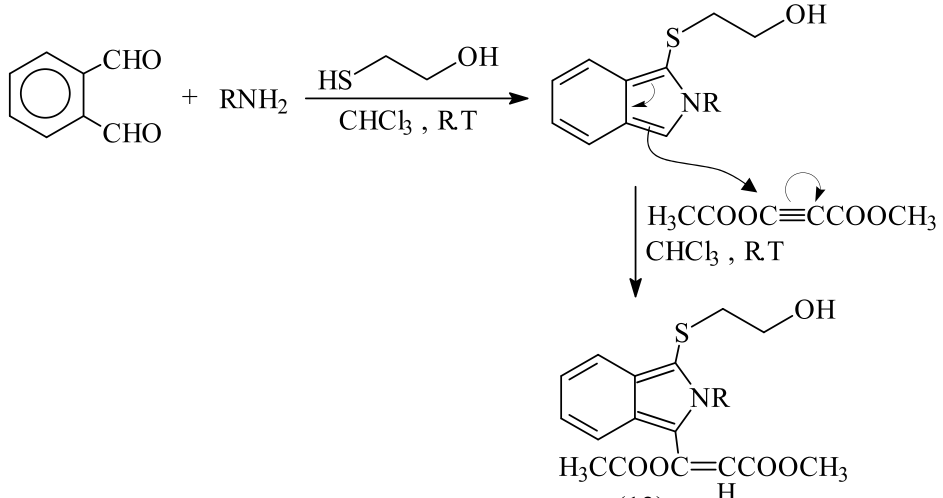
(10)

(11)

It is apparent from simple valence bond consideration as well as from calculation of electron density that isoindoles should be susceptible to electrophilic attack at carbon No. 1(15).

Also when substituted amines were added to phthalaldehyde and mercaptoethanol in chloroform, isoindole could be produce as a yellow precipitate which was to fluorescent. The structure was confirmed on the same basic properties of isoindoles and non of the products isolated like that of Diels-Alder.

The presence of isoindole was inferred from the formation of adduct with dimethyl acetylene dicarboxylate to give a red-black adduct. A substitution product with extended conjugation.



(13)

The structure of adduct (13) were suggested by spectra data. The infrared spectra showed absorption band of carbonyl group around (1735 cm^{-1}) and OH group around 3500 cm^{-1}. The physical properties and spectral data are listed in Table (I).

Further information about the isolated products was obtained from theoretical calculation which made by means of quantum mechanical semiempirical method (SCF) and molecular mechanics method (MM2). Table II and III give the calculated relevant physical properties of the products of Diels-Alder and the substitution product. The steric energy of the Diels-Alder reaction as well as their steric energies are by far higher than those for substitution reaction also another factor play an important rule on the isolated product were the differences in heat of formation. These results explain the preference of the substitution reaction as compared to the Diels-Alder reaction.

The 3D-configuration for isoindole and the product of substitution are shown in Fig. 1 as example.

Table (I): Physical and spectroscopic data of isoindole adducts (13)

Comp. 13	R	Molecular formula	m.p. °C	Yield %	IR (cm^{-1}) KBr disc				U.V (EtOH)
					O-H	C-H	C=O	C=N	□$_{max}$ (nm)
a	N-4-pyridyl	$C_{21}H_{20}N_2O_5S$	116-114	41	3450	3000	1745	1580	512,402,290
b	N-2-[4-methyl pyridyl]	$C_{22}H_{22}N_2O_5S$	109-112	35	3500	3000	1740	1590	530,402,298
c	N-2-[5-nitro pyridyl]	$C_{21}H_{19}N_3O_7S$	166-168	52	3400	3010	1740	1580	510,406,290

Table (II): Physical properties of isoindole (3)

	Heat of formation Kcal/mole	Stretch	Bend	Stretch-bend	Torsion	Non-1,4 VDW	1.4VDW	Dipole/dipole	Total steric energy Kcal/mole
Substitution	14.4701	0.6228	21.8913	-0.2443	-9.0080	-3.6484	7.5176	6.4048	12.2805
Diels-Alder	156.512	1.3973	-1.0001	-1.0001	-12.2169	-4.8795	6.7856	6.7856	46.1774

Table (III): Physical properties of isoindole adduct (5)

	Heat of formation Kcal/mole	Stretch	Bend	Stretch-bend	Torsion	Non-1,4 VDW	1.4VDW	Dipole/dipole	Total steric energy Kcal/mole
Substitution	-111.1508	1.3107	28.4632	-0.0325	1.2858	0.3062	7.5176	0.7601	39.6112
Diels-Alder	-100.6119	18.2318	108.0909	-6.1657	4.1431	-0.9331	18.4385	5.2964	147.1017

Table (IV): Physical properties of isoindole adduct (13)

	Heat of formation Kcal/mole	Stretch	Bend	Stretch-bend	Torsion	Non-1,4 VDW	1.4VDW	Dipole/dipole	Total steric energy Kcal/mole
Substitution	27.13265	0.6481	12.7189	-0.0510	-13.9986	-3.2968	10.0165	0.0000	6.0371
No sub no diels	157.26494	0.5766	12.8045	-0.0497	-6.5499	-5.3102	13.1681	0.0000	14.6394

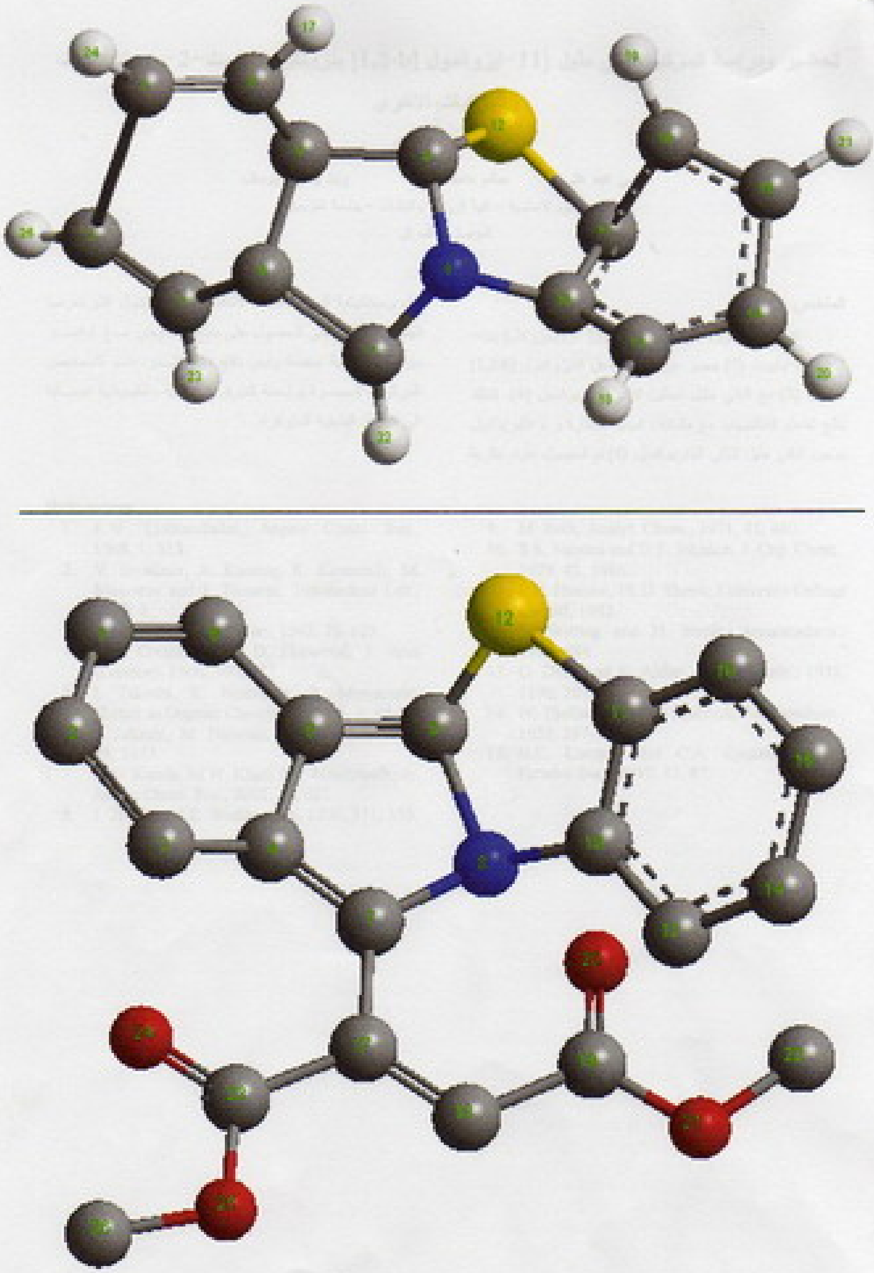


Figure 1: The 3D configuration of Isoindole and the product of substitution

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