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Synthesis of some N-Aryl- p-Toluene Sulfonamide Compounds

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ABSTRACT

A number of acetylenic amine (4a-e) were synthesis from propagyl p-(p-toluene sulfonamido) benzoate (3) with secondary amines via Mannich reaction. The carbonyl isothiocynate compound (5) was synthesized from the reaction of the corresponding benzoyl chloride with potassium thiocynate. This compound was converted to the corresponding thiourea compounds (6a-e), thiocarbomate (7a-d) and (8a-e) by their reaction with different amines, alcohols and phenols respectively. The structure of the synthesized compounds have been elucidated by their physical and spectral methods.

Keywords: Mannich reaction, sulfonamides, acetylenic amine, thiourea, thiocarbamate, Isothiocyanate compounds.

تحضير بعض معوضات N-اريل- بارا – تلوين سلفونامید

الملخص

حضر عدد من الامينات الاستيلينية (4a-e) من (بارا-تولوين سلفونامیدو بنزوات) البروباجيل (3) مع أمينات ثانوية من خلال تفاعل مانخ. كما حضر مركب ايزوثايوسيانات البنزويل (5). كلوريد البنزويل المقابل مع ثايوسيانات البوتاسيوم حول المركب (5) الى مركبات الثاشيويوريا (6a-e) والثايوكارباميت (7a-d) و (8a-e) بتفاعله مع امينات وكحولات وفينولات مختلفة على التوالي. شخصت المركبات المحضرة باستخدام الطرائق الفيزياوية والطيفية .

الكلمات الدالة: تفاعل مانخ، مركبات السلفونامید,الامينات الاستلينية , مركبات الثايويوريا و ثايو كارباميت و ايزوثايوسيانات.

INTRODUCTION

Thiourea compounds are excellent bioactive agents. A number of biological activities are associated with substituted thiourea derivatives, and some N-substituted –N\-alkoxycarbonyl thiourea have been used as antifungal agents (Liang *et al.,* 2004; Hai-Tang *et al.,* 2008), antimicrobial (Al-Haiza *et al.,* 2005; Zhony *et al.,* 2008).Several thiourea derivatives have been found to inhibit cytochrome (Underwater *et al.,* 1999), herpes simplex virus type l DNA cleavage (Zeijl *et al.,* 2000), varicella Zoster virus (Visalli *et al.,* 2003), reverse transcriptase enzyme (RT) (Venkatachalam *et al.,* 2005), the platelet- derived growth factor (PDGF) receptor (Furuta *et al.,* 2006). Quinoline thiourea derivatives also showed antitumor activity (Li *et al.,* 2006). It was used as anti – oxidants that prevent drying and cracking of neoprene (Sakata *et al.,* 2006), as accelerated stability tests on distillate fuels (Juyal and Anand 2002), and as fluorescent ligand carbonyl thiourea derivative with $Cu(ClO_4)_2$ or strong acids (Bricks *et al.,* 2000). Substituted thiocarbamates were known to posses, various biological activities, such as antiepileptics (Ludwig and Piech, 1951), inhibition of acetylcholinesterase (Casida, 1963), antineo- plastic (Stewart and Gammans, 1974) and antimicrobial agents, (Ray *et al.,* 2005). Furthermore carbamate derivatives can be used as starting compounds in a large variety of heterocyclic synthesis (Shutalev and Kurochkin, 2004). Finally acteylenic amines were known to be hypertensive agents (Wilson *et al.,* 1975), antispasmodics (Dahlbom *et al.,* 1963), anticancer agents (Fujiki and Zasshi, 1966; Khuthier; Al-Abachi, 1993; Al-Omari, 1996; Mahmood, 1997) and anti bacterial (Sheat and Dawood, 2003). Therefore, many investigaters reported the synthesis of this type compounds, [isothiocynate (Kearney *et al.*,1989 and Kulkarni, 2002), thiourea (Beyer, 1963; Count *et al.*,1977 and Sasaki *et al.*,1980), carbamate (March, 1977 and D'Amico *et al.*,1985) and acetylinic amine (Al-Ajely *et al.,* 2002 and Sheat and Dawood , 2003)] derivatives owing to their practical significance.

EXPERIMENTAL

Uncorrected melting points were determined using Electrothermal 9300 melting point apparatus. IR spectra were recorded by Infrared spectrophotometer Model Tensor 27 Bruker Co. using KBr discs. UV spectra were measured on Shimadzu UV-1650 pc, UV-Visible Spectrophotometer.

Preparation of 4-(p-Toluene Sulfonamido) benzoic acid (2) : (Bergeim *et al.*,1947)

Tosyl chloride (0.01 mole, 1.90 g) was added gradually pulsed to a solution of (0.01 mole, 1.37g) p-amino benzioc acid in pyridine (20 mL). This mixture was stirred and refluxed for 1hr ,then the hot mixture was poured on ice water, filtered off and recrystalized from ethanol. The physical and spectral data were illustrated in Table (1).

Preparation of (4-Amino But-2-ynyl)-p-Touene Sulfonamido benzoate (3): (Al-Ajely *et al.*, 2002)

A mixture of (0.01 mole, 2.91g) of compound (2) and (0.01 mole, 3mL) of thionylchloride was refluxed for 2 hrs. After cooling, (0.01 mole, 0.58mL) of propargyl alcohol was added then the mixture was refluxed for 3hrs. The mixture was diluted with

water and the precipitate was filtered and recrystallized from ethanol. The physical and spectral data were illustrated in Table (1).

Preparation of (4-Disubstituted Amino)-But-ynyl-4-(p-Toluene Sulfon- amido) Benzoate (4a-e) : (Karlen *et al.*, 1970)

To a cooled (0ºC), stirred mixture of acetylenic compound (3) (0.03 mole, 9.8g) and secondary amine (a-e) (0.03 mol), paraformaldehyde (0.03 mole) and cuprous chloride (0.03 mole, 0.06g) in 50ml of dry peroxide-free dioxane, then glacial acetic acid (0.03 mole, 4.5 ml) was added with cooling. The reaction mixture was stirred for 5 minutes at room temperature then refluxed for 3hrs at (0ºC). The mixture was hot filtrated, and the solvent was evaporated and the solid material was recrystallized from ethanol to give compounds (4a-e). The physical and spectral data were indicated in Table (1).

Preparation of 4-(p-Toluene Sulfonamido) benzoyl isothiocyante (5): (Sasaki *et al.*, 1980)

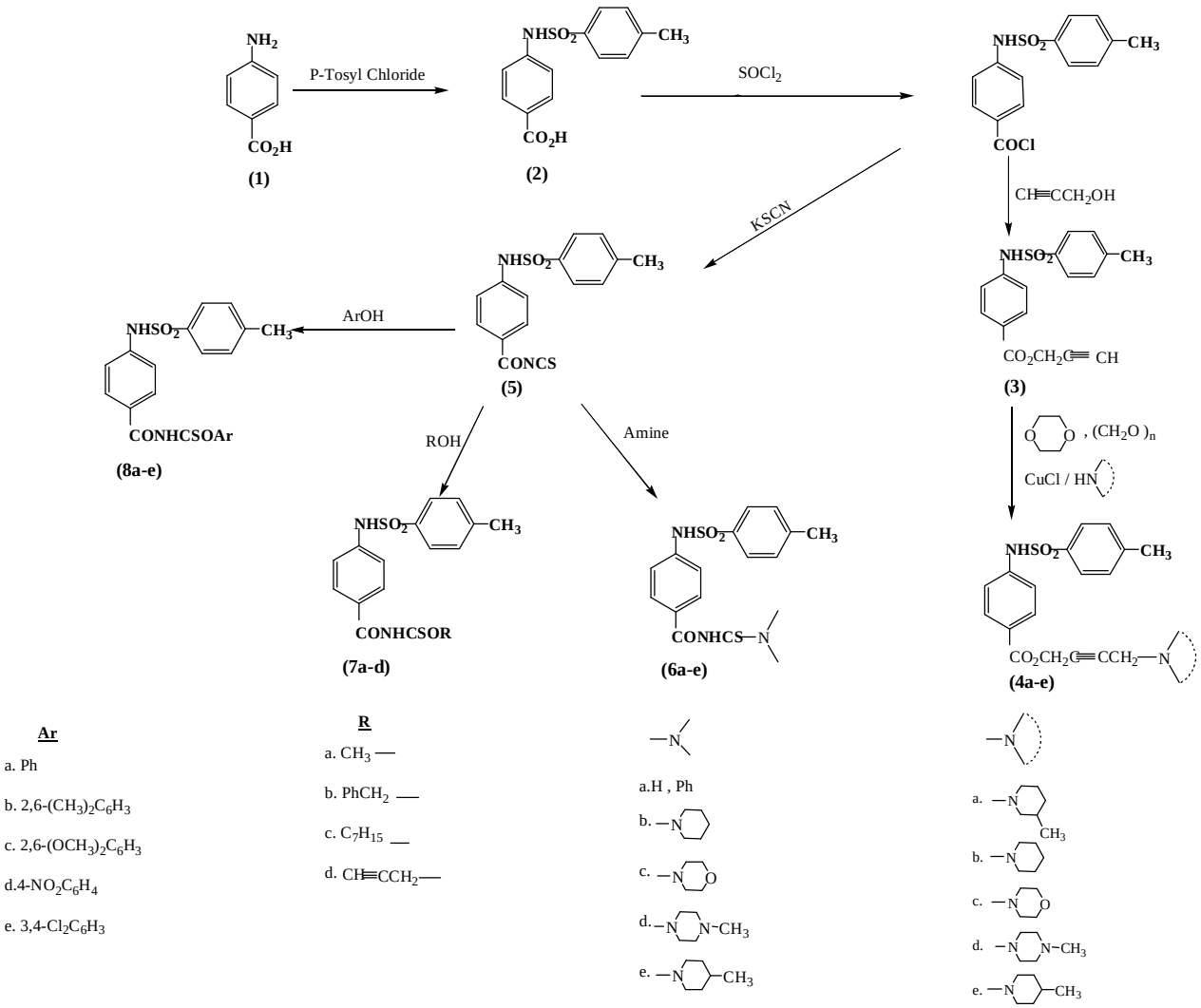
To a solution of 4-(p- Toluene Sulfonamido) benzoyl chloride (10mmole, 3.09g) in (10 ml)of anhydrous ethyl acetate, potassium isothicyanete (11 mmole,1.07g) was added. The reaction mixture was refluxed for 4hrs. The precipitate was filtered off, and recrystallized from thanol. The physical and spectral data were illustrated Table (2).

Preparation of N-[4-(p-Toluene Sulfonamido) benzoyl]-N$^{\backslash}$-Substituted thiourea (6a-e) : (Sasaki *et al.*, 1980)

To a solution of compound (5) (0.01 mole, 3.32g) in methylene chloride (15 ml), a suitable amine (0.01 mole) was added dropwise with stirring. The mixture was reflexed for (24) hrs, then filtered and the filtrate was poured on crushed ice. The precipitated material was filtered off, washed with cold water and recrystallized from ethanol – water. The physical and the spectral data were listed in Table (2).

Preparation of N-[4-(p-Toluene Sulfonamido) benzoyl]-O-Substituted thiocarbamate (7a-d) and(8a-e): (March, 1977 and Sasaki *et al.*, 1980)

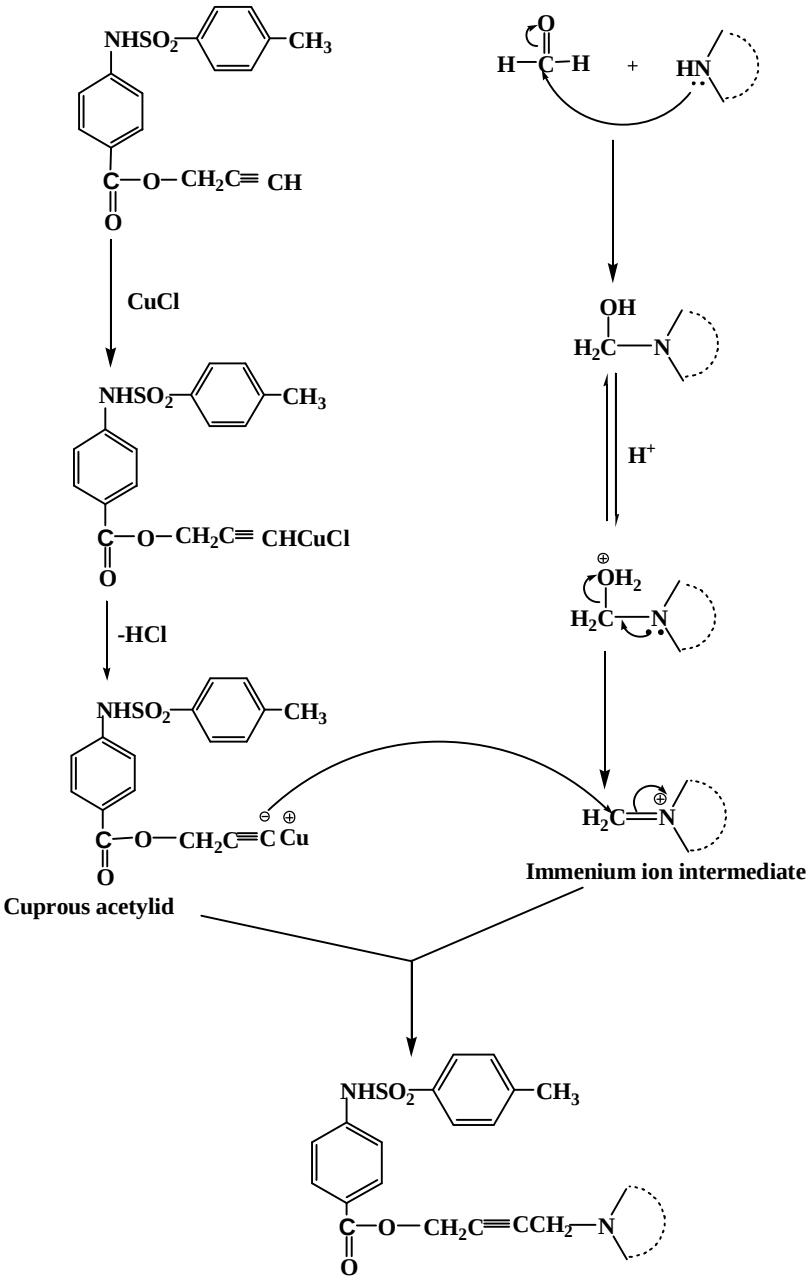
A mixture of compound (6) (0.01 mole, 3.32g), alcohol or phenol compound (0.01 mole) and potassium hydroxide (2 mg) in toluene 3ml was refluxed for 4hrs. The mixture was cooled and the precipitate was filtered off, washed with water and recrystallized from ethanol. The physical and the spectral data were listed in Table (2).



Scheme (1)

RESULTS AND DISCUSSION

Many of sulfonamide compounds, which are well known as sulfa drug (Kutzuig,1992), possessing biological activity (Ossman and Pharmazi, 1975; Ahuja *et al*., 1989). Accordingly, some new sulfonamide compounds containing acetylenic amino, thiourea and thiocarbamate moieties have been synthesized. The aim of the introducing such moieties in the skeleton structure of the sulfonamido compounds might prove the biological activity of these compounds. Therefore acetylenic compound (3) was synthesized by the reaction of the corresponding acid chloride with propagyl alcohol. The structure of compound (3) was confirmed by it's IR spectrum, which showed a characteristic weak band at 2100 cm^{-1} related to the terminal C≡C bond stretching and a weak band at 3305 cm^{-1} for ≡C−H bond stretching. Compounds (3) was converted to the corresponding acetylinic amine (4a-e) through mannich reaction (Karlen *et al.*,1970), by its reaction with secondary amine and paraformaldehyde in presence of catalytic amount of cuprous chloride .The formation of acetylinic amine derivatives were obtained according to the mechanism of mannich reaction (March, 1977) , Scheme (2).

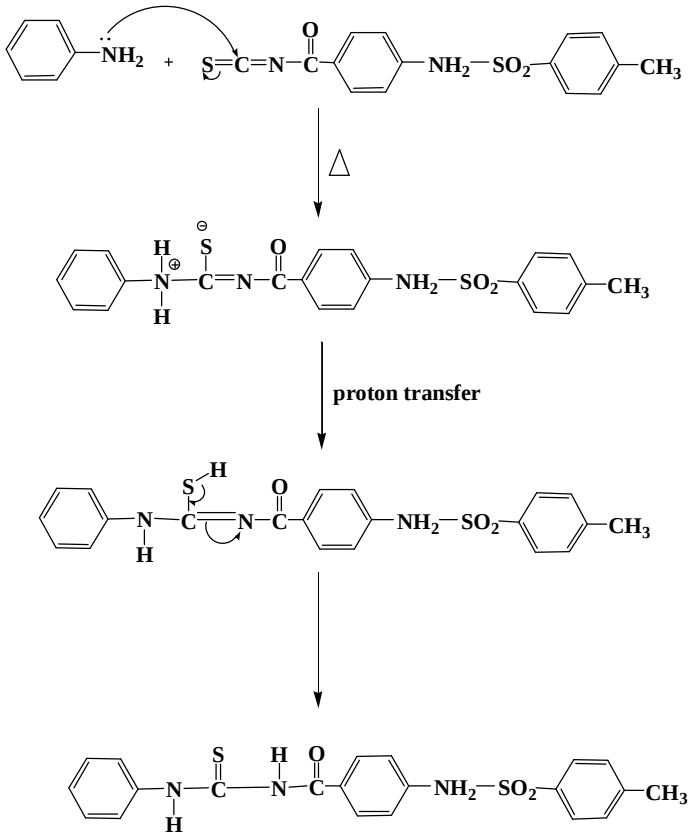


Scheme (2)

The structure of compound(4a-e) were confirmed by their IR spectra (Table 1), which showed strong absorption band for esteric υC=O at (1688 -1702 cm^{-1}), weak band at(2110-2310 cm^{-1}) for υC≡C bond stretching and a absorption band at (3241-3212 cm^{-1}) for υN−H bond stretching. Moreover, the IR spectra indicate the disappearance the absorption band for the terminal acetylinic hydrogen (≡C−H bond). The UV spectra of compounds (4a-e) showed absorption band at λmax (286-301 nm) related to the electronic transition ($n\rightarrow\pi^*$) (Finer, 1977).

The benzoyl isothiocyanate (5) was synthesized by the reaction of 4-(p-toluene sulfonamido) benzoyl chloride with potassium isothiocyanate. The IR spectral data of this compound were given in Table (2). The main absorption bands are for N=C=S which appeared at (2554 and 1925 cm^{-1}) related to asymtric and symmetric vibration respectively (Kearney *et al.*, 1998). While the UV spectrum showed λmax at (286 nm) related to ($n\rightarrow\pi^*$) transition (Finar, 1977). The compound (5) was used as synthone for compounds (6a-e) and (7a-e).

The thiourea compounds (6a-e) were synthesized by treatment of compound (5) with various amines. The reaction was carried out through the suggested nucleophilic addition mechanism (Scheme 3) (Smith, 2006).

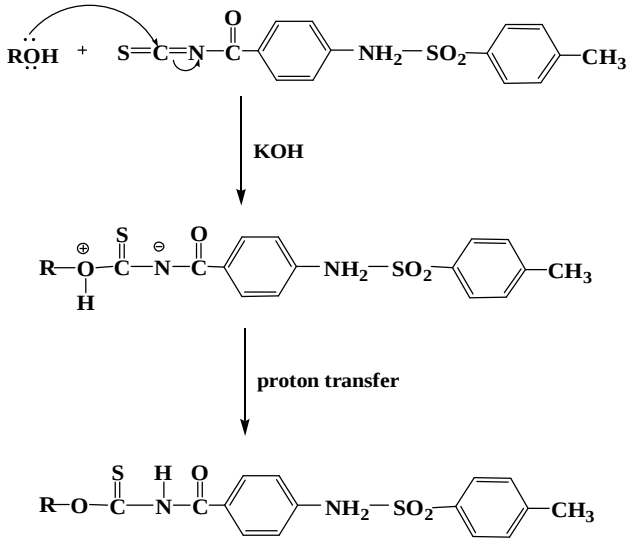


Scheme (3)

The IR spectral data of these compounds showed absorption band at (1158-1160 cm^{-1}), (1337-1339 cm^{-1}), (1090-1093 cm^{-1}), (1691-1693 cm^{-1}), (3216-3221 cm^{-1}) which are related to bond stretching of S=O(asym& sym), C=S, C=O and N-H groups respectively. The UV spectra of these compounds showed absorption band at λmax (288-316 mm), due to the ($n\rightarrow\pi^*$) transition (Finar, 1977).

The thiocarbomate derivatives (7a-d), (8a-e) were prepared by treatment of compound (5) with various alcohols and phenols respectively. The mechanism of this reaction

involved nucleophilic addition of alcohol or the phenolate anion to the isothiocynate group according to Scheme (4) (Smith, 2006).



Scheme (4)

The IR spectra of compounds (7a-d) and (8a-e) showed a characteristic bands Table (2) at (1153-1161 cm^{-1}), (1337-1339 cm^{-1}), (1091-1093 cm^{-1}), (1689-1693 cm^{-1}) and (3212-3237 cm^{-1}) related to the bond stretching of S=O (asym. & sym.), C=S, C=O and N−H group respectively.The UV specra of these compounds showed absorpition band at λmax (286-308 nm) related to the ($n\rightarrow\pi^{*}$) transition (Finer, 1977).

Table 1: Physical properties and spectral data for compounds (3) and (4a-e)

Comp. No.	m.p(°C)	Color	Yield (%)	UV ($CHCl_3$) λmax(nm)	I.R (KBr) υ (cm^{-1})					
					S=O asym.	S=O sym.	C=O	C≡C	N-H	≡C-H
3	233-235	Faint Yellow	60	296	1156	1339	1693	2100	3218	3305
4a	210-212	Yellow	45	294	1156	1341	1697	2306	3241	—
4b	187-190	Brown	40	286	1161	1337	1688	2310	3212	—
4c	199-200	Yellow	50	290	1156	1339	1702	2300	3229	—
4d	193-195	Faint Brown	35	295	1159	1338	1692	2306	3217	—
4e	185-187	Brown	55	301	1150	1336	1680	2300	3221	—

Table 2: Physical properties and spectral data for compounds (6a-e), (7a-d) and (8a-e)

Comp. No.	m.p(°C)	Colour	Yield (%)	UV ($CHCl_3$) λmax(nm)	IR (KBr) υ (cm^{-1})					
					S=O asym.	S=O sym.	C=S	C=O	N-H	Others
5	150-153	Faint Yellow	66	286	1159	1292	–	1680	3246	N=C=S 1925sym,2554asym
6a	188-190	Faint Brown	55	308	1160	1313,1337	1090	1693	3220	–
6b	182-184	Brown	60	294	1160	1315,1338	1092	1692	3221	–
6c	192-193	Yellow	45	316	1160	1315,1338	1091	1692	3218	–
6d	198-200	Faint Brown	35	288	1158	1315,1338	1093	1692	3216	–
6e	185-187	Brown	50	308	1160	1314,1339	1092	1691	3220	–
7a	233-235	Yellow	30	300	1153	1314,1337	1091	1690	3237	–
7b	180-182	Faint Yellow	45	306	1160	1316,1337	1092	1689	3213	–
7c	200-202	Yellow	35	308	1159	1315,1339	1093	1692	3217	–
7d	195-197	Faint Brown	60	294	1160	1315,1338	1092	1693	3216	C≡C 2309
8a	185-187	White	40	294	1160	1314,1337	1093	1691	3214	–
8b	201-204	Faint Yellow	55	300	1160	1316,1338	1093	1691	3212	–
8c	228-230	Brown	30	286	1161	1316,1337	1092	1689	3212	–
8d	197-198	Faint Brown	45	308	1160	1315,1338	1093	1690	3214	–
8e	182-184	Yellow	35	302	1159	1315,1338	1092	1691	3214	–

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