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Improved Synthesis of 3-(α , α-diphenyl –α- hydroxymethyl)- 4-amino 1,2,4-triazoline-5-thione and Facile Route to 3,6-Disubstituted 1,2,4-triazolo [3,4-b][1,3,4] thiadiazoles(*)

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ABSTRACT

The reaction of thiocarbohydrazide (1) with benzilic acid (2) at the melting temperature (160-170 °C) allows an improved preparation of 3-(α,α-diphenyl-α-hydroxymethyl)-4-amino-1,2,4-triazoline-5-thione (3).

The compound (3) reacts easily with suitable carboxylic acids in presence of phosphorous oxychloride to afford 1,2,4-triazolo [3,4-b] [1,3,4] thiadiazole ring systems (4a-g). The synthesized products were confirmed by physical and spectral methods.

Key words: Heterocyclic, fused rings, triazole, thiadiazole.

طريقة محسنة لتحضير 3- (الفا – ألفا – ثنائي فينيل – الفا – هيدروكسي مثيل)-4- أمينو -4,2,1 ترايازولين-5- ثايون كمادة أولية لتحضير 6,3 – ثنائي معوضات -4,2,1 – ترايازولو[4,3- b] [4,3,1] ثايادايازول

الملخص

يتضمن البحث طريقة محسنة من خلال تسخين الثايوكاربوهيدرازيد (1) مع حامض البنزيليك (2) إلى الإنصهار الكامل للحصول على 3-(الفا، الفا- ثنائي فينيل- الفا – هيدروكسي مثيل)-4-أمينو -4,2,1- ترايازولين-5-ثايون (3). يتفاعل المركب (3) بسهولة مع أحماض كاربوكسيلية مناسبة بوجود اوكسي كلوريد الفسفور ليعطي 4,2,1-ترايازولو [3,4-b] [1,3,4] ثايادايازول (4a-g).

تم إثبات الصيغ التركيبية للمركبات المحضرة باستخدام الطرق الفيزياوية والطيفية.

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INTRODUCTION

3,6-Disbustituted –1,2,4-triazolo [3,4-b] [1,3,4] thiadiazoles constitute a class of compounds scarcely studied. Literature survey revealed that these systems have emerged as potential biological active and are know to posses a broad pharmacological spectrum (Hazarika and Kataky, 1996) ; (Almousawi and Shmustaf, 2007).

Alkyl and aryl substituted derivatives of fused heterocyclic system were obtained first (Kanaoka, 1957) both through dehydrative ring closure of 4-acylamino-5-triazole-5-thiols or by the reaction of 1,3,4-thiadiazole-2-yl hydrazine with ortho esters. The similar compounds were prepared by ring closure of 5-substituted-4-amino-3-mercapto(4H)-1,2,4-triazoles using acyl chlorides in the presence of phosphoryl chloride (Potts and Huseby, 1966).

In this paper, an improved method to prepare 3-(α, α-diphenyl-α-hydroxymethyl)-4-amino-1,2,4-triazoline-5-thione (3) from thiocarbohydrazide (1) with benzilic acid (2), which was used to synthesis the title compounds (4a-f) in a high overall yield in a shorter working time.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point and are uncorrected. Infrared spectra (ν cm^{-1}) were recorded on a Pye Unicam SP200 Perkin-Elmer spectrophotometer using KBr disk. ^{1}H-NMR spectra were determined on Hitachi Perkin-Elmer spectrophotometer (60MHz) using TMS as internal reference. UV spectra were measured in a Shimadzu UV. 160 spectrophotometer. Elemental analysis were performed on a Carlo Erba type 1106 CHN Analyzer.

Preparation of 3 - (α,α –diphenyl -α- hydroxymethyl) -4- amino-1,2,4-triazoline-5-thione (3): (Invidiata *et al.*, 1997)

A mixture of thiocarbohydrazide (1) (1.06 gm, 0.01 mole) and benzilic acid (2) (2.28 gm, 0.01 mole)was heated carefully to 160-170 ^{o}C until melting occurred, then it was heated at 60 ^{o}C for 15 minutes in water-bath. The reaction mixture was cooled, mixed with water (80 ml) and acidified with concentrated hydrochloric acid. The precipitate was filtered, washed with water and dried to give (2.85 gm, 95%) of compound(3), m. p. 243-45 ^{o}C ; UV λmax (MeOH) (265 nm); I.R (KBr) ν(cm^{-1}), 3158 (NH), 1616 (C=N), 1070 (C=S), 1H-NMR δ (ppm) (CD_3OD) 4.65 (s, 2H, NH_2), 6.15 (bs, 1H, OH), 6.6-6.8 (m, 10H, 2ph).

General procedure for the preparation of 3-(α,α-diphenyl-α-hydroxymethyl)-1,2,4-triazolo[4,5-b][1,3,4]-5-substituted thiadiazoles (4a-g): (Invidiata *et al.*, 1997)

A mixture of 4-amino triazole (3) (0.29 gm, 0.001 mole) and appropriate carboxylic acid (0.001 mole) in phosphorous oxychloride (5ml) was heated at 90 ^{o}C for 30 minutes. The reaction mixture was cooled and gradually poured with stirring into ice cooled sodium bicarbonate solution (0.05%). The precipitated product was filtered, washed with water, dried and crystallized from ethanol to give the corresponding products (4a-g).
Physical and spectroscopic data are listed in Table (1).

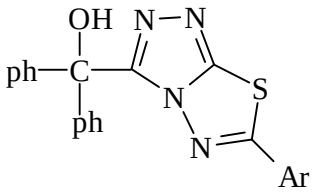


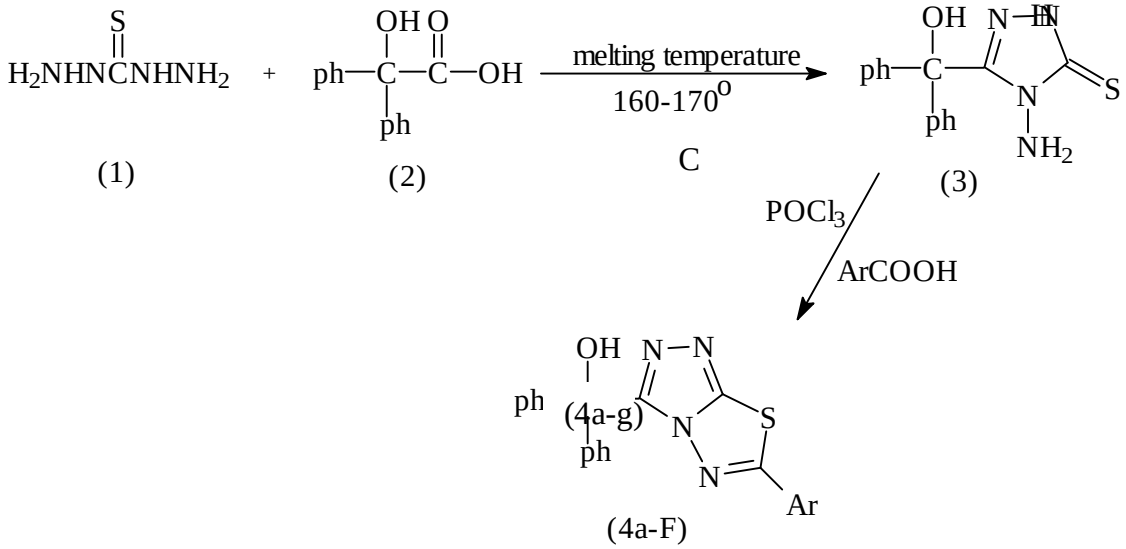
Table 1: Physical data for compounds (4a-g)

Compd. No.	Ar	m. p. °C	Yield %	Molecular formula	Analysis % found (Calcd.)		
					C%	H%	N%
4a	C_6H_5-	147-49	75	$C_{22}H_{16}N_4OS$	68.58 (68.75)	4.01 (4.16)	14.39 (14.58)
4b	4-ClC_6H_4	193-94	85	$C_{22}H_{15}ClN_4OS$	62.89 (63.08)	3.43 (3.58)	13.41 (13.38)
4c	4-$NO_2C_6H_4$	225-27	82	$C_{22}H_{15}N_5O_3S$	62.02 (61.53)	3.43 (3.49)	16.35 (16.31)
4d	3-$CH_3C_6H_4$	183-85	60	$C_{23}H_{18}N_4OS$	69.22 (69.34)	4.55 (4.52)	13.88 (14.07)
4e	2,5$(OH)_2C_6H_3$	234-36	64	$C_{22}H_{16}N_4O_3S$	63.25 (63.46)	3.71 (3.84)	13.33 (13.46)
4f	C_6H_5CH=CH-	189-91	70	$C_{24}H_{18}N_4OS$	70.11 (70.24)	4.44 (4.39)	13.49 (13.65)
4g	2-ClC_6H_4CH=CH	199-201	68	$C_{24}H_{17}ClN_4OS$	69.64 (64.79)	3.70 (3.82)	12.62 (12.59)

RESULTS AND DISCUSSION

In order to synthesis various biological active bridgehead nitrogen heterocyclic compounds (Gogoi and Kataky, 1991), the 4-amino triazole was synthesized. Thus, the reaction of thiocarbohydrazide (1) with benzilic acid (2) at the melting temperature afforded 3-(α,α-diphenyl- α-hydroxymethyl)-4-amino-1,2,4-triazoline-5-thione (3). This method resulted in higher overall yields and shorter time comparing very favorably with the alternative methodology. The structure of compound (3) was assigned on the basis of spectroscopic data. UV spectrum showed absorption at λ_{max} (MeOH) (252 nm), and the I.R spectrum was characterized by the presence of a band at (1616 cm^{-1}) due to C=N band stretching and a band at (1070 cm^{-1}) due to C=S groups. ^{1}H-NMR spectra showed a typical resonance for 1,2,4-triazole with NH_2 signal at δ (4.65 ppm) as a singlet.

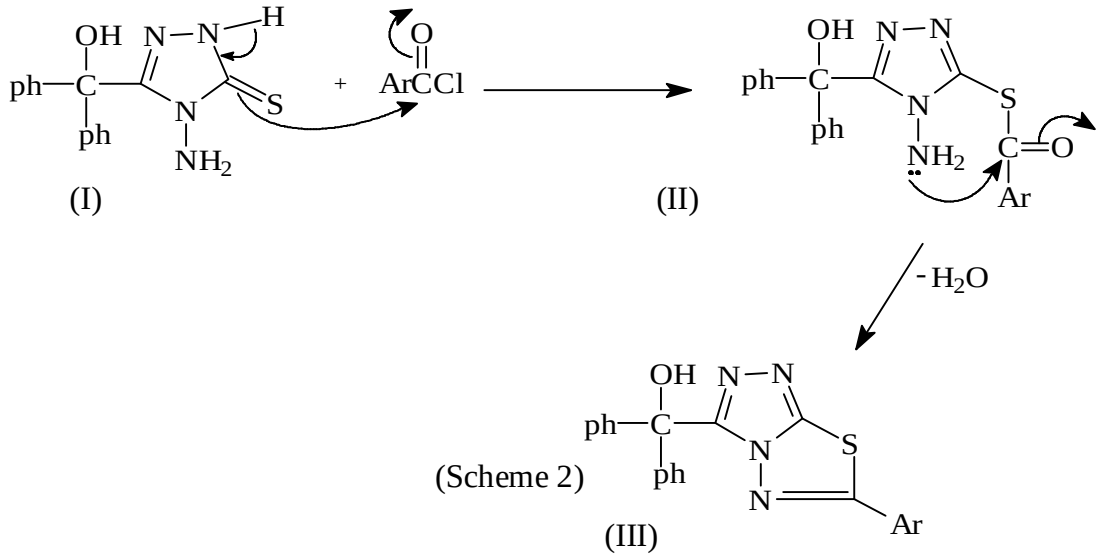
Interestingly, it was observed that 1,2,4-triazolo [3,4-b] [1,3,4] thiadiazole derivatives (4a-g) can easily be obtained in good yields directly from 1,2,4-triazole intermediate (3) by refluxing with suitable carboxylic acids in the presence of phosphorus oxychloride (Scheme 1).



a = C_6H_5- , b = 4-Cl C_6H_4 , c = 4-$NO_2C_6H_4$, d = 3-$CH_3C_6H_4$-
e = 2,5$(OH)_2C_6H_3$, f = C_6H_5CH=CH- , g = 2-ClC_6H_4CH=CH

(Scheme 1)

The first step of the reaction involves the conversion of carboxylic acid to the corresponding acid chloride by phosphorus oxychloride, followed by nucleophilic attack of sulfur atom of triazole (I) the carbonyl group of the acid chloride. The intramolecular acylation is the driving force for the formation of the products (4a-g) from the thioamido intermediate (II) as shown in scheme 2.



(Scheme 2)

The structural evidences of compounds (4a-g) were obtained from various spectroscopic data such as UV, I.R and ^{1}H-NMR. These data came in an agreement with those published in literature for similar compounds (El-Kahwass and Habib, 1989) Table (2).

Table 2: Spectral data for compounds (4a-g)

Compd. No.	UV(MeOH) λ_{max} (nm)	I.R(KBr) υ cm^{-1}		^{1}H-NMR δ(ppm) DMSO-d_6
		C=N	C-S-C	
4a	247	1630	1092	6.3(s, 1H, OH); 6.6-7.4(m,15H, 3ph)
4b	254	1645	1085	6.2(bs, 1H, OH); 6.9(s, 10H, 2ph); 7.0-7.4(m, 4H, Ar-H)
4c	256	1642	1078	6.4(bs, 1H, OH); 7.2(s, 10H, 2ph); 7.3-7.8(m, 4H, Ar-H)
4d	251	1633	1099	2.6(bs, 3H, CH_3); 6.2(bs, 1H, OH); 6.6-7.2(m, 10H, 2ph); 7.3-7.5(m, 4H, Ar-H)
4e	264	1655	1075	6.1(bs, 1H, OH); 7.1(s, 10H, 2ph); 7.2-7.5(m, 3H, Ar-H)
4f	282	1651	1083	5.5(d, 1H, =CH); 6.1(d, 1H, phCH); 6.3 (bs, 1H, OH); 6.7-7.4(m, 10H, 2ph), 7.6-7.8 (m, 5H, Ar-H)
4g	285	1660	1115	5.7(d, 1H, =CH); 6.2(d, 1H, phCH); 6.6(s, 1H, OH); 6.8-7.2(m, 10H, 2ph); 7.3-7.6(m, 4H, Ar-H)

s = singlet , d = doublet , m = multiplet , b = broad.

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