

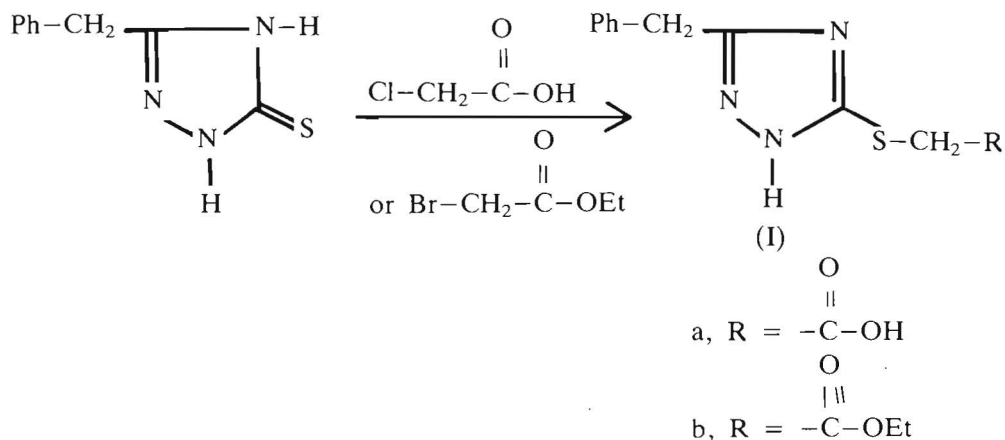
Synthesis and Some Reactions of 3-Benzyl-5-(Carboxy or Carbethoxy)-Methylthio-1,2,4-Triazole

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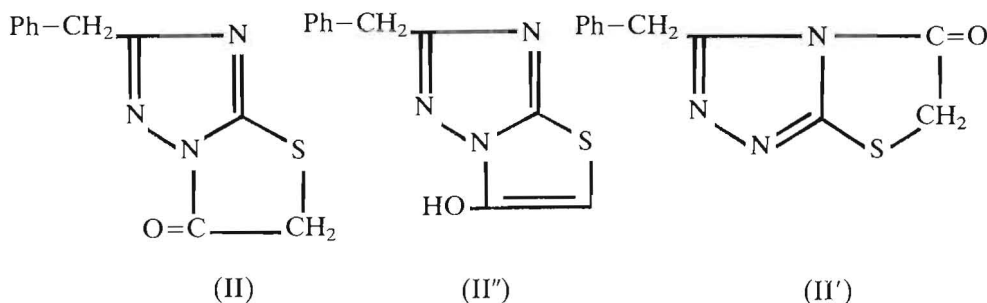
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ABSTRACT. 3-Benzyl-5-(carboxy or carbethoxy)-methylthio-triazole (Ia & b) have been prepared. (Ia) was cyclized to give 6-benzylthiazolo(3,2-b)-s-triazol-3(2H)-one (II). The reaction of the active methylene of compound (II) with aromatic aldehydes and/or arene diazonium salts gave the corresponding 2-arylidene-6-benzylthiazolo(3,2-b)-s-triazol-3(2H)-one derivatives (IIIa-c) and 2,3-dihydro-6-benzylthiazolo-(3,2-b)-s-triazol-2,3-dione-2-arylhydrazone (IVa-e). Also, hydrazinolysis of compound (Ib) and its condensation with aromatic aldehydes have been studied and gave (Va & b) and (VIa & b) respectively.

In the present investigation 3-benzyl-5-(carboxy or carbethoxy)-methylthio-1,2,4-triazole (Ia & b) have been prepared by the reaction of 3-benzyl-1,2,4-triazoline-5-thione with chloroacetic acid and/or ethyl bromoacetate in the presence of sodium acetate and acetic acid.

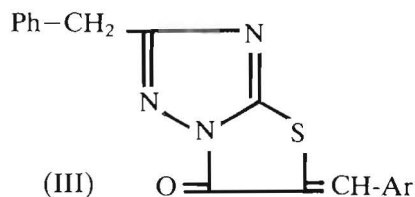


The structure of compounds (I) was proved by IR (cm^{-1}) which showed bands at 3200, 1710 attributable to ν_{OH} and $\nu_{\text{C=O}}$ of compound (Ia) and at 1735 to $\nu_{\text{C=O}}$ of compound (Ib). Compound (Ia) was cyclized by the action of acetic anhydride or phosphorous oxychloride to afford 6-benzylthiazolo-(3,2-b)-s-triazol-3-(2H)-one (II) (Hirata *et al.* 1972 and Potts and Crawford 1962) rather than (II) because compound (Ia) can be cyclized at N-1 or N-4, but N-1 is more likely involved in the cyclization reaction to give compound (II) because of its greater basicity, it is adjacent to electron donating rather than electron deficient (C_5) (Taylor and Hendess 1965). 1,2,4-Triazoles are known to be cyclized at N-1 (or N-2) (Hirata *et al.* 1972, Potts and Crawford 1962, and Chipens *et al.* 1969).



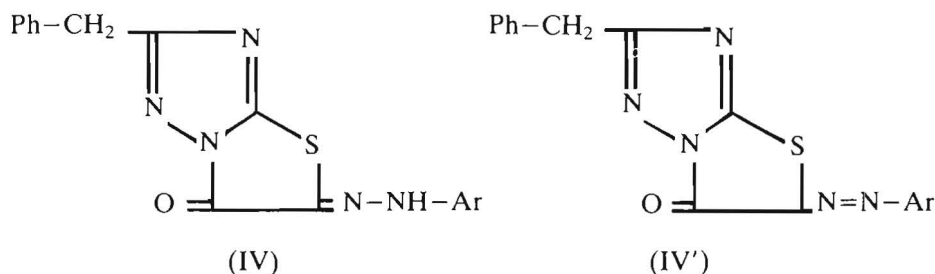
The proposed structure of (II) was confirmed by: i) IR (cm^{-1}) showing an intense band at 1770 ($\nu_{\text{C=O}}$), this carbonyl frequency is rather high, however, it has been noted that a carbonyl group attached to a triazole ring shows unusually high stretching frequency (Hirata *et al.* 1972 and Staab *et al.* 1957), ii) PMR showed signals (δ) at 3.3(s, 2H, $\text{CH}_2\text{-Ph}$), 4.8(s, 2H, $\text{-CO.CH}_2\text{-S}$) and at 7.5 (m, 5H, aromatic protons). These PMR data indicate that the product (II) exists in the keto form (II) and not in the enol form (II').

The present investigation also deals with the reaction of active methylene group of compound (II) with aromatic aldehydes to give the corresponding arylidene derivatives. Thus, compound (II) was found to condense with aromatic aldehydes (Hirata *et al.* 1972 and Potts and Crawford 1962) namely, benzaldehyde, p-nitrobenzaldehyde and/or anisaldehyde in the presence of basic catalyst to yield the corresponding 2-arylidene-6-benzylthiazolo-(3,2-b)-s-triazolo-3-one derivatives (IIIa-c) respectively.



a, $\text{Ar}=\text{C}_6\text{H}_5\text{-}$; b, $\text{Ar}=\text{C}_6\text{H}_4\text{NO}_2\text{-p}$; c, $\text{Ar}=\text{C}_6\text{H}_4\text{-OCH}_3\text{-p}$

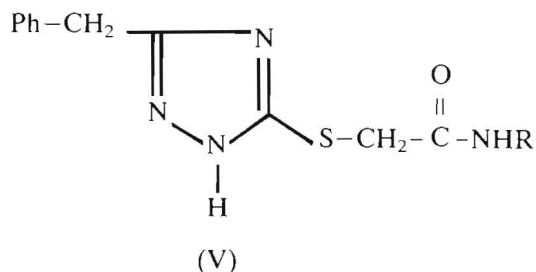
As a point of interest, these arylidene derivatives (III) were better prepared directly from 3-benzyl-1,2,4-triazoline-5-thione by the action of chloroacetic acid, and an aromatic aldehyde in the presence of acetic acid, acetic anhydride and sodium acetate mixture. On the other hand, compound (Ia) also condensed with aromatic aldehydes in the presence of acetic acid, acetic anhydride and sodium acetate mixture giving the corresponding arylidene derivatives (III). Structure of compounds (III) was supported by: i) IR (cm^{-1}) showing band at 1735 ($\nu_{\text{C=O}}$) shifted to a lower frequency compared with that of (II) due to its conjugation with the exocyclic double bond. ii) PMR of (IIIa) showed signals (δ) at 3.3(s, 2H, $\text{CH}_2\text{-Ph}$), 8.2(s, 1H, $=\text{CH-Ar}$) and at 7.4(m, 10 H, aromatic protons). The authors also investigated the reaction of thiazolo-triazolone (II) with arene diazonium salts, in sodium acetate (Taylor and Hendess 1965, Yao and Resnick 1962, and Yao 1964) buffered solution to give the corresponding 6-benzyl-thiazolo-(3,2-b)-triazolone-2-aryl hydrazones (IVa-e).



a, Ar = $\text{C}_6\text{H}_5\text{-}$; b, Ar = $\text{C}_6\text{H}_4\text{NO}_2\text{-p}$; c, Ar = $\text{C}_6\text{H}_3(\text{CH}_3)_2\text{-2,5-}$
 d, Ar = $\text{C}_6\text{H}_4\text{NO}_2\text{-m}$; e, Ar = $\text{C}_6\text{H}_4\text{NO}_2\text{-o}$

The existence of compound (IV) in the hydrazone form rather than in the azo form (IV') was supported by: i) UV spectrum of (IVa) showed band at 390 nm, it has been reported that the UV absorption of monophenyl azo-compounds differ from those of monophenylhydrazone compounds (Yao and Resnick 1962). The monophenyl azo-compounds have a strong band at 270-280 nm. The monophenylhydrazone compounds give a weak absorption band at a wavelength higher than 320 nm (Yao 1964 and Depuy and Wells 1960). ii) IR (cm^{-1}) of (IVa) showed band at 1725 ($\nu_{\text{C=O}}$). This band has undergone a shift to lower frequency compared with that of (II) due to its conjugation with a ($-\text{C=N-}$) group.

On the other hand, treatment of (Ib) with alcoholic solution of hydrazine hydrate and/or 2,4-dinitrophenylhydrazine gave the corresponding acid hydrazide derivatives (Va & b) respectively.

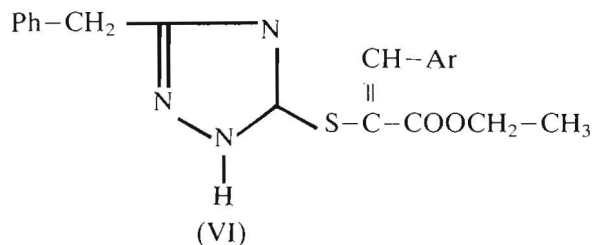


a, R = NH₂ ; b, R = -NHC₆H₃(NO₂)₂-2,4

The structure of (V) was verified from: i) IR (cm⁻¹) which showed $\nu_{C=O}$ of the hydrazide in the region (1680-1670) and broad ν_{NH} at 3200. ii) PMR of (Va) which showed signals (δ) at 3.5 (s, 2H, $\underline{CH_2}$ -Ph), 4.8 (s, 2H, -S- $\underline{CH_2}$ -C-), 7.3 (m,

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5H, aromatic protons) and at 8.1 (s, 2H, -C-NH- $\underline{NH_2}$). Also, compound (Ib) condensed with aromatic aldehydes such as anisaldehyde and p-nitrobenzaldehyde to yield the corresponding 3-benzyl-5-(α -arylidene-carbethoxymethylthio)-1,2,4-triazole (VIa & b) respectively.



a, Ar = C₆H₄-OCH₃-p ; b, Ar = C₆H₄-NO₂-p

The structure of compound (VI) was confirmed by: i) IR (cm⁻¹) showing $\nu_{C=O}$ (ester group) in the region (1690-1685), $\nu_{C=C}$ (1620) and broad band ν_{NH} (3230). ii) PMR of (VIb) showed signals (δ) at 3.2 (s, 2H, $\underline{CH_2}$ -Ph), 1.3 (t, 3H, -COOCH₂- $\underline{CH_3}$), 4.1 (q, 2H, -COOCH₂-CH₃), 8.1 (s, 1H, - \underline{CH} -Ar) and at 7.4 (m, 10 H, aromatic protons).

Experimental

All melting points reported are uncorrected. IR spectra (KBr) were determined with a Perkin-Elmer Model 297 spectrophotometer. UV spectra were determined with a Beckmann Model Acta MVI Spectrophotometer. PMR spectra

(CDCl₃) were determined with a Varian (60 MHz) Model EM 360 spectrograph.

Synthesis of 3-Benzyl-5-(Carboxy or Carbethoxy)-Methylthio-1,2,4-Triazole (Ia & b)

A mixture of 5-benzyl-1,2,4-triazoline-3-thione (0.01 mole), an excess of chloroacetic acid (0.03 mole) and/or ethyl bromoacetate, about 3 g of sodium acetate, in about 30 ml of acetic acid was refluxed for 5 hr and then the solution was evaporated, the residue was washed with little water and crystallized (*cf.* Table 1). Compound (Ia) was soluble in sodium carbonate solution (with effervescence) and in sodium hydroxide solution.

6-Benzylthiazolo-(3,2-b)-s-Triazol-3(2H)-one (II)

One gram of compound (Ia) in 10 ml of acetic anhydride or (5 ml of phosphorus oxychloride) was refluxed for 3 hr, cooled and poured into water, the product formed was collected and crystallized to give (II) (*cf.* Table 1).

2-Arylidene-6-Benzylthiazolo-(3,2-b)-s-Triazol-3-ones (IIIa-c)

(a) *General Procedure:* A mixture of (0.01 mole) of 5-benzyl-1,2,4-triazoline-3-thione, 1.5 g of chloroacetic acid, 2 g of fused sodium acetate, an equimolar amount of the appropriate aldehyde in 15 ml of acetic anhydride and 20 ml of acetic acid was refluxed for 4 hr and cooled. The precipitate formed after concentration was washed with water and crystallized from the proper solvent.

(b) A mixture of 0.01 mole of (Ia), an equimolar amount of the appropriate aldehyde in about 20 ml of acetic anhydride was refluxed for 2 hr, and worked up as above.

(c) 0.01 mole of (II) and 0.01 mole of the appropriate aldehyde were refluxed in about 20 ml of acetic anhydride for 2 hr and worked up as above (*cf.* Table 1).

6-Benzylthiazolo-(3,2-b)-s-Triazol-3-one-2-Arylhydrazones (IVa-c)

Compound (II) (0.05 mole) was dissolved in about 15 ml of ethanol containing 3 g of sodium acetate and cooled. The cold solution was treated dropwise with a cold solution of the diazonium salt (prepared from 0.05 mole of appropriate aniline in the usual way) and left for sometime in the ice bath. The precipitate formed was crystallized (*cf.* Table 1).

Hydrazinolysis of 3-Benzyl-5-Carbethoxymethylthio-1,2,4-Triazole (Ib)

A solution of compound (Ib) (0.01 mole) in 30 ml ethanol was treated with hydrazine hydrate and/or 2,4-dinitrophenylhydrazine (0.015 mole). The reaction mixture was heated under reflux for 6 hr, cooled, the solid products were filtered off and recrystallized from the suitable solvents to give the hydrazide (Va & b) (*cf.* Table 1).

Condensation of (Ib) with Aromatic Aldehydes: Formation of 5-Benzyl-3-(α -Anisylidene Carboethoxymethylthio)-1,2,4-Triazole (VIa) and 5-Benzyl-3-(α -p-Nitrobenzylidene Carboethoxymethylthio)-1,2,4-Triazole (VIb)

A mixture of (Ib) (0.01 mole) in 50 ml ethyl alcohol, sodium ethoxide (prepared from 0.35 g of metallic sodium in 15 ml absolute ethanol (0.15 mole) and an aromatic aldehyde (0.01 mole) such as anisaldehyde and/or p-nitrobenzaldehyde, was refluxed for 10 hr. The reaction mixture was left to cool, diluted with water (100 ml) and HCl (10%) was added dropwise till the solution became acidic. The solid product so obtained was crystallized from the proper solvent to give (VIa & b) (*cf.* Table 1).

Table 1. Physical data of various compounds prepared

Compound	M.p.°C Colour	Yield % solvent of crystn.*	Mol. formula (M.Wt.)	Analysis (%)	
				Calc.	Found
Ia	140 Colourless	60 (M)	C ₁₁ H ₁₁ O ₂ N ₂ S (249)	C 53.01 H 4.42 N 16.87	53.03 4.45 16.83
Ib	120 Colourless	70 (M)	C ₁₃ H ₁₅ O ₂ N ₃ S (277)	C 56.32 H 5.42 N 15.16	56.41 5.39 15.13
II	40 Colourless	55 (P)	C ₁₁ H ₉ N ₃ OS (231)	C 57.14 H 3.89 N 13.85	57.20 3.85 13.83
IIIa	141 Buff	66 (A)	C ₁₈ H ₁₃ N ₃ OS (319)	C 67.71 H 4.08 N 13.17	67.69 4.12 13.20
IIIb	190 Gray	70 (A)	C ₁₈ H ₁₂ N ₄ O ₃ S (364)	C 59.34 H 3.30 N 15.38	59.35 3.28 15.36
IIIc	154 Yellow	72 (A)	C ₁₈ H ₁₅ N ₃ O ₂ S (337)	C 64.09 H 4.45 N 12.46	64.13 4.50 12.48
IVa	80 Orange	50 (P)	C ₁₇ H ₁₃ N ₅ OS (335)	C 60.89 H 3.88 N 20.89	60.84 3.82 20.85
IVb	105 Red	52 (P)	C ₁₇ H ₁₂ N ₆ O ₃ S (380)	C 53.68 H 3.16 N 22.12	53.64 3.20 22.14

Table 1.—(Continued) Physical data of various compounds prepared

Compound	M.p.°C Colour	Yield % solvent of crystn.*	Mol. formula (M.Wt.)	Analysis (%)	
				Calc.	Found
IVc	240 Brown	55 (P)	C ₁₉ H ₁₇ N ₅ OS (363)	C 62.81 H 4.68 N 19.28	62.79 4.65 19.30
IVd	164 Red	48 (P)	C ₁₇ H ₁₂ N ₆ O ₃ S (380)	C 53.68 H 3.16 N 22.12	53.65 3.20 22.16
IVe	110 Red	55 (P)	C ₁₇ H ₁₂ N ₆ O ₃ S (380)	C 53.68 H 3.16 N 22.12	53.63 3.20 22.14
Va	63 Colourless	75 (A)	C ₁₁ H ₁₃ N ₅ OS (263)	C 50.19 H 4.94 N 26.62	50.17 4.89 26.65
Vb	85 Orange	70 (E)	C ₁₇ H ₁₅ N ₇ O ₅ S (429)	C 47.55 H 3.50 N 22.84	47.50 3.48 22.85
VIa	80 Yellow	48 (A)	C ₂₁ H ₂₁ N ₃ O ₃ S (395)	C 63.80 H 5.32 N 10.63	63.79 5.35 10.59
VIb	180 Red	50 (A)	C ₂₀ H ₁₈ N ₄ O ₄ S (410)	C 58.54 H 4.39 N 13.66	58.50 4.40 13.61

* E = ethanol; M = methanol; P = light petrol (60-80°)

A = acetic acid

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تخليق وبعض تفاعلات ٣ - بنزاييل - ٥ - (كربوكسي أو كريبثوكسي) - مثيل - ثيو - ١ و ٢ و ٤ - ترايازول

عبد النبي عيسوي و عادل منصور الجندي و ماهر الصفتي و سعيد علي سعيد

قسم الكيمياء - كلية العلوم - جامعة الزقازيق - الزقازيق - مصر

يشتمل هذا البحث على تحضير المركب ٣ - بنزاييل - ٥ - (كربوكسي أو كريبثوكسي) مثيل ثيو - ١ و ٢ و ٤ - ترايازول (Ia & b). ولقد تم تحويل المركب (Ia) إلى الشكل الحلقي ٦ - بنزاييل ثيازولو (٣ ، ٢ ب) ترايازول - ٣ (٢ يد) - أون (II) بواسطة تفاعله مع انهدريد حمض الخليك. وقد وجد أن مجموعة المثيلين النشطة الموجودة في المركب (II) تتفاعل مع الألدهيدات الأروماتية في وجود حافز قاعدي معطية مشتقات الأريليدين المقابلة (III a-c) كذلك يتفاعل المركب (II) مع أملاح الديازونيم معطياً مركبات الهيدرازونات المقابلة (IV a-c). كما وجد أن التحلل الهيدرازيني للمركب (Ia) يعطي مشتقات الهيدرازيد (V a & b) وبالمثل يتكاثف المركب (Ia) مع الألدهيدات الأروماتية معطياً مشتقات الأريليدين المقابلة (VI a & b). ولقد أمكن التوصل إلى تركيب النواتج بدراسة طيف الأشعة تحت الحمراء والفوق بنفسجية والرنين المغناطيسي.