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Cyanoethylation of 2-Mercaptoimidazoles. A Novel Synthesis of Thiazines and Thiazoles

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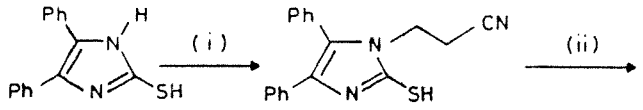
1,3-THIAZINE derivatives have found application in clinical medicine due to their strong analgesic muscle relaxing properties. and hypothermic activities. These reports promoted me to udertake the synthesis of fused heterocycles of the type imidazo [2,1-b] 1,3-thiazine for pharmacological studies.

Cyanoethylation of each of 4,5-diphenyl-2-mercaptoimidazole [1-3] and 5,5-diphenyl-2-mercapto-4-imidazolinone (7)[4] with equimolecular amounts of acrylonitrile in aqeuous pyridine gives 3-N-(β-cyanoethyl)-2-mercapto-4,5-diphenylimidazole (2) and 3-N-(β-cyanoethyl)-2-mercapto-5,5-diphenyl-4-imidazolinone (8) respectively. Cyclization of 2and 8 with acetic/ hydrochloric acid mixture afforded products formulated as 6,7-



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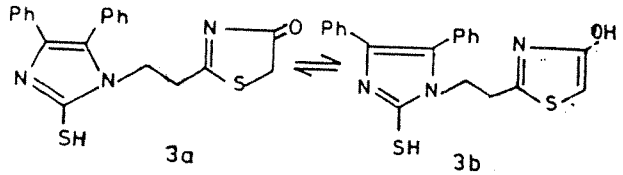
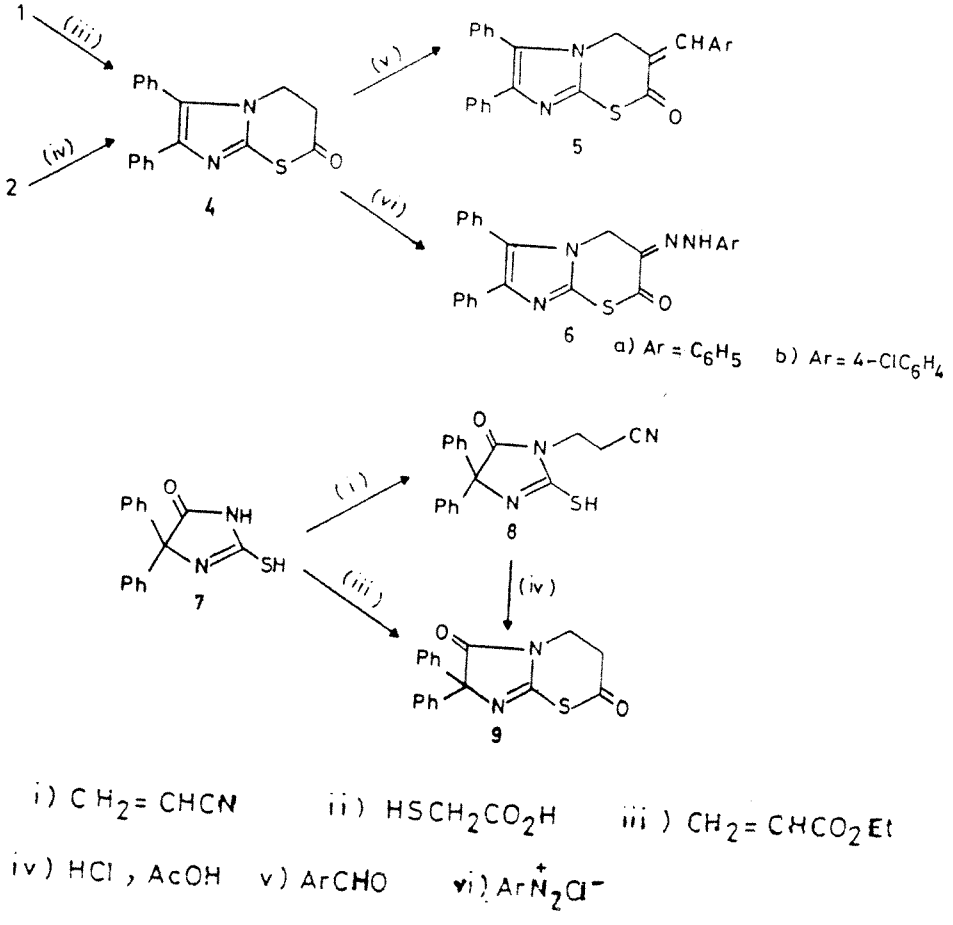


3a 3b

diphenylimidazo [2,1-b]-1,3-thiazine-2-one (4) and 7.7-diphenylimidazo [2,1-b]-1,3-thiazine-2,6-diones (9). Compounds 4 and 9 were identical in all respects with those obtained from the reaction of each of 1 and 7 with ethyl acrylate (by melting point and rnixed melting point determinations, analytical and spectral data). It has been reported that nitriles reacted with thioglycollic acid to give thiazolones (5-7). Compound 2 underwent reaction with thioglycollic acid in dry pyridine to yield a thiazole derivative. Two tautomeric structures 3a and 3b for this thiazole seemed to be possible. Since the IR spectrum of the compound revealed the absence of the OH group and the presence of a strong absorption band at 1725 cm^{-1} (C=O), structure 3b was excluded.



Aromatic aldehydes condensed readily with compound 4 to give the corresponding arylidene derivatives (5a,b). Compound 4 also reacted with aryldiazonium chloride to afford 6a,b, which exist in hydrazo rather than in the azo form (cf. Experimental Part).

Experimental Section

All melting points are uncorrected. IR spectra were recorded on a Pye Unicam SP-1100 spectrophotometer using KBr discs. The ^{1}HNMR spectra were recorded on a Varian EM-390-90 MHz spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are expressed as δ ppm units. The microanalyses were performed by the Micro Analytical Centre of Cairo University.

Synthesis of 3-N-(β-cyanoethyl)-2-mercapto-4,5-diphenylimidazole (2) and 3-N- (β-cyanoethyl)-2-mercapto-5,5-diphenyl-4-imidazolinone (8)

A mixture of each of 1 (2.52 g) and 7 (2.68 g) (0.01 mole) and 3 ml acrylonitrile in pyridine (50 ml) and water (10 ml) was refluxed for 5 hr. The reaction mixture was then reduced to half its volume by evaporation and then diluted with water (30 ml), then the separated soild was filtered off, washed with ethanol and crystallised from ethanol as pale yellow crystals of (2) and (8) respectively.

2, mp. 142°; yield 72%.

Anal. Calcd. for $C_{18}H_{15}N_3S$: C, 70.81; H, 4,91; N, 13.77; S, 10.49

Found: C, 70.62; H, 5.11;N, 13.. 1; S, 10.73

IR (cm^{-1}); 2520 (SH), 2220 (C∫ N) and 1640 (C = N ..

8, mp. 133°; yield 78%.

Anal. Calcd. for $C_{18}H_{15}N_3OS$: C, 67.28; H, 4.67; N, 13.08; S, 9.96

Found: C, 67.53; H, 4.94; N, 12.88; S, 10.12

IR (cm^{-1}); 2225 (C∫ N) ; 1720 (C = O) and 1635 (C = N).

Synthesis of imidazo [2,1-b]-1,3-thiazine derivatives (4) and (9)

A mixture of the appropriate cyanoethyl derivative 2 (3.05 g) and 8 (3.21 g) (0.01 mole), glacial acetic acid (30 ml) and concentrated hydrochloric

acid (37.3%, 10 ml) was refluxed for 4 hr. The solution was concentrated to 15 ml by evaporation, then the separated solid was filtered off, washed with ethanol and crystallised from the proper solvent as yellow crystals of 4 and 9 respectively.

4 was crystallised from acetic acid, mp. 262°, yield 68%.

Anal. Calcd. for $C_{18}H_{14}N_2OS$:C, 70.58; H, 4.57; N, 9.15; S,10.45

Found: C, 70.31; H, 4.83; N, 8.92; S, 10.70

IR (cm^{-1}); 2980 (saturated CH) 1690 (C = O) and 1645 (C = N).

^1H NMR (δ ppm): 3.7, 4.3 (2t, 2H, 2$\underline{CH_2}$ each at C_3 and C_4) and 7.2-7.5 (m, 10 H, Ar$\underline{H}$).

9 was crystallised from ethanol, mp. 211°, yield 70%.

Anal. Calcd. for $C_{18}H_{14}N_2O_2S$: C, 67.08; H, 4.35; N, 8.69;S,9.93

Found: C, 67.31; H, 4.53; N, 8.52; S, 9.73

IR (cm^{-1}); 2995 (Sat. CH) 1725, 1685 (2C = O) and 1640 (C = N).

^1H NMR (δ ppm): 3.6, 4.1 (2t, 2H, 2$\underline{CH_2}$ each at C_3 and C_4) and 7.1-7.4 (m, 10 H, Ar$\underline{H}$).

Action of ethyl acrylate on (1) and (7)

A mixture of each of 1 (2.52 g) and 7 (2.68 g) (0.01 mole) and 3 ml ethylacrylate in pyridine (50 ml) and water (10 ml). The reaction was worked up as described above to give 4 and 9 (showing no depression in melting points and mixed melting points when admixed with samples of 4 and 9 prepared as described above).

Reaction of 2 with thioglycollic acid

Thioglycollic acid (0.92 g, 0.01 mole) is added to a solution of 2 (3.05 g, 0.01 mole) in pyridine (30 ml) and the reaction mixture is heated under reflux for 5 hr. The reaction mixture was cooled to room temperature, poured over ice cold water, the solution was acidified with hydrochloric acid to

complete the precipitation. Crude product was collected and crystallised from dioxane to give yellow substance of 3a.

3a, mp. 288°; yield 60%.

Anal. Calcd. for $C_{20}H_{17}N_3OS_2$: C, 63.32; H, 4.48; N, 11.08: S, 16.88

Found: C, 63.13; H, 4.72; N, 10.85; S, 16.62

IR (cm^{-1}); 2995 (sat. CH) 1725, (C=O) and 1640 (C = N)

Action of aromatic aldehydes on 4

To a solution of 4 (3.06 g, 0.01 mole) and triethylamine (3 drops) in ethanol (50 ml) a each of benzaldehyde (1.06 ml) and p-chlorobenzaldehyde (1.41 g) (0.01 mole) was added and the mixture was heated to reflux for 2 hr- and then allowed to cool. The solid precipitate was isolated by suction and crystallized from ethanol as yellow crystals 5a,b.

5a, mp. 217°; yield 68%.

Anal. Calcd. for $C_{25}H_{18}N_2OS$: C, 76.14; H, 4.56; N, 7.10: S,8.12

Found: C, 76.43; H, 4.72; N, 6.83; S, 8.30

IR (cm^{-1}); 2990 (sat. CH) 1695, (C = O) and 1640 (C = N).

^1H NMR (δ ppm): 3.1 (s 2H, $\underline{CH_2}$); 6.1 (s, 1H, Ar$\underline{CH}$=C) and 7.2-7.4 (m, 15H, Ar-$\underline{H}$).

5b, mp. 235°; yield 70%.

Anal. Calcd. for $C_{25}H_{17}ClN_2OS$: C,70.01; H,3.96; N,6.53 ;S,7.46; Cl,8.28

Found: C,70.30; H,4.21; N,6.73; S,7.22; Cl,8.54

IR (cm^{-1}); 2980 (sat. CH) 1685, (C = O) and 1635 (C = N).

^1H NMR (δ ppm): 3.3 (s, 2H, $\underline{CH_2}$); 6.2 (s, 1H, Ar$\underline{CH}$=C) and 7.1-7.4 (m, 14 H, Ar-$\underline{H}$).

Action of aryldiazonium salt on 4

The aromatic amine (0.65 ml aniline, 0.88 g p-chloroaniline, 0.0068 mole) dissolved in concentrated hydrochloric acid (6 ml) and water (6 ml)

was cooled to 0° and then treated with a cold solution of sodium nitrite (0.6 g) in water (6 ml). The diazotised amine was added gradually to an ice-cold solution of 4 (1.83 g) (0.006 mole) dissolved in 50 ml pyridine. After the addition was completed, the reaction mixture was left aside in a cold chest for 4 hr. The product separated was filtered off, washed with water and crystallised from the proper solvent as reddish brown crystals 6a,b.

6a, was crystallised from ethanol, m.p. 231°; yield 64%.

Anal. Calcd. for $C_{24}H_{18}N_4OS$: C, 70.24; H, 4.39; N, 13.65; S, 7.80

Found: C, 70.53; H, 4.11; N, 13.40; S, 8.01

IR (cm^{-1}); 3390 (NH); 1690, (C = O) and 1640 (C = N).

^1H NMR (δ ppm): 3.5 (s, 2H, $\underline{CH_2}$); 7.1-7.4 (m, 15H, Ar-H) and 9.4 (s, 1H, exchangeable with D_2O).

6b, was crystallised from acetic acid, m.p. 253°; yield 62%.

Anal. Calcd. for $C_{24}H_{17}ClN_4OS$: C,64.79; H,3.82; N,12.59; S,7.19; Cl,1.98

Found: C,64.50; H,4.02; N,12.83; S,7.42; Cl,7.73

IR (cm^{-1}); 3410 (NH); 1695, (C = O) and 1635 (C = N).

^1H NMR (δ ppm): 3.6 (s, 2H, CH_2); 7.2-7..5 (m, 14H, Ar-H) and 9.4 (s, 1H, NH exchangeable with D_2O).

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تحضير مشتقات الثيارين والثيازول ذات النشاط البيولوجى

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أمكن تحضير العديد من مركبات اميدازو (١,٢ -ب) - ٣,١ - ثيازين وذلك من خلال تفاعل مشتقات الاميدازول مع مركب اكربلو نيتريل فى محلول البريدين المائى ثم تجرى عملية القفل باستخدام مخلوط من حمض الهيدروكلوريك وحمض الخليك .

كذلك أمكن تحضير العديد من مركبات الثيازول من خلا تفاعل مشتقات النيتريل مع حمض ثيوجليكوليك .

أمكن اثبات التركيب البنائى لكل المركبات الجديدة من خلال طرق التحليل العنصرى ودراسة أطياف الأشعة تحت الحمراء والرنين النووى المغناطيسى .