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REACTION OF PHENYLTRICHLOROMETHANE WITH SEMICARBAZIDE AND THIOSEMICARBAZIDE DERIVATIVES.

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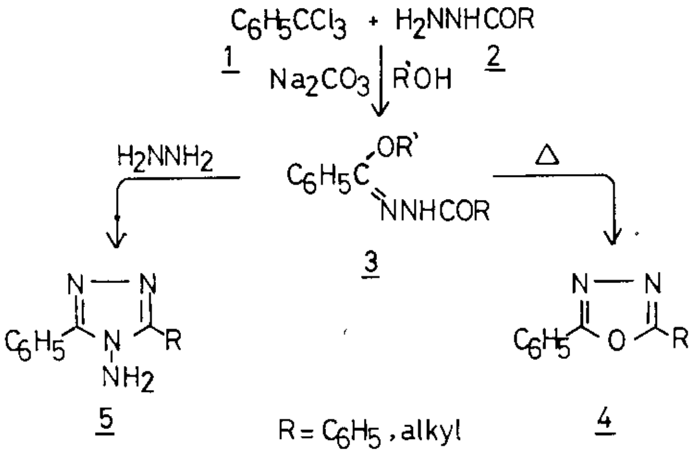
Abstract - Phenyltrichloromethane 1 reacts with 4-phenylsemicarbazide and yields ethyl N-phenylcarbamoylmethane hydrazonate 10. Thermolysis of 10 yields 3,4-diphenyl-1H-1,2,4-triazolin-5-one 9a, identified by its alternate synthesis from the amidrazone 14 and diphenyl carbonate. Hydrazinolysis of 10 and N-ethoxycarbonylbenzhydrazidoyl chloride 13 gives in both cases the tetrahydrotetrazene derivative 12. Reaction of 1 with thiosemicarbazide and its 4-phenyl derivative afforded the corresponding 2-phenyl-1,3,4-thiadiazole derivatives 16a and 16b, respectively.

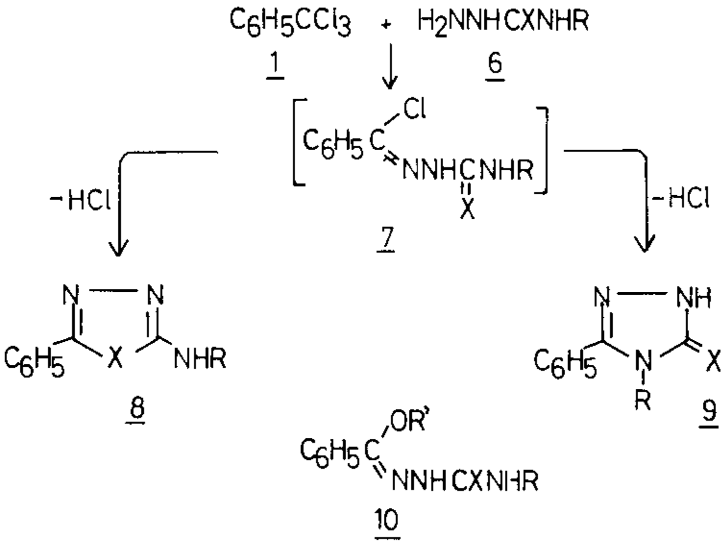
INTRODUCTION

Recently it has been reported that phenyltrichloromethane 1 reacts with acylhydrazines 2 (R = aryl or alkyl group) in alcohols to give the hydrazonate esters 3, which undergo cyclization upon heating to yield the corresponding oxadiazole derivatives 4 (Scheme 1).[1] In an attempt to investigate the effect of varying the structure of the R group in 2, we examined the reaction of 1 with the semicarbazides 6a-c (Scheme 2). Each of these semicarbazides has two nucleophilic centers and is therefore expected to give products of type 8 and 9 upon its reaction with 1. The success of getting 8 and/or 9 by this reaction would provide a one-pot synthesis which would be more convenient than their reported multi-step preparations[2-4]. Moreover, the thiosemicarbazone esters of type 10 have not yet been reported and it would be interesting to investigate their chemical behaviour if they were isolated from the reactions under investigation.



R = C_6H_5, alkyl

Scheme 1



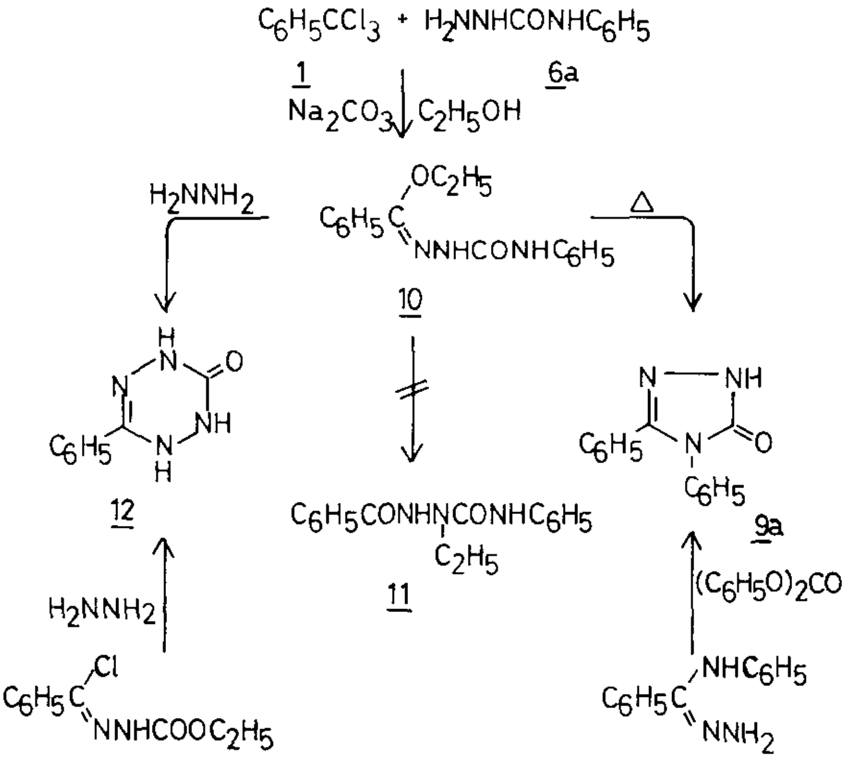
X/R : a, O/C_6H_5 , b, S/H , c, S/C_6H_5

Scheme 2

RESULTS AND DISCUSSION

Treatment of 4-phenylsemicarbazide 6a with an equimolar amount of phenyltrichloromethane 1 under reflux for 5 hr in absolute ethanol in presence of anhydrous sodium carbonate gave ethyl N-phenylcarbamoylmethanohydrazonate 10. The structure of the latter ester was deduced from its spectral and analytical data together with its chemical reactions described below (Scheme 3). The pmr spectrum of 10 in deuterated chlroform showed signals at δ 0.8 (t, 3H, $\underline{CH_3}CH_2O$), 3.5 (q, 2H, $CH_3\underline{CH_2}O$) and an aromatic proton multiplet in the region 6.4 - 8.0 ppm. Its mass spectrum revealed a molecular ion peak at m/e 283 with relative intensity 100%. The infrared spectrum of 10 in potassium bromide showed bands at 3385 (NH), 1680 (CO), 1600 (C=N) and two characteristic bands near 1225 and 1070 cm^{-1} assignable to an ether linkage.

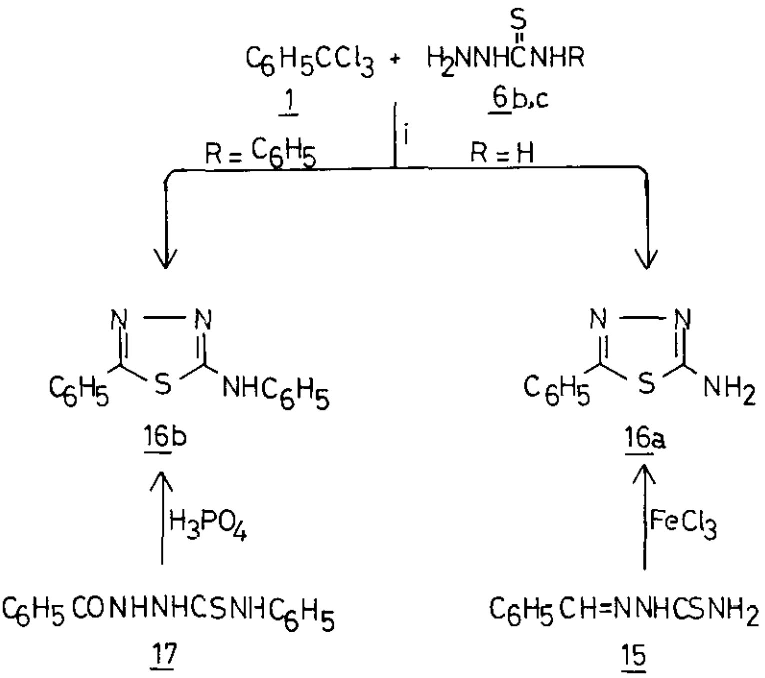
Thermolysis of 10 in the absence of solvent gave a product identified as 3,4-diphenyl-1H-1,2,4-triazolin-5-one 9a. The structure of the latter follows its elemental analysis, spectral data and its alternate synthesis from the amidrazone 14 and diphenyl carbonate[5]. The Chapman-like rearrangement product 11 has not been identified among thermolysis products. This difference between 10 and 3 is further



Scheme 3

confirmed by the results of their reaction with hydrazine hydrate. For example, in our hands treatment of 10 with hydrazine hydrate yielded 12 whereas hydrazinolysis of 3 was reported to give the triazole derivative 5. The structure of the product 12 was substantiated by its alternate synthesis from N-ethoxycarbonylbenzhydrazidoyl chloride and hydrazine hydrate. Both elemental analysis and spectral data of 12 agree with its structure. Its mass spectrum shows a molecular ion peak m/e 176 with relative intensity 100%.

Reaction of 1 with thiosemicarbazide 6b in refluxing ethanol in presence of anhydrous sodium carbonate afforded a pale yellow solid identified as 16 (Scheme 4). The structure of 16a was proved by comparison of its properties (m.p., mixed m.p., spectra) with those of an authentic sample of 2-phenyl-5-amino-1,3,4-thiadiazole obtained by oxidation of benzaldehyde thiosemicarbazone with ferric chloride[3]. Similarly, compound 1 reacts with 4-phenylthiosemicarbazide in ethanol in presence of anhydrous sodium carbonate and gives the thiadiazole derivative 16b. The structure of 16b follows its spectra and its elemental analysis and its identity with an authentic sample of 2-phenyl-5-phenylamino-1,3,4-thiadiazole prepared by dehydration of 1-benzoyl-4-phenylthiosemicarbazide 17 with phosphoric acid[7] (Scheme 4).



$i = Na_2CO_3 / C_2H_5OH$

Scheme 4

EXPERIMENTAL

Proton magnetic resonance spectra were recorded on Varian A-60 spectrometer using tetramethylsilane as an internal standard. Infrared spectra were obtained on Perkin Elmer 257 grating spectrophotometer. Melting points were obtained using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith laboratory, Knoxville, Tennessee 37916, USA. The semicarbazide 6a and its thio analog 6c were prepared as described previously[8,9]. N-Ethoxycarbonylbenzhydrazidoyl chloride 13 was prepared by chlorination of benzaldehyde N-ethoxycarbonylhydrazone[10].

Preparation of ethyl N-phenylcarbamoylmethane hydrazonate (10) - A mixture of phenyltrichloromethane (9.5 g, 0.05 mole), 4-phenylsemicarbazide (7.5 g, 0.05 mole), anhydrous sodium carbonate (10.6 g, 0.1 mole) in absolute ethanol (250 ml) was refluxed on a steam bath for 5 hr, cooled and then poured on crushed ice. After 3 hr, the solid that precipiated was collected and crystallized from ethanol to give 10 (75%), m.p. 162°C, $C_{16}H_{17}N_3O_2$, Anal. Found (Calcd.): C, 67.71 (67.82), H, 6.00 (6.04), N, 14.71 (14.83)%; ms : m/e (rel. intensity) 283 (100.0), 238 (6.6), 164 (39.7), 163 (33.7), 136 (16.9), 122 (9.9), 105 (34.0), 104 (24.6), 93 (21.8).

Thermolysis of (10) - Ethyl N-phenylcarbamoylmethane hydrazonate 10 (0.3 g) was heated at 200°C in a sealed tube in absence of solvent for 30 min during which it melted and resolidified. Recrystallization was effected from ethanol to give 9a in 97% yield, m.p. 258-260°C (lit. m.p. 260°C)[5], mixed m.p. with an authentic sample of 9a[5] showed no depression.

Hydrazinolysis of (10) and (13) - A mixture of compound 10 (0.3 g, 0.001 mole) and hydrazine hydrate (1 ml) in ethanol (10 ml) was refluxed for 10 hr and cooled. The solid formed was collected and crystallized from ethanol. The tetrazene 12 was obtained in 70% yield, m.p. 240°C, $C_8H_8N_4O$, Anal. Found (Calcd.) : C, 54.5 (54.53), H, 4.6 (4.57), N, 31.5 (31.8); ms spectrum m/e (relative intensity) 176 (100.0), 104 (58.0), 103 (14.7), 91 (9.2), 77 (30.5).

Similar treatment of hydrazidoyl chloride 13 (0.38 g, 0.002 mole) with hydrazine hydrate (1 ml) in ethanol (10 ml) and work up the reaction mixture yielded 12, identical in all respects (m.p., mixed m.p., spectra) with the sample prepared by hydrazinolysis of 10.

Preparation of 2-phenyl-5-amino-1,3,4-thiadiazole (16a) - A mixture of phenyltrichloromethane 1 (1.95 g, 0.01 mole), thiosemicarbazide 6b (0.9 g, 0.01 mole) and anhydrous sodium carbonate (1.5 g, 0.014 mole) in ethanol (50 ml) was refluxed for

24 hr. The reaction mixture was filtered while hot, the solvent was evaporated and the residue was dissolved in water. To the resulting solution, an aqueous solution of sodium carbonate was added till alkaline and the precipitated thiadiazole derivative was collected. Crystallization of the crude product from methanol gave 16a, mp. 225°C, not depressed when mixed with an authentic sample of 16a prepared by oxidation of benzaldehyde semicarbazone 15 by literature method[3].

Preparation of 2-phenyl-5-phenylamino-1,3,4-thiadiazole (16b)- This was prepared following the method described above for 16a. Phenyltrichloromethane 1 (2.0 g, 0.01 mole), 4-phenylthiosemicarbazide 6c (1.6 g, 0.01 mole) and anhydrous sodium carbonate (2.15 g, 0.02 mole) were refluxed in absolute ethanol (50 ml) for 5 hr, and the reaction mixture was poured on ice. The solid that precipitated was collected and crystallized from ethanol to give 16b in 70% yield, m.p. 198°C, not depressed when mixed with authentic sample of 16b prepared by dehydration of 1-benzoyl-4-phenylthiosemicarbazide 17 with phosphoric acid as described previously[7].

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