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REACTIONS WITH THIOHYDANTOINS: NEW ROUTES FOR SYNTHESIS OF IMIDAZOQUINAZOLINES AND IMIDAZO-1,2,4-TRIAZOLES

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Abstract - A new route for synthesis of new imidazoquinazoline derivatives via reaction of anthranilic acid with 4-thiohydantoin, 5-arylidene-4-methylmercaptohydantoins and 5-arylidene-2-ethylmercaptohydantoins is reported. Synthesis and characterization of new imidazo-1,2,4-triazoles via reaction of aldehydes with new 2- and 4-phenylhydrazonohydantoin derivatives is also reported and discussed.

The considerable biological and medicinal activities of imidazoquinazolines and imidazotriazoles have stimulated recent interest in the synthesis of derivatives of these ring systems.[1-3] In continuation of our previous work,[4] we have investigated some new routes for synthesis of these heterocyclic systems. The work has resulted in synthesis of several new imidazoquinazolines and imidazo-1,2,4-triazoles from the readily accesible thiohydantoin derivatives. The products were obtained in good yields under mild reaction conditions.

A mixture of 4-thiohydantoin (1a) (0.004 mole) and anthranilic acid (0.004 mole) was heated in an oil bath at 150-160°C till evolution of H_2S ceased (ca. 2 hr), then cooled and triturated with ethanol, or a solution of 4-methylthio derivative of 1a [3.6 g of 1a in aqueous sodium hydroxide (16 ml, 12%), methanol (90 ml) and 3.5 ml of methyl iodide were mixed. The mixture was stirred for 1 hr and left aside overnight at room temperature, then evaporated to one half of its volume] and 3.7 g of anthranilic acid in ethanol (20 ml) was refluxed for 90 min on a water bath till precipitation of brown product was completed. In both cases, the same product of molecular formula $C_{10}H_7O_2N_3$ was afforded. The IR spectrum of the product revealed the presence of C=N, 2C=O and NH groups. Two structures, imidazo[5,1-b]quinazoline-1,9-dione (2) and imidazo[4,5-b]quinoline-2,9-dione (3), were possible for the reaction product. Structure 3 was eliminated since the reaction product (0.01 mole) readily condensed with aromatic aldehydes (0.01 mole) in presence of glacial acetic acid (30 ml) and anhydrous sodium acetate (3 g). The reaction mixture was refluxed for 2 hr, cooled, and then poured into cold water to give the arylidene derivatives 4a,b. The structure of 4a,b was confirmed by independent synthesis from 5-arylidene-4-methylmercaptohydantoins 5a,b with anthranilic acid. Thus, in a typical procedure, each of 5a,b (0.004 mole) was refluxed with anthranilic acid (0.004 mole) in presence of acetic acid (20 ml) till the bad odour of methane thiol could not be detected. The products obtained after cooling and filtration were proved to be 4a,b by m.p. and mixed m.p. Compound 4c could be also synthesised from reaction of 5c with anthranilic acid in an oil bath at 150-160°C as described above (cf. Chart 1). The IR spectra of 4a,b showed absorption peaks characteristic for C=N, 2C=O and NH groups.

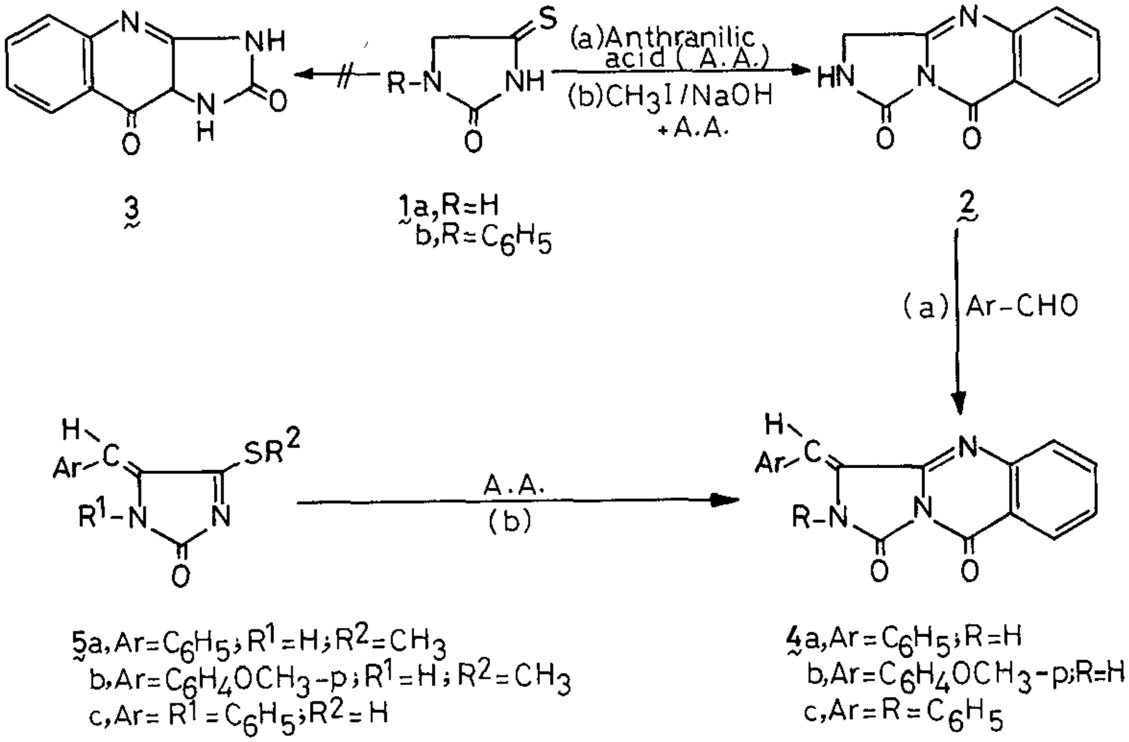
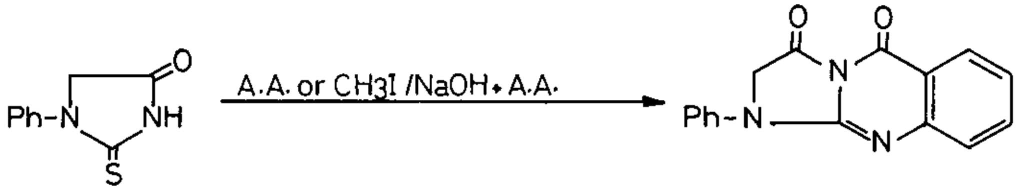


Chart 1

Attempts to prepare 1-phenylimidazo[2,1-b]quinazoline-3,5(1H,2H)-dione (7) via the reaction of 1-phenyl-2-thiohydantoin (6) or its 2-methylthio derivative with anthranilic acid, as described above, were unsuccessful. On the other hand, 2-arylidene derivatives 9a,b were directly synthesised by refluxing 5-arylidene-1-phenyl-2-ethylmercaptohydantoins (8a,b) (0.004 mole) with anthranilic acid (0.004 mole) in glacial acetic acid (20 ml). The structure of 9a,b was inferred from analytical data and IR spectra which revealed, in each case, the presence of the absorption bands characteristic for two carbonyl groups.



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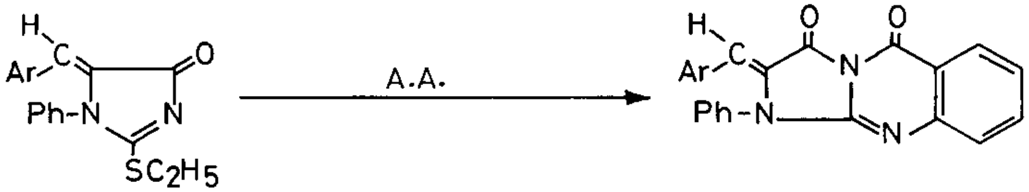
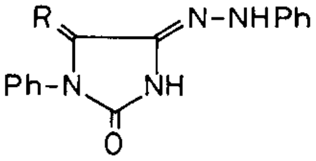


8a, Ar=C_6H_5
b, Ar=$C_6H_4OCH_3$-p

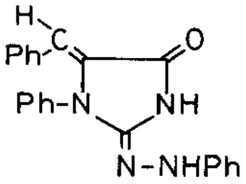
9a, Ar=C_6H_5
b, Ar=$C_6H_4OCH_3$-p

In continuation of this work, we attempted to prepare imidazo-1,2,4-triazoles. A synthetic approach well documented for the preparation of ring fused s-triazoles was investigated.[5,6] Thus, each of 1b, 5c and 8a (0.01 mole) was refluxed with phenylhydrazine (0.01 mole) in ethanol (30 ml) till the odour of H_2S (or C_2H_5SH in case of 8a) ceased (ca. 1 hr). The solid obtained by cooling (or dilution with water in case of 8a) was proved to be phenylhydrazone derivatives 10a,b and 11. The IR spectrum of 11 as a typical example of phenylhydrazone derivatives showed absorption bands characteristic for C=N, C=O, NH ring and NH hydrazone groups. (cf. Chart 2).

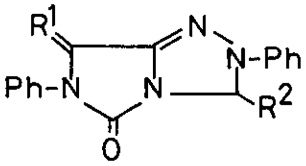
A mixture of each of 4-phenylhydrazone derivatives 10a,b and 2-phenylhydrazone derivative 11 (0.01 mole) and formaldehyde (5 ml, 40%) in ethanol (20 ml) was refluxed till the solid separated (ca. 30 min) to afford imidazo-1,2,4-triazole derivatives 12a,b and 13a. On the other hand, when a mixture of each of 10a,b and 11 (0.01 mole) and benzaldehyde (0.01 mole) was heated in an oil bath at 150-160°C for 2 hr, cooled and triturated with ethanol, 12c,d and 13b were obtained (cf. Chart 2). Imidazo[5,1-c]-1,2,4-triazole derivatives 12a-d and imidazo[2,1-c]-1,2,4-triazole derivatives 13a,b could be assigned to the reaction products based on analytical data and IR spectra which showed disappearance of characteristic band of NH group and also showed absorption bands characteristic for C=N and C=O groups.



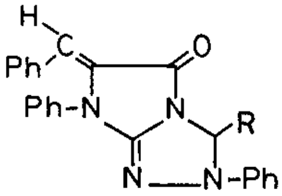
10a, $R=H_2$
b, $R=CHPh$



11



12a, $R^1=H_2$; $R^2=H$
b, $R^1=CHPh$; $R^2=H$
c, $R^1=H_2$; $R^2=C_6H_5$
d, $R^1=CHPh$; $R^2=C_6H_5$



13a, $R=H$
b, $R=C_6H_5$

Chart 2

Table 1: List of imidazo[5,1-b]quinazolines (**2**,**4**a-c), imidazo[2,1-b]quinazolines (**9**a,b), 4- and 2-phenylhydrazonohydantoins (**10**a,b, **11**), imidazo[5,1-c]-1,2,4-triazoles (**12**a-d) and imidazo[2,1-c]-1,2,4-triazoles (**13**a,b).

Comp.*	M.p.** (°C)	Yield (%)	Formula	Comp.*	M.p.** (°C)	Yield (%)	Formula
2	282	80(a) 70(b)	$C_{10}H_7O_2N_3$	11	110	60	$C_{22}H_{18}ON_4$
4a	>300	70(a) 75(b)	$C_{17}H_{11}O_2N_3$	12a	120	60	$C_{16}H_{14}ON_4$
4b	>300	75(a) 77(b)	$C_{18}H_{13}O_3N_3$	12b	201	62	$C_{23}H_{18}ON_4$
4c	240	70	$C_{23}H_{15}O_2N_3$	12c	265	65	$C_{22}H_{18}ON_4$
9a	232	70	$C_{23}H_{15}O_2N_3$	12d	172	68	$C_{29}H_{22}ON_4$
9b	252	65	$C_{24}H_{17}O_3N_3$	13a	210	60	$C_{23}H_{18}ON_4$
10a	196	60	$C_{15}H_{14}ON_4$	13b	195	70	$C_{29}H_{22}ON_4$
10b	121	65	$C_{22}H_{18}ON_4$				

*Satisfactory elemental analyses for the newly synthesised compounds were obtained.

Compound **2 crystallised from AcOH, **4**a,b from DMF and other products from EtOH.

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