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SYNTHESIS AND SOME REACTIONS OF 6-(4-CHLORO-3-METHYL)-PHENYL-4-ARYL-3-OXO-2, 3, 4, 5-TETRAHYDROPYRIDAZINES

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The present work deals with the synthesis of 6-(4-chloro-3-methyl)-phenyl-4-aryl-3-oxo-2, 3, 4, 5-tetrahydropyridazines (2) involving the interaction of α-aryl-β-(4-chloro-3-methyl)-benzoylpropionic acids (1) with hydrazines in boiling butanol. The reaction of the pyridazines (2) with $PCl_5/POCl_3$, P_2S_5 and secondary amines has been investigated. The reaction of the products with many other reagents has also been described. Dehydrogenation of the pyridazinone derivative (2b) with Br_2/AcOH afforded a hydropyridazine derivative (9). Different aspects of regioselective behaviour of organomagnesium reagents toward pyridazine derivative (9) has been investigated.

INTRODUCTION

α-Aryl-β-(4-chloro-3-methyl)-benzoylpropionic acids (1) reacts with hydrazines to give 6-(4-chloro-3-methyl)-phenyl-4-aryl-3-oxo-2, 3, 4, 5-tetrahydropyridazines (2). Some reactions of the latter compound were studied, since compounds similar to 5, 6-diarylpyridazin-3-ones lower the blood pressure of the spontaneously hypertensive rat (SHR). The objective of our project was to explore the structure-activity relationship with the newly synthesized compounds which contain the 4, 6-diaryl part on the pyridazinone nucleus.

Thus the acid (1) condensed with hydrazines in the presence of *n*-butanol and afforded the pyridazinones (2).

The structure of compounds (2a-f) was confirmed by microanalyses and ir spectral data. The ir. spectra show bands characteristic of the C=O stretching vibrations of cyclic carboxamides (1650-1660 cm^{-1}), C=N (1630-1635 cm^{-1}) and bands of the NH group (~ 3200 cm^{-1}) for (2a-d). The H^1 N.M.R. spectrum of (2f) ($CDCl_3$): δ 2.1 (*d*, 6H); δ- 2.25 (*s*, 3H, *o*-CH_3); δ 2.27 (*s*, 3H, *m*-CH_3); δ 2.3 (*s*, 3H), N-CH_3); δ 2.6-3 (quintet, non-equivalent protons of methylene group); δ 3.9-4 (*q*, methine proton); δ 7.1 (*m*), δ 7.2 (*m*); δ 7.25 (*s*) and δ 7.6 ppm (*d*) corresponding to 6H.

As a point of interest, the presence of the pyridazinone derivatives (2a-d) in lactam-lactim tautomeric equilibrium has been investigated. Thus, the pyridazinone (2d) reacts with a mixture of $PCl_5/POCl_3$ (1) on a water bath to give 6-(4-chloro-3-methyl)-phenyl-3-chloro-4-(2-methyl-5-isopropyl)-phenyl-4, 5-dihydropyridazine (3). The reaction of (3) with sodium azide in boiling D.M.F. (2) afforded the tetrazole derivative (4).

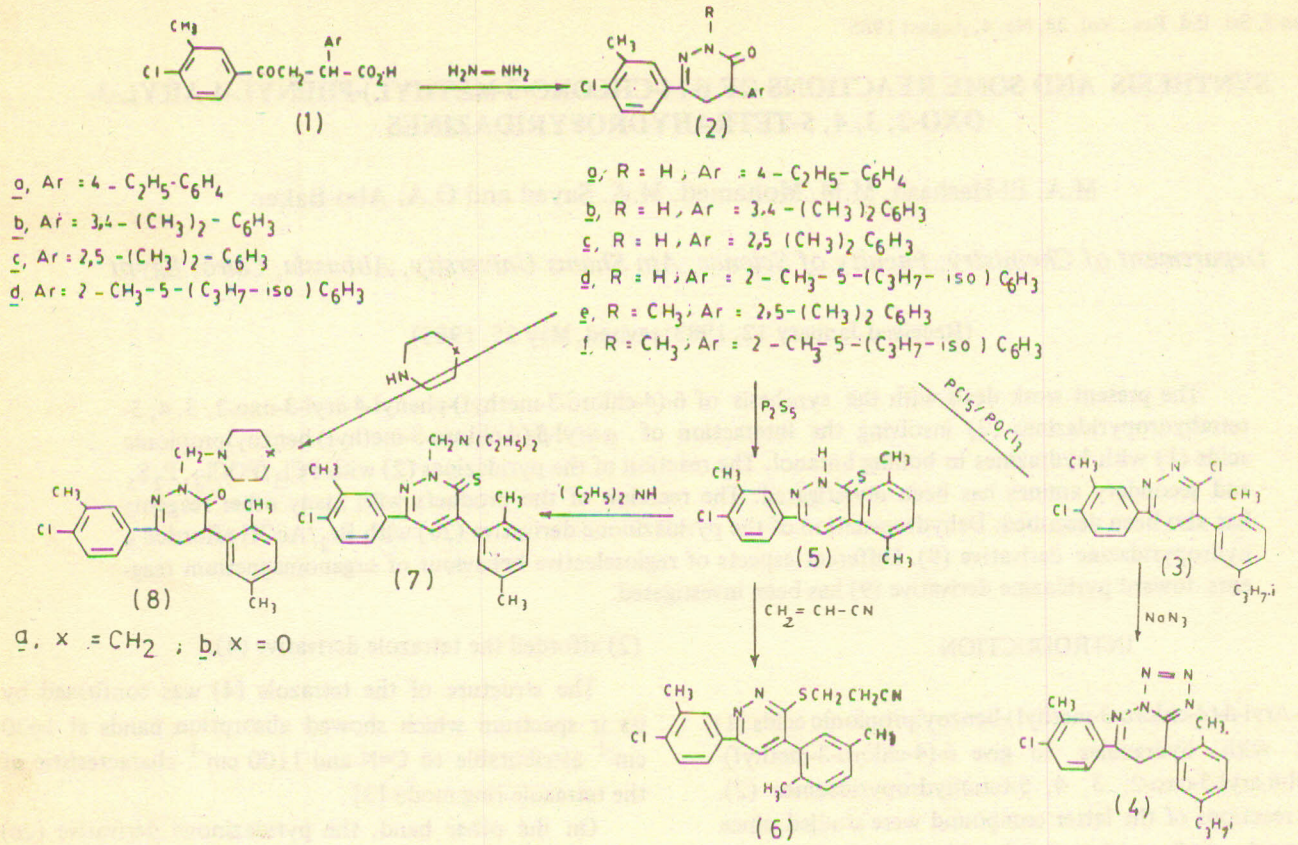
The structure of the tetrazole (4) was confirmed by its ir spectrum which showed absorption bands at 1630 cm^{-1} attributable to C=N and 1100 cm^{-1} characteristic of the tetrazole ring mode [3].

On the other hand, the pyridazinone derivative (2c) reacts with phosphorous pentasulphide (4) in boiling xylene to give 6-(4-chloro-3-methyl)-phenyl-4-(2, 5-dimethyl)-phenyl-3-(2H)-pyridazine thione (5) in which thionation together with dehydrogenation takes place. The ir spectrum of the thione (5) showed bands at 1630 cm^{-1} (C=N), 1300 cm^{-1} (C=S) and 2570 cm^{-1} (S-H). Such ir data show that the thione (5) really exists on the thioamide (-NH-C=S)-iminothil -N=C-SH dynamic equilibrium.

Also this paper reports the results obtained from the reaction of 3-mercaptopyridazine (5) with acrylonitrile [5]. Thus, when compound (5) is allowed to react with acrylonitrile in refluxed pyridine, S-cyanoethyl derivative (6) is obtained. The ir spectrum of compound (6) shows bands characteristic of C=N at 2225 cm^{-1} and C=N at 1625 cm^{-1}. This shows that the 3-mercaptopyridazine derivative exists in thiol form in solution.

However, when compound (5) was submitted to reaction with diethylamine in the presence of aqueous formaldehyde in boiling ethanol (6), the product was a Mannich base [7]. The ir spectrum of compound (7) shows absorption bands at 1635 cm^{-1} and 1350 cm^{-1} attributable to C=N and C=S respectively.

Similarly, compound (2c) reacts with secondary amines, viz. piperidine and/or morpholine to give the Mannich bases (8a and 8b) respectively. The assigned



structure for the Mannich bases (8) supported from ir spectra which showed bands at the regions 1660-1670 cm^{-1} and 1620-1630 cm^{-1} due to C=O and C=N respectively.

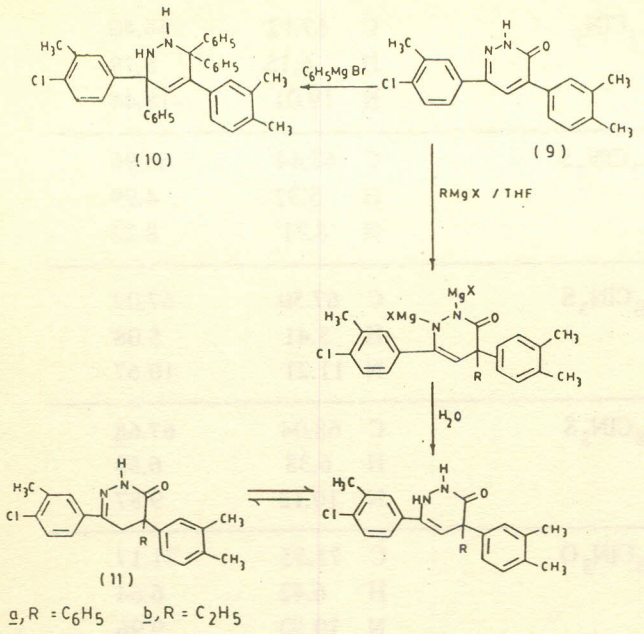
Recently, it has been reported that tetrahydropyridazin-3-one underwent dehydrogenation upon treatment with bromine and acetic acid [1], and therefore, the reaction of the pyridazinone derivative (2b) with bromine and acetic acid afforded 6-(4-chloro-3- methyl) -phenyl-4-(3,4-dimethyl)-phenyl-3-oxo-2, 3-dihydropyridazine (9). The ir spectrum of compound (9) was fully consistent with the proposed structure which showed bands at 1655, 1630, 1600 and 3240 cm^{-1} (C=O, C=N, C=C and NH groups) stretching frequencies.

The reaction of 6-(4-chloro-3-methyl)-phenyl-4-(3,4-dimethyl)-phenyl-3-oxo-2,3-dihydropyridazine (9) with phenylmagnesium bromide (3 equivalent) afforded 6-(4-chloro-3-methyl)-phenyl-4-(3,4-dimethyl)-phenyl-3,3,6 triphenyl-1,2,3,6-tetra-hydropyridazine (10), i.e., the product formed by 1,2-addition to both carbonyl and the azomethine group of (9). The ir spectrum of compond (10) agrees well with the proposed structure (1620 cm^{-1} and 3200 cm^{-1} and 3200 cm^{-1}, attributable to C=C and NH respectively) and no absorptions for C=O or C=N has been observed.

However, when compound (9) was submitted to reaction with phenyl magnesium bromide or ethyl magnesium iodide (4 equivalent) in tetrahydrofuran, the products were 6-(4-chloro-3-methyl)-phenyl-4-(3,4-dimethyl)-phenyl-4-(phenyl or ethyl)-3-oxo-2,3,4,5-tetrahydropyridazines (11a and 11b), i.e., the products are formed by the 1,4-addition to (–C=C-C=N) system of (9).

The ir spectra of compounds (11) showed strong absorption bands at 1650, 1620, 3200 and 3400 cm^{-1} attributable to C=O, C=N and NH or OH. Such ir spectral data explain that the products (11) actually exist in the lactam-lactim tautomeric equilibrium.

The failure of organomagnesium reagents to add to the carbonyl group may be due to the presence of pyridazin-3-one in the lactim form. It might also be due to the deactivation of the carbonyl group in the lactam form sketch by the negative charge on the nitrogen atom in the magnesium halide salt, which is the primary product of the interaction between the pyridazin-3-one and the organomagnesium reagents.



EXPERIMENTAL

All melting points reported are uncorrected. The infrared absorption spectra were determined with a Beckman infrared spectrophotometer using KBr wafer technique (ν max in cm^{-1}). H^1N.M.R. spectra were carried out using Varian s-60 spectrometer in $CDCl_3$ and TMS as internal standard; chemical shifts in δ-scale. Physical data are group in Table 1.

Synthesis of pyridazin-3-one derivatives. A solution of the α-aryl-γ-(4-chloro-3-methyl)-benzoylproionic acids (1) (0.01 mole) in *n*-butanol (50 ml) was treated with hydrazine hydrate or methyl hydrazine (0.01 mole) and refluxed for 6 hr. The solids that separated after concentration and cooling were crystallized from a suitable solvent to give the tetrahydro-pyridazinone derivatives (2a-f) as colourless crystals. The results are listed in Table 1.

Table 1. Pyridazinone derivatives (2), chloropyridazine (3), tetrazole (4), thio derivatives (5, 6); Mannich bases (7, 8) and tetrahydropyridazine (10 and 11)

Compd.	Yield %	m.p.° solvent	Molecular formula	Analysis % Found	Calcd.
2a	92	172	$C_{19}H_{19}ClN_2O$	C 69.94	69.83
				H 5.21	5.81
		Toluene		N 8.08	8.57
2b	95	165	$C_{19}H_{19}ClN_2O$	C 70.17	69.83
		(P.E. 60-80)		H 5.57	5.81
				N 8.11	8.57
2c	85.8	169	$C_{19}H_{19}ClN_2O$	C 70.18	69.83
		(P.E. 100-120)		H 5.41	5.81
				N 7.99	8.57
2d	93	167	$C_{21}H_{23}ClN_2O$	C 70.85	71.08
		(P.E. 80-100)		H 6.22	6.48
				N 8.00	7.89
2e	94	113	$C_{20}H_{21}ClN_2O$	C 70.12	70.48
		(P.E. 80-100)		H 6.26	6.16
				N 8.61	8.22
2f	81	103	$C_{22}H_{25}ClN_2O$	C 72.02	71.64
		(P.E. 60-80)		H 6.15	5.97
				N 8.05	7.59
3	76	179	$C_{21}H_{22}Cl_2N_2$	C 67.36	67.56
				H 6.11	5.89
		Butanol		N 8.04	7.50

Contd.

4	54	192 Butanol	$C_{21}H_{22}ClN_5$	C 67.12 H 6,15 N 19.01	66.40 5.79 18.44
5	88	215 Benzene	$C_{19}H_{17}ClN_2S$	C 67.44 H 5.32 N 8.71	66.96 4.99 8.22
6	30	152 (P.E. 100-120)	$C_{22}H_{20}ClN_3S$	C 67.5u H 5.41 N 11.21	67.09 5.08 10.67
7	72.9	160 Benzene	$C_{24}H_{28}ClN_3S$	C 68.04 H 6.33 N 10.12	67.68 6.58 9.87
8a	57	139 (P.E. 100-12)	$C_{25}H_{30}ClN_3O$	C 71.55 H 6.42 N 10.50	71.17 6.64 9.96
8b	78	148 Benzene	$C_{24}H_{28}ClN_3O_2$	C 67.72 H 6.18 N 9.61	68.00 6.13 9.91
9	92.5	226 (P.E. 100-120)	$C_{19}H_{17}ClN_2O$	C 70.11 H 5.11 N 9.11	70.26 5.23 8.62
10	42.5	191 Benzene	$C_{37}H_{33}ClN_2$	C 82.67 H 6.51 N 5.33	82.14 6.10 5.18
11a	50	215 Methanol	$C_{25}H_{23}ClN_2O$	C 75.06 H 5.52 N 7.13	74.53 5.71 6.95
11b	45	241 Toluene	$C_{21}H_{23}ClN_2O$	C 70.93 H 6.65 N 7.41	71.08 6.48 7.89

Synthesis of 3-chloropyridazine derivative (3). A suspension of (2d (1 g, 0.003 mile), $POCl_3$ (3 ml) and PCl_5 (0.5 g) was heated on a steam bath for 2 hr. The reaction mixture was poured gradually on to crushed ice (*ca* 150 g), the solid that separated was filtered off and crystallized from the proper solvent to give compound (3) as yellowish crystals. The results are listed in Table 1.

Action of sodium azide on chloropyridazine derivative (3). Synthesis of tetrazole derivative (4). A solution of (3) (1.1 g; 0.003 mole), sodium azide (0.5 g), water (5 ml) and dimethyl formamide (30 ml) was boiled under reflux for 3 hr., cooled and then water (100 ml) was added. The solid which separated was filtered off and crystallized from the proper solvent to give the tetrazole (4) as grey crystals (cf. Table 1).

Action of P_2S_5 on the pyridazinone (2c) Synthesis of the pyridazine thione 5. A solution of (2c) (3,3 g; 0.01 mole), P_2S_5 (0.02 mole) and dry xylene (50 ml) was boiled under reflux for 1 hr. The reaction mixture was filtered while hot and the solid that separated upon concentration and cooling was crystallized from the proper solvent to give the thione (5) as yellow crystals (cf. Table 1).

Reaction of 3-mercaptopyridazine 5 with acrylonitrile: formation of S-cyanoethyl derivative (6). A solution of

(5) (3.4 g; 0.01 mole) and acrylonitrile (0.02 mole) in pyridine (30 ml) was refluxed for 3 hr. The reaction mixture was diluted with water (100 ml) and the solid that separated was filtered off and crystallized from the suitable solvent to give compound (6) as colourless crystals (cf. Table 1).

Reaction of secondary amines with thione 5 and pyridazinone (2c): formation of Mannich bases (7 and 8). A solution of (5) or (2c) (0.01 mole) and secondary amines, viz. diethylamine, piperidine or morpholine (0.02 mole), formaldehyde (2.5 ml) in methanol (30 ml) was refluxed on a steam bath for 1 hr. The solid obtained by cooling was crystallized from the proper solvent to give (7) as yellow crystals and (8) as colourless crystals (cf. Table 1).

Dehydrogenation of 2b with Br_2/AcOH: formation of (9): A vigorously stirred solution of (2b) (3.3 g; 0.01 mole) in glacial acetic acid (50 ml) was heated to 50-60° and then treated portionwise with bromine (0.01 mole) during a period of 15 min. The mixture was further stirred for 3 hr. and then poured on ice/water. The solid that separated was filtered off and crystallized from the suitable solvent to give (9) as colourless crystals (cf. Table 1).

Reaction of phenylmagnesium bromide with pyridazinone (9). A solution of phenyl magnesium bromide (3 moles) in sodium-dried ether (50 ml) was added dropwise to a stirred hot solution of compound (9) (1 mole) in dry ether/benzene (25:25 ml). The resultant solution was heated under reflux for 8 hr. and then allowed to stand at room temperature overnight. The mixture was hydrolysed by the addition of saturated aqueous ammonium chloride (100 ml). The organic layer was separated, washed with water, and then dried with sodium sulphate. The solvent was distilled off and the residual product recrystallized from the suitable solvent to give (10) as colourless crystals (cf. Table 1).

Reaction of the pyridazinone (9) with organomagnesium reagents. A solution of phenylmagnesium bromide or ethylmagnesium iodide (4 moles) in tetrahydrofuran (50 ml) was added dropwise to a stirred hot solution of compound (9) (1 mole) in tetrahydrofuran (50 ml). The solution was heated on a steam bath for 6 hr., and then allowed to stand at room temperature overnight. The mixture was then added to ice-cold saturated aqueous ammonium chloride (100 ml) with stirring. The organic layer was extracted with ether, washed with water and then dried over sodium sulphate (anhydrous). Slow evaporation of the solvent left the desired products which crystallized from the suitable solvent to give (10 (cf. Table 1).

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