SYNTHESIS OF SOME NOVEL 3-(2-CHLORO-3-QUINOLYL)-5-PHENYL [1,3] THIAZOLO [2,3-c] [1,2,4] TRIAZOLES.

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Abstract: Various acetanilides (**1**) were treated with DMF and $POCl_3$ complex (Vilsmeier's reagent) to obtain 2-chloro-3-quinolinecarboxaldehydes (**2**). The latter on condensation with thiosemi- carbazide in alcohol gave the corresponding thiosemicarbazones (**3**), which on treatment with substituted phenacyl bromides (**4**) in alchol gave quinoline substituted thiazoles (**5**). The dehydrogenative cyclisation of 5 was achieved with chloranil in refluxing toluene resulting in novel 3-(2-chloro-3-quinolyl)-6-phenyl [1,3] thiazolo [2,3-c] [1,2,4] triazoles (**6**) whose structures are supported by spectral data.

Introduction: In recent years, the chemistry of quinolines[1-3] and their derivatives has gained increasing attention, particularly because substituted quinolines are associated with immense biological activities[4-14]. Likewise, a triazolothiazole system as substituent on quinoline ring may also be found to confer a wide range of biological activities[15-18] on quinoline derivatives. We report herein the synthesis of 3-(2-chloro-3-quinolyl)-6-phenyl [1,3]thiazolo[2,3-c][1,2,4]triazole (6) incorporating three biologically active moieties - quinoline, thiazole and triazole - in a single molecule. The title compounds will be evaluated for their biological activities in course of time, the results of which will be published elsewhere.

Results & Discussions:

Substituted acetanilides 1 were treated with dimethylformamide-phosphorous oxychloride complex (Vilsmeier reagent) to obtain the known[19] 2-chloro-3-quinolinecarboxaldehydes (2). 2a (i.e., 2,R=CH_3) on treatment with thiosemicarbazide in

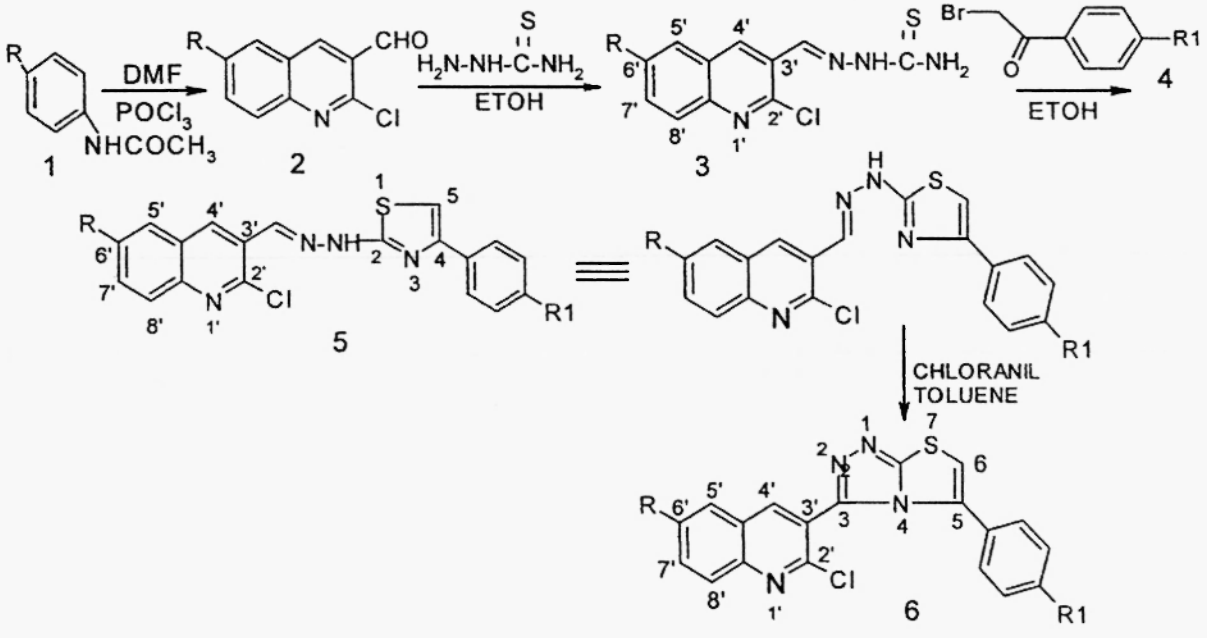
alcohol at reflux temperature gave, in a facile manner, the corresponding thiosemicarbazone 3a (i.e.,R=CH_3), whose structure has been established on the basis of its spectral data. Thus, its IR (KBr) spectrum, showed peaks at 3394 & 3280 cm^{-1} (doublet of unequal and medium intensity due to –NH_2 grouping), at 3143 cm^{-1} (broad but medium band due to –NH-group) and no absorption in the carbonyl region indicating absence of aldehyde group. Its ^1H NMR spectrum revealed signals at δ 2.60 (s, 3H,6′-CH_3), 3.20(s,2H,-NH_2), 7.60(d,J=8 Hz,1H,7′-H), 7.70(d,J=8 Hz,1H,8′-H), 8.00(s,1H,-CH=N), 8.60(s,1H,5′-H), 9.00(s,1H,4′-H), 11.80(s,1H,-NH). This data supports the formation of thiosemicarbazone (Table-I). Treatment of 3a with phenacyl bromide (4a,i.e., 4,R1=H) in alcohol at reflux temperature gave, in a facile manner, a substituted thiazole 5a(i.e., 5,R=CH_3, R1=H) whose structure has been established on the basis of its spectral data. Thus, its IR (KBr) spectrum showed a peak at 3055 cm^{-1} (broad, medium, due to –NH-group) and no absorption due to –NH_2 group. Its ^1H NMR spectrum revealed signals at δ 2.60 (s, 3H, 6′-CH_3), 6.00-7.00(broad hump, 1H, -NH-), 7.50(s, 1H,thiazole-H). 7.90(s, 1H,-CH=N), 8.70(s,1H,5′-H), 8.90(s,1H,4′-H), 7.75-8.00(m,7H,Ar-H, five protons of the phenyl group at 4th position of thiazole and 7′,8′ protons). This data supports the formation of thiazole ring (Table-II). Similar sequence of reactions was done on a different substrate[20] earlier to prepare fused thiazoles.

Chloranil is a compound widely used for oxidations and dehydrogenations[21, 22,23]. It was considered worthwhile to carryout dehydrogenative cyclisation of 5 to 6 using chloranil. Thus, reaction of 5a (i.e., 5,R=CH_3, R1=H) with chloranil in refluxing toluene gave 6a (i.e., 6,R=CH_3, R1=H), whose structure has been established on the basis of its spectral and analytical data. Thus, its IR (KBr) spectrum showed the absence of absorption at 3055 cm^{-1}due to -NH that was present in the IR spectrum of 5a. Its ^1H NMR spectrum showed signals at δ 2.6(s, 3H, 6′-CH_3), 7.30-7.50(m, 5H,phenyl hydrogens at the 5th position to thiazolotriazole ring), 7.80(s,1H,5′-H), 8.10(d,J=8Hz,1H,8′-H), 8.20(d,J=8Hz,1H, 7′-H), 8.50(s,1H,6-H), 8.65(s,1H, 4′-H). The peak at δ6.00-7.00 (-NH

proton broad hump) which was present in the spectrum of 5a was absent in the ^1H NMR of 6a, which supports the triazole ring formation. The mass spectrum of 6a showed M^+ at 376 and the other peaks at m/z 246,209,194,183,173,168,155142, 137,128,111, 102, 89,75,64,48. All the above data supports the structure of 6a (scheme).

The dehydrogenative cyclisation of 5 to 6 using chloranil has been studied in different solvents such as dichloromethane, benzene, dichloro ethane etc. and it has been found that the reaction is either incomplete or very slow in all the solvents as monitored by TLC. It was found that during workup of reaction, i.e., in the convesion of 5e to 6e using chloranil in refluxing toluene, tetrachloro-1,4-dihydroquinone could be isolated in quantitative yield by simple extraction of the reaction mixture with 10% alkali. This indi -cates that chloranil itself gets reduced to tetrachloro-1,4-dihydroquinone after dehydroge -natively cyclising 5a to 6a. Thus, chloranil, apart from being an excellent reagent for dehydrogenative cyclisation offers the advantage of easy recovery and recyclisability. The reaction of 5a to 6a has been extended to several substituted 5 and the products obtained have all been assigned structures 6 on the basis of spectral data (Table -III).

Scheme



Experimental Section:

IR spectra were recorded as KBr pellets on a Perkin Elmer System 2000 F.T. I.R. spectrometer. ^{1}H NMR spectra were recorded on a 100 MHz or 200 MHz Varian Instrument using TMS as internal standard. Melting points are uncorrected and were determined in open capillaries. TLC was recorded on glass plates coated with silica Gel G and spotting was done using iodine chamber or UV lamp.

Preparation of 3 (General procedure): A mixture of **2** (0.01 mole) and thiosemicarbazide (0.01 mole) in ethanol (20 ml) was heated under reflux with mechanical stirring for 3 hrs. At the end of this period, the reaction mixture was cooled, the separated solid was filtered, recrystallised from methanol to obtain pure **3**.

Preparation of 5 (General procedure): A mixture of **3** (0.01mole) and phenacyl bromide **4** (0.01mole) in ethanol (25ml) was heated under reflux, with mechanical stirring, forl hr. During the course of the reaction, the mixture became clear and solid started separating out from the solution. At the end of this period, when the reaction is complete(as shown by disappearance of the starting material **3** on TLC), the mixture was cooled, filtered, recrystallised from methanol to yield pure **5**.

Preparation of 6 (General procedure): A mixture of chloranil (0.01mole) and **5** (0.01mole) in toluene (25ml) was heated under reflux with constant stirring for 2 hrs. At the end of this period, the reaction mixture was cooled, filtered, the insoluble product washed with cold toluene and dried to obtain pure **6**. The toluene filtrate from above was washed with sodium hydroxide solution to remove hydroquinone, (hydroquinone is obtained by acidifying the aqueous alkali solution) and the toluene distilled to obtain second crop of **6** which was recrystallised from a suitable solvent.

Table I

Reaction of 2 with Thiosemicarbazide to obtain 3

SI No.	Quinolines (2) used	Product(3) obtained	Yield (%)	M.P (°C)
a.	R=CH_3	R=CH_3	91	234-236
b.	R=H	R=H	90	208-210

Table II

Reaction of 3 with Phenacyl bromides (4) to obtain 5

Sl No.	3 used	Phenacyl Bromide 4 used	Product obtained (5)	Yield (%)	M.P. (°C)
a.	$R=CH_3$	R1=H	$R=CH_3$ R1=H	90	184-86
b.	R=H	$R1=CH_3$	R=H $R1=CH_3$	88	188-90
c.	R=H	R1=Cl	R=H R1=Cl	90	190-92
d.	R=H	R1=Br	R=H R1=Br	91	200-02
e.	R=H	R1=H	R=R1=H	89	184-86
f.	$R=CH_3$	$R1=CH_3$	$R=CH_3$ $R1=CH_3$	89	180-82
g.	$R=CH_3$	R1=Cl	$R=CH_3$ R1=Cl	88	183-85
h.	$R=CH_3$	R1=Br	$R=CH_3$ R1=Br	91	182-84

Table-III

Physical and spectral data of compd. 6(a-h) obtained from 5(a-h)

Compd.,	Yield (%)	mp° C	^{1}H-NMR (200 MHz, $CDCl_3$), ppm
6a	75	146-48	2.6(s,3H,CH_3-6′), 7.30-7.50(m,5H,ph-H), 7.80(s,1H,H-5′),8.10(d,1H,H-8′),8.20(d,1H,H-7′), 8.50(s,1H,H-6),8.65(s,1H,H-4′).
6b	68	148-50	2.2(s,3H,ph-Me),7.6(m,4H,ph-H),7.7(dd,1H,H-7'), 7.90(dd,1H,H-6'),8.3(d,1H,H-5'),8.60(s,1H,H-6), 8.65(d,1H,H-8'), 8.75(s,1H,H-4').
6c	68	182-84	7.5(m,4H,ph-H),7.60(dd,1H,H-7'), 7.7(d,1H,H-8'), 7.9(dd,1H,H-6'),8.35(d,1H,H-5'),8.70(s,1H,H-6), 8.80(s,1H,H-4').
6d	72	188-90	7.55(m, 4H,ph-H), 7.65(dd,1H,H-7'), 7.75(d,1H,H-8'), 7.85(dd,1H,H-6'),8.45(d,1H,H-5'),8.65(s,1H,H-6), 8.75(s,1H,H-4').
6e	70	166-68	7.5(m,5H,ph-H), 7.65(dd,1H,H-7'), 7.7(d,1H,H-8'), 7.95(dd,1H,H-6'),8.4(d,1H,H-5'),8.65(s,1H,H-6), 8.8(s,1H,H-4').
6f	69	197-99	2.25(s,3H,Me-6'), 7.65(m,4H,ph-H),7.80(d,1H,H-7'), 7.90(d.1H,H-8'),8.45(s,1H,H-5'),8.70(s,1H,H-6), 8.80(s,1H,H-4').
6g	70	196-98	2.2(s,3H,Me-6'), 7.60(m,4H,ph-H), 7.75(d,1H,H-7'), 7.80(d,1H,H-8'),8.50(s,1H,H-5'),8.75(s,1H,H-4'), 8.80(s,1H,H-6).
6h	68	210-12	2.3(s,3H,Me-6'), 7.65(m,4H,ph-H), 7.85(d,1H,H-7'), 7.95(d,1H,H-8'),8.45(s,1H,H-5'),8.75(s,1H,H-6), 8.85(s,1H,H-4').

Satisfactory I.R's were obtained for all compounds

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