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BEHAVIOUR OF THE HETERO-RING IN SUBSTITUTED 2-PHENYLIMINO-4-THIAZOLIDINONES TOWARDS THE ACTION OF ORGANOMAGNESIUM COMPOUNDS

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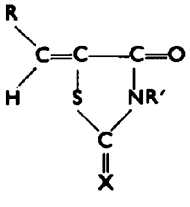
Abstract—Treatment of 5-arylidene derivatives of 2-phenylimino-4-thiazolidinones with Grignard reagents does not open the hetero-ring, the double bond of the lateral chain, the C=C bond and the C=N bond of Ic, enter into reaction, yielding colourless products, believed to have structure III. On the other hand, 5-benzylidene-3-phenyl-2-phenylimino-4-thiazolidinone (Id) on treatment with Ph Mg Br undergoes addition to the C=C bond of the lateral chain with the formation of 5-diphenylmethyl-3-phenyl-2-phenylimino-4-thiazolidinone (IIc).

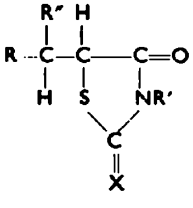
Whereas, the Grignard reagents do not attack the carbonyl group of the thiazolidine ring in Ic and Id, the carbonyl group in 5-methyl-2-phenylimino-4-thiazolidinone undergoes 1,2-addition with Ph Mg Br, followed by loss of water upon hydrolysis of the reaction mixture to yield Va. Elucidation of the structure of the latter has been proved by an independent synthesis. Hetero-ring opening by the action of Ph Mg Br in the thiazolidine system, has been found upon treatment of 5-methyl-3-phenyl-2-phenylimino-4-thiazolidinone with the same reagent, yielding N,N'-diphenylbenzamidine.

The discrepancy in the melting points of the 5-arylidene derivatives of 2-phenylimino-4-thiazolidinone and of 3-phenyl-2-phenylimino-4-thiazolidinone is discussed.

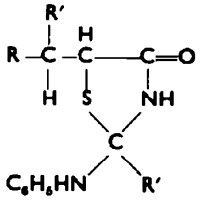
RECENTLY, it has been shown[1] that Grignard reagents do not open the hetero-ring in 5-arylidene derivatives of 3-arylrhodanines (Ia) and 3-aryl-2,4-thiazolidinediones (Ib), and in addition to reaction with the active hydrogen atom of rhodanine, the carbanion of the Grignard reagent attacks the exocyclic electrophilic carbon atom



Ia, X = S
b, X = O
c, X = NC_6H_5 ; R' = H
d, X = NC_6H_5 ; R = R' = C_6H_5



IIa, X = S
b, X = O
c, X = NC_6H_5 ; R = R' = R'' = C_6H_5



III

[1] *a* A. Mustafa, W. Asker, A. F. A. Shalaby, and M. E. Sobhy, *J. Org. Chem.* 23, 1992 (1958); *b* A. Mustafa, W. Asker, S. Khattab, M. E. Sobhy, A. M. Fliefel, and K. Abu-Elazayem, *J. Amer. Chem. Soc.* 82, 2029 (1960).

with the formation of IIa-b, respectively. The Grignard reagent does not attack the carbonyl or thione group of the thiazolidine ring; rhodanine and 3-aryl-2,4-thiazolidinedione are stable to this reagent.

In this investigation the study of the behaviour of the hetero-ring in substituted 2-phenylimino-4-thiazolidinones toward the action of Grignard reagents has been undertaken. During treatment of 5-arylidene-2-phenylimino-4-thiazolidinones (Ic; cf. Table 1) with Grignard reagents only addition of the reagents takes place to the conjugation, created by the attachment of an exocyclic C=C bond in the 5-position of a heterocyclic ring having a carbonyl function, and to the endocyclic C=N (cf. the possible tautomeric form of Ic[2]), with the formation of 2-anilino-2-aryl-5-diarylmethyl-4-thiazolidinones (III; cf. Table II). On the other hand, the carbanion of phenylmagnesium bromide attacks the exocyclic carbon atom of 5-benzylidene-3-phenyl-2-phenylimino-4-thiazolidinone (Id), and not the exocyclic C=N bond, with the formation of 5-diphenyl-methyl-3-phenyl-2-phenylimino-4-thiazolidinone (IIc). During treatment of Ib ($R = C_6H_5$; $R' = H$) with phenylmagnesium bromide, only 1,4-addition of the reagent takes place to the conjugation created by the attachment of an exocyclic C=C bond in the 5-position of a heterocyclic ring having a carbonyl function, with the formation of IIb ($R = R'' = C_6H_5$; $R' = H$), this behaviour being analogous to that of ($R = R' = C_6H_5$) towards the same reagent.[1a]

The structure of III ($R = R' = C_6H_5$) which is taken as typical of the Grignard products, is inferred from the fact that it is colourless, gives the correct analytical values, and yields benzophenone upon oxidation with chromic acid. The IR spectrum of III ($R = R' = C_6H_5$) exhibits absorption bands at 1650 cm^{-1} and 1532 cm^{-1} (imide I and II bands), 3325 cm^{-1} (—NH stretching), and 3680 cm^{-1} (—OH stretching). Compound Ic has an intense band at 1690 cm^{-1} (C=O stretching) and 1645 cm^{-1} (C=N stretching). The shift in carbonyl absorption is consistent with the removal of the exocyclic double bond in the 5-position and the disappearance of the C=N band is in favour of the proposed structure.

The assigned structure for the adduct IIc is supported by the fact that it is colourless, gives the correct analytical values, and the formation of benzophenone upon oxidation with chromic acid. Hydrolytic cleavage of the exocyclic C=N bond takes place upon treatment with a mixture of hydrochloric and acetic acids, yielding the known IIb ($R = R' = C_6H_5$).[1a] Additional support for the structure is given by the presence of a band of medium intensity at 1610 cm^{-1} (C=O stretching), 1645 cm^{-1} (C=N stretching,) and the absence of —NH absorption. The IR spectrum of Id exhibits absorption at 1750 cm^{-1} (C=O stretching). This shift in carbonyl absorption is consistent with removal of the exocyclic double bond in the 5-position.

Further study of the behaviour of IVa and IVb toward the action of phenylmagnesium bromide has also been undertaken. 1,2-Addition of the reagent to the carbonyl group of the hetero-ring in IVa takes place, followed by elimination of water upon hydrolysis, with the formation of 5-methyl-4-phenyl-2-phenylaminothiazole (Va, or its tautomeric form). On the other hand, the hetero-ring opening in IVb

[2] Cf. the alkylation of the salts of stable isomers of 2-arylimino-4-thiazolidinones to a mixture and the predominance of the acid-soluble 2-substituted amino-2-thiazolin-4-ones [F. B. Dains and S. I. Davis, *Univ. Kansas Sci. Bull.* **24**, 25 (1936); *Chem. Abstr.*, **32**, 3397 (1938); F. B. Dains and F. F. Eberly, *J. Amer. Chem. Soc.* **55**, 3859 (1933); *Ibid.* **57**, 2627 (1935); *Ibid.* **58**, 2544 (1936)].

TABLE 1. 5-ARYLIDENE-2-PHENYLIMINO-4-THIAZOLIDINONES (Ic)

Arylidene derivative (Ic) R=	Time of reflux hr.	Colour	M.p.,[a]	Yield, %	Formula	Carbon, % Found	Carbon, % Calc.	Hydrogen, % Found	Hydrogen, % Calc.	Nitrogen, % Found	Nitrogen, % Calc.	Sulphur, % Found	Sulphur, % Calc.
C_6H_5	2	yellow	254	73	$C_{16}H_{12}ON_2S$	68·33	68·57	4·44	4·29	9·71	10·00	11·33	11·43
$C_6H_4CH_3$-*m*	3	pale yellow	220	75	$C_{17}H_{14}ON_2S$	68·98	69·39	4·95	4·76	9·65	9·52	10·61	10·88
C_6H_4OH-*o*	1	yellow	255	71	$C_{16}H_{12}O_2N_2S$	64·42	64·86	4·11	4·05	9·25	9·46	10·55	10·81
C_6H_4OH-*p*	1	yellow	304	72	$C_{16}H_{12}O_2N_2S$					9·18	9·46	10·62	10·81
$C_6H_4OCH_3$-*o*	4	pale brown	228	75	$C_{17}H_{14}O_2N_2S$	65·46	65·81	4·66	4·52	8·91	9·03	9·95	10·33
$C_6H_4OCH_3$-*p*	2	yellow	252	72	$C_{17}H_{14}O_2N_2S$	65·64	65·81	4·61	4·52	9·32	9·03	10·06	10·33
$C_6H_4OC_2H_5$-*o*	3	orange	225	69	$C_{18}H_{16}O_2N_2S$					8·41	8·64	9·59	9·88
C_6H_4Cl-*o*	3	pale yellow	222	74	$C_{16}H_{11}ON_2SCl$[b]					*8·68*	*8·90*	9·96	*10·11*
C_6H_4Cl-*p*	3	pale brown	290	75	$C_{16}H_{11}ON_2SCl$	61·18	61·05	3·72	3·50	8·54	8·90	9·96	10·11
$C_6H_4NO_2$-*m*	1	pale brown	292	70	$C_{16}H_{11}O_3N_3S$					12·76	12·92	9·75	9·85
$CH=CHC_6H_5$	2	yellow	245	68	$C_{18}H_{14}ON_2S$					9·01	9·15	10·31	10·46

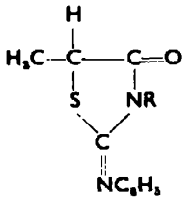
[a] M.ps. are uncorrected. [b] Cl, found: 11·18; Calc.: 11·29

TABLE 2. 2-ANILINO-2-ARYL-5-DIARYLMETHYL-4-THIAZOLIDINONES (III)

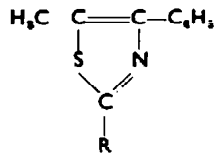
Grignard product (III) R=	R'=	Solvent of crystallization	M.p.,[a]	Yield %	Formula	Carbon, % Found Calc.	Hydrogen, % Found Calc.	Nitrogen, % Found Calc.	Sulphur, % Found Calc.
C_6H_5	C_6H_5	A	225	71	$C_{28}H_{24}ON_2S$	77·13 77·06	5·39 5·50	6·34 6·42	7·33 7·34
C_6H_5	$C_6H_4CH_3$-*p*	A	146	68	$C_{29}H_{26}ON_2S$	77·24 77·59	5·96 6·03	5·91 6·03	5·91 6·89
C_6H_5	$CH_2C_6H_5$	B	270	71	$C_{29}H_{26}ON_2S$	77·24 77·59	5·96 6·03	5·91 6·03	7·28 6·89
C_6H_5	$C_{10}H_7$-α	B	255	65	$C_{32}H_{26}ON_2S$			5·18 5·22	6·11 5·97
$C_6H_4CH_3$-*m*	C_6H_5	B	208	72	$C_{29}H_{26}ON_2S$	76·88 77·33	5·53 5·78	6·16 6·22	6·63 7·11
$C_6H_4OCH_3$-*p*	C_6H_5	A	234	66	$C_{29}H_{26}O_2N_2S$			5·69 6·01	7·22 6·87
$C_6H_4OC_2H_5$-*o*	C_6H_5	B	128	64	$C_{30}H_{28}O_2N_2S$			5·91 5·83	5·94 6·67
C_6H_4Cl-*o*	C_6H_5	B	282	70	$C_{28}H_{23}ON_2SCl$[c]				6·89 6·80
C_6H_4Cl-*p*	C_6H_5	B	215	71	$C_{28}H_{23}ON_2SCl$	71·28 71·41	5·06 4·89	5·96 5·95	6·53 6·80
C_6H_4Cl-*p*	$CH_2C_6H_5$	B	238	69	$C_{29}H_{25}ON_2SCl$[d]			5·76 5·62	6·40 6·42

[a] M.ps. are uncorrected. [b] A, alcohol; B, acetic acid. [c] Found: Cl, 7·78; Calc.: 7·55. [d] Found: Cl, 7·10; Calc.: 7·10.

has been effected by treatment with the same reagent and formation of N,N'-diphenylbenzamidine.



IVa, R = H
b, R = C_6H_5



Va, R = NHC_6H_5
b, R = OH

The structure of Va, established by analytical and spectral data as well as by independent synthesis, is supported by the presence of a band of medium intensity at 1640 cm^{-1} (C=N stretching) and the absence of C=O absorption. Compound Va was synthesized, according to the procedure for 2-aminothiazoles,[3] via treatment of phenylthiourea and propiophenone with sulphuryl chloride.[4] Trials to effect the hydrolytic cleavage of the exocyclic C=N bond (Cf. the tautomeric form of Va), by the action of a mixture of hydrochloric and acetic acids to yield 2-hydroxy-5-methyl-4-phenylthiazole (Vb) were unsuccessful. Compound Vb has been synthesized independently by treatment of α-bromopropiophenone with potassium thiocyanate, followed by isomerization of the α-thiocyanatopropiophenone formed to Vb[5] (or the possible tautomeric form). There is a discrepancy in the melting points reported for 5-arylidene-2-phenylimino-4-thiazolidinones (Ic). The melting points found for the arylidenes (Ic, R = C_6H_5, and $C_6H_4NO_2$-*m*) are consistent with those reported by Wheeler and Jamieson,[7] and do not agree with those reported by Bhargava *et al.*[6] Moreover, (R = $C_6H_5CH=CH$—) upon treatment with aqueous sodium hydroxide, yielded α-mercapto-β-styryl-acrylic acid, m.p. 148–151°, which agrees with that reported by Campaigne and Cline[8] and differs from that reported by Bhargava *et al.*[6] In the case of Id Ladna[9] reported m.p. 208–211°; Ahuja and Dutt[10] reported for the same substance m.p. 158° and in our hands, Id melts at 217°. In this investigation a mixture of glacial acetic acid and fused sodium acetate was used as the condensing agent.

EXPERIMENTAL

5-Arylidene-2-phenylimino-4-thiazolidinones (Ic)

General procedure. A mixture of 2-phenylimino-4-thiazolidinone[11] (1·92 g, 0·01 mole), the appropriate aromatic aldehyde (0·01 mole), fused sodium acetate (1·5 g), and glacial acetic acid

[3] Cf. R. C. Elderfield, *Heterocyclic Compounds* Vol. V, p. 557. Wiley and Sons, New York, N.Y. (1957).
[4] L. H. Conover and D. S. Tarbell, *J. Amer. Chem. Soc.* **72**, 5221 (1950).
[5] Cf. J. T. Gregory and R. A. Mathes, *J. Amer. Chem. Soc.* **74**, 1719 (1952).
[6] P. N. Bhargava, K. N. P. Permeswaran, and S. Venkatarman, *J. Indian Chem. Soc.* **35**, 161 (1958).
[7] H. L. Wheeler and J. S. Jamieson, *J. Amer. Chem. Soc.* **25**, 366 (1903).
[8] E. E. Campaigne and R. E. Cline, *J. Org. Chem.* **21**, 32 (1956).
[9] L. Y. Ladna, *Farm. Zh.* **15**, No. 1, 9 (1960); *Chem. Abstr.* **55**, 14432 (1961).
[10] D. F. Ahuja and S. Dutt, *J. Indian. Chem. Soc.* **28**, 12 (1951).
[11] H. K. Pujari and M. K. Rout, *J. Indian Chem. Soc.* **82**, 431 (1955).

(20 ml) was refluxed for the time recorded in Table 1, and left overnight. The crystals which separated, were washed with hot water, and recrystallized from glacial acetic acid. The compounds (Ic) listed in Table 1, are all insoluble in NaOH aq. and give orange colour with conc H_2SO_4.

According to the procedure of Bhargava *et al.*[6] for the preparation of Ic (R = C_6H_4 OH-*o*), the solid insoluble after extraction with alcohol was crystallized from acetic acid, m.p. 255°. Evaporation of the alcohol gave a small amount of solid material which was crystallized from acetic acid, m.p. 255° and not 192° as reported by Bhargava *et al.*

Compound Ic (R = C_6H_5CH = CH—) was hydrolysed with NaOH according to Bhargava *et al.*[6], and the m.p. of the crude α-mercapto-β-styrylacrylic acid obtained, was 148–151°, in agreement with that reported by Campaigne and Cline,[8] and not as described by Bhargava *et al.*

Action of Grignard reagents on Ic. To a Grignard solution (prepared from 1·0 g Mg and the appropriate quantity of the aryl halide in 150 ml dry ether), was added a suspension of the 5-arylidene-2-phenylimino-4-thiazolidinone (1·5 g) in dry benzene (50 ml). The reaction mixture was refluxed for 1 hr and kept overnight at room temp. It was then decomposed with saturated NH_4Cl aq. (100 ml) extracted with ether and the latter dried and evaporated. The oily residue was washed with pet. ether (b.p. 40–60°) till it solidified and then crystallized from the proper solvent (cf. Table 2).

The Grignard products (III), listed in Table 2, are all colourless, give no colour with $FeCl_3$, and develop a red colour with conc H_2SO_4.

Action of chromic acid on III (R = R′ = C_6H_5). A mixture of 2-anilino-5-diphenylmethyl-2-phenyl-4-thiazolidinone (1·0 g) chromic acid (1·0 g) and glacial acetic acid (20 ml) was heated on a water-bath for 2 hr and left overnight. The reaction mixture was then poured into ice-cold water and extracted with ether. The oily residue, obtained on evaporating the ether, was dissolved in alcohol and the solution treated with 2,4-dinitrophenylhydrazine. The yellow crystals (0·5 g) obtained, proved to be benzophenone 2,4-dinitrophenylhydrazone (m.p. and mixed m.p.).

Attempted hydrolysis of 2-anilino-5-diphenylmethyl-2-phenyl-4-thiazolidinone

(a) *With sulphuric acid.* A solution of the thiazolidinone (0·5 g) in conc H_2SO_4 (10 ml) after keeping overnight at room temp, was poured over crushed ice. The solid, which separated, recrystallized from acetic acid, and proved to be unchanged thiazolidinone (m.p. and mixed m.p.).

(b) *With sodium hydroxide.* To a suspension of the thiazolidinone (0·5 g) in alcohol (10 ml), 10 ml NaOH aq. (10%) was added and the mixture refluxed 1 hr. The product as before, proved to be unchanged thiazolidinone.

(c) *With acetic-hydrochloric acid mixture.* A suspension of the thiazolidinone (0·5 g) in a mixture of acetic acid (10 ml) and conc HCl aq. (10 ml) was refluxed for 2 hr and allowed to cool. The hydrochloride of 2-anilino-5-diphenylmethyl-2-phenyl-4-thiazolidinone, which separated, was recrystallized from acetic acid, m.p. 210° (yield, 0·4 g) (Found: N, 5·88; Cl, 7·31. $C_{28}H_{25}ON_2SCl$ requires: N, 5·93; Cl, 7·51%).

Action of Ph Mg Br *on* Id. To a solution of Ph Mg Br (prepared as above), a suspension of Id (2 g), prepared after Ladna,[12] was added in dry ether (100 ml). The reaction mixture after keeping overnight at room temp, yielded a solid which crystallized from alcohol, m.p. 198° (yield 1·5 g) (Found: C, 77·31; H, 5·11; N, 6·15; S, 7·17. $C_{28}H_{22}ON_2S$ requires: C, 77·42; H, 5·05; N, 6·45; S, 7·37%).

Compound IIc is insoluble in NaOH aq. and gives no colour with either $FeCl_3$ or conc H_2SO_4.

Action of chromic acid on IIc. Treatment of IIc with chromic acid afforded benzophenone which was identified as its 2,4-dinitrophenylhydrazone.

Action of acetic-hydrochloric acid mixture on IIc. A suspension of IIc (0·5 g) in a mixture of acetic acid (10 ml) and conc HCl aq. (10 ml) was refluxed for 2 hr, allowed to cool, and poured into ice-cold water. The product (0·3 g) recrystallized from alcohol m.p. 156°, alone or when mixed with an authentic sample of IIb (R = R′ = R″ = C_6H_5).[13a]

Action of Ph Mg Br *on* Ib (R = C_6H_5; R′ = H). To a solution of Ph Mg Br, a suspension of 5-benzylidene-2,4-thiazolinedione (2·0 g)[13] in dry benzene (100 ml) was added, the mixture refluxed for 3 hr, and after standing kept overnight at room temp yielded a solid (1·4 g) which crystallized

[12] Ladna,[9] reported m.p. 208–211°; Ahuja and Dutt,[10] reported m.p. 158° for Id; found m.p. for Id 217°.

[13] D. Liebermann, J. Himbert, and L. Hengl, *Bull. soc. Chim.*, 4, 1120 (1948).

from benzene as pale yellow crystals, m.p. 154° (Found: C, 68·26; H, 4·42; N, 5·09; S, 11·39. $C_{16}H_{13}O_2NS$ requires: C, 67·84; H, 4·63; N, 4·95; S, 11·30%).

Compound IIb (R = R″ = C_6H_5, R′ = H) is insoluble in NaOH aq. and gives an orange colour with H_2SO_4.

Action of PhMgBr *on* IVa. The reaction was carried out and worked up as described for Ic. The product was crystallized from alcohol, m.p. 168° (Found, C, 72·27; H, 5·27; N, 10·43; S, 11·94. $C_{16}H_{14}N_2S$ requires: C, 72·18; H, 5·26; N, 10·53; S, 12·03%).

Compound Va is insoluble in NaOH aq. and gives a pale brown colour with H_2SO_4. An authentic sample of Va was prepared according to Conover and Tarbell[4] as follows: Sulphuryl chloride (11·3 g) was added dropwise, with cooling, to a stirred mixture of propiophenone (6·7 g), phenylthiourea (15·2 g) and chloroform (50 ml). After the addition was complete and standing 12 hr the mixture was heated on a water-bath to remove the solvent and SO_2 leaving a sticky mass, which was treated with excess NaOH aq. (5%), and extracted with ether. The solid, after evaporation of the ether crystallized from alcohol, m.p. 168°, alone or when mixed with the Grignard product (Va).

2-Hydroxy-5-methyl-4-phenylthiazole (Vb). To a hot solution of α-bromopropiophenone (21 g) in alcohol (100 ml), saturated KCNS aq. was added. The mixture was heated on a boiling water-bath for 1 hr, cooled, poured into ice-cold water and extracted with ether. Evaporation of the ether yielded the oily α-thiocyanatopropiophenone (16 g). A mixture of crude α-thiocyanatopropiophenone (11 g), glacial acetic acid (15 ml), and conc HCl aq. (2 ml) was refluxed for 8 hr, and then poured into ice-cold water. The mixture was extracted with ether. The oily residue, obtained upon evaporating the ether, solidified on trituration with alcohol. The solid (5·0 g) was filtered off and recrystallized from alcohol, m.p. 169° (Found: C, 63·07; H, 4·91; S, 16·80. $C_{10}H_9ONS$ requires: C, 62·83; H, 4·71; S, 16·75%).

Action of PhMgBr *on* IVb. The product crystallized from alcohol, m.p. 144°, alone or when mixed with an authentic sample of N,N′-diphenylbenzamidine.[14]

The IR spectra were measured using a Perkin-Elmer model 137 B.

[14] O. Doebner, *Ber. Dtsch. Chem. Res.* **15**, 233 (1882).