A NEW APPROACH TO 5-ARYLIDENETHIAZOLIDIN-4-ONES

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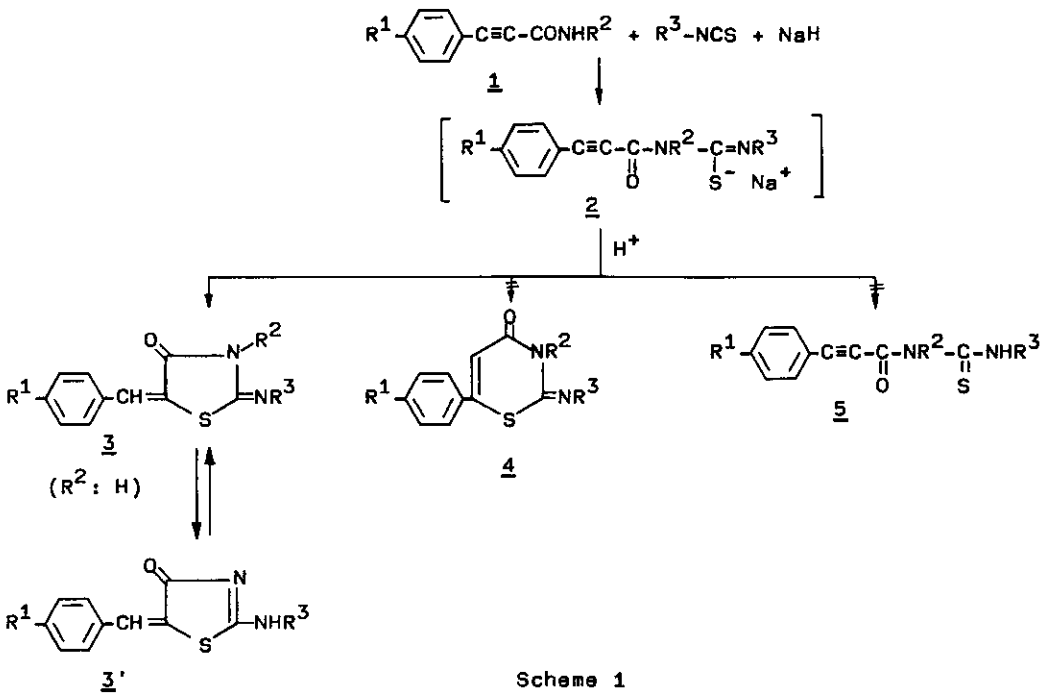
Abstract - Reaction of 3-phenylpropynamides with heterocumulenes in the presence of a base yields 5-arylidenethiazolidin-4-ones by intramolecular nucleophilic addition to the α-carbon of the C≡C triple bond.

Since the reaction of methyl phenylpropynoate with N-substituted or N,N'-disubstituted thioureas leads to 2,3-dihydro-2-alkyl(aryl)imino-6-phenyl-1,3-thiazin-4-ones (4)[1], 3-phenylpropynamides (1) should also be appropriate building blocks for the synthesis of this class of substances. Contrary to expectations based on the preparation of 2-thioxoperhydro-1,3-thiazin-4-ones by dithiocarboxylation of cinnamamides [2] and on studies of the reaction of heterocumulenes with 2-arylacetylene-1-sulfonamides [3] the reaction of 1 with isothiocyanates in the presence of a base (NaH or KOH) does not give the desired 2,3-dihydro-1,3-thiazin-4-ones (4). The alternative formation of the acyl thioureas 5 can also be excluded (Scheme 1). Surprisingly, it appeared that intramolecular nucleophilic addition of the sulfur atom in 2 had actually occurred to the α-carbon of the C≡C triple bond to provide 2-alkyl(aryl)imino-5-arylidenethiazolidin-4-ones (3). They were isolated as the only reaction products. The formation of five-membered ring products was confirmed by comparison with thiazolidin-4-ones prepared *via* independent methods from haloacetic acid or their derivatives and thioureas followed by condensation with aromatic aldehydes [4,5]. The structures of 3 are also consistent with the ir, ^{1}H nmr and mass spectroscopic data. Comparing these data of the compounds 3 and 4 [1] shows significant differences. There is a downfield shift of the olefinic proton in 3 (δ 7.70-7.85 ppm) whereas the H_5-signal of the 1,3-thiazin-4-ones 4 appears at δ 6.80-6.95 ppm. In the mass spectra of 3 the fragment R^1-C_6H_4-$CS^{]+\cdot}$, typical for 4, is missing.

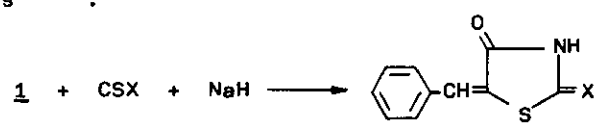


Scheme 1

The existence of the tautomeric amino form 3' (R^2: H) depends on the substituent R^3 and the solvent used [6,7].

The compounds 3i-k are also available from the unsubstituted 3-phenylpropynamide (1; R^1=R^2: H), an isothiocyanate in the basic system sodium hydride/dimethylformamide and methylation.

Replacing isothiocyanate by carbon disulfide or carbon oxide sulfide yields 2-thioxothiazolidin-4-one 6a and thiazolidine-2,4-dione 6b, respectively (Scheme 2). These compounds are identical with those prepared after well-known procedures [8-10].



6a (X: S)

(R^1=R^2: H) 6b (X: O)

Scheme 2

The fact that all reactions took a course to five-membered rings is in accordance with the recently described first example of an intramolecular anti-Michael addition of a carbanion to an acetylenic amide to produce pyrrolidinones [11].

EXPERIMENTAL

2-Alkyl(aryl)imino-5-arylidenethiazolidin-4-ones (3a-h); General Procedure. Sodium hydride (0.24 g, 10 mmol) is added portionwise to a stirred solution of 3-phenylpropynamide (1; 10 mmol) and of the isothiocyanate (10 mmol) in dry dimethylformamide (40 ml). Stirring is continued at room temperature for 3 h. The mixture is poured into ice-water (400 ml) and carefully acidified to pH 5 with 10% aqueous hydrochloric acid precipitating the products 3a-h. They are filtered, dried, and recrystallized from an appropriate solvent.

2-Alkyl(aryl)imino-5-benzylidene-3-methylthiazolidin-4-ones (3i-k). Method A: 3-Phenylpropynamide (1; 2.9 g, 20 mmol) and isothiocyanate (20 mmol) are dissolved in dry dimethylformamide (80 ml) adding sodium hydride (0.48 g, 20 mmol), and stirring is continued for 30 min. After having added some more sodium hydride (0.48 g, 20 mmol) methyl iodide (2.9 g, 20 mmol) is added dropwise to the reaction mixture that should be stirred at room temperature for 1 h and worked up as mentioned above.
Method B: A solution of N-methyl-3-phenylpropynamide (1; 3.2 g, 20 mmol) in dry dimethylformamide (80 ml) is stirred and the appropriate isothiocyanate (20 mmol) is added. Sodium hydride (0.48 g, 20 mmol) is added in portions and stirring is continued at room temperature for 3 h. Working up as described for 3a-h.

5-Benzylidene-2-thioxothiazolidin-4-one (6a). According to the preparation of 3, a solution of 3-phenylpropynamide (1; 2.2 g, 15 mmol) in dry dimethylformamide (45 ml) reacts with carbon disulfide (1.14 g, 15 mmol) and sodium hydride (0.36 g, 15 mmol); yield: 1.85 g (57%); mp 204-206°C (water or carbon tetrachloride); lit.[8] mp 200°C; ms: m/z 221 (M^+); ^{1}H nmr (acetone-d_6/HMDS$_{int.}$) δ 7.40-7.60 ppm (m, 6H, arom, -CH=); ^{13}C nmr (acetone-d_6) δ 126.8, 130.2, 131.3, 131.5, 132.6, 134.3, 169.6, 196.0 ppm; Anal. Calcd. for $C_{10}H_7NOS_2$: C, 54.24; H, 3.19; N, 6.33. Found: C, 54.02; H, 3.19; N, 6.21.

Table 1. 5-Arylidene-thiazolidin-4-ones 3a-k

3	R^1	R^2	R^3	Yield %	mp °C (solvent)	Molecular Formula	Microanalyses Calcd. (Found) C	H	N
a	H	H	CH_3	59	231-233 (methanol)	$C_{11}H_{10}N_2OS$ (218.3)	60.53 (60.57)	4.62 (4.62)	12.84 (12.75)
b	H	H	n-C_3H_7	65	183-185 (benzene)	$C_{13}H_{14}N_2OS$ (246.3)	63.39 (63.57)	5.73 (5.90)	11.37 (11.01)
c	H	H		68	259-261 (ethanol)	$C_{16}H_{18}N_2OS$ (286.4)	67.10 (67.15)	6.34 (6.49)	9.78 (9.56)
d	H	H	CH_2=CH-CH_2	58	168-170 (benzene/ ether) lit.[5] 165	$C_{13}H_{12}N_2OS$ (244.2)	63.91 (63.66)	4.95 (5.07)	11.47 (11.46)
e	H	H	C_6H_5	74	261-263 (methanol) lit.[6] 261	$C_{16}H_{12}N_2OS$ (280.3)	68.55 (68.56)	4.31 (4.34)	9.99 (9.83)
f	H	H	3-CH_3-C_6H_4	60	201-203 (benzene/ hexane)	$C_{17}H_{14}N_2OS$ (294.4)	69.36 (69.59)	4.79 (4.77)	9.52 (9.25)
g	CH_3O	H	C_6H_5	57	256-258 (ethanol)	$C_{17}H_{14}N_2O_2S$ (310.3)	65.79 (65.65)	4.55 (4.52)	9.02 (8.68)
h	CH_3O	H	CH_2=CH-CH_2	65	185-186 (benzene)	$C_{14}H_{14}N_2O_2S$ (274.3)	61.29 (61.03)	5.14 (5.16)	10.21 (9.98)
i	H	CH_3	n-C_3H_7	76(A) 61(B)	85-87 (ethanol/ water)	$C_{14}H_{16}N_2OS$ (260.3)	64.58 (64.48)	6.19 (6.45)	10.76 (10.64)
j	H	CH_3	C_6H_5	68(A) 56(B)	132-134 (ethanol) lit.[6] 130	$C_{17}H_{14}N_2OS$ (294.4)	69.35 (69.62)	4.79 (4.84)	9.52 (9.43)
k	H	CH_3	CH_3	50(B)	111-112 (ethanol/ water) lit.[12] 113	$C_{12}H_{12}N_2OS$ (232.3)	62.04 (61.86)	5.21 (5.10)	12.06 (12.00)

Table 2. Spectroscopic data for compounds listed in table 1

3	ir (Nujol)[a] ν [cm^{-1}]	^{1}H nmr (DMSO-d_6/HMDS int.)[b] δ [ppm]	ms[c] m/z (rel. intensity, %)
a	1600, 1635, 1690	3.31 (s,3H,CH_3); 7.60-7.85 (m,6H,arom,-CH=)	218 (M^+,75); 162 (11); 134 (100)
b[d,e]	1605, 1640, 1695	0.95 (t,3H,CH_3); 1.66 (m,2H, CH_2); 3.55 (t,2H,NCH_2); 7.20-7.50 (m,5H,arom); 7.62 (s,1H,-CH=); 9.30 (br,s,NH)	246 (M^+,72); 231 (6); 217 (76); 204 (54); 162 (40); 134 (100)
c	1580, 1630, 1680	1.35-2.24 (m,11H,C_6H_{11}); 7.51-7.80 (m,6H,arom,-CH=)	286 (M^+,17); 204 (17); 162 (5); 134 (100)
d	1605, 1625, 1695	4.35 (m,2H,CH_2); 5.25-5.55 (m,2H,CH_2=); 6.00-6.31 (m,1H,-CH=CH_2); 7.50-7.81 (m,5H,arom); 7.84 (s,1H,-CH=)	244 (M^+,63); 217 (27); 162 (29); 134 (100)
e	1645, 1680	7.10-7.80 (m,11H,arom,CH=)	280 (M^+,73); 163 (51); 134 (100)
f	1600, 1650, 1700, 3100-3180	2.50 (s,3H,CH_3); 6.95-7.90 (m,10H,arom,-CH=)	294(M^+,83); 163 (33); 135 (38); 134 (100)
g	1640, 1675	3.98 (s,3H,CH_3); 7.10-7.80 (m,10H,arom,-CH=)	310 (M^+,35); 193 (18); 164 (100); 149 (31)
h	1600, 1630, 1690	4.00 (s,3H,CH_3); 4.37 (m, 2H,CH_2); 5.30-5.58 (m,2H, CH_2=); 5.94-6.28 (m,1H, -CH=); 7.19-7.31 (m,2H, arom); 7.61-7.80 (m,3H, arom,-CH=)	274 (M^+,41); 192 (58); 164 (100)
i[d,f]	1605, 1650, 1705	0.95 (t,3H,CH_3); 1.68 (m,2H, CH_2); 3.20 (s,3H,NCH_3); 3.28 (t,2H,NCH_2); 7.20-7.45 (m,5H,arom); 7.61 (s,1H,-CH=)	260 (M^+,21); 231 (55); 134 (100)

j[g]	1605, 1645, 1710	3.34 (s,3H,NCH_3); 6.75-7.40 (m,10H,arom); 7.52 (s,1H, -CH=)	294 (M^+,84); 134 (100); 132 (86)
k	1610, 1655, 1705	3.18 (s,3H,CH_3); 3.23 (s, 3H,CH_3); 7.20-7.50 (m,5H,arom); 7.61 (s,1H,-CH=)	232 (M^+,95); 162 (3); 134 (100)

[a] Recorded on a C. Zeiss Specord ir spectrometer.

[b] Measured at 100 MHz using a Varian HA-100 spectrometer.

[c] Recorded on a EA-spectrometer (v. Ardenne, Dresden).

[d] ^1H nmr in $CDCl_3$.

[e] ^{13}C nmr ($CDCl_3$, 50.327 MHz, Bruker WP-200): δ 11.3; 22.6; 47.3; 126.7; 129.0; 129.5; 129.8; 131.5; 134.1; 177.1; 179.3 ppm.

[f] ^{13}C nmr ($CDCl_3$, 50.327 MHz, Bruker WP-200): δ 11.7; 23.9; 29.3; 54.7; 121.8; 128.8; 129.3; 129.7; 134.0; 148.1; 166.6 ppm.

[g] ^1H nmr in CCl_4.

5-Benzylidenethiazolidine-2,4-dione (6b). Sodium hydride (0.36 g, 15 mmol) is added in portions to a cooled solution of 3-phenylpropynamide (1; 2.2 g, 15 mmol) in dry dimethylformamide (45 ml). After 0.5 h a moderately strong stream of carbon oxide sulfide (2.4 g, 40 mmol) is bubbled through the reaction mixture at 0°C. Stirring is continued at room temperature for 3 h and the mixture is worked up as described above; yield: 1.5 g (47%); mp 244-246°C (ethanol); lit.[10] mp 242°C; ms: m/z 205 (M^+); ^1H nmr (DMSO-d_6/HMDS int.) δ 7.40-7.65 (m,5H,arom); 7.83 ppm (s,1H,-CH=); Anal. Calcd. for $C_{10}H_7NO_2S$: C, 58.53; H, 3.44; N, 6.83. Found: C, 58.65; H, 3.41; N, 6.71.

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