A Facile, One-Step Synthesis of 3-Alkyl- or 3-Aryl-4-methyl-2-(substituted-methylene)-2,3-dihydro-1,3-thiazoles

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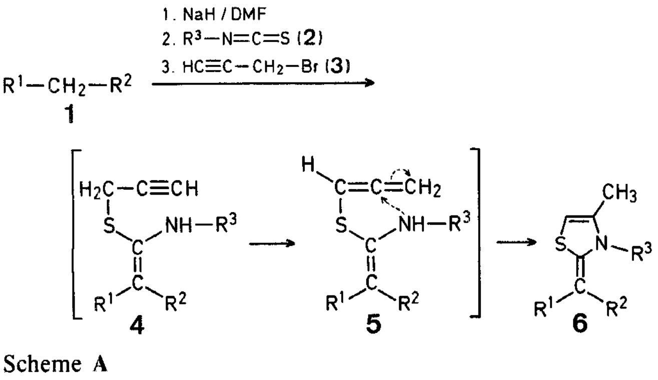
In connection with our previous work[1], it was intended to prepare and study the sigmatropic rearrangements of *S,N*-propargyl acetals **4**. However when acetophenone (**1a**) was reacted with phenyl isothiocyanate (**2**; $R^3=C_6H_5$) and propargyl bromide (**3**) in the presence of sodium hydride, the product obtained was characterised as 3-phenyl-4-methyl-2-(benzoylmethylene)-2,3-dihydro-1,3-thiazole (**6a**). Apparently, the thiazoline **6a** is formed by isomerisation and ring closure of the *S,N*-propargyl acetal **4** (Scheme A). The reaction was found to be general and the thiazolines **6b-d** were obtained from the respective ketones in good yields (Table).

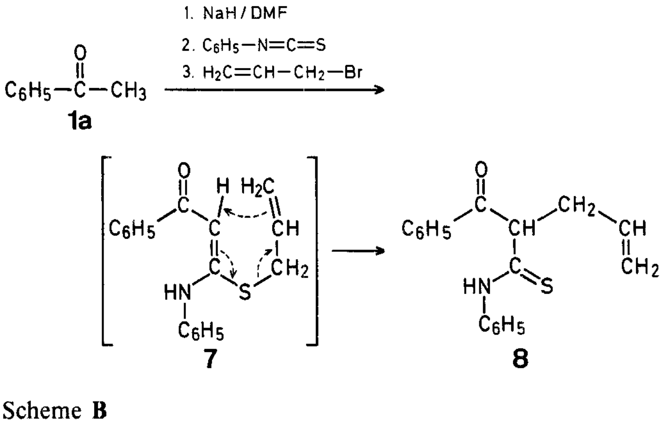


Scheme A

Other active methylene compounds like phenylacetonitrile and acetylacetone gave the corresponding thiazolines **6e** and **6f** respectively. The 3-*N*-ethylthiazoline derivatives **6g-j** were obtained from the corresponding **1**, ethyl isothiocyanate (**2**; $R^3=C_2H_5$) and propargyl bromide (**3**) in the presence of sodium hydride.

Reactions of acetone and nitromethane under similar conditions yielded untractable complex reaction mixtures, from which the desired thiazolines could not be isolated.

When **1a** was reacted with phenyl isothiocyanate and allyl bromide in the presence of sodium hydride, the corresponding α-benzoyl-α-allylthioacetanilide **8** was obtained. The thioacetanilide **8** is formed by thio-Claisen rearrangement of the *S,N*-allyl acetal **7** (Scheme **B**).



Scheme **B**

Three methods for the preparation of these thiazoline derivatives are reported in the literature. In the first method[2], the corresponding *N*-substituted thioamides are condensed with the respective α-halocarbonyl compounds. However, this method requires prior preparation of thioamides and yields are low in the case of 4-methyl derivatives. In the second method[1], 3-alkyl- or 3-aryl-4,5-substituted-2-(benzoylmethylene)-dihydro-1,3-thiazoles are obtained in low yields by base-catalysed elimination of sulfur from the corresponding 2-phenacylthiothiazolium salts. The third method[4] involves acylation of 2-methylthiazolium salts with dialkyl 1-oxoalkanephosphonates.

The present method, therefore, provides a novel route to the hitherto inaccessible 3-aryl- or 3-alkyl-4-methylthiazolineylidene derivatives directly from the active methylene compounds in good yields.

3-Alkyl- or 3-Aryl-4-methyl-2-(substituted-methylene)-2,3-dihydro-1,3-thiazoles 6a-j; General Procedure:

To an ice-cooled and well stirred suspension of sodium hydride (2.0 g, 0.04 mol, 50% suspension) in dry dimethylformamide (40 ml), compound **1** (0.04 mol) in dimethylformamide (5 ml) is added followed by subsequent addition of aryl or alkyl isothiocyanate **2** (0.04 mol) in dimethylformamide (8 ml). The ice-cooled reaction mixture is further stirred for 2 h and propargyl bromide (**3**; 4.8 g, 0.041 mol) in dimethylformamide (10 ml) is slowly added during 30 min. After further stirring with cooling for 1.5-2 h, the reaction mixture is poured over crushed ice (250 g) and extracted with chloroform (3 × 150 ml). The organic layer is washed with water (3 × 150 ml), dried with sodium sulfate and evaporated to give a brown viscous residue. Pure thiazolines are isolated either by trituration with hexane and dichloromethane (**6a-6f, 6j**) or by passing through silica gel column and eluting with 3 : 7 ethyl acetate/hexane (**6g-i**). The thiazolines **6a-j** are recrystallised from dichloromethane/hexane.

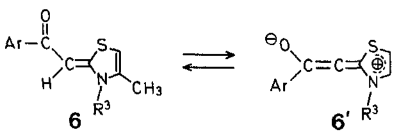
Table. 3-Alkyl- or 3-Aryl-4-methyl-2-(substituted-methylene)-2,3-dihydro-1,3-thiazoles **6a–j**

Product No.	R^1	R^2	R^3	Yield[a] [%]	m.p. [°C]	Molecular formula[b]	I.R. (nujol) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$) δ [ppm]	M.S. m/e (M$^+$)
6a	C_6H_5—CO	H	C_6H_5	71	159–160°	$C_{18}H_{15}NOS$ (293.4)	1590 (w); 1560 (m)[c]	1.92 (s, 3 H); 5.92 (br. s, 1 H); 6.14 (s, 1 H); 7.05–7.85 (m, 10 H)	293
6b	4-H_3C—C_6H_4—CO	H	C_6H_5	68	188–190°	$C_{19}H_{17}NOS$ (307.4)	1595 (w); 1585 (w); 1550 (m)[c]	1.90 (s, 3 H); 2.32 (s, 3 H); 5.88 (s, 1 H); 6.10 (s, 1 H); 6.75–7.8 (m, 9 H)	307
6c	4-H_3CO—C_6H_4—CO	H	C_6H_5	73	154–155°	$C_{19}H_{17}NO_2S$ (323.4)	1601 (w); 1585 (w); 1550 (m)[c]	1.87 (s, 3 H); 3.72 (s, 3 H); 5.80 (s, 1 H); 5.72 (br. s, 1 H); 5.98 (s, 6.5–7.4 1 H); (A_2B_2, 4 H); 7.45–7.7 (m, 5 H)	323
6d	4-Cl—C_6H_4—CO	H	C_6H_5	65	174–175°	$C_{18}H_{14}ClNOS$ (327.8)	1601 (w); 1584 (w); 1552 (m)[c]	1.90 (s, 3 H); 5.82 (s, 1 H); 6.15 (s, 1 H); 7.05–7.75 (m, 9 H)	327 (^{35}Cl)
6e	C_6H_5	—CN	C_6H_5	83	153°	$C_{18}H_{14}N_2S$ (290.4)	2172 (CN); 1595 (m); 1547; 1520	1.80 (s, 3 H); 5.63 (s, 1 H); 7.05–7.6 (m, 10 H)	290
6f	H_3C—CO	H_3C—CO	C_6H_5	75	146–147°	$C_{15}H_{15}NO_2S$ (273.4)	1695 (m); 1622 (s)	1.90 (s, 3 H); 1.98 (s, 3 H); 6.45 (s, 1 H); 7.1–7.55 (m, 5 H)	273
6g	C_6H_5—CO	H	C_2H_5	67	112°	$C_{14}H_{15}NOS$ (245.3)	1682 (w); 1600 (w); 1560 (s)[c,d]	1.35 (t, 3 H); 2.28 (s, 3 H); 3.89 (q, 2 H); 5.92 (s, 1 H); 6.15 (br. s, 1 H); 7.15–7.5 (m, 3 H); 7.7–8.0 (m, 2 H)	245
6h	4-H_3CO—C_6H_4—CO	H	C_2H_5	72	149–150°	$C_{15}H_{17}NO_2S$ (275.3)	1600 (w); 1587 (m); 1550 (s)[c,d]	1.31 (t, 3 H); 2.18 (s, 3 H); 3.80 (s, 3 H); 3.85 (q, 2 H); 5.95 (s, 1 H); 6.20 (s, 1 H); 6.5–7.5 (m, 4 H)	275
6i	4-Cl—C_6H_4—CO	H	C_2H_5	69	145°	$C_{14}H_{14}ClNOS$ (279.8)	1600 (m); 1593 (m); 1585 (s)[c,d]	1.22 (t, 3 H); 2.13 (s, 3 H); 3.60 (q, 2 H); 5.98 (s, 1 H); 6.15 (s, 1 H); 6.65–6.95, 7.15–7.9 (2 m, 4 H)	279 (^{35}Cl)
6j	C_6H_5	—CN	C_2H_5	82	118°	$C_{14}H_{14}N_2S$ (242.3)	2160 (CN); 1610 (w); 1595 (w); 1572 (w)	1.47 (t, 3 H); 2.15 (s, 3 H); 4.21 (q, 2 H); 5.53 (s, 1 H); 7.0–7.5 (m, 5 H)	242

[a] Yield of pure, isolated product.

[b] Satisfactory microanalyses obtained: C ±0.37, H ±0.47, N ±0.38.

[c] Absence of carbonyl group due to the existence of the dipolar form[2] **6'**:



[d] In KBr.

α-Allyl-α-benzoyl-thioacetanilide (8):

Prepared as described above from acetophenone (**1a**; 4.8 g, 0.04 mol), phenyl isothiocyanate (5.4 g, 0.04 mol), sodium hydride (2.0 g, 0.04 mol, 50% suspension), and allyl bromide (4.84 g, 0.04 mol); yield: 8.5 g (72%); m.p. 115–116 °C (from benzene/hexane); bright yellow crystals.

$C_{18}H_{17}NOS$	calc.	C 73.22	H 5.76	N 4.74
(295.4)	found	73.54	5.42	4.41

M.S.: $m/e = 295$ (M^+).

I.R. (KBr): $\nu = 3200$ (NH), 1690 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.88$ (t, 2H, $-C\underline{H}_2-CH=CH_2$); 5.0–5.9 (m, 4H, $-C\underline{H}=C\underline{H}_2$ and $CO-C\underline{H}-$); 7.2–8.2 ppm (m, $10H_{arom}$).

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