Synthesis, Crystal Structure of Some New 2-(4-Methylbenzoylimino)-3-aryl-4-methyl-1,3-thiazolines

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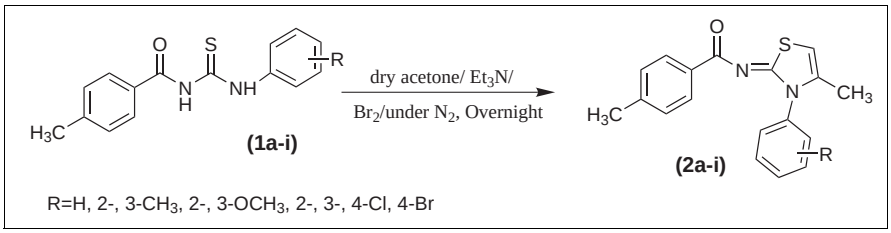

An efficient, straightforward synthesis of some new 2-(4-methylbenzoylimino)-3-aryl-4-methyl-1,3-thiazolines (**2a-i**) is described. The methodology involves the cyclization of 1-(4-methylbenzoyl)-3-arylthioureas with acetone in the presence of bromine and triethylamine. The structures were confirmed by spectroscopic data, elemental analyses and in one case (**2i**) by the single crystal X-ray diffraction data.

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Introduction.

Various 2-imino-1,3-thiazolines are associated with diverse pharmacological activities such as antimicrobial, anti-inflammatory, antihistaminic, antihypertensive, hypnotic, and anticonvulsant activity [1-6]. Thiazolidinone derivatives of rhodanine are reported to have antibacterial, antiviral, pesticidal, anti-inflammatory and anti-diabetic properties [7-10]. Synthesis of an arylalkylidene rhodanine library and the modification of the rhodanine side chain resulted in increased selectivity towards hepatitis C virus (HCV) NS3 protease [11], and bis-thiazole derivatives showed promising anticancer activity against human cell lines [12]. In addition, thiazolines have been found to display acaricidal, insecticidal, and plant growth regulators activities [13] and have also been used for the identification of human cells with positive myeloperoxidase reactivity [14]. 2-Phenylimino-1,3-thiazoline-4-acetanilides have shown significant antifungal activity against rice blast *Pyricularia oryzae*, thus can be used as agrochemical fungicides [15]. The condensation products of 3-aryl-4-phenyl-2-imino-4-thiazolines with 9-chloro-2,4-(un)substituted acridines exhibited interesting anti-inflammatory and analgesic activities [16]. Atropisomerism has been observed in some *N*,*N*-diaryl-2-iminothiazoline derivatives. The optically pure atropisomers were obtained by resolution and their potential use as new non-biaryl ligands for enantio-selective metal catalysis has been suggested [17]. The synthetic strategies for 2-iminothiazoles reported in the literature include the reaction of 1,2-diaza-1,3-butadienes with rhodanine affording 2-(mercaptoacetyl)imino-thiazoline derivatives and by reaction of the same reagents with chiral 1,3-oxazolidine-2-thione derivatives [7,8], alkylation of 2-aminothiazoles obtained from condensation of α-haloketones with thiourea [18], reaction of α-bromoketimines with potassium thiocyanate [19], reaction of ketones with *N*-alkyl rhodanamines or bisbenzyl formamidine disulfide [20], reaction of α-chloroketones with thiosemicarbazide in acidic medium [21] and the more recently reported synthesis of 2-imino-1,3-thiazolines from 1-arylmethyl-2-(bromomethyl) aziridines *via* ring transformation of 1-arylmethyl-2-(thiocyanomethyl)aziridines [22].

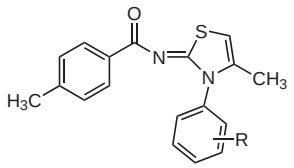


Figure 1. 2-(4-Methylbenzoylimino)-3-aryl-4-methyl-1,3-thiazolines

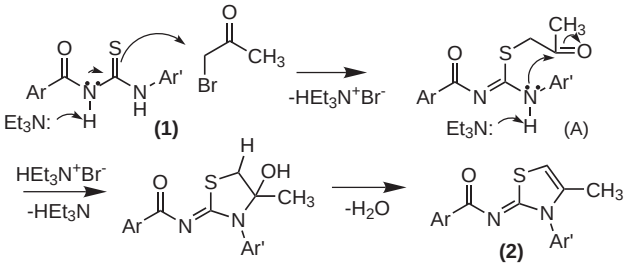
In this article, we wish to report a facile, efficient and straightforward synthesis of some new 2-(4-methylbenzoylimino)-3-aryl-4-methyl-1,3-thiazolines by cyclization of corresponding 1-(4-methylbenzoyl)-3-aryl thioureas with acetone in the presence of bromine and triethyl amine in high overall yields and without the formation of undesired side products. The crystal structure of compound (**2i**) was determined by single-crystal X-ray diffraction data.

Results and Discussion.

The synthesis of 1-(4-methylbenzoyl)-3-arylthio-ureas was carried out according to the published

procedure [23] involving treatment of 4-methyl-benzoyl chloride with potassium thiocyanate in acetone followed by reaction with suitably substituted anilines. The thioureas were characterized by typical IR absorptions at 3351, 3200 cm^{-1} for free and associated NH, at 1667 for carbonyl and at 1230-1250 for thiocarbonyl groups. The characteristic broad singlets at *ca* δ 9.0 and 12 for HN(1) and HN(3) and peaks at 170, 179 for carbonyl and thiocarbonyl were observed in the ^{1}H and $^{13}CNMR$ spectra respectively. The base-catalyzed cyclization of 1-aroyl-3-aryl-thioureas with acetone was easily achieved in presence of bromine. Thus, triethyl amine was added to a solution of 1-(4-methylbenzoyl)-3-arylthioureas (**1a-i**) in dry acetone followed by the treatment with an acetone solution of bromine to furnish the 2-(4-methylbenzoyl)imino-3-aryl-4-methyl-1,3-thiazo-lines (**2a-i**) in good to high yields (Scheme 1).

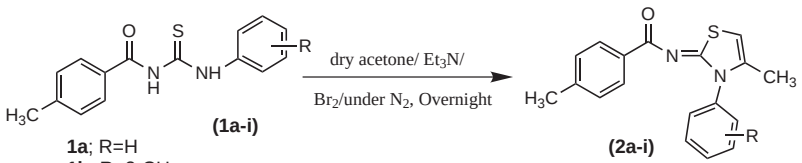
Scheme 2



Mechanism of cyclcondenation of (**1a-i**) with acetone to afford (**1a-i**)

There have been reports in literature of S/N regioselective nucleophilic competition in the synthesis of heterocycles by intramolecular cyclization reactions from the same precursor. Thus, same resonance stabilized anionic thiourea species may lead to either the 2-aroyl-imino-3-aryl-4-methyl-1,3-thiazolines (**2**)

Scheme-1



1a; R=H
1b; R=2-CH_3
1c; R=3-CH_3
1d; R=2-OCH_3
1e; R=3-OCH_3
1f; R=2-Cl
1g; R=3-Cl
1h; R=4-Cl
1i; R=4-Br

Synthesis of 2-(4-methylbenzoylimino)-3-aryl-4-methyl-1,3-thiazolines

The compounds were characterized by the absence of NH absorptions of the thiourea moiety and the appearance of the characteristic C=O and C=N absorptions at 1635-1680 and 1560-1590 cm^{-1}, respectively in the IR spectra.

In the ^{1}H-NMR spectra, the singlet for H-C(5) appeared at δ 6.30-6.45, for Me-C(4) at δ 2.0 and the AA'BB' system at 7.65-7.77 and 7.35-7.90 for the aromatic protons. $^{13}CNMR$ showed the peak for Me-C(4) at δ 15.4-15.8 ppm. In the mass spectrum, in addition to the molecular ion peak $M^{+\cdot}$ the major fragments corresponded to $[M\text{-}91]^{+}$, and the base peak at *m/z* 119 for the 4-methybenzoyl cation (Table 1).

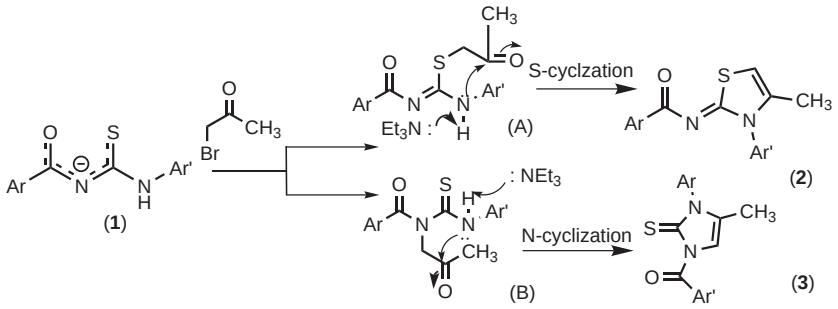
The mechanism of reaction involves the attack of anion (generated by the transfer of N-1 proton to base) to the α-carbon of the α-bromoacetone produced *in situ* to afford the intermediate (A) followed by the attack of anion from N-3 to the carbonyl group resulting in the intramolecular cyclization and dehydration to yield (**2**) (Scheme 2).

(*S*-cyclization products) *via* intermediate (A) or to the isomeric 1-aroyl-3-arylimida-zole-2-thiones (**3**) (*N*-cyclization products) *via* intermediate (B) under the conditions of thermodynamic and kinetic controls respectively (Scheme 3).

In principle, a similar cyclization of 1-aroyl-3-arylthioureas with acetaldehyde and acetophenone should also furnish the 2-aroylimino-3-aryl-1,3-thiazolines, and 2-aroylimino-3-aryl-4-phenyl-1,3-thiazolines respectively.

The crystal structure of compound (**2i**) is depicted in Figure 2. Table-2 gives the crystal data and structure refinement and the selected bond lengths and angles appear in Table-3. It crystallizes in the monoclinic space group $P2_1/c$ with unit cell parameters a = 6.905(2) Å, b = 10.839(2) Å, c = 21.906(4) Å and, α= 90°, β= 91.495(13)°, γ = 90°. The C8-O1 and C1-N2 bonds show a typical double-bond character with bond lengths

Scheme 3



Mechanism of S or N cyclization from same thiourea precursor (**1**)

1.242(3) and 1.313(3) Å, respectively and C8-N2 with bond length of 1.375(3) Å indicates a partial double-bond character.

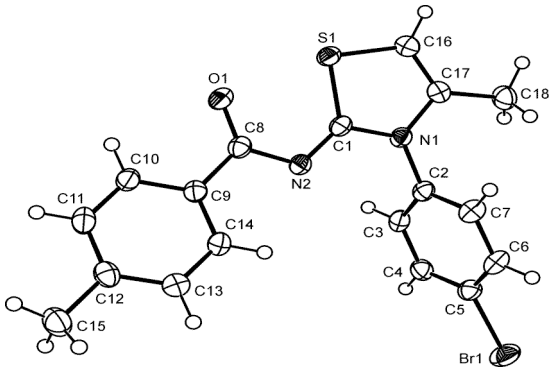


Figure 2. An ORTEP drawing of 2-(4-methylenbenzoylimino)-3-(4-bromophenyl)-4-methyl-1,3-thiazoline (**2i**) with displacement ellipsoids plotted at 50% probability level.

Table 1

Physical and spectral data for compounds **(2a-2i)**

Compd	M.P. (ºC)	Yield (%)	υ max (cm^{-1}) C=O	C=N	δ ppm C_4-H	C_5-Me	EIMS *(m/z)* M^+, M-91, $MeC_6H_4CO^+$
(2a)	178	70	1665	1591	6.38	2.06	308, 217, 119
(2b)	194	60	1680	1552	6.34	2.05	322, 231, 119
(2c)	135	58	1670	1587	6.34	2.05	322, 231, 119
(2d)	214	60	1656	1563	6.28	2.03	328, 291, 119
(2e)	222	61	1679	1581	6.30	2.02	328, 291, 119
(2f)	240	69	1639	1560	6.42	2.02	342, 253, 119
(2g)	180	65	1679	1596	6.40	2.02	342, 253, 119
(2h)	164	72	1660	1590	6.40	2.02	342, 253, 119
(2i)	182	75	1673	1562	6.45	2.07	386, 297, 119

Recrystallization Solvents: [a] ethanol, [b] ethyl acetate

Table 2

Crystal data and structure refinement for (**2i**).

Empirical formula	$C_{18}H_{15}BrN_2OS$
Formula weight	387.29
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Table 2 (continued)

Space group	$P2_1/c$
Unit cell dimensions	a = 6.905(2) Å, α = 90°. b = 10.839(2) Å, β = 91.495(13) °. c = 21.906(4) Å, γ = 90°.
Volume	1639.0(6) Å^3 Z, 4
Density (calculated)	1.570 Mg/m^3
Absorption coefficient	2.64 mm^{-1}
F(000)	784
Crystal size	0.08 x 0.06 x 0.04 mm^3
Theta range for data collection	3.5 to 27.5°.
Index ranges	-8<=h<=8, -14<=k<=14, -27<=l<=28
Reflections collected	13740
Independent reflections	3740 [R(int) = 0.045]
Completeness to theta = 27.5°	99.6 %
Absorption correction	Multi-scan method
Max. and min. transmission	0.902 and 0.817
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3740 / 0 / 209
Goodness-of-fit on F^2	1.03
Final R indices [I>2sigma(I)]	R1 = 0.034, wR2 = 0.080
R indices (all data)	R1 = 0.053, wR2 = 0.088

Table 3

Selected bond lengths [Å] and angles [°] for (**2i**).

Br(1)-C(5)	1.900(2)
S(1)-C(16)	1.736(2)
S(1)-C(1)	1.739(2)
O(1)-C(8)	1.242(3)
N(1)-C(1)	1.368(3)
N(1)-C(17)	1.413(3)
N(1)-C(2)	1.438(3)
N(2)-C(1)	1.313(3)
N(2)-C(8)	1.375(3)
C(16)-S(1)-C(1)	90.96(10)
C(1)-N(1)-C(17)	114.58(17)
C(1)-N(1)-C(2)	122.51(17)
C(17)-N(1)-C(2)	122.90(17)
C(1)-N(2)-C(8)	115.52(18)
N(2)-C(1)-N(1)	121.78(19)
N(2)-C(1)-S(1)	128.53(16)
N(1)-C(1)-S(1)	109.65(15)

Table 3 (continued)

C(7)-C(2)-C(3)	120.7(2)
C(7)-C(2)-N(1)	119.85(18)
C(3)-C(2)-N(1)	119.45(19)
C(6)-C(5)-Br(1)	118.61(18)
C(4)-C(5)-Br(1)	119.53(17)
O(1)-C(8)-N(2)	124.4(2)
O(1)-C(8)-C(9)	120.46(19)
N(2)-C(8)-C(9)	115.13(18)
N(1)-C(17)-C(18)	121.17(19)

EXPERIMENTAL

Melting points were recorded using a MEL TEMP MP-D apparatus and are uncorrected. ^{1}H NMR and the ^{13}C NMR spectra were determined in $CDCl_3$ at 400 MHz and 100 MHz respectively using a Bruker AM-400 machine. FTIR spectra were recorded on an FTS 3000 MX spectrophotometer. Mass Spectra (EI, 70eV) on a MAT 312 instrument, and elemental analyses were conducted using a LECO CHNS analyzer. Single crystal structure determination of (**2i**) was made on a Nonius KappaCCD diffractometer.

The general experimental procedure for the synthesis of compounds **2a-i** is illustrated by the synthesis of **2i**. The physical and spectral data for compounds **2a-i** are given in Table 1.

3-(4-Bromophenyl)-2-(4-methylbenzoylimino)-4-methyl-1,3-thiazoline (**2i**).

To a stirred solution of 1-(4-methylbenzoyl)-3-(4-bromophenyl)thiourea (**1i**) 0.5g (0.002 mol) in 20 ml acetone containing 0.3 ml (0.002 mol) triethylamine, was added dropwise, a solution of bromine 0.1 ml (0.002 mol) in acetone (10 ml) under nitrogen. After the addition was complete, the solution was stirred at room temperature overnight. The reaction mixture was filtered and concentrated to leave a crude solid. Recrystallization with aqueous ethanol afforded (**2i**) as colorless crystals, 0.5g (75 %), mp 182°. R_f 0.14 (petrol ether / EtOAc 7/3); ir (potassium bromide): 2938, 1673 (CO), 1600 (C=C), 1514, 1572 (C=N), 1265, 1152, 1050, 783, 736, 700 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.07 (s, 3H, C5-Me); 2.48 (s, 3H, Ar-Me); 6.45 (s, 1H, C4-H), 7.14 (2H, AA'BB'); 7.24 (2H, AA'BB'); 7.35 (2H, AA'BB'); 7.67 (2H, AA'BB'); ^{13}C nmr (deuteriochloroform): δ 15.1, 21.3, 105.2, 123.7, 128.1, 129.2, 130.0, 132.7.0, 133.8, 134.0, 137.5, 170.1, 179.0 ms: m/z 388 (7.3), 386 (7.0) (M^+), 297 (16.8), 215 (36.0), 119 (100), 91 (51), 65 (22).

Anal. Calcd for $C_{18}H_{15}BrN_2OS$: C, 55.8; H 3.90; N 7.23, S 8.28. Found: C 55.80; H 3.96; N 7.32; S 8.21.

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REFERENCES

[1] D. M. Vittoria, O. Mazzoni, E. Piscopo, A. Caligmano and A. Bolognese, *J. Med. Chem.*, **35**, 2910 (1992).

[2] A. M. Omar, N. H. Eshba, *J. Pharm. Sci.* **73**, 1166 (1984); P. B. Patel, J. T. Trivedi, *Indian Chem. Soc.*, **54**, 765 (1987).

[3] M. Chaudhary, S. S. Parmar, S. K. Chaudhari, and B. V. Ramasastry, *J. Pharm. Sci.*, **65**, 443 (1976).

[4] F. A. Ragab, M. M. Hussain, M. M. Hanna and G. S. Hassan, *J. Pharm. Sci.*, **82**, 387 (1993).

[5] H. Y. Hassan, N. A. El-Koussi and Z. S. Farghaly, *Chem. Pharm. Bull.*, **46**, 863 (1998).

[6] G. Turan-Zitouni, D. M. Sivaci, Z. A. Kaplancikli and A. Ozdemir, *Farmaco*, **57**, 569 (2002).

[7] C. L. Lee and M. M. Sim, *Tetrahedron Lett*., **41**, 5729 (2000).

[8] I. Inamori, Y. Okamoto, Y. Takegawa, H. Tsujibo, Y. Sakagami, Y. Kumeda, M. Shibata and Numata, *Biosci. Biotechnol. Biochem*., **62**, 1025 (1998).

[9] N. S. Habib, S. M. Rida, E. A. M. Badawey, H. T. Y. Fahmy and H. Ghozlan, *Eur. J. Med. Chem*., **32**, 759 (1997).

[10] T. W. Sing, L. C. Lee, S. L. Yeo, S. P. Lim and M. M. Sim, *Biorg. Med. Chem. Lett*., **11**, 91 (2001).

[11] H. T. Y. Fahmy and A. A. Bekhit, *Pharmazie*, **57**, 800 (2002).

[12] F. Nagasaki, T. Yamada, E. Takahashi, Y. Kitagawa, R. Hatano, Japanese Patent JP 63250371 (1988); *Chem. Abstr.*, **110**, 192810 (1989).

[13] H. Hoelzel, D. Creuzburg, P. Stohr, H. Dehne, J. Teller, L. Kranz, H. Luthardt, T. Roethling and A. Kaestner**,** German Patent DD 258168 (1988); *Chem. Abstr.*, **111**, 2681 (1989).

[14] C. G. Bonde and N. J. Gaikwad, *Bioorg. Med. Chem.*, **12**, 2151 (2004); A. Bodtke, W.-D Pfeiffer, N. Ahrens, P. Langer, *Bioorg. Med. Chem. Lett.*, **14**, 1509 (2004).

[15] S. Bae, H-G. Hahn and K.D. Nam, *J. Comb. Chem.*, **7**, 7 (2005).

[16] S. M. Sondhi, G. Bhattacharjee, R. K. Jameel, R. Shukla, R. Raghubir, O. Lozach, and L. Meijer, *Cent. Eur. J. Chem.*, **2**, 1 (2004).

[17] M. Bouchekara, A. Djafri, N. Vanthuyne, and C. Roussel, *ARKIVOC*, **72** (2002).

[18] S. E. Bramley, V. Dupplin, D. G. Goberdhan and G. D. Meakins, *J. Chem. Soc., Perkin Trans. 1*, 639 (1987); N. De Kimpe, W. De Cock, M. Keppens, D. De Smaele and A. Meszaros, *J. Heterocyclic Chem.*, **33**, 1179 (1996).

[19] H. Beyer, W. Lassig and E. Bulka, *Chem. Ber*., **87**, 1385 (1987); H. Beyer, and G. Wolter, *Chem. Ber.*, **89**, 1652 (1956).

[20] E. Schmitz, and H. Striegler, *J. Prakt. Chem.,* **312**, 359 (1970); A. K. Bhattacharya, *J. Indian Chem. Soc*., **44**, 57 (1967).

[21] T. H. Kim, N. Lee, G-J. Lee and J. N. Kim, *Tetrahedron*, **57**, 7137 (2001).

[22] M. D'hooghe, A. Waterinckx, and N. De Kimpe, *J. Org. Chem*., **70**, 227 (2005).

[23] B. Liu, H. Gao, and X. Zhou, *Hauxe Yangbao,* **5**, 42 (1994); A. Saeed, and M. Parvez, *Cent. Eur. J. Chem.* **3,** 780 (2005).