Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Novel and Expedient Regioselective Synthesis of 2-Imino-3-methyl-2,3-dihydrothiazoles

Ranjana Aggarwal [a] & Rajiv Kumar [a]
[a] Department of Chemistry, Kurukshetra University, Kurukshetra, Haryana, India
Published online: 18 Aug 2008.

To cite this article: Ranjana Aggarwal & Rajiv Kumar (2008): Novel and Expedient Regioselective Synthesis of 2-Imino-3-methyl-2,3-dihydrothiazoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:13, 2096-2102

To link to this article: http://dx.doi.org/10.1080/00397910802029356

Synthetic Communications®, 38: 2096–2102, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802029356

Taylor & Francis
Taylor & Francis Group

Novel and Expedient Regioselective Synthesis of 2-Imino-3-methyl-2,3-dihydrothiazoles

Ranjana Aggarwal and Rajiv Kumar
Department of Chemistry, Kurukshetra University,
Kurukshetra, Haryana, India

Abstract: Cyclization of α-tosyloxyacetophenones **1** and N-methylthiourea **2** in acidic medium affords a novel and expedient method to synthesize 2-imino-3-methyl-2,3-dihydrothiazoles **3** with excellent level of regiocontrol.

Keywords: Acidic medium; 2-imino-3-methyl-2,3-dihydrothiazoles; N-methylthiourea; Regioselective synthesis; α-tosyloxyacetophenones

INTRODUCTION

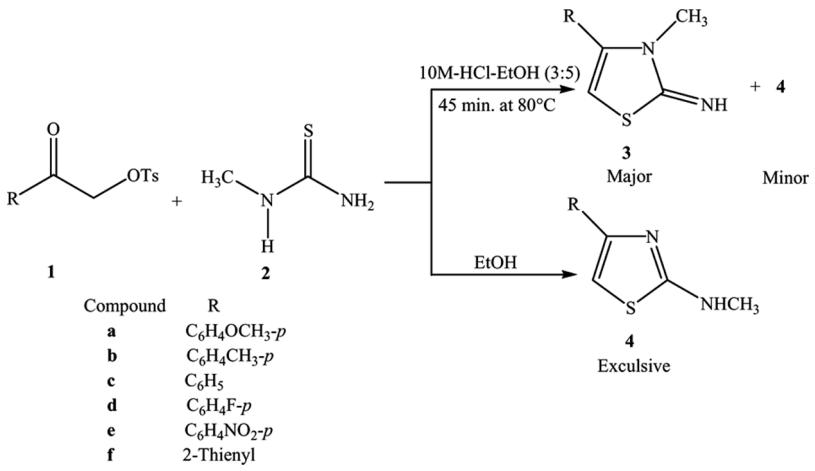
Recently, while studying the reaction of heteroarylhydrazines with fluorinated β-diketones,[1] we observed that regiochemistry of the products was altered when the reaction medium was changed from neutral to acid. Whereas 5-hydroxy-5-trifluoromethyl-Δ^2-pyrazolines (hydrated form of 5-trifluoromethylpyrazoles) were the major product in a neutral medium, formation of 3-trifluoromethylpyrazoles occurred in the acidic medium. This observation prompted us to explore the possibility of synthesis of 2-imino-3-methyl-2,3-dihydrothiazole **3**, a regioisomer of 2-methylaminothiazole **4**, by modifying the conditions of Hantzsch thiazole synthesis. In contrast to several methods available for the synthesis of 2-aminothiazoles,[2–6] there are only a few reports that describe the synthesis of 2-imino-2,3-dihydrothiazole derivatives,[7–10]

Received October 11, 2007.
Address correspondence to Ranjana Aggarwal, Department of Chemistry, Kurukshetra University, Kurukshetra 136119, Haryana, India. E-mail: ranjana67in@yahoo.com

despite the clear opportunity to introduce an additional handle for chemical diversity. The most commonly reported routes to 2-imino-2,3-dihydrothiazole derivatives involve reaction of α-thiocyanatoketones with anilines,[7] reaction of bis-methylformamidine disulphide dihydrochloride with ketones,[8] reaction of 2-aminothiazoles with alkyl halides,[9] and reaction of α-haloketones with substituted thioureas.[10] However, these methods involve a multistep synthesis, prolonged reaction time, use of lachrymatory substrates, and finally yields of the products are moderate at best. Consequently, there is need for an alternative procedure involving milder conditions and simpler substrates. We describe here a novel and expedient method for regioselective synthesis of 2-imino-3-methyl-2,3-dihydrothiazoles **3** involving reaction of α-tosyloxyacetophenones **1** and N-methylthiourea **2** in an acidic medium.

RESULTS AND DISCUSSION

Hantzsch thiazole synthesis involves reaction of α-haloketones with thioamides and thioureas, and it provides a useful method for the synthesis of a wide variety of 2-alkyl/arylamino-4-substituted thiazoles.[6,11] A large variety of different thiazoles have been synthesized by us using an efficient modification utilizing α-tosyloxyketones, obtained by the oxidation of enolizable ketones with [hydroxy(tosyloxy)iodo]benzene (HTIB) in place of highly lachrymatory α-haloketones.[12,13] In the present study, initially, the reaction between α-tosyloxyacetophenones **1**



Scheme 1. Reaction of α-tosyloxacetophenones 1 and N-methylthiourea 2 with or without HCl.

and N-methylthiourea **2** was carried out with or without adding HCl to refluxing ethanol. Although the reaction in neutral conditions afforded the exclusive formation of 2-methylaminothiazole **4**, the thin-layer chromatography (TLC) and ^{1}H NMR of the crude reaction mixture of the acidic medium indicated the formation of an additional compound, 2-imino-3-methyl-2,3-dihydrothiazole **3**, along with **4** (Scheme 1). Encouraged by this preliminary result, we attempted to optimize the reaction conditions for the formation of **3** as the major product. We envisaged accomplishing a set of experiments by varying the concentration of HCl in ethanol and the temperature of the reaction taking α-tosyloxy-*p*-methoxyacetophenone **1a** as a typical compound.

As evident in Table 1, the optimum condition of concentration of HCl and temperature for the formation of **3a** in 88% proportion was established as 10 M HCl– EtOH (3:5) at 80 °C for 45 min. To check the scope of this method, other α-tosyloxyacetophenones **1b–f** were made to react with **2** under similar conditions of concentration and temperature. The ratios of **3** and **4** were calculated on the basis of an analysis of ^{1}H NMR of the crude reaction mixture. The results summarized in Table 2 indicate the generality of this reaction with respect to various α-tosyloxyacetophenones **1**. The method is mild, and except for α-tosyloxy-*p*-nitroacetophenone **1e**, tolerates several substituted aryl and thienyl groups at 4-position and affords the desired products in isolated yields ranging from 67 to 79%.

Hydrochloride salts of two isomers **3** and **4** were purified by fractional crystallization. **3**-HCl, being less soluble in ethanol, crystallized out first, was neutralized with aq. NaOH, and recrystallized from ethanol to give **3**. The mother liquor, on basification followed by extraction with ethyl acetate and recrystallization from ethanol, provided **4** as a free base. 2-Imino-3-methyl-4-(*p*-nitrophenyl)-2,3-dihydrothiazole **3e** could not be completely purified because of its low yield. Finally, the known products were identified by comparison of mp's with those reported in

Table 1. Ratio of **3**[a] at different temperatures and concentrations of HCl in ethanol

Temperature (°C)	10M HCl–EtOH	Ratio of 3[a]
95	1:2	75
95	3:5	80
80	3:5	88
60	3:5	84
30	3:5	68

[a]Ratio calculated from the ^{1}H NMR of the crude reaction mixture.

Table 2. ^{1}H NMR data, proportion, and physical data of **3** and **4** in 10M HCl–EtOH (3:5) at 80 °C for 45 min

Compound	δ (5-H) ($CDCl_3$)	δ (CH_3) ($CDCl_3$)	Proportion (%) in mixtures[a]	Mp (°C) (lit.)	Yields[b] (%)
3a	5.65	3.20	88	76–78	79
3b	5.70	3.22	85	72–74	78
3c	5.89	3.29	80	78–80[10]	73
3d	5.85	3.27	71	70–71[10]	67
3e	5.92	3.27	4	Cannot be isolated	—
3f	5.76	3.21	79	76–78	76
4a	6.58	3.00	12	120–122[15]	9
4b	6.66	3.02	15	126–128[16]	12
4c	6.63	2.94	20	132–134[10]	13
4d	6.64	2.96	29	136–138[10]	14
4e	6.95	3.06	96	184–186[10]	88
4f	6.57	2.96	21	120–122	10

[a]Ratio calculated from the ^{1}H NMR of the crude reaction mixture.
[b]Isolated yields.

the literature. The structures of other unknown compounds were confirmed on the basis of their IR, ^{1}H NMR, and elemental analyses.

^{1}H NMR proved to be an important tool in distinguishing the structure of the isomers **3** and **4** on the basis of two sharp singlets due to 5-H of thiazole ring and N-CH_3 of methyl protons. The difference in the chemical shift of the proton at 5-position of the two isomers is about δ 0.9 units. In the case of **3**, the 5-H proton resonated upfield at about δ 5.7, whereas in **4** it resonated at about δ 6.6. Such a shielding in **3** can be attributed to the less aromatic character of the 2,3-dihydrothiazole ring. Similarly, the proton signal of N-CH_3 of the two isomers exhibited the difference of around δ 0.2 units. This deshielding is because in case of **3**, CH_3 is attached to a sp^3 hybridized nitrogen, which is the part of ring (Table 2). In IR, N-H stretch of these two isomers **3** and **4** appears at about 3050 and 3350 cm^{-1}, respectively.

Murav'eva and Shchukina[14] have reported that in an acidic medium, **3** rearranges to **4**. However, when **3b** and **4b** were separately subjected to these conditions of temperature and concentration, no such isomerization was observed.

In summary, we have developed an efficient and high-yielding protocol for the regioselective synthesis of **3** from readily available α-tosyloxyacetophenones **1** and N-methylthiourea **2** under acidic

conditions. These results are from our preliminary experiments, further studies concerning the full scope of this reaction and its mechanism are in progress.

EXPERIMENTAL

The IR spectra of the compounds were recorded on a Buck Scientific IR M-500 spectrophotometer using KBr pellets (ν_{max} in cm^{-1}): ^1H NMR spectra were recorded on a Bruker instrument at 300 MHz; and chemical shifts are expressed in δ-scale downfield from TMS as an internal standard.

General Procedure

(a)Reaction between α-tosyloxyacetophenones **1** and N-methylthiourea **2**: α-tosyloxyacetophenones **1** (2 m mol) was added to the solution of N-methylthiourea **2** (0.18 g, 2 m mol) in 10 M HCl (6 ml)-EtOH (10 ml). The resulting solution was stirred for 45 min. at a temperature of 80 °C. On cooling slowly, a solid separated out, which was filtered, washed with aq. NaOH, and recrystallized from ethanol to afford 2-imino-3-methyl-2,3-dihydrothiazole **3**. The filtrate was neutralized using aq. NaOH and extracted with ethyl acetate (3×20 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, and concentrated. The solid thus obtained was recrystallized from ethanol to give 2-methylaminothiazole **4**.

(b) A solution of 2-imino-3-methyl-4-(*p*-methylphenyl)-2,3-dihydrothiazole (**3b**) (0.5 g) in 10 M HCl (6 ml)–EtOH (10 ml) was stirred 45 min. at 80 °C. Workup of the reaction as in the previous experiment gave unreacted **3b** (0.46 g), identified by comparison with an authentic sample. Similarly, the 2-methylamino-4-(*p*-methylphenyl)-thiazole (**4b**) was recovered unchanged when subjected to the previous conditions.

Data

Compound **3a** (found N, 12.63;$C_{11}H_{12}N_2OS$ required N, 12.73). IR (cm^{-1}) 3045 (N-H); ^1H NMR ($CDCl_3$): 3.20 (s, 3H, N-CH_3), 3.86 (s, 3H, OCH_3), 5.65 (s, 1H, 5-H), 6.94 (d, $J = 8.4$ Hz, 2H, 3′, 5′-H), 7.26 (d, $J = 8.4$ Hz, 2H, 2′, 6′-H).

Compound **3b** (found N, 13.65; $C_{11}H_{12}N_2S$ required N, 13.72) IR (cm^{-1}) 3047 (N-H); ^1H NMR ($CDCl_3$): 2.41 (s, 3H, CH_3), 3.22 (s, 3H, N-CH_3), 5.70 (s, 1H, 5-H), 7.24–7.29 (m, 4H, 2′, 3′, 5′, 6′-H).

Compound **3f** (found N, 14.25; $C_8H_8N_2S_2$ required N, 14.29) IR (cm^{-1}) 3055 (N-H); ^1H NMR ($CDCl_3$): 3.21 (s, 3H, N-CH_3), 5.76 (s, 1H, 5-H), 6.99–7.03 (m, 2H, 3′, 4′-H), 7.29 (dd, $J = 5.1$ Hz, $J = 1.5$ Hz, Hz, 1H, 5′-H).

Compound **4f** (found N, 14.22; $C_8H_8N_2S_2$ required N, 14.29) IR (cm^{-1}) 3550 (N-H); ^1H NMR ($CDCl_3$): 2.96 (s, 3H, NH-CH_3), 6.57 (s, 1H, 5-H), 6.94–7.35 (m, 3H, 3′, 4′, 5′-H).

ACKNOWLEDGMENTS

We thank the Council of Scientific and Industrial Research, New Delhi, for financial assistance and a junior research fellowship to Rajiv Kumar. Thanks are also due to Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute (RSIC, CDRI), Lucknow, India, for providing elemental analysis. We also thank Professor S. P. Singh for helpful suggestions.

REFERENCES

1. Singh, S. P.; Kumar, V.; Aggarwal, R; Elguero, J. The reaction of aryl and heteroarylhydrazines with aryl-trifluoromethyl β-diketones. *J. Heterocycl. Chem.* **2006**, *43*, 1003–1014.
2. Schulman, S. Fluorene derivatives for cancer research. *J. Org. Chem.* **1949**, *14*, 382–387.
3. Djerassi, C.; Scholz, C. R. 2-(Aryloxymethyl)thiazolines and penthiazolines. *J. Org. Chem.* **1950**, *15*, 694–699.
4. Parkash, O.; Saini, S.; Saini, N.; Parkash, I.; Singh, S. P. Use of [hydroxy-(tosyloxy)iodo]benzene in the synthesis of ethyl 4-(2-substitutedamino-4-thiazolyl)phenoxyacetates and acids as anti-inflammatory agents. *Indian J. Chem.* **1995**, *34B*, 660–663.
5. Ochiai, M.; Nishi, Y.; Hashimoto, S.; Tsuchimoto, Y.; Chen, D. Synthesis of 2,4-disubstituted thiazoles from (*Z*)-(2-acetoxyvinyl)phenyl-λ^3-iodanes: Nucleophilic substitution of α-λ^3-iodanyl ketones with thioureas and thioamides. *J. Org. Chem.* **2003**, *68*, 7887–7888.
6. Metzger, J. V. *Thiazole and its derivatives, part 1*; Wiley: New York, 1979; chap. 2.
7. Sharma, G. M.; Sachdev, H. S.; Ralhan, N. K.; Singh, H.; Sandhu, G. S.; Gandhi, K.; Narang, K. S. Thiopegan derivatives, XXI: A mechanism for the formation of 9:10 and 10:11 thiopegan derivatives. *Tetrahedron* **1961**, *15*, 53–59.

8. Bhattacharya, A. K. Interaction of bis-methyl/benzyl formamidine disulphide dihydrobromides with certain ketones: Formation of thiazoles and thiazolines. *J. Indian Chem. Soc.* **1967**, *44*, 57–63.
9. Werbel, L. M.; Degnan, M. B.; Harger, G. F.; Capps, D. B. 1-Alkyl-3-(3-alkyl-5-nitro-4-thiazolin-2-ylidene)ureas and related compounds as schistosomicides. *J. Med. Chem.* **1972**, *15*, 955–963.
10. Bramley, S. E.; Dupplin, V.; Goberdhan, D. G. C.; Meakins, G. D. The Hantzsch thiazole synthesis under acidic conditions: Change of regioselectivity. *J. Chem. Soc. Perkin Trans. 1* **1987**, 639–643.
11. Hantszch, A. Über die oxy-thiazole oder thiazolone. *Ber. Dtsch. Chem. Ges.* **1927**, *60b*, 2537–2545.
12. Singh, S. P.; Naithani, R.; Aggarwal, R.; Parkash, O. A convenient synthesis of 4-substituted-4′-(2-thienyl)-2,2′-bithiazoles as potential phototoxic agents. *Synth. Commun.* **2001**, *31*, 3747–3751.
13. Aggarwal, R.; Pundeer, R.; Kumar, V.; Chaudhari, V.; Singh, S. P.; Parkash, O. A facile synthesis of thiazole-2(3H)-thione through [hydroxy(tosyloxy)iodo]benzene. *Synth. Commun.* **2004**, *34*, 2659–2664.
14. Murav'eva, K. M.; Shchukina, M. N. Synthesis and rearrangement of the thiazolinimine series. *Doklady Akad. Nauk SSSR* **1959**, *126*, 1274–1277; *Chem. Abstr.* **1960**, *54*, 498.
15. Hampel, W.; Mueller, I. Reaction with diazoketones, VI: Synthesis of some 2-alkylamino-and 2-arylamino-4-arylthiazole. *J. Praktische Chemie.* **1968**, *38*, 320–326; *Chem. Abstr.* **1969**, *70*, 37690w.
16. Kabalka, G. W.; Mereddy, A. R. Microwave-promoted synthesis of functionalized 2-aminothiazoles. *Tetrahedron Lett.* **2006**, *47*, 5171–5172.