Organoiodine(III) mediated one-pot synthesis of *N*-substituted 2-aminothiazoles^Ψ

Om Prakash*, Rashmi Pundeer and Vishwas Chaudhri

Department of Chemistry, Kurukshetra University, Kurukshetra-136 119, India

E-mail : oprakash50@sify.com

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The synthesis of *N*-substituted 2-aminothiazoles has been achieved in one-pot by the successive treatment of acetophenones with [hydroxy(tosyloxy)iodo]benzene (HTIB), potassium thiocyanate and appropriate aniline.

2-Aminothiazoles are utilized as agents based on cyclo-genase inhibition and also have application in therapy¹, e.g. one of the first commercial synthetic drugs containing thiazole, 'sulphathiazole', (a sulphamide antibiotic) was derived from a 2-aminothiazole. There are two important routes which are commonly employed for the synthesis of 2-amino/substituted aminothiazoles. The first one is well-known Hantzsch thiazole synthesis making the use of α -haloketones (HK) which are made to react with thioureas². The second method involves preparation of α -thiocyanato ketones from the reaction of α -haloketones and potassium/ammonium thiocyanate. The thiocyanatoketones on reaction with amines give *N*-substituted 2-aminothiazoles. This method is known as Tcherniac's synthesis³. Since both of these routes involve HK which are associated with problems of handling and preparation due to highly lachrymatory nature, synthetic methods avoiding the use of HK are always preferred.

With this objective in mind, we have earlier shown that the use of α -tosyloxyketones readily accessible through the oxidation of enolizable ketones with [hydroxy-(tosyloxy)iodo]benzene (HTIB) can offer a superior replacement of HK in the Hantzsch thiazole synthesis. An important advantage of TK mediated syntheses reported by us is that it is possible to carry out these syntheses by using one-pot procedure starting from ketones⁴.

In continuation of our previous results involving HTIB/TK, we now report a new synthesis of *N*-substituted 2-aminothiazoles as a superior alternative to the reported Tcherniac's synthesis.

Results and discussion

Based on our earlier strategies, it was expected that α -

tosyloxyacetophenone (**1a**) accessible through the oxidation of acetophenone with HTIB⁵, might undergo nucleophilic displacement by the attack of potassium thiocyanate to form α -thiocyanatoacetophenone (**2a**)⁶. α -Thiocyanatoacetophenone should then conveniently provide 4-phenyl-2-(*N*-phenylamino)thiazole (**3a**) by the action of aniline.

To examine the feasibility of the proposed strategy, acetophenone was subjected to oxidation with one equivalent of HTIB in acetonitrile to afford **1a**. The latter was treated with one equivalent of potassium thiocyanate in ethanol. α -Thiocyanatoacetophenone (**2a**), thus obtained, was made to react with aniline. The reaction gave **3a** in excellent yield (81%) (Method A) (Scheme 1).

Method A

Method B

Scheme 1

Encouraged by successful preparation of **3a** according to Method A involving separation of the intermediates **1a** and **2a**, we carried out the conversion **1a**→**3a** in one-pot generating the intermediates **1a** and **2a** *in situ* (Method B). The method, indeed, afforded **3a** in 74% yield.

The approach was further generalized by using different acetophenones, propiophenone and anilines to obtain variously *N*-substituted 2-aminothiazoles.

^ΨDedicated to Professor S. M. Mukherji for his outstanding contribution to Chemistry Department, Kurukshetra University, Kurukshetra, India.

The known products were identified by comparing their melting points and spectral data with those reported in literature. It is to be noted that the compound **3d** is already known in literature. However, the reported m.p. (110°)⁷ did not agree with the m.p. of the product obtained from the present study. So, we confirmed the structure by its spectral and analytical data (Experimental). The structures of new thiazoles **3e-h** obtained from this study were confirmed by spectral and analytical data (¹H NMR and HRMS).

In conclusion, the I^{III} mediated approach involving TK offers a new example of one-pot convenient synthesis of *N*-substituted 2-aminothiazoles.

Experimental

Melting points were taken in open capillaries and are not corrected. ¹H NMR were taken on a Bruker 300 MHz instrument using TMS as internal standard.

Method A. Synthesis of 4-phenyl-2-(*N*-phenylamino)-thiazole (3a) via isolation of intermediates 1a and 2a :

α-Tosyloxyacetophenone (1a) : A solution of acetophenone (1.2 g, 10 mmol) with HTIB (4.31 g, 11 mmol) in acetonitrile (20 cm³) was refluxed for 2 h. The solvent was distilled off and 2 cm³ of ethanol was added to the residual solution. Solid α-tosyloxyacetophenone (**1a**), separated as crystalline compound, was filtered and washed with cold ethanol, m.p. 90° (lit. 90°), yield 2.03 g (70%).

α-Thiocyanatoacetophenone (2a) : To α-tosyloxyacetophenone (1.45 g, 5 mmol) in ethanol (20 cm³) was added potassium thiocyanate and the reaction mixture was refluxed for 10 min. A crystalline solid separated out on cooling, was filtered, washed with cold ethanol and recrystallized from ethanol to afford pure α-thiocyanatoacetophenone, m.p. 75° (lit. 75–76°), yield 0.63 g (71%).

4-Phenyl-2-(*N*-phenylamino)thiazole (3a) : A solution of α-thiocyanatoacetophenone (1.77 g, 10 mmol) in methanol with aniline (0.93 g, 10 mmol) was refluxed for 5 h. Most of the solvent was distilled off and to the residual mixture was added cold water. A solid was separated off which after recrystallization from ethanol gave pure **3a**, m.p. 138° (lit. 139°), yield 2.05 g (81%).

Method B. One-pot synthesis of 4-phenyl-2-(*N*-phenylamino)thiazole (3a) :

To a solution of acetophenone (1.20 g, 10 mmol) in acetonitrile (20 cm³) was added HTIB (4.31 g, 11 mmol) and the resulting solution was refluxed for 2 h. The solvent was distilled off *in vacuo* and 20 cm³ of methanol was added to it. To the resulting suspension was added KSCN (0.97 g, 10 mmol) and the mixture was refluxed for 10 min. Subsequent addition of aniline (0.93 g, 10 mmol) followed by

refluxing for 5 h and usual work up (as given in Method A) gave **3a**, m.p. 137° (lit. 139°), yield 1.86 g (74%).

Adopting the same procedure, other derivatives of the title compounds (**3**) were synthesized by taking different acetophenones, propiophenone and anilines.

4-Phenyl-2-(*N*-phenylamino)thiazole (3a) : Yield 74 %; m.p. 137° (lit.⁸ 139°); ¹H NMR δ (CDCl₃) 6.82 (1H, s, 5-H), 7.29–7.43 (10H, m, NC₆H₅, C₆H₅).

2-(*N*-4-Methoxyphenylamino)-4-phenylthiazole (3b) : Yield 79%; m.p. 164° (lit.⁸ 167°); ¹H NMR δ (CDCl₃) 3.82 (3H, s, OCH₃), 6.72 (1H, s, 5-H), 6.73–7.14 (4H, m, NC₆H₄), 7.27–7.36 (m, 5H, C₆H₅).

5-Methyl-4-phenyl-2-(*N*-phenylamino)thiazole (3c) : Yield 67%; m.p. 168° (lit.⁹ 168°); ¹H NMR δ (CDCl₃) 2.46 (3H, s, CH₃), 7.32–7.65 (10H, m, C₆H₅, NC₆H₅).

4-Fluorophenyl-2-(*N*-4-fluorophenylamino)thiazole (3d) : Yield 76%; m.p. 156–158° (lit. 110°); ¹H NMR δ (CDCl₃) 6.71 (1H, s, 5-H), 7.00–7.09 (4H, m, 2,6-H, NC₆H₄F, C₆H₄F), 7.30–7.37 (2H, m, 3,5-H, NC₆H₄F), 7.62–7.75 (2H, m, 3,5-H, C₆H₄F); *m/z* 288 (M⁺).

2-(*N*-3-Chloro-4-fluorophenylamino)-4-phenylthiazole (3e) : Yield 80%; m.p. 154–158°; ¹H NMR δ (CDCl₃) 7.03 (1H, s, 5-H), 7.16–7.18 (2H, m, 2,6-H, NC₆H₃FCI), 7.28–7.39 (5H, m, C₆H₅), 7.68–7.71 (1H, m, 5-H, NC₆H₃FCI); HRMS (*m/z*); Calcd. for C₁₅H₁₀ClFN₂S : 304.02372, Found : 304.02263.

2-(*N*-4-Fluorophenylamino)-5-methyl-4-phenylthiazole (3f) : Yield 68%; m.p. 242°; ¹H NMR δ (CDCl₃) 2.40 (3H, s, CH₃), 7.06–7.11 (2H, m, 2,6-H, NC₆H₄F), 7.25–7.38 (5H, m, C₆H₅), 7.55–7.59 (2H, m, 3,5-H, NC₆H₄F); HRMS (*m/z*); Calcd. for C₁₆H₁₃FN₂S : 284.07834, Found : 284.07886.

2-(*N*-3-Chloro-4-fluorophenylamino)-5-methyl-4-phenylthiazole (3g) : Yield 72%; m.p. 202°; ¹H NMR δ (CDCl₃) 2.42 (3H, s, CH₃), 7.15–7.18 (2H, m, 2,6-H, NC₆H₃FCI), 7.25–7.39 (5H, m, C₆H₅), 7.55–7.59 (1H, m, 5-H, NC₆H₃FCI); HRMS (*m/z*); Calcd. for C₁₆H₁₂ClFN₂S : 318.03937, Found : 318.03969.

2-(*N*-3-Chloro-4-fluorophenylamino)-4-fluorophenylthiazole (3h) : Yield 72%; m.p. 230–234°; ¹H NMR δ (CDCl₃) 6.65 (1H, s, 5-H), 7.12–7.18 (4H, m, 2,6-H, NC₆H₃FCI, C₆H₄F), 7.56–7.63 (1H, m, 5-H, NC₆H₃FCI), 7.70–7.72 (2H, m, 3,5-H, C₆H₄F); HRMS (*m/z*); Calcd. for C₁₅H₉ClF₂N₂S : 322.01430, Found : 322.01357.

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