# A One-Pot Synthesis of 2-Amino- and 2-(Arylamino)-Substituted Thiazoles and Selenazoles using [Hydroxy(tosyloxy)iodo]benzene, Carbonyl Compounds and Thioureas or Selenoureas: A Modification of the Hantzsch Synthesis

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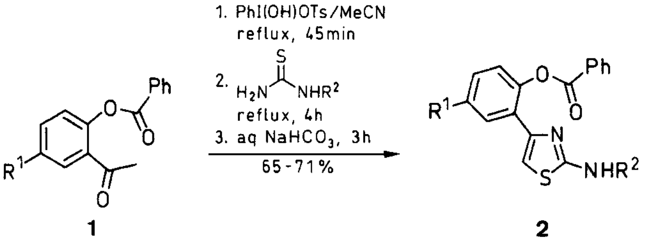
A one-pot synthesis of 4-substituted 2-amino- or 2-(arylamino)thiazoles has been achieved via treatment of ketones with [hydroxy(tosyloxy)iodo]benzene and thioureas in refluxing acetonitrile. 1,3-Dicarbonyl compounds yield (5-acyl-4-methylthiazol-2-yl)-ammonium tosylates and the corresponding selenazol-2-yl compounds, respectively, upon reaction with [hydroxy(tosyloxy)iodo]benzene followed by the addition of thiourea or selenourea. The tosylate salts are converted to the corresponding free bases by treatment with sodium bicarbonate. This synthesis is an important modification of the Hantzsch synthesis.

Due to the importance of thiazole derivatives in medicinal chemistry, considerable effort has been invested in their preparation.[1-3] Although several routes with variable yields have been reported for the synthesis of this heterocyclic nucleus, the Hantzsch synthesis continues to prevail as the method of choice.[4] This method involves the reaction of α-halocarbonyl compounds, which are lachrymators, with an appropriate thiourea or thioamide.

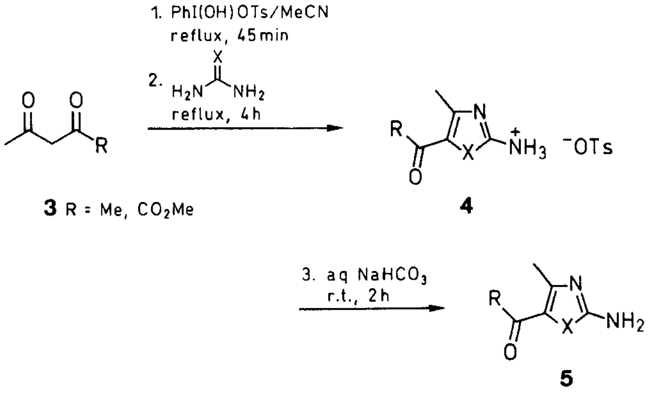
As an extension of our studies on the utility of hypervalent iodine compounds as synthetic reagents,[5-7] we have become interested in the synthesis of thiazoles and selenazoles. We now report a one-pot synthesis of thiazoles starting from carbonyl compounds, [hydroxy(tosyloxy)iodo]benzene [PhI(OH)OTs] and thioureas.

Refluxing 4-substituted 2-benzoyloxyacetophenones **1** with PhI(OH)OTs in acetonitrile, followed by addition of thioureas yielded the corresponding thiazolylammonium tosylates, which were converted to the free bases by treatment with saturated sodium bicarbonate.



| **2** | R$^1$ | R$^2$ | **2** | R$^1$ | R$^2$ |
|---|---|---|---|---|---|
| **a** | H | H | **e** | MeO | Ph |
| **b** | H | 4-MeOC$_6$H$_4$ | **f** | MeO | 4-MeC$_6$H$_4$ |
| **c** | H | 4-ClC$_6$H$_4$ | **g** | MeO | 4-MeOC$_6$H$_4$ |
| **d** | Cl | 4-MeOC$_6$H$_4$ | **h** | MeO | 4-ClC$_6$H$_4$ |

Treatment of β-dicarbonyl compounds **3** (pentane-2,4-dione or methyl 2,4-dioxopentanoate) under similar conditions yielded (5-acyl-4-methylthiazol-2-yl)ammonium tosylates **4a,b** and the corresponding selenazol-2-yl compounds **4c,d**, respectively, which were then converted to their free bases by treatment with saturated sodium bicarbonate.



| **4,5** | R | X | **4,5** | R | X |
|---|---|---|---|---|---|
| **a** | Me | S | **c** | Me | Se |
| **b** | CO$_2$Me | S | **d** | CO$_2$Me | Se |

The reaction proceeds via the formation of an α-tosyloxy ketone intermediate, which may be prepared separately by the treatment of ketones with PhI(OH)OTs.[8] From this intermediate, which is comparable in its chemical reactivity to that of an α-halo ketone, the heterocyclic reaction with thio or selenourea is completely mechanistically analogous to that seen in the Hantzsch synthesis.[4,7-13] The advantages of the present modification of the Hantzsch synthesis are: (a) avoidance of α-halo carbonyl compounds and (b) it is a one-pot synthesis of thiazole derivatives which can potentially be significantly broadened in its scope and general synthetic utility.

All melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained using a Unicam SP 1000 spectrophotometer. $^1$H NMR spectra were obtained using a Bruker WP 400 MHz spectrometer.

**Synthesis of 4-Substituted 2-Amino- or 2-(Arylamino)thiazoles; General Procedure:**

Acetophenone (**1**; 0.010 mol) was added to a solution of PhI(OH)OTs (3.92 g, 0.010 mol) in MeCN, (60 mL) and the resulting solution was refluxed for 45 min. Then, thiourea or a substituted thiourea (0.010 mol) was added and the mixture refluxed for 4 h, during which time the thiazole tosylate precipitated from solution, and was isolated by vacuum filtration, washing the solid with hexanes to remove any residual iodobenzene. The tosylate salt was then suspended in sat. aq NaHCO$_3$ (100 mL) and stirred for 3 h, during which time the product **2** precipitated, and was isolated by vacuum filtration and air-dried.

**Table 1.** Synthesis of 2-Amino- and 2-(Arylamino)thiazoles **2** from acetophenones **1** using PhI(OH)OTs and Thiourea

| Prod-uct | Yield (%) | mp (°C) | Molecular Formula[a] | IR(Nujol) ν (cm$^{-1}$) | $^1$H NMR (DMSO-$d_6$) δ |
|---|---|---|---|---|---|
| **2a** | 66 | 88–90 | $C_{16}H_{12}N_2O_2S$ (296.3) | 3475, 3350, 1730 | 6.65 (s, 1H), 7.10–8.30 (m, 9H), 9.70 (br, 2H) |
| **2b** | 68 | 133–136 | $C_{23}H_{18}N_2O_2S$ (386.4) | 3360 (sh), 1735 (sh) | 2.30 (s, 3H), 6.91 (s, 1H), 6.93–8.30 (m, 13H) |
| **2c** | 66 | 194–196 | $C_{22}H_{14}ClN_2O_2S$ (405.8) | 3360 (sh), 1735 (sh) | 6.70 (s, 1H), 6.71–8.31 (m, 12H), 10.17 (s, 1H) |
| **2d** | 68 | 153–155 | $C_{23}H_{17}ClN_2O_3S$ (436.8) | 3340 (sh), 1725 (sh) | 3.95 (s, 3H), 6.70 (s, 1H), 6.71–8.30 (m, 13H) |
| **2e** | 71 | 184–186 | $C_{23}H_{18}N_2O_3S$ (402.4) | 3330 (sh), 1730 (sh) | 3.82 (s, 3H), 6.74 (s, 1H), 6.75–8.30 (m, 13H), 9.80 (br, 1H) |
| **2f** | 65 | 188–189 | $C_{24}H_{20}N_2O_3S$ (416.4) | 3350 (br), 1725 (sh) | 2.30 (s, 3H), 3.94 (s, 3H), 6.78 (s, 1H), 6.80–8.30 (m, 12H), 9.89 (s, 1H) |
| **2g** | 69 | 171–173 | $C_{24}H_{20}N_2O_4S$ (432.4) | 3340 (br), 1720 (sh) | 3.94 (s, 3H), 3.96 (s, 3H), 6.76 (s, 1H), 6.77–8.32 (m, 12H), 9.85 (br, 1H) |
| **2h** | 68 | 204–205 | $C_{23}H_{17}ClN_2O_3S$ (436.8) | 3340 (br), 1720 (sh) | 3.94 (s, 3H), 6.72 (s, 1H), 6.79–8.31 (m, 12H) |

[a] Satisfactory microanalyses obtained: C ±0.13, except for **2a**: C −1.05.

**Table 2.** Synthesis of (5-Acyl-4-methylthiazol-2-yl[selenazol-2-yl])-ammonium tosylates **4** and their free bases **5** using PhI(OH)OTs and thiourea or selenourea

| Prod-uct | Yield (%) | mp (°C) | Molecular Formula[a] or Lit. mp (°C) | IR (KBr) ν (cm$^{-1}$) | $^1$H NMR (DMSO-$d_6$) δ |
|---|---|---|---|---|---|
| **4a** | 78 | 257–259 | $C_{13}H_{16}N_2O_4S_2$ (328.3) | 3320 (br), 1690 (sh) | 2.20 (s, 3H), 2.42 (s, 3H), 2.45 (s, 3H), 7.25 (d, 2H), 7.75 (d, 2H), 7.89 (br, 3H) |
| **4b** | 78 | 186–190 | $C_{14}H_{18}N_2O_5S_2$ (358.2) | 3330 (br), 1690 (sh) | 1.30 (t, 3H), 2.31 (s, 3H), 2.45 (s, 3H), 4.15 (s, 2H), 7.76 (br, 3H) |
| **4c** | 74 | 225–227 | $C_{13}H_{16}N_2O_4SSe$ (375.3) | 3235 (br), 1685 (sh) | 2.30 (s, 3H), 2.41 (s, 3H), 2.45 (s, 3H), 7.23 (d, 2H), 7.65 (d, 2H), 8.23 (br, 3H) |
| **4d** | 79 | 185–187 | $C_{14}H_{18}N_2O_5SSe$ (405.3) | 3330 (br), 1690 (sh) | 1.32 (s, 3H), 2.31 (t, 3H), 2.45 (s, 3H), 4.15 (s, 2H), 7.26 (d, 2H), 7.75 (d, 2H), 8.86 (br, 3H) |
| **5a** | 78 | 268–270 | known in Lit.[14] but, no mp reported | 3350, 3330 (sh), 1690 (sh) | 2.30 (s, 3H), 2.4 (s, 3H), 7.7 (br, 2H) |
| **5b** | 78 | 173–174 | 177[14] | 3350, 3330 (sh), 1690 (sh) | 1.45 (t, 3H), 2.30 (s, 3H), 4.15 (s, 2H), 7.76 (br, 2H) |
| **5c** | 74 | 242–245 | | 3350, 3330 (sh), 1685 (sh) | 2.30 (s, 3H), 2.40 (s, 3H), 7.71 (br, 2H) |
| **5d** | 79 | 179–180 | 180–181[14] | 3350, 3330 (sh), 1690 (sh) | 1.45 (t, 3H), 2.30 (s, 3H), 4.15 (s, 2H), 7.76 (br, 2H) |

[a] Satisfactory microanalyses obtained

**Synthesis of 5-Acyl-2-amino-4-methylthiazoles 5a,b and the Corresponding selenazoles 5c,d; General Procedure:**

The carbonyl compound **3** (0.010 mol) was dissolved in MeCN (60 mL) and PhI(OH)OTs (3.92 g, 0.010 mol) was then added; the mixture was refluxed for 45 min. Then, thiourea or selenourea (0.760 g or 1.23 g, 0.010 mol) was added and the mixture refluxed additional 4 h, during which time the product precipitated from solution, and was isolated by vacuum filtration, dried, and crystallized from MeOH. The salt **4** was then suspended in sat. aq $NaHCO_3$ (60 mL) and stirred at r.t. for 2 h. The resulting solid **5** was isolated by vacuum filtration and washed with $H_2O$.

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