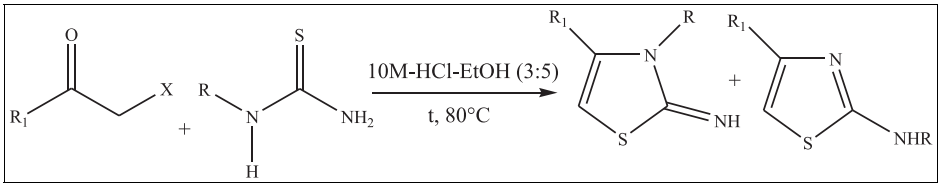
# Effect of Substituents on the Regioselectivity of the Reaction of α-Tosyloxyketones with Thioureas in Acidic Medium: Access to 2-Aminothiazoles and 2-Imino-2,3-dihydrothiazoles

Ranjana Aggarwal,[a]* Rajiv Kumar,[a] Dionisia Sanz,[b] and Rosa M. Claramunt[b]

[a]Department of Chemistry, Kurukshetra University, Kurukshetra 136 119, Haryana, India
[b]Departamento de Quimica Organica y Bio-organica, UNED, Madrid, Spain
*E-mail: ranjana67in@yahoo.com

Received December 15, 2011
DOI 10.1002/jhet.1676
Published online 26 November 2013 in Wiley Online Library (wileyonlinelibrary.com).




Regioselective condensation of α-tosyloxyacetophenones **1** and *N*-substituted thioureas **2** in acidic medium to give regioisomers 2-aminothiazoles **I** and 2-imino-2,3-dihydrothiazoles **II** is largely influenced by the substituents present on **1** and **2**. A mechanism, supported by DFT calculations has been proposed to explain the observed regioselectively.

*J. Heterocyclic Chem.*, **51**, 598 (2014).

## INTRODUCTION

Pharmacologically, 2-aminothiazoles **I** are among the most important classes of organic compounds (Fig. 1). These compounds possess versatile biological activities; some of these, for instance, Fentiazac [1] and Meloxicam [2], are associated with anti-inflammatory activities. Compounds such as Nizatidine possess anti-ulcer activity [3]. Also, their regioisomers, that is, 2-imino-2,3-dihydrothiazoles (2-iminothiazolines) **II** [4–7] (Fig. 1), although less common as compared with 2-aminothiazoles **I** [8–12], possess an additional point of structural diversity in a thiazoline-based pharmacophore and are known to have anti-inflammatory, analgesic, anticancer activity [13], and used as neuroprotective agents [14]. The most common reported routes to 2-imino-2,3-dihydrothiazole derivatives **II** involve the reaction of bisbenzyl as well as bismethyl formamidine disulphide dihydrobromide with ketones [15], reaction of α-thiocyanatoketones with anilines [4], reaction of α-haloketones with anilines followed by potassium thiocyanate [6], and reaction of *N*-aryl-α-oxo-α-arylethanehydrazonoyl bromides with monosubstituted thioureas [16]. However, these methods involve multistep synthesis, prolonged reaction time, and use of lachrymatory substrates, and finally, yields of the products are moderate at the best.

The use of 2-imino-2,3-dihydrothiazoles **II** as precursors to synthesize a wide variety of compounds also makes them compounds of interest [4,17], so an efficient and simple method is needed to synthesize 2-imino-2,3-dihydrothiazoles by which we can vary substituents present at various positions.

Recently, we have reported an efficient modification to the Hantzsch thiazole reaction for the regioselective synthesis of 2-imino-3-methyl-2,3-dihydrothiazole from *N*-methylthiourea and α-tosyloxyacetophenones (α-TK) under acidic conditions [18]. The optimum condition of concentration of HCl and temperature to obtain 2-imino-2,3-dihydrothiazoles in maximum ratio was established as 10M HCl:EtOH (3:5) at 80°C for 45 min (Scheme 1, for R═Me).

This mild and efficient method for the synthesis of 2-imino-2,3-dihydrothiazoles seems to be quite general as several substituted aryl and thienyl groups could be incorporated at 4-position, and the desired isomers were achieved in 71–88% yield (2-aminothiazoles were present in 12–29% as calculated from $^1$H NMR spectra of the crude reaction mixtures) [18]. However, with α-tosyloxy-*p*-nitroacetophenone, a complete reversal of regioselectivity was observed as the corresponding 2-aminothiazole **4** was obtained in 96% yield, and the desired isomer could not be isolated from the reaction mixture (only 4%).

This observation promoted us to think that the electronic effect of the substituent in **1**, that is, electron-withdrawing $NO_2$ group present on the phenyl ring of α-TK, is playing a significant role in controlling the regiochemical outcome of the reaction. Therefore, it was decided, in the present study, to investigate a set of reactions between various thioureas and differently substituted α-TK to establish the role of electronic factors of the substituents on the ratio of the two regioisomers and to provide an insight into the mechanistic path of the reaction.

## RESULTS AND DISSCUSSION

In the present investigation, differently substituted α-TK **1a–i** and thioureas **2a–d** were made to react under the

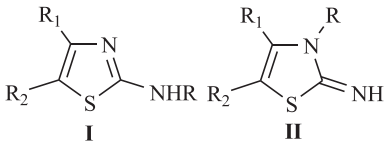


**Figure 1.** General structure of 2-aminothiazoles (**I**) and 2-imino-2,3-dihydrothiazoles (**II**).

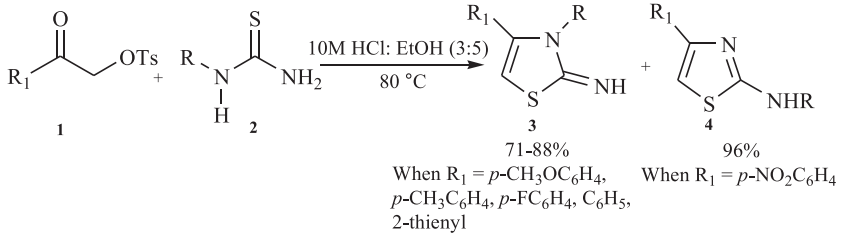
aforementioned optimum conditions of temperature and concentration, that is, 10M HCl–EtOH (3:5) at 80°C for 45 min (Scheme 2). The ratio of 2-imino-2,3-dihydrothiazoles **3** and 2-aminothiazoles **4** was determined on the basis of an analysis of $^1$H NMR spectra of the crude reaction mixture and is summarized in Table 1.

The $^1$H NMR spectra proved to be an important tool in distinguishing the structure of the isomers **3** and **4** on the basis of the sharp singlet because of the 5-H of the thiazole ring. The difference in the chemical shift of the proton at 5-position of the two isomers is about δ 0.9 units. In case of **3**, 5-H proton resonated upfield at δ 5.65–5.99, whereas in **4**, it resonated at δ 6.58–6.98. This shielding in **3** can be attributed to the nonaromatic character of the 2,3-dihydrothiazole ring.

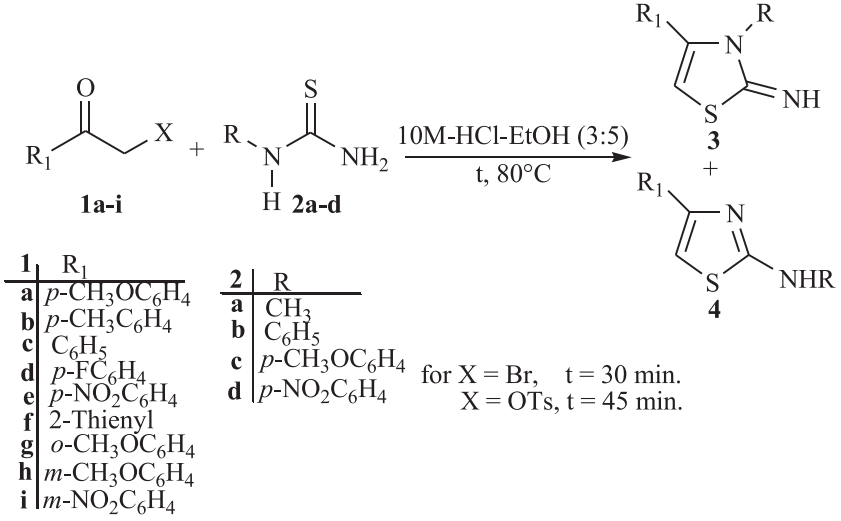
The proton signal of N–$CH_3$ of the two isomers (**3** and **4 aa–ia**) also provides a tool to distinguish between them and exhibited the difference of around δ 0.2 units. This difference is due to the fact that in case of **3**, the methyl attached to the ring nitrogen experiences more deshielding than the methylamino [18]. In IR spectra, N–H stretch of these two isomers **3** and **4** is at about 3050 and 3560 $cm^{-1}$, respectively. The known products were identified by comparison of their melting points with those reported in literature. The structure of all unreported compounds was confirmed on the basis of their IR, $^1$H NMR spectra, and elemental analysis.

A careful analysis of the results of our study (Table 1) indicates that the ratio of 2-imino-2,3-dihydrothiazole **3aa** was the maximum (88%) when methylthiourea **2a** was condensed with α-tosyloxy-*p*-methoxyacetophenone (Entry 1, Table 1). However, it was found that by changing the position of $OCH_3$ from *para* to *ortho*, the ratio of 2-imino-2,3-dihydrothiazole **3** in the reaction mixture decreased from 88 to 77% (Entry 7, Table 1), and with *m*-$OCH_3$, its ratio further decreased to 66% (Entry 8, Table 1). The drop in the ratio of **3** may be accounted because of the steric factor in the case of *ortho* and the loss of mesomeric effect in case of *meta* orientation.

**Scheme 1**




**Scheme 2**




| 1 | $R_1$ |
|---|---|
| a | *p*-$CH_3OC_6H_4$ |
| b | *p*-$CH_3C_6H_4$ |
| c | $C_6H_5$ |
| d | *p*-$FC_6H_4$ |
| e | *p*-$NO_2C_6H_4$ |
| f | 2-Thienyl |
| g | *o*-$CH_3OC_6H_4$ |
| h | *m*-$CH_3OC_6H_4$ |
| i | *m*-$NO_2C_6H_4$ |

| 2 | R |
|---|---|
| a | $CH_3$ |
| b | $C_6H_5$ |
| c | *p*-$CH_3OC_6H_4$ |
| d | *p*-$NO_2C_6H_4$ |

**Table 1**

Physical data, $^1$H NMR of **3** and **4**, and ratio of **3** in reaction mixture in 10M HCl–EtOH (3:5) at 80°C.

| Entry | Compound | $R^1$ | R | Ratio (%) of **3** in mixture[a] using | | δ (5-H) | | Yields (%) | | mp (°C) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | α-TK | α-BK | 3 | 4 | 3 | 4 | 3 | 4 |
| 1 | **aa** | *p*-$CH_3OC_6H_4$ | $CH_3$ | 88 | 83 | 5.65 | 6.58 | 79 | 9 | 76–78 [21] | 120–122 [20] |
| 2 | **ba** | *p*-$CH_3C_6H_4$ | $CH_3$ | 85 | 79 | 5.70 | 6.66 | 78 | 12 | 72–74 [18] | 126–128 [22] |
| 3 | **ca** | $C_6H_5$ | $CH_3$ | 80 | 69 | 5.89 | 6.63 | 73 | 13 | 78–80 [7] | 132–134 [7] |
| 4 | **da** | *p*-$FC_6H_4$ | $CH_3$ | 71 | 64 | 5.85 | 6.64 | 67 | 14 | 70–71 [7] | 136–138 [7] |
| 5 | **ea** | *p*-$NO_2C_6H_4$ | $CH_3$ | 4 | 6 | 5.92 | 6.95 | — | 88 | Cannot | 184–186 [7] |
| 6 | **fa** | 2-Thienyl | $CH_3$ | 79 | — | 5.76 | 6.57 | 76 | 10 | 76–78 [18] | 120–122 [18] |
| 7 | **ga** | *o*-$CH_3OC_6H_4$ | $CH_3$ | 77 | — | 5.93 | 6.40 | 65 | 13 | 84–86 | 112–114 |
| 8 | **ha** | *m*-$CH_3OC_6H_4$ | $CH_3$ | 66 | — | 5.95 | 6.70 | 59 | 25 | 92–94 | 144–146 [23] |
| 9 | **ia** | *m*-$NO_2C_6H_4$ | $CH_3$ | 30 | — | 5.90 | 6.88 | 24 | 56 | 100–102 | 145–156 [20] |
| 10 | **ab** | *p*-$CH_3OC_6H_4$ | $C_6H_5$ | 23 | 24 | 5.82 | 6.67 | 19 | 68 | 122–124 [4] | 136–138 [20] |
| 11 | **bb** | *p*-$CH_3C_6H_4$ | $C_6H_5$ | 12 | 14 | 5.86 | 6.69 | 10 | 78 | 100–102 [4] | 134–136 [22] |
| 12 | **cb** | $C_6H_5$ | $C_6H_5$ | 7 | 10 | 5.99 | 6.81 | 6 | 81 | 108–110 [7] | 130–132 [7] |
| 13 | **db** | *p*-$FC_6H_4$ | $C_6H_5$ | 4 | 7 | 5.89 | 6.73 | 4 | 84 | 134–136 [7] | 114–116 [7] |
| 14 | **eb** | *p*-$NO_2C_6H_4$ | $C_6H_5$ | 0 | 0 | — | 6.97 | 0 | 87 | — | 196–198 [7] |
| 15 | **hb** | *m*-$CH_3OC_6H_4$ | $C_6H_5$ | 18 | — | 5.94 | 6.82 | 15 | 65 | 114–116 | 145–147 |
| 16 | **ib** | *m*-$NO_2C_6H_4$ | $C_6H_5$ | 0 | 0 | — | 6.98 | 0 | 86 | — | 120–122 [20] |
| 17 | **ac** | *p*-$CH_3OC_6H_4$ | *p*-$CH_3OC_6H_4$ | 69 | 70 | 5.95 | 6.60 | 59 | 18 | 144–146 | 156–160 |
| 18 | **cc** | $C_6H_5$ | *p*-$CH_3OC_6H_4$ | 28 | 38 | 5.87 | 6.67 | 16 | 67 | 112–114 [4] | 162–164 [24] |
| 19 | **ec** | *p*-$NO_2C_6H_4$ | *p*-$CH_3OC_6H_4$ | 0 | 0 | — | 6.96 | 0 | 79 | — | 174–176 |
| 20 | **ad** | *p*-$CH_3OC_6H_4$ | *p*-$NO_2C_6H_4$ | 0 | 0 | — | 6.73 | 0 | 81 | — | 184–186 [25] |
| 21 | **cd** | $C_6H_5$ | *p*-$NO_2C_6H_4$ | 0 | 0 | — | 6.62 | 0 | 74 | — | 196–198 |
| 22 | **ed** | *p*-$NO_2C_6H_4$ | *p*-$NO_2C_6H_4$ | 0 | 0 | — | 6.95 | 0 | 77 | — | 306–308 [22] |

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

The reaction of α-tosyloxy-*p*-nitroacetophenone **1e** with *N*-methylthiourea **2a** (Entry 5, Table 1) gave altogether different result, and 2-imino-2,3-dihydrothiazole **3ea** was found to be the minor product (only 4%). However, by placing $NO_2$ group to *m*-position, the electron-withdrawing mesomeric effect of $NO_2$ group diminished, and the ratio of 2-imino-2,3-dihydrothiazole **3ia** in the reaction mixture increased from 4 to 30% (Entry 9, Table 1). These results clearly show that electronic factors on α-TK are governing the course of the reaction.

To see the effect of substituents present on thiourea, the reaction was further investigated by taking several substituted phenylthioureas. With *N*-phenylthiourea **2b**, there is a change in regioselectivity, and 2-aminothiazole **4** becomes the dominant product. For instance, in the reaction of α-tosyloxy-*p*-methoxyacetophenone **1a** and *N*-phenylthiourea **2b** under the optimum reaction conditions, the proportion of 2-imino-2,3-dihydrothiazole **3ab** in the reaction mixture is only 23% (Entry 10, Table 1), whereas it was 88% by using *N*-methylthiourea **2a** (Entry 1, Table 1). Effect of substituents on the product composition was again observed when **2b** was made to react with **1b–e**, **h–i** (Entries 11–16, Table 1) under the same reaction conditions. For instance, with *m*-$OCH_3$ group on the aryl ring of α-TK **1h**, the ratio of 2-imino-2,3-dihydrothiazole **3hb** decreases to 18% (Entry 15, Table 1), whereas replacing it with *p*-$NO_2$ group, 2-imino-2,3-dihydrothiazole **3** did not form at all (Entry 14, Table 1). These results show that the regiochemistry of the reaction depends not only on the nature and position of substituents present on the aryl group of α-TK but also on the nature of the substituent present on thiourea.

Afterwards, the reaction was also explored with *N*-(*p*-methoxyphenyl)thiourea **2c** (Entries 17–19, Table 1) and *N*-(*p*-nitrophenyl)thiourea **2d** (Entries 20–22, Table 1) with various α-TK. The reaction afforded 2-imino-2,3-dihydrothiazole **3** in greater ratio (69%) when **2c** was made to react with **1a** as compared with that obtained in the corresponding reaction of **1a** with **2b** (23%). The presence of $NO_2$ group on phenylthiourea **2d** again shifted the regioselectivity in favor of 2-aminothiazole, and **3** was not detected. This shows that electron-releasing/withdrawing groups on the phenyl ring of the thiourea also play a significant role in regiochemistry of the reaction and result in an increase in the ratio of **3** in case of electron-releasing groups and in favor of **4** when electron-withdrawing groups are present.

Because this reaction is a modification of Hantzsch thiazole synthesis, a study was undertaken to draw a comparison between α-TK and α-bromoacetophenones (α-BK). Some of these reactions were then performed using α-BK in place of α-TK under identical reaction conditions. It was found that although the reaction with α-BK proceeds faster (30 min) as compared with that with α-TK (45 min), the results summarized in Table 1 show that the reaction with α-TK is slightly more regioselective as

compared with the former. This may be attributed to the slow reactivity of α-tosyloxy group as compared with that of α-bromo, thus, making the reaction more selective.

A plausible mechanism of the reaction is given in Scheme 3. It was assumed that in acidic medium, the thioureas get protonated to give two forms, **A** and **B**, existing in equilibrium. DFT calculations at the hybrid B3LYP/6-31G** level of the relative energies of the protonated thioureas **A** and **B** (Table 2) show that for **2a** (Me), **2b** ($C_6H_5$), and **2c** ($p$-$CH_3OC_6H_4$), the **A** form is stabilized with respect to **B**, but for **2d** ($p$-$NO_2C_6H_4$), **B** becomes slightly favored, so affording an explanation for the experimental results.

2-Aminothiazoles **4** were thought to be forming through the protonated thioureas **B**, by involving substituted nitrogen (NHR) in the first attack of sulfur followed by intramolecular attack of the $NH_2$ group on the carbonyl in the second step that would afford the cyclic intermediate **C**. Subsequent dehydration of this tertiary alcohol leads to the formation of the thiazole nucleus **4**.

However, in case of 2-imino-2,3-dihydrothiazoles **3**, protonated thioureas **A** are involved; firstly, the carbon of the tosyloxymethyl group is attacked by the sulfur of thioureas involving the $NH_2$ nitrogen. Then, in the second step, NHR nitrogen of the open chain intermediate attacks on the carbonyl group to give the cyclic 4-hydroxythiazolidine intermediate **D**, which on further loss of water and proton give 2-imino-2,3-dihydrothiazoles **3** (Scheme 3). This mechanism seems reasonable because the thiazolidene-2-imine derivative has been prepared by the condensation of acyl and arylacyl thioureas with α-haloketones [19].

**Scheme 3**

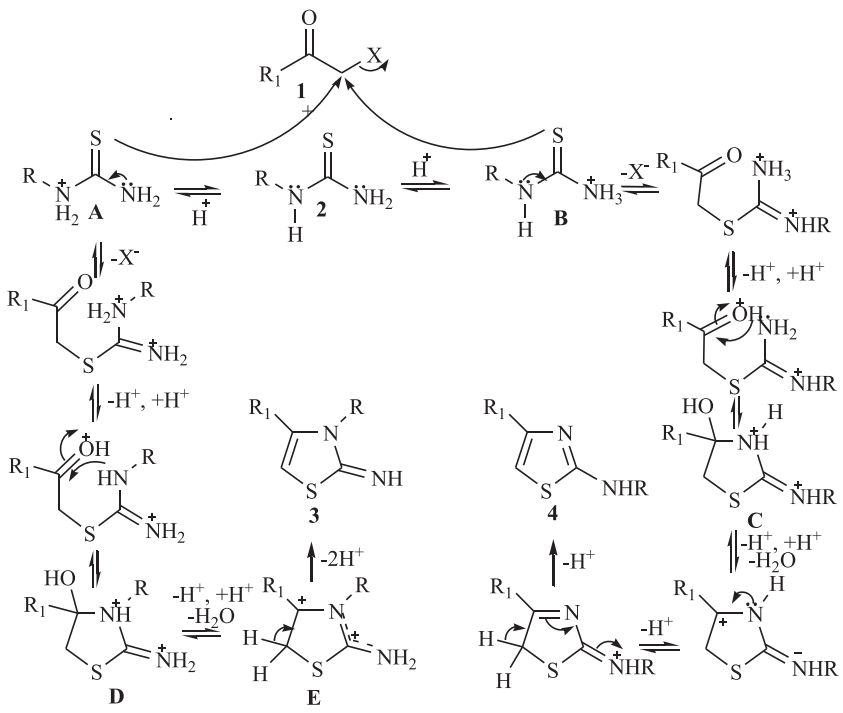


**Table 2**

Absolute energies (hartrees) and relative energies (kJ/mol) of structures **2aH$^+$–2dH$^+$**.

| Protonated thioureas | | A | B |
|---|---|---|---|
| **2aH$^+$** (R=$CH_3$) | | −587.87367 (0.0) | 29.841 |
| | +ZPE | −587.84899 (0.0) | 27.518 |
| **2bH$^+$** (R=$C_6H_5$) | | −779.62228 (0.0) | 19.216 |
| | +ZPE | −779.58509 (0.0) | 18.763 |
| **2cH$^+$** (R=$p$-$CH_3OC_6H_4$) | | −894.15313 (0.0) | 28.846 |
| | +ZPE | −894.10816 (0.0) | 28.442 |
| **2dH$^+$** (R=$p$-$NO_2C_6H_4$) | | 2.435 | −984.10385 (0.0) |
| | +ZPE | 2.304 | −984.06615 (0.0) |

Accordingly, it was thought that **2a** and **2c** are reacting mainly through protonated form **A**, whereas **2d** through form **B** and **2b** is the borderline mechanism. Furthermore, on changing the methyl group by a phenyl group, the equilibrium shifts towards protonated thioureas **B** because of the increase in steric hindrance between substituents R and $R_1$ in dication **D** as compared with dication **C**; as a result, the equilibrium shifts in favor of 2-aminothiazoles **4**, and the ratio of 2-aminothiazoles increases.

Finally, as the ratio of **3** increases with electron-donating groups and lowers with electron-withdrawing groups on $R_1$, it was thought that electron-withdrawing group present on $R_1$ facilitates the nucleophilic attack on the carbonyl group to give **D**, but instability of the resulting dication **E** again shifts the equilibrium towards **4**. In a similar manner, electron-donating groups present on R also favor the formation of **4** as compared with electron-withdrawing group that favors **3**.

## CONCLUSIONS

From our work, we have established that the reaction of α-TK **1a–i** with differently substituted thioureas **2a–d** affords 2-iminothiazolines and/or aminothiazoles depending on the nature of the substituents. A plausible mechanism, supported by DFT/B3LYP/6-31G** calculations, is proposed.

In a more detailed manner, we can conclude that (i) with α-TK having strong electron-donating substituents on *para* position of the phenyl group, the ratio of 2-iminothiazolines was the maximum with all thioureas. When such group was located in *ortho* and *meta*, the ratio of 2-iminothiazolines decreases; (ii) with α-TK having strong electron-withdrawing groups on *para* position, the ratio of 2-iminothiazolines was either zero or negligible with all thioureas. Changing the position of the electron-withdrawing group to *meta* increases the proportion of 2-iminothiazolines; (iii) the ratio of 2-iminothiazolines was maximum with *N*-methylthiourea comparatively with arylthioureas; (iv) arylthioureas substituted in *para* position of phenyl ring by electron-donating groups increased the amount of 2-iminothiazolines, and with strong electron-withdrawing groups in the same position, 2-iminothiazolines did not form at all.

## EXPERIMENTAL

**General.** Melting points were determined in open capillaries in electrical apparatus and are uncorrected. IR spectra were recorded on a ABB HORIZON MB3000 (Quebec, Canada) instrument. $^1$H NMR spectra were run on a Brucker instrument at 300 MHz using TMS as an internal standard. α-TK were synthesized according to literature procedure [26].

**DFT calculations.** The optimization of the structures of all compounds discussed in this paper was carried out at the hybrid B3LYP/6-31G** level [27–31] with basis sets of Gaussian type functions using Spartan '02 for Windows [32].

**General procedure for the reaction between α-tosyloxyacetophenones 1a–i (X=OTs) and *N*-substituted thioureas 2a–d.** To the solution of *N*-substituted thiourea **2** (2 mmol) in 10M HCl (6 mL)–EtOH (10 mL) was added α-TK **1** (X=OTs) (2 mmol). Resulting solution was stirred for 45 min at a temperature of 80°C. On cooling slowly, a solid separated out and was neutralized using aq. NaOH and extracted with ethyl acetate (3 × 20mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered,\ and concentrated. The TLC and the $^1$H NMR spectra of the reaction mixture showed the formation of two products **3** and **4** in the ratio given in Table 1. The mixture thus obtained was separated by column chromatography using silica gel (100–200 mesh) with petroleum ether:ethyl acetate (99:3) afforded **3**, and further elution of column with petroleum ether:ethyl acetate (98:5) afforded **4**.

**2-Imino-3-methyl-4-(*o*-methoxyphenyl)-2,3-dihydrothiazole (3ga).** IR (cm$^{-1}$): 3050 (N–H). $^1$H NMR ($CDCl_3$) δ: 3.24 (s, 3H, N–$CH_3$), 3.85 (s, 3H, $OCH_3$), 5.93 (s, 1H, 5-H), 6.97–7.05 (m, 2H, 3′, 5′-H), 7.24 (d, 1H, *J* = 9.6 Hz, 6′-H), 7.47 (t, 1H, *J* = 7.5 Hz, 4′-H). *Anal*. Calcd for $C_{11}H_{12}N_2OS$: N 12.72, found: N 12.54.

**2-Imino-3-methyl-4-(*m*-methoxyphenyl)-2,3-dihydrothiazole (3ha).** IR (cm$^{-1}$): 3051 (N–H). $^1$H NMR ($CDCl_3$) δ: 3.28 (s, 3H, N–$CH_3$), 3.84 (s, 3H, $OCH_3$), 5.83 (s, 1H, 5-H), 6.86–6.87 (m, 1H, 2′-H), 6.91–6.99 (m, 2H, 5′, 6′-H), 7.35–7.37 (m, 1H, 4′-H). *Anal*. Calcd for $C_{11}H_{12}N_2OS$: N 12.72, found: N 12.62.

**2-Imino-3-methyl-4-(*m*-nitrophenyl)-2,3-dihydrothiazole (3ia).** IR (cm$^{-1}$): 3045 (N–H). $^1$H NMR ($CDCl_3$) δ: 3.43 (s, 3H, N–$CH_3$), 5.90 (s, 1H, 5-H), 7.64-7.70 (m, 1H, 5′-H), 8.12–8.15 (m, 2H, 4′, 6′-H), 8.80–8.83 (m, 1H, 2′-H). *Anal*. Calcd for $C_{10}H_9N_3O_2S$: N 17.86, found: N 17.92.

**2-Imino-3-phenyl-4-(*m*-methoxyphenyl)-2,3-dihydrothiazole (3hb).** IR (cm$^{-1}$): 3052 (N–H). $^1$H NMR ($CDCl_3$) δ: 3.81 (s, 3H, $OCH_3$), 5.95 (s, 1H, 5-H), 6.73–6.76 (m, 1H, 2′-H), 6.96–6.99 (m, 1H, 4″-H ), 7.10–7.13 (m, 1H, 4′-H), 7.15–7.21 (m, 2H, 3″, 5″-H), 7.33–7.36 (m, 1H, 6′-H), 7.43–7.50 (m, 1H, 5′-H), 7.52–7.55 (m, 2H, 2″, 6″-H). *Anal*. Calcd for $C_{16}H_{14}N_2OS$: N 9.92, found: N 9.84.

**2-Imino-3,4-bis-(*p*-methoxyphenyl)-2,3-dihydrothiazole (3ac).** IR (cm$^{-1}$): 3062 (N–H). $^1$H NMR ($CDCl_3$) δ: 3.75 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 5.95 (s, 1H, 5-H), 6.72 (d, 2H, *J* = 8.7 Hz, 3″, 5″-H), 6.83 (d, 2H, *J* = 8.7 Hz, 3′, 5′-H), 7.07 (d, 2H, *J* = 8.7 Hz, 2″, 6″-H), 7.95 (d, *J* = 8.7 Hz, 2H, 2′, 6′-H). *Anal*. Calcd for $C_{17}H_{16}N_2O_2S$: N 8.97, found: N 8.75.

**2-(*N*-Methylamino)-4-(*o*-methoxyphenyl)thiazole (4ga).** IR (cm$^1$): 3556 (N–H) $^1$H NMR ($CDCl_3$) δ: 3.00 (s, 3H, N–$CH_3$), 3.92 (s, 3H, $OCH_3$), 6.40 (s, 1H, 5-H), 6.95–7.03 (m, 2H, 3′, 5′-H), 7.26–7.28 (m, 1H, 6′-H), 7.44–7.47 (m, 1H, 4′-H). *Anal*. Calcd for $C_{11}H_{12}N_2OS$: N 12.72, found: N 12.65.

**2-(*N*-Methylamino)-4-(*m*-methoxyphenyl)thiazole (4ha).** IR (cm$^{-1}$): 3550 (N–H). $^1$H NMR ($CDCl_3$) δ: 3.00 (s, 3H, N–$CH_3$), 3.86 (s, 3H, $OCH_3$), 6.71 (s, 1H, 5-H), 6.88–6.90 (m, 1H, 2′-H), 6.92–7.00 (m, 2H, 5′, 6′-H), 7.36–7.42 (m, 1H, 4′-H). *Anal*. Calcd for $C_{11}H_{12}N_2OS$: N 12.72, found: N 12.57.

**2-(*N*-Methylamino)-4-(*m*-nitrophenyl)thiazole (4ia).** IR (cm$^{-1}$): 3558 (N–H). $^1$H NMR ($CDCl_3$) δ: 3.05 (s, 3H, N–$CH_3$), 6.88 (s, 1H, 5-H), 7.52–7.57 (m, 1H, 5′-H), 8.26–8.32 (m, 2H, 4′, 6′-H), 8.66–8.69 (m, 1H, 2′-H). *Anal*. Calcd for $C_{10}H_9N_3O_2S$: N 17.86, found: N 17.75.

**2-(*N*-Phenylamino)-4-(*m*-methoxyphenyl)thiazole (4hb).** IR (cm$^{-1}$): 3564 (N–H). $^1$H NMR ($CDCl_3$) δ: 3.86 (s, 3H, $OCH_3$), 6.82 (s, 1H, 5-H), 6.85–6.88 (m, 1H, 4″-H), 7.05–7.09 (m, 2H, 3″,

5″-H), 7.29–7.31 (m, 1H, 4′-H), 7.32–7.41 (m, 3H, 2′, 5′, 6′-H), 7.42–7.49 (m, 2H, 2″, 6″-H). *Anal*. Calcd for $C_{16}H_{14}N_2OS$: N 9.92, found: N 9.87.

**2-(*N*-*p*-Methoxyphenylamino)-4-(*p*-methoxyphenyl)thiazole (4ac).** IR ($cm^{-1}$): 3570 (N–H). $^1H$ NMR ($CDCl_3$) δ: 3.83 (s, 3H, $OCH_3$), 3.85 (s, 3H, $OCH_3$), 6.62 (s, 1H, 5-H), 6.87–6.94 (m, 4H, 3′, 5′, 3″, 5″-H), 7.32 (d, 2H, $J = 8.7$ Hz, 2″, 6″-H), 7.76 (d, 2H, $J = 9$ Hz, 2′, 6′-H). *Anal*. Calcd for $C_{17}H_{16}N_2O_2S$: N 8.97, found: N 8.75.

**2-(*N*-*p*-Methoxyphenylamino)-4-(*p*-nitrophenyl)thiazole (4ec).** IR ($\nu_{max}$, $cm^{-1}$): 3566 (N–H). $^1H$ NMR (300 MHz, $CDCl_3$), δ: 3.81 (s, 3H, $OCH_3$), 6.96 (s, 1H, 5-H), 6.93 (d, $J = 8.7$ Hz, 2H, 3″, 5″-H), 7.34 (d, 2H, $J = 8.7$ Hz, 2″, 6″-H), 7.95 (d, 2H, $J = 9$ Hz, 2′, 6′-H), 8.22 (d, 2H, $J = 9$ Hz, 3′, 5′-H). *Anal*. Calcd for $C_{16}H_{13}N_3O_3S$: N 12.84, found: N 12.59.

**2-(*N*-*p*-Nitrophenylamino)-4-phenylthiazole (4cd).** IR ($\nu_{max}$, $cm^{-1}$): 3560 (N–H). $^1H$ NMR (300 MHz, $CDCl_3$), δ: 6.62 (d, 2H, $J = 9.0$ Hz, 2″, 6″-H), 6.96 (s, 1H, 5-H), 7.39–7.43 (m, 3H, 3′, 4′, 5′-H), 7.63–7.74 (m, 2H, 2′, 6′-H), 8.04 (d, 2H, $J = 9.0$ Hz, 3″, 5″-H). *Anal*. Calcd for $C_{15}H_{11}N_3O_2S$: N 14.13, found: N 14.06.

**General procedure for the reaction between α-bromoacetophenones 1a–i (X=Br) and *N*-substituted thioureas 2a–d.** To the solution of *N*-substituted thiourea **2** (2 mmol) in 10M HCl (6 mL)–EtOH (10 mL) was added α-BK **1** (X = Br) (2 mmol). Resulting solution was stirred for 30 min at a temperature of 80°C. On cooling slowly, a solid separated out and was neutralized using aq. NaOH and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The TLC and the $^1H$ NMR spectra of the reaction mixture showed the formation of two products **3** and **4** in the ratio given in Table 1.

**Acknowledgments.** We thank the Council of Scientific and Industrial Research, New Delhi of India and MICINN of Spain (Grant CTQ2010-16122) for financial assistance. Thanks are also due to RSIC, CDRI, Lucknow, India for providing elemental analysis. We also thank Prof. S. P. Singh for helpful suggestions.

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