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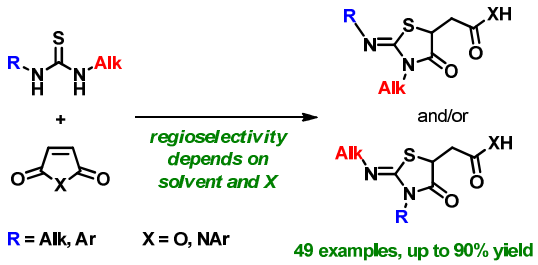
The regioselectivity of the reaction between unsymmetric thioureas and maleic acid derivatives has been studied, and general regularities have been established.



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ARTICLE TYPE

# Synthesis of thiazolidines via regioselective addition of unsymmetric thioureas to maleic acid derivatives†

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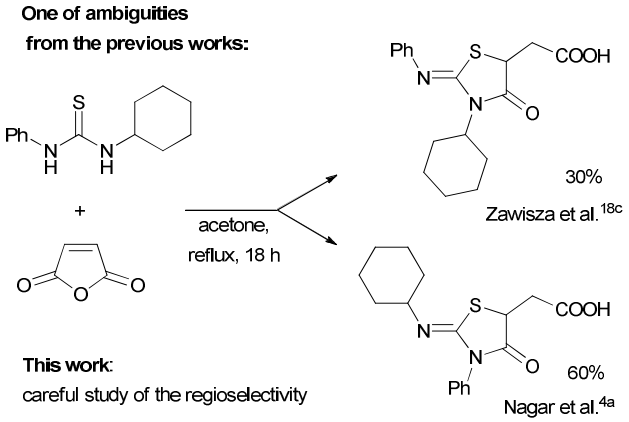
A wide range of unsymmetric thioureas has been studied in reaction with *N*-arylmaleimides and maleic anhydride. The regioselectivity of the addition depends not only on steric factors but on both solvent polarity and type of maleic acid derivative (imide or anhydride). The general regularities have been established providing practical guidelines to control the reaction result .The unequivocal structural assignment of all products has been done using NMR spectroscopy including $^{15}$N-$^{1}$H HMBC experiments.

## Introduction

Thiazolidine derivatives and, in particular, thiazolidinylacetic acids are highly valuable scaffolds for medicinal and bioorganic chemistry as can be exemplified by a central penicillin core that contains fused β-lactam and thiazolidine rings.[1] Various substituted thiazolidines exhibit anti-inflammatory,[2] antiviral,[3] anticonvulsant and cardiovascular properties.[4] Several thiazolidine derivatives were explored as anti-*Toxoplasma gondii*,[5] anticancer,[6] antibiofilm,[7] and antioxidant agents,[8] as well as sFRP-1[9] and MMPs[10] inhibitors for the treatment of bone related disorders. Thus, thiazolidine derivatives feature exclusively broad range of biological activities that warrants a constant interest in preparing new thiazolidines and studying their properties.[11]

Such a wealth of research activities is enabled by a facile synthesis of these compounds and ready availability of starting materials. For example, addition of thiourea derivatives to maleic anhydride or maleimides was used to get a rich functionalized thiazolidinylacetic acid framework. This approach was described for thiosemicarbazones,[2a,5,6,12] thiosemicarbazides,[5b] thiocarbonohydrazides,[13] and some alkyl and aryl (aroyl) mono-[14] and disubstituted (both *N*,*N*-[15] and *N*,*N*'-[4a,16]) thioureas. On the other hand, this method is also applicable to maleic acid[17] and its monoamides[9] including those with various functional groups at the C=C bond[18] that affords products ready for further modifications.[19]

It is accepted that this reaction begins with a nucleophilic attack of thiourea's sulfur atom on the C=C bond of maleimide or maleic anhydride followed by a proton transfer and a nucleophilic attack of a nitrogen atom on any of the two carbonyl groups and the latter step is considered rate-determining.[14a] Formation of the five-membered 4-oxo-1,3-thiazolidines is usually observed instead of the six-membered 4-oxo-1,3-thiazinanes[16c] (although the factors governing this preference remain unclear).



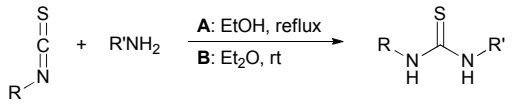

**Scheme 1**

The next question pertains to the regioselectivity of the nucleophilic attack of the nonequivalent nitrogen atoms of the thiourea. While for thiosemicarbazones ($R^1$ = –N=CRR') formation of 2-hydrazono-1,3-thiazolidines was reported for a wide range of substrates, the literature on addition of thioureas (especially *N*,*N*'-disubstituted) contains some controversial data. For example, Zawisza and coworkers[18c] reported that the reaction of *N*-cyclohexyl-*N*'-phenylthiourea with maleic anhydride in refluxing acetone led to 2-(3-cyclohexyl-4-oxo-2-phenylimino-1,3-thiazolidin-5-yl)acetic acid in 30% yield, whereas isomeric 2-(2-cyclohexylimino-4-oxo-3-phenyl-1,3-thiazolidin-5-yl)acetic acid was obtained in 60% yield by Nagar et al.[4a] for the same reaction under identical conditions (Scheme 1). It is important to mention that unambiguous evidence for the structural identity was given in neither article. Furthermore, Marrian and coworkers reported[15] a surprising result that the regioselectivity of the thiazolidine formation depends on a substituent at the maleimide's nitrogen atom. Summarizing the literature data, addition of unsymmetric thioureas to maleimides has not been carefully studied. We therefore decided to thoroughly investigate

factors governing the regioselectivity of this process, and our results are reported herein.

## Results and discussion

We used addition of amines **2** to isothiocyanates **1** in refluxing ethanol to synthesize a number of thioureas **3** (Scheme 2).[20] This simple procedure provides a convenient route to a wide range of various alkyl- and arylsubstituted thioureas. A series of *N*-substituted maleimides **4** (Table 1) was prepared from maleic anhydride and amines.[21]




**1** **2** **3**, 62-87%

**A**: R = Et, R' = Ph, 4-$MeOC_6H_4$, 4-$H_3CC_6H_4$, 4-$ClC_6H_4$, 4-$FC_6H_4$, 4-$O_2NC_6H_4$
R = $CH_3$, R' = 2,6-dimethylphenyl
R = Ph, R' = *i*-Pr, *c*-Hex, *t*-Bu
**B**: R = Et, R' = *i*-Pr

**Scheme 2** Synthesis of *N*-alkyl-*N*'-arylthioureas

We first used the reaction of *N*-aryl-*N*'-ethylthioureas **3a-f** and *N*-arylmaleimides **4a-g** to study the influence of the electronic factors on the ease and regioselectivity of the thiazolidine ring formation (Table 1, entries 1-36). In order to find the optimal reaction medium, we compared solvents of different nature yet with similar boiling points: polar protic isopropyl alcohol (bp 82 °C), polar aprotic acetonitrile (bp 81 °C) and nonpolar benzene (bp 80 °C). We found no significant solvent effect when equimolar mixtures of thioureas and maleimides **3a**/**4f** and **3c**/**4c** were refluxed in each solvent for an equal amount of time. The conversion of the starting material increased rapidly during the first 3-4 hours, but further heating did not improve the yield of the single reaction product. The remaining thiourea and maleimide can be easily removed after aqueous work up and subsequent product recrystallization from 50% aqueous ethanol. Due to simplicity of product isolation, isopropyl alcohol was chosen for further experiments.

In all cases 2-arylimino-3-ethyl-4-oxo-1,3-thiazolidines **5aa-ff** were isolated in good yields (the average yield for 36 reactions is 72%) with a single well reproducible exception of compound **5fa** (Table 1, entries 1-36). All obtained products share common characteristic features in their NMR spectra and the proton signals of the $CH^AH^B$-CH-S fragment are particularly diagnostic. The diastereotopic methylene protons signals appear as doublets of doublets in the range $\delta$ 2.7-2.8 ($CDCl_3$) (2.9-3.1 (DMSO-$d_6$)) and 3.3-3.4 ($CDCl_3$) (3.2-3.3 (DMSO-$d_6$)) ppm with the geminal coupling constant $^2J$ = 16.0-17.7 Hz and vicinal constants $^3J$ = 9.1-10.1 Hz for the high field signals and 3.2-4.4 Hz for the low field ones. The signal of the methyne proton is observed as a doublet of doublets with the corresponding vicinal constants at $\delta$ 4.4-4.5 ($CDCl_3$) (4.5-4.7 (DMSO-$d_6$)) ppm. In the $^{13}C$ NMR spectra the signals of SCH and C=N atoms are usually observed at $\delta$ 43.2-44.0 and 153-157 ppm, respectively. The signal of the *ipso*-carbon atom of the former thiourea aryl ring usually appears in the lower field than one from the starting maleimide ($\delta$ 141-156 versus 130-144 ppm, respectively).

However the NMR spectra patterns of 2-arylimino-3-ethyl-4-oxo-1,3-thiazolidines **5aa-ff** presented above can be expected for the isomeric 3-aryl-2-ethylimino-4-oxo-1,3-thiazolidines as well. Given the obvious different nucleophilicity of the thiourea's nitrogen atoms with aryl and ethyl groups, we expected formation of thiazolidines with the *endo*-cyclic alkyl group and unambiguously confirmed this inference using X-ray analysis data for compound **5af** (Fig. 1).[22] This thiazolidine features (*Z*)-configuration of the C=N bond to minimize the steric strain between the neighboring groups.

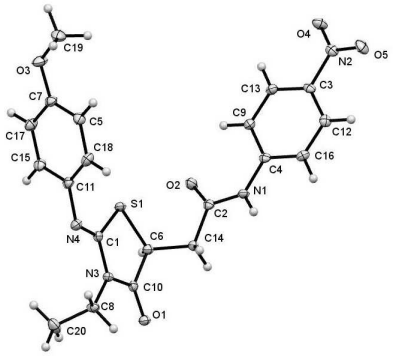



**Fig. 1** *ORTEP* representation of thiazolidine **5af**. Thermal ellipsoids are drawn at the 50% probability level

The $^1H$ NMR spectra of the reaction mixtures confirm that 2-arylimino-3-ethyl-4-oxo-1,3-thiazolidines **5aa-ff** were the single products in all cases except reactions with *N*-(4-methoxyphenyl)maleimide **4a,** where minor products (not exceeding 10% of the main product) were detected *in situ*. Based on the very similar, slightly shifted characteristic signals of the $CH^AH^B$-CH-S fragment, we speculate that they can be the regioisomeric 2-alkyliminothiazolidines.

As variation of substituents in both thiourea and maleimide aromatic rings showed that the electronic factors do not have a significant effect on the reaction selectivity, we decided to evaluate the steric factors. First, we examined thiourea **3g** with a sterically crowded *N*-(2,6-dimethylphenyl) group (Table 1, entries 37-41). Expectedly, 2-(2,6-dimethylphenylimino)-3-methyl-4-oxo-1,3-thiazolidines **5ga-gf** with the *endo*-cyclic position of a methyl group were obtained as single regioisomers. Their characteristic spectral features are consistent with those of 2-arylimino-3-ethyl-4-oxo-1,3-thiazolidines **5aa-ff**.

Next we assessed the influence of the alkyl group size on the reaction regioselectivity by comparing four *N*-alkyl-*N*'-phenylthioureas **3c,h-j** (Alk = Et, *i*-Pr, *c*-Hex, *t*-Bu) in reaction with *N*-phenylmaleimide **4c**. Experiments in isopropyl alcohol showed that isomers with *exo*-cyclic position of an alkyl group become more favoured with increasing the alkyl size (Table 2). Mixtures of two isomers **6h**,**7h** and **6i**,**7i** were obtained for reactions with isopropyl- and cyclohexylthioureas **3h** and **3i**, respectively. Bulky *N*-alkyl substituents on the thiourea impede the approach to the electrophilic carbonyl carbon atom of the maleimide, and in the case of the most sterically crowded *tert*-butyl group only 2-*tert*-butylimino-4-oxo-3-phenyl-1,3-thiazolidine **7j** was isolated. In line with this, the reaction time increases

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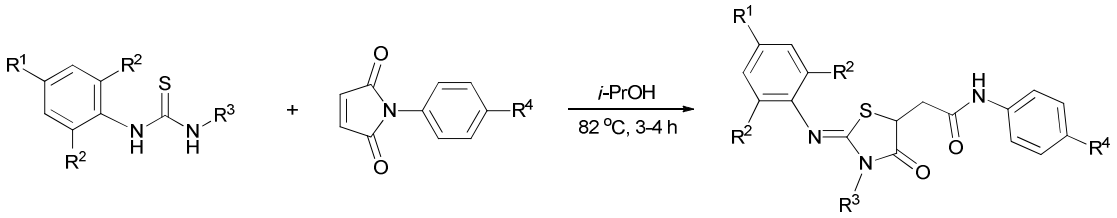
**Table 1** Substrate scope for the synthesis of 3-alkyl-2-arylimino-4-oxo-1,3-thiazolidines




**3a-g** **4a-g** **5aa-gf**

| Entry | Thiourea | $R^1$ | $R^2$ | $R^3$ | Maleimide | $R^4$ | Thiazolidine | Isolated yield, % |
|---|---|---|---|---|---|---|---|---|
| 1 | **3a** | OMe | H | Et | **4a** | OMe | **5aa** | 77 |
| 2 | **3a** | OMe | H | Et | **4b** | Me | **5ab** | 76 |
| 3 | **3a** | OMe | H | Et | **4c** | H | **5ac** | 80 |
| 4 | **3a** | OMe | H | Et | **4d** | Cl | **5ad** | 68 |
| 5 | **3a** | OMe | H | Et | **4e** | F | **5ae** | 80 |
| 6 | **3a** | OMe | H | Et | **4f** | $NO_2$ | **5af** | 78 |
| 7 | **3b** | Me | H | Et | **4a** | OMe | **5ba** | 69 |
| 8 | **3b** | Me | H | Et | **4b** | Me | **5bb** | 80 |
| 9 | **3b** | Me | H | Et | **4c** | H | **5bc** | 73 |
| 10 | **3b** | Me | H | Et | **4d** | Cl | **5bd** | 76 |
| 11 | **3b** | Me | H | Et | **4e** | F | **5be** | 74 |
| 12 | **3b** | Me | H | Et | **4f** | $NO_2$ | **5bf** | 79 |
| 13 | **3b** | Me | H | Et | **4g** | $CO_2Et$ | **5bg** | 56 |
| 14 | **3c** | H | H | Et | **4a** | OMe | **5ca** | 71 |
| 15 | **3c** | H | H | Et | **4b** | Me | **5cb** | 78 |
| 16 | **3c** | H | H | Et | **4c** | H | **5cc** | 69 |
| 17 | **3c** | H | H | Et | **4d** | Cl | **5cd** | 73 |
| 18 | **3c** | H | H | Et | **4e** | F | **5ce** | 77 |
| 19 | **3c** | H | H | Et | **4f** | $NO_2$ | **5cf** | 78 |
| 20 | **3d** | Cl | H | Et | **4a** | OMe | **5da** | 62 |
| 21 | **3d** | Cl | H | Et | **4b** | Me | **5db** | 70 |
| 22 | **3d** | Cl | H | Et | **4c** | H | **5dc** | 70 |
| 23 | **3d** | Cl | H | Et | **4d** | Cl | **5dd** | 81 |
| 24 | **3d** | Cl | H | Et | **4e** | F | **5de** | 63 |
| 25 | **3d** | Cl | H | Et | **4f** | $NO_2$ | **5df** | 68 |
| 26 | **3e** | F | H | Et | **4a** | OMe | **5ea** | 72 |
| 27 | **3e** | F | H | Et | **4b** | Me | **5eb** | 75 |
| 28 | **3e** | F | H | Et | **4c** | H | **5ec** | 86 |
| 29 | **3e** | F | H | Et | **4d** | Cl | **5ed** | 73 |
| 30 | **3e** | F | H | Et | **4e** | F | **5ee** | 71 |
| 31 | **3e** | F | H | Et | **4f** | $NO_2$ | **5ef** | 74 |
| 32 | **3f** | $NO_2$ | H | Et | **4a** | OMe | **5fa** | 36 |
| 33 | **3f** | $NO_2$ | H | Et | **4c** | H | **5fc** | 62 |
| 34 | **3f** | $NO_2$ | H | Et | **4d** | Cl | **5fd** | 72 |
| 35 | **3f** | $NO_2$ | H | Et | **4e** | F | **5fe** | 78 |
| 36 | **3f** | $NO_2$ | H | Et | **4f** | $NO_2$ | **5ff** | 69 |
| 37 | **3g** | H | Me | Me | **4a** | OMe | **5ga** | 66 |
| 38 | **3g** | H | Me | Me | **4c** | H | **5gc** | 75 |
| 39 | **3g** | H | Me | Me | **4d** | Cl | **5gd** | 71 |
| 40 | **3g** | H | Me | Me | **4e** | F | **5ge** | 66 |
| 41 | **3g** | H | Me | Me | **4f** | $NO_2$ | **5gf** | 81 |

from 3 h for ethylthiourea **3c** to 25-28 h for thioureas **3i,j**.

Comparison of the NMR spectroscopic data of two isomers **6h**,**7h** and **6i,7i** shows that the proton signals of the $CH^AH^B$-CH-S fragment of the isomer **A** appear in higher field than those of the isomer **B**. Thus, the signals of methylene protons in $CDCl_3$ are observed at $\delta$ 2.80, 3.33 ppm for isomer **A** and at $\delta$ 2.94, 3.45 ppm for isomer **B**, while that of the SCH proton appears at $\delta$ 4.37 ppm and 4.60 ppm, respectively. A chemical shift of the *N*-alkyl α-proton is even more characteristic, since a replacement of the *endo*-cyclic amide-position of an alkyl substituent for an *exo*-

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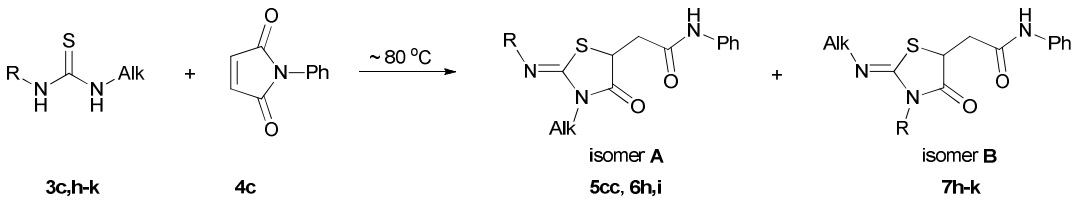
**Table 2** Reaction of thioureas **3c,h-k** with *N*-phenylmaleimide (**4c**) in different solvents. Ratio of isomers **A**:**B** is given according to the $^1$H NMR spectra of reaction mixtures




**3c,h-k** **4c** **5cc, 6h,i** **7h-k**

| Entry | Thiourea | R | Alk | Thiazolidines | Time, h | *i*-PrOH | $CH_3CN$ | $C_6H_6$ |
|---|---|---|---|---|---|---|---|---|
| 1 | **3c** | Ph | Et | **5cc** | 3 | 1:0 (69)[a] | 1:0 | 1:0 |
| 2 | **3h** | Ph | *i*-Pr | **6h/7h** | 17 | 1: 1.5 (25:39)[a] | 1:2.8 | 4.3:1 |
| 3 | **3i** | Ph | *c*-Hex | **6i/7i** | 28 | 1:2.1 (18:36)[a] | 1:4.2 | 2.6:1 |
| 4 | **3j** | Ph | *t*-Bu | **7j** | 25 | 0:1 | 0:1 | 0:1 (55)[a] |
| 5 | **3k** | Et | *i*-Pr | **7k** | 15 | 0:1 (83)[a] | 0:1 | 0:1 |

[a] Isolated yields, %

cyclic imino-position shifts it upfield by ~1.5 ppm (from $\delta$ 4.5-4.9 (**A**) to 3.15-3.5 (**B**) ppm, respectively). Some features of the $^{13}$C NMR spectra of the two isomers are instructive as well. For isomers **A** (**5cc**, **6h,i**), the signal of the *ipso*-carbon atom of the phenyl ring originally present in thiourea is observed at $\delta$ ~148 ppm whereas for isomers **B** (**7h-j**) it appears at $\delta$ ~136 ppm. For 3-phenylthiazolidines **7h-j**, the signal of the C=N carbon atom is found at $\delta$ ~149-150 ppm, while for 3-alkylthiazolidines **5cc**, **6h,i** it is at $\delta$ ~154 ppm. Besides that, the thiazolidines with *exo*-cyclic alkyl group are less soluble in common organic solvents than their isomers.

All the spectroscopic signatures mentioned above aid to the structural assignment of regioisomers, but they are not definite. We therefore used X-ray analysis to confirm the structures of isomers **6h** and **7h** (Fig. 2).[23] However, the X-ray analysis is not an express structural method, and we therefore used $^{15}$N-$^1$H HMBC NMR spectroscopy for structure determination of isomeric thiazolidines. In a typical spectrum of thiazolidine **6h** presented in the Supporting Information, the correlation between the C=N nitrogen signal at $\delta$ ~262 ppm and the signal of *ortho*-protons of the phenyl ring at $\delta$ ~6.9 ppm occurs via three bonds and is indicative of the *exo*-cyclic position of an aryl substituent. The correlation between *endo*-cyclic CON nitrogen signal at $\delta$ ~169 ppm and proton signals at $\delta$ ~1.54 ppm ($CH_3$ protons) confirms the *endo*-cyclic position of the isopropyl group (the vicinal coupling constant $^3J$ (*N*-CH-(C$H_3$)$_2$) is larger than the geminal $^2J$ (*N*-C*H*-(C$H_3$)$_2$)). In the $^{15}$N-$^1$H HMBC spectrum of thiazolidine **7h** the inverse correlations are found: C=*N* ($\delta$ ~274 ppm) gives a cross-peak with C$H_3$ ($\delta$ ~1.1 ppm), and CO*N* ($\delta$ ~167 ppm) with H$^o$ ($\delta$ ~7.3 ppm). Likewise $^{15}$N-$^1$H HMBC spectra of cyclohexyl isomers **6i** and **7i** provide analogous data thus confirming generality of this straightforward method for unambiguous structure assignment of isomeric thiazolidines.

Surprisingly, the replacement of isopropyl alcohol by aprotic nonpolar benzene in a reaction of *N*-alkyl-*N'*-phenylthioureas **3h,i** with *N*-phenylmalimide **4c** dramatically altered the regioselectivity in favor of 3-alkyl-2-arylimino-4-oxo-1,3-thiazolidines (Table 2, entries 2,3). On the other hand, aprotic but

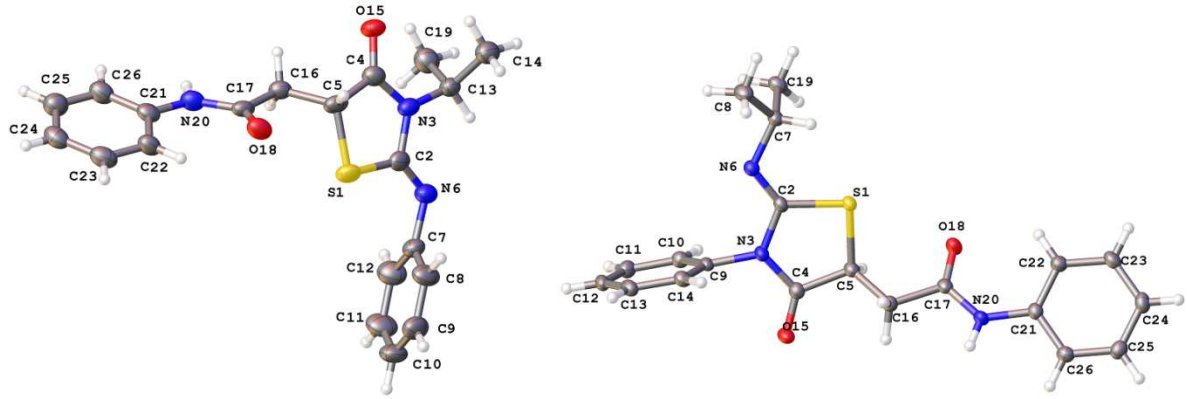



**Fig. 2** *OLEX2* representation of thiazolidines **6h** and **7h**. Thermal ellipsoids are drawn at the 50% probability level

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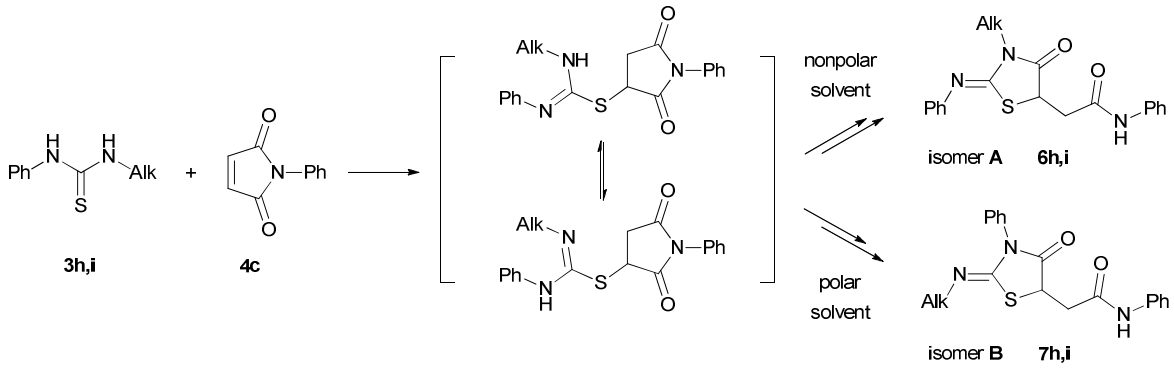


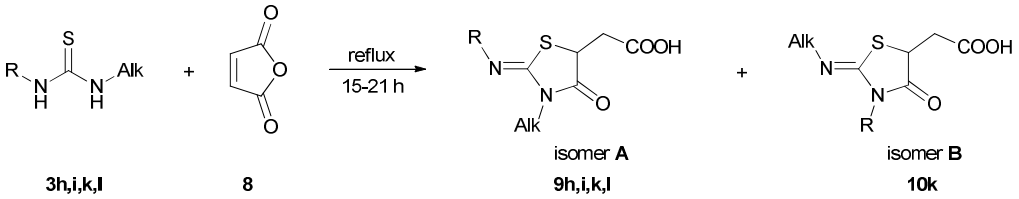

**Scheme 3** Solvent effect on regioselective formation of thiazolidines **6,7h,i**

polar acetonitrile gave even higher conversion to 2-alkylimino-3-aryl-4-oxo-1,3-thiazolidines **7h,i** as compared to isopropyl alcohol. Only for reactions with ethyl- and *tert*-butylthioureas **3c,j** the change of solvent had no influence on the reaction regioselectivity.

The influence of a solvent polarity on this reaction is clear, but it does not allow to draw any certain conclusions about the reaction mechanism remembering that a significant change of products ratio corresponds only to a small change in activation energy barriers difference (*e.g.*, from 1:1 to 1:4 by ~1 kcal/mol via the Boltzmann factor). As was mentioned earlier, the initial attack of a sulfur atom on the maleimide's C=C bond can be followed by a nucleophilic attack onto the carbonyl carbon atom by any of the two nitrogen atoms (Scheme 3). In general, the choice between these two reaction pathways is determined by the nucleophilicity of nitrogen atoms and steric preferences. However, for thioureas **3h,i** the transition state leading to isomer **B** is apparently more polar as polar solvents (isopropyl alcohol and acetonitrile) facilitate its formation, and the reaction seems to be kinetically controlled. In order to check the reversibility of the reaction steps we executed three experiments heating the pure isomer **7h** under reaction conditions in all solvents used before (during 18 h in isopropyl alcohol, acetonitrile, and benzene). No changes were observed in benzene solution, while in isopropyl alcohol ~11% of the second isomer was revealed along with the comparable quantities of the starting thiourea **3h** and *N*-phenylmaleimide (**4c**), and in acetonitrile - the same result to a lesser extent (~2-3%). Thus in general, this reaction appears to be reversible but under applied conditions the ratio of regioisomers is determined kinetically.

The expected result was obtained for unsymmetric dialkylthiourea **3k** in reaction with *N*-phenylmaleimide (**4c**). Only one product was formed independently of the solvent used (Table 2, entry 5), and its structure was assigned to **7k**. In the NMR spectra of thiazolidine **7k** the signal of the $CH_2$ protons of ethyl group is observed at $\delta$ ~3.79 ppm - the same position as for 3-ethylthioureas **5aa-ff**, and the proton and carbon signals of the methine fragment of isopropyl group ($\delta_H$ 3.45 ppm, $\delta_C$ 53.5 ppm) confirm its *exo*-cyclic position (compare with thiazolidine **7h**). Thus, the regioselectivity of this reaction if two different alkyl groups are introduced in the thiourea seems to be determined by steric factors but not by solvent polarity.

**Table 3** Reaction of thioureas **3h,i,k,l** with maleic anhydride (**8**) in different solvents. Ratio of isomers **A**:**B** is given according to the $^1$H NMR spectra of reaction mixtures




| Entry | Thiourea | R | Alk | Thiazolidine | Acetone | $C_6H_6$ |
|---|---|---|---|---|---|---|
| 1 | **3i** | Ph | *c*-Hex | **9i** | 1:<0.2 (60:0) | 1:0 (87)[a] |
| 2 | **3h** | Ph | *i*-Pr | **9h** | 1:<0.2 | 1:0 (71)[a] |
| 3 | **3l** | Ph | $CH_2Ph$ | **9l** | 1:<0.15 | 1:0 (76)[a] |
| 4 | **3k** | Et | *i*-Pr | **9k/10k** | 1.3:1 | 1:1.8 (90)[a] |

[a] Isolated yields, %

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# ARTICLE TYPE

Finally, we reproduced the before mentioned (Scheme 1) controversial reaction of *N*-cyclohexyl-*N*'-phenylthiourea (**3i**) with maleic anhydride (**8**) (Table 3, Entry 1). The first experiment was carried out in refluxing acetone exactly as in both articles[4a,18c] and only one product was isolated after recrystallization (according to the $^1$H NMR spectrum of the reaction mixture a small amount of a second isomer was detected). The spectral features of the main product ($\delta$ (NC*H*) ~4.35 ppm, $\delta$ (N*C*H) 54.9 ppm, $\delta$ (C$^i$) 148.5 ppm) correspond to the structure of 2-(3-cyclohexyl-4-oxo-2-phenylimino-1,3-thiazolidin-5-yl)acetic acid (**9i**). In addition, the structure of thiazolidine **9i** was verified by $^{15}$N-$^1$H HMBC NMR spectroscopy (see Supporting Information). In this way we have confirmed the result of Zawisza and coworkers.[18c] The noticeably lower yield given in their paper (30%) may be addressed to the careless product isolation.

Remembering our previous observations of solvent-dependent regioselectivity in the reaction of thiourea **3i** with *N*-phenylmaleimide (**4c**) (Table 2) we had tried nonpolar solvent here too. But no change of regioselectivity was detected! Only one regioisomer **9i** was formed in benzene that was confirmed by the $^1$H NMR spectrum of the reaction mixture. The same result was also obtained for isopropyl-**3h** and benzyl-**3l** thioureas (Table 3). This remarkable outcome shows that despite of steric factors this reaction leads preferentially to the obviously more sterically hindered isomer with the *endo*-cyclic position of bulky alkyl group.

But even more outstanding is the reaction of *N*-ethyl-*N*'-isopropylthiourea (**3k**) with maleic anhydride (**8**) because in this particular case we again established solvent-dependent regioselectivity and mixtures of isomeric thioureas **9k**/**10k** were obtained (Table 3, entry 4). In polar acetone the isomer with *endo*-cyclic position of bulkier isopropyl group **9k** is formed preferentially whereas in nonpolar benzene the regioselectivity changes in favor of 3-ethyl-2-isopropyliminothiazolidine **10k**. These similar compounds are hardly separated by column chromatography therefore we characterized them in mixture thanks to our knowledge about spectral features discussed before.

Thus, the reaction of *N*-alkyl-*N*'-phenylthioureas **3h,i,l** with bulky alkyl groups with maleic anhydride (**8**) proceeds in regioselective manner giving preferentially or exclusively 3-alkyl-2-phenyliminothiazolidines **9h,i,l** independently of the solvent polarity (Table 3) that absolutely differ from the reaction with *N*-phenylmaleimide (**4c**) with variable regioselectivity (Table 2). And on the contrary, *N*,*N*'-dialkylthiourea **3k** with different substituents in reaction with *N*-phenylmaleimide (**4c**) gives only one isomer **7k** independently of the solvent but with maleic anhydride (**8**) - variable mixtures of isomers **9k**/**10k**. Steric factors solely evidently failed to explain these really surprising regularities where more sterically hindered products are often formed preferentially and the regioselectivity of the process depends on both solvent polarity and type of maleic acid derivative (imide or anhydride). This reaction, so simple at first sight, demonstrates some intriguing features being more ambiguous than it seems though still controllable.

## Conclusions

The addition of *N*-aryl-*N*'-ethyl(methyl)thioureas to *N*-arylmaleimides proceeds regioselectively providing 2-(3-ethyl(methyl)-2-arylimino-4-oxo-1,3-thiazolidin-5-yl)-*N*-arylacetamides in good yields. It is applicable for a wide range of substituents in aromatic rings and the product selectivity does not depend on the solvent used. A remarkable dependence of the reaction regioselectivity on the solvent polarity was revealed with more sterically hindered alkyl thioureas. In nonpolar benzene 3-alkyl-2-arylimino-4-oxo-1,3-thiazolidines are formed preferentially, whereas in polar isopropyl alcohol and acetonitrile the reaction regioselectivity changes in favor of 2-alkylimino-3-aryl-4-oxo-1,3-thiazolidines. In the case of the most bulky *N*-*tert*-butyl-*N*'-phenylthiourea, the only isomer with *exo*-cyclic position of an alkyl group is formed. But in reaction with maleic anhydride sterically hindered *N*-alkyl-*N*'-phenylthioureas demonstrate preferred formation of 3-alkyl-2-phenyliminothiazolidines.

*N*-Ethyl-*N*'-isopropylthiourea gives opposite regioselective outcome: one product in the reaction with *N*-phenylmaleimide and solvent-dependent mixtures of isomers with maleic anhydride.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: [representative experimental details, characterization data for compounds, copies of the $^1$H and $^{13}$C NMR spectra for compounds **5aa-ff**, **5ga-gf**, **6h,i**, **7h-k**, **9h,i,l** and **9k/10k**, copies of the $^{15}$N-$^1$H HMBC NMR spectra for compounds **6h,i**, **7h,i** and **9i**]. See DOI: 10.1039/b000000x/

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23 CCDC 936389 and 993722 contain the supplementary crystallographic data for compounds **6h** and **7h**, respectively. These data can be obtained free of charge from The Cambrige Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.