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Reaction of *N*-benzyl azomethine ylide with aryl isothiocyanates: synthesis of (*Z*)-*N*-aryl-3-benzylthiazolidine-5-imines

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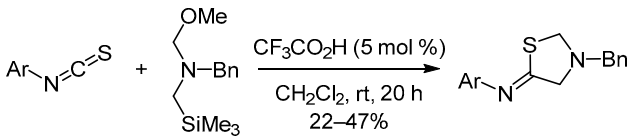


Ar = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-BrC$_6$H$_4$

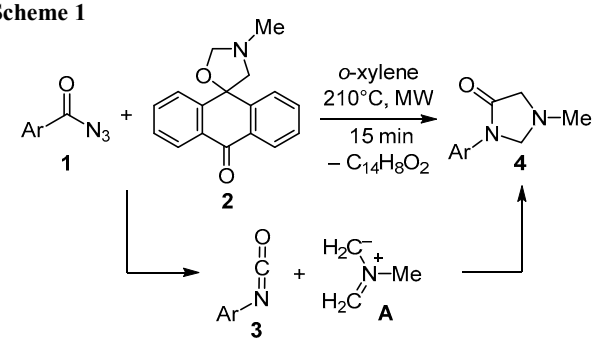
The reaction of aryl isothiocyanates with nonstabilized azomethine ylides generated *in situ* by various methods was studied. It was established that the use of *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine in the presence of trifluoroacetic acid in the role of a catalyst led to the formation of (*Z*)-*N*-aryl-3-benzylthiazolidin-5-imines in 22–47% yields.

Keywords: azomethine ylides, isothiocyanates, thiazolidines, [3+2] cycloaddition.

Nonstabilized azomethine ylides are commonly employed by organic chemists for the synthesis of various nitrogen heterocycles *via* [3+2] cycloaddition reactions to activated alkenes.[1] Recently, there has been a growing interest by researchers toward using the cycloaddition reactions of azomethine ylides to heterodipolarophiles C = X (where X = N, O, S), leading to the formation of imidazolidines, oxazolidines, and thiazolidines.[2] For this reason, it is important to characterize the chemoselectivity of such reactions when the starting dipolarophile contains two different double bonds. For example, it was found that 1,3-dipolar cycloaddition proceeded more readily at an activated C=C double bond compared to a C=O bond.[3]

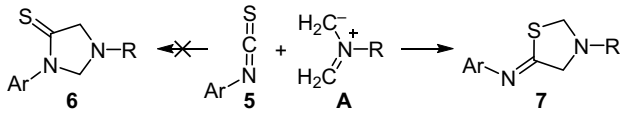
We recently studied spiro[anthracene-9,5'-oxazolidine] **2** as a precursor of azomethine ylides **A** in reactions with aroyl azides **1**, which underwent a Curtius rearrangement upon heating in a microwave reactor and *in situ* formed aryl isocyanates **3** that reacted with azomethine ylide **A** present in the reaction medium (Scheme 1).[4] As a result, imidazolidin-4-ones **4** were isolated as products of ylide addition at the C=N bond, while adducts at the C=O bond were not detected. Unsubstituted phenyl isocyanate reacted analogously.

Scheme 1



In a continuation of that work, we were interested in any changes in the selectivity of this reaction as a result of replacing the oxygen atom in the molecule of isocyanate **3** with a sulfur atom. Taking into account the fact that the cycloaddition reaction of azomethine ylides with thiones proceeds easier than with ketones,[2a] one could expect the formation of both imidazolidines **6** (adducts at the C=N bond) and thiazolidines **7** (adducts at the C=S bond) upon the use of isothiocyanates[5] **5** (Scheme 2). The reactions of isothiocyanates **5** with nonstabilized azomethine ylides have not been previously studied.

Scheme 2



At the same time, related reactions of aryl isothiocyanates with stabilized azomethine ylides, generated from ninhydrin and proline, have been described in the literature,[6a] as well as there are reports about reactions with aziridines containing electron-withdrawing substituents.[6b–d] The latter reactions[6b–d] depend on the structure of the starting substrates and lead to the formation of both azomethine ylide adducts at the C=N or C=S bonds and imidazolidine-2-thiones resulting from an initial nucleophilic attack by nitrogen atom, followed by a recyclization step.

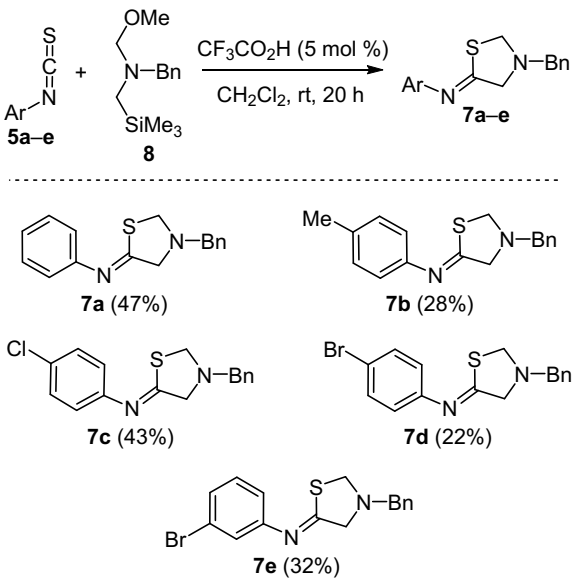
We selected phenyl isothiocyanate (**5a**) as a model substrate. The reaction conditions that were previously developed for phenyl isocyanate were initially applied also in this case, by heating an excess of substrate with spiro-[anthracene-9,5'-oxazolidine] **2** in a microwave reactor at 210°C (Scheme 2, Table 1, entry 1). However, the reaction produced an intractable product mixture under these conditions. Refluxing of phenyl isothiocyanate (**5a**) with sarcosine and formaldehyde in benzene medium in a flask equipped with a Dean–Stark adapter also was not successful, as the major product was 1,1-dimethyl-3-phenylthiourea (Table 1, entry 2). The use of *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**8**) as a precursor of nonstabilized azomethine ylide in the presence of trifluoroacetic acid as catalyst allowed to obtain 3-benzylthiazolidin-5-imine **7a**, which was isolated by column chromatography in 47% yield (Scheme 3, Table 1, entry 3).

Table 1. Optimization of the reaction conditions for the synthesis of product **7** (Ar = Ph)

Entry	Reaction conditions	Yield, %
1	**5a** (1.5 equiv), **2** (1 equiv), *o*-xylene, MW, 210°C, 15 min	–*
2	**5a** (1 equiv), sarcosine (1.2 equiv), CH_2O (1.8 equiv), PhH, reflux, 3 h	–*
3	**5a** (1 equiv), **8** (1.25 equiv), CF_3CO_2H (0.05 equiv), CH_2Cl_2, 0–25°C, 20 h	47**

* R = Me, intractable product mixture.
** R = Bn.

Scheme 3



Aryl isothiocyanates **5b–e** containing methyl or halogen substituents at the benzene ring also participated in this reaction, forming corresponding *N*-aryl-3-benzylthiazolidin-5-imines **7b–e** in 22–43% yields (Scheme 3). The reactions with 3,4-dimethoxyphenyl and 3-nitrophenyl isothiocyanates produced intractable product mixtures, pointing to the deleterious effect of strong electron-donating or -withdrawing substituents in the starting substrate.

The structures of the obtained adducts **7a–e** were established by IR spectroscopy and two-dimensional NMR (^1H–^{15}N HMBC) experiments. Thus, IR spectrum of 3-benzylthiazolidin-5-imine **7a** contained an absorption band at 1670 cm^{-1} due to the stretching vibrations of imino group in imidothioate structure **7** and contradicting the alternative thioamide structure **6**. ^1H–^{15}N HMBC spectrum of cycloadduct **7b** featured a cross peak of nitrogen signal at 170.4 ppm with the protons at position 4 of thiazolidine ring, which gave a signal at 4.04 ppm (Fig. 1). The absence of an analogous cross peak with protons at position 2 of compound **7b**, separated by 4 bonds from the same nitrogen atom, also supported the assignment of thiazolidine structure to this compound.

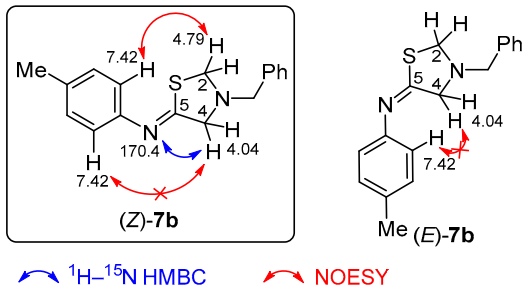


Figure 1. The main correlations in 2D NMR spectra of adduct **7b**.

The stereoconfiguration of imino group was established on the basis of NOESY spectrum of product **7b**, which featured a cross peak of proton signal at 4.79 ppm, belonging to the 2-CH_2 group of thiazolidine ring, with the *ortho* protons of the *N*-aryl substituent at 7.42 ppm. Also, the NOESY spectrum showed an absence of cross peak of the latter protons with the 4-CH_2 group giving a signal at 4.04 ppm, confirming the existence of adduct **7b** in a (*Z*)-configuration. In the isomeric structure (*E*)-**7b**, on the other hand, a strong coupling through space would be expected between the *ortho*-aniline protons and the protons at position 4. The (*Z*)-configuration of cycloadducts **7** was entirely expected, since the attack by azomethine ylide proceeded from the less sterically congested side of aryl isothiocyanate **5**.

Thus, we have explored the reaction of aryl isothiocyanates with *N*-benzyl azomethine ylide, leading to the formation of (*Z*)-*N*-aryl-3-benzylthiazolidin-5-imines. It was shown that, upon changing the starting materials from aryl isocyanates to aryl isothiocyanates, the chemoselectivity of [3+2] cycloaddition was altered.

Experimental

IR spectra were recorded on a Bruker Alpha spectrometer equipped with an ATR accessory (ZnSe crystal). ^{1}H NMR spectra were acquired on a Bruker Avance 500 instrument (500 MHz) for samples in $CDCl_3$ solutions, with TMS as internal standard. ^{13}C NMR spectra were acquired on Bruker Avance 400 and Bruker Avance 500 instruments (101 and 126 MHz, respectively) for samples in $CDCl_3$ solutions, with the solvent signal used as internal standard (77.2 ppm). NOESY and ^{1}H–^{15}N HMBC spectra were acquired on a Bruker Avance 400 instrument. High-resolution mass spectra were recorded by using a Bruker maXis Impact HD mass spectrometer (TOF ESI). Column chromatography was performed on Merck silica gel (40–63 μm), with quality meeting the ASTM specification.

All solvents were dried and distilled according to the standard procedures.

Synthesis of (*Z*)-*N*-aryl-3-benzylthiazolidin-5-imines 7a–e (General method). A mixture of the appropriate aryl isothiocyanate **5a**–**e** (1.0 mmol) and *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**8**) (296 mg, 1.25 mmol) in anhydrous CH_2Cl_2 (3 ml) was cooled to 0°C and treated by dropwise addition of CF_3CO_2H (6 mg, 0.05 mmol) as a solution in anhydrous CH_2Cl_2 (1 ml). The mixture was warmed to room temperature and stirred for 20 h. The solution was washed with concd $NaHCO_3$ solution, H_2O, and then dried over anhydrous Na_2SO_4. The solvent was removed by evaporation on a rotary evaporator. The obtained oily product was purified by column chromatography (eluent CH_2Cl_2–hexane or EtOAc–hexane).

(*Z*)-3-Benzyl-*N*-phenylthiazolidin-5-imine (7a). The crude product was purified by column chromatography (eluent CH_2Cl_2–hexane, 5:1), R_f 0.33 (CH_2Cl_2). Yield 0.126 g (47%), yellow oil. IR spectrum, ν, cm^{-1}: 1670. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.85 (2H, s, NCH_2Ph); 4.06 (2H, t, *J* = 1.1, 4-CH_2); 4.82 (2H, t, *J* = 1.1, 2-CH_2); 7.29–7.34 (2H, m, H Ph); 7.34–7.37 (4H, m, H Ph); 7.45 (2H, t, *J* = 7.9, H Ph); 7.55–7.58 (2H, m, H Ph). ^{13}C NMR spectrum (126 MHz), δ, ppm: 59.2; 70.6; 78.7; 124.1; 127.9; 128.0; 128.9 (2C); 129.4; 137.2; 138.4; 198.2. Found, *m*/*z*: 269.1107 $[M+H]^+$. $C_{16}H_{17}N_2S$. Calculated, *m*/*z*: 269.1103.

(*Z*)-3-Benzyl-*N*-(*p*-tolyl)thiazolidin-5-imine (7b). The crude mixture was treated with 1:4 EtOAc–hexane mixture (2 ml), and the insoluble precipitate of urea was removed by filtration. The crude product was purified by column chromatography (eluent EtOAc–hexane, 1:4), R_f 0.35 (EtOAc–hexane, 1:2). Yield 0.08 g (28%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.36 (3H, s, CH_3); 3.84 (2H, s, NCH_2Ph); 4.04 (2H, t, *J* = 1.1, 4-CH_2); 4.79 (2H, t, *J* = 1.1, 2-CH_2); 7.24 (2H, d, *J* = 8.3, H Ar); 7.28–7.33 (1H, m, H Ph); 7.34–7.36 (4H, m, H Ph); 7.42 (2H, d, *J* = 8.3, H Ar). ^{13}C NMR spectrum (101 MHz), δ, ppm: 21.3; 59.1; 70.5; 78.7; 124.0; 127.9; 128.8; 128.9; 129.9; 135.8; 137.2; 138.0; 197.9. Found, *m*/*z*: 283.1263 $[M+H]^+$. $C_{17}H_{19}N_2S$. Calculated, *m*/*z*: 283.1263.

(*Z*)-3-Benzyl-*N*-(4-chlorophenyl)thiazolidin-5-imine (7c). The crude mixture was treated with 1:4 mixture of EtOAc–hexane (2 ml), and the insoluble precipitate of urea was removed by filtration. The crude product was purified by column chromatography (eluent EtOAc–hexane, 1:4), R_f 0.38 (EtOAc–hexane, 1:2). Yield 0.13 g (43%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.84 (2H, s, NCH_2Ph); 4.04 (2H, t, *J* = 1.1, 4-CH_2); 4.80 (2H, t, *J* = 1.1, 2-CH_2); 7.29–7.33 (1H, m, H Ph); 7.33–7.37 (4H, m, H Ph); 7.40 (2H, d, *J* = 8.8, H Ar); 7.54 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum (101 MHz), δ, ppm: 59.1; 70.6; 78.4; 125.3; 128.1; 128.9; 129.5; 133.3; 136.9; 137.0; 198.5. Found, *m*/*z*: 303.0717 $[M+H]^+$. $C_{16}H_{16}ClN_2S$. Calculated, *m*/*z*: 303.0714.

(*Z*)-3-Benzyl-*N*-(4-bromophenyl)thiazolidin-5-imine (7d). The crude mixture was treated with 1:4 mixture of EtOAc–hexane (2 ml), and the insoluble precipitate of urea was removed by filtration. The crude product was purified by column chromatography (eluent EtOAc–hexane, 1:4), R_f 0.32 (EtOAc–hexane, 1:2). Yield 0.076 g (22%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.84 (2H, s, NCH_2Ph); 4.03 (2H, s, 4-CH_2); 4.80 (2H, s, 2-CH_2); 7.30–7.38 (5H, m, H Ph); 7.48 (2H, d, *J* = 8.8, H Ar); 7.56 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum (101 MHz), δ, ppm: 59.1; 70.6; 78.3; 121.2; 125.5; 128.1; 128.9; 132.4; 137.0; 137.4; 198.5. Found, *m*/*z*: 347.0212 $[M+H]^+$. $C_{16}H_{16}BrN_2S$. Calculated, *m*/*z*: 347.0207.

(*Z*)-3-Benzyl-*N*-(3-bromophenyl)thiazolidin-5-imine (7e). The crude mixture was treated with 1:4 mixture of EtOAc–hexane (2 ml), and the insoluble precipitate of urea was removed by filtration. The crude product was purified by column chromatography (eluent EtOAc–hexane, 1:4), R_f 0.22 (EtOAc–hexane, 1:3). Yield 0.111 g (32%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.84 (2H, s, NCH_2Ph); 4.04 (2H, s, 4-CH_2); 4.81 (2H, s, 2-CH_2); 7.29–7.33 (1H, m, H Ph); 7.31 (1H, t, *J* = 8.1, H Ar); 7.34–7.38 (4H, m, H Ph); 7.45 (1H, d, *J* = 8.1, H Ar); 7.56 (1H, d, *J* = 8.1, H Ar); 7.75 (1H, t, *J* = 1.9, H Ar). ^{13}C NMR spectrum (126 MHz), δ, ppm: 59.1; 70.6; 78.4; 122.6; 122.7; 126.9; 128.1; 128.9; 130.5; 130.8; 137.0; 139.6; 198.7. Found, *m*/*z*: 347.0212 $[M+H]^+$. $C_{16}H_{16}BrN_2S$. Calculated, *m*/*z*: 347.0208.

Supplementary information file containing IR spectrum of compound **7a**, ^{1}H and ^{13}C NMR spectra of compounds **7a**–**e**, as well as NOESY and ^{1}H–^{15}N HMBC spectra of compound **7b** is available at the journal website at http://link.springer.com/journal/10593.

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