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Stereoselective synthesis of 2-pyrrolinyl- and 2-imidazolinylthiazoles

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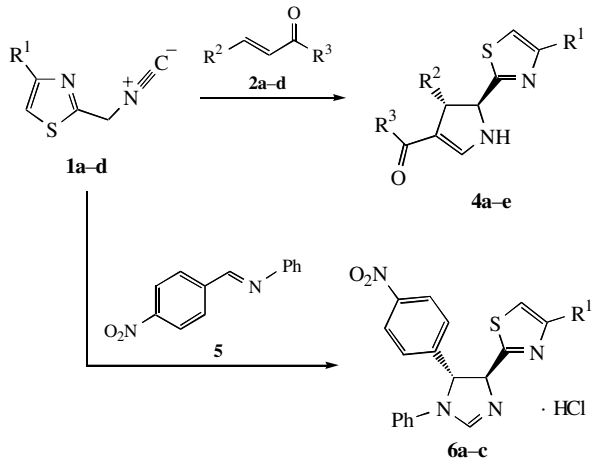
The reaction of 2-isocyanomethylthiazoles with *trans*-chalcone or aromatic azomethines in the presence of copper compounds results in only *trans*-pyrrolines or *trans*-imidazolines with thiazole substituents, as evidenced by ^{1}H NMR and mass spectrometry.

The thiazole structure is an important part in a great number of biologically active compounds. One of the promising methods for the preparation of various thiazole derivatives is based on the use of 2-isocyanomethylthiazoles (*e.g.*, the one-step synthesis of demethyldysidenin by the Passerini reaction).[1] The presence of acidic hydrogen at the -carbon atom of the isocyanomethyl group opens wide opportunities for performing a variety of cyclyzation reactions of the generated ylides with carbonyl compounds, , -unsaturated nitriles and azomethines[2–4] in the presence of catalysts such as bases,[2] copper(I) oxide[3] and gold(I) tetrafluoroborate.[4] Cycloaddition reactions of this type usually result in a mixture of diastereoisomers.[2–4] Thus, Ito *et al.*[5] reported a diastereoselective and enantioselective synthesis of 2-oxazolines using a gold(I)-catalysed aldol reaction in the presence of chiral ferrocenylamine ligands. Schollkopf *et al.*[6] observed the base-catalysed epimerization of *cis*-oxazolines into thermodynamically more stable *trans*-oxazolines. Therefore, *trans*-oxazoline is the major product of base-catalysed cyclization.

We have found that the refluxing of 4-(4-chlorophenyl)-2-isocyanomethylthiazole **1a** in benzene with *trans*-chalcone **2a** in the presence of copper(I) acetylacetonate **3** results in the formation of only one of six possible diastereoisomeric 2-pyrrolinylthiazoles† (Scheme 1). The structure of *trans*-2-(3-benzoyl-4-phenyl- 2-pyrrolin-5-yl)-4-(4-chlorophenyl)thiazole **4a** was assigned to this product on the basis of NMR and mass spectrometry data. The *cis*-isomer has not been detected in the reaction mixture by NMR. The NMR spectrum of **4a** exhibited



1a R^1 = 4-ClC_6H_4
1b R^1 = 4-$MeOC_6H_4$
1c R^1 = Ph
1d R^1 = 4-BrC_6H_4

2a R^2 = R^3 = Ph
2b R^2 = R^3 = 4-ClC_6H_4
2c R^2 = R^3 = 4-$NO_2C_6H_4$
2d R^2 = 3-pyridinyl, R^3 = Ph

4a R^1 = 4-ClC_6H_4, R^2 = R^3 = Ph
4b R^1 = R^2 = R^3 = 4-ClC_6H_4
4c R^1 = 4-ClC_6H_4, R^2 = R^3 = 4-$NO_2C_6H_4$
4d R^1 = 4-ClC_6H_4, R^2 = 3-pyridinyl, R^3 = Ph
4e R^1 = 4-$MeOC_6H_4$, R^2 = R^3 = Ph

6a R^1 = Ph
6b R^1 = 4-BrC_6H_4
6c R^1 = 4-$MeOC_6H_4$

Scheme 1

the resonance signals of three non-equivalent aromatic rings at δ 7.35-8.01 ppm, a broad singlet of the NH group at δ 8.33 ppm, and a singlet of the thiazole ring at δ 8.15 ppm. Moreover, the signals of three protons of the pyrroline ring are observed: a doublet at δ 4.47 ppm (J 4.7 Hz), a doublet of doublets at δ 5.07 ppm (J 4.7 Hz and 1.6 Hz) and a doublet at δ 7.56 ppm (J 1.6 Hz). Mass-spectrometric analysis confirmed the molecular formula of this compound, while the NMR data enabled us to determine the stereochemical features of 2-pyrrolines. The presence of NH group peaks suggests that we prepared 2-pyrrolines. A value of 4.7 Hz for the coupling constant between 4- and 5-protons of the pyrroline ring allows us to conclude that the obtained compound exists as the *trans*-isomer.[4] The reaction of 4-aryl-2-isocyanomethylthiazoles **1a**,**b** with substituted *trans*-chalcones **2a–d** proceeds in a similar way thus leading to corresponding *trans*-2-pyrrolines **4a–e**. The introduction of electron-withdrawing substituents in *trans*-chalcones results in shortening the reaction time and increasing yield of the product. In contrast, the introduction of electron-donating substituents decreases yields of the target compounds. For example, the use of 4,4′-dimethoxychalcone **2e** does not result in the corresponding pyrroline.

Similarly, the reaction of 4-nitrobenzylideneaniline **5** with 4-aryl-2-isocyanomethylthiazoles **1b–d** in the presence of copper(I) acetylacetonate **3** results in the formation of only *trans*-2-imidazolinylthiazoles **6a–c**‡ (Scheme 1). Since imidazolines **6a–c** are easily oxidised by atmospheric oxygen, they were isolated as hydrochlorides. The structure of compounds **6a–c** was established by NMR and mass spectrometry. The NMR spectrum of the hydrochloride of *trans*-2-[5-(4-nitro-

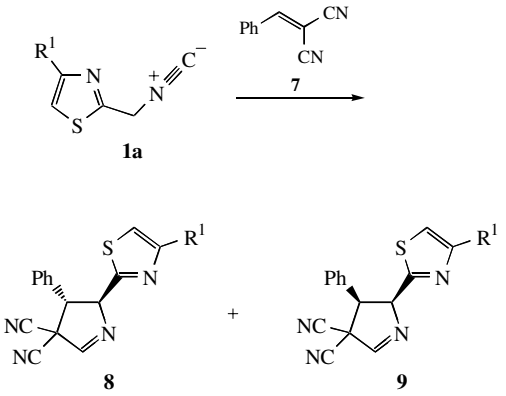
† *General procedure for the synthesis of trans-2-pyrrolines* **4a–e**: A solution of 4-(4-chlorophenyl)-2-isocyanomethylthiazole **1a** (0.24 g, 1 mmol), chalcone **2a** (0.23 g, 1.1 mmol) and copper(I) acetylacetonate **3** (5 mg, 0.03 mmol) in benzene was refluxed for 1 h. The product was collected by filtration, washed with benzene and dried to yield **4a** (0.25 g, 56%), mp 273–275 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.47 (d, 1H, 5-H, $J_{4\text{-H},5\text{-H}}$ 4.7 Hz), 5.07 (dd, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 4.7 Hz, $J_{4\text{-H},2\text{-H}}$ 1.6 Hz), 7.56 (d, 1H, 2-H, $J_{4\text{-H},2\text{-H}}$ 1.6 Hz), 7.59-8.01 (m, 14H, PhCO + Ph + + PhCl), 8.15 (s, 1H, 5-H thiazole), 8.33 (br. s, 1H, NH). MS, *m*/*z*: 442 (23%, M$^+$), 365 (42), 337 (65), 168 (21), 105 (100), 77 (92). Some physical characteristics for other compounds (melting point, yield, reaction time, NMR and mass-spectral data) are given below.

4b: mp 220–221 °C, 58%, 0.5 h. ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.47 (d, 1H, 5-H, $J_{4\text{-H},5\text{-H}}$ 4.8 Hz), 5.09 (d, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 4.8 Hz), 7.65 (s, 1H, 2-H), 7.49-7.60 (m, 12H, ClPhCO + 2PhCl), 8.16 (s, 1H, 5-H thiazole), 8.52 (br. s, 1H, NH). MS, *m*/*z*: 512 (2%, [M + 2]$^+$), 510 (3%, M$^+$), 371 (24), 266 (25), 223 (100), 168 (32), 139 (45), 111 (25).

4c: mp 242–245 °C, 89%, 0.2 h. ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.68 (d, 1H, 5-H, $J_{4\text{-H},5\text{-H}}$ 5.1 Hz), 5.23 (dd, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 5.1 Hz, $J_{4\text{-H},2\text{-H}}$ 1 Hz), 7.64 (d, 1H, 2-H, $J_{4\text{-H},2\text{-H}}$ 1 Hz), 7.49-8.29 (m, 12H, NO_2PhCO + + PhNO$_2$ + PhCl), 8.25 (s, 1H, 5-H thiazole), 8.90 (br. s, 1H, NH). MS, *m*/*z*: 532 (57%, M$^+$), 530 (100), 500 (30), 382 (55), 168 (34), 150 (86), 120 (83), 104 (57).

4d: mp 245–246 °C, 65%, 0.7 h, ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.52 (d, 1H, 5-H, $J_{4\text{-H},5\text{-H}}$ 5.1 Hz), 5.16 (d, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 5.1 Hz), 7.63 (s, 1H, 2-H), 7.39-8.01 (m, 13H, PhCO + PhCl + pyridinyl), 8.16 (s, 1H, 5-H thiazole), 8.47 (br. s, 1H, NH). MS, *m*/*z*: 443 (19%, M$^+$), 338 (78), 249 (17), 168 (12), 105 (74), 78 (100), 77 (67).

4e: mp 272–273 °C, 30%, 8 h, ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.80 (s, 3H, OMe), 4.47 (d, 1H, 5-H, $J_{4\text{-H},5\text{-H}}$ 4.9 Hz), 5.06 (dd, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 4.9 Hz, $J_{4\text{-H},2\text{-H}}$ 1.5 Hz), 7.56 (d, 1H, 2-H, $J_{4\text{-H},2\text{-H}}$ 1.5 Hz), 6.99-7.91 (m, 14H, PhCO + Ph + PhOMe), 7.92 (s, 1H, 5-H thiazole), 8.32 (br. s, 1H, NH). MS, *m*/*z*: 438 (12%, M$^+$), 422 (17), 338 (55), 164 (12), 105 (99), 77 (100).



Scheme 2

phenyl)-1-phenyl- [2]-imidazoline-4-yl]-4-(4-bromophenyl)thiazole **6a** exhibits resonance signals of three non-equivalent aromatic rings at δ 7.39–8. 30 ppm, a singlet of the thiazole ring at δ 8.37 ppm and the signals of the imidazoline ring: a singlet at δ 7.24 ppm, a doublet at 6.03 ppm and a doublet at δ 6.63 ppm. A value of 6.7 Hz of the coupling constant between protons of the imidazoline ring suggests that the compound exists as the *trans*-isomer. The mass spectrum of **6a** exhibits a molecular ion peak of *m*/*z* 505.

‡ *General procedure for the synthesis of trans-2-imidazolinylthiazoles* **6a–c**: A solution of 4-(4-bromophenyl)-2-isocyanomethylthiazole **1a** (0.15 g, 0.5 mmol), 4-nitrobenzylideneaniline **5** (0.13 g, 0.6 mmol) and copper(I) acetylacetonate **3** (3 mg, 0.02 mmol) in benzene was refluxed for 5 h. The reaction mixture was saturated with hydrogen chloride. The hydrochlorides were collected by filtration, washed with benzene and dried to yield **6a** (0.21 g, 85%), mp 153–154 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 5.40 (d, 1H, 5-H, $J_{4\text{-H},5\text{-H}}$ 6.7 Hz), 6.84 (d, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 6.7 Hz), 7.36 (s, 1H, 2-H), 7.24–8 .30 (m, 13 H, Ph + PhBr + $PhNO_2$), 8.18 (s, 1H, 5-H thiazole). MS, *m*/*z*: 506 (23%, [M + 2]$^+$), 504 (22%, M$^+$), 280 (52), 278 (51), 266 (100), 214 (14), 212 (14), 182 (39), 180 (41), 134 (31), 89 (69), 77 (74). Some physical characteristics for other compounds (melting point, yield, NMR and mass-spectral data) are given below.

6b: mp 142–145 °C, 70%. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.81 (s, 3 H, OMe), 6.08 (br. s, 1H, 5-H), 6.63 (br. s, 1H, 4-H), 7.36 (s, 1H, 2-H), 7.02–8.30 (m, 13 H, $PhNO_2$ + Ph + PhOMe), 8.13 (s, 1H, 5-H thiazole). MS, *m*/*z*: 456 (17%, M$^+$), 334 (42), 266 (100), 164 (53), 122 (37), 77 (65).

6c: mp 121–122 °C, 73%. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.07 (d, 1H, 5-H, *J* 6.0 Hz), 6.68 (d, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 6.0 Hz), 7.35 (s, 1H, 2-H), 7.40–7.31 (m, 15 H, 2Ph + 5-H thiazole + $PhNO_2$). MS, *m*/*z*: 426 (5%, M$^+$), 303 (24), 200 (100), 189 (78), 134 (64), 102 (24), 77 (29).

In contrast, the reaction of 4-(4-chlorophenyl)-2-isocyanomethylthiazole **1a** with benzylidenemalononitrile **7** in the presence of **3** affords a mixture of *trans*- and *cis*-isomers of 4-(4-chlorophenyl)-2-(4-phenyl-3-dicyano- [1]-pyrroline-5-yl)-thiazole **8** and **9** in the ratio 11:9§ (Scheme 2). We found that *cis*- [1]-pyrroline **9** was not converted into *trans*- [1]-pyrroline **8** even under heating in benzene in the presence of triethylamine, for a long time.

Thus, the observed ratio of *cis*- and *trans*-isomers in this reaction depends on the structure of the starting materials rather than on epimerization. We suggest that the carbonyl groups of chalcones or the imino groups of azomethines are coordinated with copper and take an active part in the formation of intermediate complex,[3] thus leadind to 2-pyrrolinyl- and 2-imidazolinylthiazoles with the *trans*-configuration.

Starting 4-aryl-2-isocyanomethylthiazoles **1a–d** were obtained according to a well-known method.[1]

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§ *trans*- and *cis*- 4-(4-Chlorophenyl)-2-(4-phenyl-3-dicyano- [1]-pyrroline-5-yl)thiazoles **8** and **9** were prepared in a manner similar to that for 2-pyrrolines. Each of the two configurational isomers was isolated by column chromatography. The isomer ratio was calculated from the intensity ratio of the corresponding signals in the NMR spectra of the isomer mixture. The NMR data for **8**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.78 (d, 1H, 5-H, $J_{4\text{-H},5\text{-H}}$ 8.5 Hz), 5.95 (dd, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 8.5 Hz, $J_{4\text{-H},2\text{-H}}$ 3 Hz), 6.45 (d, 1H, 2-H, $J_{4\text{-H},2\text{-H}}$ 3 Hz), 7.40–7.75 (m, 9 H, Ph + PhCl), 8.25 (s, 1H, 5-H thiazole).

For **9**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 5.0 (dd, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 17 Hz, $J_{4\text{-H},2\text{-H}}$ 1.5 Hz), 5.18 (d, 1H, 5-H, $J_{4\text{-H},5\text{-H}}$ 17 Hz), 5.80 (d, 1H, 2-H, $J_{4\text{-H},2\text{-H}}$ 1.5 Hz), 7.48–7.5 2 (m, 9H, Ph + PhCl), 8.40 (s, 1H, 5-H thiazole). MS, *m*/*z*: 388 (72%, M$^+$), 361 (100), 233 (56), 168 (61), 77 (85).