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NOVEL SYNTHESIS OF DIHYDROTHIOPHENE-2,5-DIIMINE DERIVATIVES BY THE THREE-COMPONENT REACTION OF ISOCYANIDES WITH ENAMINES AND ARYLISOTHIOCYANATES

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Abstract – A distribution of the products in the reaction of aryl isothiocyanates with isocyanides and 2,2-dialkylenamines has been studied in details. In range 55-60 °C this reaction results in the formation of dihydrothiophene-2,5-diimine derivatives, constitutions of which are proved by an X-ray analysis. In contrast at high temperature (above 110 °C) the major products in the present reaction are 2-imino-5-thiopyrrolidones. A one step pathway to dihydrothiophene structure has been elaborated.

INTRODUCTION

During last decade isocyanide based multicomponent reactions (IMCR) are becoming a powerful tool in heterocyclic chemistry to create complex and diverse compound libraries.[1] The main advantage of the syntheses of heterocycles using IMCR is a possibility to realize short pathways to hundreds of heterocyclic systems on the basis of commercially available starting compounds. Progress in this field would not be possible without the pioneer work of Prof. Ivar Ugi devoted to cyclic variants of four component condensation, which was discovered by his group in 60thies.[2] Tetrazoles,[3] β-lactams[4] and triazinones[5] were the first example of heterocycles obtained with the help of IMCR that opened the way to further discoveries. In fact, several cyclic products can be synthesized in IMCR with bifunctional starting compounds or in secondary reactions. The overall number of possible cyclizations is depended on dimension of the reaction and may be calculated with the easy equation $(n^2 – n)/2$, where n is number of starting compounds.[6] Thus, a hypothetical seven component reaction would be able to give access to 21 different cyclizations that is very interesting with the view point of diversity-oriented synthesis.[7] Other important aspect is varying of atom

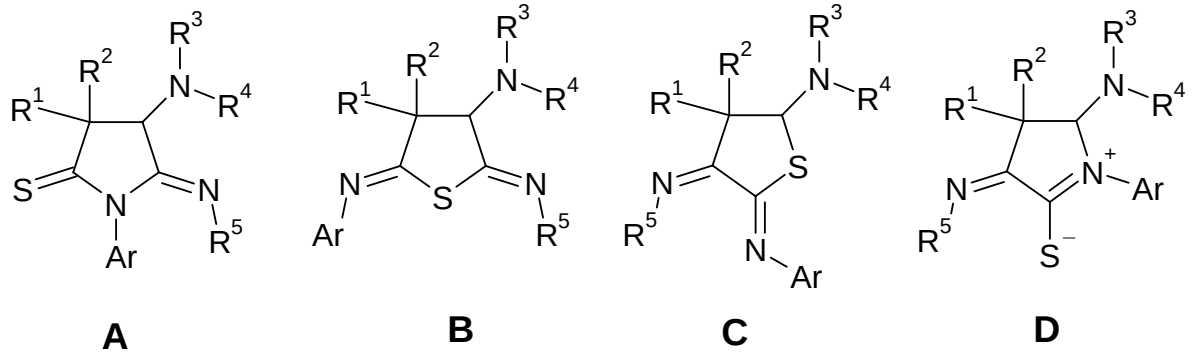
connectivity in a target cycle, that may be possible with design of novel IMCR.[8] On the other hand, multitude of combinations leading to different cycles is a real obstacle for identification of structures yielded from IMCR; so some well-known reactions should be rediscovered to reveal its real scope.

In the past five years our research group focused his efforts on development of new methodology for IMCR finding.[6] Several algorithms based on reorganization of an existing reaction were presented that allowed us to find novel MCRs with minimal input of work.[9] One of our objects was three component system which includes isothiocyanates, isocyanides and second nucleophile.[10] Using various reaction conditions and changing nucleophiles it is possible to obtain here different products, for example: fused imidazoles, thioamides, thiopyrrolidones and other structures. The present work is a part of our research devoted to this interesting system, where we describe a novel synthesis of dihydrothiophene-2,5-dimine derivatives. A starting point for our investigation was the observation that depending on reaction conditions aromatic isothiocyanates **1** react with isocyanides **2** and 2,2-dialkyl enamines **3** in particular ways giving a new product **4** together with 2-imino-5-thiopyrrolidones **5**. It should be noted that synthesis of compounds **5** was previously described by Ley and Nast.[11] Keeping this in mind we carried out an experiment, where various reaction conditions were tested to obtain a new product **4** exclusively and prove its structure.

RESULTS AND DISCUSSION

At first, we have refused the reaction conditions described in the initial article,[11] that is refluxing in acetonitrile over 5-6 h, owing to obstacles connecting with control on the distribution of products. Therefore, the reaction was carried out at room temperature in acetonitrile, but it was found that starting compounds **1-3** were recovered from the reaction mixture even after one week of stir. The better results were obtained at temperature in range 55-60 °C, so we have reached both the acceptable reaction rate and high selectivity. At this conditions we have fixed only one product in reaction mixture in contrast to refluxing, where two products with equal molecular weight were distributed. Concentration of the reagents is also a very important factor in IMCR. As a rule, all reactions of this type proceed better if the reactants are presented in high concentration that is 0.5 to 1 molar, because dilution favors two component side reactions. We have also observed the significant increase of the reaction time in relative diluted (0.1-0.2 molar) acetonitrile solution. However, in absence of a solvent it was impossible to mount the reaction rate higher than one in 0.5 molar acetonitrile solution. Other solvents were tested as medium for the reaction (benzene, methanol, DMF), but the yields of **4** was lower than one in acetonitrile. Thus, it may be concluded that an addition of polar solvent has a positive effect on the reaction rate. The next factor, which should be considered, is a relative high sensibility of the reactions to a trace remains of water in reaction mixture. The best way to carry out the reaction is the use of anhydrous solvent and reagents.

The next step was structural investigations for the compounds yielded from the present reaction. The structure of a product was determined on the basis of X-ray analysis, NMR-spectroscopy and mass-spectrometry. The crude analysis of reaction mixture with the help of LS-MS confirmed assembly of all three educts **1-3** with the formation of two isomeric structures **4** and **5**, one of them could be assigned to an major product at temperature 55-60 °C. Taking into account the published results[10-12], it was possible to propose several theoretical structures for **4** and **5** (Scheme 1). Two of them (**A** and **B**) are based on initial interaction of isothiocyanates with enamines, whereas **C** and **D** on the formation of isothiocyanate-isocyanide zwitterion. In addition, two type of cyclization can be considered as most probable: towards the N or S atoms.



Scheme 1 Possible structures of **4** and **5**.

The NMR data allowed us to except some structures. Thus, the ^{13}C NMR spectrum of compound **4a** exhibited a series of signals in a 120-168 ppm region, that can be assigned to aromatic ring and thioimidate part of structures **B**. In contrast, extremely downfield ^{13}C signal of thiolactams group in a 200-210 ppm region was absent, that is an evidence again the structure **A**.[13] In addition, this compound contains a CH group, which shows the characteristic signal in ^{1}H NMR spectrum. The location of this resonance in the region of 3.30-3.60 ppm allows us to decline the structure **C**. On the other hand, the NMR data give us no information to help distinguish two isomeric structures **B** and **D**. Therefore, the structure **B** for compound **4a** (R^1, R^2 = Me; R^3, R^4 = -$(CH_2)_5$-; R^5 = *c*-C_6H_{11}; Ar = 3-$CF_3C_6H_4$) at the temperature 55-60 °C has been established by a single crystal X-ray analysis (Figure 1). According to these data, the dihydrothiophene-2,5-diimine moiety is non-planar (dihedral angle C1-C2-C3-C4 is 49.2°) with high degree of localization of the double C=N bond. Thus, bond length C1-N2 is 1.253 Å, whereas C1-C2 is 1.526 Å. The angle N2-C1-C2 is 122.9°, whereas N1-C4-C3 is 122.6° that open the way to existence of four isomers for this structure. Note, that we registered the signals of only one isomer in ^{1}H NMR spectra for all obtained compounds **4a-m**. In general, structural investigation has shown that in contrast to previously

reported data[11] the reaction of **1** with **2** and **3** results in the formation of **4** (Scheme 2). Therefore an original method for construction of this heterocyclic system has been discovered.

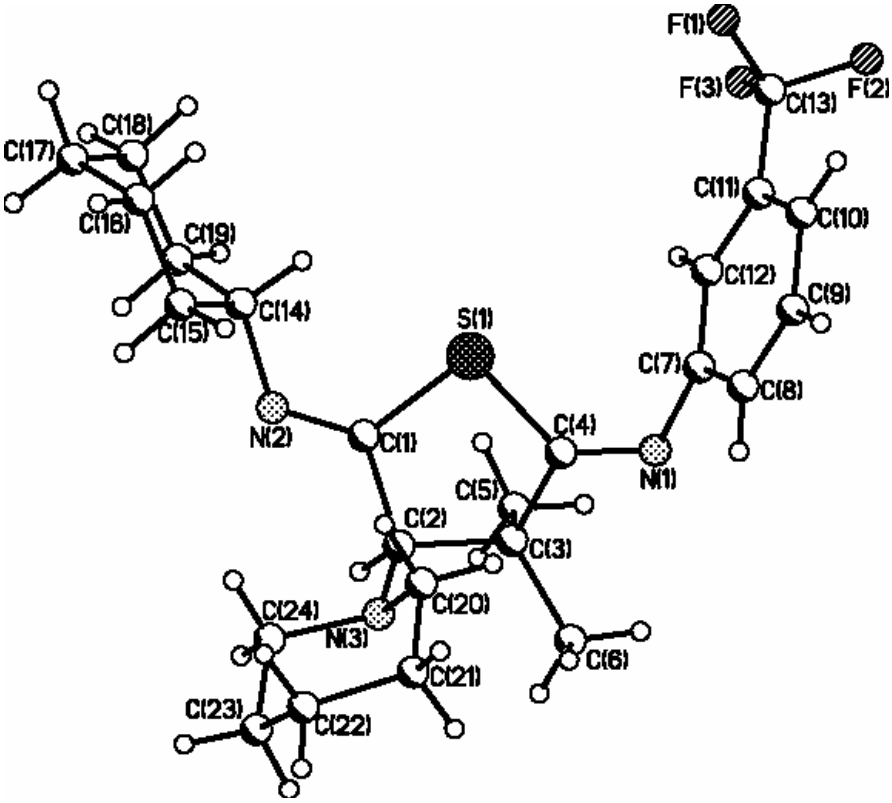
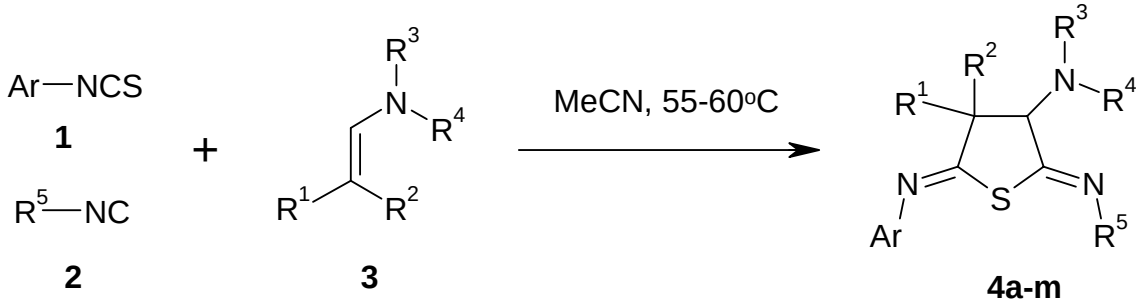


Figure 1 Structure of **4a** according the X-ray analysis data.



R^1,R^2 = Me, -$(CH_2)_5$-

R^3, R^4 = -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_2O(CH_2)_2$-, -$(CH_2)_2S(CH_2)_2$-, -$(CH_2)_2NMe(CH_2)_2$-

R^5 = *t*-Bu, *c*-C_6H_{11}, Ad, 4-ClC_6H_4, 4-$MeOC_6H_4$

Scheme 2 Synthesis of dihydrothiophene-2,5-diimine derivatives **4**.

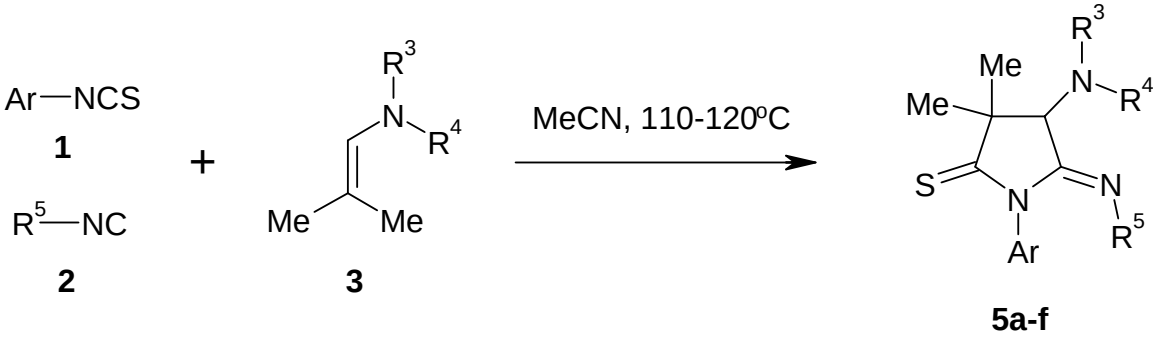
The rate of the reaction is critically depended on the structure of isothiocyanates **1**. Thus, the introduction of electron-withdrawing substituents (CN or NO_2) in aromatic isothiocyanates results in shortening of the reaction time and increasing yields of the products **4**. In contrast, the introduction of electron-donating substituents decreases the yield of the target compound. Therefore, we have not used

4-methoxyisothocyanate as a starting reagent in the present reaction. Moreover, due to very low reaction rates, no products could be isolated using aliphatic isothiocyanates. These results are summarized in Table 1. On the other hand, the nature of isocyanides has the insignificant influence on the reaction. Interestingly it was found that aromatic isocyanide with electron-withdrawing group gives target compounds **4c,e** in moderate yields (Table 1). In that way, isocyanides with electron-donating and electron-withdrawing groups demonstrate similar reactivity in this IMCR. In contrast to isocyanides the reaction is sensitive to choice of enamines; only 2,2-dialkyl derivatives **3** give the target products **4** in good yields. Representative examples with various substituents at 2,3,4 and 5 positions are summarized in Table 1. 2-Monoalkylated analogs give only a mixture of polymers in this reaction.

Table 1 Isolated yields of the MCR products **4**.

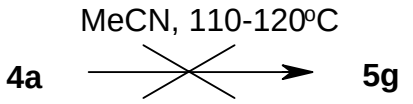
Compd	Ar	R^1, R^2	R^3, R^4	R^5	Yield, (%)
4a	3-$CF_3C_6H_4$	Me, Me	-$(CH_2)_5$-	*c*-C_6H_{11}	84
4b	3-ClC_6H_4	Me, Me	-$(CH_2)_5$-	*t*-Bu	93
4c	4-NCC_6H_4	Me, Me	-$(CH_2)_5$-	4-ClC_6H_4	63
4d	3-$CF_3C_6H_4$	Me, Me	-$(CH_2)_2O(CH_2)_2$-	Ad	67
4e	3-$CF_3C_6H_4$	Me, Me	-$(CH_2)_2O(CH_2)_2$-	4-ClC_6H_4	49
4f	Ph	Me, Me	-$(CH_2)_4$-	*c*-C_6H_{11}	34
4g	3-ClC_6H_4	Me, Me	-$(CH_2)_2S(CH_2)_2$-	Ad	74
4h	4-NCC_6H_4	Me, Me	-$(CH_2)_2NMe(CH_2)_2$-	*t*-Bu	65
4i	Ph	-$(CH_2)_5$-	-$(CH_2)_5$-	Ad	42
4j	4-NCC_6H_4	-$(CH_2)_5$-	-$(CH_2)_5$-	4-$MeOC_6H_4$	68
4k	3-$CF_3C_6H_4$	-$(CH_2)_5$-	-$(CH_2)_2O(CH_2)_2$-	*t*-Bu	56
4l	Ph	-$(CH_2)_5$-	-$(CH_2)_4$-	*c*-C_6H_{11}	58
4m	3-ClC_6H_4	-$(CH_2)_5$-	-$(CH_2)_4$-	4-$MeOC_6H_4$	64

We have found that high temperature favors the formation of 2-imino-5-thiopyrrolidones **5**, which became a major product in range 110-120 °C. The reaction was carried out in sealed vessels under pressure. This reaction was previously described by Ley and Nast,[11] but no structural investigation concerning the final product **5** was published. Therefore, we have used X-ray analysis, NMR-spectroscopy and mass-spectrometry that are necessary for the reliable assignment. While the structure of one of the products **5a** was proved with the help of X-ray analysis, other structures **5b-f** were confirmed with the help of NMR-spectroscopy. All our findings have confirmed the formation of 2-imino-5-thiopyrrolidones (Scheme 3) as a major product in reaction of **1** with **2** and **3** at the temperature 110-120 °C.



R^3, R^4 = -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_2O(CH_2)_2$-, -$(CH_2)_2S(CH_2)_2$-, -$(CH_2)_2NMe(CH_2)_2$-

R^5 = *t*-Bu, *c*-C_6H_{11}, Ad



Scheme 3 Synthesis of 2-imino-5-thiopyrrolidones **5**.

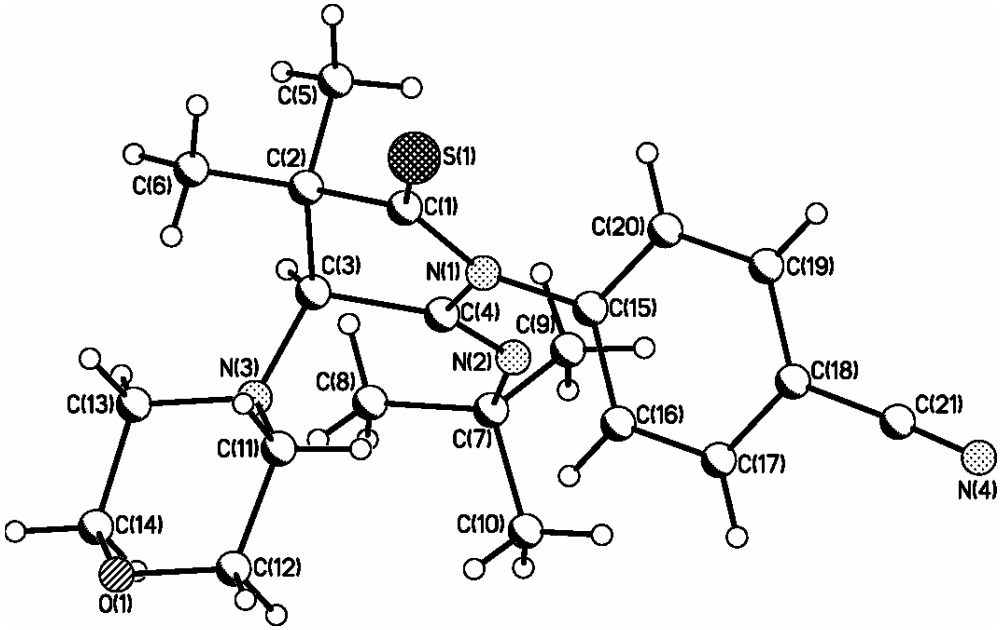


Figure 2 Structure of **5a** according the X-ray analysis data.

Thus, the ^{13}C NMR spectrum of the compound **5a** exhibited the signal of thiolactam group in the region 205 ppm. The signals of CH group for all compounds **5a-f** were observed in the region 3.80 – 4.20 ppm in contrast to structure **4** that help distinguish between these two products. The parent mass peak for all compounds **5a-f** corresponds with the sum of three initial educts. On the other hand, we have marked the absence of the peak [amine+isocyanide+S+CH], which is characteristic for mass-spectra of **4**. X-ray analysis for compound **5a** has given us the next proof of cyclization with the formation C-N bound instead C-S (Figure 2.). A distinctive feature of the examined structure is non-planar pyrrolidine cycle (dihedral

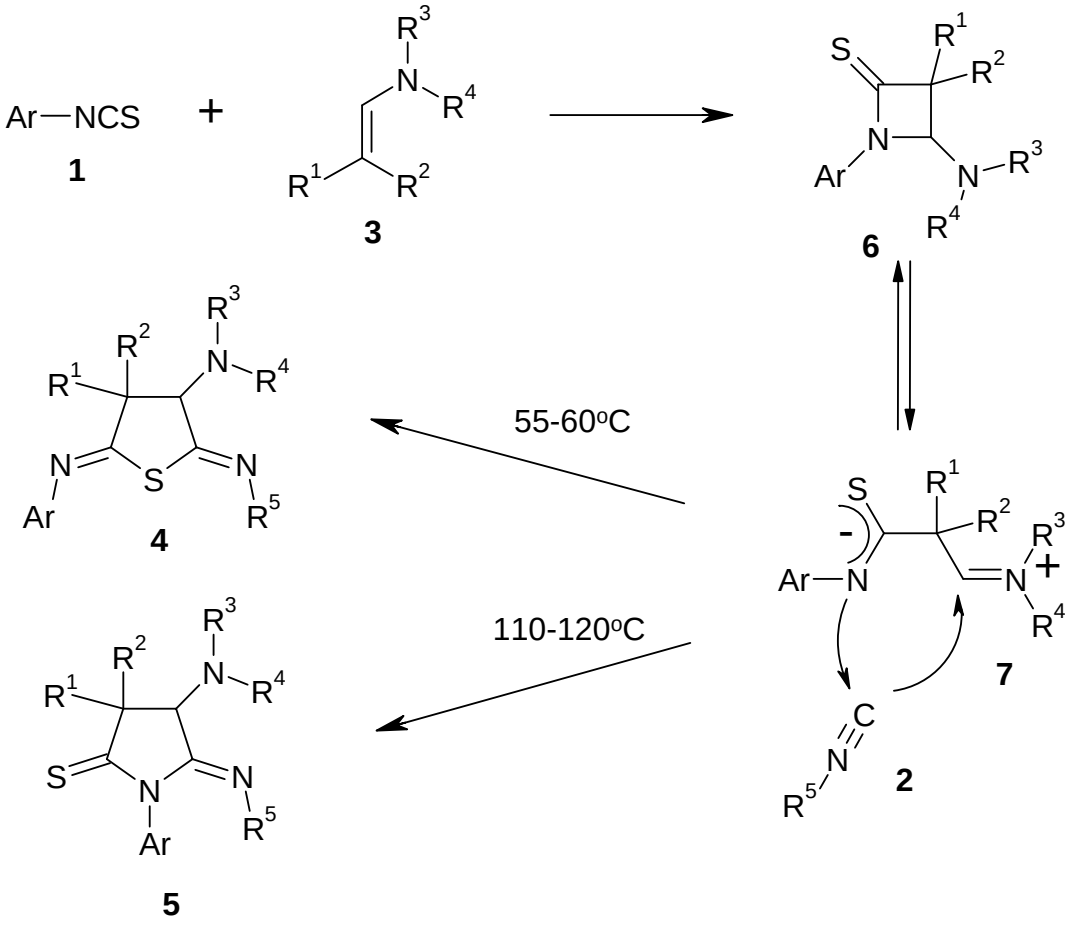
angle C1-C2-C3-C4 is 32.9°) with high degree of localization of the double C=N bond (1.251 Å). In contrast, bond lengths in the system NCS (1.632 Å for C1-S1 and 1.363 Å for C1-N1) reflects a remarkable electronic delocalization in thiolactam moiety. It should be noted that the reaction proceeded gladly only in the case of isothiocyanates bearing electron-withdrawing groups. Therefore, phenyl isothiocyanate leads to the corresponding product **5b** in low yield (Table 2). It should be noted that we have not succeeded in obtaining of compounds **5** with enamines containing cyclohexane ring. In this cases temperature has a little influence on the distribution of both products **4** and **5**, so in range of 110-120 °C the mixture of **4** (major products) and **5** (minor products) is formed.

Table 2 Isolated yields of the MCR products **5**.

Compd	Ar	R^3, R^4	R^5	Yield, (%)
5a	4-NCC_6H_4	-$(CH_2)_2O(CH_2)_2$-	*t*-Bu	79
5b	Ph	-$(CH_2)_2O(CH_2)_2$-	*c*-C_6H_{11}	25
5c	3-ClC_6H_4	-$(CH_2)_5$-	Ad	57
5d	3-$CF_3C_6H_4$	-$(CH_2)_2NMe(CH_2)_2$-	*c*-C_6H_{11}	49
5e	4-NCC_6H_4	-$(CH_2)_4$-	Ad	92
5f	4-NCC_6H_4	-$(CH_2)_2S(CH_2)_2$-	*t*-Bu	90

Taking into account all aforementioned experiments it might be proposed that 2-imino-5-thiopyrrolidones **5** could be a product of a Dimroth-type rearrangement and dihydrothiophene-2,5-diimine derivatives **4** were starting compounds for it. To prove this suggestion we carried out the experiment, where pure dihydrothiophene-2,5-diimine **4a** was heated in acetonitrile at temperature 120 °C. Interestingly it was found that no considerable amount of corresponding dihydrothiophene-2,5-diimine was formed at these conditions. In that way, the both products **4** and **5** can be obtained independently starting from three initial educts **1-3**. Previously it was found that interaction of 2,2-dimethyl enamines with isothiocyanates or isocyanates resulted in the formation of instable 2-azetidinthiones **6** [12] or 2-azetidinones[14] which were registered in reaction mixtures. High reactivity of these intermediates opens the way to several transformations through the ring opening and formation of zwitter-ion **7** (Scheme 4). Although mechanism of the reaction is not studied by us in detail it may be agreed with this scheme, which can clear up all observed facts. Following such of mechanism 2-imino-5-thiopyrrolidones **5** are thermodynamically more preferable products which can be formed at high temperature. In contrast, in range of 55-60 °C it is possible to carry up the cyclization leading to dihydrothiophene-2,5-diimine **4** exclusively. Owing to low rate of a Dimroth-type rearrangement the distribution of the product cannot be changed by further heating that

allows us to find an optimal reaction conditions for obtaining of dihydrothiophene-2,5-diimine derivatives and 2-imino-5-thiopyrrolidones in separate ways.



Scheme 4 Possible mechanism of the reaction.

In summary, we have studied the reaction of aromatic isothiocyanates with isocyanides and 2,2-dialkyl enamines more preciously than it was made before. The significant influence of temperature on this reaction has been revealed. We have found that dihydrothiophene-2,5-diimine derivatives are formed at the temperature 55-60 °C. The scope and limitations of novel method for preparation of this structure have been defined. In general, derivatives of dihydrothiophene-2,5-diimine can be obtained in case of various starting reagents including aromatic and aliphatic isocyanides, aromatic isothiocyanates substituted with electron-withdrawing groups. In addition, the various alkyl groups may be presented in structure of starting 2,2-dialkyl enamines. In that way, a next heterocycle system becomes accessible with the help of IMCRs.

EXPERIMENTAL

All heterocumulenes and enamines were obtained from commercial sources and used without further

purification. Isocyanides were synthesized according well-known method.[15]

NMR spectra were recorded on a Bruker DRX-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C). ^{13}C NMR spectra have been obtained for selected compounds. MS were recorded on Varian MAT 311A. Preliminary examination and data collection for crystal structure analysis were carried out on a diffractometer Xcalibur 3 CCD. Melting points are uncorrected values.

General procedure for the synthesis of dihydrothiophene-2,5-diimines **4**. A mixture of 0.5 mmol of each of the compounds: isothiocyanate, isocyanide, 2,2-dialkyl enamine in anhydrous acetonitrile (0.6 mL) were mixed together and stirred at the temperature in range 55-60 °C for 5 h. After cooling the product were filtered out. Additional amount of the product was obtained by extraction of filtrate with hexane. Hexane solution was treated with CuBr to remove excess of isocyanide and after that was evaporated to dryness. The crude product from both sources was purified by crystallization from ethanol or flash chromatography (silica gel 40μ, $CHCl_3$).

4a Crystal structure analysis: $C_{24}H_{32}F_3N_3S$, M = 451.59, triclinic, space group P1, a = 10.8588(5), b = 11.3439(8), c = 11.5255(7) Å, V = 1225.74(13) Å3, Z = 2, ρ_{calcd} = 1.224 g cm^{-3}, μ = 0.170 mm^{-1}, F(000) = 480. Data collection was performed at 295 K within the Θ-range from 2.79 to 31.75°; a total of 7114 (of which 3979 were unique) reflections were collected (R(int) = 0.0196) and used to refine 280 parameters. The structure was solved with the program SHELXS-97[16] and refined using SHELXL-97[17] to R1 = 0.0483 and wR2 = 0.1350 [I > 2σ (I)]. Crystallographic data have been deposited with the Cambridge Crystallographic Centre as supplementary publication[18]. Mp 128-129 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.33 (3H, s, Me), 1.37 (3H, s, Me), 1.25-1.75 (16H, m, 8CH_2), 2.31-2.37 (2H, m, NCH_2), 2.59-2.65 (2H, m, NCH_2), 2.83-2.93 (1H, m, CH), 3.36 (1H, s, CH), 6.95-7.05 (2H, m, CH_{Ar}), 7.28-7.56 (2H, m, CH_{Ar}). ^{13}C NMR (100MHz, DMSO-d_6) δ: 23.2 (CH_2), 23.6 (Me), 25.9 (CH_2), 26.2 (CH_2), 27.6 (Me), 28.1 (CH_2), 32.5 (CH_2), 48.4 (CH_2N), 49.1 (Cquat.), 56.8 (CH), 74.5 (CH), 120.2 – 142.5 (6C-Ar), 122.3 (CF_3), 165.3 (C=N), 168.1 (C=N). MS (m/z, %): 451 (M^+, 23), 367 (27), 342 (19), 238 (100), 164 (31), 141 (44). Anal. Calcd for $C_{24}H_{32}F_3N_3S$: C, 63.83; H, 7.14; N, 9.30. Found: C, 63.80; H, 6.99; N, 9.36.

4b Mp 95-96 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.25 (9H, s, *t*-Bu), 1.28 (3H, s, Me), 1.33 (3H, s, Me), 2.32-2.37 (2H, m, NCH_2), 2.60-2.66 (2H, m, NCH_2), 3.28 (1H, s, CH), 6.65-6.76 (2H, m, CH_{Ar}), 7.08-7.34 (2H, m, CH_{Ar}). MS (m/z, %): 391 (M^+, 31), 393 (M+2, 11), 334 (54), 308 (43), 307 (51), 212 (100). Anal. Calcd for $C_{21}H_{30}ClN_3S$: C, 64.34; H, 7.71; N, 10.72. Found: C, 64.45; H, 7.68; N, 10.75.

4c Mp 164-165 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.41 (6H, s, 2Me), 1.42-1.68 (6H, m, 3CH_2), 2.49-2.53 (2H, m, NCH_2), 2.72-2.78 (2H, m, NCH_2), 3.60 (1H, s, CH), 6.81 (2H, d, *J* = 8.5 Hz, CH_{Ar}), 6.86 (2H, d, *J* = 8.5 Hz, CH_{Ar}), 7.29 (2H, d, *J* = 8.5 Hz, CH_{Ar}), 7.67 (2H, d, *J* = 8.5 Hz, CH_{Ar}). MS (m/z, %): 436 (M^+, 27), 438 (M+2, 9), 352 (17), 299 (21), 266 (76), 169 (100). Anal. Calcd for $C_{24}H_{25}ClN_4S$: C, 65.96; H, 5.77; N, 12.82. Found: C, 66.14; H, 5.69; N, 12.79.

4d Mp 137-138 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.32 (3H, s, Me), 1.37 (3H, s, Me), 1.65 (6H, broad s, 3CH_2), 1.79-1.93 (6H, m, 3CH_2), 2.08 (3H, broad s, 3CH), 2.36-2.42 (2H, m, NCH_2), 2.65-2.72 (2H, m, NCH_2), 3.31 (1H, s, CH), 3.56 (4H, t, J = 4.5 Hz, 2OCH_2), 7.00-7.08 (2H, m, CH_{Ar}), 7.39-7.57 (2H, m, CH_{Ar}). MS (m/z, %): 505 (M^+, 11), 419 (34), 370 (26), 344 (15), 292 (100), 149 (64), 135 (13). Anal. Calcd for $C_{27}H_{34}F_3N_3OS$: C, 64.14; H, 6.78; N, 8.31. Found: C, 63.98; H, 6.85; N, 8.36.

4e Mp 175-176 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.44 (3H, s, Me), 1.46 (3H, s, Me), 2.53-2.61 (2H, m, NCH_2), 2.78-2.84 (2H, m, NCH_2), 3.62 (1H, s, CH), 3.64 (4H, t, J = 4.4 Hz, 2OCH_2), 6.84 (2H, d, J = 8.5 Hz, CH_{Ar}), 6.96-7.04 (2H, m, CH_{Ar}), 7.29 (2H, d, J = 8.5 Hz, CH_{Ar}), 7.36-7.52 (2H, m, CH_{Ar}). MS (m/z, %): 481 (M^+, 22), 483 (M+2, 8) 395 (17), 344 (19), 268 (100), 192 (25). Anal. Calcd for $C_{23}H_{23}ClF_3N_4OS$: C, 57.32; H, 4.81; N, 8.72. Found: C, 57.48; H, 4.70; N, 8.62.

4f Mp 103-104 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.33 (3H, s, Me), 1.36 (3H, s, Me), 1.25-1.71 (14H, m, 7CH_2), 2.52-2.56 (2H, m, NCH_2), 2.76-2.82 (2H, m, NCH_2), 2.86-2.91 (1H, m, CH), 3.60 (1H, s, CH), 6.72-6.76 (2H, m, CH_{Ar}), 7.05-7.33 (3H, m, CH_{Ar}). ^{13}C NMR (100MHz, DMSO-d_6) δ: 23.6 (CH_2), 24.3 (Me), 25.2 (CH_2), 26.9 (Me), 28.4 (CH_2), 30.8 (CH_2), 48.6 (Cquat.), 49.5 (CH_2N), 56.0 (CH), 75.7 (CH), 119.8 – 148.2 (6C-Ar), 164.7 (C=N), 167.8 (C=N). MS (m/z, %): 369 (M^+, 42), 299 (33), 260 (29), 224 (100), 141 (52). Anal. Calcd for $C_{22}H_{31}N_3S$: C, 71.50; H, 8.45; N, 11.37. Found: C, 71.39; H, 8.38; N, 11.57.

4g Mp 162-163 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.29 (3H, s, Me), 1.32 (3H, s, Me), 1.66 (6H, broad s, 3CH_2), 1.80-1.93 (6H, m, 3CH_2), 2.09 (3H, broad s, 3CH), 2.57 (4H, broad s, 2SCH_2), 2.63-2.69 (2H, m, NCH_2), 2.90-2.95 (2H, m, NCH_2), 3.30 (1H, s, CH), 6.67-6.77 (2H, m, CH_{Ar}), 7.08-7.35 (2H, m, CH_{Ar}). MS (m/z, %): 487 (M^+, 14), 489 (M+2, 6), 382 (17), 352 (28), 326 (21), 308 (31), 149 (100). Anal. Calcd for $C_{26}H_{34}ClN_3S_2$: C, 63.97; H, 7.02; N, 8.61. Found: C, 64.06; H, 6.93; N, 8.71.

4h Mp 154-155 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.26 (9H, s, *t*-Bu), 1.31 (3H, s, Me), 1.34 (3H, s, Me), 2.14 (3H, s, NMe), 2.29 (4H, broad s, 2NCH_2), 2.34-2.41 (2H, m, NCH_2), 2.65-2.69 (2H, m, NCH_2), 3.34 (1H, s, CH), 6.91 (2H, d, J = 8.2 Hz, CH_{Ar}), 7.71 (2H, d, J = 8.2 Hz, CH_{Ar}). MS (m/z, %): 397 (M^+, 26), 382 (34), 340 (26), 314 (16), 227 (83), 212 (100). Anal. Calcd for $C_{22}H_{31}N_5S$: C, 66.46; H, 7.86; N, 17.61. Found: C, 66.37; H, 7.75; N, 17.79.

4i Mp 196-197 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.20-1.55 (16H, m, 8CH_2), 1.64 (6H, broad s, 3CH_2), 1.71-1.96 (6H, m, 3CH_2), 2.06 (3H, broad s, 3CH), 2.29-2.43 (2H, m, NCH_2), 2.62-2.72 (2H, m, NCH_2), 3.54 (1H, s, CH), 6.69-6.74 (2H, m, CH_{Ar}), 7.07-7.33 (3H, m, CH_{Ar}). MS (m/z, %): 475 (M^+, 14), 391 (32), 314 (41), 290 (100), 257 (37), 149 (52). Anal. Calcd for $C_{30}H_{41}N_3S$: C, 75.74; H, 8.69; N, 8.83. Found: C, 75.66; H, 8.77; N, 8.74.

4j Mp 206-207 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.32-1.98 (16H, m, 8CH_2), 2.49-2.56 (2H, m, NCH_2), 2.76-2.81 (2H, m, NCH_2), 3.73 (3H, s, MeO), 3.86 (1H, s, CH), 6.74 (2H, d, J = 8.2 Hz, CH_{Ar}), 6.78 (2H, d,

J = 8.6 Hz, CH_{Ar}), 6.84 (2H, d, *J* = 8.2 Hz, CH_{Ar}), 7.66 (2H, d, *J* = 8.6 Hz, CH_{Ar}). MS (m/z, %): 472 (M^+, 19), 388 (17), 339 (15), 262 (74), 228 (43), 165 (100). Anal. Calcd for $C_{28}H_{32}N_4OS$: C, 71.15; H, 6.82; N, 11.85. Found: C, 71.12; H, 6.67; N, 12.00.

4k Mp 139-140 °C. ^{1}H NMR (400MHz, DMSO-*d*$_6$) δ: 1.27 (9H, s, *t*-Bu), 1.30-1.97 (10H, m, $5CH_2$), 2.36-2.45 (2H, m, NCH_2), 2.70-2.78 (2H, m, NCH_2), 3.52 (1H, s, CH), 3.58 (4H, t, *J* = 4.2 Hz, $2OCH_2$), 6.95-7.00 (2H, m, CH_{Ar}), 7.34-7.55 (2H, m, CH_{Ar}). MS (m/z, %): 467 (M^+, 29), 410 (35), 384 (42), 381 (67), 214 (100), 178 (26). Anal. Calcd for $C_{24}H_{32}F_3N_3OS$: C, 61.65; H, 6.90; N, 8.99. Found: C, 61.48; H, 6.89; N, 9.05.

4l Mp 122-123 °C. ^{1}H NMR (400MHz, DMSO-*d*$_6$) δ: 1.25-1.98 (24H, m, $12CH_2$), 2.48-2.54 (2H, m, NCH_2), 2.80-2.85 (2H, m, NCH_2), 2.86-2.91 (1H, m, CH), 3.91 (1H, s, CH), 6.71-6.74 (2H, m, CH_{Ar}), 7.04-7.32 (3H, m, CH_{Ar}). MS (m/z, %): 409 (M^+, 48), 339 (19), 332 (22), 300 (38), 224 (100), 141 (56). Anal. Calcd for $C_{25}H_{35}N_3S$: C, 73.30; H, 8.61; N, 10.26. Found: C, 73.17; H, 8.65; N, 10.20.

4m Mp 194-195 °C. ^{1}H NMR (400MHz, DMSO-*d*$_6$) δ: 1.32-1.98 (14H, m, $7CH_2$), 2.67-2.72 (2H, m, NCH_2), 2.93-2.98 (2H, m, NCH_2), 3.73 (3H, s, MeO), 4.12 (1H, s, CH), 6.60-6.72 (2H, m, CH_{Ar}), 6.74 (2H, d, *J* = 8.2 Hz, CH_{Ar}), 6.84 (2H, d, *J* = 8.2 Hz, CH_{Ar}), 7.05-7.28 (2H, m, CH_{Ar}). MS (m/z, %): 467 (M^+, 37), 469 (M+2, 13), 397 (33), 334 (41), 248 (100), 165 (82). Anal. Calcd for $C_{26}H_{30}ClN_3OS$: C, 66.72; H, 6.46; N, 8.98. Found: C, 66.65; H, 6.66; N, 9.07.

General procedure for the synthesis of 2-imino-5-thiopyrrolidones **5**. A mixture of 0.5 mmol of each of the compounds: isothiocyanate, isocyanide, 2,2-dialkyl enamine in anhydrous acetonitrile (0.6 mL) were mixed together in sealed vessel and stirred at the temperature in range 110-120 °C for 3 h. After cooling the product were filtered out. Additional amount of the product was obtained by extraction of filtrate with hexane. Hexane solution was treated with CuBr to remove excess of isocyanide and after that was evaporated to dryness. The crude product from both sources was purified by crystallization from ethanol or flash chromatography (silica gel 40μ, $CHCl_3$).

5a Crystal structure analysis: $C_{21}H_{28}N_4OS$, M = 384.53, monoclinic, space group P2(1)/c, a = 8.7848(10), b = 10.3756(7), c = 23.3888(7) Å, V = 2116.9(3) Å3, Z = 4, ρ_{calcd} = 1.207 g cm^{-3}, μ = 0.170 mm^{-1}, F(000) = 824. Data collection was performed at 295 K within the Θ-range from 2.63 to 31.73°; a total of 6668 (of which 4218 were unique) reflections were collected (R(int) = 0.0249) and used to refine 248 parameters. The structure was solved with the program SHELXS-97[16] and refined using SHELXL-97[17] to R1 = 0.0524 and wR2 = 0.1425 [I > 2σ (I)]. Crystallographic data have been deposited with the Cambridge Crystallographic Centre as supplementary publication[19]. Mp 148-149 °C. ^{1}H NMR (400MHz, DMSO-*d*$_6$) δ: 1.27 (9H, s, *t*-Bu), 1.32 (3H, s, Me), 1.52 (3H, s, Me), 2.78-2.89 (4H, m, $2NCH_2$), 3.55 (4H, t, *J* = 4.3 Hz, $2OCH_2$), 3.99 (1H, s, CH), 7.33 (2H, d, *J* = 8.5 Hz, CH_{Ar}), 7.82 (2H, d, *J* = 8.5 Hz, CH_{Ar}). ^{13}C NMR (100MHz, DMSO-*d*$_6$) δ: 26.1 (Me), 29.5 (Me), 30.6 (Me), 49.8 (Cquat.), 52.3 (Cquat.), 52.9(CH_2N), 60.1

(CH), 66.7 (CH_2O), 112.1 – 138.4 (6C-Ar + CN), 148.9 (C=N), 205.6 (C=S). MS (m/z, %): 384 (M^+, 54), 327 (100), 301 (19), 281 (21), 223 (16). Anal. Calcd for $C_{21}H_{28}N_3OS$: C, 65.59; H, 7.34; N, 14.57. Found: C, 65.41; H, 7.33; N, 14.39.

5b Mp 216-217 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.25 (3H, s, Me), 1.26-1.70 (10H, m, $5CH_2$), 1.39 (3H, s, Me), 2.56-2.64 (4H, m, $2NCH_2$), 3.38-3.45 (1H, m, CH), 3.58 (4H, t, J = 4.0 Hz, $2OCH_2$), 3.80 (1H, s, CH), 7.08-7.12 (2H, m, CH_{Ar}), 7.35-7.45 (3H, m, CH_{Ar}). ^{13}C NMR (100MHz, DMSO-d_6) δ: 22.7 (CH_2), 26.8 (Me), 27.8 (CH_2), 28.9 (Me), 31.7 (CH_2), 50.6 (Cquat.), 53.3 (CH_2N), 56.2 (CH), 59.4 (CH), 67.8 (CH_2O), 121.0 – 147.2 (6C-Ar), 149.2 (C=N), 205.1 (C=S). MS (m/z, %): 385 (M^+, 42), 308 (34), 299 (100), 276 (13), 250 (17). Anal. Calcd for $C_{22}H_{31}N_3OS$: C, 68.53; H, 8.10; N, 10.90. Found: C, 68.60; H, 7.98; N, 10.88.

5c Mp 127-128 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.24 (3H, s, Me), 1.32 (3H, s, Me), 1.48 (6H, broad s, $3CH_2$), 1.60-1.95 (12H, m, $6CH_2$), 2.07 (3H, broad s, 3CH), 2.79-2.86 (4H, m, $2NCH_2$), 3.84 (1H, s, CH), 7.03-7.12 (2H, m, CH_{Ar}), 7.28-7.42 (2H, m, CH_{Ar}). MS (m/z, %): 469 (M^+, 10), 471 (M+2, 4), 385 (16), 310 (34), 308 (100), 149 (73), 135 (25). Anal. Calcd for $C_{27}H_{36}ClN_3S$: C, 68.98; H, 7.72; N, 8.94. Found: C, 68.07; H, 7.65; N, 8.86.

5d Mp 185-186 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.27 (3H, s, Me), 1.30-1.72 (10H, m, $5CH_2$), 1.37 (3H, s, Me), 2.14 (3H, s, NMe), 2.32 (4H, broad s, $2NCH_2$), 2.56-2.63 (4H, m, $2NCH_2$), 3.38-3.42 (1H, m, CH), 3.84 (1H, s, CH), 7.42-7.47 (2H, m, CH_{Ar}), 7.51-7.67 (2H, m, CH_{Ar}). MS (m/z, %): 466 (M^+, 38), 451 (59), 342 (46), 321 (42), 306 (100). Anal. Calcd for $C_{24}H_{33}F_3N_4S$: C, 61.78; H, 7.13; N, 12.01. Found: C, 61.66; H, 7.18; N, 11.91.

5e Mp 165-166 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.27 (3H, s, Me), 1.38 (3H, s, Me), 1.64 (6H, broad s, $3CH_2$), 1.68-1.90 (10H, m, $5CH_2$), 2.07 (3H, broad s, 3CH), 2.85-2.94 (4H, m, $2NCH_2$), 4.16 (1H, s, CH), 7.29 (2H, d, J = 8.5 Hz, CH_{Ar}), 7.81 (2H, d, J = 8.5 Hz, CH_{Ar}). MS (m/z, %): 446 (M^+, 12), 376 (21), 285 (24), 149 (100), 135 (34). Anal. Calcd for $C_{27}H_{34}N_4S$: C, 72.61; H, 7.67; N, 12.54. Found: C, 72.57; H, 7.72; N, 12.60.

5f Mp 181-182 °C. ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.26 (9H, s, *t*-Bu), 1.29 (3H, s, Me), 1.51 (3H, s, Me), 2.56 (4H, broad s, $2SCH_2$), 3.11 (4H, broad s, $2NCH_2$), 3.97 (1H, s, CH), 7.33 (2H, d, J = 8.3 Hz, CH_{Ar}), 7.83 (2H, d, J = 8.3 Hz, CH_{Ar}). MS (m/z, %): 400 (M^+, 52), 402 (M+2, 4), 343 (47), 317 (100), 298 (29), 241 (45). Anal. Calcd for $C_{21}H_{28}N_4S_2$: C, 62.96; H, 7.05; N, 13.99. Found: C, 63.05; H, 6.98; N, 14.03.

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