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CARBON-CARBON AND CARBON-HETEROATOM CONJUGATE ADDITION OF N-SUBSTITUTED MALEIMIDES TO 4*H*-1,2,4-TRIAZOL-3-THIOLES, 2-AMINO-1,3-THIAZOLES, 1*H*-IMIDAZOLE AND 2-PHENYLINDOLIZINE CATALYZED BY LEWIS ACIDS

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Key words: Michael addition; catalyst; maleimide; Lewis acids; succinimide, regioselectivity

In the paper the cheap and effective method of the synthesis of 3-heteryl substituted succinimides via catalytic Michael addition are presented. Lewis acids have been found to be effective catalysts for conjugate addition of N-aryl substituted maleimides to the heterocycles with donor-heteroatoms or CH-active function. Catalytic reactions proceed in mild conditions without formation of by-products that are often present in the classical Michael reaction. The compounds synthesized are promising and interesting substrates for biological evaluation since numerous natural products, drugs and drug candidates bear the succinimide core. Moreover, regioselectivity of addition of ambident heterocyclic nucleophiles such as 4H-1,2,4-triazole-3-thiole, 1H-imidazole and 2-amino-1,3-thiazole to maleimides have been investigated. Lewis acids such as aluminium chloride, zinc chloride and lithium perchlorate have been tested on different heterocyclic substrates as catalysts. Interestingly, depending on nucleophilicity of the substrate different Lewis acids have shown significantly varying efficacy. In this respect aluminium chloride was identified as the most effective catalyst for C–C addition among the Lewis acids tested. Lithium perchlorate appears to be the most efficient in the case of C–N addition with the endocyclic nitrogen atom of the hererocycle. Zinc chloride shows a good catalytic efficacy in addition of maleimides to the exocyclic amino group of 2-aminothiazole. Finally, the advantages of the catalytic approach developed such as mild reaction conditions, easy handling, low toxicity of the catalysts and their low cost make this method useful for the synthesis of new 3-heteryl substituted succinimides, which, in turn, are interesting substrates in medicinal chemistry.

КАТАЛІТИЧНЕ КАРБОН-КАРБОН ТА КАРБОН-ГЕТЕРОАТОМ СПРЯЖЕНЕ ПРИЄДНАННЯ N-ЗАМІЩЕНИХ МАЛЕЇНІМІДІВ ДО 4H-1,2,4-ТРИАЗОЛ-3-ТІОЛІВ, 2-АМІНО-1,3-ТІАЗОЛІВ, 1H-ІМІДАЗОЛУ ТА 2-ФЕНІЛІНДОЛІЗИНУ В ПРИСУТНОСТІ КИСЛОТ ЛЬЮЇСА

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Ключові слова: *приєднання за Міхаелем; каталізатор; малеїнімід; кислоти Льюїса; сукцинімід; регіоселективність*

В даній публікації представлений простий та економний метод синтезу похідних 3-гетерилзаміщених піролідин-2,5-діонів за допомогою каталітичної реакції Міхаеля. В якості каталізаторів були використані кислоти Льюїса, які показали високу каталітичну ефективність у реакціях приєднання N-арил заміщених малеїнімідів до донорних та CH-активних гетероциклів. Представлені реакції перебігають в основному при кімнатній температурі і м'яких умовах, що дозволяє уникнути утворення небажаних побічних продуктів. Синтезовані речовини є цікавими та перспективними об'єктами з точки зору медичної хімії, оскільки відомо, що сполуки із сукцинімідним ядром проявляють антибактеріальну, протитуберкульозну та антиепілептичну активність. Відомі також природні сполуки з піролідин-2,5-діоновим фрагментом, що використовуються як ефективні та селективні антибіотики. У даній роботі було досліджено регіоселективність приєднання малеїнімідів до гетероциклічних субстратів з двома альтернативними донорними центрами. В якості каталізаторів були використані хлориди алюмінію та цинку, а також літію перхлорат. Було виявлено, що випробувані кислоти Льюїса проявляють різну каталітичну активність на різних субстратах, що вочевидь залежить від нуклеофільності гетероциклу. Найбільш ефективним каталізатором для C–C приєднання виявився алюмінію хлорид. У свою чергу, літію перхлорат показав високу каталітичну активність для C–N приєднання, а цинку хлорид був ідентифікований, як найбільш ефективний у випадку приєднання малеїнімідного кільця до екзоциклічної аміногрупи 2-амінотіазолу. Перевагами даного каталітичного методу є м'які реакційні умови, низька токсичність каталізаторів та їх низька ціна, що робить даний підхід синтетично вигідним для отримання 3-гетерилзаміщених піролідин-2,5-діонів.

КАТАЛИТИЧЕСКОЕ УГЛЕРОД-УГЛЕРОД И УГЛЕРОД-ГЕТЕРОАТОМ СОПРЯЖЕННОЕ ПРИСОЕДИНЕНИЕ N-ЗАМЕЩЕННЫХ МАЛЕИНИМИДОВ К 4H-1,2,4-ТРИАЗОЛ-3-ТИОЛАМ, 2-АМИНО-1,3-ТИАЗОЛАМ, 1H-ИМИДАЗОЛУ И 2-ФЕНИЛИНДОЛИЗИНУ В ПРИСУТСТВИИ КИСЛОТ ЛЬЮИСА

Т.В.Матвиюк, М.В.Горичко, К.Лербет, М.Бальтас, З.В.Войтенко

Ключевые слова: *присоединение по Михаэлю; катализатор; малеинимид; кислоты Льюиса; сукцинимид; региоселективность*

В настоящей статье представлен простой и эффективный экономный метод синтеза 3-гетарилзамещенных пирролидин-2,5-дионов с помощью каталитической реакции Михаэля. В качестве катализаторов были использованы кислоты Льюиса, которые показали высокую каталитическую активность в ре-

акциях присоединения N-арилзамещенных малеинимидов к донорным гетероциклам. Представленные реакции протекают в большинстве случаев при комнатной температуре и мягких условиях, что позволяет избегать образования нежелательных побочных продуктов. Синтезированные соединения являются перспективными в области медицинской химии, поскольку хорошо известно, что производные пиролидин-2,5-дионов обладают антибактериальной, антиэпилептической и противотуберкулезной активностью. Также известны продукты природного происхождения, содержащие сукцинимидное ядро, которые являются эффективными и селективными антибиотиками. В представленной работе была исследована региоселективность присоединения малеинимидов к гетероциклическим субстратам. В качестве катализаторов были использованы хлориды алюминия, цинка и перхлорат лития. Оказалось, что апробированные кислоты Льюиса имеют разную каталитическую активность на разных субстратах, что, вероятно, зависит от нуклеофильности гетероцикла. Наиболее эффективным катализатором для C–C присоединения оказался хлорид алюминия, тогда как перхлорат лития показал высокую каталитическую активность при C–N присоединении, а хлорид цинка позволил получить высокие выходы аддуктов в случае присоединения малеинимидов к экзоциклической аминогруппе 2-аминотиазола. Представленный здесь оптимизированный каталитический метод позволяет синтезировать новые 3-гетарилзамещенные пирролидин-2,5-дионы.

Michael and conjugated addition reactions are well known as efficient methods for the construction of carbon-carbon and carbon-heteroatom bonds with wide applications in organic synthesis [1, 2]. These reactions have been widely used in the synthesis of pharmaceutical intermediates, peptide analogues, antibiotics, and other drugs [3-5]. On the other hand, maleimides are an important class of substrates, which have been successfully used in the wide range of organic transformations. They have emerged as excellent dienophiles/dipolarophiles in cycloaddition reactions, as well as Michael acceptors. Traditionally, conjugate additions are performed under the influence of strong bases, but basic conditions often lead to formation of undesirable side products by polymerization, self-condensation, and other reactions.

Due to the presence of two carbonyl groups conjugated with a double bond and nitrogen imide atom maleimides have excellent opportunity to formation of complexes with heavy Lewis acids. In this context the search of new and efficient catalysts for various organic transformations is a relevant area of research nowadays. Various alternative catalysts, such as phase-transfer catalysts, transition-metal complexes, lanthanides, alumina [6], have been proposed [1, 7]. Despite the broad research and scientific attention to this field only a few catalysts can be used for a preparative synthesis due to high costs, difficulties related to their recovery and reuse, and often a complicated procedure of synthesis. Thus, development of new methods using cheap, commercially available, nontoxic catalysts capable of generating products in good yields is of paramount importance.

In the course of our previous study of Michael reaction on heterocyclic substrates with maleimides as electron-deficient dienophiles [8-11] we were trying to expand the boundaries of this reaction and find the optimal experimental conditions. Herein we report results of our research on conjugate addition of maleimides to nucleophilic heterocyclic substrates under the mild catalytic conditions. In this respect, we used Lewis acids because of their efficacy, low cost, ease of handling and low toxicity. Only a few examples of using aluminum chloride, as well as other Lewis acids were reported for the activation of maleimides [12] and the potency of those catalysts in the field of Michael addition has not been developed yet. Our interest on maleimides as Michael acceptors is also specified because of a large number of reported pharmaceutical substances bearing the pyrrolidine-2,5-dione fragment. For example, Phensuximide and Suclophenide are already more than 40 years in use as effective anticonvulsant and antiepileptogenic drugs [13, 14] and they are still actual nowadays (Fig. 1). Moreover, succinimide is the core structural unit found in natural products. [15, 16]. Since Komura and coworkers in 1987 reported isolation of Andrimid as a new and highly specific antibiotic, 1,3-substituted and 3,4-disubstituted succinimides emerged as a new class of natural products with the important biological activity [17]. Andrimid and Moiramide B (Fig.) exhibit a potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* and a number of other antibiotic-resistant human pathogens. Those natural antibiotics have been described in the target fatty acid biosynthesis system (FAS) that is the primary target for antitubercular drugs [18]. Futhermore, Hirsutellone A, a natural product bearing the succinimide ring (Fig. 1) displayed a significant growth inhibitory activity against *Mycobacterium tuberculosis* [19]. Due to the wide spectrum of bioactivity of pyrrolidine-2,5-dione derivatives we have synthesized a number of new 3-heteryl substituted succinimides using the optimized catalytic conditions.

Results and Discussion

In our research we have used *N*-aryl maleimides as electron-deficient reactants in conjugate addition with 4*H*-1,2,4-triazole-3-thioles, 2-amino-1,3-thiazoles, 1*H*-imidazole and 2-phenylindolizine. The reactions, in general, proceed smoothly at the room temperature, and the products are in good yields. C–C, C–N and C–S adducts have been synthesized using aluminum chloride, lithium perchlorate and zinc chloride as catalysts. Regioselectivity of maleimide addition in the presence of two alternative nucleophilic centres in a heterocyclic substrate has been investigated. For example, addition of 4*H*-1,2,4-triazole-

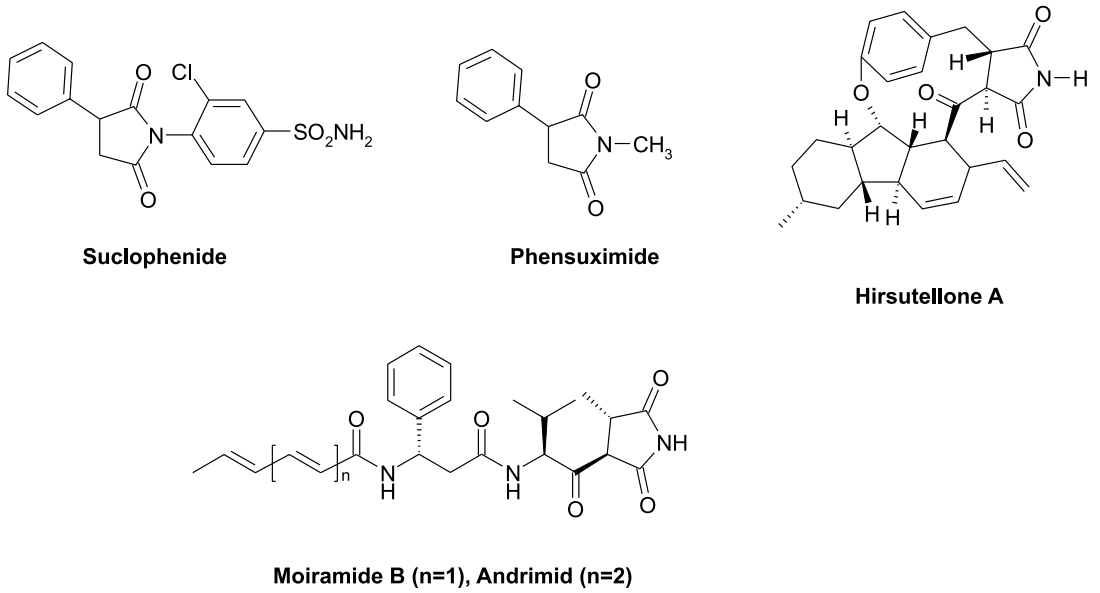


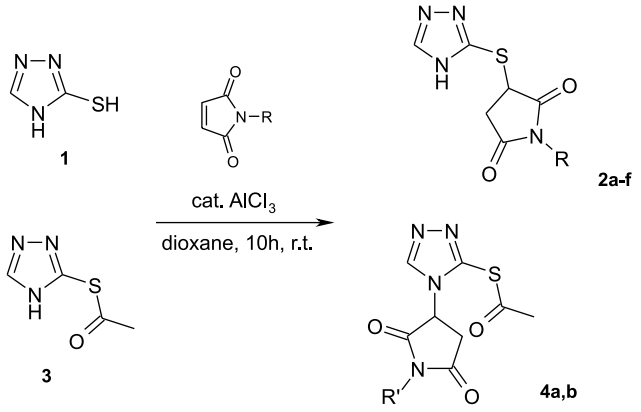
Figure. Structures of anticonvulsant drugs (Phensuximide and Suclophenide), natural antibiotics (Moiramide B and Andrimide) and antimycobacterial alkaloid Hirsutellone A.

3-thiol (**1**) with maleimides gives the conjugated products *via* a highly nucleophilic mercapto group as a single type of products (Scheme 1) in good yields (Table 1). In the case of the blocked mercapto function (compound **3**) the reaction proceeds *via* the 4-*NH*-position of the heterocycle forming only one product **4a,b,** respectively.

Regioselectivity of Michael addition of maleimides to 2-amino-1,3-thiazoles has been also investigated. Recently we have reported the double conjugate addition of maleimides to 2-amino-1,3-thiazole and 3-substituted-2-aminopyridines in the presence of the catalytic amount of lithium perchlorate [19]. In contrast, the presence of the catalytic amount of zinc chloride leads to formation of C-N mono Michael adducts (**6a,b**) *via* the exocyclic nitrogen atom of the heterocycle (Scheme 2, Table 2). Aluminum chloride appears to be not effective catalyst in this reaction. Only the trace amounts of mono addition products were isolated. In this case regioselectivity of the reaction depends on the catalyst used. *N*-Acylated derivative of 2-amino-1,3-thiazole (**7**) reacts with maleimide *via* C-5 ring position forming C–C adduct **8**. The reaction proceeds in the presence of aluminum chloride. After refluxing of the reaction mixture for 5 hours, compound **8** was isolated as a single product in 76% yield.

Subsequently imidazole has been selected as a substrate for our further investigation of catalytic conjugate addition since it combines the imido group and a CH-active fragment as alternative reactive positions in one ring. The addition occurs on the nitrogen atom of the heterocycle forming carbon-heteroatom adducts **10a-c** in good yields (Scheme 3, Table 3). The reaction proceeds at the room temperature in the presence of the catalytic amount of lithium perchlorate with full conversion of the starting products in 2 hours. Aluminum and zinc chlorides appear to be not appropriate catalysts, mixtures of hardly identified products were isolated in both cases.

Thereafter 2-phenylindolizine (**11**) was selected as a less reactive substrate that contains only CH-active fragment. Unlike previously used conditions, this

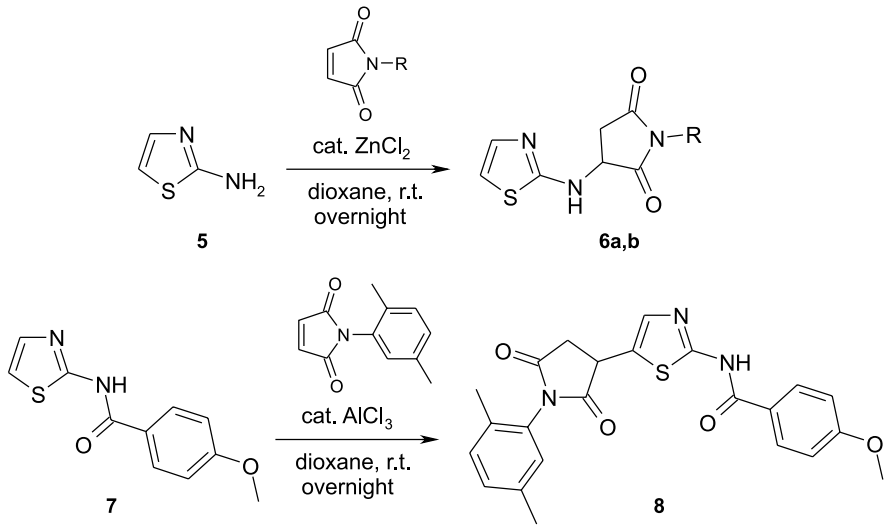


Scheme 1. Carbon–heteroatom conjugate addition of maleimides to 4*H*-1,2,4-triazole-3-thiol **1** and its acetyl derivative **3**.

Table 1

The compounds synthesized

Cmpd	R	Yield %
2a	*p*-$(NO_2)C_6H_4$	80
2b	*m*-$(NO_2)C_6H_4$	60
2c	*p*-$(OCH_3)C_6H_4$	63
2d	*m*-$(Br)C_6H_4$	80
2e	$-C_6H_5$	62
2f	$-CH_2-Ph$	50
4a	*p*-$(NO_2)C_6H_4$	57
4b	*p*-$(OCH_3)C_6H_4$	40



Scheme 2. Michael addition of maleimides to 2-aminothiazoles **5** and **7**.

Table 2

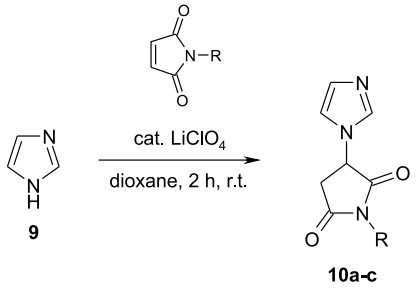
The compounds synthesized

Cmpd	R	Yield %
6a	C_6H_5	44
6b	CH_2–C_6H_5	38

Table 3

The compounds synthesized

Cmpd	R	Yield %
10a	C_6H_5	95
10b	C_6H_4–*p*(OCH_3)	92
10c	C_6H_4-*p*(NO_2)	90



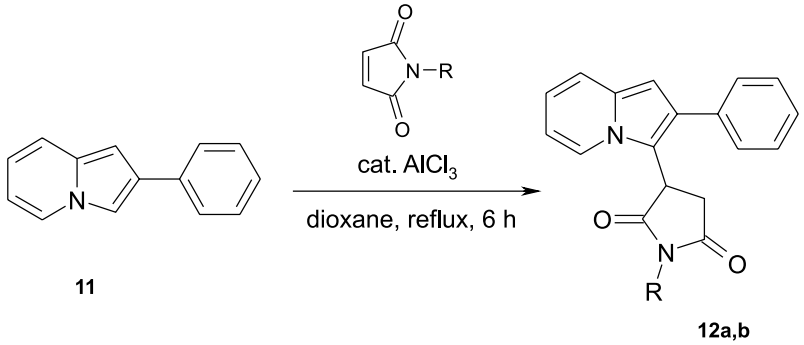
Scheme 3. Synthesis of imidazole derivatives **10a-c**.

reaction requires refluxing of the reaction mixture for 6 hours. The products **12a,b** were isolated in good yields only when aluminum chloride was used as a catalyst (Scheme 4, Table 4).

Experimental Part

All chemicals were obtained from Aldrich or Acros Organics and used without further purification. All solvents were distilled before use. Compounds **3**, **7** and **11** have been synthesized according to the literature procedures and completely characterized using ^{1}H and ^{13}C NMR, MS and C,H,N analysis with all the results obtained fitting the previously reported literature data (details are not reported here) [22, 23, 24]. Nuclear magnetic resonance spectra were recorded on a 'Mercury 400' Varian spectrometer (^{1}H and ^{13}C NMR), TMS signal was used as an internal standard for calibration of spectral data. Melting points were measured on a Mettler Toledo MP50 melting point system and are uncorrected.

General procedure for the synthesis of derivatives **2a-f**, **4a,b** and **8**: 100 mg (0,99 mmol) of 4*H*-1,2,4-triazole-3-thiole (**1**) or 143 mg (0,1 mmol) of *S*-(4*H*-1,2,4-triazol-3-yl)ethanethioate (**3**) and 1 mmol of *N*-substituted maleimide were dispersed in a dry dioxane. The mixture was stirred for 15 minutes for dissolving of maleimide. Thereafter 2,0 mg of anhydrous aluminum chloride (0,015 mmol) was quickly added. The reaction mixture was stirred at the room temperature for 10 hours. The progress of the reaction was monitored by TLC. After its completion the solvent was evaporated. Then the residue was washed two times with distilled water and the crude product was purified by crystallization.



Scheme 4. Synthesis of 2-phelylindolizine derivatives **12a,b**.

Table 4

The compounds synthesized

Cmpd	R	Yield %
12a	C_6H_5	84
12b	CH_2–C_6H_5	71

1-(4-Nitrophenyl)-3-(4H-1,2,4-triazol-3-ylsulfanyl)-2,5-pyrrolidinedione (2a)

A crude product was crystallized from methyl alcohol to give a purple powder. Yield 80%; m.p.: 165-166°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.94 dd (1H, J 18.4 Hz, J 3.6 Hz,); 3.45 dd (1H, J 18.4 Hz, J 9.6 Hz); 4.62 dd (1H, J 3.6 Hz, J 9.6 Hz); 7.60 d (2H, J 8.2 Hz); 8.34 d (2H, J 8.2 Hz); 8.45 s (1H); 14.16 br. s (1H). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 36.5, 41.6, 128.1, 145.2, 145.8, 158.0, 159.8, 162.5, 174.5, 174.8.

1-(3-Nitrophenyl)-3-(4H-1,2,4-triazol-3-ylsulfanyl)-2,5-pyrrolidinedione (2b)

A crude product was crystallized from methyl alcohol to give a white powder. Yield 60%; m.p.: 171-173°C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.93 dd (1H, J 18.4 Hz, J 4.6 Hz); 3.57 dd (1H, J 18.4 Hz, J 9.6 Hz); 4.72 dd (1H, J 4.6 Hz, J 9.6 Hz); 7.78-7.82 m (2H); 8.19 s (1H); 8.31 d (1H, J 8.2 Hz); 8.42 s (1H); 14.17 s (1H).

1-(4-Methoxyphenyl)-3-(4H-1,2,4-triazol-3-ylsulfanyl)-2,5-pyrrolidinedione (2c)

A crude product was crystallized from isopropyl alcohol to give light yellow crystals. Yield 63%; m.p.: 162-163°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.93 dd (1H, J 16.8 Hz, J 2.4 Hz); 3.40 dd (1H, J 16.8 Hz, J 9.4 Hz); 3.82 s (3H); 4.54 dd (1H, J 2.4 Hz, J 9.4 Hz); 6.98 d (2H, J 8.2 Hz); 7.19 d (2H, J 8.2 Hz); 8.04 s (1H);14.17 br. s (1H).

1-(3-Bromophenyl)-3-(4H-1,2,4-triazol-3-ylsulfanyl)-2,5-pyrrolidinedione (2d)

Yield 80%; m.p.: 178-180°C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.93 dd (1H, J 18.4 Hz, J 4.6 Hz); 3.57 dd (1H, J 18.4 Hz, J 9.6 Hz); 4.72 dd (1H, J 4.6 Hz, J 9.6 Hz); 7.80-7.83 m (2H); 8.19 s (1H); 8.31 d (1H, J 8.2 Hz); 8.42 s (1H); 14.16 br. s (1H).

1-Phenyl-3-(4H-1,2,4-triazol-3-ylsulfanyl)-2,5-pyrrolidinedione (2e)

Yield 62%; m.p.: 154-155°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.92 dd (1H, J 18.0 Hz, J 4.8 Hz); 3.42 dd (1H, J 18.0 Hz, J 9.6 Hz); 4.67 dd (1H, J 4.8 Hz, J 9.6 Hz); 7.26 d (2H, J 7.2 Hz); 7.40-7.53 m (3H); 8.56 s (1H); 14.08 br. s (1H). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 36.5, 41.3, 127.0, 128.5, 128.9, 132.8, 145.8, 155.4, 174.3, 174.8.

1-Benzyl-3-(4H-1,2,4-triazol-3-ylsulfanyl)-2,5-pyrrolidinedione (2f)

A crude product was crystallized from isopropyl alcohol to give a white powder. Yield 62%; m.p.: 154-155°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.92 dd (1H, J 18.4 Hz, J 4.0 Hz); 3.27 dd (1H, J 18.4 Hz, J 9.6 Hz); 4.56-4.58 m (3H); 7.24-7.28 m (5H); 8.58 s (1H); 14.12 br. s (1H).

S-{4-[1-(4-Nitrophenyl)-2,5-dioxo-3-pyrrolidinyl]-4H-1,2,4-triazol-3-yl} ethanethioate (4a)

A crude product was crystallized from ethanol to give white crystals. Yield 57%; m.p.: 183-184°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.80 s (3H); 2.90 dd (1H, J18.0 Hz, J 4.8 Hz); 3.36 dd (1H, J 18.0 Hz, J 9.6 Hz); 4.65 dd (1H, J 4.8 Hz, J 9.6 Hz); 7.03 d (2H, J 8.8 Hz); 7.16 d (2H, J 8.8 Hz); 8.56 s (1H). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 37.2, 41.2, 55.4, 114.15, 125.3, 128.2, 145.4, 152.7, 159.0, 174.5, 174.9, 175.4.

S-{4-[1-(4-Methoxyphenyl)-2,5-dioxo-3-pyrrolidinyl]-4H-1,2,4-triazol-3-yl} ethanethioate (4b)

A crude product was crystallized from ethanol to give a light yellow powder. Yield 40%; m.p.: 167-169°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.82 s (3H); 3.37 dd (1H, J 18.4 Hz, J 3.6 Hz); 3.80 dd (1H, J 18.4 Hz, J 9.6 Hz); 3.81 s (3H); 4.53 m (1H); 6.99 d (2H, J 8.8 Hz); 7.18 d (2H, J 8.8 Hz); 8.44 s (1H).

N-{5-[1-(2,5-Dimethylphenyl)-2,5-dioxo-3-pyrrolidinyl]-1,3-thiazol-2-yl}-4-methoxybenzamide (8).

A crude product was crystallized from the mixture of isopropyl alcohol and ethyl acetate (1:1) to give a white powder. Yield 62%; m.p.: 138-139°C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.48 s (3H); 2.58 s (3H); 2.91 dd (1H, J 18.0 Hz, J 1.2 Hz); 3.17 s (3H); 3.23 dd (1H, J 18.0 Hz, J 9.2 Hz); 4.56 dd (1H, J 1.2 Hz, J 9.2 Hz); 3.57 s (3H); 7.22–7.28 m (7H); 8.29 s (1H); 11.08 br. s (1H).

General procedure for the synthesis of derivatives **6a, b**: 80 mg (0,80 mmol) of 1,3-thiazol-2-amine was dissolved in 7 mL of dry dioxane. Then *N*-substituted maleimide (0,82 mmol) was added to the solution. The resulting mixture was stirred for 10 min for complete dissolution of the reagents. Thereafter 2,0 mg (0,015 mmol) of anhydrous zinc chloride was quickly added and the flask was fitted with a calcium chloride tube. The reaction mixture was stirred overnight at the room temperature. After the solvent was evaporated, to the residue 8 mL of brain was added. The mixture was extracted 3 times with ethyl acetate. Combined organic layers were dried with sodium sulphate, filtered and the solvent was evaporated. A crude product was then purified by crystallization.

1-Phenyl-3-(1,3-thiazol-2-ylamino)-2,5-pyrrolidinedione (6a)

A crude product was crystallized from the small amount of isopropyl alcohol to give a creamy powder. Yield 44%; m.p.: 119-120°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.85 dd (1H, J 18.0 Hz, J 3.6 Hz); 3.31 dd (1H, J 18.0 Hz, J 9.2 Hz); 4.53 dd (1H, J 3.6 Hz, J 9.2 Hz); 6.78-7.38 m (6H); 7.41 d (1H, J 4.8 Hz); 8.01 s (1H). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 38.9, 54.9, 115.6, 125.6, 127.3, 133.0, 138.9, 165.0, 169.6, 170.3, 172.2.

1-Benzyl-3-(1,3-thiazol-2-ylamino)-2,5-pyrrolidinedione (6b)

A crude product was crystallized from the small amount of isopropyl alcohol to give a creamy powder. Yield 38%; m.p.: 138-140°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.91 dd (1H, J 18.4 Hz, J 4.0 Hz); 3.27 dd (1H, J 18.4 Hz, J 9.2 Hz); 4.27 s (2H); 4.58 dd (1H, J 4.0 Hz, J 9.2 Hz); 6.73 d (1H, J 7.6 Hz); 7.22 d (1H, J 7.6 Hz); 7.24-7.33 m (5H); 8.12 br. s (1H).

General procedure for the synthesis of derivatives **10a-c**: 80 mg (1,18 mmol) of imidazole was dissolved in 7 mL of dry dioxane. After that *N*-substituted maleimide (1,18 mmol) was added. The resulting mixture was stirred for complete dissolution of the reagents. Then the catalytic amount of lithium perchlorate 2,0 mg (0,019 mmol) was added and the reaction mixture was stirred for 2h at the room temperature. Then 18 mL of distilled water was added. The precipitate obtained was filtered and washed with isopropyl alcohol and diethyl ether to give a white powder.

3-(1H-Imidazol-1-yl)-1-phenyl-2,5-pyrrolidinedione (10a)

Yield 95%; m.p.: 161-163°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.16 dd (1H, J 16.8 Hz, J 6.4 Hz); 3.40 dd (1H, J 16.8 Hz, J 9.2 Hz); 5.68 dd (1H, J 9.2 Hz, J 6.4 Hz); 6.92 s (1H); 7.36-7.49 m (5H); 7.57 s (1H); 7.80 s (1H). ^{1}H NMR (400 MHz, CF_3CO_2D), δ, ppm: 2.9 dd (1H, J 16.8 Hz, J 6.4 Hz); 3.26 dd (1H, J 16.8 Hz, J 9.2 Hz); 5.38 dd (1H, J 9.2 Hz, J 6.4 Hz); 6.54-6.57 m (2H); 6.80-6.88 m (3H); 6.9 s (1H); 7.08 s (1H); 7.51 s (1H). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 36.88, 54.79, 118.56, 127.3, 128.59, 128.93, 129.34, 132.47, 137.96, 172.94, 173.35.

3-(1H-Imidazol-1-yl)-1-(4-methoxyphenyl)-2,5-pyrrolidinedione (10b)

Yield 92%; m.p.: 154-155°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.18 dd (1H, J 16.8 Hz, J 6.8 Hz); 3.37 dd (1H, J 16.8 Hz, J 4.2 Hz), 3.83 s (3H); 5.64 dd (1H, J 4.2 Hz, J 6.8 Hz); 6.94 s (1H); 7.00-7.26 m (4H); 7.40 s (1H); 7.83 s (1H).

3-(1H-Imidazol-1-yl)-1-(4-nitrophenyl)-2,5-pyrrolidinedione (10c)

Yield 90%; m.p.: 170-171°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.16 dd (1H, J 17.6 Hz, J 8.8 Hz); 3.36 dd (1H, J 17.6 Hz, J 9.2 Hz); 5.63 dd (1H, J 8.8 Hz, J 9.2 Hz); 6.92 s (1H); 7.27 d (2H, J 7.2 Hz); 7.33 d (2H, J 7.2 Hz); 7.38 s (1H); 7.80 s (1H).

General procedure for the synthesis of derivatives **12a,b**: 2-Phenylindolizine 100 mg (0,52 mmol) was dispersed in dry dioxane. Then 0,53 mmol of *N*-substituted maleimide was added. The mixture was stirred for 15 minutes. After that the catalytic amount of aluminum chloride 1.5 mg (0,011 mmol) was added. The reaction mixture was refluxed for 6 hours. The reaction progress was monitored by TLC. After completion, the solvent was evaporated and the crude product was purified by crystallization.

1-Phenyl-3-(2-phenyl-3-indolizinyl)-2,5-pyrrolidinedione (12a)

The crude product was recrystallized from absolute ethanol. Yield: 84%; mp: 210-212°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 3.06 dd (1H, J 6.9 Hz, J 17.7 Hz); 3.36 m (1H); 5.13 t (1H, J 6.9 Hz); 6.60-7.54 m (14H); 7.97 d (1H, J 6.6 Hz). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 33.6, 37.4, 99.6, 111.3, 114.5, 117.5, 119.1, 122.8, 126.9, 127.1, 128.4, 128.7, 128.9, 129.0, 129.8, 132.3, 132.5, 135.7, 174.5, 175.8.

1-Benzyl-3-(2-phenyl-3-indolizinyl)-2,5-pyrrolidinedione (12b)

The crude product was recrystallized from absolute ethanol. Yield: 71%; mp: 192-194°C. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 3.14 dd (1H, J 6.3, Hz, J 16.8 Hz); 3.35 m (1H); 4.12 s (2H); 5.07 m (1H); 6.67-7.53 m (14H); 7.95 d (1H, J 6.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 33.6, 37.5, 46.6, 99.8, 111.5, 114.3, 117.1, 118.9, 122.8, 124.9, 126.4, 127.1, 128.4, 128.7, 128.9, 129.0, 129.8, 132.3, 132.5, 135.7, 174.1, 175.6.

Conclusions

We have demonstrated that Lewis acids can be effective catalysts for carbon-carbon and carbon-heteroatom Michael addition. The advantages of this method such as mild reaction conditions, simple experimental procedure, low toxicity of the catalysts and their low cost can make this method synthetically useful. Moreover, it is an easy way to synthesize 3-heteryl substituted pyrrolidine-2,5-diones, which are attractive synthetic compounds in the field of medicinal chemistry.

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