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Michael addition of heteronucleophilic substances to N – Ar substituted maleimides: green approach

Oleh Vybornyi[a], Tetiana Matviiuk[a], Tatyana Yegorova[a], Michel Baltas[b], Zoia Voitenko[a]

[a]*Department of Chemistry, Taras Shevchenko National University of Kyiv, 64/13 str. Volodymyrska, Kyiv, 01601, Ukraine*

[b]*Université Paul Sabatier, UPS, LSPCMIB, 118 route de Narbonne, F-31062 Toulouse cedex 9, France*

vybornyy@mail.ru

A new method for the preparation of the adducts of aromatic hetero nucleophiles (NH, SH, OH) to the activated C=C bond of N-aryl-substituted maleimides using Michael reaction was developed. A possibility to obtain mono-adducts was demonstrated for 2-aminopyridine derivatives. It was proven that in the case of amino phenols, which possess three potential nucleophilic centers, only the addition to amino group occurs. Utility of the method for the formation of C–C bond in Michael reaction was also demonstrated.

Introduction

Michael reaction is a convenient method for the formation of different covalent bonds (C–C or C – heteroatom) [1–5]. The classical conditions for this reaction include the use of base catalysis (KOH, etc). Unfortunately, the basic conditions often lead to unwanted results due to the occurrence of side reactions, such as hydrolysis of maleimide ring or cleavage of base-labile functional groups [6]. These effects inevitably decrease the overall yields and purity of the product. Currently, either Lewis acids or aliphatic amines are commonly used as the catalysts in Michael addition. Using these conditions allowed to extend already high synthetic possibilities of the Michael reaction, and it is widely used in the field of bioconjugate chemistry (for linking biologically relevant species like peptides, DNA), as well as for the synthesis of the biologically active compounds containing maleimide moiety [7–9]. For example, pharmacologically active pyrrolidine-2,5-dione derivatives are synthesized from maleimides. Moreover, cyclic imides are an important class of molecules with diverse array of bioactivities: antagonists of α-1A adrenergic and androgen receptors, anxiolytic, antiviral, antibacterial, anti-inflammatory, and antitumor properties. Also, succinimide derivatives exhibit potent hypolipidaemic and fungicidal properties [10–14].

Methods for the preparation of pyrrolidine-2,5-dione derivatives which are C–C Michael's adducts are well-known in literature [15, 16]. On the contrary, the addition of the aromatic heteronucleofilic species (NH, SH, OH derivatives) to the maleimides is less studied [17–19]. In our previous reports, we have described the studies on the regioselectivity and reactivity of N- and S-nucleophiles in the addition to maleimide. Although these results have demonstrated the utility of the Michael addition for the synthesis of various heterocycles, which are hardly achievable by alternative methods, some of the compounds are not reactive under the conditions reported.

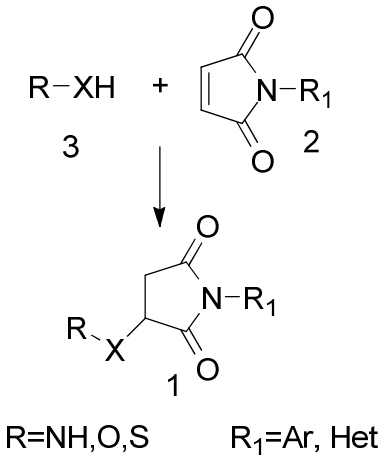
Therefore, a research aimed at the elaboration of novel synthetic procedures,

which could allow controlling of selectivity and increasing reactivity (or decreasing reaction time) looks promising.

Results and discussion

The main purpose of the study was to develop a convenient and preparative method for the synthesis of different pyrrolidine-2,5-dione derivatives of general formula **1** (Scheme 1).

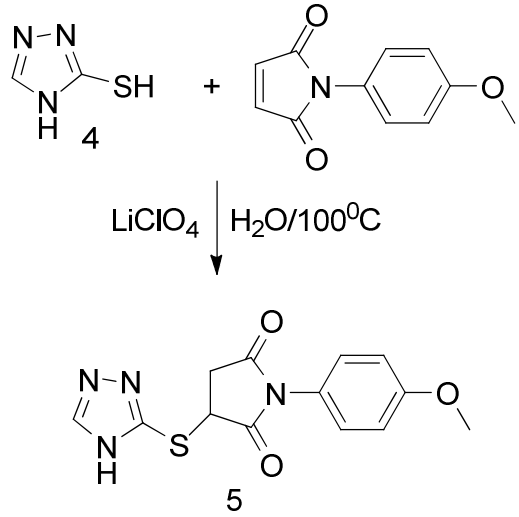
In order to improve the selectivity (*i. e.* exclusive formation of 1:1 adduct), the yield of the reaction and to avoid the use of organic solvents, it was decided to test influence of various catalysts and solvents on the reaction outcome.



Scheme 1. Synthesis of pyrrolidine-2,5-diones **1**

The experimental data clearly show that the reaction time and yields depend strongly on the polarity of the solvent. For example, average yields in dioxane are usually higher than in apolar solvents like toluene. Preliminary experiments on the use of more polar solvents showed that in this case, the reaction time was shortened significantly. It was found that water is an optimal solvent. Several commonly used Lewis acids such as AlCl3, TiCl4 and BiCl3 were impossible to use due to their hydrolysis. On the contrary, the use of LiClO4 – a weaker Lewis acid – was beneficial due to the complete dissociation of the salt. The optimized conditions for the reaction in water were 100 °C, catalytic amount of $LiClO_4$, 2–4 hours.

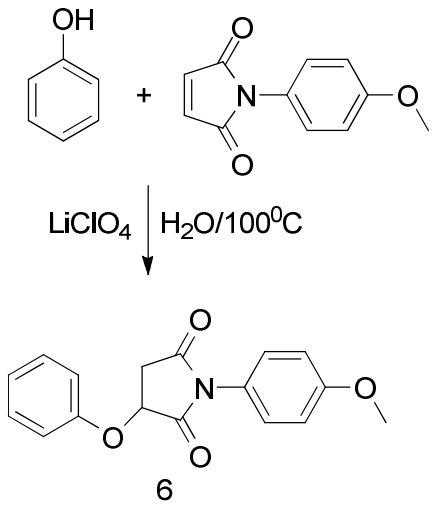
To demonstrate the scope of this reaction, an S-nucleophile **4** were introduced into the reactions with N-arylmaleimides. The corresponding product **5** was obtained in 93% yield.



Scheme 2. Reaction with S-nucleophiles

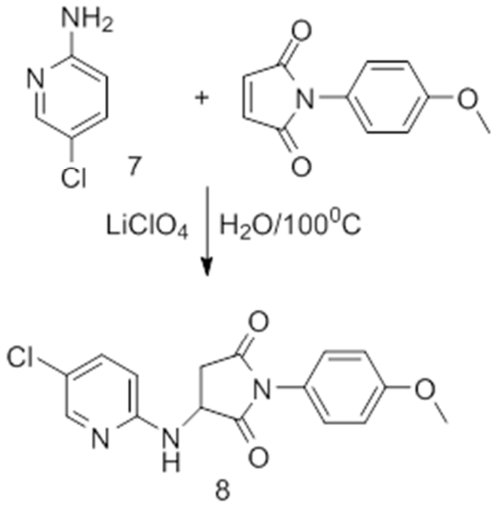
The synthesis of the know compound **5** allowed us to demonstrate the benefits of the method. The use of LiClO4 allowed to shorten the reaction time from 24 to 2 h and to improve the yield from 70% to 93%. The spectral characteristics of **5** were identical to those described in the literature [18].

To demonstrated the utility of the method for O-nucleophiles, preparation of the compound **6** was performed. By applying our procedure, we were able to decrease reaction time from 72 to 6 h, and to increase the yield from 50% to 82%. Again, the spectral data of the were identical to those described in the literature [19].



Scheme 3. Reaction with O-nucleophiles

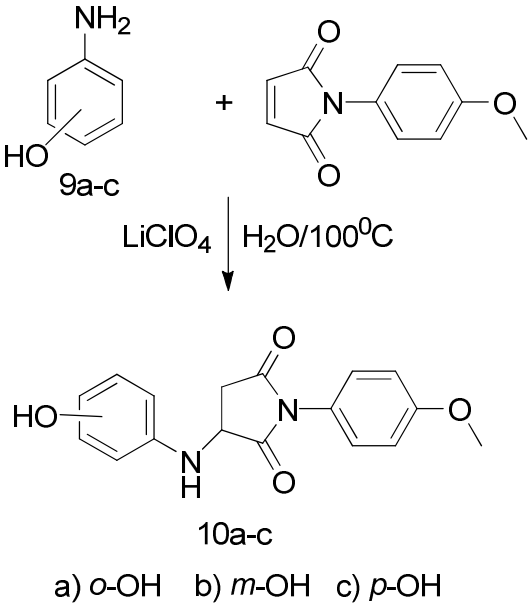
The possibility of using *N*-nucleophiles in the reaction studied was demonstrated for the case of 4-chloro-2-aminopyridine **7**.



Scheme 4. Reaction with N-nucleophiles

Unexpectedly, the reaction changed its selectivity in water compared to the literature results [17]. The reaction of **7** with 4-methoxyphenylmaleimide in the presence of lithium perchlorate in dioxane gave a product of *bis*-addition with the opening of the maleimide ring in 50% yield. Using the method developed in this work, only the product of mono addition was obtained.

After it was found that even the replacement of dioxane by water could lead to the drastic changes in the reaction outcome, it was interesting to study the effect of the use of lithium perchlorate in water at 100 °C on the regioselectivity of the reaction. For the first time, *ortho*-, *meta*- and *para*-aminophenols **9a–c**, which contain three potential nucleophilic centers: –NH2, –OH and –CH, were introduced into the reaction.

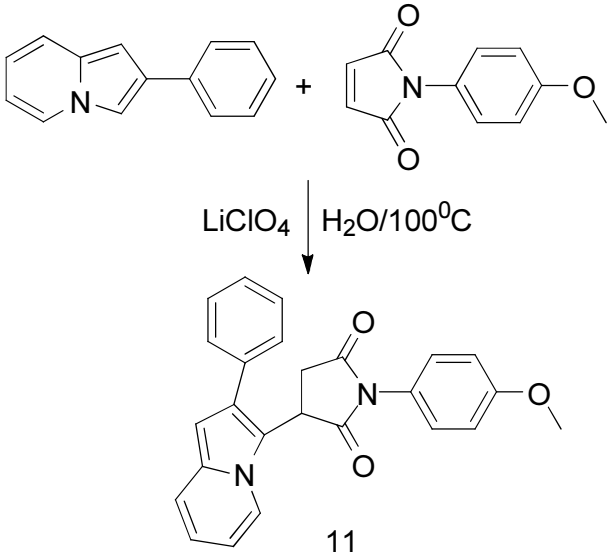


Scheme 5. Reaction with N-nucleophiles

The spectral data have shown that only the products of mono-addition **10a–c** are formed in the reaciont. For example, in the 13C NMR spectrum of compound **10a,** the signal of the carbon atom, which is linked to the nitrogen, has a chemical shift of 56.0 ppm. If it was linked to other atom, the chemical shifts for them would be ~86 or ~38 ppm for the O–C and C–C bonds, respectively. It was also found that the rate of reaction is affected by nucleophilicity of **9**. Thus, the reaction with **9a** and **9c** was much faster than in the case of **9b**.

To further demonstrate the possibilities of the synthetic method developed, apart from introducing heterocyclic nucleophiles,

formation of the classical C–C bond in the Michael reaction was studied, preparation of 1-phenyl-3-(2-fenilindolizyn-3-yl)pyrrolidine-2,5-dione **11** [20] being used as an example. As in the case of hetero-nucleophiles, the method allowed to shorted the reaction time by two folds.



Scheme 6. Reaction with C-nucleophiles

Conclusions

The method for the synthesis of pyrrolidine-2,5-diones was developed, which allows to increase the yield of the reaction products, to reduce time of the reaction, to avoid the formation of the products of *bis*-addition or ring opening, and to improve the reaction regioselectivity. The method was used successfully for hetero-nucleophiles (NH, SH, OH), in particular, 2-aminopyridine derivatives and amino phenols, as well as for the C-nucleophiles. The advantages of the method include avoiding the use of organic solvents, thus making it environmentally and economically beneficial.

Acknowledgments

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Experimental part

The NMR spectra (400.396 MHz) were recorded with a Varian Mercury 400 with TMS as internal standard.

*Procedure for the synthesis of **1**.* A mixture of 5 mmol 1-aryl-1H-pyrrole-2,5-dione **2**, 5 mmol of heteronucleophile **3**, 0.5 mmol of lithium perchlorate and 15 mL of water was heated with constant stirring. The reaction progress was monitored by TLC. After the reaction was complete, water was evaporated in vacuum. Then, 10 mL of isopropanol were added, the reaction mixture was refluxed for 10 min, and then cooled. The crystalline precipitate formed was filtered.

*1-(4-methoxyphenyl)-3-(4H-1,2,4-triazol-3-ylthio)pyrrolidine-2,5-dione **5**.*

Yield 91%. The constants and spectral data are indentical to those described in the literature [18].

*1-(4-methoxyphenyl)-3-phenoxypyrrolidine-2,5-dione **6**.*

Yield 82%. The constants and spectral data are indentical to those described in the literature [19].

*3-[(5-chloropyridin-2-yl)amino]-1-(4-methoxyphenyl)pyrrolidine-2,5-dione **8**.*

1H NMR (DMSO *d*6, 400 MHz), δ, ppm: 2.614 (dd 1Ha, 3J=18 Hz, 2J=4,6 Hz), 3.196 (dd. 1Hc, 3J=18 Hz, 3'J=8,4 Hz), 3.808 (s. 3H), 4.586 (dd. 1Hb, 2J=4,6 Hz, 3J=8,4 Hz), 6.118 (d. 1H),

7.204 (m. 4H), 7.278 (d. 1H), 7.822 (s. 1H). 13C NMR (400 MHz, DMSO *d*6) ppm: 36.82; 52.91; 55.46; 113.43; 114.06; 122.38; 126.42; 127.20; 137.12; 143.22; 159.79; 161.84; 174.49; 176.74. Yield: 73%.

3-[(2-hydroxyphenyl)amino]-1-(4-methoxyphenyl)pyrrolidine-2,5-dione ***10a***.

1H NMR (DMSO *d*6, 400 MHz), δ, ppm: 2.656 (dd. 1Ha, 3J=18 Hz, 2J=4,6 Hz), 3.205 (dd. 1Hc, 3J=18 Hz, 3'J=8,4 Hz), 3.808 (s. 3H), 4.667 (dd. 1Hb, 2J=4,6 Hz, 3J=8,4 Hz), 5.261 (s. 1H –NH), 6.629 (m. 4H), 6.971 (s. 2H), 7.183 (s. 1H), 9.152 (s. 1H -OH). 13C NMR (400 MHz, DMSO *d*6) ppm: 37.31; 52.22; 56.03; 111.33; 114.49; 114.77; 117.60; 120.27; 125.81; 128.93; 136.67; 145.09; 159.55; 175.38; 177.73. Yield: 93%.

3-[(3-hydroxyphenyl)amino]-1-(4-methoxyphenyl)pyrrolidine-2,5-dione ***10b***.

1H NMR (DMSO *d*6, 400 MHz), δ, ppm: 2.645 (dd 1Ha, 3J=18 Hz, 2J=4,6 Hz), 3.195 (dd. 1Hc, 3J=18Hz, 3'J=8,4 Hz), 3.815 (s. 3H), 4.603 (dd. 1Hb, 2J=4,6 Hz, 3J=8,4 Hz), 5.551 (s. 1H –NH), 6.090 (m. 2H), 6.654 (dd 2H), 6.987 (t. 1H), 7.197 (dd. 3H), 8.792 (s. 1H -OH). 13C NMR (400 MHz, DMSO *d*6) ppm: 36.99; 53.20; 56.02; 100.62; 105.19; 114.77; 115.24; 125.63; 128.84; 130.29; 141.98; 152.22; 159.56; 175.23; 177.31. Yield: 84%.

3-[(4-hydroxyphenyl)amino]-1-(4-methoxyphenyl)pyrrolidine-2,5-dione ***10c***.

1H NMR (DMSO *d*6, 400 MHz), δ, ppm: 2.598 (dd 1Ha, 3J=18 Hz, 2J=4,6 Hz), 3.193 (dd 1Hc, 3J=18 Hz, 3'J=8,4 Hz), 3.816 (s. 3H), 4.519 (dd. 1Hb, 2J=4,6 Hz, 3J=8,4 Hz), 5.327 (s. 1H –NH), 6.539 (d 2H), 6.681 (d 2H), 6.980 (d 2H), 7.190 (d 2H), 8.300 (d 1H -OH). 13C NMR (400 MHz, DMSO *d*6) ppm: 37.08; 53.47; 56.04; 114.81; 115.21; 116.37; 125.66; 128.88; 140.57; 149.95; 159.55; 175.38; 177.61. Yield: 90%.

1-(4-methoxyphenyl)-3-(2-phenyl-3aH-inden-3-yl)pyrrolidine-2,5-dione ***11.***

Yield 86%. The constants and spectral data are indentical to those described in the literature [20].

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