chemistry proceedings

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Cycloaddition of Thiourea- and Guanidine-Substituted Furans to Dienophiles: A Comparison of the Environmentally-Friendly Methods †

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† Presented at the 24th International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2020; Available online: https://ecsoc-24.sciforum.net/.

Abstract: The cycloaddition strategy was employed in order to obtain a 7-oxanorbornene framework substituted with a guanidine moiety or its precursor functional groups: protected amine or thiourea. In order to optimize the conditions for the cycloaddition, several environmentally-friendly methods—microwave assisted organic synthesis, high pressure synthesis, high speed vibrational milling, and ultrasound assisted synthesis—were employed. The outcomes of the cycloaddition reactions were interpreted in terms of *endo*/*exo* selectivity, the conversion of the reactants to the product, and the isolated yields. In general, our results indicated the HP and HSVM approaches as the methods of choice to give good yields and conversions.

Keywords: cycloaddition; guanidine; microwave assisted organic reactions; high pressure; high speed vibrational milling; ultrasound

Citation: Barešić, L.; Margetić, D.; Glasovac, Z. Cycloaddition of Thiourea- and Guanidine-Substituted Furans to Dienophiles: A Comparison of the Environment Friendly Methods. *Chem. Proc.* **2021**, *3*, 57. https://doi.org/10.3390/ecsoc-24-08380

Academic Editors: Julio A. Seijas and M. Pilar Vázquez-Tato

Published: 14 November 2020

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1. Introduction

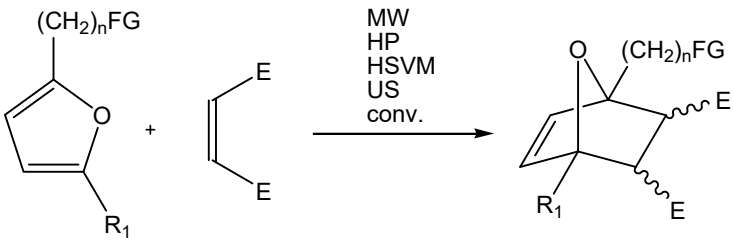
Cycloaddition reactions represent an excellent tool for the construction of cyclic systems in a highly regioselective and stereoselective manner [1]. Of particular interest are rigid polycyclic structures, due to their well-defined spatial orientation of the functional groups. Attaching one or more superbasic groups to such a skeleton would lead to the interesting target molecules, as shown by Margetić et al. [2]. While a complex polycyclic backbone could be difficult to obtain, the preparation of a norbornene- and bicyclo[2.2.2]octene-type of scaffold is a simple, one-step process, and is therefore suitable even for large-scale synthesis. Many biologically and technologically interesting systems were built upon such rigid scaffolds, consisting of one or more norbornene and/or its oxa and aza analogues, to mention only the -turn mimics and bisporphyrine tweezer-like receptors [3,4].

In continuation of our interest in the guanidine-type of superbases [5,6], we were attracted by the paper of Calmes and coworkers, who proved that cycloaddition could be a good approach toward chiral diamines [7]. They also suggested that such diamines could be excellent building blocks for the synthesis of novel bifunctional catalysts, or could be used as ligands. Indeed, diamines have often been used in the synthesis of novel basic organocatalysts [8–10] or fluorophores [11]. Triggered by these results, we became interested in using guanidine-substituted dienes in cycloaddition reactions [12].

Cycloaddition reactions have been successfully conducted under variety of conditions, and were beneficially assisted by high pressure (HP) [13], microwave irradiation (MW) [14], ball milling in a solid state (HSVM) [15], and to a lesser extent by ultrasound

activation (US) [16,17]. Employing these modern techniques allowed us to pursue successfully one of our long-standing goals: performing organic synthesis under environmentally-friendly conditions using a minimal amount of solvent and energy.

In this paper, we present the results of cycloaddition reactions of 2-substituted furans to *N*-phenylmaleimide (NPMI) and maleic anhydride (Scheme 1). The 2-Substituted furans were selected to bear protected amino, thioureido or guanidine substituents either directly attached to the furan ring or separated by a methylene linker (furfuryl derivatives). Protected amino and thioureido derivatives were selected as the common precursors in guanidine synthesis [8].



n = 0 (furanyl derivatives) or 1 (furfuryl derivatives)
FG = guanidine, thiourea or NHBoc containing substituent
E = electron withdrawing group
R_1 = H or COOMe

Scheme 1. General representation of the reaction conducted under various conditions.

2. Materials and Methods

The structures of the starting dienes are schematically given in Figure 1, while *N*-phenylmaleimide (NPMI) and maleic anhydride (MA) were used as the dienophiles.

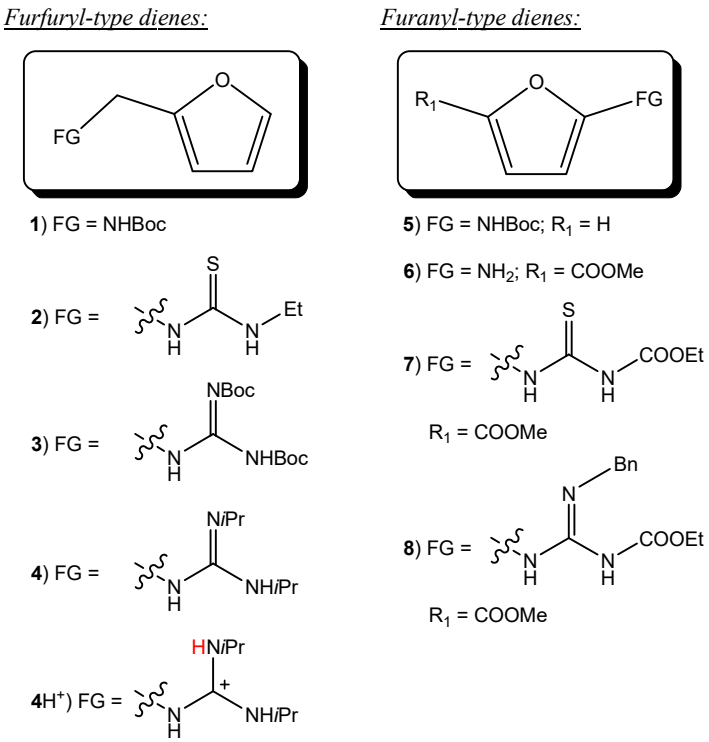


Figure 1. Structures of the starting dienes **1–8.**

N-Phenylmaleimide (NPMI) and maleic anhydride (MA) were purchased from Sigma, and were used as dienophiles without further purification. Furanyl- and furfuryl

derivatives **1** [18], **5** [19] and **6** [19] were prepared according to the literature procedures. Thioureas **2** and **7** were obtained by the addition of furan **6** or furfurylamine to the corresponding isocyanates at room temperature. Guanidines **3** [20] and **8** [21] were prepared in analogy to the literature procedures. Guanidine **4** was prepared by the microwave-assisted addition of furfurylamine to diisopropylcarbodiimide under solvent-free conditions, in analogy to the previously-described procedure [22]. Its hydrochloride salt (**4**H$^+$) was obtained by stirring equimolar amounts of neutral guanidine and ammonium chloride in methanol at room temperature for 24 h. The desired salt precipitated upon treating the crude mixture with acetonitrile. The solvents (dichloromethane, diethylether, acetonitrile, ethyl acetate and light petroleum (b.p. 40–60 °C)) were used as purchased. The reaction products were identified by one-dimensional and/or two-dimensional ^{1}H and ^{13}C spectroscopy, using Bruker Avance 300 MHz and Bruker Avance 600 MHz spectrometers.

Reaction Conditions

C (conventional approach): stirring at room temperature in dichloromethane for 24 h using a 1:1 molar ratio of the reactants.

US (ultrasound): sonification for 2 h, by which time the reaction temperature rises to 53 °C. The reactions were performed in chloroform using a diene:dienophile 1:1.33 molar ratio.

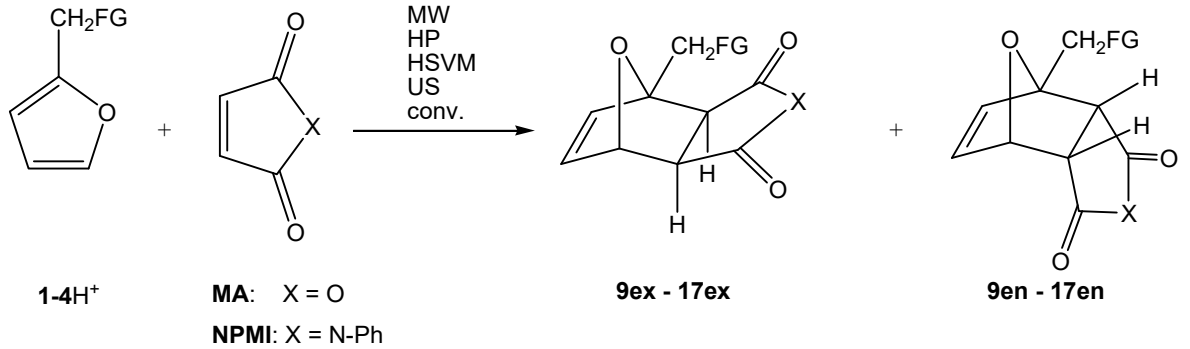
HSVM (high speed vibrational milling): ball-milling in a 10 mL stainless steel jar for 3 h at 30 MHz using one 12 mm steel ball. The reactions were performed using a diene:dienophile 1:3 molar ratio.

HP (high pressure): the reaction mixture (in dichloromethane, 0.5 mL) was pressurized at 5–7 kbar at room temperature for 24 h. The reactions were performed using a diene:dienophile 1:2 molar ratio.

MW (microwave assisted): heating at 80 °C for 15 min in acetonitrile using 100W of initial microwave power. The reactions were performed using a diene:dienophile 1.1:1 molar ratio.

3. Results and Discussion

In most cases, the cycloaddition reactions of furfuryl-type dienes **1**-**4**H$^+$ (Figure 1) with dienophiles *N*-phenylmaleimide (**NPMI**) or maleic anhydride (**MA**) produced a mixture of *endo* and *exo* isomers, as expected (Scheme 2).



Scheme 2. Reaction scheme for the formation of *endo* (**9en**-**17en**) and *exo* (**9ex**-**17ex**) cycloadducts. The meaning of FG is given in Figure 1.

The reactions were conducted as described in the Materials and Methods section. The conversion of the reactions was determined from the ratios of the characteristic signals observed in ^{1}H NMR of the crude reaction mixture. For the cycloadducts, the signals at the bridgehead position, as well as those at ring junction positions, were found to be suitable and sufficiently separated from the other signals. In the case of overlapping of *endo* and *exo* signals, they were integrated together. In several instances, a substantial amount of unidentified side-products were formed, giving an unrealistically high conversion.

Such cases were accompanied by relatively low yields, and were parenthesized. The results of the cycloaddition reactions are collected in Table 1.

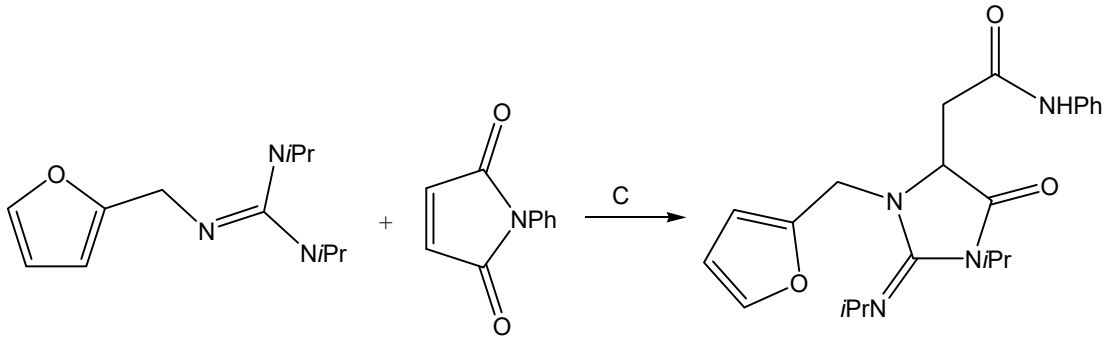
Cycloaddition reactions using furfuryl derivatives as dienes proceed in a more consistent manner than those which employ furan dienes. This could be easily rationalized by considering the structure of furan dienes **5–8,** which have free or amino groups directly attached to the furan ring, which destabilizes the structure.

Table 1. Conversions, isolated yields, and the *endo*/*exo* ratio of the cycloadducts obtained by the reactions of dienes **1–8**H$^+$ and **NPMI** or **MA** as dienophiles using environmentally-friendly methods.[1]

Entry	Diene/ Adduct	Dienophile	Method	*exo*: *endo*	Conv./%	Yield/%
	Furfuryl derivatives					
1	**1/9**	**MA**	C	1: 0.1	66	62
2	**1/9**	**MA**	HSVM	1: 0.0	91	90
3	**1/9**	**MA**	US	1: 0.1	77	63
4	**1/9**	**MA**	HP	1: 0.2	97	92
5	**1/9**	**MA**	MW	1: 0.5	69	67
6	**1/10**	**NPMI**	C	1: 1.4	79	57
7	**1/10**	**NPMI**	HSVM	1: 1.3	(>98) [2]	57
8	**1/10**	**NPMI**	US	1: 1.1	>98	83
9	**1/10**	**NPMI**	HP	1: 1.8	50	42
10	**1/10**	**NPMI**	MW	1: 0.8	>98	84
11	**2/11**	**MA**	HP, HSVM	n/d [3]	n/d [3]	n/d [3]
12	**2/12**	**NPMI**	C	1: 1.1	93	81
13	**2/12**	**NPMI**	HSVM	1: 1.0	>98	74
14	**2/12**	**NPMI**	US	1: 1.8	(>98) [2]	52
15	**2/12**	**NPMI**	HP	1: 1.1	89	78
16	**2/12**	**NPMI**	MW	1: 1.1	(87)	53
17	**3/13**	**MA**	C	1: 2.0	25	20
18	**3/13**	**MA**	HSVM	1: 2.6	(83)	46
19	**3/13**	**MA**	US	1: 0.2	46	n/d
20	**3/13**	**MA**	HP	1: 2.0	73	68
21	**3/13**	**MA**	MW	1: 0.4	21	n/d
22	**3/14**	**NPMI**	C	1: 1.0	36	33
23	**3/14**	**NPMI**	HSVM	1: 1.4	>98	62
24	**3/14**	**NPMI**	US	1: 1.0	77	75
25	**3/14**	**NPMI**	HP	1: 0.7	>98	88
26	**3/14**	**NPMI**	MW	1: 0.8	75	70
27	**4/15**	**MA**	C	n/o	(>98) [2]	11 [4]
28	**4/16**	**NPMI**	C	n/o	(>98) [2]	57 [4]
29	**4**H$^+$**/17**	**NPMI**	C	1: 1.4	31	n/d [5]
30	**4**H$^+$**/17**	**NPMI**	HSVM	1: 1.5	>98	n/d [5]
31	**4**H$^+$**/17**	**NPMI**	US	1: 1.6	30	n/d [5]
32	**4**H$^+$**/17**	**NPMI**	HP	1: 1.0	30	n/d [5]
33	**4**H$^+$**/17**	**NPMI**	MW	1: 0.5	46	n/d [5]
	Furanyl derivatives					
34	**5/18**	**MA**	C or HP	n/d	n/d	44 (ar) [1,6]
35	**5/19**	**NPMI**	C	1: 0.08 [7]	n/d	38.[7]
36	**6/20**	**NPMI**	HP	n/o [8]	~75 [8]	n/d [8]
37	**7/21**	**NPMI**	all methods	n/d	0	n/r
38	**8/22**	**NPMI**	C	n/d	(>98)	64 (ar) [1]

[1] n/d = not determined; n/o = not observed; n/r = no reaction; ar = aromatization. [2] No measurable signals of the starting diene were observed. [3] Reactions of thiourea **2** with maleic anhydride gave a viscous oil with no defined signals either of reactants or cycloadducts. [4] The product of the aza-Michael reaction was isolated (Scheme 3). [5] Unable to determine due to the similar solubilities of the diene and cycloadduct. [6] Approximately 40% of the Achmatowicz-like product was also obtained as a product of oxidation. [7] Isolated after the washing with diethylether. [8] A mixture of two products formed upon the epoxy bridge cleavage.

Furfuryl derivatives **1**–**4**H$^+$ produce cycloadducts in good to excellent yields, with guanidine **4** being an exception. In this case, the aza-Michael reaction with the subsequent cyclization of the formed adduct to a creatinine derivative took place (Scheme 3). The aza-Michael addition of nucleophiles to conjugated enones is known to take place [23–25]. In order to overcome this problem, we used the guanidine salt **4**xHCl as the diene, which proved sufficient to prevent the aza-Michael addition.



4 **23**

Scheme 3. Schematic representation of the aza-Michael reaction of guanidine **4**.

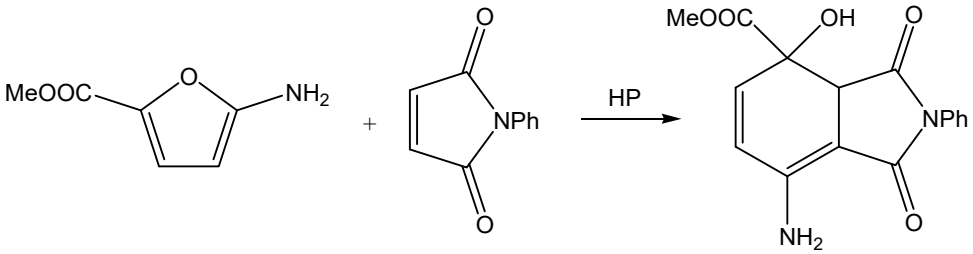
Comparing the different methods, the tabulated data clearly indicate better conversion and yields if the reactions are performed using HSVM and HP with respect to the other employed synthetic approaches. Heating with microwaves also provides good conversions, but the reaction times should be optimized very carefully. Namely, on the prolonged heating of the reaction of thiourea **2** with NPMI (entry 16), the conversion increases, but the ^{1}H NMR of the crude reaction mixture becomes more complex due to the partial decomposition of the product. The *endo*:*exo* ratio is generally between 1:1 and 1:2 in favor of the *endo* product, except in MW-assisted reactions, in which the *exo* product slightly dominates. This could be explained by the higher reaction temperature, which speeds up the formation of the thermodynamically more stable *exo* product.

The reactions with maleic anhydride (MA) gave, in general, lower yields, but also a highly-preferred formation of the *exo* adduct, as expected. The exception is diene **3** (Table 1, entries 17–21) in which, in certain cases, the *endo* adduct prevails. While these results indicate a slower retroDA reaction under HSVM and HP conditions, the reactions needs to be investigated more thoroughly before drawing any definite conclusion. Among the tested furfuryl-based derivatives, Boc-protected amines and guanidines proved to be the optimal for obtaining the desired oxanorbornenes. Thiourea **2** is suitable for the reactions with NPMI but not with MA, in which case it gives a mixture of products which are difficult to separate.

Within the furanyl series, the efficiency of the tested reactions varied significantly. In 1997, Padwa and coworkers performed cycloaddition reactions of dienes **5** and **6** with both NPMI and MA, yielding 77 and 79% of the *exo* cycloadduct, respectively [19]. In our hands, the reaction with **NPMI** (Table 1, entry 35) resulted in a significantly lower yield (38%), while the cycloaddition with MA (Table 1, entry 34) furnished a mixture of compounds of which product of aromatization (44%) and Achmatowicz-like rearrangement was identified in spite of the use of dry diethylether or dichloromethane under a dry argon atmosphere. The same reaction was also tested under solvent-free conditions by grinding

the reactants in the mortar. The thin-layer chromatography (TLC) analysis of the mixture indicated the formation of the same side-products as the reaction in the solution. Interestingly, Achmatowicz-like rearrangement was not detected in the reaction with NPMI.

Reaction of **6** with NPMI under the HP conditions gave two main products, one of which corresponded to partially-opened oxanorbornene **24,** as described by Padwa and coworkers [19]. Apparently, the changing reaction conditions from the reflux in benzene to the pressurized system at the room temperature did not prevent an unwanted side reaction. A study on the nature and mechanism of the formation of the other side product is under way.



6 **24**

Amongst the last three tested dienes, thiourea 7 did not react with NPMI under any of the tested conditions, while guanidine 8 yielded a product identified as 2,5-disubstituted *N*-phenylphthalimide, with a 64% yield.

4. Conclusions

The tested methods of the HSVM and HP approaches gave, in general, better results in the cycloaddition reactions of furfuryl derivatives over others in terms of conversion and yields. A certain advantage of HSVM over HP was noticed in the cycloaddition of guanidinium salt to NPMI, indicating the broader applicability of this approach.

Boc-protected amine **1** underwent cycloaddition with NPMI and MA equally or better than the other derivatives. Furfurylthioureas showed unexpected sensitivity toward the method employed. The cleavage of the oxa-bridge leading to a partially or fully aromatized product turned out to be the main side-reaction when furanyl dienes **5–8** were used. The application of the high pressure did not prevent the partial cleavage of the oxa-bridge, as evidenced by the formation of the diene **24**.

Author Contributions: Experimental work and tabulation of data, L.B.; writing, Z.G.; supervision, reviewing and editing, D.M.; project administration, D.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Croatian Science Foundation, grant No. IP-2018-01-3298, Cycloaddition strategies towards polycyclic guanidines (CycloGu).

Institutional Review Board Statement: Not applicable

Informed Consent Statement: Not applicable.

Acknowledgments: The authors acknowledge funding by the Croatian Science Foundation grant No. IP-2018-01-3298, Cycloaddition strategies towards polycyclic guanidines (CycloGu). The work of doctoral student Luka Barešić was fully supported by the 'Young researchers' career development project – training of doctoral students' of the Croatian Science Foundation.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

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