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

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Abstract: Cycloaddition strategy was employed to obtain 7-oxanorbornene framework substituted with guanidine moiety or its precursor functional group: protected amine or thiourea. To optimize 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 outcome of cycloaddition reactions was interpreted in terms of *endo*/*exo* selectivity, conversion of reactants to product and isolated yields. In general, our results indicate HP and HSVM approaches as the methods of choice giving good yields and conversions.

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

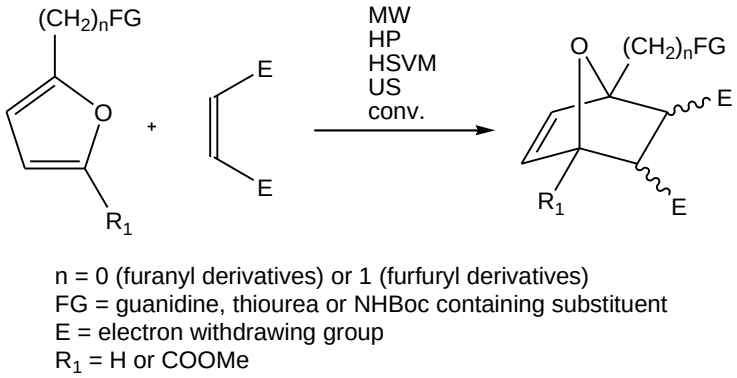
1. Introduction

Cycloaddition reaction represent an excellent tool for constructing 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 skeleton would lead to the interesting target molecules as shown by Margetić et al. [2]. While complex polycyclic backbone could be difficult to obtain, preparation of norbornene- and bicycle[2.2.2]octene-type of scaffold is simple, one-step process and therefore suitable even for the large-scale synthesis. Many biologically and technologically interesting systems were built upon such rigid scaffolds consisting one or more norbornene and/or its oxa and aza analogues, to mention only the -turn mimics and bisporphyrine tweezers-like receptors [3,4].

In continuation of our interest in 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 synthesis of novel bifunctional catalysts or used as ligands. Indeed, diamines have often been used in 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 were successfully conducted under variety of conditions and 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 environment friendly conditions using minimal amount of solvent and energy.

In this paper, we are presenting results of cycloaddition reactions of 2-substituted furans to *N*-phenylmaleimide (NPMI) and maleic anhydride. 2-Substituted furans were selected to bear protected amino, thioureido or guanidine substituent either directly attached to furan ring or separated by methylene linker (furfuryl derivatives). Protected amino and thioureido derivatives are selected as common precursors in guanidine synthesis [Error! Bookmark not defined.].



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

2. Materials and Methods

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

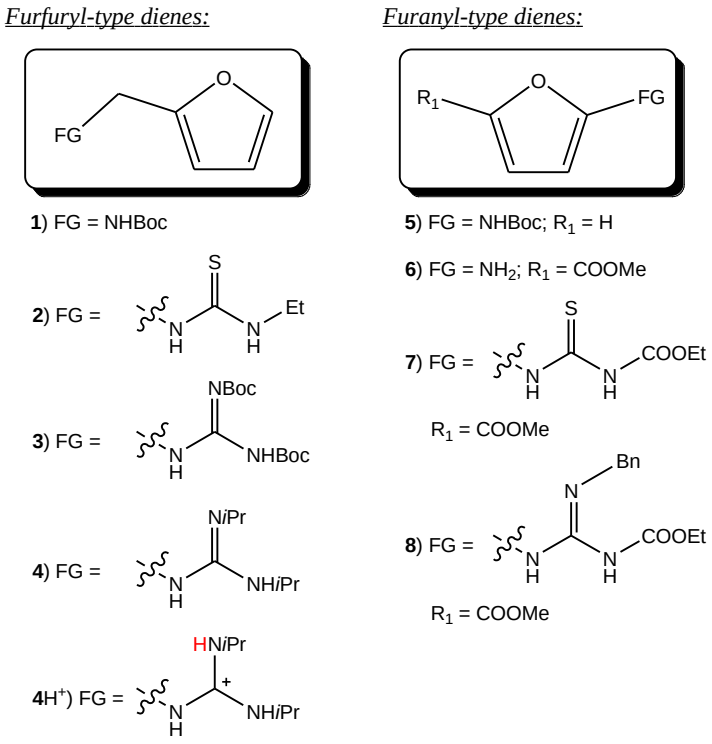


Figure 1. Structures of the starting dienes **1**-**8.**

N-Phenylmaleimide (**NPMI**) and maleic anhydride (**MA**) were purchased from Sigma and used as dienophiles without further purification. Furanyl- and furfuryl derivatives **1** [18], **5** [19] and **6** [**Error! Bookmark not defined.**], were prepared according to literature procedures. Thioureas **2** and **7** were obtained by 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 microwave-assisted addition of furfurylamine to diisopropylcarbodiimide under solvent free conditions in analogy to 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. Desired salt precipitated upon treating the crude mixture with acetonitrile. 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.

Reacions Conditions

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

US (Ultrasound): Sonification for 2 h by which time reaction temperature rises to 53 °C. Reactions were performed using diene: dienophile = 1: 1.33 molar ratio in chloroform.

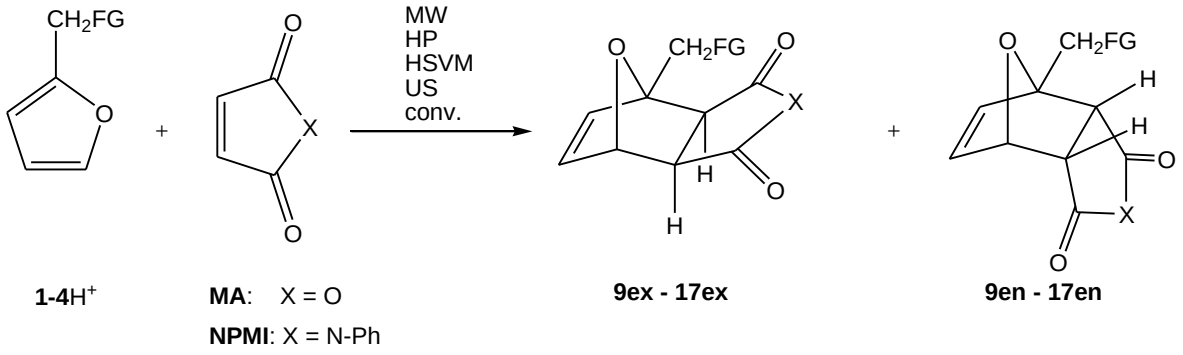
HSVM (High speed vibrational milling): Ball-milling in a 10 mL stainless steel jar for 3 h at 30 MHz using one 12 mm steel ball. Reactions were performed using diene: dienophile = 1: 3 molar ratio.

HP (High pressure): Reaction mixture (in dichloromethane, 0.5 mL) was pressurized at 5-7 kbar at room temperature during 24 h. Reactions were performed using diene: dienophile = 1: 2 molar ratio.

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

3. Results and Discussion

In most cases, cycloaddition reactions of furfuryl-type dienes **1**-**4**H$^+$ (Figure 1) with dienophiles *N*-phenylmaleimide (**NPMI**) or maleic anhydride (**MA**) produced 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. Meaning of FG is given in Figure 1.

The reactions were conducted as described in Material and Methods section. 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 bridgehead position as well as those at ring junction positions were found to be suitable and sufficiently separated from 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 was formed giving unrealistically high conversion. Such cases are accompanied with relatively low yields and 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 with employed furan dienes. This could be easily rationalized by considering structure

of furan dienes **5**-**8** which have free or amino group directly attached to furan ring what destabilizes the structure.

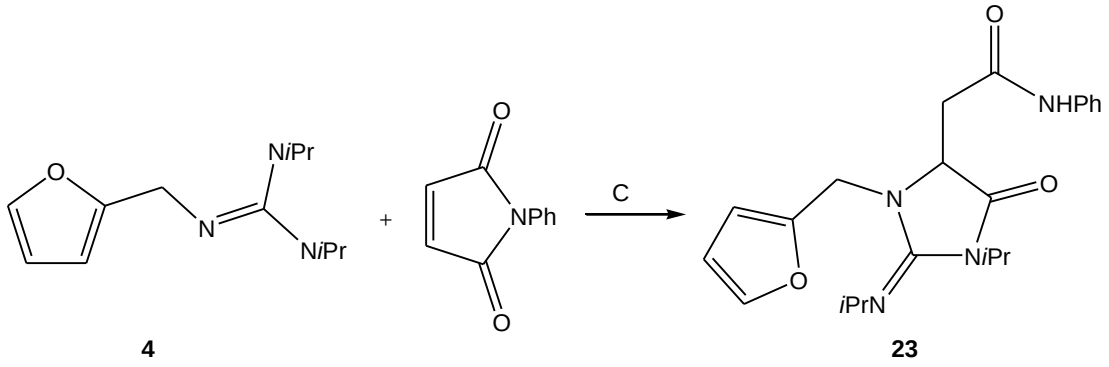
Table 1. Conversions, isolated yields and *endo*/*exo* ratio of cycloadducts obtained by reactions of dienes **1**-**8**H^+ and **NPMI** or **MA** as dienophiles using environment friendly methods.[1]

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 cycloadduct. [4] product of the aza-Michael reaction was isolated (Scheme 3). [5] unable to determine due to 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 epoxy bridge cleavage.

Furfuryl derivatives **1**-**4**H^+ produce cycloadducts in good to excellent yields with guanidine **4** being an exception. In this case, aza-Michael reaction with subsequent cyclization of formed adduct

to creatinine derivative took place (Scheme 3). Aza-Michael addition of nucleophiles to conjugated enones is known to take place [23–25]. To overcome this problem, we used the guanidine salt **4**xHCl as the diene what proved sufficient to prevent the aza-Michael addition.



4 **23**

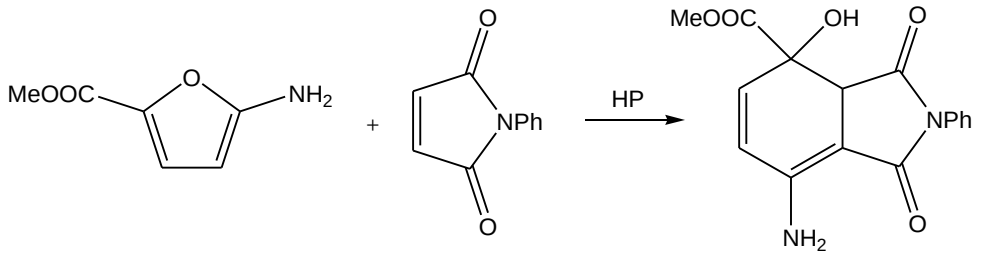
Scheme 3. Schematic representation of the aza-Michael reaction of guanidine **4**.

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

Reactions with maleic anhydride (**MA**) gave, in general lower yields but highly preferred formation of the *exo* adduct, as expected. The exception is diene **3** (Table 1, entries 17-21) where in certain cases, *endo* adduct prevails. While these results indicate 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 desired oxanorbornenes. Thiourea **2** is suitable for the reactions with **NPMI** but not with **MA** in which case it gives a mixture of products difficult to separate.

Within furanyl series, 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 [**Error! Bookmark not defined.**]. In our hands, the reaction with **NPMI** (Table 1, entry 35) resulted with significantly lower yield (38 %) while the cycloaddition with **MA** (Table 1, entry 34) furnished mixture of compounds of which product of aromatization (44 %) and Achmatowicz-like rearrangement was identified in spite of using dry diethylether or dichloromethane under dry argon atmosphere. The same reaction was also tested under solvent-free conditions by grinding reactants in the mortar. TLC analysis of the mixture indicated formation of same side-products as the reaction in solution. Interestingly, Achmatowicz-like rearrangement was not detected in reaction with **NPMI**.

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



6 **24**

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

4. Conclusions

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

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

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