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Tandem [4+2]/[4+2] cycloaddition of bis-furyl dienes with fumaric and maleic esters at ultra-high pressure

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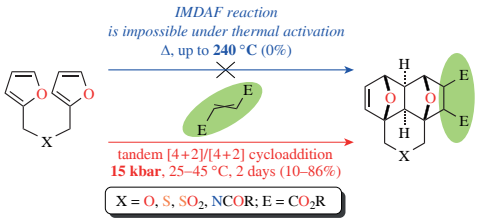
Employment of ultra-high pressures (15 kbar) at room temperature makes it possible to prepare 1,4:5,8-diepoxynaphthalenes annulated with other heterocycles from bis-furfuryl derivatives and fumaric/maleic esters. Such a reaction does not proceed under ordinary thermal conditions.



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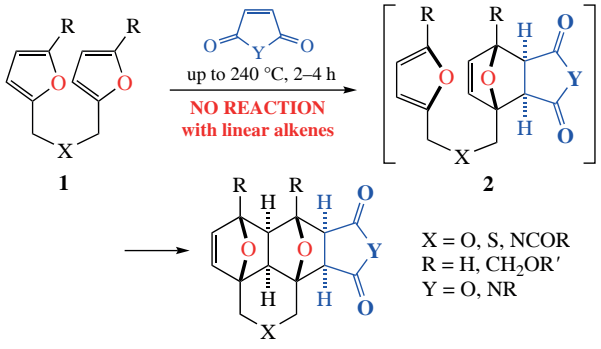
The intramolecular Diels–Alder reaction of furans (IMDAF reaction) is a powerful tool in organic and medicinal chemistry opening up a convenient way to valuable heterocyclic compounds;[1–5] it is often used to obtain natural products,[6–8] polymers,[9,10] pharmaceuticals and biomedical materials.[11–15] Furan derivatives, being active dienes, readily enter into the Diels–Alder (DA) reactions with diverse dienophiles to form six-membered rings containing an 1,4-epoxy bridge of 7-oxabicyclo[2.2.1]heptene type.[16–20] In turn, the thus obtained compounds are used for the stereoselective synthesis of practically useful products and functional materials.[21–24] While thermal conditions are most often employed for the IMDAF reaction, the application of ultra-high pressures (8–15 kbar) provides an easier and green alternative. High pressure can significantly lower the activation energy of the DA reaction, reducing the need for extreme temperatures and minimizing the formation of by-products.[25,26]

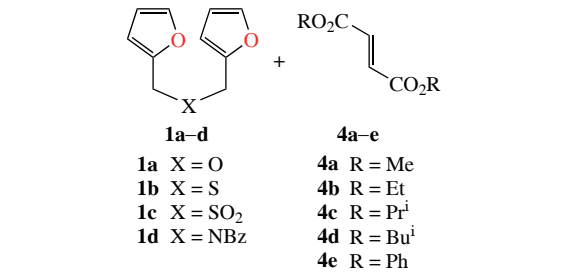
Previously,[27–29] we performed the tandem DA/IMDAF reaction between bis-furan dienes **1** (Scheme 1) and a series of activated alkynes and cyclic alkenes. The cycloaddition with cyclic derivatives of maleic acid proceeded stepwise through the formation of intermediate **2** and readily afforded final adducts **3**.[21] However, we were unable to obtain analogous products from acyclic fumaric acid esters by simple heating of reactants.

In this study we succeeded in fulfilling the cycloaddition of a series of bis-furan derivatives **1** with acyclic fumaric/maleic esters **4** under ultra-high pressure conditions (Scheme 2). Importantly, the majority of furan derivatives used in this and



1 **2** **3** (26–90%)

Scheme 1



1a–d **4a–e**

1a X = O
1b X = S
1c X = SO_2
1d X = NBz

4a R = Me
4b R = Et
4c R = Pr^i
4d R = Bu^i
4e R = Ph

5a–p **6a–p**

5a, 6a X = O, R = Me
5b, 6b X = O, R = Et
5c, 6c X = O, R = Pr^i
5d, 6d X = O, R = Bu^i
5e, 6e X = S, R = Me
5f, 6f X = S, R = Et
5g, 6g X = S, R = Pr^i
5h, 6h X = S, R = Bu^i
5i, 6i X = S, R = Ph
5j, 6j X = SO_2, R = Me
5k, 6k X = SO_2, R = Et
5l, 6l X = SO_2, R = Pr^i
5m, 6m X = SO_2, R = Bu^i
5n, 6n X = NBz, R = Et
5o, 6o X = NBz, R = Pr^i
5p, 6p X = NBz, R = Bu^i

Scheme 2

cited above works can be prepared from furfural, 5-hydroxymethylfurfural and 2-furoic acid, renewable materials available in almost unlimited quantities through the processing of biomass, agricultural and woodworking industry waste. Bis-furans **1a**–**d**, required for this study, are either commercially available substances or were obtained by known methods.[16,17,27] Fumaric acid esters were synthesized *via* an esterification reaction from fumaric acid and the corresponding alcohols.

For the model reaction, we selected inexpensive diethyl fumarate **4b** as a dienophile and difurfuryl ether **1a** as a bis-diene (see Scheme 2). This choice was also explained by their excellent solubility in methanol and their liquid aggregate state, which minimized the precipitation during the high-pressure experiment. Initially we retested the thermal and/or catalytic activation and ascertained that both methods do not lead essentially to cycloadducts **5b** and **6b** (Table 1, entries 1–5). Therefore, ultra-high pressure had to be applied. For these experiments, methanol was selected as a solvent due to its low freezing point under elevated pressure (at room temperature, it remains liquid at pressures of up to 35 kbar[30]). Considering the sharp deceleration of reactant diffusion in viscous liquids, the reactions under pressure were carried out for not less than two days. The ratios of the starting components **1a/4b** was 1 : 1.1, the test experiments were carried out at room temperature. In fact, pressures of up to 5 kbar were not enough to initiate the cycloaddition; the best results were achieved at 15 kbar (entries 9 and 10). Under lower pressure (10–13 kbar, entries 6–8), the DA reaction was also possible, but the conversion of the bis-diene **1a** was noticeably lower (^{1}H NMR of the crude reaction mixtures).

The duration of the experiment also affects the completeness of the reaction. An increase in the reaction time from 1 to 2 days led to a noticeable increase in conversion of bis-diene **1a**, while doubling the reaction time to 4 days showed only a slight improvement of conversion (see Table 1, entries 9 and 10). For these reasons, we chose the exposure time of 2 days as the optimal one. Under chosen conditions, the ratio of the diastereomers **5a/6a** was ~2 : 1. Pressure variations and replacement of the solvent with dichloromethane (at 12 kbar) have little effect on this ratio.

As it was shown previously,[21,27,28] the tandem [4 + 2]/[4 + 2] cycloaddition proceeds *via* an initial intermolecular DA step followed by an intramolecular DA reaction (see Scheme 1, intermediate **2** for the case of cyclic maleic derivatives). In the case of acyclic fumarates **4a**–**e** the first step of the process is not diastereospecific (see Online Supplementary Materials, Scheme S1, intermediates **A** and **B**), the IMDAF reaction results in a mixture of two diastereomers **5** and **6** differing in the arrangement of the ester groups relative to the bridged oxygen atoms.

Table 1 Optimization of the reaction conditions for Scheme 2.

Entry	*P*/kbar	*t*/days	*T*/°C	Solvent	Conversion of **1a** (%)	**5a/6a** ratio
1	1×10^{-3}	4	80	PhH	–	–
2	1×10^{-3}	4	110	PhMe	–	–
3	1×10^{-3}	4	180[a]	*o*-xylene	–	–
4	1×10^{-3}	0.17	240[a]	MeCN	–[c]	–
5	1×10^{-3}	2	~20	CH_2Cl_2[b]	–[c]	–
6	5	2	~20	MeOH	–	–
7	10	2	~20	MeOH	57	67 : 33
8	15	2	~20	MeOH	75	67 : 33
9	15	2	~20	MeOH	88	70 : 30
10	15	4	~20	MeOH	92	66 : 34

[a] Microwave irradiation (600 W) was applied for activation. [b] $AlCl_3$ (20 mol%) was used as an additive. [c] Degradation of the reactants was observed.

After determining the optimal conditions, we carried out the tandem DA/IMDA reaction with other substrates **1a**–**d** and **4a**–**e** (see Scheme 2 and Table 2). As a result, a series of diastereomeric mixtures of 1,4:5,8-diepoxynaphthalenes **5a**–**p** and **6a**–**p** was obtained. As indicated above, the solid starting materials **1** and **4**, despite their good solubility in MeOH at atmospheric pressure, have a risk of crystallizing under pressure of 15 kbar, which can lead to a sharp decrease in conversion, which truly occurred in several experiments. To get around this obstacle, in some cases (see Table 2, entries 1, 5, 9–13) we performed the cycloaddition in a mixture of MeOH/CH_2Cl_2 at 40–45 °C. However, even under these conditions, the conversions remained moderate.

All IMDAF adducts were isolated as diastereomer mixtures **5** and **6** differing in the orientation of the ester groups with a *syn*-arrangement of the bridged oxygen atoms. The ratios of the diastereomers were close to 70 : 30 in all cases; *i.e.* the bulkiness of the ester groups in the dienophile component does not appreciably affect the diastereoselectivity of the [4 + 2]/[4 + 2] cycloaddition. Due to their similar structure and close retention factors, it turned out to be difficult to separate the diastereomers by column chromatography. Luckily, one isomer **5b** was isolated from the enriched mixture by fractional crystallization from ethyl acetate. This adduct has been fully characterized by NMR methods; additionally its structure was previously confirmed by XRD analysis.[31] The obtained data allowed us to assign the diastereomers to the series **5** or **6** based on their NMR spectra. For the **5** series, the most representative signals in ^{1}H NMR spectra are doublets of H^5 and H^4 at δ ~ 2.1 and 1.7 ppm (J ~ 6.5 Hz). For compounds **6**, the mentioned above protons resonate at δ_H ~ 1.9 and 1.8 (doublets with J ~ 6.5 Hz).

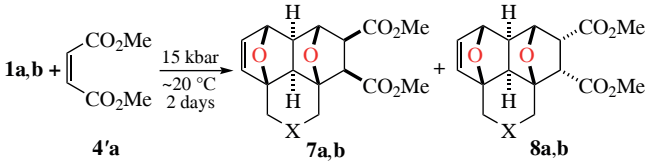
In addition, we successfully involved dimethyl maleate **4′a** into the same tandem reaction (Scheme 3), which provided mixtures of both possible diastereomers **7** and **8** with an essential predominance of the *endo*,*endo*-isomers **8**. The structures of the diastereomers were assigned based on the NOE experiments. Note that the reaction between bis-furans **1** and maleic esters is also impossible at atmospheric pressure; heating at 210 °C in MeCN (microwave irradiation) does not provide the target cycloadducts **7**, **8**.

In summary, an efficient protocol for the synthesis of annelated 1,4:5,8-diepoxynaphthalenes through a tandem DA/

Table 2 Conversion of **1**, isomer ratios and yields of cycloadducts **5** and **6**.

Entry	Reactants	Solvent[a]	*T*/°C	Conversion of **1** (%)	Products	Total yield[b] (%) (**5/6** ratio)
1	**1a** + **4a**	MeOH/CH_2Cl_2	40–45	45	**5a** + **6a**	40 (67 : 33)
2	**1a** + **4b**	MeOH	~20	88	**5b** + **6b**	80 (70 : 30)
3	**1a** + **4c**	MeOH	~20	83	**5c** + **6c**	78 (69 : 31)
4	**1a** + **4d**	MeOH	~20	82	**5d** + **6d**	76 (66 : 34)
5	**1b** + **4b**	MeOH/CH_2Cl_2	40–45	39	**5e** + **6e**	35 (63 : 37)
6	**1b** + **4a**	MeOH	~20	75	**5f** + **6f**	70 (62 : 38)
7	**1b** + **4c**	MeOH	~20	90	**5g** + **6g**	79 (66 : 34)
8	**1b** + **4d**	MeOH	~20	89	**5h** + **6h**	77 (65 : 35)
9	**1b** + **4e**	MeOH/CH_2Cl_2	40–45	48	**5i** + **6i**	39 (66 : 34)
10	**1c** + **4e**	MeOH/CH_2Cl_2	40–45	51	**5j** + **6j**	42 (70 : 30)
11	**1c** + **4a**	MeOH/CH_2Cl_2	40–45	70	**5k** + **6k**	61 (72 : 28)
12	**1c** + **4c**	MeOH/CH_2Cl_2	40–45	69	**5l** + **6l**	58 (73 : 27)
13	**1c** + **4d**	MeOH/CH_2Cl_2	40–45	65	**5m** + **6m**	53 (69 : 31)
14	**1d** + **4a**	MeOH	~20	74	**5n** + **6n**	66 (71 : 29)
15	**1d** + **4c**	MeOH	~20	57	**5o** + **6o**	46 (73 : 27)
16	**1d** + **4d**	MeOH	~20	63	**5p** + **6p**	52 (72 : 28)

[a] Due to poor solubility of the reactants in MeOH and a low reaction rate under high pressure, a mixture of MeOH/CH_2Cl_2 (v/v = 50 : 50) was used as a solvent at 40–45 °C. [b] Isolated yields.



a X = O (Σ 51%, **7a/8a** = 20 : 80)
b X = S (Σ 40%, **7b/8b** = 16 : 84)

Scheme 3

IMDA reaction under ultra-high pressure is proposed. The reactions which do not proceed under heating and normal pressure take place at pressure of 15 kbar and at almost room temperature. In particular, the cycloaddition between fumaric or maleic acid esters and bis-furyl dienes provides a mixture of diastereomeric adducts in ~70 : 30 ratios and 40–86% total yields. Probably, the proposed method is general and it will allow involving other alkenes into the [4 + 2] cycloaddition with bis-dienes. This work provides an outstanding example of the advantages of high pressure activation over thermal activation in pericyclic [4 + 2] cycloaddition reactions.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7673.

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