High-Pressure Chemistry

Diels–Alder Reaction of Thiophene: Dramatic Effects of High-Pressure/Solvent-Free Conditions[**]

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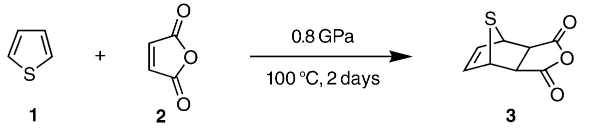
For a long time since the discovery of the Diels–Alder reaction in 1936[1] it was known that thiophene (**1**) is highly aromatic and hence does not undergo the Diels–Alder reaction, even with relatively strong dienophiles such as maleic anhydride (**2**).[2] However, almost 25 years ago we found that when the reaction was conducted at high pressure (1.2–2.0 GPa) and at a temperature of 100 °C, **1** did react with **2** to afford the *exo* adduct **3** in around 40 % yield.[3] Surprisingly, there have been no reports since then on the development of an alternative method to synthesize **3**. Thus, we decided to reinvestigate the Diels–Alder reaction of **1**.

Our previous work showed the unusual effect of the solvent in the Diels–Alder reaction of **1** with **2**, and dichloromethane was chosen as the best solvent mainly because of its low freezing point.[4] At that time we also recognized that it was necessary to raise the pressure above 1.0 GPa to attain a satisfactory result. We thus decided to investigate the solvent effects at high pressure under different conditions.[5] The results are summarized in Table 1.

As expected, decreasing the pressure to 0.8 GPa gave disappointingly low yields (entries 1 and 2). Changing the solvent from dichloromethane to perfluorohexane considerably improved the yield to 77 %, although the reaction rate was still slow (entry 4); the fluorophobic effect should play a crucial role in rate enhancement.[6] After extensive experiments to identify other effective solvents, we finally concluded that a solvent-free system might be beneficial.[7] Thus, treatment of a 4:1 mixture of **1** and **2** at 0.8 GPa and 100 °C for 2 days afforded the desired *exo* adduct **3** in almost quantitative yield (entry 5).[8] A 2:1 mixture of these substrates gave a slightly decreased yield (87 %), thus indicating severe interference by a solid-phase-like reaction (entry 6).

To better understand the reaction profile of the present system we conducted further investigations to determine the effects of pressure and temperature under solvent-free conditions (Figures 1 and 2). The results show that both pressure and temperature have strong effects: pressures above 0.6 GPa and temperatures above 80 °C are both necessary to achieve synthetically useful results.[9] The sharp increase in product yields between 0.4 and 0.6 GPa suggests

Table 1: High-pressure Diels–Alder reaction of thiophene (**1**) with maleic anhydride (**2**).



Entry	Solvent	1:2	Yield [%][a]	Recovery [%][b]
1	CH_2Cl_2	1:1[c]	19	64[d]
2	CH_2Cl_2	4:1[c]	21	29[d]
3	$Cl_2CHCHCl_2$	4:1[c]	23	16[d]
4	$CF_3(CF_2)_4CF_3$	4:1[c]	77	19[d]
5	solvent-free	4:1	93	0
6	solvent-free	2:1	87	7

[a] Yield of isolated product. [b] Recovery of **2**. [c] Approximately 1.5 M solution. [d] A considerable amount of unidentified insoluble substance was formed.

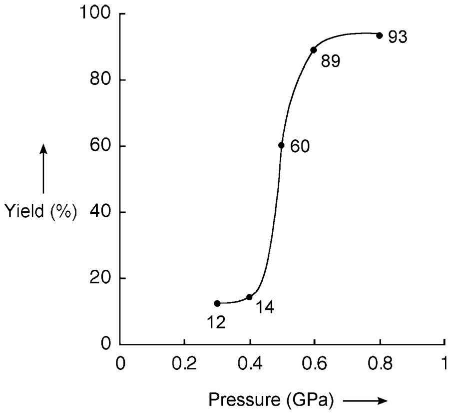


Figure 1. Effect of pressure on the Diels–Alder reaction of **1** with **2** at a constant temperature of 100 °C (2 days).

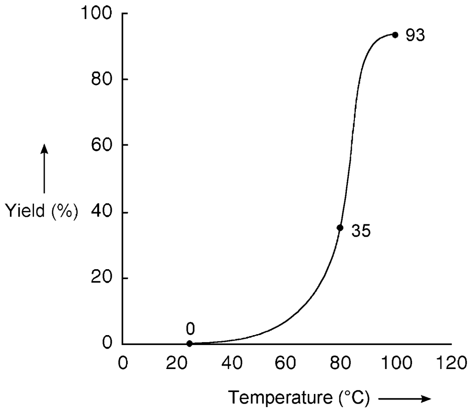


Figure 2. Effect of temperature on the Diels–Alder reaction of **1** with **2** at a constant pressure of 0.8 GPa (2 days).

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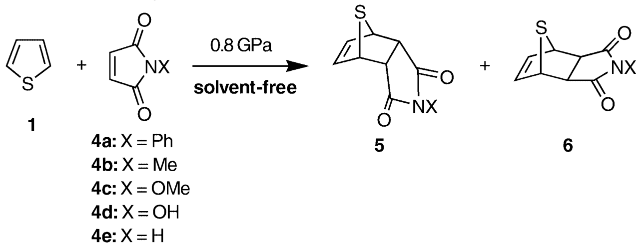
that the present reaction might be promoted kinetically by high pressure.

The extraordinary power of a high-pressure/solvent-free system was further demonstrated by successful reactions using maleimide dienophiles **4**, such as *N*-phenyl-, *N*-methyl-, *N*-methoxy-, *N*-hydroxy-, and NH-substituted maleimides (Table 2). Interestingly, in contrast to **2**, a mixture of *endo* and *exo* isomers (**5** and **6**) was consistently obtained in an approximately 1:1 ratio in these cases.[10] The structures of these adducts were confirmed by ^{1}H NMR measurements, for example, the H_2/H_3 protons of **5a** were observed at $\delta = 4.04$ ppm, whereas those of **6a** were, as expected, shifted upfield to $\delta = 3.32$ ppm. We intend to explore this significant difference in stereoselectivity between **2** and **4** in future studies.

Table 2: High-pressure Diels–Alder reaction of thiophene (**1**) with maleimide dienophiles **4**.



Entry	4	Conditions		Yield [%][a]		Recovery [%][b]
		T [°C]	*t* [days]	5	6	
1	**4a**	100	2	51	48	1
2	**4b**	80	7	47	34	17
3	**4c**	80	7	58	35	3
4	**4d**	80	7	47	34	3
5	**4e**	80	7	54	30	16

[a] Yield of isolated product. [b] Recovered starting compound **4**.

Finally, we investigated the results of Diels–Alder reactions between **1** and acrylic dienophiles such as acryloyl chloride (**7a**), methyl acrylate (**7b**), and acrylonitrile (**7c**). Although these dienophiles show only slight reactivity, we could prepare the desired Diels–Alder adducts **8** and **9** (*endo*/*exo* ca. 1:1) under high-pressure/solvent-free conditions (Table 3).[11] The major problem in these reactions is unavoidable polymerization of the acrylic dienophiles, even in the presence of a radical inhibitor,[12] and we are still trying to overcome this difficulty.

In summary, the remarkable effects of a combination of high-pressure and solvent-free conditions led to a) a significant lowering of the reaction pressure required for the Diels–Alder reaction of thiophene, b) a considerable improvement in the product yields to an almost quantitative level of conversion, and c) new findings that less reactive dienophiles such as methyl acrylate and acrylonitrile could be used. This technique will have potential utility in drug synthesis as well as in materials development.

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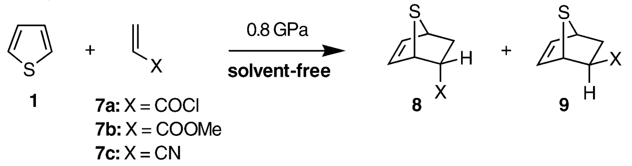
Table 3: High-pressure Diels–Alder reaction of thiophene (**1**) with acrylic dienophiles **7**.[a]



Entry	7	Conditions		Total yield [%] (**8**:**9**)[b]
		T [%]	*t* [days]	
1	**7a**	40	3	9 (56:44)[c,d]
2	**7b**	100	2	2.0 (61:39)[d]
3	**7c**	100	12	11 (50:50)[d]

[a] A catalytic amount of *N*-nitorosodiphenylamine (0.5 mol %) was used as a radical inhibitor. [b] Yield of isolated product. [c] Yield was determined after conversion into **8b** and **9b** by esterification with methanol/pyridine. [d] A considerable amount of polymeric substances was obtained.

Keywords: cycloaddition · high-pressure chemistry · solvent effects · thiophene

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[8] At the end of the reaction most of **3** was precipitated in the mixture as a result of its very low solubility. Typical experimental procedure: A mixture of thiophene (1.495 g, 17.8 mmol) and maleic anhydride (441 mg, 4.5 mmol) was placed in a teflon reaction vessel (volume: 3.9 mL), and the mixture was treated at 0.8 GPa and 100 °C for 2 days. After cooling the reaction mixture and releasing the pressure, the excess of thiophene was evaporated and the crude solid product (785 mg) was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) to give *exo* adduct **3** (761 mg, 93 %) as a colorless solid.

[9] Theoretical calculations have revealed a very large activation energy for thiophene cycloaddition reactions: a) B. S. Jursic, Z. Dzravkovski, S. L. Whittenburg, *J. Phys. Org. Chem.* **1995**, *8*, 753; b) B. S. Jursic, *J. Mol. Struct. THEOCHEM* **1998**, *454*, 105.

[10] **5a**: M.p. 174–175 °C (recryst from AcOEt); FTIR (KBr): $\tilde{\nu} = 1706, 1499, 1388, 1204, 1191\ \text{cm}^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.04$ (2H, dd, $J = 2.4, 1.2$ Hz), 4.60 (2H, m), 6.59 (2H, t, $J = 2.2$ Hz), 7.10–7.13 (2H, m), 7.35–7.46 ppm (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 50.99$ (×2), 52.98 (×2), 126.39 (×2), 128.86, 129.16 (×2), 131.37, 136.78 (×2), 173.97 ppm (×2). **6a**: M.p. 201–202 °C (recryst from CH_2Cl_2); FTIR (KBr): $\tilde{\nu} = 1711, 1496, 1395, 1381, 1195\ \text{cm}^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.32$ (2H, s), 4.58 (2H, t, $J = 2.0$ Hz), 6.64 (2H, t, $J = 2.0$ Hz), 7.25–7.28 (2H, m), 7.38–7.42 (1H, m), 7.44–7.49 ppm (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 50.12$ (×2), 53.89 (×2), 126.54 (×2), 128.87, 129.18 (×2), 131.85, 139.94 (×2), 175.17 ppm (×2).

[11] **8b**: Colorless oil; FTIR (neat): $\tilde{\nu} = 1735, 1435, 1313, 1204, 1038, 708\,\text{cm}^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.99$ (1H, ddd, $J = 12.1, 3.4, 1.0$ Hz), 2.54 (1H, ddd, $J = 12.1, 9.0, 3.2$ Hz), 3.57 (1H, dt, $J = 9.0, 3.4$ Hz), 3.66 (3H, s), 4.18 (1H, m), 4.41 (1H, m), 6.29 (1H, dd, $J = 6.1, 3.4$ Hz), 6.47 ppm (1H, dd, $J = 6.1, 3.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.13, 48.14, 51.87, 51.92, 53.11, 135.24, 139.15, 173.04$ ppm. **9b**: Colorless oil; FTIR (neat): $\tilde{\nu} = 1735, 1435, 1310, 1281, 1214, 1037, 716\,\text{cm}^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.99$ (1H, ddd, $J = 12.2, 8.1, 1.0$ Hz), 2.55 (1H, dt, $J = 12.2, 3.4$ Hz), 2.84 (1H, ddd, $J = 8.1, 3.4, 0.7$ Hz), 3.75 (3H, s), 4.19 (1H, m), 4.50 (1H, m), 6.39 (1H, dd, $J = 6.1, 3.7$ Hz), 6.45 ppm (1H, ddd, $J = 6.1, 3.4, 0.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.26, 46.99, 51.27, 52.20, 54.55, 137.09, 140.17, 173.69$ ppm.

[12] The acrylic dienophiles have a strong tendency to polymerize at high pressure, and this can sometimes be very dangerous. Particular attention should be paid to these reactions.