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Behaviour of selenophenes substituted with electron-withdrawing groups in polar Diels–Alder reactions

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Abstract—The normal electron-demand Diels–Alder reactions between substituted selenophenes, nitro being one of these groups, and dienes of diverse reactivity give benzoselenophenes derivatives.

1. Introduction

Selenium is an essential micronutrient for animals and humans. In recent years, organoselenium chemistry has emerged as an exceptional class of structures, due to its pivotal role in the synthesis of a large number of biological compounds and important therapeutic products ranging from antiviral and anticancer agents to naturally occurring food supplements. Over the last decade, considerable efforts have been directed towards the development of stable organoselenium compounds that could be used as antioxidants, enzyme inhibitors, antitumour and anti-infective agents, cytokine inducers and immunomodulators. In addition, many organoselenium compounds have been studied as biological models capable of simulating catalytic functions demonstrated by natural enzymes.[1]

The design and synthesis of organoselenium compounds with biological activity currently constitute fundamental problems in applied chemistry in both pharmaceutical and academic laboratories. Therefore, every effort to increase the knowledge of selenium chemistry would contribute to those purposes.

As a follow-up of our research on the behaviour of five-membered aromatic heterocycles in cycloaddition reactions, and considering that compounds such as benzofurans, benzothiophenes and benzopyrroles have been synthetized by Diels–Alder (DA) reactions,[2] it is of interest to investigate the cycloaddition reactions of substituted selenophene with electron-withdrawing groups in the presence of strong and poor dienes.

In this Letter, our aim has been to explore and to compare the behaviour of nitroselenophenes in their exposure to dienes under thermal conditions. Moreover we report a new and simple route for the construction of benzoselenophenes.

2. Results and discussion

The experiments were carried out using the following compounds as dienophile: 2-nitroselenophene (**1a**), 3-nitroselenophene (**1b**),[3] 2-acetyl-5-nitroselenophene (**1c**) and 2-acetyl-4-nitroselenophene (**1d**).[4] Isoprene (**2**) and 1-diethyl-amino-3-*tert*-butyldimethyl-siloxy-1,3-butadiene (Rawal's diene) (**3**) were chosen as the diene components (Scheme 1).

The results of cycloaddition studies between nitroselenophenes with the above mentioned dienes under different reaction conditions,[5] shows their behaviour as normal dienophiles.

The reactions of **1a** with isoprene proceeded to produce the mixture of isomeric cycloadducts **4a** and **4b**. The ease of thermal extrusion of nitrous acid accompanying the DA reaction of nitroselenophenes and of the dehydrogenation of the resultant dihydrobenzoselenophenes makes this reaction sequence a simple way to produce

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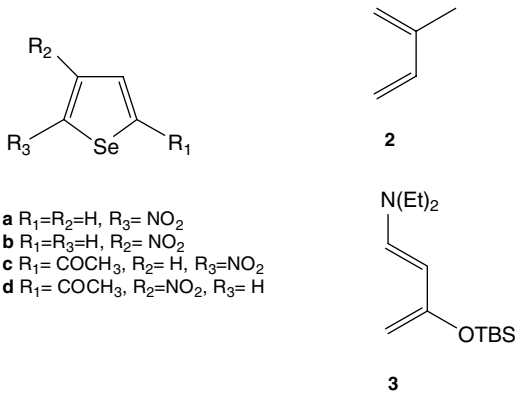


Scheme 1.

benzoselenophenes. In these conditions the step of the dehydrogenation would be a thermal process via radical intermediates.[6]

Similarly, the treatment of **1b** with **2** afforded a mixture of **4a** and **4b** with moderate yields (Scheme 2, Table 1, entries 1–4).[8]

The DA reactive behaviour of nitroselenophenes appears as opposed to that reported for nitrothiophenes when isoprene was used as diene. [2b] No pyrrolyl-derivatives from hetero DA were detected.

On the other hand, exposure of disubstituted selenophene **1c** to isoprene yielded the mixture of isomeric benzoselenophenes **6a** and **6b** with moderate yields (Scheme 3). In a similar way, reactions of **1d** with **2** cycloadducts **6a** and **6b** were obtained (Table 1, entries 5–8).[8] These reactions proceeded by the selective addition of the diene to the nitro-substituted double bond of the selenophene. No bis-adduct from the double cycloaddition of the diene was detected. Attempts to isolate the primary adducts were not successful because of their instability.

Table 1. Diels–Alder reactions of nitroselenophenes and isoprene

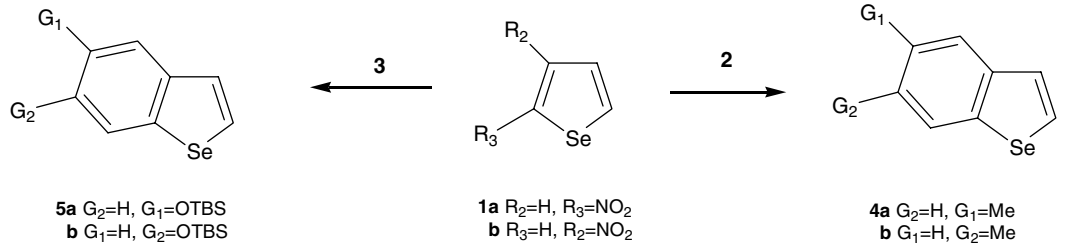
Entry	Dienophile	Conditions[a]	Products	Product ratio	Yield[b] (%)
1	**1a**	200 °C, 72 h	**4a**,**b**	1.5:1	60
2		150 °C, 72 h	**4a**,**b**	1.5:1	55
3	**1b**	200 °C, 72 h	**4a**,**b**	1:1	58
4		150 °C, 72 h	**4a**,**b**	1:1	54
5	**1c**	200 °C, 72 h	**6a**,**b**	1:1	55
6		150 °C, 72 h	**6a**,**b**	1:1	50
7	**1d**	200 °C, 72 h	**6a**,**b**	1.5:1	59
8		150 °C, 72 h	**6a**,**b**	1.5:1	54

[a] 12 equiv of isoprene in benzene.
[b] Based on consumed dienophile.

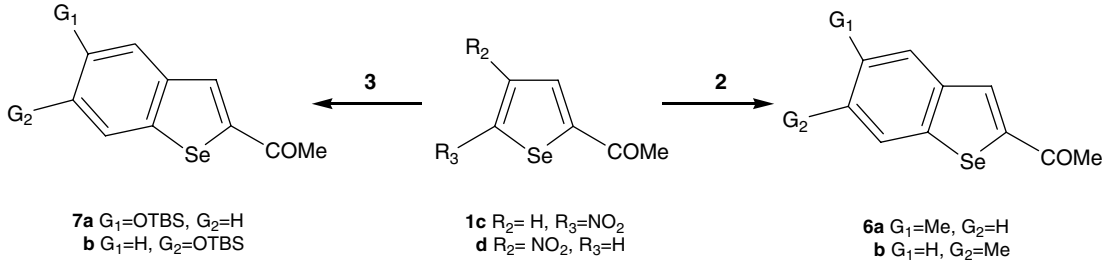
When 1-diethyl-amino-3-*tert*-butyldimethyl-siloxy-1,3-butadiene (Rawal's diene) reacted with **1a** it afforded aromatic cycloadduct **5a** with loss of the nitro group. Similarly, in the reactions of **3** with **1b** benzoselenophene, **5b** was obtained with moderate to high yield and complete regioselectivity (Scheme 2, Table 2).[8]

Exposure of **1c** and **1d** to **3** gave benzoselenophenes **7a** and **7b**, respectively.[8] The reactions proceeded for dienophiles **1c** and **1d** by addition of the diene selectively to the nitro-substituted double bond of the selenophene, indicating the strong directing effect of the nitro group. In these reactions, only 1:1 adducts whose structure revealed site selectivity and regioselectivity were obtained. All cycloaddition products shows extrusion of the nitro group as nitrous acid.

By analogy,[7] the reactions of nitroselenophenes with dienes **2** and **3** could be considered a domino process that is initialized by a polar DA reaction; the latter con-



Scheme 2. Reactivity of nitroselenophenes with different dienes.



Scheme 3. Reactivity of 2-acetyl-nitroselenophenes with different dienes.

Table 2. Diels–Alder reactions of nitroselenophenes with Rawal's diene

Entry	Dienophile	Conditions[a]	Product	Yield[b] (%)
1	**1a**	200 °C, 72 h	**5a**	52
2		150 °C, 72 h	**5b**	50
3	**1b**	200 °C, 72 h	**5a**	55
4		150 °C, 72 h	**5b**	50
5	**1c**	200 °C, 72 h	**7a**	56
6		150 °C, 72 h	**7b**	50
7	**1d**	200 °C, 72 h	**7a**	53
8		150 °C, 72 h	**7b**	53

[a] 3 equiv of Rawal's diene in benzene.
[b] Based on consumed dienophile.

certed elimination of nitrous acid from the [2+4] cycloadduct yields the corresponding benzoselenophenes. The irreversible character of the extrusion of nitrous acid makes the domino reaction thermodynamically feasible.

3. Conclusions

We have described the first synthesis of benzoselenophene by D–A reactions. This study indicates a properly substituted selenophene function as a normal dienophile. A very strong electron-acceptor group, such as a nitro group, induces similar reactivity at 2- and 3-positions in the selenophene ring.

The results are consistent with previously published reactions of nitrofurans and nitropyrroles with different dienes, that proceed to yield benzofurans and indoles as the main products.[2a,c]

Finally, these reactions provide a clean one-pot synthesis of benzoselenophenes from readily available nitroselenophenes with diverse dienes.

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3. The synthesis of **1a** and **1b** were performed starting from selenophene following a procedure proposed by Yur'ev, Yu. K.; Zaitseva, E. L.; Rosantev, G. G. *Zh. Obshch. Khim.* **1960**, *30*, 2207. After the reaction was completed, the mixture was poured on to crushed ice. The aqueous mixture was extracted with ethyl ether, the organic layers combined were washed twice with water, dried with Na_2SO_4, and then the solvent removed. The residue was purified by column chromatography in silica gel using hexane–ethyl acetate mixtures as the eluent.
4. The synthesis of **1c** and **1d** were performed starting from selenophene following a procedure proposed by Kataev, E. G.; Palkina, M. V. *Uch.Zap. Kasan, Gosudarst. Univ. Im. V.I. Ulyanova-Lenina, Khim.* **1953**, *113*, 115, [*Chem. Abstr.* **52**, 3762 (1958)] for the synthesis of 2-acetylselenophene. Then, this compound was nitrated following the procedure given in Ref. 3.
5. *General procedure*: The temperature, the length of the reaction and the diene/dienophile ratio are given in Tables 1 and 2. An ampoule containing 1.0 mmol of the dienophile and the required amount of diene in 0.5 ml of dry benzene were cooled in liquid nitrogen, sealed and then heated in an oil bath. After the reaction time was completed, it was cooled once more in liquid nitrogen and opened. The solution was evaporated and the residue purified by column chromatography in silica gel or alumina using hexane–ethyl acetate mixtures as the eluent. Biolatto, B.; Kneeteman, M.; Paredes, E.; Mancini, P. *J. Org. Chem.* **2001**, *66*, 3906–3912; Paredes, E.; Brasca, R.; Kneeteman, M.; Mancini, P. M. E. *Tetrahedron* **2007**, *63*, 3790–3799.
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8. *Spectral data*: ^1H and ^{13}C NMR spectroscopy aided in the determination of the cycloaddition products, with two-dimensional ^1H–^{13}C COSY (HMBC) and NOE correlated spectral analysis being especially helpful in this connection. Compound **4a**: δ ^1H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H); 6.95 (d, 1H, $J = 4.4$ Hz); 7.26 (d, 1H, $J = 4.4$ Hz); 7.72 (m, 2H); 7.76 (dd, 1H, $J = 8.4$ Hz, $J = 2.2$ Hz). ^{13}C NMR (75 MHz): δ 25.2; 127.5; 127.9; 128.9; 129.5; 132.4; 138.3; 140.2; 144.3. HRMS *m/z* 195.1232 (Calcd C_9H_8Se, 195.1225). Compound **4b**: ^1H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H); 7.02 (d, 1H, $J = 4.3$ Hz); 7.28 (d, 1H, $J = 4.3$ Hz); 7.69 (d, 1H, $J = 8.3$ Hz); 7.75 (m, 2H). ^{13}C NMR (75 MHz): δ 25.2; 126.6; 127.4; 130.0; 131.6; 132.7; 137.5; 139.4; 143.5. Compound **5a**: ^1H NMR (300 MHz, $CDCl_3$): δ 0.20 (s, 6H); 1.05 (s, 9H); 6.85 (dd, 1H, $J = 8.6$ Hz, $J = 2.3$ Hz); 6.95 (d, 1H, $J = 4.5$ Hz); 7.35 (d, 1H, $J = 2.4$ Hz); 7.40 (d, 1H, $J = 4.4$ Hz); 7.72 (d, 1H, $J = 8.5$ Hz). ^{13}C NMR (75 MHz): δ −4.6; 18.8; 25.7; 117.3; 120.5; 127.6; 130.2; 133.7; 136.4; 143.0; 157.1. HMRS *m/z* 311.3585 (Calcd $C_{14}H_{20}OSiSe$, 311.3577). Compound **5b**: ^1H NMR (300 MHz, $CDCl_3$): δ 0.20 (s, 6H); 1.05 (s, 9H); 7.05 (d, 1H, $J = 4.3$ Hz); 7.22 (m, 2H); 7.30 (d, 1H, $J = 4.4$ Hz); 7.68 (d, 1H, $J = 8.2$ Hz). ^{13}C NMR: δ −4.6; 18.8; 25.7; 112.3; 120.2; 127.3; 127.6; 131.4; 135.8; 144.2; 158.6. Compound **6a**: ^1H NMR (300 MHz, $CDCl_3$): δ 2.458 (s, 3H); 2.639 (s, 3H); 7.766 (dd, 1H, $J = 8.2$ Hz, $J = 2.2$ Hz); 7.719 (m, 2H); 8.087 (s, 1H). ^{13}C NMR (75 MHz): δ 24.5, 30.1, 126.9, 129.5, 132.6, 133.8, 139.3, 139.9, 142.5, 149.3, 229.7. IR (C=O) 1651.5 cm^{-1}. HMRS *m/z* 237.1606 (Calcd $C_{11}H_{10}OSe$, 237.1598). Compound **6b**: ^1H NMR (300 MHz, $CDCl_3$): δ 2.457 (s, 3H); 2.637 (s, 3H); 7.792 (d, 1H, $J = 8.4$ Hz); 7.765 (dd, 1H, $J = 8.4$ Hz, $J = 2.1$ Hz); 7.715 (d, 1H, $J = 2.1$ Hz); 8.086 (s, 1H). ^{13}C

NMR (75 MHz): δ 24.5, 30.1, 127.2, 128.8, 131.4, 134.2, 137.2, 139.5, 145.1, 149.2, 230.3. IR (C=O) 1652 cm^{-1}. Compound **7a**: ^1H NMR (300 MHz, $CDCl_3$): δ 0.20 (s, 6H); 1.05 (s, 9H); 2.46 (s, 3H); 7.765 (dd, 1H, $J = 8.3$ Hz, $J = 2.1$ Hz); 7.712 (m, 2H); 8.08 (s, 1H): ^{13}C NMR (75 MHz): δ −4.6; 18.8; 25.7; 30.1; 112.5; 122.1; 128.4; 132.1; 135.2; 144.0; 147.7; 156.4; 229.2. IR (C=O) 1651.5 cm^{-1}. HMRS m/z 337.3962 (Calcd $C_{17}H_{22}OSeSi$, 337.3955). Compound **7b**: ^1H NMR (300 MHz, $CDCl_3$): δ 0.20 (s, 6H); 1.05 (s, 9H); 2.46 (s, 3H); 7.78 (d, 1H, $J = 8.5$ Hz); 7.75 (dd, 1H, $J = 8.3$ Hz, $J = 2.2$ Hz); 7.70 (d, 1H, $J = 2.2$ Hz); 8.087 (s, 1H). ^{13}C NMR (75 MHz): δ −4.6; 18.8; 25.7; 30.1; 117.3; 120.5; 132.4; 133.5; 136.4; 143.0; 149.2; 157.3; 228.4. IR (C=O) 1652 cm^{-1}.