

Synthesis of naphthothiophene derivatives through polar Diels-Alder reactions employing 5-nitrobenzothiophene as electrophile. Microwave irradiation vs classical thermal conditions

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Abstract. Herein we report a simple, economical and efficient one-step procedure to synthesize the naphtho[2,1-b]thiophene ring system in good to excellent yield through the polar Diels-Alder reactions of 5-nitro-3-acetylbenzothiophene and dienes of different nucleophilicity. In thermal conditions the reactions were developed in molecular solvents; moreover the reaction system was exposed to microwave irradiation as a complement of reaction conditions.

Keywords: Nitrobenzothiophene, electrophile, Diels-Alder

Introduction

Naphthothiophene has been reported as a promising p-type semiconductor. The development of high-performance n-type semiconductors is highly desirable.¹

On the other hand, in the hierarchy of carbon-carbon bond constructions, the Diels-Alder (DA) reaction has attained a preminent position. Its potential in heterocyclic chemistry synthesis is very well known. This process is in one step inter or intramolecular from aspects diene and dienophile bearing an almost unlimited number of variants.^{2,3}

Recently we have reported a simple scheme to synthesize the dibenzothiophene ring system in good yield through the DA reaction of 2- and 3-nitrobenzothiophenes and different dienes.⁴

Herein we report a simple, economical and efficient one-step procedure to synthesize the naphtho[2,1-b]thiophene ring system in good yield through the polar DA reactions of 5-nitrobenzothiophene and electron-rich (ER) dienes. A very strong EW group, such as nitro group, push the nucleophilic character of these heterocyclic compounds and owing to this substituent is easily extruded under thermal conditions make this reaction sequence a simple method of organic compound's families with heteroatom rings preparation.

Results and Discussion

The study of P-DA reactions was carried out employing 5-nitro-3-acetylbenzothiophene **1a** as electrophilic dienophile, whereas 1-methoxy-3-trimethylsilyloxy-1,3-butadiene **2**, 1-trimethylsilyloxy-1,3-butadiene **3** and isoprene **4** were chosen as ER diene partners (Figure 1). The selection of dienes took into account the type of substitution present in their structures and the relative nucleophilicity.

5-nitro-3-acetylbenzothiophenes **1a** were prepared by acylation and nitration of benzothiophene, and subsequent chromatographic separation.

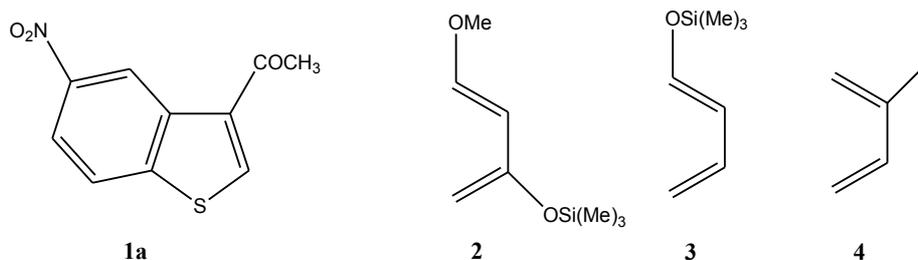
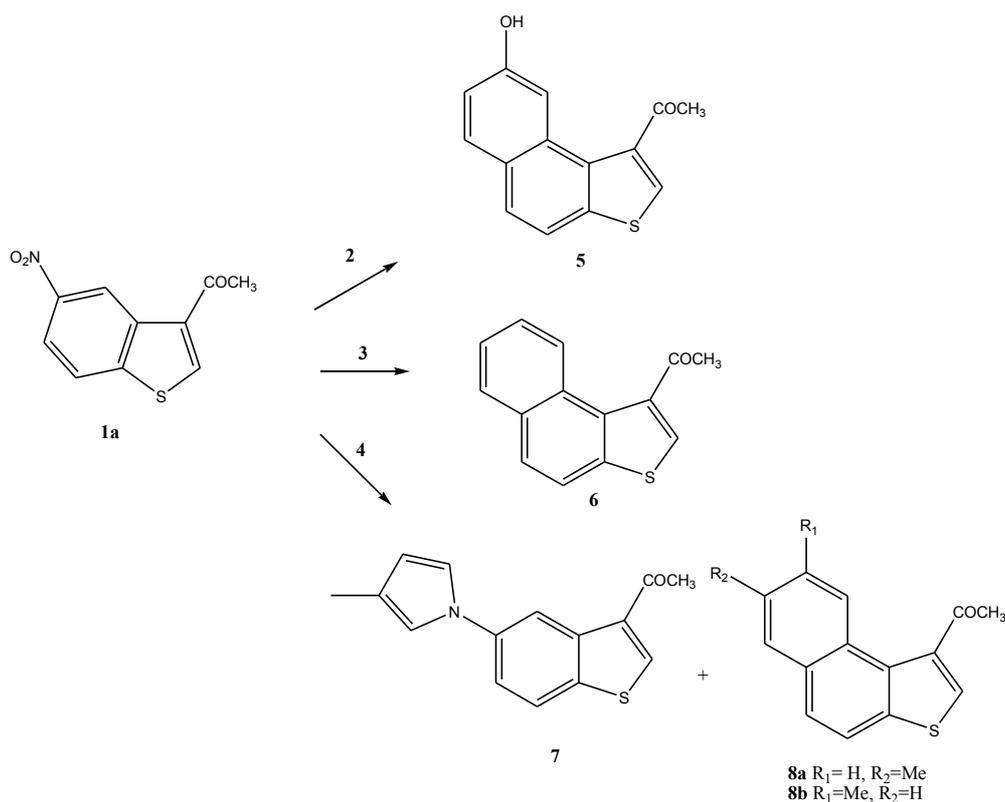


Figure 1

When 5-nitro-3-acetylbenzothiophene **1a** reacted with Danishefsky's diene **2** in a sealed ampoule at 150 °C and 120 °C for 72 h using benzene as solvent the reaction proceeded to produce hydroxylated naphthothiophene **5** with acceptable yield and complete regioselectivity (Scheme 1, Table 1). These results indicate a properly substituted benzothiophene functions as a normal dienophile with an activated 1,3-butadiene.

Exposure of **1a** to 1-trimethylsilyloxy-1,3-butadiene **3** (150°C and 120°C, 72 h, Bz anh) afforded naphthothiophene **6** with reasonable yield (53% and 50%). When **1a** was then heated with less reactive isoprene **4** (150°C and 120°C, 72 h, Bz anh), it gave pyrrolylbenzothiophene **7** in low yield formed by an assumed hetero cycloaddition followed by thermal rearrangement and isomeric naphthothiophenes **8a** and **8b** (Scheme 1, Table 1).⁵



Scheme 1

Considering that microwave irradiation (MW) has been used to enhance organic reactions, we realized some experiences in this P-DA reactions using molecular solvent (benzene) and solvent-free conditions.

With microwave irradiation (150 °C and 180°C, 60 min) and benzene as reaction media was chosen, **1a** react with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene **2** afforded **5**. The reactions of **1a** with diene **3** in similar conditions produced naphthothiophene **6** in reasonable yield (entries 1,2,5,6 Table 2).

On the other hand, when **1a** react with isoprene and MW irradiation using benzene as solvent product **7**, **8a** and **8b** were obtained (entries 9,10; Table 2). These results are coincident with those previously obtained.⁶

Diels-Alder cycloaddition of **1a** with Danishefsky's diene under microwave irradiation in solvent-free condition (180°C and 150°C) gave **5** with very good yield (entries 3 and 4, Table 2). On the other hand, when **3** reacted with **1a** under microwave irradiation in solvent-free condition afforded naphthothiophene **6** (entries 7,8; Table 2) after elimination of the nitro group and in situ aromatization.

Finally, treatment of **1a** with isoprene **8a**, **8b** and **7** are obtained when microwave irradiation in solvent-free condition are used (entries 11, 12; Table2).

Table 1. Thermal reactions of nitrobenzothiophenes with dienes of different reactivity

Entry	Dienoph.	Diene	Conditions. ^a	Product, yield ^b
1	1a	2 , 2 eq.	150°C	5 , 55%
2			120°C	5 , 52%
3		3 , 2 eq.	150°C	6 , 53%
4			120°C	6 , 50%
5		4 , 12 eq	150°C	7 , 10%; 8a,b , 15%
6			120°C	7 , 5%; 8a,b , 12%

^a Reaction time 72 h; reaction media: benzene anh.

^b Based on consumed nitrobenzothiophene.

Table 2. Diels-Alder reactions of nitrobenzothiophenes with different dienes employing microwave irradiation.

Entry	Dienoph.	Diene	Conditions ^a	Product, yield ^b
1	1a	2 , 2 eq.	180°C, Bz anh.	5 , 56%
2			150°C, Bz anh.	5 , 54%
3			180°C, Solv. Free	5 , 70%
4			150°C, Solv. Free	5 , 68%
5		3 , 2 eq.	180°C, Bz. anh.	6 , 50 %
6			150°C, Bz. anh.	6 , 48%
7			180°C, Solv. Free	6 , 58%
8			150°C, Solv. Free	6 , 55%
9		4 , 12 eq.	180°C, Bz. anh.	7 , 10%; 8a,b ; 17%
10			150°C, Bz. anh.	7 , 8%; 8a,b ; 12%
11			180°C, Solv. Free	7 , 12%; 8a,b ; 20%
12			150°C, Solv. Free	7 , 8%; 8a,b ; 18%

^a Reaction time 60 min.

^b Based on consumed nitrobenzothiophene.

Conclusions

The reactions between 5-nitro-3-acetylbenzothiopheno **1a** and different dienes, developed in benzene as solvent to yield naphthothiophenes derivatives permit to conclude that a properly substituted benzothiophene functions as a normal dienophile with an activated 1,3-butadiene.

With microwave irradiation and benzene as reaction media, **1a** react with **2**, **3** and **4**, respectively, to yield the same products than before. Reaction of dienes **2** and **3** with 5-nitrobenzothiophenes **1a** under microwave irradiation in solvent-free condition give good yields of the aromatic naphthothiophenes through elimination of the nitro group and subsequent aromatization.

The use of MW irradiation decreases the time of reaction for similar yields.

Acknowledgments

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References and notes

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- 5- The temperature, the length of the reaction, and the diene/dienophile ratio were dependent on the starting material and are indicated in Table 1. An ampule containing a solution of 1.0 mmol of the dienophile and the required amount of diene in 1 ml of dry benzene was cooled in liquid nitrogen, sealed (under nitrogen atmosphere), and then heated with stir in a 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 on silica gel or alumina using hexane/ethyl acetate mixtures as eluent.
- 6- Microwave irradiation was performed in a Anton Parr Monowave 300, microwave reactor in standard closed vessels. The temperature, the length of the reaction, and the diene/dienophile ratio were dependent on the starting material and are indicated in Table 2. After the reaction time was completed, the solution was evaporated and the residue purified by column chromatography on silica gel or alumina using hexane/ethyl acetate mixtures as eluent.