



International Research Journal of Pure & Applied Chemistry
8(4): 229-235, 2015, Article no. IRJPAC.2015.088
ISSN: 2231-3443



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Polar Diels-Alder Reactions Using Heterocycles as Electrophiles. Influence of Microwave Irradiation

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IRJPAC/2015/18867

Editor(s):

(1) Wolfgang Linert, Institute of Applied Synthetic Chemistry Vienna University of Technology Getreidemarkt, Austria.

Reviewers:

(1) Anonymous, Wrocław University of Technology, Poland.

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(3) Anonymous, Madras University, India.

Complete Peer review History: <http://www.sciencedomain.org/review-history.php?iid=1052&id=7&aid=9590>

Short Research Article

Received 13th May 2015

Accepted 26th May 2015

Published 4th June 2015

ABSTRACT

In this work we studied a series of polar Diels-Alder reactions using different heterocycles derivatives acting as electrophiles joint to dienes of different nucleophilicity, analyzing the effect of the microwave irradiation in these processes. We employ the technique in two conditions: benzene as solvent and solvent free reactions. The last one presents the better yield in shorter time of reaction. Using microwave heating the aromatic cycloadducts are clearly predominant. It is possible to demonstrate that the microwave irradiation has a better influence on these cycloaddition reactions respect to those developed in thermal classical conditions.

Keywords: Aromatic heterocycles; electrophiles; microwave irradiation; solvent free; Diels-Alder.

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1. INTRODUCTION

The Diels-Alder (DA) reaction is a very useful tool as organic transformation. Its use in natural products synthesis is very well known. This reaction underlines the synthesis of diverse carbo- and heterocyclic compounds [1-2]. Due to our interest in the cycloaddition chemistry of substituted aromatic heterocycles with electron-withdrawing groups, we have reported studies on the electrophilic character of aromatic compound with adequate substitution in their reactions with different dienes developed in benzene as the reaction medium and under conventional heating. These electrophiles react with dienes through polar Diels-Alder (P-DA) reactions to obtain in one step the respective cycloadducts aromatized [3-14]. Normally the reaction products are useful due to their biological activity [15-17].

The microwave-assisted controlled heating has become a powerful tool in organic synthesis, being increasingly used to accelerate organic reactions and to increase yields. As it is known it reduces reaction times or even offers desired products in minutes and the further formation of by-products is eliminated [18]. In a conventional synthesis, to reach the optimal reaction conditions to obtain a desired specific product one or more heating stages are required. This way of heating a reaction mixture is slow and inefficient. Application of microwaves in organic synthesis has been improved over the last years. This methodology results in better reaction rates and very high yields. In our case, the heating depends on the capability of the molecules present in a cycloaddition process of irradiation absorption. The reaction mixture undergoes heating by a combination of thermal effect, dipolar polarization and ionic conduction. Then the polar compound can absorb energy very efficiently [19]. A number of authors had used successfully this proceeding observing even modifications of the selectivity, although the microwave effect is a topic of discussion yet [20].

Taking into account that microwave irradiation (MW) helps to improve organic reactions we carry out some experiments of this polar process using this methodology. Then, the principal aim of this work is to study the cycloaddition reactions of nitro substituted pyrroles, indoles, thiophenes and benzothiophenes, exposed to dienes of different nucleophilicity using MW irradiation in two experimental conditions, in presence of benzene as molecular solvent and

complementary in solvent-free conditions. One of the tosylindoles derivatives used presents the nitro group as a substituent in the benzene ring to test the director effect of the substituent. We choose this type of electrophiles due to the behavior that they demonstrated participating in polar cycloaddition reactions when we use normal experimental conditions. The projected aromatic cycloadducts have shown a great potential in pharmaceutical research and could be used as versatile scaffolds in experimental drug design.

2. MATERIALS AND METHODS

General Procedure: The following dienophiles were used: 1-tosyl-2-nitropyrrole (1a), 1-tosyl-3-nitropyrrole (1b), 1-tosyl-2-nitroindole (2a), 1-tosyl-3-nitroindole (2b), 1-tosyl-5-nitroindole (2c), 2-nitrothiophene (3a), 3-nitrothiophene (3b), 2-nitrobenzothiophene (4a) and 3-nitrobenzothiophene (4b). These were prepared by nitration of the corresponding heterocyclic compound following a procedure proposed by H. Anderson et al. [21] with some modifications: A mixture of 70% nitric acid (4.15 ml) and acetic anhydride (60 ml), cooled under -10°C is added drop wise over a 30 min period to a stirred mixture of heterocyclic compound (19.56 mmol) and acetic anhydride (60ml). The mixture was stirred for further 2 h, let warm to room temperature and the poured onto crushed ice. The aqueous mixture was extracted with methylene chloride, the organic layers combined were washed twice with water, dried with Na_2SO_4 , and then the solvent removed. The residue purified by column chromatography on silica gel using hexane/ethyl acetate mixtures as eluent. Isoprene (5) and 1-trimethylsilyloxy-1,3-butadiene (6) were chosen as diene components (Fig. 1). The selection of the dienes took into account the type of substitution presents in their structures and the relative nucleophilicity.

In the case of pyrroles and indoles derivatives the introduction of the tosyl protecting group was further carried out by the technique reported by E. Wenkert et al. [22] with some modifications: a 50% potassium hydroxide solution (1.0 mL) was added dropwise to a stirring mixture of 1.0 mmol of the requisite indole or pyrrole and 0.1 mmol of tetra-*n*-butylammonium bromide in 3.0 mL of benzene at room temperature and the stirring continued for 5 min. 4-toluenesulfonyl chloride (190.65 mg, 1.0 mmol) was added dropwise and the mixture stirred for 2 h. It was poured into 20 mL of water and extracted with 60 mL of

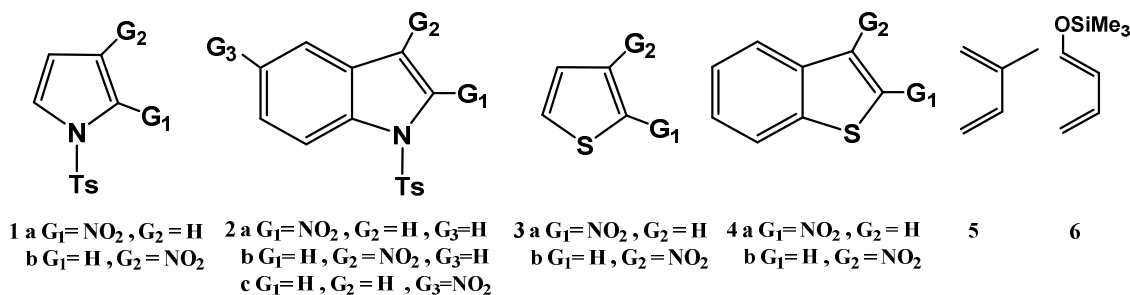


Fig. 1. Dienophiles and dienes

methylene chloride. The extract was dried and evaporated and the residue chromatographed.

Microwave irradiation was performed in an Anton Paar 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 Tables. After the reaction time was completed, the solution was evaporated and the residue purified by column chromatography.

3. RESULTS AND DISCUSSION

To test the efficacy of nitro substituted heterocycles as dienophile in DA reactions, the following compounds were used: (1a), (1b), (2a), (2b), (2c), (3a) y (3b). Moreover, the reactive behavior of 2-nitrobenzothiophene (4a) and 3-nitrobenzothiophene (4b) were reported as part of a theoretical study [13].

Usually, thermal DA transformations using molecular solvents require harsh conditions (high temperatures and longer reaction times or high pressure). In the experiences developed in normal thermal conditions the product with the tosylnitropyroles and tosylnitroindoles were a mixture of tosyldihydroindoles and tosylindoles derivatives and tosyldihydrocarbazoles and tosylcarbazoles, respectively, specially working a lower temperature (90°C, 48 h). Only using tosylnitropyroles in its reaction with the Danishefsky's diene (high pressure conditions) was possible to insulate the primary cycloadducts [3]. In this conditions the reactivity of the nitrothiophenes with both dienes offers the corresponding pyrrolil derivatives (hetero DA process). Instead, the behavior of nitrobenzothiophenes is different. In its reaction with isoprene produce the hetero DA products but when react with 1-trimethylsilyloxy-1,3-butadiene the corresponding dibenzothiophene were obtained as principal product [4,13].

The reactions of 1a and 1b with isoprene 5 under MW irradiation and benzene as reaction medium, yielded the mixture of isomeric indoles 7a and 7b (Table 1, entries 1-4). Similar results were obtained using MW irradiation in absence of solvent, but in this case with better yields in a shorter time of reaction. We can observe that this condition induces the aromatization of the cycloadducts and in general improve the yields respect to the normal thermal experiences. On the other hand the treatment of 1a y 1b with 6 under the same conditions, afforded the indole 7c (Table 1, entries 5-8). In the last case the best results were obtained in solvent-free conditions which showing the high yields. In this process the reaction times were shorter compared to the reactions performed with these electrophiles in normal conditions using benzene as solvent [11]. All the products are the result of the nitro group elimination and subsequent aromatization. This step is irreversible.

In turn exposure of indoles 2a and 2b to isoprene using MW irradiation in both conditions -benzene as reaction media and solvent free- yielded the mixture of carbazoles 8a and 8b with good yield. Moreover, in the reactions with diene 6 cycloadduct 8c was obtained in good yield. (Table 2, entries 1, 2, 3, 4 and 7, 8, 9, 10) [3].

When tosylnitroindole 2c react under MW irradiation both conditions, with the dienes 5 and 6 the products observed were induced by the nitro group position and it were the benzo[e]indoles 9a and 9b, and 9c, respectively. The yields were moderates (Table 2, entries 5, 6 and 11, 12). This behavior is similar to nitronaphthalenes [11] and remark the importance in the reaction course of the nitro group. Once again we observe the loss of the nitro group and product aromatization.

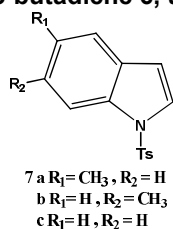
When 2- and 3-nitrothiophene 3a and 3b were heated by MW irradiation in the presence of cited

dienes, using both reaction conditions, offer the pyrrolyl thiophene derivatives 10a, 10b y 11a, 11b, respectively, in moderate yield. The products are formed assuming hetero cycloaddition process followed by thermal rearrangement (Table 3, entries 1-8).

Probably the major aromatic character of these heterocycles is responsible of the observed

reactive behavior. This reactive behavior was also observed with nitronaphthalenes [11] and when the nitrobenzene reacts with the dienes 5 and 6 in presence of benzene as solvent and in solvent free conditions, using microwave irradiation at 190°C afforded 12 and 13 respectively (see Scheme 1).

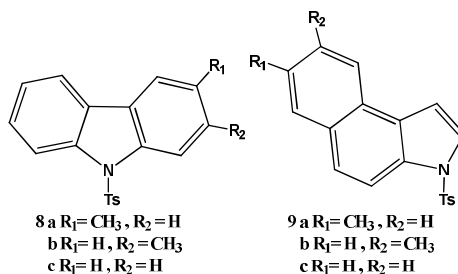
Table 1. P-DA reactions of nitro-substituted pyrroles 1a and 1b with isoprene 5 and 1-trimethylsilyloxy-1,3-butadiene 6, under MW irradiation



Entry	Dienophile	Diene	Conditions ^a	Prod.	Yield (%) ^b
1	1a	5 , 12 equiv	Benzene, 120 min	7a, 7b	30
2	1a	5 , 12 equiv	Free-solv., 50 min	7a, 7b	55
3	1b	5 , 12 equiv	Benzene, 120 min	7a, 7b	24
4	1b	5 , 12 equiv	Free-solv., 50 min	7a, 7b	51
5	1a	6 , 3 equiv	Benzene, 50 min	7c	51
6 ^c	1a	6 , 3 equiv	Free-solv., 20 min	7c	68
7	1b	6 , 3 equiv	Benzene, 50 min	7c	42
8 ^c	1b	6 , 3 equiv	Free-solv., 20 min	7c	63

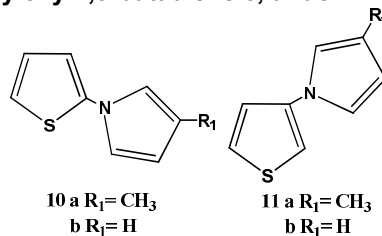
^aReaction temperature: 180°C, ^bBased on consumed dienophile. ^cMaximum yield of the reaction

Table 2. P-DA reactions of nitro indoles 2a, 2b and 2c with isoprene 5 and with 1-trimethylsilyloxy-1,3-butadiene 6, under MW irradiation



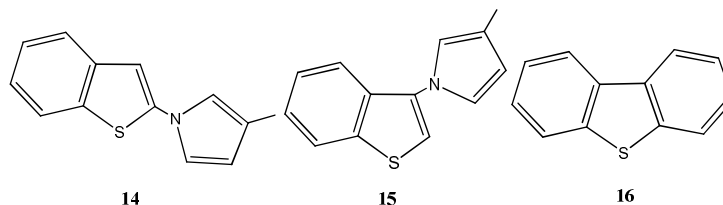
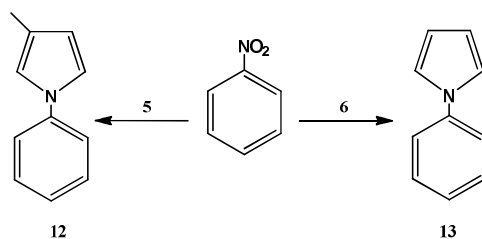
Entry	Dienophile	Diene	Conditions ^a	Prod.	Yield (%) ^b
1	2a	5 , 12 equiv	Benzene, 30 min	8a, 8b	50
2	2a	5 , 12 equiv	Free-solv., 30 min	8a, 8b	62
3	2b	5 , 12 equiv	Benzene, 30 min	8a, 8b	57
4	2b	5 , 12 equiv	Free-solv., 30 min	8a, 8b	67
5	2c	5 , 12 equiv	Benzene, 60 min	9a, 9b	51
6	2c	5 , 12 equiv	Free-solv., 30 min	9a, 9b	58
7	2a	6 , 3 equiv	Benzene, 30 min	8c	61
8 ^c	2a	6 , 3 equiv	Free-solv., 30 min	8c	73
9	2b	6 , 3 equiv	Benzene, 30 min	8c	66
10 ^c	2b	6 , 3 equiv	Free-solv., 30 min	8c	75
11	2c	6 , 3 equiv	Benzene, 60 min	9c	62
12 ^c	2c	6 , 3 equiv	Free-solv., 30 min	9c	70

^aReaction temperature: 180°C, ^bBased on consumed dienophile. ^cMaximum yield of the reaction

Table 3. P-DA reactions of nitro thiophenes 3a and 3b with isoprene 5 and with 1-trimethylsilyloxy-1,3-butadiene 6, under MW irradiation.

Entry	Dienophile	Diene	Conditions ^a	Prod.	Yield(%) ^b
1	3a	5 , 12 equiv	Benzene, 120 min	10a	23
2	3a	5 , 12 equiv	Free-solv., 30 min	10a	28
3	3b	5 , 12 equiv	Benzene, 120 min	11a	22
4	3b	5 , 12 equiv	Free-solv., 30 min	11a	25
5	3a	6 , 3 equiv	Benzene, 50 min	10b	33
6 ^c	3a	6 , 3 equiv	Free-solv., 20 min	10b	39
7	3b	6 , 3 equiv	Benzene, 50 min	11b	31
8 ^c	3b	6 , 3 equiv	Free-solv., 20 min	11b	35

^aReaction temperature: 180°C, ^bBased on consumed dienophile. ^cMaximum yield of the reaction

**Fig. 2. Reactions products of the P-DA cycloaddition between 4a and 4b with dienes 5 and 6**

Recently we reported that the exposure of benzothiophenes 4a and 4b with 5 under MW irradiation -both reaction conditions-, offer the heterocycle adducts 14 and 15, respectively, in moderate yield. Instead when these electrophiles react with diene 6 the product was dibenzothiophene 16 with good yields which have greater nucleophilicity (Fig. 2, above) [13]

4. CONCLUSION

The use of microwave irradiation in this type of P-DA reactions presents advantages in relation with those developed in normal conditions

observing lower reaction times and better yields. In the process developed with nitropyrrroles and nitroindoles it was observed that in all cases the nitro group is responsible to the orientation and the selectivity. The nitro group extrusion as nitrous acid occurs. The same behavior was noted for the reaction between nitrobenzothiophene and the diene 1-trimethylsilyloxy-1,3-butadiene. Other cases studied showed hetero cycloaddition, specially using nitrobenzene. In general, using MW irradiation the behavior of the different pair diene/dienophile were similar to the reactions carried out with conventional heating in benzene

as the reaction medium, but the use of MW decreased the reaction times significantly and the tendency of the product to aromatization improved. It is important to note that MW in solvent-free conditions yielded the best result. The methodology explored could be used in commercial form. However, it would be necessary to have the required equipment for this purpose.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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