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MICROWAVES ASSSITED CYCLOADITION REACTIONS OF UNSATURATED PHENOTHIAZINE DERIVATIVES

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ABSTRACT. Microwaves assisted *aza*Diels-Alder cycloaddition reactions using aromatic and heteroaromatic Schiff bases as heterodienes and 3,4-dihydro-2*H*-pyrane (DHP) as dienophyle in the presence of iodine catalyst, afforded stable cycloaddition adducts, as well as their oxidation products. The structures of the new hexahydro-2*H*-pyrano[3,2-*c*]quinoline and 3-(3-hydroxypropyl)-quinoline derivatives were assigned based on spectroscopic methods (high resolution NMR and mass spectrometry).

Keywords: *Phenothiazine, Ferrocene, aza-Diels-Alder cycloaddition, Schiff base, 3,4-dihydro-2H-pyrane.*

INTRODUCTION

Many published papers, several books [1,2] and review articles [3,4] indicate the microwaves irradiation as an alternative technique for achieving almost all types of thermally induced reactions, including synthesis of heterocyclic compounds. Particularly efficient heating processes induced by the dielectric heating afford shorter reaction times and sometimes better yields or increased selectivities.

[4+2] Cycloaddition reaction is an extremely useful route to generate six-membered ring compounds with advanced stereocontrol [5,6]. The reaction proceeds under thermal conditions and application of high pressure, catalysts and solvent variation increase the reaction rate and selectivity [7,8]. Six member ring heterocycles (containing oxygen or nitrogen) may also be obtained by using the appropriate heterodienes or heterodienophiles. Tetrahydroquinoline derivatives were prepared by aza-Diels-Alder reactions based on [4+2] cycloaddition between *N*-arylimines (electron-poor azadiene) and electron-rich dienophiles. Among other catalysts employed in pyrano-quinoline derivatives preparation from imines and 3,4-dihydro-*2H*-pyrane, iodine was capable to reduce the reaction time and to increase the yields acting as a Lewis acid that coordinate to the nitrogen atom of the polar C=N bond [9,10].

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Our previous results regarding formal *aza*-Diels-Alder cycloaddition reactions between Schiff bases containing highly electron-donating phenothiazinyl- or ferrocenyl groups and 3,4-dihydro-2*H*-pyrane (DHP) in the presence of iodine catalyst, highlighted the formation of quinoline derivatives by a multistep reaction mechanism and a characteristic substituent-dependence for the subsequent transformation of the reaction adduct [11]. Depending on the substitution pattern of the N-phenyl group the reactions of phenothiazine-containing imines afforded 2*H*-pyrano[3,2-*c*]quinolines or 3-(3-hydroxypropyl)quinolines. Irrespectively of the electronic properties of the N-phenyl substituent the less reactive ferrocene-based imines were converted into quinoline products. The theoretical calculations allowed predicting reliable structure-reactivity relationships which must be taken into account when setting up procedures for related cycloaddition reactions.

In order to bring more experimental evidence for supporting these theoretical predictions regarding structure-reactivity relationships, three additional Schiff bases containing aryl, phenothiazinyl and respectively ferrocenyl units were employed as heterodienes in cycloaddition reactions performed under microwaves assisted conditions.

Schiff bases containing phenothiazine units can be obtained by the condensation of 10-alkyl-3-formylphenothiazine with aromatic amines [12], aromatic diamines or heteroaromatic amines [13]. Alternative precursors for such heterocyclic Schiff bases were N-alkyl-3-aminophenothiazine derivatives and benzaldehyde derivatives [14]. Schiff bases containing phenothiazine units appear as stable yellow solids with green-yellow fluorescence in solution [12].

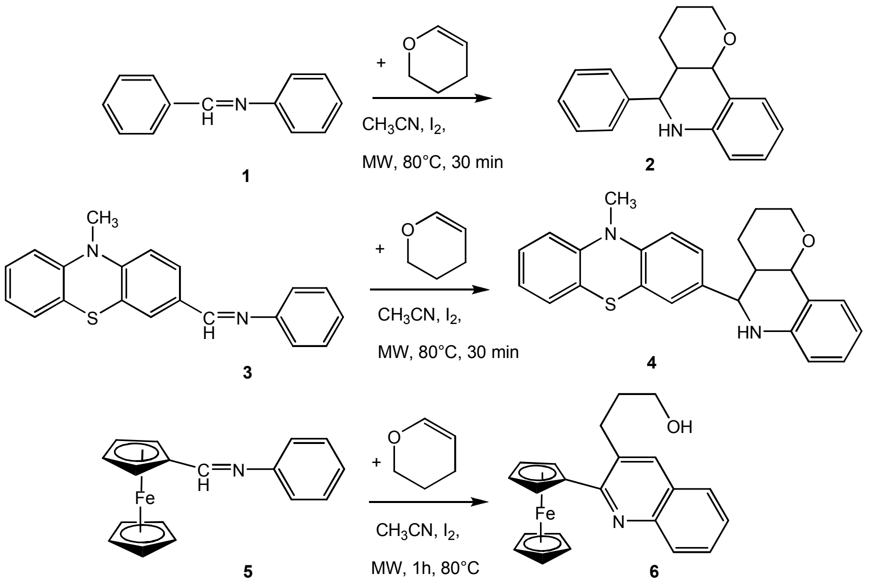
Schiff bases containing ferrocene units have been conventionally prepared by heating several hours under reflux a solution of ferrocenylcarbaldehyde and an aromatic amine in the presence of a polar solvent such as alcohol [15], a non-polar solvent such as toluene with azeotropic water removal [16] and under solvent free conditions [17] which gave the best yields. Microwave assisted synthesis in the presence of different dehydrating reagents such as zinc chloride, titanium chloride, molecular sieves, alumina [1], or using solvent free reaction conditions, greatly increased the reaction rate, prevented the formation of decomposition products and gave good reaction yields of ferrocenyl Schiff bases [18].

RESULTS AND DISCUSSION

Schiff bases **1, 3** and **5** were prepared according to previously reported procedures by the condensation of the corresponding (hetero)aromatic aldehyde with aniline in ethanol under reflux. Thus, high yields of **1** were prepared starting with benzaldehyde, **3** was obtained from 10-methyl- 10*H*phenothiazine-3-carbaldehyde [12] and **5** was obtained from ferrocenyl-carbaldehyde [17].

Schiff bases **1, 3,** and **5** were tested as heterodienes in *aza*-Diels-Alder cycloaddition reactions. No cycloaddition adduct was obtained in reaction with cyclopentadiene dienophile, no matter what reaction conditions were employed: various catalysts (I_2, KH_2PO_4, F_3C-COOH, *p*H_2N-C_6H_4-SO_3H, or $FeCl_3$), classical heating, or microwave irradiation.

Good results were obtained when, in the presence of catalytic amounts of iodine, Schiff bases **1, 3,** or **5** acted as electron poor azadienes in reaction with the electron rich dienophile 3,4-dihydro-*2H*-pyrane (DHP) leading to the formation of 2-phenyl-hexahydro-2*H*-pyrano[3,2-*c*]quinoline **2**, 2-(10-methyl-3-phenothiazinyl)-hexahydro-2*H*-pyrano[3,2-*c*]quinoline **4** and 2-ferrocenyl-3-(3-hydroxypropyl)quinoline **6** respectively (scheme 1).



Scheme 1

The syntheses were performed under microwaves irradiation using a CEM Discover Lab Mate microwave reactor equipped with temperature and power control. Several experimental conditions were tested in order to set up the optimal reaction parameters. The selected polar solvent was acetonitrile, which ensured an efficient dielectric heating of the reaction mixture. Unfortunately the cycloaddition reaction was accompanied by other thermally induced transformations of the sensitive Schiff base substrates and thus, the cycloaddition adducts could be isolated in 50-60% yields after 30-60 minutes reaction time (monitored by TLC). The cyclization of the less reactive ferrocenyl-Schiff base **3** required the longest reaction time. Nevertheless, the microwave assisted synthesis of these new quinoline derivatives **2, 4** and **6** by microwave assisted aza-Diels-Alder cycloaddition appears advantageous when taking into consideration green chemistry principles such as: atom economy, mild reaction conditions and energy saving.

Structural analysis of the cycloadducts was performed by high resolution NMR experiments which revealed the formation of stable 2-phenyl-hexahydro-2*H*-pyrano[3,2-*c*]quinoline **2** and 2-(10-methyl-3-phenothiazinyl)-hexahydro-2*H*-pyrano[3,2-*c*]quinoline **4** respectively**.** Analysis of the coupling pattern shown by the protons attached to the carbon atoms participating to the fused tetrahydropyrane and tetrahydroquinoline rings, revealed a *cis* annelation of these heterocyclic rings. ^{1}H-NMR spectrum of 2-ferrocenyl-3-(3-hydroxypropyl)quinoline **6** indicate the presence of a 2,3-disubstituted quinoline unit by showing a deshielded signal (situated at 7.89 ppm) which may be assigned to the proton in position 4 of the heterocycle and of a propyl side chain indicated by the three signals situated in the aliphatic region of the spectrum (3.84, 3.25 and 2.01 ppm). Consequently, **6** was formed by the facile oxidation of the cycloaddition adduct, accompanied by the tetrahydropyrane ring opening.

CONCLUSIONS

Under microwaves assisted conditions, Schiff bases containing aryl, 3-phenothiazinyl and respectively ferrocenyl units attached to the methine group, acted as heterodienes in azaDiels-Alder cycloaddition reactions in the presence of DHP filodiene and iodine catalyst, in acetonitrile solvent. The presence of rich π-electron moieties phenothiazinyl or ferrocenyl, decreases the reactivity of the Schiff bases as compared to the phenyl substituted one. Structural analysis performed by spectroscopic methods indicates the formation of stable cycloadducts containing phenyl- or phenothiazinyl substituents and the formation of highly unstable ferrocenyl substituted cycloadduct, which undergoes rapid aromatization in similar reaction conditions.

EXPERIMENTAL SECTION

FT-IR spectrometer Bruker Vector 22, 300 MHz NMR spectrometer Bruker, Shimadzu MS Spectrometer, Merck reagents were used.

General procedures for the microwaves assisted synthesis of Schiff bases

Carbaldehyde derivative (2.0 mmol) was dissolved in MeCN (4 mL) in a 10 ml microwave reaction vessel. The reaction mixture was sealed and subjected to microwave irradiation using 100 W power levels at 80°C for 30-60 min. After cooling the product was filtered and recrystallized from ethanol.

[(10-Methyl-10*H*phenothiazin-3-yl)methylene]aniline (3)

Dark brown oil, yield: 0.546 g, 83% **IR:** 2894, 1707, 1437, 1330, 1079 cm^{-1}.

^{1}H NMR, 300 MHz, $CDCl_3$: δ= 3.33 ppm (s, 3H, **-**CH_3); 7.60 ppm, (d, ^3J= 7.8 Hz, 1H, H_2); 8.65 ppm, (s, 1H CH=N); 7.72 ppm, (s, 1H H_4); 7.21 ppm, (d, ^3J= 8 Hz, 1H H_6); 6.97 ppm, (t, ^3J= 8 Hz,1H H_7); 7.26 ppm, (t, ^3J= 8 Hz, 1H H_8); 6,75 ppm, (d, ^3J= 8.4 Hz, 2H, $H_{1,9}$); 7.66 ppm, (m, 4H $H_{2',3',5',6'}$); 7.76 ppm, (d, ^3J= 8.1 Hz, 1H); 7.73 ppm, (s, 1H); **^{13}C NMR,** $CDCl_3$ δ ppm**:** 35.6 (-CH_3), 126.7 (C_1), 129.4 (C_2), 130.3 (C_3), 161.3 ($\underline{C}$H=N), δ= 129.3 (C_4), 123.7 (C_{5a}), 127.5 (C_6), 123.8 (C_7), 123.8 (C_8), 117.9 (C_9), 146.2 (C_{9a}), 148.6 (C_{10a}), 124.4 (C_{4a}) 151.4 ($C_{1'}$), 121.9 ($C_{2',6'}$), 130.8 ($C_{3'5'}$), 127.2 ($C_{4'}$);

MS (EI, 70eV) m/z= 316 (100%) $M^{+\cdot}$

(Ferrocenylmethylene)aniline (5)

Dark brown oil yield: 0.453 g, 75% **IR:** 1620, 1435, 2956 cm^{-1}; **^{1}H NMR** 300 MHz, $CDCl_3$: δ=8.35 ppm (s, 1H, C$\underline{H}$=N); 7.40 ppm (d, 2H, ^3J=9 Hz $H_{2,6}$) 7.23 ppm (tr, 3H, J=7.5 Hz $H_{3,4,5}$) 4.83 ppm (s, 2H, $H_{2',5'}$); 4.51 ppm (s, 2H,$H_{3',4'}$), 4.27 ppm (s, 5H, Cp ring, Fc) **^{13}C NMR** δ 161.3, (CH=N), 152.7 (C1), 129.1 (C3,5), 125.1 (C4), 120.6 (C2,6), 80.3 (C1'), 71.2 (C3',4'), 69.2 (C2',5'), **MS** (EI, 70eV) m/z= 302 (100%) $M^{+\cdot}$

General procedure for the microwaves assisted azaDiels-Alder cyclization of Schiff bases with 3,4-dihydro-2H-pyrane(DHP)

To a solution of Schiff base (2.85 mmol) in 4 mL CH_3CN, 3,4-dihydro-2*H*-pyrane (0.24 g, 2.85 mmol) and catalytic ammounts of iodine were added. The resulting mixture was irradiated in the microwave reactor for 30 min. at 80°C using max. 100 W power levels. Water (15 mL) was added to the reaction mixture and then extraction with CH_2Cl_2 (3×10 mL) was performed. The organic layer was dried over anhydrous sodium sulfate and then filtered. After solvent evaporation to dryness, the crude product was obtained and it was further purified by column chromatography (using silicagel support and eluent CH_2Cl_2:MeOH 80:1) to afford the cycloadducts.

5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (2)

Dark yellow oil; yield: 0.453 g, 60%; **^{1}H NMR** 300 MHz, $CDCl_3$: δ= 4.33 ppm (s,1H NH), 3.86 ppm (t, 1H H_2), 2.05 ppm (m, 1H, H_3), 4.57 ppm (d, 1H, J= 2.4 Hz H_{2p}), 1.65 ppm (m, 1H) H_{3a}, 6.86 ppm (1H, d, J=8.7 Hz) H_6, 6.66 ppm (1H, d, J=9.0 Hz) H_8, 7.19 ppm (1H, dd, J=9, 8.7 Hz) H_7, 7.34 ppm (3H, m) $H_{2',4',6'}$, 7.44 ppm (2H, m) $H_{1',3'}$, 3.65 ppm (1H, d, J=10 Hz, H_{2eq}), 3.47 (1H, dt, J=10, 2.1 Hz) H_{2ax}, 1.82 ppm (1H, q, J=11.2, 2.1 Hz) $H3_{ax}$, 1.40 ppm (1H, d, J=11.2 Hz) $H3_{eq}$, 1.70 ppm (1H, tt, J=11.2, 2.1 Hz) H_{4ax}, 1.55 ppm (1H, d, J=11.2 Hz) H_{4eq} **^{13}C NMR** *δ* 69.6 (C6), 24.5 (C5), 23.9 (C4), 48.5 (C3), 63.1 (C2), 119.7 (C4a), 128.1 (C5), 120.5 (C6), 126.3 (C7),110.3 (C8), 144.9 (C8a), 141 (C5'), 129.8 (C6',C4'), 128.6 (C1',C3'), 126.5 (C2') **MS** (EI 70eV) m/z= 206 (100%), 265 (35%) $M^{+\cdot}$

5-(10-methyl-10*H*phenothiazin-3-yl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (4)

Dark brown oil; yield: 0.570 g, 50%; **IR**: 3376, 2932, 1546, 1464, 1331, 1256, 1083 cm^{-1}; **^{1}H NMR** 300 MHz, $CDCl_3$: δ= 1.55 ppm (m, 1H,*J*=10.5 Hz, H_{5ax}) 1.65 ppm (m, 1H, *J*=10.6 Hz,H_{4ax}), 1.76 ppm (m, 1H,*J*=10.6 Hz) H_{4eq}, 1.90 ppm (m, 1H,*J*=10.5 Hz H_{5eq}), 2.59 ppm (m, 1H, *J*=2.5 Hz H_{3ax}), 3.40 ppm (s, 3H, N-CH_3), 3.65 ppm (d, 1H, *J*=11.5 Hz H_{6ax}), 3.89 ppm (d, 1H, *J*=2.5 Hz H_{2axp}); 4.10 ppm (d, 1H,*J*=11.5 Hz, H_{6eq}), 4.40 ppm (s, 1H NH), 6.84 ppm (d, 2H, *J*=8.5 Hz, $H_{1',9'}$), 6.97 ppm (t, 1H, *J*=7.5 Hz $H_{7'}$), 7.10 ppm (m, 4H $H_{5,6,7,8\ Q}$) 7.21 ppm (t, 1H, *J*=8.5 Hz), $H_{8'}$, 7.23 ppm (t, 1H, *J*=7.5 Hz $H_{6'}$), 8.03 ppm (s, 1H $H_{4'}$), 7.86 ppm (d, 1H, *J*=8.5 Hz, $H_{2'}$), 7.99 ppm (dd, 1H, *J*=7.0 Hz, H_7), **^{13}C NMR** δ 35.4 (CH_3), 113.7 (C1'), 114 (C9'), 127.2, 127.5, 126.5 (C2', C4', C6'), 122.5 (C7'), 128.3 (C8'), 125.3 (C4'a), 123.2 (C5'a), 61.9 (C2ch), 37.8 (C3ch), 69.6 (C2p), 119.7 (C4ach), 124.4 (C5ch), 126.7 (C6ch), 123.5 (C7ch), 114.5 (C8), 119.8 (C8a), 69.2 (C2p), 24.2 (C5), 69.05 (C6), 24.1 (C4), 38.7 (C3); **MS** (EI 70eV) m/z= 400 (100%) $M^{+\cdot}$

2-Ferrocenyl-3-(3-hydroxypropyl)quinoline (6)

Dark brown oil, 0.553 g, 58%; **IR:** 3139, 2998, 2935, 2832, 1721, 1291, 1038 cm^{-1}; **^{1}H NMR,** 300 MHz, CDCl3 *δ* = 2.01 (2H, t, *J*=7.2 Hz, -CH2-); 3.25 (2H, t, *J*=7.2 Hz, CH2), 3.84 (2H, t, *J*=7.2 Hz, CH2), 4.13 (5H, s, Cp ring, Fc), 4.43 (2H, s, H3',4'), 5.01 (2H, s, H2',5'), 7.46 (1H, d, *J*=7.5 Hz, H7), 7.63 (1H, d, *J*=7.5 Hz, H6), 7.72 (1H, d, *J*=7.5 Hz, H5), 7.89 (1H, s, H4), 8.05 (1H, d, *J*=8.4 Hz, H8). **^{13}C NMR** *δ* 158.7 (C2), 126.1 (C6), 146.9 (C8a), 133.7 (C3), 135.8 (C4), 129.2 (C4a), 129.0 (C8), 127.0 (C7), 127.2 (C5), 85.8 (C1'), 70.8 (C3',4'), 70.08 (C2',5'), 70.02 (Cp ring, Fc), 62.6 (C11), 34.2 (C10), 29.7 (C9); **MS** (EI 70eV) m/z= 371 (100%) $M^{+\cdot}$, 340 (20%).

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REFERENCES

1. A. Loupy (Ed), “Microwaves in Organic Chemistry”, Wiley-VCH Weinheim **2002**.
2. P. Lidstrom, J. P. Tierney (Eds), “Microwave-Assisted Organic Synthesis”, Blackwell, Oxford, **2004**.
3. P. Lidstrom, J. Tierney, B. Wathey and J. Westman, *Tetrahedron* **2001**, *57*, 9225.
4. C. O. Kappe, *Angew. Chem.*, **2004**, *43*, 6250.

5. W. Carruters “Cycloaddition reactions in Organic Synthesis” Pergamon Press Oxford **1990**.
6. F. Fringuelli, A. Taticchi, “The Diels Alder Reaction. Selected practical methods” Wiley, Chichester, UK **2002**.
7. A. Kumar, *Chem Rev.,* **2001**, *101*, 1.
8. G. Metha, R. Uma. *Acc. Chem. Res.*, **2000**, *33*, 278.
9. Li Yun-Cheng, Zhang Jun-Min, Dong Li-Ting, *Chinese Journal of Chemistry*, **2006**, *24*, 929.
10. G. Jin, J. Zhao, J. Han, S. Zhu, J. Zhang, *Tetrahedron,* **2010**, *66*, 913.
11. E. Gál, C. Cristea,L. Silaghi-Dumitrescu,T. Lovász, A. Csámpai, *Tetrahedron* **2010**, *66* (52), 9938.
12. E. Gál, L. Găină, T. Lovász, C. Cristea, L. Silaghi-Dumitrescu *Studia Universitatis Babeş-Bolyai, Chemia*, **2009**, *4,* 17.
13. L. Gaina, T. Lovasz, I.A. Silberg, C. Cristea, S. Udrea, *Heterocycl. Commun.*, **2001**, *7*(6), 549.
14. V.A. Skorodumov, S.V. Zhuravlev, *Russian J. Org. Chem.,* **1965**, *2*(1), 363.
15. C. Imrie, P. Engelbrecht, C. Loubser, C.W. McCleland, V.O. Nyamori, R. Bogardi, D.C. Levendis, N. Tolom, J.L. van Rooyen, N. Williams, *J. Organomet. Chem*. **2002**, *65*, 645.
16. S.K. Pal, A. Krishnan, P.K. Das, A.G. Samuelson, *J. Organomet. Chem.,* **2000**, *604*, 248-259.
17. C. Imrie, V.O. Nyamori, T.I.A. Gerber, *J. Organomet. Chem.,* **2004**, *689,* 1617.
18. G. Öztürk, A. Petit, C. Kouklovsky, *Synthetic Communications*, **2008**, *38*, 2707.