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Synthesis of New Pyrazole Derivatives via Diketonic Michael Adducts

Diketonik Michael Katılma Ürünlerinden Yeni Pirazol Bileşiklerinin Sentezi

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ABSTRACT

Pyrazole ring containing heterocyclic molecules have been known to show biological activity. In this work, by realizing the cyclization reactions of diketonic Michael adducts, synthesis of new pyrazole compounds was accomplished. Diketonic Michael adducts were prepared in low-good yields by the addition reactions of acetylacetone to nitrovinyl arene compounds in the presence of piperidine. Pyrazole compounds were obtained in high yields via the cyclization reactions of these molecules. Structures of all the addition and the cyclization products were clarified by using ^{1}H NMR, ^{13}C NMR and HRMS techniques.

Key Words

Nitrovinyl arene, Michael addition, cyclization, pyrazole.

ÖZ

Pirazol halkası içeren heterohalkalı bileşiklerin biyolojik aktivite gösterdikleri bilinmektedir. Bu çalışmada, diketonik Michael katılma ürünlerinin halkalaşma tepkimeleri çalışılarak yeni pirazol bileşiklerinin sentezi gerçekleştirilmiştir. Nitrovinil aren bileşikleri ile asetilaseton bileşiğinin piperidin varlığındaki katılma tepkimelerinden diketonik Michael katılması ürünleri orta-iyi verimlerle sentezlenmiştir. Katılma ürünlerinin hidrazin hidrat ile olan halkalaşma tepkimeleri ile pirazol bileşikleri yüksek verimlerle sentezlenmiştir. Elde edilen katılma ve halkalaşma ürünlerinin yapıları ^{1}H NMR, ^{13}C NMR ve HRMS teknikleri kullanılarak aydınlatılmıştır.

Anahtar Kelimeler

Nitrovinil aren, Michael katılması, halkalaşma, pirazol.

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INTRODUCTION

Among heterocyclic compounds, pyrazoles with two adjacent nitrogen atoms are considerably important members of five-membered ring systems due to their diverse biological activities. The presence of a pyrazole group on a structure allows them to be used in a variety of application areas such as medicine and agriculture. In particular, they are known to have anticancer, antiinflammatory, antibacterial, antidepressant, antifungal, antioxidant as well as antiviral activities [1-7]. These wide range biological properties have made pyrazoles target molecules in synthetic organic chemistry. A plenty of methods have been developed for the synthesis of pyrazole-derived heterocyclic systems. These methods include the reaction of 1,3-diketones with hydrazines [8,9], reaction of acetylenic ketones with hydrazine [10], reaction of methylenemalononitriles with hydrazines [11] or 1,3-dipolar cycloadditions [12,13].

Nitroalkene compounds are versatile class of molecules due to the strongly electron withdrawing nature of nitro group. Easy functionalization of nitro group to amines [14], ketones [15], or oximes [16] has made nitroalkenes one of the essential precursors in synthetic chemistry. They also have found use as building blocks in carbon-carbon bond formation reactions in accordance with having an electron deficient double bond [17,18].

Herein, we report the synthesis of pyrazole compounds having both the nitro and the aromatic/aliphatic cyclic units on its skeleton via the cyclization reactions of hydrazine hydrate and 1,3-diketonic Michael adducts. Synthesis of 1,3-diketonic molecules were carried out by Michael addition reactions of acetylacetone to heterocyclic nitroalkenes. Structures of all the addition and the cyclization products were identified by using ^{1}H NMR, ^{13}C NMR and HRMS techniques.

MATERIALS and METHODS

Chemicals and Instrument

All solvents and chemicals were purchased from Sigma Aldrich, Fisher Scientific or Acros Organics and used without further purification. Thin layer chromatography (TLC) was conducted on aluminium sheets coated with silica gel 60 F254 (Merck, Darmstadt, Germany), with visualisation by UV lamp (254 or 360 nm). Products were purified by silica gel flash column chromatography (0.05-0.63 mm 230-400 mesh ASTM, E.Merck). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) spectra were recorded on a Bruker 400, Ultra Shield high performance digital FT-NMR spectrometer. Data for ^{1}H NMR, ^{13}C NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, m = multiplet, dd = doublet of doublet, bs = broad singlet). Mass spectra were recorded on a Agilent 1200/6210 High Resolution Mass Time-of-Flight (TOF) LC/MS spectrometer. Nitrostyrene compounds were synthesized according to the literature procedures [19,20].

General method for the synthesis of Michael adducts (3a-e): Nitrostyrene **1a** (3.0 mmol, 0.564 g) and acetylacetone (3.3 mmol, 0.330 g) were combined in toluene (5 mL). Piperidine (0.1 mmol, 0.010 mL) was then added into this solution. The reaction was stirred at room temperature for 24h. After completion of the reaction (followed by TLC), reaction mixture was treated with 0.1 M HCl (5 mL), extracted with ethyl acetate, dried over $MgSO_4$ and the solvent was evaporated to dryness. The crude product was purified using column chromatography with EtOAc:hexanes (1:5).

3-(1-(1H-indol-3-yl)-2-nitroethyl)pentane-2,4-dione (3a): Yield: 26%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm= 1.95 (s, 3H, C***H***$_3$), 2.32 (s, 3H, C***H***$_3$), 4.59 (s, 2H, C***H***$_2$), 4.65 – 4.78 (m, 2H, C***H***, C***H***), 7.02 (d, *J*= 2.5 Hz, 1H, C***H***$_{indol}$), 7.15-7.25 (m, 2H, C***H***$_{phenyl}$), 7.38 (d, *J*= 8.0 Hz, 1H, C***H***$_{phenyl}$), 7.63 (d, *J*= 7.8 Hz, 1H, C***H***$_{phenyl}$), 8.21 (bs, 1H, N***H***); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm= 28.3, 30.6, 34.4, 70.3, 77.8, 110.4, 111.8, 117.9, 120.5, 123.0, 123.2, 125.6, 136.1, 201.8, 202.8. HRMS (ESI-TOF) m/z $[M+H]^+$ for $C_{15}H_{17}N_2O_4$ calcd: 289.1183, found: 289.1170.

3-(2-nitro-1-(thiophen-2-yl)ethyl)pentane-2,4-dione (3b): Yield: 30%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm= 2.08 (s, 3H, C***H***$_3$), 2.30 (s, 3H, C***H***$_3$), 4.41 (d, *J*= 10.1 Hz, 1H, C***H***), 4.52 – 4.57 (m, 1H, C***H***), 4.65 – 4.67 (m, 2H, C***H***$_2$), 6.89 – 6.95 (m, 2H, C***H***$_{thiophene}$), 7.24 (d, *J*= 4.9 Hz, 1H, C***H***$_{thiophene}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm= 29.6, 30.6, 38.2, 71.0, 78.5, 125.8, 127.4, 127.4, 138.4, 200.7, 201.5. HRMS (ESI-TOF) m/z $[M+Na]^+$ for $C_{11}H_{13}NO_4SNa$ calcd: 278.0457, found: 278.0467.

3-(1-(furan-2-yl)-2-nitroethyl)pentane-2,4-dione (3c): Yield: 70%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm= 2.09 (s, 3H, C***H***$_3$), 2.29 (s, 3H, C***H***$_3$), 4.33 – 4.41 (m, 2H, C***H***, C***H***), 4.67 (d, *J*= 5.4 Hz, 2H, C***H***$_2$), 6.18 (d, *J*= 3.2 Hz, 1H, C***H***$_{furan}$),

6.30 – 6.31 (m, 1H, C*H*$_{furan}$), 7.36 (s, 1H, C*H*$_{furan}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm= 29.3, 30.7, 36.6, 67.9, 75.8, 108.9, 110.8, 142.9, 149.4, 200.8, 201.5. HRMS (ESI-TOF) m/z $[M+Na]^+$ for $C_{11}H_{13}NO_5Na$ calcd: 262.0686, found: 262.0699.

3-(2-nitro-1-(p-tolyl)ethyl)pentane-2,4-dione (3d): Yield: 28%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm= 1.96 (s, 3H, C*H*$_3$), 2.31 (s, 3H, C*H*$_3$), 2.32 (s, 3H, C*H*$_3$), 4.20 – 4.25 (m, 1H, C*H*), 4.38 (d, *J*= 10.9 Hz, 1H, C*H*), 4.58 – 4.63 (m, 2H, C*H*$_2$), 7.08 (d, *J*= 7.6 Hz, 2H, C*H*$_{phenyl}$), 7.15 (d, *J*= 7.6 Hz, 2H, C*H*$_{phenyl}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm= 21.1, 29.5, 30.4, 42.5, 70.8, 78.4, 127.8, 130.0, 132.8, 138.4, 201.2, 201.9. HRMS (ESI-TOF) m/z $[M+Na]^+$ for $C_{14}H_{17}NO_4Na$ calcd: 286.1055, found: 286.1068.

General method for the synthesis of pyrazole derivatives (4a-c): Michael adduct **3a** (0.20 mmol, 0.0576 g) and hydrazine hydrate (0.4 mmol, 0.020 mL) were combined in ethanol (1 mL). The reaction was stirred at room temperature for 2h. After completion of the reaction (followed by TLC), reaction solvent was evaporated to dryness. The crude product was purified using column chromatography with EtOAc:hexanes (1:1).

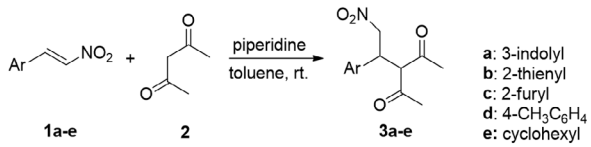
3-(1-(3,5-dimethyl-1H-pyrazol-4-yl)-2-nitroethyl)-1H-indole (4a): Yield: 85%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm= 2.18 (s, 6H, C*H*$_3$), 4.80 – 4.86 (m, 1H, C*H*), 5.08 – 5.13 (m, 2H, C*H*$_2$) 6.91 (s, 1H, C*H*$_{indole}$), 7.05 – 7.09 (m, 1H, C*H*$_{phenyl}$), 7.18 – 7.21 (m, 1H, C*H*$_{phenyl}$), 7.34 – 7.37 (m, 2H, C*H*$_{phenyl}$), 8.00 (bs, 1H, N*H*), 8.35 (bs, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm= 11.4, 31.8, 77.9, 111.5, 112.4, 113.2, 118.7, 119.9, 121.3, 122.7, 126.0, 136.6, 142.6. HRMS (ESI-TOF) m/z $[M+H]^+$ for $C_{15}H_{17}N_4O_2$ calcd: 285.1346, found: 285.1364.

3,5-dimethyl-4-(2-nitro-1-(thiophen-2-yl)ethyl)-1H-pyrazole (4b): Yield: 75%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm= 2.22 (s, 6H, C*H*$_3$), 4.83 – 4.89 (m, 1H, C*H*), 5.02 – 5.09 (m, 2H, C*H*$_2$), 6.81 (s, 1H, C*H*$_{thiophene}$), 6.92 – 6.95 (m, 1H, C*H*$_{thiophene}$), 7.21 (d, *J*= 4.9 Hz, 1H, C*H*$_{thiophene}$), 7.89 (bs, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm= 11.5, 35.0, 78.4, 112.7, 124.2, 125.0, 127.0, 142.6, 142.8. HRMS (ESI-TOF) m/z $[M+H]^+$ for $C_{11}H_{14}N_3O_2S$ calcd: 252.0801, found: 252.0809.

4-(1-(furan-2-yl)-2-nitroethyl)-3,5-dimethyl-1H-pyrazole (4c): Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm= 2.21 (s, 6H, C*H*$_3$), 4.74 (dd, *J*= 12.3, 9.0 Hz, 1*H*, C*H*), 4.88 – 4.92 (m, 1H, C*H*), 5.04 (dd, *J*= 12.3, 7.0 Hz, 1H, C*H*), 6.02 (d, *J*= 2.8 Hz, 1H, C*H*$_{furan}$), 6.31 (s, 1H, C*H*$_{furan}$), 7.36 (s, 1H, C*H*$_{furan}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm= 11.4, 33.8, 76.5, 107.0, 110.5, 142.2, 142.9, 151.6. HRMS (ESI-TOF) m/z $[M+H]^+$ for $C_{11}H_{14}N_3O_3$ calcd: 236.1030, found: 236.1040.

3,5-dimethyl-4-(2-nitro-1-(p-tolyl)ethyl)-1H-pyrazole (4d): Yield: 78%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm= 2.11 (s, 6H, C*H*$_3$), 2.24 (s, 3H, C*H*$_3$), 4.75 – 4.81 (m, 2H, C*H*$_2$), 4.91 – 4.98 (m, 1H, C*H*), 6.97 (d, *J*= 7.9 Hz, 2H, C*H*$_{phenyl}$), 7.04 (d, *J*= 7.8 Hz, 2H, C*H*$_{phenyl}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm= 21.1, 29.5, 30.4, 42.5, 70.8, 78.4, 127.8, 130.0, 132.8, 138.4, 201.2, 201.9. HRMS (ESI-TOF) m/z $[M+H]^+$ for $C_{14}H_{18}N_3O_2$ calcd: 260.1399, found: 260.1407.

Table 1. Synthesis of Michael adducts.[a,b]

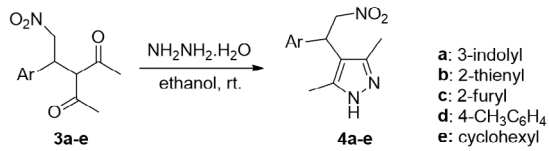


1a-e 2 3a-e

Entry	Compound	Aryl	Yield (%)[b]
1	**3a**	3-indolyl	26
2	**3b**	2-thienyl	30
3	**3c**	2-furyl	70
4	**3d**	4-$CH_3C_6H_4$	28
5	**3e**	cyclohexyl	-

[a]Styrene:acetylacetone ratio (1:1.1), piperidine (10%mol). [b]Isolated yields after flash column chromatography.

Table 2. Synthesis of pyrazole compounds.[a]



Entry	Compound	Aryl	Yield (%)[b]
1	**4a**	3-indolyl	85
2	**4b**	2-thienyl	75
3	**4c**	2-furyl	99
4	**4d**	4-$CH_3C_6H_4$	87
5	**4e**	cyclohexyl	-

[a]Adduct: hydrazine hydrate ratio (1:2). [b]Isolated yields after flash column chromatography.

RESULTS and DISCUSSION

As the bioactivity of pyrazole compounds is important for synthetic organic chemistry, in this work, we focused on the synthesis of new pyrazole derivatives having nitro and aromatic/aliphatic cyclic groups on the structure. 3-Indolyl, 2-thienyl, 2-furyl, 4-methylphenyl and cyclohexyl groups were chosen as the cyclic groups on nitrostyrene compounds. Firstly, synthesis of 1,3-diketonic Michael adducts **3a-e** were studied by the addition reactions of acetylacetone (**2**) to nitrostyrenes **1a-e** in the presence of piperidine as catalyst. The Michael adducts **3a-d** were successfully obtained in low to good yields (26-70%) (Table 1). Adducts **3b-d** have not been described in literature and synthesized for the first time in this study. However, the desired cyclohexyl substituted adduct **3e** could not be obtained.

With the synthesized Michael adducts **3a-d** in hand, these compounds were subjected to cyclization with hydrazine hydrate. Cyclization reactions have produced the targeted pyrazole rings **4a-d** in good-excellent yields (Table 2). Pyrazoles **4b-d** were synthesized for the first time in this study and have not been described in literature yet. Structures of the pyrazole compounds have been identified by spectroscopic methods.

The ^{1}H NMR spectrum of pyrazole **4b** given in Figure 1 is in agreement with the structure. Characteristic NH proton signal of pyrazole ring was observed at 7.98 ppm and the aromatic thiophenyl CH signals were seen in between 6.81–7.21 ppm range. Aliphatic CH_2 and CH signals were observed as multiplets respectively in the 5.02–5.09 ppm and 4.83–4.90 ppm range. The CH_3 protons gave a singlet at 2.22 ppm. The ^{13}C NMR spectrum of **4b** is also in agreement with the structure (Figure 2). Characteristic pyrazole carbon signals were seen at 112.7 and 142.6 ppm. Aromatic thiophene signals were observed in 120-145 ppm range and aliphatic CH_2, CH and CH_3 carbon signals have come at 78.4, 34.9 and 11.5 ppm, respectively.

CONCLUSION

In conclusion, we have successfully synthesized the pyrazole compounds **4a-d** having both the aliphatic nitro group and aromatic rings on the skeleton via the cyclization reactions of Michael adducts with hydrazine hydrate. Novel pyrazoles **4b-d** were synthesized for the first time and obtained in good to excellent yields (75-99%). For the synthesis of pyrazole compounds, Michael adducts **3a-d** were prepared at first. Structures of all the addition and the cyclization products were identified by using ^{1}H NMR, ^{13}C NMR and HRMS techniques.

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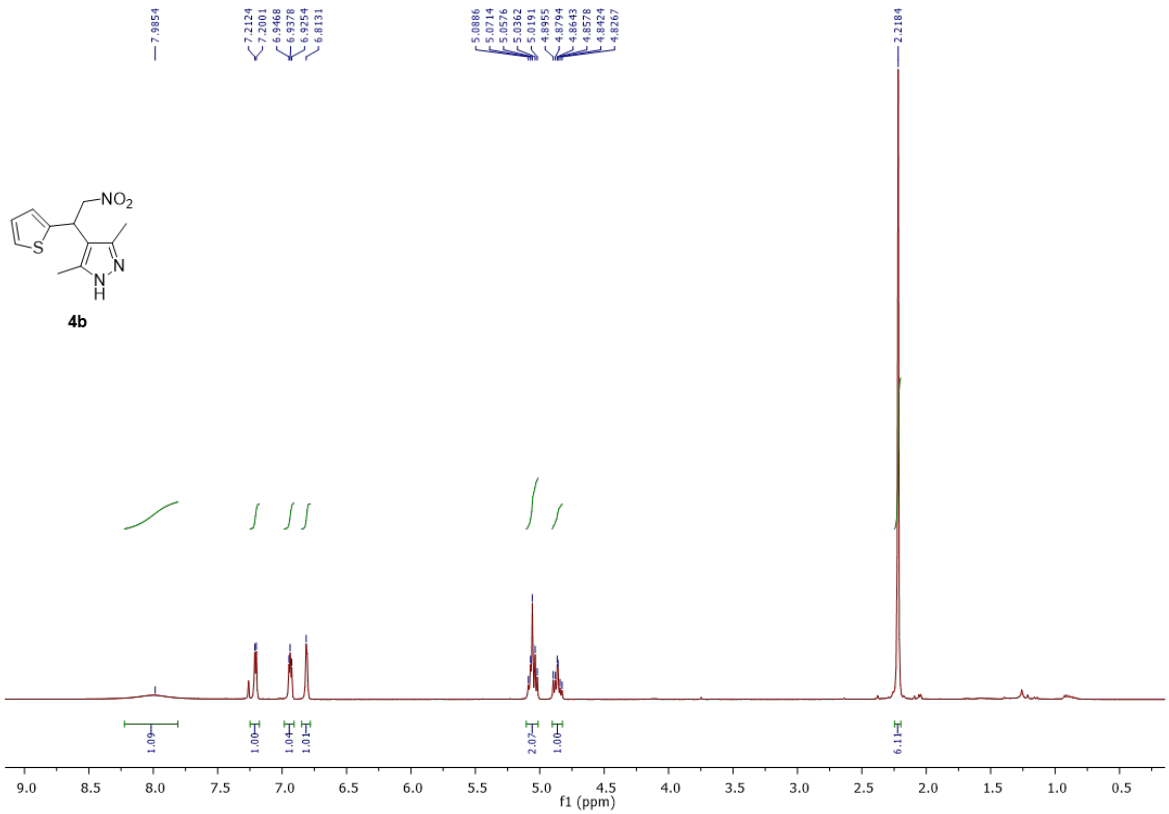

Figure 1. ^{1}H NMR spectrum of pyrazole **4b.**

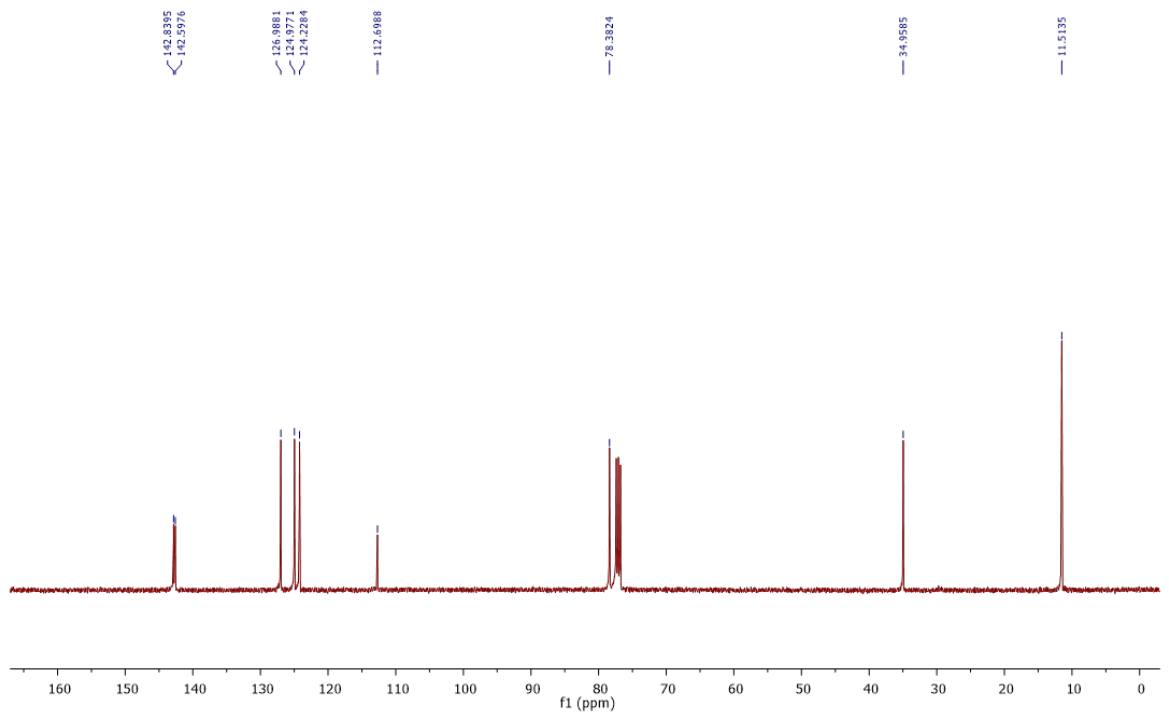

Figure 2. ^{13}C NMR spectrum of pyrazole **4b**

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