Karaelmas Fen ve Mühendislik Dergisi
Journal home page: http://fbd.beun.edu.tr

Research Article
Received / Geliş tarihi : 25.11.2016
Accepted / Kabul tarihi : 09.03.2017

Synthesis of Some New Pyrazoles

Bazı Yeni Pirazollerin Sentezlenmesi

Adnan Çetin

Muş Alparslan Üniversitesi, Eğitim Fakültesi, Matematik ve Fen Bilimleri Bölümü, Muş, Türkiye

Abstract

In this paper, firstly, 2-(2-(4-bromophenyl)hydrazino)-1-(2-(hydroxyphenyl)-3-phenylpropane-1,3-dione (1), which is a starting material, was synthesized. Then, the new substituted pyrazoles derivatives (2a-e) were obtained via the reaction-starting material and various hydrazines. The structures of newly-synthesized compounds were determined by spectroscopic methods.

Keywords: Heterocyclic compounds, Hydrazine, 1,3-diketone, Pyrazoline

Öz

Bu makalede; ilk olarak, başlangıç materyali olan 2-(2-(4-bromofenil)hidrazin)-1-(2-(hidroksifenil)-3-fenilpropan-1,3-dion (1) sentezlendi. Sonra, başlangıç materyali ve çeşitli hidrazinlerin reaksiyonu vasıtasıyla yeni substitue pirazol türevleri (2a-e) elde edildi. Yeni sentezlenen bileşiklerin yapıları spektroskopik yöntemler tarafından belirlendi.

Anahtar Kelimeler: Heterosiklik bileşikler, Hidrazin, 1,3-diketon, Pirazolin

1. Introduction

Pyrazole is a simple aromatic ring and an organic compound of the heterocyclic series. It is characterized by a five-unit ring structure which comprises of adjacent two nitrogen atoms and three carbon atoms. Since the beginning of this century, pyrazole, which is an important class of heterocyclic compounds, has increasingly received attention in the literature because of wide-spread use in biological activities (Makriyannis et al. 1999, Bondock et al. 2010). Pyrazole and their derivatives are very rare in natural products (Toure and Hall, 2009). Generally, substituted pyrazoles have been obtained with common synthetic applications (Bekhit and Abdel-Aziem 2004, Cetin 2016, Cetin and Bildirici 2016). The pyrazole and its derivatives are used in the industrial applications such as agricultural and medicinal drugs (Terrett et al. 1996, Talley et al. 1997). Hence, they are popular targets for synthetic chemists. 1,3-diketones and hydrazines are widely used for the preparation of substituted pyrazole compounds (Heller and Natarajan, 2006; Fustero et al. 2008). Among the available samples including synthetics, Deracoxib is used as a veterinary medicine with its anti-inflammatory effects (McCann et al. 2004). Fezolamine is used as an antidepressant drug (Bailey et al. 1985). Fipronil is used as insecticide (Hainzl and Casida 1996) and Celecoxib is used in the treatment of inflammation (Penning et al. 1997), as shown in Figure 1.

Classic methods for the synthesis of pyrazoles have involved a suitable cyclocondensation and various alkyl or aryl substituents including the 1,3-dicarbonyl compounds, and derivatives and hydrazines as nucleophile in the medium. In the present study, a new type of substituted pyrazole was synthesized and these compounds were characterized by spectroscopic methods such as IR, NMR and Elemental analysis.

2. Materials and Method

2.1. General

All of the solvents and chemical reactive were purchased from Sigma Aldrich. These materials were used without purification. Melting points were identified on an Electro thermal IA9000 instrument. IR spectra were recorded on a Shimadzu instrument. NMR spectra were recorded on Bruker NMR spectrometers. $CDCl_3$ solvent was performed

*Corresponding Author: a.cetin@alparslan.edu.tr

Adnan Çetin orcid.org/0000-0001-6487-9489

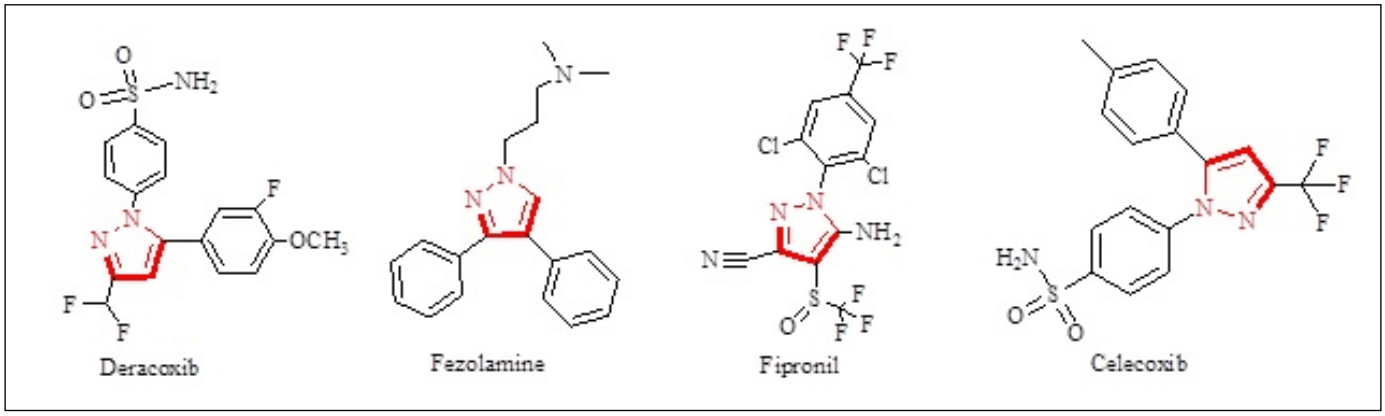


Figure 1. Some of the important uses of synthetic pyrazole.

for NMR spectra. Chemical shifts δ were expressed as ppm. The elemental composition was determined using a LECO TruSpec CHN Elemental Analyzer.

2.2.2-(2-(4-bromophenyl)hydrazino)-1-(2-(hydroxyphenyl)-3-phenylpropane-1,3-dione

4-bromo aniline (0.043 g, 0,25 mmol) was dissolved in conc. sulfuric acid (0,25 mmol) and $NaNO_2$ (0.05 g, 0,75 mmol) was dissolved in 5 mL water. These two solutions were kept in ice bath for 10 minutes below 0 °C and then $NaNO_2$ solution was added dropwise to the solution of 4-bromo aniline over a period of 30 minutes with constant stirring at 0 °C. The diazonium salt of 4-bromo aniline generated was immediately used for coupling reaction with 1-(2-(hydroxyphenyl)-3-phenylpropane-1,3-dione (0,06 g, 0,25 mmol). The 1-(2-(hydroxyphenyl)-3-phenylpropane-1,3-dione was taken in 2,5 mL methanol. The solution was added dropwise to the solution of diazonnium salt over a period 30 minutes when it was continuous stirring below 0 °C. The reaction was allowed to cool to ambient temperature. The mixture was stirred 10 hours. The product was washed with water, filtered, dried and it was crystallized using acetone (0.08 g, 81%); mp 142-144 °C, ^{1}H-NMR (400 MHz, $CDCl_3$) d (ppm): 8.5 (s, 1H, -NH), 8.2–6.4 (m, 13H, Ar-H), 4.2 (br, 1H, -OH). ^{13}C-NMR (100 MHz, $CDCl_3$) d (ppm): 196.1, 192.5, 154.2, 150.6, 146.1, 141.3, 139.4, 135.9, 133.6, 132.5, 131.6, 130.3, 129.6, 124.7, 123.1, 111.2. IR (ν, cm^{-1}): 3456, 3215, 3060, 2921, 1695, 1703, 1596, 1498, 1436, 1315. Anal. calcd. for $C_{21}H_{15}BrN_2O_3$ (423.30): C, 59.59; H, 3.57; N, 6.62. Found: C, 59.65; H, 3.53; N, 6.60.

2.3.General Procedure for Synthesis New Substituted Pyrazole Derivatives

The starting material 1 (0.16 g, 0,25 mmol) dissolved in ethanol solution (5 ml) and an equivalent of sulfuric acide (0,25 mmol) were put to in a 50 ml flask. The mixture was added drop wise appropriate hidrazines (0,25 mmol) (methyl hydrazine, phenyl hydrazine, 2,5-dimethyl phenyl hydrazine, 3,4-dimethyl phenyl hydrazine and 4-bromophenylhydrazine, respectively) in ethanol (10 ml). The mixture was refluxed in ethanol solution for 6 hours. The reaction mixture was allowed to cool to ambient temperature. The obtained product was filtered, dried and it was crystallized from ethanol.

2.4.1-(4-bromophenyl)-2-(1-methyl-3-phenol,5-phenyl-1H-pyrazol-4-yl)diazene

1 and methyl hydrazine were employed. **2a** was synthesized according to general procedure. (0.12 g, 72%); mp 181-183 °C, ^{1}H-NMR (400 MHz, $CDCl_3$) d (ppm): 8.2–6.5 (m, 13H, Ar-H), 3.9 (s, 1H, -OH), 2.5 (s, 3H, $-CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) d (ppm): 151.6, 145.2, 141.0, 139.2, 135.8, 131.8, 130.1, 129.1, 128.1, 122.3, 109.1 and 29.1. IR (ν, cm^{-1}): 3368, 3065, 2932, 1607, 1500, 1436, 1321. Anal. calcd. for $C_{22}H_{17}BrN_4O$ (433.35): C, 60.98; H, 3.95; N, 12.93. Found: C, 60.95; H, 4.01; N, 12.99.

2.5.1-(4-bromophenyl)-2-(1,5-diphenyl-3-phenol)-1H-pyrazol-4-yl)diazene

1 and phenyl hydrazine were employed. **2b** was synthesized according to general procedure. (0.16 g, 75%); mp 188-201 °C, ^{1}H-NMR (400 MHz, $CDCl_3$) d (ppm): 8.1-6.3 (m, 18H, Ar-H), 4.1 (s, 1H, -OH). ^{13}C-NMR (100 MHz, $CDCl_3$) d (ppm): 153.4, 149.0, 143.3, 140.7, 136.3, 135.2, 131.6, 130.1, 129.8, 129.1, 128.4, 127.3, 126.8, 124.8, 122.1 and 110.3. IR (ν, cm^{-1}): 3394, 3060, 2945, 1611, 1498, 1442, 1315. Anal. calcd. for $C_{22}H_{17}BrN_4O$ (495.37): C, 65.46; H, 3.87; N, 11.31. Found: C, 65.51; H, 3.92; N, 11.38.

2.6.1-(4-bromophenyl)-2-(2,5-dimethylphenyl-3-phenol)-1H-pyrazol-4-yl)diazene

1 and 2,5-dimethyl phenyl hydrazine were employed. **2c** was synthesized according to general procedure. (0.13 g, 68%); mp 184-186 °C, ^{1}H-NMR (400 MHz, $CDCl_3$) d (ppm): 8.3-6.4 (m, 16H, Ar-H), 4.0 (s, 1H, -OH), 2.0 (s, 3H, -CH_3), 1.7 (s, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) d (ppm): 153.7, 150.1, 145.4, 138.0, 137.3, 135.1, 134.0, 133.8, 132.9, 131.5, 130.6, 129.3, 128.4, 127.7, 126.4, 122.1, 109.5, 22.3, 16.1. IR (ν, cm^{-1}): 3413, 3065, 2934, 1607, 1499, 1441, 1318. Anal. calcd. for $C_{22}H_{17}BrN_4O$ (523.42): C, 66.54; H, 4.43; N, 10.70. Found: C, 66.59; H, 4.44; N, 10.65.

2.7.1-(4-bromophenyl)-2-(3,4-dimethylphenyl-3-phenol)-1H-pyrazol-4-yl)diazene

1 and 3,4-dimethyl phenyl hydrazine were employed. **2d** was synthesized according to general procedure. (0.14 g, 70%); mp 187-189 °C, ^{1}H-NMR (400 MHz, $CDCl_3$) d (ppm): 8.2-6.6 (m, 16H, Ar-H), 3.9 (s, 1H, -OH), 2.1 (s, 3H, -CH_3), 1.6 (s, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) d (ppm): 152.1, 149.6, 144.2, 142.0, 138.1, 137.9, 136.3, 135.2, 134.4, 133.9, 131.2, 130.3, 129.6, 128.5, 127.1, 122.3, 121.6, 109.3, 20.1, 15.6. IR (ν, cm^{-1}): 3385, 3064, 2972, 1610, 1498, 1442, 1321. Anal. calcd. for $C_{29}H_{23}BrN_4O$ (523.41): C, 66.54; H, 4.43; N, 10.70. Found: C, 66.61; H, 4.42; N, 10.65.

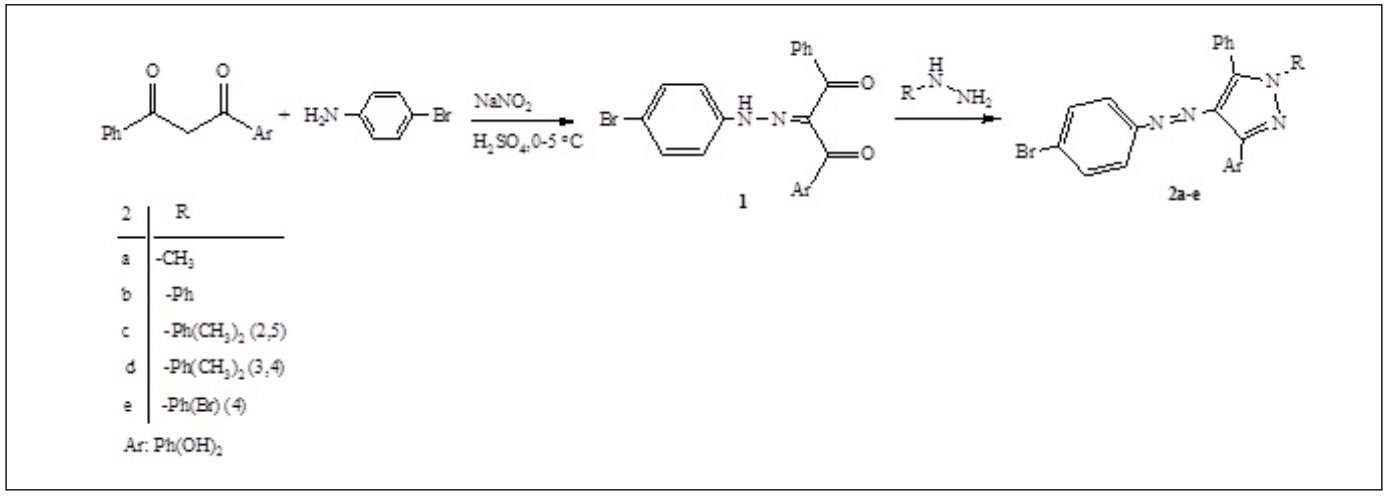
2.8.1-(4-bromophenyl)-2-(4-bromophenyl-3-phenol)-1H-pyrazol-4-yl)diazene

1 and 4-bromo phenyl hydrazine were employed. **2e** was synthesized according to general procedure. (0.12 g, 60%); mp 205-208 °C, ^{1}H-NMR (400 MHz, $CDCl_3$) d (ppm): 8.3-6.7 (m, 17H, Ar-H), 4.2 (s, 1H, -OH). ^{13}C-NMR (100 MHz, $CDCl_3$) d (ppm): 154.3, 150.1, 146.5, 141.3, 140.5, 137.2, 135.0, 133.8, 131.3, 130.0, 129.4, 129.0, 128.6, 127.7, 126.9, 123.1, 122.4 and 111.4. IR (ν, cm^{-1}): 3441, 3080, 2985, 1612, 1496, 1442, 1319. Anal. calcd. for $C_{27}H_{18}Br_2N_4O$ (574.30): C, 56.47; H, 3.16; N, 9.76. Found: C, 56.52; H, 3.19; N, 9.71.

3. Results and Discussion

The aim of this study is to prepare substituted pyrazole derivatives because they have wide applications. To illustrate, these compounds are used both pharmaceuticals and in the agricultural industry (Hernández-Vázquez et al. 2016, Zahaoai et al. 2015). So, syntheses of methods are important take attention for chemist and pharmacist. In this present work, the decomposition temperatures of all the synthesized compounds **1** and **2a-e** are ranging from between 142-144 and 181-208 °C, respectively. These compounds were checked with the help of a digital melting point apparatus and were uncorrected. The structure of the synthesized compounds (**1** and **2a-e**) were determined by using various spectra techniques such as IR, NMR and elemental analysis. The various substituted pyrazoles were synthesized via reaction cyclocondensation of compound including 1,3-diketone and some hydrazines. Initially, 2-(2-(4-bromophenyl)hydrazino)-1-(2-(hydroxyphenyl)-3-phenylpropane-1,3-dione was obtained with coupling reaction 1-(2-(hydroxyphenyl)-3-phenylpropane-1,3-dione and 4-bromoaniline with sodium nitrite solution on the ice bath in figure 2.

The hydrazono compound 1, which was diazotized and coupled with starting material, showed IR bands at



2	R
a	-CH_3
b	-Ph
c	-Ph$(CH_3)_2$ (2,5)
d	-Ph$(CH_3)_2$ (3,4)
e	-Ph(Br) (4)

Figure 2. Synthesis of **1** and **2a-e.**

appropriate frequencies as the other resemble compounds. It showed characteristic band 3215 cm^{-1} due to the presence hydrazono (–NH) groups. Hydrazono (1) also showed that characteristic bands 1685-1700 cm^{-1} due to the presence of the C=O groups. Characteristic^{1}H NMR spectrum was investigated; -NH peak of hydrozono group was observed at 8.5 ppm. After synthesized compound **1**, the substituted pyrazole derivatives (2a-e) were prepared with in the usual way (see experimental). IR spectra for all the synthesized substitued pyrazoles showed important IR bands at appropriate frequencies as expected. When IR spectrums of the substituted pyrazoles are investigated, One of the significant signals to be expected that disappeared carbonyls (-C=O) groups to related hydrazono compound after formation of the pyrazole ring. Also, the band of C=N stretching vibration of pyrazole rings appeared around between 1498 and 1442 cm^{-1} in the IR spectra. Characteristic ^{13}C NMR of the **2a-e** signals aromatic carbons of the pyrazole groups were observed at ~153.0 (C-3), ~109.0 (C-4) and ~145.0 (C-5) ppm, respectively. Besides, When the ^{1}H NMR spectra was investigated, Characteristic ^{1}H NMR signal of the **2a-e** the multiplied signals (-CH) protons of aromatic ring in the region between 8.4 and 6.3 ppm. Hydroxyl (-OH) group of phenol ring system appeared as a singlet signals between d 4.2 and 3.9 ppm. Finally, the new synthesized compounds have been agreement with our previous findings (Cetin and Bildirici 2016).

4. Conclusion

In summary, this article has shown more than one important rings (substitued group) and a plenty of examples have been provided for synthesis of pyrazoles. I think, this guidance document may be used for most research studies and researches.

5. Acknowledgement

The author is indebted to the Scientific Research Projects Chairmanship (BAP) of Muş Alparslan University for its financial support of this study. Project Number: MŞÜ15-EMF-G04.

5. References

Bailey, DM., Hansen, PE., Hlavac, AG., Baizman, ER., Pearl, J., DeFelice, AF., Feigenson, ME. 1985. 3, 4-Diphenyl-1H-pyrazole-1-propanamine antidepressants. *J Med. Chem.*, 28: 256-260.

Bekhit, AA., Abdel-Aziem, T. 2004. Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory-antimicrobial agents. *Bioorg. Med. Chem.*, 12: 1935-1945.

Bondock, S., Fadaly, W., Metwally, MA. 2010. Synthesis and antimicrobial activity of some new thiazole, thiophene and pyrazole derivatives containing benzothiazole moiety. *Euro. J. Med. Chem.*, 45: 3692-3701.

Cetin, A. 2016. Synthesis of Pyrazoles via Electrophilic Cyclization of Alkynes Containing Thiophene. *Lett. Org. Chem.*, 13: 310-315.

Çetin, A., Bildirici, İ. 2016. A study on synthesis and antimicrobial activity of 4-acyl-pyrazoles. *J.Saud. Chem. Soc*,.

Du, S., Tian, Z., Yang, D., Li, X., Li, H., Jia, C., Qin, Z. 2015. Synthesis, Antifungal Activity and Structure-Activity Relationships of Novel 3-(Difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic Acid Amides. *Molecules*, 20: 8395-8408.

Fustero, S., Román, R., Sanz-Cervera, J. F., Simón-Fuentes, A., Cunat, A. C., Villanova, S., Murguia, M. 2008. Improved regioselectivity in pyrazole formation through the use of fluorinated alcohols as solvents: synthesis and biological activity of fluorinated tebufenpyrad analogs. *J. Org. Chem.*, 73: 3523-3529.

Hainzl, D., Casida, JE. 1996. Fipronil insecticide: novel photochemical desulfinylation with retention of neurotoxicity. *Proc Natl Acad Sci.*, 93: 12764-12767.

Heller, S. T., Natarajan, SR. 2006. 1, 3-Diketones from acid chlorides and ketones: A rapid and general one-pot synthesis of pyrazoles. *Org. Let.*, 8: 2675-2678.

Hernández-Vázquez, E., Salgado-Barrera, S., Ramírez-Espinosa, JJ., Estrada-Soto, S., Hernández-Luis, F. 2016. Synthesis and molecular docking of N′-arylidene-5-(4-chlorophenyl)-1-(3, 4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carbohydrazides as novel hypoglycemic and antioxidant dual agents. *Bioorg. Med. Chem.*, 24: 2298-2306.

Lan, R., Liu, Q., Fan, P., Lin, S., Fernando, SR., McCallion, D., Makriyannis, A. 1999. Structure-activity relationships of pyrazole derivatives as cannabinoid receptor antagonists. *J. Med. Chem.*, 42: 769-776.

McCann, ME., Donald, R., Zhang, D., Brideau, C., Black, WC., Hanson, PD., Hickey, GJ. 2004. In vitro effects and in vivo efficacy of a novel cyclooxygenase-2 inhibitor in dogs with experimentally induced synovitis. *Am. J Vet. Res.*, 65: 503-512.

Penning, TD., Talley, JJ., Bertenshaw, SR., Carter, JS., Collins, PW., Docter, S., Rogers, RS. 1997. Synthesis and biological evaluation of the 1, 5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1 H-pyrazol-1-yl] benzenesulfonamide (SC-58635, celecoxib). *J. Med. Chem.*, 40: 1347-1365.

Terrett, NK., Bell, AS., Brown, D., Ellis, P. 1996. Sildenafil (Viagra TM), a potent and selective inhibitor of type 5 cGMP phosphodiesterase with utility for the treatment of male erectile dysfunction. *Bioorg. Med. Chem.*, 6: 1819-1824.

Toure, BB., Hall, DG. 2009. Natural product synthesis using multicomponent reaction strategies. *Chem. Rev.*, 109: 4439-4486.