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Sübstitüe Pirazol Karboksilik Asit Sentezi, Siklizasyonu ve Nükleofilik Yer Değiştirme Reaksiyonları

İsrafil TOZLU[1], Volkan TAŞDEMİR[2], Aycan GÜNER ÇELİK[1], Hasan GENÇ[1*]

ÖZET: Substitüe pirazol karboksilik asit 2a-b türevleri 2,3-furandion 1 ve benzaldehit hidrazon 11a-b elde edildi. Pirazol karboksilik asit türevleri asit klorürlerine 3a-b dönüştürüldü. Pirazol karboksilik asitin asit klorürü çeşitli alkoller, üre ve aminlerle reaksiyonundan karşılık gelen ester 6a-b, üre 7a-b ve amid 4a-b, 8a-b türevleri elde edildi. Ek olarak, amid türevlerinden (SOCl2/DMF) ile su çekilerek karşılık gelen nitril türevleri 5 elde edildi. Ayrıca pirazol karboksilik asit türevlerinin hidrazin ile siklizasyon reaksiyonlarından 9 ve dekarboksilasyonu sonucu 10 türevlerinin eldesi reaksiyonları araştırılmıştır.

Anahtar Kelimeler: Siklizasyon, Dekarboksilasyon, Pirazol karboksilik asit, Pirazol.

Synthesis, Cyclization and Nucleophilic Substitution Reactions of Substituted Pyrazole Carboxylic Acid

ABSTRACT: Substituted pyrazole carboxylic acid 2a-b derivatives, obtained from 2,3-furandione 1 and benzaldehyde hydrazone 11a-b was converted via reactions of its acid chloride 3a-b. The corresponding ester 6a-b, urea 7a-b, and amide derivatives 4a-b, 8a-b were obtained from the reaction of the acyl chloride of the pyrazole carboxylic acid with various alcohols, urea, and amines. Additionally, the corresponding nitrile derivatives 5 were obtained by extracting water from the amide derivatives (SOCl2 / DMF). Furthermore, cyclization reactions of substituted pyrazole carboxylic acid derivatives using hydrazine were investigated 9 and reaction of 2b decarboxylation product 10.

Keywords: cyclization, decarboxylation, pyrazole carboxylic acid, pyrazole.

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INTRODUCTION

The reaction of 2,3-furandiones in apolar solvents with various hydrazines and hydrazones at 70–80 °C directly produces pyrazole-3-carboxylic acids (Şener et al., 2007). Through the investigation of advanced reactions, various derivatives of pyrazole skeletons, such as ester, amide, ureide, nitrile, pyrazolopyridazine, and their new derivatives, have been synthesized (Şener et al., 2002; Yıldırım et al., 2005; Şener et al., 2008; Korkusuz and Yıldırım, 2011). Today, pyrazole carboxylic acids and their derivatives have various bioactive properties such as antidiabetic, antiviral, antiobesity, anticancer, and antibacterial (Kamal et al., 2015), and their pyridazinone-containing compounds have cardiovascular, anti-inflammatory, and antiseptic properties (Frizzo et al., 2013), which have various applications in the agricultural and pharmaceuticals areas (Joule and Mills, 2010; Matyus, 1998; Tewari and Mishra, 2001).

Carbon-fluorine bonds are necessary pharmacophore units in medicine and are found in naturally occurring organic molecules (Harper et al., 2003) (Figure 1). Furthermore, most pharmaceutical and chemical products that possess fluorine atoms show biological activities and can be used in agriculture (Hagmann, 2008; Banks et al., 1994). In this work, we aimed to prove the reproducibility of the reaction of substituted pyrazole-3-carboxylic acid 2 a-b to produce some known and unknown pyrazole derivatives (Şener et al., 2004; Bildirici et al., 2009). This work is concerned with the synthesis and various reactions of heterocyclic compounds containing a new pyrazole ring (Akçamur et al., 1986; Shawali, 1977).

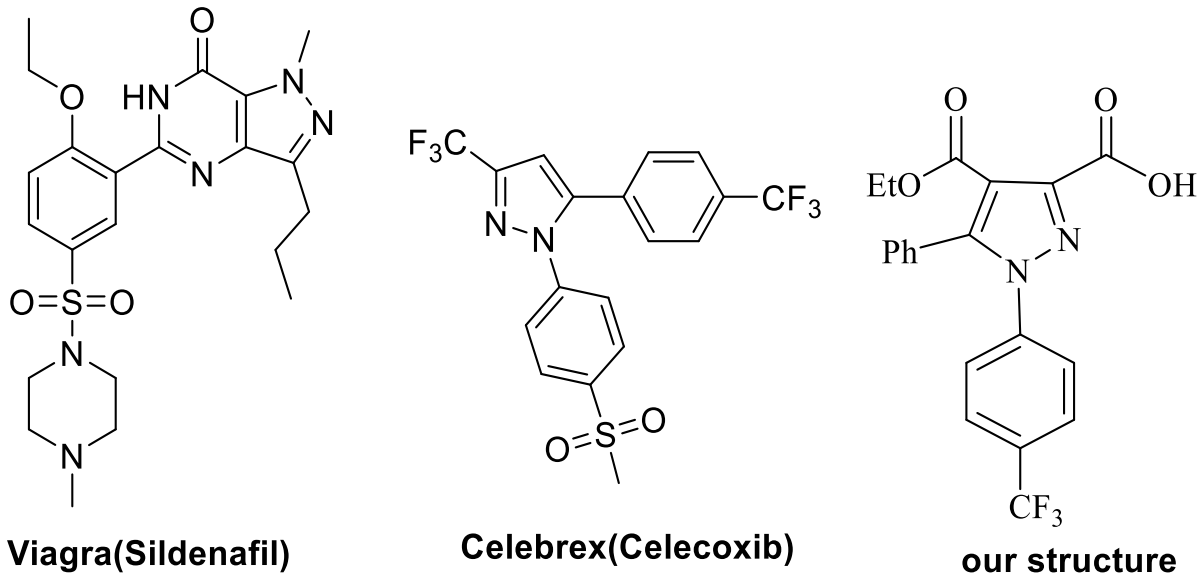


Figure 1. Essential medicines which include pyrazole and CF_3 groups and our structure

MATERIALS AND METHODS

Materials

All chemicals and solvents were commercially obtained from Sigma-Aldrich with analytical grade. The solutions were distilled and dried with suitable agents. The Electrothermal Gallenkamp apparatus is used to determine the melting points. FT-IR (Thermo Nicolet iS10) spectra were determined in ATR mode. Elemental compositions of samples were obtained using a Thermo Scıentific Flash 2000 machine. ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a 400 MHz Agilent using TMS (tetramethylsilane) as the internal standard. All experiments were followed by TLC (thin layer chromatography) using DC Alufolien Kieselgel 60 F254 and a Camag TLC lamp (254/366 nm).

Experimental procedure

General procedure for 4-(ethoxycarbonyl)-aryl-5-phenyl-1H-pyrazole-3-carboxylic acid 2a-b

I. It was refluxed in 10 mL of dry benzene by adding **1** (4 ethoxycarbonyl-5-phenyl-2,3-furandione) and **11a-b** (benzaldehyde-phenyl hydrazone) in a stochiometric ratio 1:1 ratio into a 50mL flask for 6 hours. TLC control defined the starting compounds finished and the product formed. Dry benzene was removed and treated with diethyl ether. The crude product was crystallized from toluene by filtration 0.218 g (60%) of 2. M.p.: 165 °C.

II. In a 25 mL beaker, **1** and **11a-b** were mixed in a stochiometric ratio with the help of a spatula in an oil bath at 110 °C for 40 minutes. The crude product was brought to room temperature and treated with diethyl ether. Then, the crude product was crystallized using toluene.

General procedure for 3a-b

I. Compound **2a** (1 mmol) was soluted in excess of $SOCl_2$ (2 mL). The reaction flask was stirred at room temperature for 2 days. The resulting product was crystallized using toluene to get compound **3a.**

II. PCl_5 was added to the solution of compound **2b** (1mmol) in CCl_4 (10 ml). The mixture in the reaction chamber was heated to 80°C and stirred. It was observed that the starting material was finished after 4 hours by TLC. After removing the solvent, the crude product was crystallized with cyclohexane to form compound **3b**

Ethyl 3-carbamoyl-aryl-5-phenyl-1H-pyrazole-4-carboxylate 4a-b

General Procedure

Aqueous ammonia (8 ml, 2 mmol) was added to a cold solution of acid chloride **3a-b** (1 mmol) in toluene at 0–5 °C, and the reaction flask was stirred for 24 h. The white precipitate was isolated by filtration and recrystallized using methanol.

Ethyl 3-cyano-1-(3,4-dimethylphenyl)-5-phenyl-1H-pyrazole-4-carboxylate 5

To a mixture of DMF (1.4 ml) and $SOCl_2$ (0.30 ml) was added a cold solution of acid amide **4a** (1 mmol) at 0–5 °C for 24 h. After determining by TLC that the starting material was finished in the reaction mixture, the mixture was poured into ice in a 100 mL beaker. The solid product formed was crystallized in toluene by filtration 0.165 g (75%) of **5.**

4-Ethyl 3-methyl-aryl-5-phenyl-1H-pyrazole-3,4-dicarboxylate 6a-b

General Procedure

A cold solution of pyrazole acid **2a-b** (0.364 g, 1 mmol) in 3 drops sulfuric acid was added 10 mL in methanol with stirring. The reaction mixture was refluxed for 3 hours. When the starting material was finished, the mixture was filtered after cooling to 5 °C. The crude product obtained was crystallized from the same alcohol.

Ethyl 1-(3,4-dimethylphenyl)-3-((methylcarbamoyl)carbamoyl)-5-phenyl-1H-pyrazole-4-carboxylate 7 a-b

General Procedure

Acid chloride **3a-b** and methyl urea were refluxed at a stereometric ratio of 1:2 in 10 mL xylene for 6 hours. When the starting material was finished, the reaction mixture was evaporated. The oily product obtained was treated with diethyl ether. It was crystallized in a mixture of methanol and ethanol(1:1).

Ethyl 3-(benzylcarbamoyl)-1-(3,4-dimethylphenyl)-5-phenyl-1H-pyrazole-4-carboxylate 8 a-b

Acid chloride **3a** (0,150 g, 1 mmol) and benzyl amine (0.22 g, 2 mmol) were refluxed in toluene for about 5 h. After evaporation, the oily residue was treated with dry diethylether and the crude product was crystallized using by toluene to furnish compound **8**

2-(3,4-dimethylphenyl)-4-ethoxy-6-(2-nitrophenyl)-3-phenyl-2,6-dihydro-7H-pyrazolo[3,4-d] pyridazin-7-one 9a

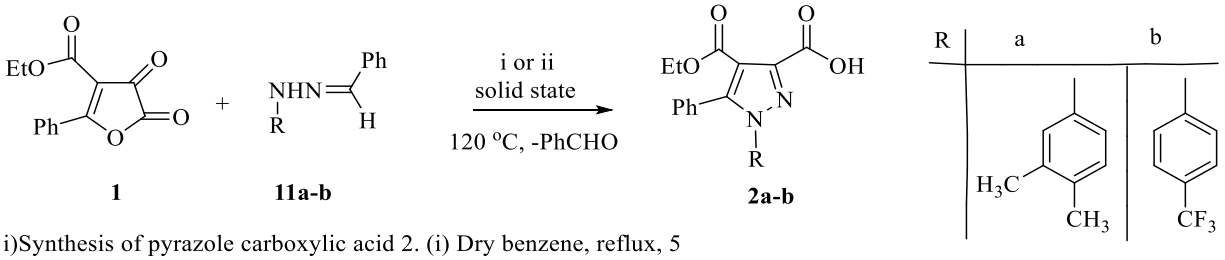
Compound **2a** (0.103 g, 1 mmol) and 2-nitrophenyl hydrazine (0.043 g, 1 mmol) were refluxed in 10 mL xylene for 5 h. Then, the white precipitated solid was filtered off and crystallized using xylene to form 0.108 g (80%) of compound **9**

5-phenyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole 10

The **2b** (0.404 g, 1 mmol) molecule was taken into a 25 mL beaker mixed with a spatula in the oil bath and heated for 45 minutes to 240 °C. The reaction was brought to room temperature and treated with cyclohexane.

RESULTS AND DISCUSSION

Adsorption In this investigation, 4-ethoxycarbonyl-5-phenyl-2,3-furandione **1** (Yıldırım et al., 1995; Kappe et al., 1995) and (E)-1-benzylidene-2-(3,4-dimethylphenyl) hydrazone **1a** were refluxed in dry benzene for 6 hours to produce 2 (Akçamur et al., 1997; Tewari and Mishra, 2001; Mahajan al., 1991). When the reaction was carried out at 110 °C for 50 minutes in an oil bath in the absence of any solvent, the same substance was obtained more quickly and in greater yield (70%; Figüre 2).



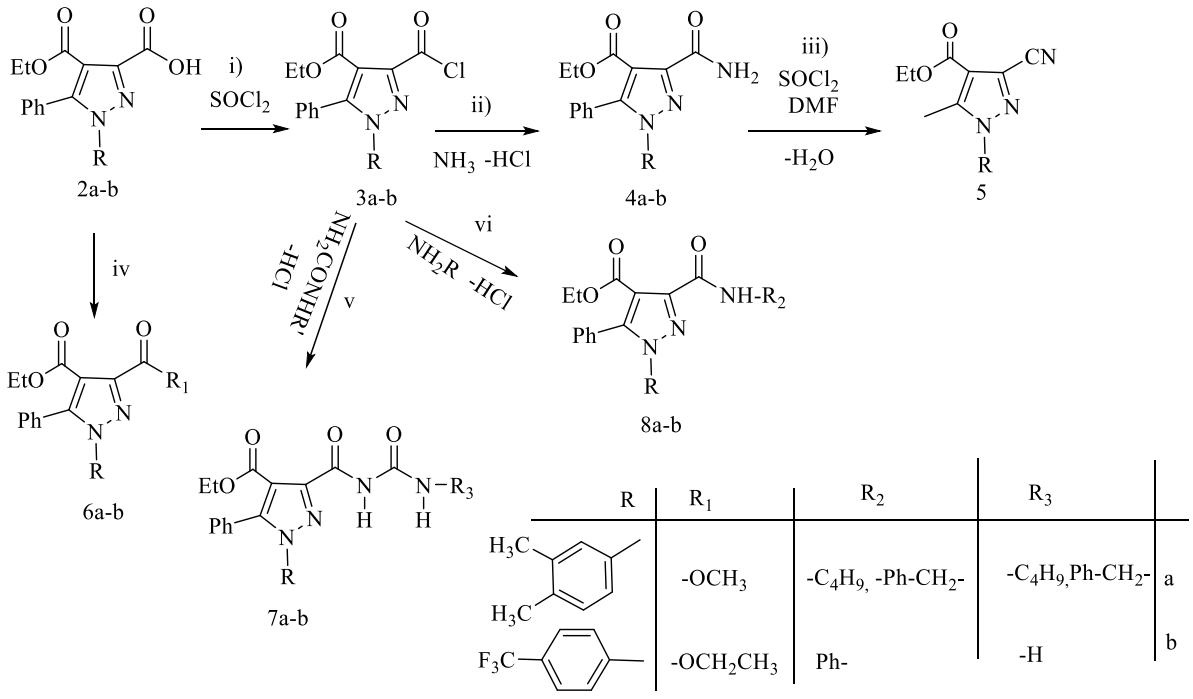
i)Synthesis of pyrazole carboxylic acid 2. (i) Dry benzene, reflux, 5 hours; (ii) solid state, grinding of 1 and 1a-b in a reaction pot for 40 minutes.

Figure 2. Proposed reaction mechanism for compound 2

The reaction between compound 2 and ethyl alcohol using the Fischer esterification method gave compound 4 (Figure 3). Compound **2a** in excess thionyl chloride was stirred at room temperature for 3 days to produce acyl chloride **3a** (Şener et al., 2007; Genç et al., 2010). The acyl chloride was then reacted with different nucleophiles, such as benzylamine (for **7b**), n-butyl amine (for **7a**), methyl urea (for **8**), and ammonia (for **5**). Compound **5**, which contains an amide group**,** was reacted with a mixture of DMF and $SOCl_2$, a water-removing reagent, resulting in compound **6**, which contains a nitrile unit.

The ring closure reaction between compound **2a** and 2-nitro phenylhydrazine in xylene gave compound **9** (Şener et al., 2008; Tozlu et al., 2019) (Figure 4). Unexpectedly, the final product of the reaction was found to carry an EtO group on the pyridazinone ring. The final product, **9**, was confirmed by NMR data. To understand the forming of compound **9**, we have progressed the same reaction under 50 °C for 50 min. The experiment gave an intermediate which was confirmed by LC-MS/MS data. After increasing the temperature of reaction media to the reflux temperature of xylene, compound **9** was yielded, which was also confirmed by NMR and LC-MS/MS data (Figure 4).

Decarboxylation of **2b**, which possess ester and carboxylic acid, gave unexpected product resulting in C-3 and C-4 unsubstituted pyrazole ring (Figure 5). Previous decarboxylation reactions of the similar skeleton by us (Genç et al., 2019) and (Taslimi et al., 2019) did not give the same result as we have observed.



i)a)$SOCl_2$(extreme) stirred for 3 days. b)PCl_5 in CCl_4 refluxed for 4 h,ii) add NH_3 at 0-5°C for 24h,iii) DMF+$SOCl_2$ stirred at 0- 5°C for 24h,iv) H_2SO_4, Alcohol, ref. 3h,v) urea refluxed in xylene for 5 vi) amine refluxed in toluene for 4h.

Figure 3. Further reactions of compound 2a-b

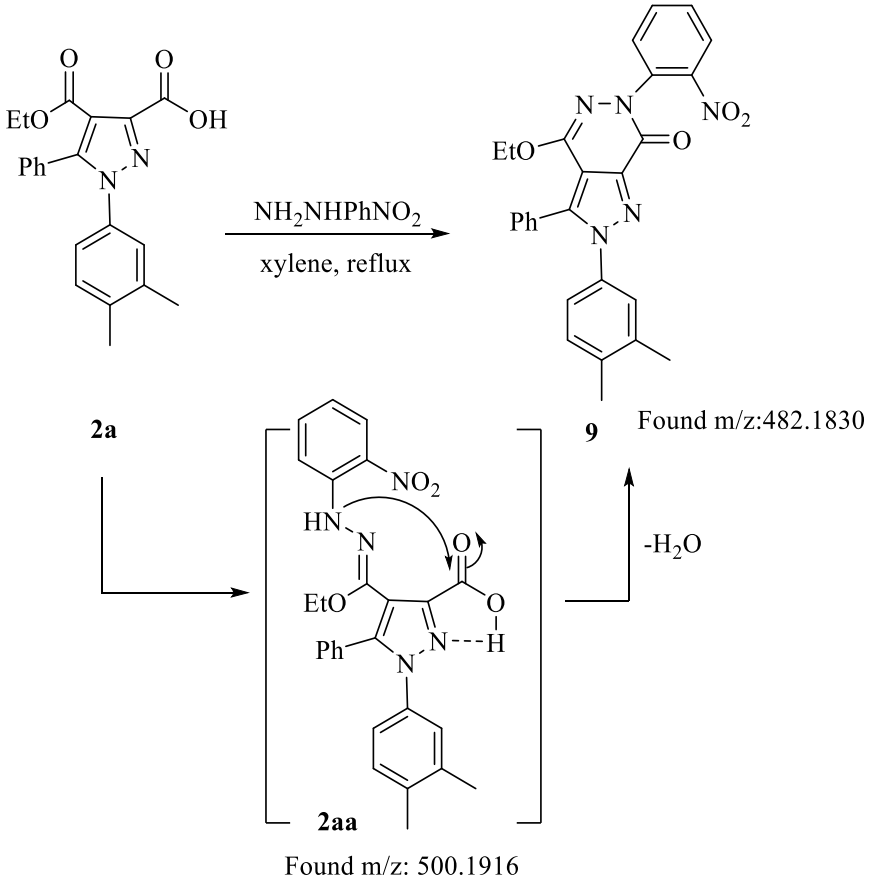


Figure 4. Synthesis of pyrazolopyridazine 9

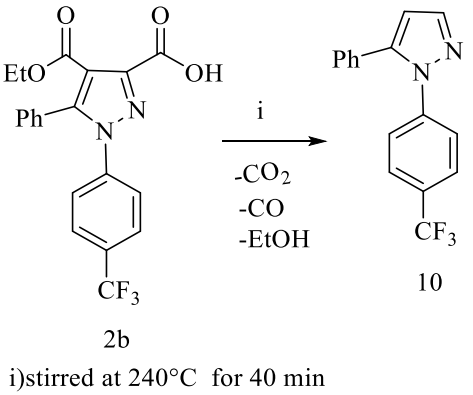


Figure 5. Decarboxylation of 2b

In the literature, decarboxylation of malonic acid monoester gives ethyl acetate. The resonance structure of dicarbonyl molecules is the driving force for decarboxylation. However, in our decarboxylated product, either ester or carboxylic acid was removed from the ring. It might be due to the inductive effect of CF_3 group (Figure 6). We have proposed that under high temperature, decarboxylation of carboxylic acid and ethoxy groups occurs simultaneously. We have progressed the reaction under open-air, and H_2O molecules assist it. We have assumed that after removing carbon dioxide from the ethoxy unit, water molecules attach to the Et group and protonated ethanol gives a proton to the C-4 position of pyrazole ring, which emerged the compound **10** (Baird, 2003). The driving force of this reaction might be a negative inductive effect of CF_3.

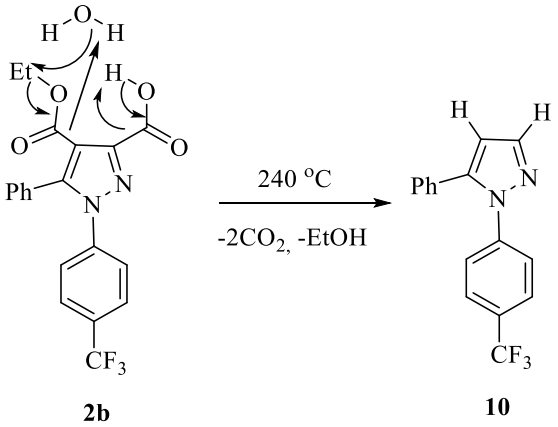


Figure 6. Proposed mechanism for decarboxylation of compound 2

CONCLUSION

In this work, the reaction between 4-ethoxycarbonyl-5-phenyl-2,3-furandione 1 and two different hydrazone derivatives, one of them has CF_3 group, in both solvent and solid-phase were investigated. Synthesis of novel derivatives with various functional groups from the obtained compound was achieved. Because the reaction of acid chloride can easily convert new functional groups with nucleophiles, the carboxylic acid was converted into acyl chloride. Spectroscopic studies carried out structural analysis of the synthesized pyrazole carboxylic acid derivatives. Besides the nucleophilic substitutions of the pyrazole carboxylic acid, pyrazolopyridazine derivatives bearing the nitrophenyl unit were formed. It is known that nitro phenylhydrazine derivatives exhibit biological activity with pyrazole carboxylic acid ring-forming derivatives.

Conflict of Interest

The article authors declare that there is no conflict of interest between them.

Author's Contributions

The authors declare that they have contributed equally to the article.

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