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Seryum Amonyum Nitrat Varlığında Yeni 3-Oksobutanohidrazid Türevlerinin Sentezi

Furgan ASLANOĞLU

ÖZET: Bu çalışmada, yeni 3-oksobutanohidrazid türevleri için yeni bir sentetik yöntem geliştirilmiştir. Bu sentetik yöntem iki adımdan oluşmaktadır. İlk aşamada aldehit fenil hidrazon türevleri sentezlendi. Daha sonra, bu bileşikler 2,2,6-trimetil-4*H*-1,3-dioksin-4-on (TMD) bileşiği ile katalitik miktarda seryum amonyum nitrat varlığında reaksiyona sokularak hedef moleküller olan 3-okzobutanohidrazit türevleri sentezlendi. Sentezlenen 3-oksobutanohidrazid türevlerinin yapıları 1H-NMR ve 13C-NMR ile karakterize edildi.

Anahtar Kelimeler: 3-Oksobutanohidrazid, seryum amonyum nitrat, asetil keten

Synthesis of Novel 3-Oxobutanohydrazide Derivatives in the Presence of Cerium Ammonium Nitrate

ABSTRACT: In this study, a new synthetic method was developed for new 3-oxobutanohydrazide derivatives. This synthetic method consists of two steps. In the first step, aldehyde phenyl hydrazone derivatives were synthesized. Then, these compounds were reacted with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (TMD) compound in the presence of the catalytic amount of cerium ammonium nitrate and 3-oxobutanohydrazide derivatives, which are new target molecules, were synthesized. The structures of the synthesized 3-oxobutanohyidrazide derivatives were characterized by 1H-NMR and 13C-NMR.

Keywords: 3-Oxobutanohydrazide, serium ammonium nitrate, acetylketene

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INTRODUCTION

Organic compounds containing nitrogen atoms have attracted the attention of synthetic organic chemists in recent years due to their important biological activities. Organic compounds containing the hydrazide structure have significant biological activity such as antiviral (Şenkardes et al., 2016), antiinflammatory (Kumar et al., 2015), anticancer (Kumar et al., 2012), and anticonvulsant (Çakır et al., 2001). In addition, nitrofurantoin (Munoz-Davila, 2014), nitrofurazone (McCalla et al., 1970), and furazolidone (Ali, 1983), which are used as chemotherapeutic agents, contain the hydrazide skeleton (Figure 1).

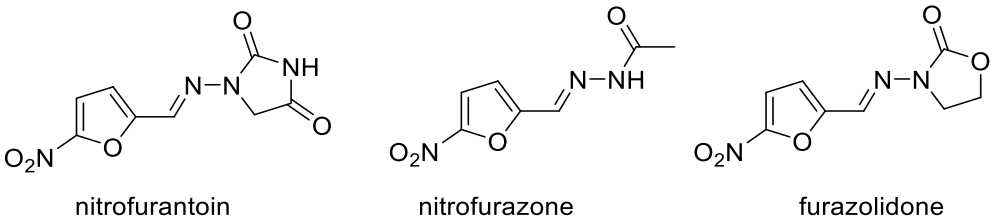


Figure 1. Chemotherapeutic agents containing the hydrazide skeleton

In this study, a new synthetic method was developed for novel hydrazide derivatives by acetoacetylating the synthesized hydrazones. As an acetoacetylating agent, 2,2,6-trimethyl-4H-1,3-dioxin-4-one (TMD) (1) was utilized. This compound is thermolysis above 100°C and turns into acetylketene intermediate. Since the acetylketene intermediate is unstable, they react very quickly with the -OH, -SH, and -NH groups in the medium and the acetoacetylation reaction occurs easily (Annibale et al. 1996) (Figure 2). Two publications have been published this year by us and studies have been still going on (Aslanoglu, 2022).

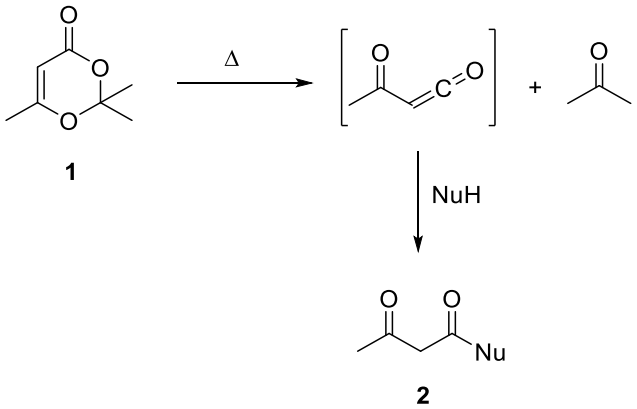


Figure 2. Decomposition and reaction of TMD (1)

One of the most popular uses of cerium ammonium nitrate (CAN) is as a one-electron oxidant (Ho, 1973). Ce (IV) is a one-electron oxidant that may form carbon-carbon bonds by generating radicals on carbon bound to acidic hydrogen (Heiba et al. 1971). Furthermore, by using catalytic amounts in synthetic organic chemistry, CAN promotes the development of synthetic methodologies.

MATERIALS AND METHODS

Materials

All commercially accessible solvents and compounds in the analytical grade were bought from Abcr, Acros, and Alfa Aesar. With the appropriate agents, The solutions were distilled and dried with the appropriate agents The melting points were obtained using the Electrothermal Gallenkamp equipment. The 1D NMR spectra were obtained using a 400 MHz Agilent and the internal standard TMS

(tetramethylsilane). TLC was used to monitor the conversion process of each experiment using a Camag TLC lamp (254/366 nm) and DC Alufolien Kieselgel 60 F254

Experimental procedure

General Procedure aldehyde phenylhydrazone (5)

The benzaldehyde derivative (1 eq) (**3**) was dissolved in 20 ml of ethanol. Afterward, phenylhydrazine (1 eq) (**4**) was added slowly and solid formation was observed when mixed slowly. The compound mixture was taken and heated at 80 °C for 30 minutes. TLC was used to monitor the conversion process once it was completed. The solvent was evaporated and then the residue was recrystallized in ethanol. Hydrazone derivatives (**5**) were filtrated and dried (Chandrika et al. 2021).

General Procedure hydrazide-hydrazone derivatives

Cerium ammonium nitrate (25 mg, 5 mmol %) was added to a stirred solution of TMD (142 mg, 1 mmol) in toluene (15 mL). The hydrazone compound (1 mmol) (**5**) was then added, and the final mixture was heated in a nitrogen environment for 3 hours at the reflux temperature. The reaction mixture was filtered and evaporated after full conversion (as indicated by TLC). The crude product was purified over silica gel eluting with hexane/EtOAc to give hydrazide derivatives (**6**).

6a. *N*-Benzylidene-*N'*-[1-(phenyl)methylidene]-3-oxobutanohydrazide

A colorless oil, yield: 92 %, R_f = 0.5 (hexane/ethyl acetate, 2:1) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60-7.55 (m, Aryl-H, 3H), 7.53-7.48 (m, Aryl-H, 3H), 7,38-7.34 (m, Aryl-H and =C-H, 3H), 7,24-7.21 (m, Aryl-H, 2H), 4.09 (s, -CH_2, 2H), 2.36 (s, -CH_3, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.72, 169.10, 142.69, 135.20, 133.82, 130.34, 130.18, 129.64, 129.17, 128.77, 127.26, 50.87, 30.03.

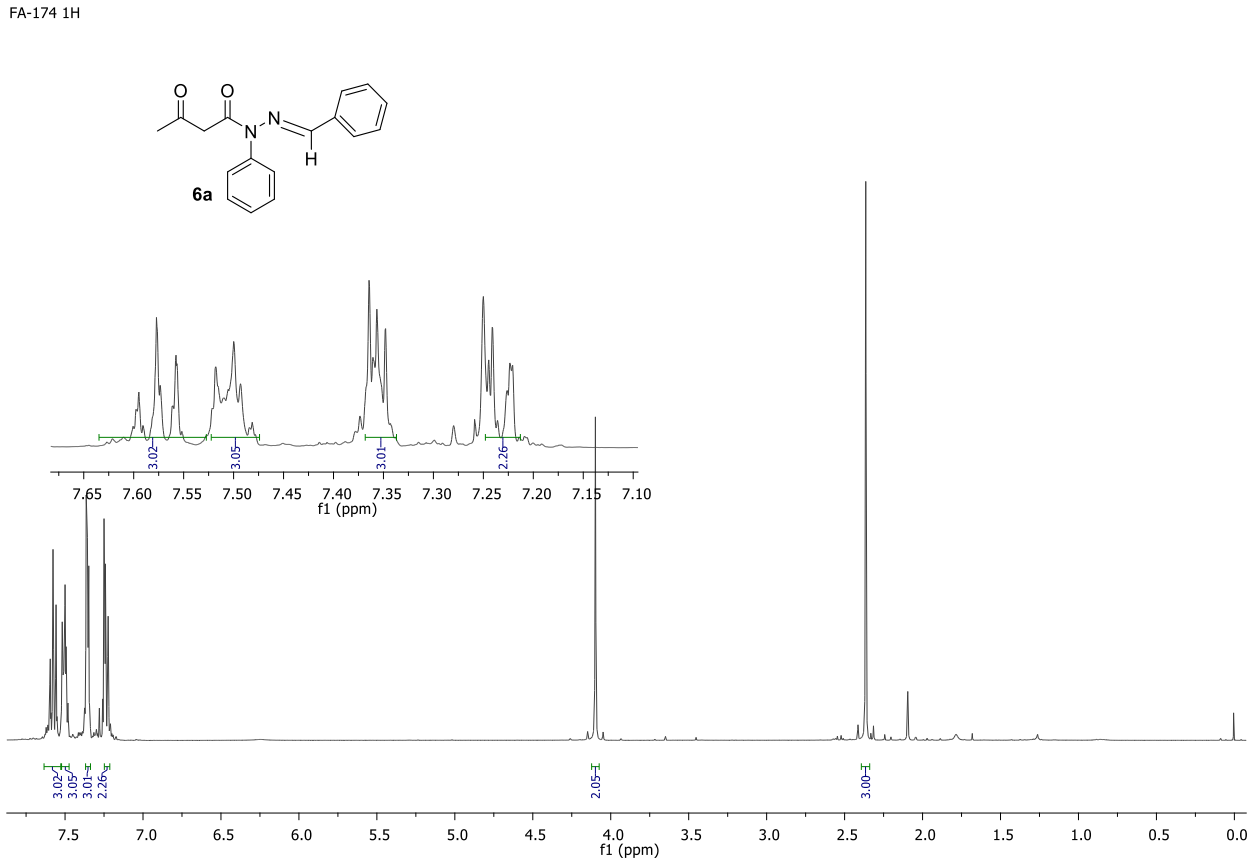


Figure 3. ^{1}H NMR Spectrum of Compound 6a in $CDCl_3$

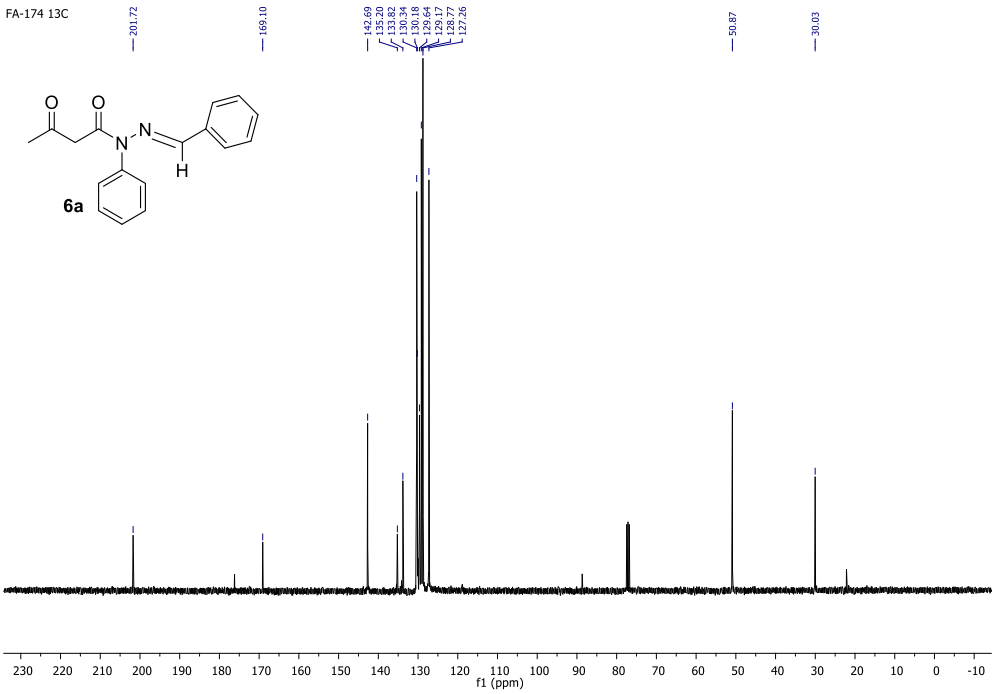


Figure 4. ^{13}C NMR Spectrum of Compound 6a in $CDCl_3$

6b. *N*-Benzylidene-*N'*-[1-(4-methyl phenyl)methylidene]-3-oxobutanohydrazide

A colorless oil, yield: 89 %, R_f = 0.4 (hexane/ethyl acetate, 2:1.) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60-7.54 (m, Aryl-H, 2H), 7.52-7.47 (m, Aryl-H, 1H), 7.42-7.37 (A-part of AA'BB'-system, Aryl-H, 2H), 7,24-7.20 (m, Aryl-H and =C-H, 3H), 7.18-7.14 (B-part of AA'BB'-system, Aryl-H, 2H), 4.07 (s, -CH_2, 2H), 2.36 (s, -CH_3, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.76, 169.01, 142.76, 140.49, 135.26, 131.08, 129.54, 129.47, 129.40, 129.19, 127.21, 50.85, 29.98, 21.46.

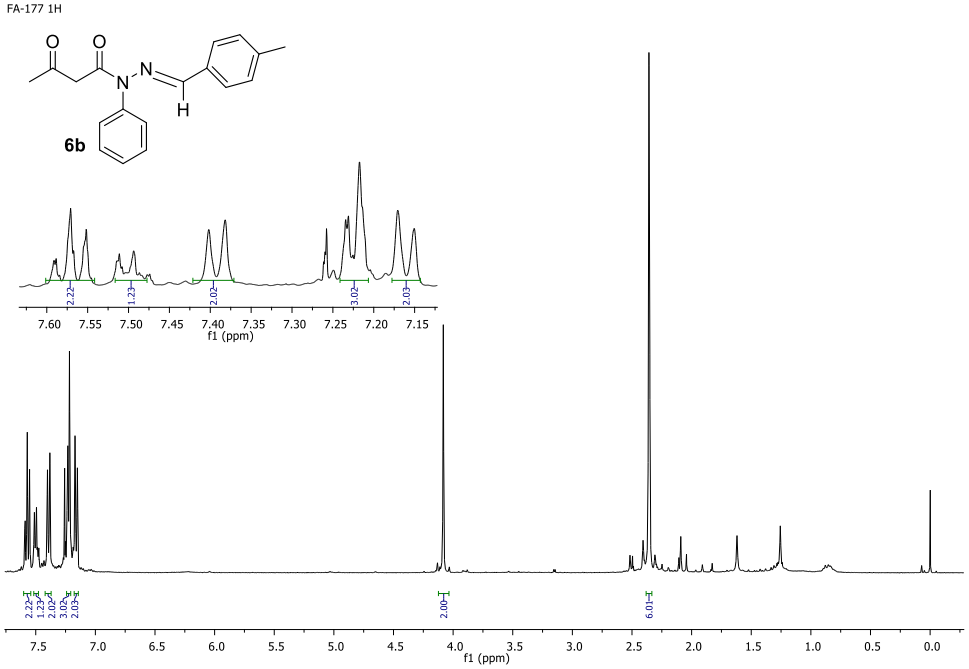


Figure 5. ^{1}H NMR Spectrum of Compound 6b in $CDCl_3$

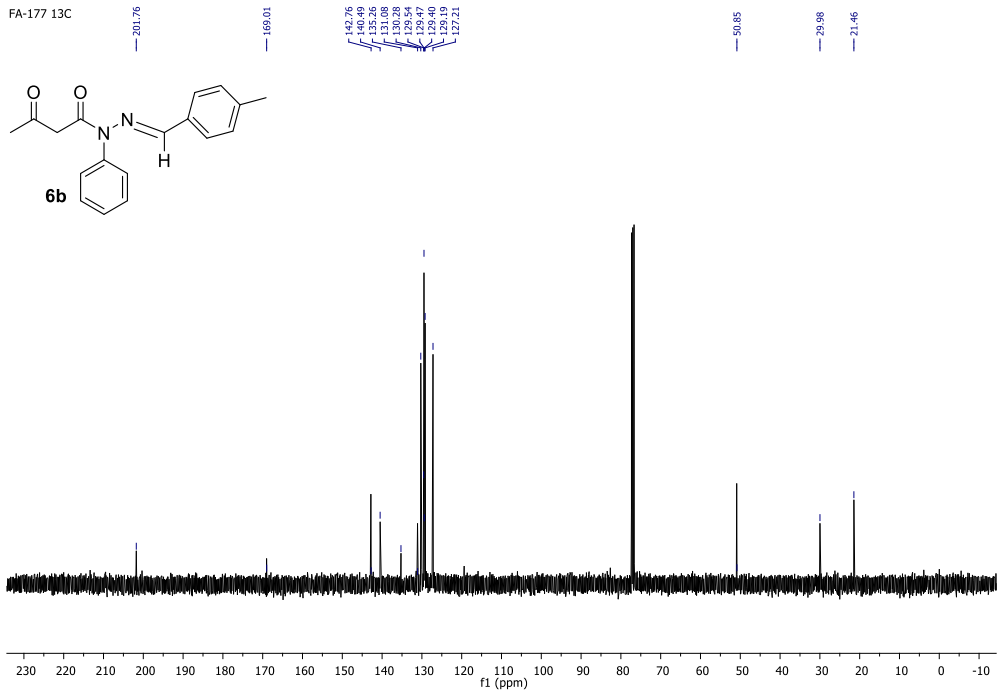


Figure 6. ^{13}C NMR Spectrum of Compound 6b in $CDCl_3$

6c. *N*-Benzylidene-*N'*-[1-(4-chlorophenyl)methylidene]-3-oxobutanohydrazide

A colorless oil, yield: 87 %, R_f = 0.6 (hexane/ethyl acetate, 2:1.) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61-7.55 (m, Aryl-H, 2H), 7.53-7.48 (m, Aryl-H, 1H), 7.45-7.41 (A-part of AA'BB'-system, arom, 2H), 7.35-7.31 (B-part of AA'BB'-system, arom, 2H), 7.23-7.19 (m, Aryl-H and =C-H, 3H), 4.08 (s, -CH_2, 2H), 2.36 (s, -CH_3, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.58, 169.02, 141.28, 136.01, 132.34, 130.38, 129.73, 129.09, 129.04, 128.40, 128.38, 50.89, 29.97.

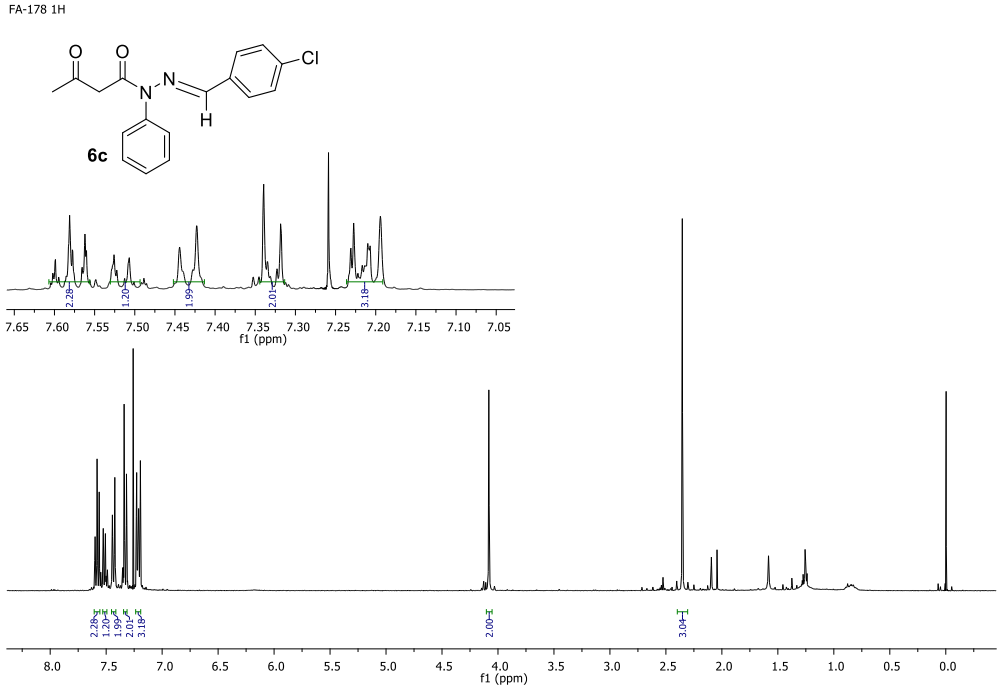


Figure 7. ^{1}H NMR Spectrum of Compound 6c in $CDCl_3$

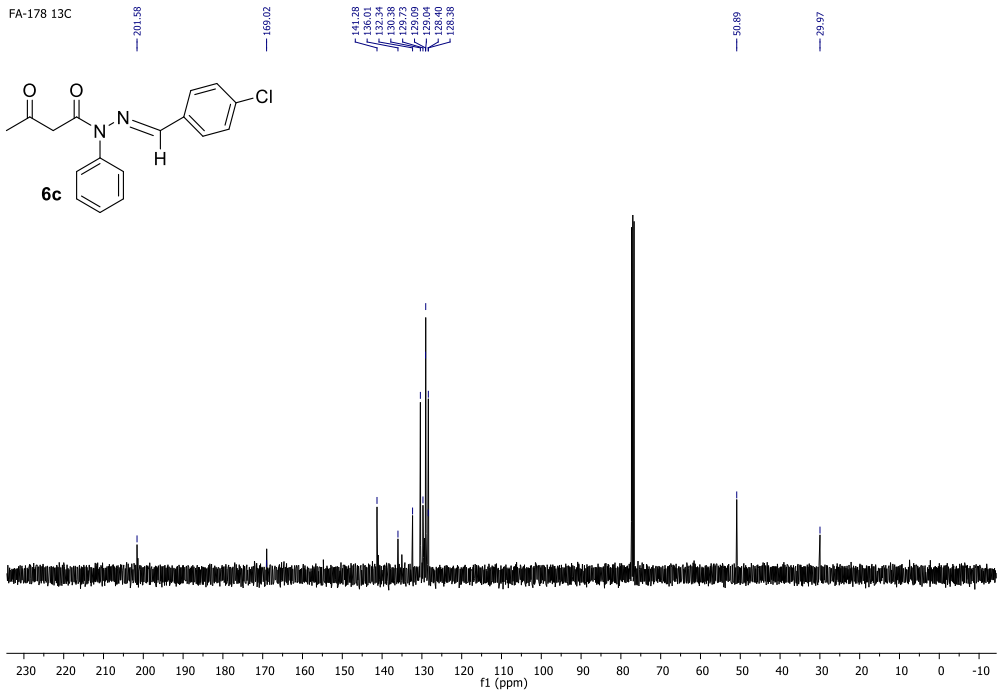


Figure 8. ^{13}C NMR Spectrum of Compound 6c in $CDCl_3$

6d. *N*-Benzylidene-*N'*-[1-(thiophene)methylidene]-3-oxobutanohydrazide

A colorless oil, yield: 83 %, R_f = 0.5 (hexane/ethyl acetate, 2:1.) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60-7.54 (m, Aryl-H, 2H), 7,53-7.48 (m, Aryl-H, 1H), 7.36 (d, *J* = 1.93 Hz, =C-H, 1H), 7.32 (bd, *J* = 7.87 Hz, =C-H, 1H), 7.24-7.21 (m, Aryl-H, 2H), 7,02 (bs, =C-H, 1H), 6.99 (m, =C-H, 1H), 4.04 (s, -CH_2, 2H), 2.39 (s, -CH_3, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.75, 168.86, 139.03, 136.79, 135.10, 130.35, 130.11, 129.67, 129.16, 127.94, 127.55, 50.55, 30.27.

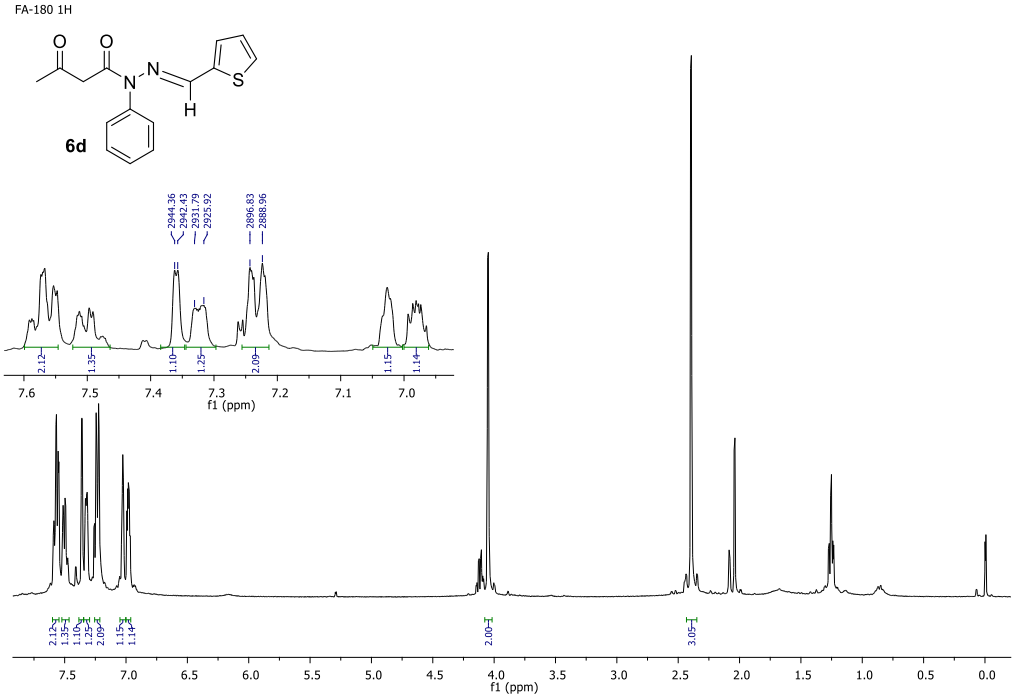


Figure 9. ^{1}H NMR Spectrum of Compound 6d in $CDCl_3$

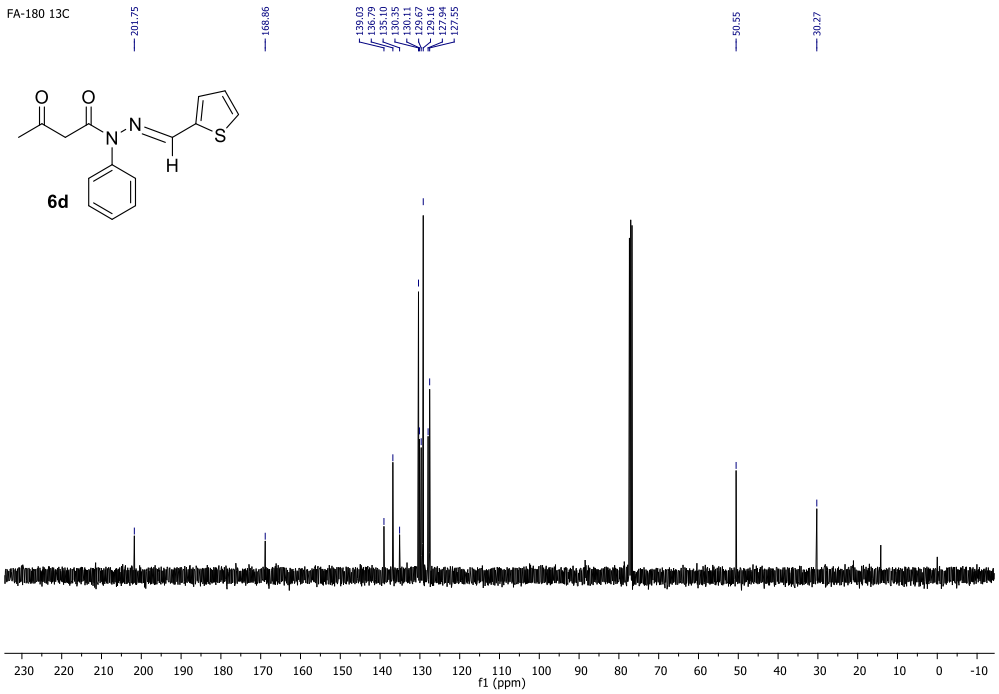


Figure 10. ^{13}C NMR Spectrum of Compound 6d in $CDCl_3$

6e. *N*-Benzylidene-*N'*-[1-(4-(trifluoromethyl)methylidene]-3-oxobutanohydrazide

A colorless oil, yield: 85 %, R_f = 0.4 (hexane/ethyl acetate, 2:1.) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (s, Aryl-H, 4H), 7.60-7.57 (m, Aryl-H, 2H), 7,55-7.49 (m, Aryl-H, 1H), 7.25-7.20 (m, Aryl-H and =C-H, 3H), 4.11 (s, -CH_2, 2H), 2.36 (s, -CH_3, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.42, 169.09, 140.72, 137.18, 134.92, 130.45, 129.86, 129.25, 129.03, 127.37, 12.71, 50.84, 29.98.

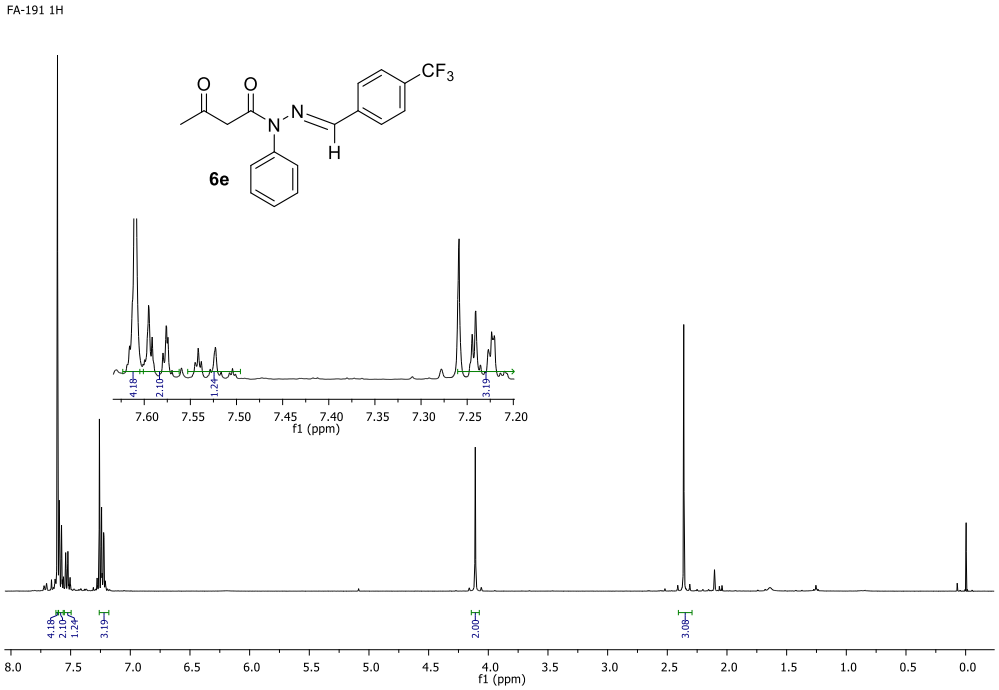


Figure 11. ^{1}H NMR Spectrum of Compound 6e in $CDCl_3$

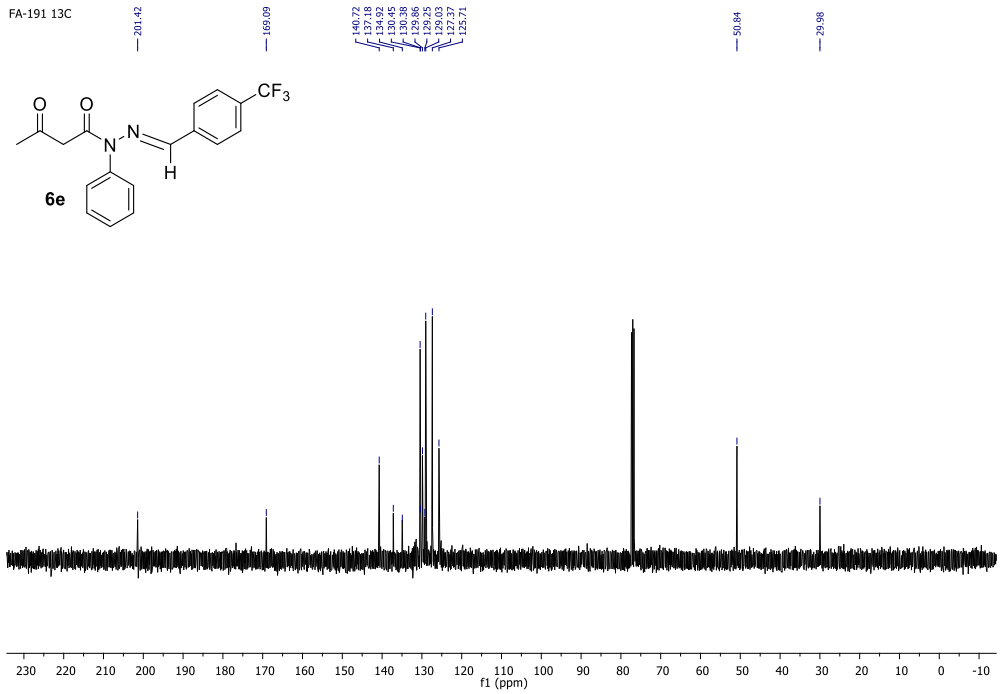


Figure 12. ^{13}C NMR Spectrum of Compound 6e in $CDCl_3$

6f. *N*-Benzylidene-*N'*-[1-(2-(chlorophenyl)methylidene]-3-oxobutanohydrazide

A colorless oil, yield: 79 %, R_f = 0.5 (hexane/ethyl acetate, 2:1.) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (s, =C-H, 1H), 7.62-7.547 (m, Aryl-H, 4H), 7,54-7.48 (m, Aryl-H, 1H), 7.32-7.28 (m, Aryl-H, 3H), 7.24-7.22 (m, Aryl-H, 2H), 4.10 (s, -CH_2, 2H), 2.35 (s, -CH_3, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.60, 169.08, 139.62, 135.05, 134.51, 131.36, 130.95, 130.40, 129.90, 129.78, 128.91, 127.07, 126.96, 50.87, 30.01.

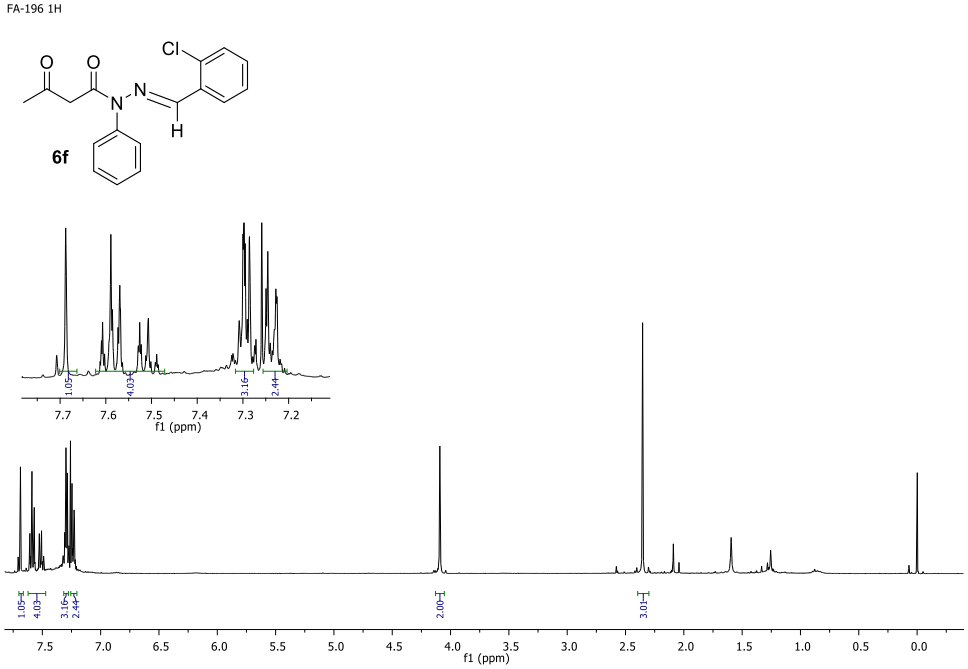


Figure 13. ^{1}H NMR Spectrum of Compound 6f in $CDCl_3$

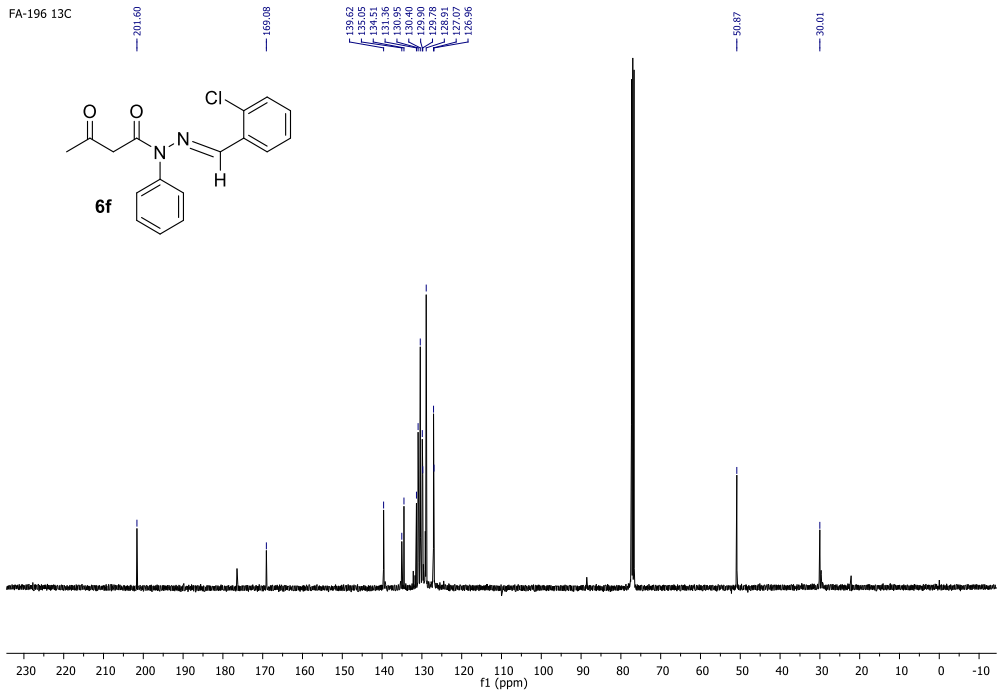


Figure 14. ^{13}C NMR Spectrum of Compound 6Fin $CDCl_3$

RESULTS AND DISCUSSION

To synthesize new hydrazide derivatives, it was necessary to synthesize various hydrazone derivatives (**5**) in the first step of the study. Because of this, various aldehyde derivatives were reacted with phenylhydrazine (**4**) and different hydrazone derivatives (**5**) were synthesized. Hydrazone derivatives (**5**) were prepared by first dissolving aldehyde derivatives in ethyl alcohol, then adding phenylhydrazine (**4**) dropwise and refluxing for 0.5 hours. (Chandrika et al. 2021) (Figure 15).

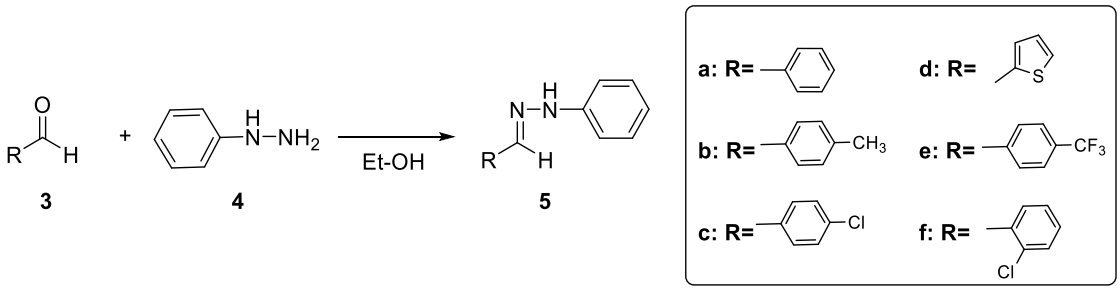
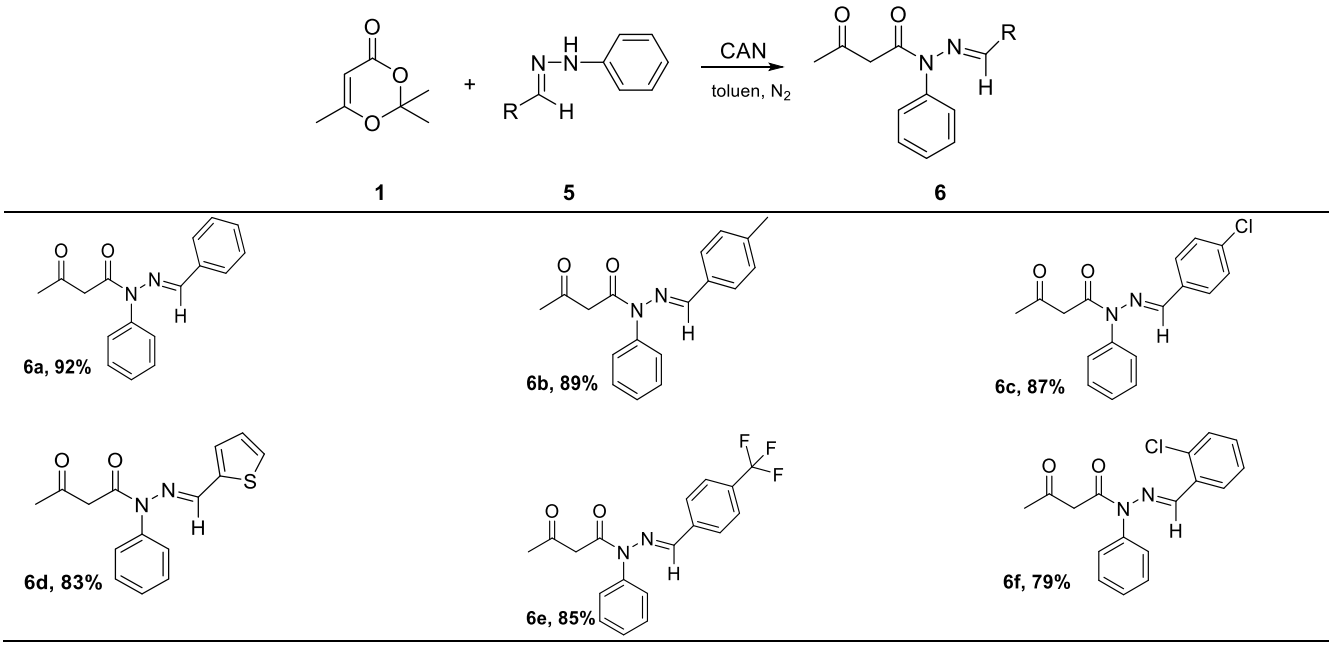


Figure 15. Synthesis of aldehyde phenylhydrazone

The direct reaction of TMD (1) with hydrazone is not known in the literature. The formation of hydrazide with TMD is very limited. Yavari et al. synthesized hydrazide derivatives with one pot reaction using microwave irradiation using a compound of aldehyde, methyl hydrazine, or 4-methylphenylhydrazine hydrochloride and TMD (**1**). However, in the same literature, when the same reaction was carried out with phenylhydrazine, the hydrazide did not form and the reaction resulted in the formation of the cyclization product.

Synthesizing with novel hydrazide derivatives by reacting phenylhydrazine-derived hydrazones with the chemical TMD (1) may fill the gap in the literature. The reaction did not occur on the first try when TMD (**1**) and hydrazone (**5**) were reacted without the use of a catalyst. Following that, the same reaction was repeated, based on the literature, with the catalytic amount of cerium ammonium nitrate (CAN) and the reaction occurred at a very high yield.

Table 1. Synthesis of hydrazide derivative (**6**)



TMD (1) (1eq), hydrazone derivatives (5) (1 eq), Cerium Ammonium Nitrate (CAN) (5 mmol %)

The structure of hydrazide compounds was identified via 1D NMR spectroscopic data **6**. For instance, the presence of a singlet peak in the ^{1}H NMR spectra of compound **6a** at 4.09 ppm existing -CH_2 and 2.36 ppm existing -CH_3 demonstrated the acetoxylation event took place. However, novel carbon signals showed in the ^{13}C NMR of **6a**, including 201.72 ppm and 169.10 ppm (Aceto acetate carbonyl carbons), 50.87 ppm (-CH_2), and 30.03 ppm (-CH_3). NMR spectra of compound **6b-f** are also in agreement with the proposed structures.

It was observed that no product was formed when phenylhydrazone was reacted with TMD without using any catalyst. When the catalytic amount of cerium ammonium nitrate was applied in the same process, however, the reaction occurred in high yields. It is thought that cerium ammonium nitrate, which is used in a catalytic amount in this reaction, increases the electrophilicity of the carbonyl group by being coordinated with the carbonyl group of intermediate (Goswami et al. 2000). Following that, the hydrazone's NH group is expected to attack the carbonyl group and produce the hydrazide compound (Goswami et al. 2000).

CONCLUSION

In this work, a novel method for acetylacetylation of phenylhydrazone was developed that had not before been published. According to this methodology the reaction, which did not occur with catalytic-free conditions, occurred when a catalytic amount of cerium ammonium nitrate was used. The reaction obtained significant yields of 3-oxobutanohydrazide derivatives that had not previously been reported in the literature.

ACKNOWLEDGEMENTS

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