

Onder Alici and Ibrahim Karatas*

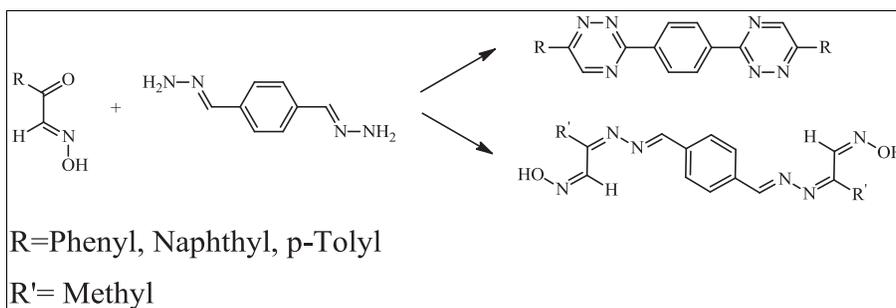
Department of Chemistry, Faculty of Science, Selcuk University, 42075 Konya, Turkey

*E-mail: ikaratas@selcuk.edu.tr

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This study describes a novel method for the synthesis of 1,2,4-triazines. Firstly, isonitrosoacetophenone, *p*-methylisonitrosoacetophenone, and isonitroso-1-acetylnaphthalene were synthesized from the reaction of butylnitrite with acetophenone, *p*-methylisonitrosoacetophenone, and 1-acetylnaphthalene, respectively. Then, symmetric derivatives of 1,2,4-triazines were prepared from the condensation reaction of keto oximes with terephthalohydrazone. However, the heteroaromatic closure was not observed in the condensation reaction of pyruvic-aldehyde-1-oxime(keto oxime) with terephthalohydrazone. Structures of the obtained products were confirmed by FTIR, ¹H-NMR, and elemental analyses techniques.

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INTRODUCTION

1,2,4-Triazines are well-known compounds, and substituted triazines represent an important class of nitrogen-containing heterocycles. A wide variety of synthetic methods for the preparation of them and their substituted derivatives are available. Some of 1,2,4-triazine compounds are yellow in color, and their nonsubstituted or alkyl-bonded derivatives have lower melting points. Moreover, lots of 1,2,4-triazine compounds are liquids. Nevertheless, it is stated in literature that aryl or heterocyclic substituted compounds of 1,2,4-triazines are solid, crystalline, and soluble in many organic solvents [1]. Compounds containing the 1,2,4-triazine moiety are found in natural materials. Also, a large number of synthetic 1,2,4-triazines have biological activity and have been used for various purposes. While only a few of these heterocyclic compounds are found in nature, a number of substituted 1,2,4-triazines have been prepared and tested as potentially active building blocks in agrochemical and medicinal fields [2]. The 1,2,4-triazine core is a versatile synthetic platform to access a wide range of condensed heterocyclic ring systems via intramolecular Diels–Alder reactions with a vast array of dienophiles. In addition, the triazine ring system is a significant component of commercial dyes, herbicides, insecticides, and more recently, pharmaceutical compositions [3–9].

The traditional thermal conditions for the synthesis of 1,2,4-triazines involve refluxing of a 1,2-diketone and an acyl hydrazide, in a 1:1 ratio, in a solution of ammonium

acetate–acetic acid for 6–24 h [10]. In addition to this, the different synthetic methods are reported as follows. (a) Condensation of acid hydrazides with benzil in a solution of acetic acid–ammonium acetate to give 5,6-diphenyl-1,2,4-triazines containing various aromatic and heterocyclic groups attached at position 3 [11]. (b) Cyclization of aliphatic, aromatic, and heterocyclic acid hydrazide with 1,2-diketone monoacylhydrazones in alcoholic ammonia under pressure [12]. (c) Condensation of aromatic monohydrazones (but not aliphatic) with 1,2-diketones to give 5,6-disubstituted 1,2,4-triazines [13]. (d) Condensation reaction of acid hydrazide and β-halo acetophenone in the presence of NaOAc or AgOAc [14,15]. (e) Reaction of β-diketones with amidrazones and *S*-methylthiosemicarbazide were also reported in the literature [16,17].

As it is seen from the above-reported methods, many synthetic ways for the synthesis of substituted 1,2,4-triazines are available. However, according to our knowledge, a keto oxime and a hydrazone have been not used as starting materials for this purpose. We have presented a new pathway for the synthesis of substituted-1,2,4-triazines by using terephthalaldehyde dihydrazone and isonitrosoketones.

RESULTS AND DISCUSSION

In this study, the isonitrosoacetophenone (**I**), isonitroso-1-acetylnaphthalene (**II**), *p*-methyl isonitrosoacetophenone

(III), and terephthalaldehydedihydrazone (V) were synthesized according to the known procedure. The melting points and other properties of those compounds were compatible with the literature knowledge [18–21]. Many synthesis methods of 1,2,4-triazine compounds are available in studies that have been performed since 1950 [1]. However, the synthesis of 1,2,4-triazine compound derivatives by using keto oxime and hydrazone compounds were not seen in the literature investigations. For this reason, a new synthetic procedure to 1,2,4-triazine derivatives is reported using different starting materials. In our previous study, five-membered heterocyclic compounds were prepared by the heteroaromatic closing reaction [22].

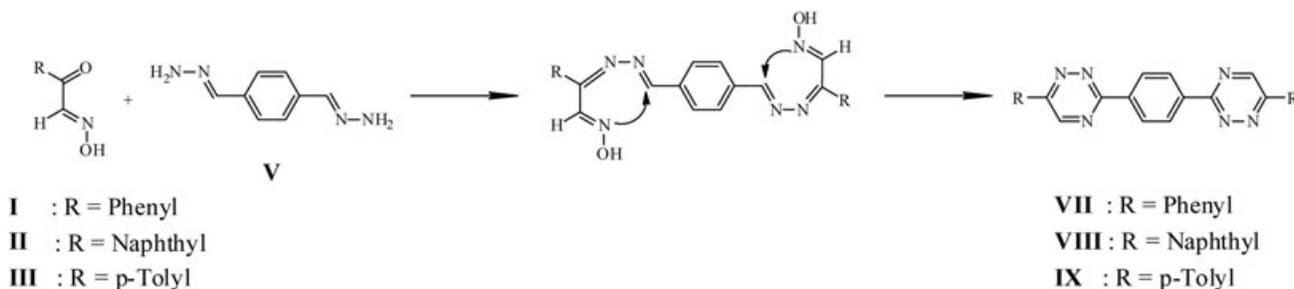
In the study, three symmetrical 1,2,4-triazine compounds were prepared by the condensation of four keto oxime derivatives with terephthalaldehydedihydrazone. The alkyl and aryl groups in keto oxime derivatives were efficient on synthesizing the 1,2,4-triazine derivatives. When the R group of keto oxime was phenyl, *p*-tolyl, and naphthyl, the triazine compound was formed (Scheme 1), but when the R group was methyl, the triazine compound was not formed (Scheme 2). Moreover, when the R group was naphthyl, it was seen that the reaction time would be shorter. When the R group was methyl, the ring closure was not observed, and this reaction was realized as normal condensation reaction. Characterization of the synthesized compounds was made by ¹H-NMR, FT-IR and elemental analysis.

Some of 1,2,4-triazine compounds are generally yellow in color and their nonsubstituted or alkyl-bonded

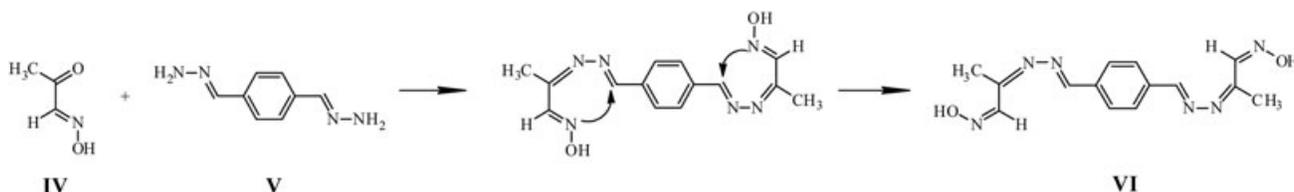
derivatives have lower melting points. Moreover, lots of 1,2,4-triazine compounds are liquids. Nevertheless, it is stated in literature that aryl or heterocyclic substituted compounds of 1,2,4-triazine compounds are solid, crystalline, very stable, and have ability to dissolve in much organic solvents [1].

By ¹H-NMR evaluation of synthesized compound VI, it is observed that —NOH peak of oxime is at 12.08 ppm (s,2H); —CH peak of oxime is at 8.52 ppm (d,2H, *J* = 6.32 Hz); —CH peak of benzene ring is at 8.11 ppm (d,4H, *J* = 12.30 Hz); —CH peak which is neighbor to benzene ring is at 7.9 ppm (s,2H), and proton peaks of methyl groups are at 2.31 ppm (s,6H). For compound VII, it is observed that —CH peaks of triazine ring is at 8.74 ppm (s,2H); the phenyl rings which are neighbor to triazines have —CH peaks at 7.90 ppm (d,4H, *J* = 8.3 Hz), 7.77 ppm (s,2H), 7.66 ppm (d,4H, *J* = 8.3 Hz) and —CH peaks of central phenyl ring is at 7.17 ppm (s,4H). Also, for compound VIII, it is observed that the —CH peak of (s,2H) triazine compound is at 8.70 ppm and both naphthalene rings which are neighbors to triazine have —CH peaks at 8.10 ppm (s,4H), 7.90 ppm (t,4H, *J* = 10.0 Hz), 7.76 ppm (s,2H), 7.65 ppm (t,4H, *J* = 8.3 Hz). In addition, the benzene ring, which is central phenyl ring, has —CH peak at 7.18 ppm (d,4H, *J* = 10.35 Hz). In the ¹H-NMR analysis of synthesized compound IX, the —CH peak of (s,2H) triazine compound is at 8.65 ppm and both *p*-tolyl rings, which are neighbors to triazine, have —CH peaks at 7.80 ppm (d, 4H, *J* = 8.41 Hz), 7.65 ppm (d, 4H, *J* = 8.34 Hz). In addition, the benzene ring, which is neighbor to both triazines, has —CH peak at 7.70 ppm (s, 4H). It is observed

Scheme 1. The ring closure reaction mechanism.



Scheme 2. The condensation reaction without ring closing.



that $-\text{CH}_3$ peak of *p*-tolyl is at 2.45 ppm (s, 6H). These values are compatible with literature values the one-sided triazine derivative [2].

The compound (VI) has yellow color and crystalline structure, can partly dissolve only in hot DMSO. The same results were obtained for corresponding compounds (VII, VIII, and IX).

The FTIR spectrum data of 1,2,4-triazine are mentioned in lots of studies. The characteristic IR peaks of 1,2,4-triazine compounds have C—H stretching frequency in 3090–3030 cm^{-1} interval. Moreover, C=N and C=C frequencies are in 1560–1295 cm^{-1} interval. Again, it is observed that the vibration peaks of (C—H, N—N) which is of triazine ring are in 1050–995 cm^{-1} [2].

With the evaluation of FT-IR spectrum of compound VI, —OH stretching vibration peak of oxime group is seen at 3159 cm^{-1} . C=N and N—O vibration peaks are observed at 1618 and 986 cm^{-1} , respectively.

For compound VII, —CH groups peaks of triazine and aromatic ring are observed at 3331 and 3182 cm^{-1} , respectively. Moreover, C=C and C=N groups of triazine ring have specific peaks in the region of 1597–1215 cm^{-1} .

For the isonitroso-1-acetylnaphtalene compound, —NO peak is observed at 971 cm^{-1} but is not observed for compound VIII. At 1670 cm^{-1} , decreased strength of —CN stretching frequency peak is observed. —OH peak, which is seen at 3287 cm^{-1} of isonitroso-1-acetylnaphtalene, is not seen for the compound VIII. —NH peak, which appeared at 3360 cm^{-1} of terephthalodihydrazone, disappeared in the spectrum of compound VIII. In addition, C=C and C=N groups of triazine ring are observed in the region of 1529–1215 cm^{-1} .

For the *p*-methyl isonitrosoacetophenone, —NO peak is observed at 971 cm^{-1} but is not observed for compound IX. At 1670 cm^{-1} , decreased strength of —CN stretching frequency peak is observed. —OH peak, which is seen at 3150 cm^{-1} of *p*-methyl isonitrosoacetophenone, is not seen for the compound IX. —NH peak, which appeared at 3360 cm^{-1} of terephthalodihydrazone, disappeared in the spectrum of compound IX. The specific peak of triazine (C=C and C=N) framework is observed in 1540–1215 cm^{-1} interval. In addition, aliphatic —CH peak is observed in 1079 cm^{-1} .

EXPERIMENTAL

Materials and measurements. Pyruvic aldehyde 1-oxime (98%) (IV), terephthalaldehyde (99%), hydrazine hydrate (80%), 2-acetonaphthalen (99%), 4'-methylacetophenone (95%), and 4-acetylbiphenyl (98%) were purchased from Merck. The starting materials, isonitrosoacetophenone (I), isonitroso-1-acetylnaphtalene (II), *p*-methylisonitrosoacetophenone (III), and terephthalaldehydedihydrazone (V) were synthesized according to the previously published methods [18–21]. The $^1\text{H-NMR}$ spectra and elemental analysis for carbon, hydrogen, and nitrogen were

carried out in the Laboratories of the Scientific and Technical Research Council of Turkey (TUBITAK). $^1\text{H-NMR}$ spectra were recorded in DMSO- d_6 solutions on a Bruker 400 MHz spectrometer using TMS as an internal reference. Infrared spectra were recorded on a Perkin Elmer Model 1605 FT-IR spectrophotometer as KBr pellets in the region of 500–4000 cm^{-1} .

General procedure for the preparation of VII–XI. A solution of 2.40 mmol of compound (I–IV) in ethanol (20 mL) was added dropwise to a solution of 0.162 g (1.0 mmol) of compound (V) in ethanol (20 mL). After completion of dropping, the mixture was stirred until the temperature is up to room temperature. The mixture was allowed to stand to crystallize for 2 days. The formed yellow solid was filtered and washed with ethanol and ether.

2-(((1-(Hydroxyimino)propan-2-ylidene)hydrazono)methyl)benzylidene)hydrazono) propanal oxime (VI). This compound was obtained as yellow color crystal. Yield 0.108 g (52%); mp >300°C (decomp.); IR: OH 3159 cm^{-1} , CH (aromatic) 3065 cm^{-1} , C=N 1618 cm^{-1} , N—O 986 cm^{-1} . $^1\text{H NMR}$: δ 12.08 (s, 2H, NOH), 8.52 (d, 2H, CH, $J = 6.32$ Hz), 8.11 (d, 4H, $J = 12.30$ Hz, aromatic CH), 7.9 (s, 2H, CH), 2.31 ppm (s, 6H, CH₃); Anal. Calcd. for C₁₄H₁₆N₆O₂: C, 56.00; H, 5.33; N, 28.00. Found: C, 57.40; H, 5.62; N, 27.60.

1,4-Bis(6-phenyl-1,2,4-triazin-3-yl)benzene (VII). This compound was obtained as yellow color crystal. Yield 0.21 g (64%); mp >300°C (decomp.); IR: CH (triazine) 3331 cm^{-1} ; CH (aromatic) 3182 cm^{-1} ; C=C 1597 cm^{-1} ; C=N 1215 cm^{-1} . $^1\text{H-NMR}$: δ 8.74 (s, 2H, triazine ring); 7.90 (d, 4H, $J = 8.3$ Hz); 7.77 (s, 2H); 7.66 (d, 4H, $J = 8.3$ Hz); 7.17 ppm (s, 4H); Anal. Calcd. for C₂₄H₁₆N₆: C, 78.60; H, 4.10; N, 18.80. Found: C, 76.71; H, 4.53; N, 18.80.

1,4-Bis(6-(naphthalen-1-yl)-1,2,4-triazin-3-yl)benzene (VIII). This compound was obtained as yellow color crystal. Yield 0.24 g (%55); mp > 300°C (decomp.); IR: CH (triazine) 3333 cm^{-1} ; CH (aromatic) 2908 cm^{-1} ; C=C 1559, 1529, 1430, 1380, 1290 cm^{-1} ; C=N 1215 cm^{-1} . $^1\text{H-NMR}$: δ 8.7 (s, 2H, triazine ring), 8.10 (s, 4H), 7.90 (t, 4H, $J = 10.0$ Hz), 7.76 (s, 2H), 7.65 (t, 4H, $J = 8.3$ Hz), 7.18 ppm (d, 4H, $J = 10.35$ Hz); Anal. Calcd. for C₃₂H₂₀N₆: C, 74.20; H, 4.20; N, 21.60. Found: C, 73.10; H, 6.70; N, 20.20.

1,4-Bis(6-*p*-tolyl-1,2,4-triazin-3-yl)benzene (IX). This compound was obtained as yellow color crystal. Yield 0.29 g (%69); mp >300°C (decomp.); IR: CH (triazine) 3333 cm^{-1} ; CH (aromatic) 2915 cm^{-1} ; C=C 1565, 1540, 1450, 1350, 1270 cm^{-1} ; C=N 1215 cm^{-1} ; CH (aliphatic) 1079 cm^{-1} . $^1\text{H NMR}$: δ 8.65 (s, 2H, triazine ring), 7.70 (s, 4H), 7.80 (d, 4H, $J = 8.41$ Hz), 7.65 (d, 4H, $J = 8.34$ Hz), 2.45 ppm (s, 6H); Anal. Calcd. for C₂₆H₂₀N₆: C, 74.98; H, 4.84; N, 20.18. Found: C, 73.62; H, 5.60; N, 20.88.

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