

ORIGINAL RESEARCH

Development of a New and Efficient Synthesis Method of 1,2,4-Triazole-5-Thione Derivatives

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ABSTRACT: 3,4-Disubstituted-2,4-dihydro-5H-1,2,4-triazole-5-thiones were synthesized by a new one-pot, two-step synthesis method which was demonstrated to be superior than the current synthesis methods. The new method involves addition of alkyl/aryl isothiocyanates to substituted hydrazides in ethanol following the refluxing process of intermediate in 4N sodium hydroxide solution. According to our new synthesis procedure, reaction has gone to completion within 6 hours by higher product yields and reduced solvent usage.

KEYWORDS: 1,2,4-triazole-5-thione, synthesis, method development

INTRODUCTION

The chemistry of 1,2,4-triazole-5-thiones has been an interesting field of study for a long time. The synthesis of novel 1,2,4-triazole-5-thione derivatives and investigation of their biological activities have gained more importance in recent years. A survey of literature revealed their potential pharmacological activity profile as antibacterial (1-4), antifungal (5, 6), antitubercular (7, 8), antiviral (9, 10), anticancer (11-13) and anticonvulsant (14, 15). Besides the pharmacological significance of this heterocyclic ring system it is also an attractive scaffold to be constituted for chemical diversity. The current process for preparation of 1,2,4-triazole-5-thiones is achieved via synthesis, isolation and recrystallization of acyl/aryl substituted thiosemicarbazides (16). The current process required long reaction times and higher solvent costs. Furthermore, using environmentally safer solvents especially water has gained prominence in recent years and in our methodology we use water and ethanol to reduce the amount of waste water and waste solvent. Through our new one-pot, two-step synthesis method which was demonstrated to be superior than the current synthesis method; 1,2,4-triazole-5-thione derivatives were

synthesized by the addition of alkyl/aryl isothiocyanates to substituted hydrazides in ethanol following the refluxing process of intermediate in 4N sodium hydroxide solution.

The synthesis of 1,2,4-triazole-5-thione derivatives has been carried out according to the steps shown in Scheme 1. In the initial step, acyl/aryl substituted thiosemicarbazides were synthesized by the addition of alkyl/aryl isothiocyanates to substituted hydrazides in ethanol. In the second step, 1,2,4-triazole-5-thione derivatives were synthesized by refluxing the reaction medium in 4N sodium hydroxide solution and then neutralization with hydrochloric acid.

EXPERIMENTAL

Chemistry

All solvents and chemicals used in this study were supplied from Aldrich, Merck and Fluka and used without purification. Melting points (°C) were measured using Schmelzpunktbestimmer SMP II melting point apparatus, uncorrected. The reactions were monitored on Merck pre-coated aluminium TLC plates 60F-254, using ethyl acetate and petroleum ether (50:50) as solvent system and the products were visual-

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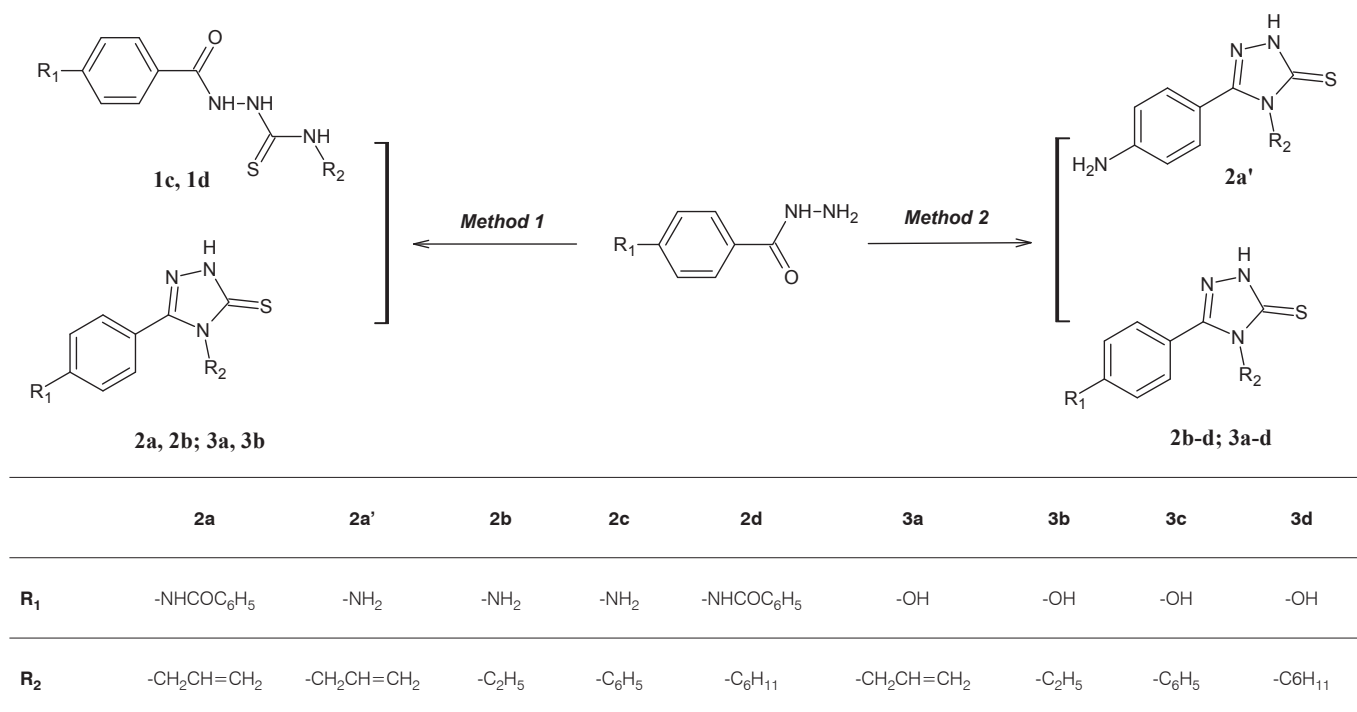
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SCHEME 1. Synthetic route to compounds 1c, 1d, 2a-d, 2a' and 3a-d

ized by using UV light. The liquid chromatographic system consists of an Agilent technologies 1100 series instrument equipped with a quaternary solvent delivery system and a model Agilent series G1315 A photodiode array detector. A Rheodyne syringe loading sample injector with a 50 μ l sample loop was used for the injection of the analytes. Chromatographic data were collected and processed using Agilent Chemstation Plus software. The separation of compounds were performed at ambient temperature by using a reversed phase Kromasil 100-5C18 (Hichrom, 4.6 x 250 mm) column. All experiments were employed in isocratic mode. The mobile phase was prepared by mixing acetonitrile and 0.1% phosphoric acid (65:35, v/v) and filtered through a 0.45 μ m membrane and degassed by ultrasonication, prior to use. Solvent delivery was employed at a flow rate of 1 ml.min⁻¹. Detection of the analytes were carried out at 254 nm. The Infra-red spectra were recorded on Shimadzu FTIR-8400S Spectrophotometer and expressed in wavenumber ν (cm⁻¹). ¹H-NMR spectra were recorded on Varian Unity Inova Spectrometer at 500 MHz and Varian Spectrometer at 300 MHz, using DMSO-*d*₆ as a solvent; tetramethylsilane (TMS) was used as internal standard. All NMR chemical shifts are reported as δ values in parts per million (ppm) and coupling constant (*J*) are given in Hertz (Hz). ¹H-NMR and Mass analyses were provided by Faculty of Pharmacy Center Laboratory (Ankara University) and the Scientific and Technical Research Council of Turkey, TÜBİTAK (Ankara).

Ethyl 4-(benzoylamino)benzoate

To the solution of ethyl 4-aminobenzoate (benzocaine; 0.03 mol) in ether benzoyl chloride (0.03 mol) was added dropwise with stirring. Shortly after the addition was completed the appearing precipitate was collected and washed with water and recrystallized from ethanol. Yield 67%, mp: 137°C (17).

4-(Benzoylamino)benzoic acid hydrazide

Ethyl 4-(benzoylamino)benzoate (0.01 mol) and hydrazine hydrate (9 ml) were heated under reflux for 30 mins. and 15 ml ethanol was added to the reaction medium. The mixture was heated under reflux for 45 mins. The crude product was filtered and washed with boiling ethanol. Yield 80%, mp: 235°C (17).

1,4-Disubstituted aroylthiosemicarbazides and 3,4-Disubstituted-2,4-dihydro-5H-1,2,4-triazole-5-thiones (Method 1)

To the solution of appropriate hydrazide (0.005 mol) in 30 ml ethanol; ethyl, allyl, phenyl, cyclohexyl isothiocyanates (0.005 mol) and 2N NaOH solution (8 ml) were added respectively under reflux for 4 h. Acidification of the reaction liquor with 2N HCl solution furnished the precipitate. The crude product was filtered and washed with distilled water until the filtrate was no longer acidic and then recrystallized from ethanol.

3,4-Disubstituted-2,4-dihydro-5H-1,2,4-triazole-5-thiones (Method 2)

After two hours of refluxing appropriate hydrazide (0.005 mol) with ethyl, allyl, phenyl, cyclohexyl isothiocyanates (0.005 mol) in 30 ml ethanol, 4N NaOH solution (15 ml) were added and the reaction medium was refluxed for an additional 4 hours. Acidification of the reaction liquor with 2N HCl solution furnished the precipitate. The crude product was filtered and washed with distilled water until the filtrate was no longer acidic and then recrystallized from ethanol.

3-[4-(Benzoylamino)phenyl]-4-allyl-2,4-dihydro-5H-1,2,4-triazole-5-thione (2a)

The compound was synthesized via method 1 by using 4-(benzoylamino)benzoic acid hydrazide as the starting compound. It was recrystallized from ethanol and obtained as yellow crys-

tals. Yield 51%, mp: 191-195°C. FTIR, (cm^{-1}): 3295 (NH str, triazole and amide), 3100 (=C-H str), 2944 (C-H str), 1653 (amide C=O str), 1597, 1558, 1512 and 1489 (C=N str and C=C str), 1185 (C=S str). $^1\text{H NMR}$: δ (ppm) 4.72 (s, 2H, N-CH₂-), 4.81-5.16 (m, 2H, =CH₂), 5.79-5.85 (m, 1H, -CH=), 7.50-7.67 (m, 4H, Ar-H), 7.89-7.97 (m, 5H, C₆H₅), 10.54 (s, 1H, CONH), 13.99 (s, 1H, NH).

3-(4-Aminophenyl)-4-allyl-2,4-dihydro-5H-1,2,4-triazole-5-thione (2a)

The compound was also synthesized via method 2 by using 4-(benzoylamino)benzoic acid hydrazide as the starting compound. It was recrystallized from ethanol and obtained as yellow crystals. Yield 59%, mp: 224°C (5). HPLC t_R (min.): 2.72. FTIR, (cm^{-1}): 3454 (NH asymmetric str), 3338 (NH symmetric str), 3213 (NH str, triazole), 3072 and 3022 (=C-H str), 1608, 1577, 1519 and 1491 (C=N str and C=C str), 1192 (C=S str).

3-(4-Aminophenyl)-4-ethyl-2,4-dihydro-5H-1,2,4-triazole-5-thione (2b)

The compound was also synthesized via method 2 by using 4-(benzoylamino)benzoic acid hydrazide as the starting compound. It was recrystallized from ethanol and obtained as yellow crystals. Yield 79%, mp: 248-250°C (5). HPLC t_R (min.): 2.63. FTIR, (cm^{-1}): 3464 (NH asymmetric str), 3352 (NH symmetric str), 3093 and 3022 (=C-H str), 1614, 1579, 1519 and 1489 (C=N str and C=C str), 1176 (C=S str).

3-(4-Aminophenyl)-4-phenyl-2,4-dihydro-5H-1,2,4-triazole-5-thione (2c)

The compound was synthesized via method 2 by using 4-(benzoylamino)benzoic acid hydrazide as the starting compound. It was recrystallized from ethanol and obtained as yellow crystals. Yield 65%, mp: 290°C (5). HPLC t_R (min.): 2.82. FTIR, (cm^{-1}): 3470 (NH asymmetric str), 3335 (NH symmetric str), 3215 (NH str, triazole), 3088 and 3016 (=C-H str), 1604, 1552, 1512 and 1496 (C=N str and C=C str), 1180 (C=S str).

3-[4-(Benzoylamino)phenyl]-4-cyclohexyl-2,4-dihydro-5H-1,2,4-triazole-5-thione (2d)

The compound was synthesized via method 2 by using 4-(benzoylamino)benzoic acid hydrazide as the starting compound. It was recrystallized from ethanol and obtained as yellow crystals. Yield 31%, mp: 200-206°C. HPLC t_R (min.): 3.53. FTIR, (cm^{-1}): 3228 (NH str), 3196 (NH str, triazole), 3090 (=C-H str), 2929 and 2852 (C-H asymmetric and symmetric str), 1672 (C=O str), 1614, 1591, 1512 and 1489 (C=N str and C=C str), 1170 (C=S str).

3-(4-Hydroxyphenyl)-4-allyl-2,4-dihydro-5H-1,2,4-triazole-5-thione (3a)

The compound was synthesized via method 2 by using 4-hydroxybenzoic acid hydrazide as the starting compound. It was recrystallized from ethanol and obtained as yellow crystals. Yield 73%, mp: 167-170°C (168-169°C (18), 176-178 (19)). HPLC t_R (min.): 2.72. FTIR, (cm^{-1}): 3345 (O-H str), 3376 and 3197 (NH str, triazole), 3074 (=C-H str), 1594, 1530, 1495 (C=N str and C=C str), 1427 (O-H bending), 1180 (C=S str). $^1\text{H NMR}$: δ (ppm) 4.64 (s, 2H, N-CH₂-), 4.81-5.14 (m, 2H, =CH₂), 5.76-5.89 (m, 1H, -CH=), 6.87 (d, $J = 9$ Hz, 2H, Ar-H protons in ortho position due to hydroxyl group), 7.46 (d, $J = 9$ Hz, 2H, Ar-H protons

in meta position due to hydroxyl group), 10.09 (s, 1H, -OH), 13.86 (s, 1H, NH).

The compound was also synthesized via method 1 by using 4-hydroxybenzoic acid hydrazide as the starting compound. It was recrystallized from ethanol and obtained as yellow crystals. Yield 52%, mp: 167-170°C (168-169°C (18), 176-178 (19)). HPLC t_R (min.): 2.71.

3-(4-Hydroxyphenyl)-4-ethyl-2,4-dihydro-5H-1,2,4-triazole-5-thione (3b)

The compound was synthesized via method 1 by using 4-hydroxybenzoic acid hydrazide as the starting compound. It was recrystallized from ethanol and obtained as white crystals. Yield 18%. HPLC t_R (min.): 2.64. FTIR, (cm^{-1}): 3309 (O-H str), 3161 (NH str, triazole), 3020 (=C-H str), 1610, 1597, 1514, 1487 (C=N str and C=C str), 1411 (O-H bending), 1180 (C=S str).

The compound was synthesized via method 2 by using 4-hydroxybenzoic acid hydrazide as the starting compound. It was recrystallized from ethanol and obtained as white crystals. Yield 86%, mp: 219°C (212-214°C (18)). HPLC t_R (min.): 2.63.

3-(4-Hydroxyphenyl)-4-phenyl-2,4-dihydro-5H-1,2,4-triazole-5-thione (3c)

The compound was synthesized via method 2 by using 4-hydroxybenzoic acid hydrazide as the starting compound. It was recrystallized from ethanol and obtained as yellow crystals. Yield 42%, mp: 260-265°C (267-268°C (18)). HPLC t_R (min.): 2.79. FTIR, (cm^{-1}): 3440 (O-H str), 3134 (NH str, triazole), 3055 (=C-H str), 1608, 1595, 1512, 1496 (C=N str and C=C str), 1433 (O-H bending), 1176 (C=S str).

3-(4-Hydroxyphenyl)-4-cyclohexyl-2,4-dihydro-5H-1,2,4-triazole-5-thione (3d)

The compound was synthesized via method 2 by using 4-hydroxybenzoic acid hydrazide as the starting compound. It was recrystallized from ethanol and obtained as white crystals. Yield 68%, mp: 253-256°C (247-249°C (18)). HPLC t_R (min.): 3.51. FTIR, (cm^{-1}): 3344 (O-H str), 3095 (NH str, triazole), 3014 (=C-H str), 2937 (C-H str), 1614, 1593, 1510, 1487 (C=N str and C=C str), 1386 (O-H bending), 1188 (C=S str). $^1\text{H NMR}$: δ (ppm) 0.92-2.16 (m, 10H, -C₆H₁₁), 4.24 (s, 1H, -C₆H₁₁), 6.89 (d, $J = 9$ Hz, 2H, Ar-H protons in ortho position due to hydroxyl group), 7.31 (d, $J = 9$ Hz, 2H, Ar-H protons in meta position due to hydroxyl group), 10.04 (s, 1H, -OH), 13.71 (s, 1H, NH).

Synthesis method for the 1,4-disubstituted aroylthiosemicarbazide standarts (lit.17)

Appropriate hydrazide (0.005 mol) was heated with ethyl, allyl, phenyl, cyclohexyl isothiocyanates (0.005 mol) under reflux for 2-2.5 h in ethanol (65 ml). The crude product was filtered and recrystallized from ethanol.

Synthesis method for 3,4-disubstituted-2,4-dihydro-5H-1,2,4-triazole-5-thione standarts (lit. 5)

A mixture of appropriate thiosemicarbazide (0.005 mol) in 2N NaOH solution (5 ml) were heated under reflux for 4h. The reaction medium was cooled and acidified by using 2N HCl solution. The precipitate was washed with distilled water until the filtrate was no longer acidic and then recrystallized from ethanol.

RESULT AND DISCUSSION

To achieve 1,2,4-triazoles, derived from 4-hydroxybenzoic acid hydrazide and 4-benzoyl-aminobenzoic acid hydrazide, the one-pot synthesis method of Shah *et al.* (18) was employed. Shah *et al.* (18), reported the synthesis of 3-phenyl-4-*n*-butyl-5-mercapto-1,2,4-triazole in yield of 50% by using benzoic acid hydrazide as starting compound. According to the method 1 (18); the ethanolic solutions of the hydrazides, mentioned above, were refluxed with ethyl-, allyl-, cyclohexyl- and phenyl isothiocyanates following 4 hours of heating in 2N NaOH. Administration of this method by using cyclohexyl and phenyl isothiocyanates, 1,4-disubstituted thiosemicarbazides were gained in stead of 3,4-disubstituted-2,4-dihydro-5H-1,2,4-triazole-5-thiones; consequently the applied method was found workable onyl for reactants ethyl- and allyl isothiocyanates. Our one-pot synthesis method (method 2) was developed to gain these failed compounds. In accordance with one-pot two-step reaction procedure; acyl/aroil substituted thiosemicarbazides were synthesized by the addition of alkyl/aryl isothiocyanates to substituted hydrazides in ethanol and in the second step, 1,2,4-triazole-5-thione derivatives were synthesized by the refluxing the reaction medium in 4N sodium hydroxide solution and then neutralization with hydrochloric acid.

The IR spectra of compounds **1c** and **1d** were characterized by the presence of a C=O absorption bands at 1670 and 1653 cm^{-1} . The signals at 7.69, 10.18 and 10.48 ppm and 7.60, 9.08, 9.98 ppm were attributed -NH- moieties of thiosemicarbazide.

In the IR spectra of compound **2a**, which was gained through method 1, absorption bands attributable to aromatic primary amine -NH₂- was not observed moreover the presence of C=O absorption band at 1653 cm^{-1} clarifying existence of 4-benzoylamino moiety. The signal at 10.54 ppm attributable to -NH- proton of 4-benzoylamino moiety provided confirmatory evidence for unhydrolyzed amide. Compounds **2b-d** were synthesized via method 2 with the yield range 31-79%. Melting points of compounds **2a-c** were found in accordance with literature (5, 20, 21). Consequential check of IR spectra of compounds **2a** and **2c** revealed absence of bands between 1650-1700 cm^{-1} appertaining C=O groups and existence of bands at 3213 and 3215 cm^{-1} attributable to triazole -NH .

Compounds **2b** and **2c** were also synthesized by using standart synthesis method (5); their retention times (Comparative retention times for compounds synthesized by method 1 and 2 were given in Table 1.) and UV spectra were matched with the compounds that were gained through our one-pot two step reaction procedure. (Overlaid UV spectra of compounds **2b** and **2c** that were gained through method 1 and 2 were given in Figure 1.). Gathering data from IR bands at 1672 and 3228 cm^{-1} corresponding to C=O and triazole N-H group of compound **2d** convinced us about cyclization of thiosemicarbazide to form triazole ring.

TABLE 1. Comparative retention times of compounds gained by different methods

Compounds	Retention time (min)	
	Products by Method 1 or Method 2 (1,2)	Standarts
1c	3.14 (1)	3.14
1d	2.79 (1)	2.80
2b	2.63 (2)	2.63
2c	2.81 (2)	2.81
3a	2.71 (2)	2.71
3b	2.63 (2)	2.63
3d	3.51 (2)	3.52

Compounds **3a-d** were synthesized by using 4-hydroxybenzoic acid hydrazide as starting compound in accordance with method 2 and their yields were detected between 42-86%. Absence of C=O stretching bands between 1650-1700 cm^{-1} and existence of N-H stretching bands between 3376-3095 cm^{-1} were also substantive content relating to triazole ring closure. (Overlaid UV spectra of compounds **3a**, **3b** and **3d** that were gained through method 1 and 2 were given in Figure 2.). Compound **3a** were synthesized by using procedures of both methods. The ¹HNMR spectra of products gained by using method 1 and method 2 were evaluated and -NH- signals of both products were detected at 13.86 ppm.

CONCLUSION

Consequently, a new method was developed for the synthesis of 3,4-disubstituted-1,2,4-triazole-5-thione derivatives from

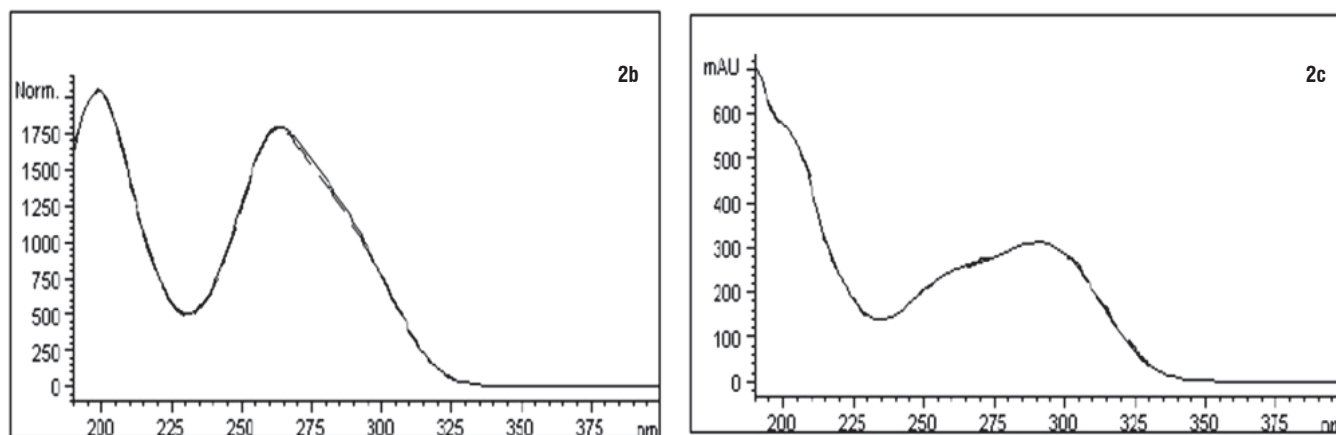


FIGURE 1. Overlaid UV spectra of compounds **2b** and **2c**. (For compounds **2b** and **2c**; dotted lines belong to the products achieved by standart synthesis method and continuous lines belong to the products achieved by using method 2)

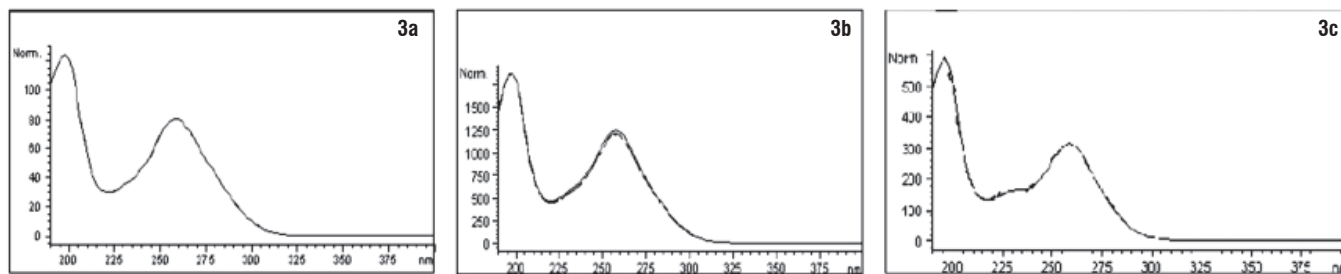


FIGURE 2. Overlaid UV spectra of compounds 3a, 3b and 3d. (For compound 3a; dotted line belongs to the product achieved by employing method 1 and continuous line belongs to the product achieved by using method 2. For compound 3b; dotted line belongs to the product achieved by employing method 2 and continuous line belongs to the product achieved by using method 3. For compound 3d; dotted line belongs to the product achieved by employing method 2 and continuous line belongs to the product achieved by standart synthesis method.)

4-hydroxybenzoic acid hydrazide and 4-benzoyl-aminobenzoic acid hydrazide. The current processes for preparation of 1,2,4-triazole-5-thiones involve synthesis, isolation and recrystallization of acyl/aryl substituted thiosemicarbazides requiring long reaction times and higher solvent costs. Our new one-pot, two-step synthesis method was demonstrated to be superior than the current synthesis methods by means of leading

desired products by higher yields within only 4 or 6 hours. The developed method has no notable advantage to current methods in terms of each reaction time but diminished experimental procedure is easily appreciable. The products of our method were compared to the products of current literature methods through experimental data gathered from high performance liquid chromatography, IR and $^1\text{H-NMR}$ spectroscopy.

1,2,4-Triazol-5-Tiyon türevi bileşiklerin elde edilmesi için yeni ve etkili bir sentez yöntemi geliştirilmesi

ÖZET: Çalışmamız kapsamında, 3,4-disubstitüe-2,4-dihidro-5H-1,2,4-triazol-5-tiyon türevi bileşiklerin elde edilebilmesi için literatürde kayıtlı bulunan diğer sentez yöntemlerinden farklı olarak aynı tepkime kabında gerçekleştirilen iki basamaklı bir sentez yöntemi geliştirilmiş ve geliştirilen yöntemin üstünlüğü diğer sentez yöntemleriyle karşılaştırılarak ispatlanmıştır. Sübstitüe hidrazitlerin etanollü çözeltilerinin alkil/aryl izotiyosiyanatlarla ısıtılmasını takiben tepkime ortamına 4N sodyum hidroksit çözeltisi ilave edilerek ısıtmaya devam edilmiştir. Oluşturulan yeni sentez yönteminde, tepkimenin 6 saat içerisinde tamamlandığı, literatürdeki diğer yöntemlerle kıyaslandığında daha yüksek verim elde edildiği ve daha az çözücü kullanıldığı tespit edilmiştir.

ANAHTAR KELİMELER: 1,2,4-triazol-5-tiyon, sentez, yöntem geliştirme

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