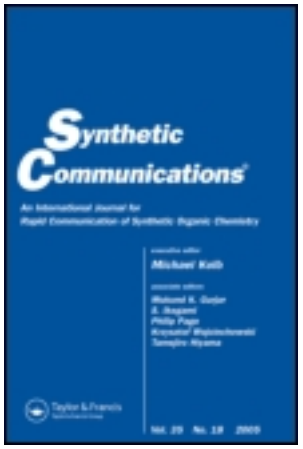

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ECOFRIENDLY SOLVENTLESS SYNTHESIS AND REDUCTION REACTION OF SOME TRIAZOLE COMPOUNDS AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITY

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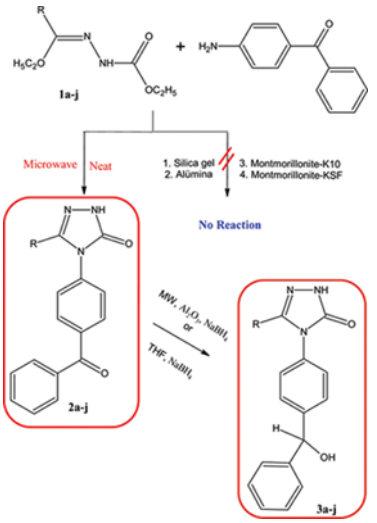
GRAPHICAL ABSTRACT



Abstract *A number of triazole-3-one compounds have been synthesized, and reduction of the carbonyl group in the molecule has been carried out to give a corresponding hydroxyl group that possesses asymmetric carbon atom in good yields and short reaction times. It is eco-friendly because it is produced by straightforward microwave irradiation in the absence of solvent. All newly synthesized compounds were also screened for their antimicrobial*

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activities. The antimicrobial activity study revealed that ***2d, 2i, 3c,*** *and* ***3g–j*** *showed good activity against a variety of microorganisms.*

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Keywords Antimicrobial activity; green chemistry; microwave-assisted synthesis; solvent-free; 1,2,4-triazole-3-one

INTRODUCTION

A dramatic increase in antibiotic resistance, especially among Gram-positive bacteria, triggered a clear need for the discovery of new antimicrobials rather than analogs of the existing ones.[1] Traditionally, small molecules have been a reliable source for discovering novel biologically active compounds.

1,2,4-Triazole compounds have been found to be useful for applications in medicine and agriculture.[2] The synthesis, reactions, and biological properties of substituted triazole constitute a significant part of modern heterocyclic chemistry.[3] Compounds with the triazole ring system have many pharmacological properties and play important roles in biochemical processes. There have been reported applications in a wide spectrum of potential biological properties, such as antifungal,[4] antitumor,[5] analgesic,[6] antibacterial,[7,8] and cancer therapy.[9] Antibacterial activity data of these structures showed considerable activity against Gram-negative and Gram-positive bacteria as well as some strains of fungi.[10–12] Thus, the heterocyclic system is an attractive scaffold to be utilized for exploiting chemical diversity.

The application of microwave (MW) irradiation as an effective energy source for activation of reactions has now become a very popular and useful technology in organic chemistry.[13] Nowadays economical and environmental conditions are forcing the chemical community to search for more efficient ways of performing chemical transformations in a single operation by reusing catalysts and avoiding toxic and costly reagents, large amounts of solvents, and expensive purification techniques.[14] Reactions using solid-supported reagents and scavengers have created considerable interest among synthetic chemists around the world.[15] Because of several advantages in terms of yield, purity, and selectivity, supported reagents have been used under solvent-free conditions for the synthesis of various important synthetic intermediates.[16]

The combination of microwave irradiation and solvent-free reaction conditions leads to enhanced reaction rates, greater yields of pure products, easier workup, and selective conversions, all advantages of the ecofriendly approach.[17,18] Consequently, this protocol should be welcomed in these environmentally conscious times.

The growing importance of triazole compounds has led to the development of new methods for their synthesis, including microwave-assisted synthesis. Thus, the development of simple, convenient, safe, and efficient methods for the preparation of these molecules still continues to be an interesting and attractive area of research in synthetic chemistry.

In the present work, we studied the triazole formation, taking different parameters of solid supports like (i) montmorillonite KSF, (ii) montmorillonite K10, (iii) alumina, and (iv) silica gel. However, no reaction occurred. Encouraged by recent focus on the green chemical theme of eliminating the use of solvents, we

extended our studies to neat reactions, those that could be made successful without any solid supports. It did not lead to any side reactions and no detectable by-product was observed. Consequently, we extended this condition to the synthesis of compounds (**2a–j**).

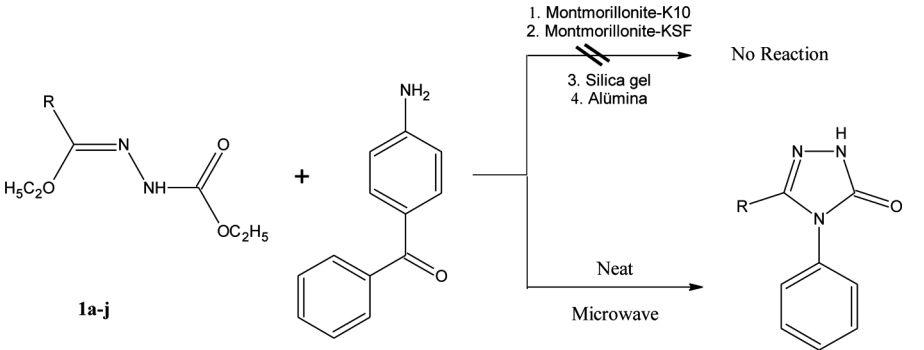
RESULTS AND DISCUSSION

Recently, we reported the synthesis of triazole compounds by both microwave irradiation and conventional heating.[19,20] However, poor reaction yields, selectivity, and long reaction times dissuade more systematic study of the reaction. Therefore, we planned to focus our study on the synthesis and reduction of triazole compounds via conventional and microwave-assisted synthesis under solvent-free media.

(*N*′-Ethoxycarbonyl)-4-alkyl(aryl)hydrazonic acid ethyl ester can be considered as useful intermediate leading to the formation of heterocycles, such as 1,2,4-triazole-3-ones. We synthesized some (*N*′-ethoxycarbonyl)-4-alkyl(aryl)hydrazonic acid ethyl ester (**1a–j**) according to the literature.[20–22]

At first, we had to optimize the reaction conditions for the synthesis of 5-aryl(alkyl)-4-(4-benzoylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**2a–j**) by the reaction of (*N*′-ethoxycarbonyl)-4-alkyl(aryl)hydrazonic acid ethyl ester (**1a–j**) with p-aminobenzophenone. We tried different reaction conditions to carry out this reaction under microwave irradiation in the absence of solvent. For this we used solid support, such as montmorillonite KSF, montmorillonite K10, alumina, and silica gel, but no reaction occurred. However, reaction occurred when heated neat above the melting points under microwave irradiation (Scheme 1).

The polarity of the system is increased during the reaction progress from the neutral ground state (GS) to the dipolar transition state (TS) for cyclization. Consequently, microwave stabilizing effects by dipole–dipole interactions with the electric



R		R	
a	$-CH_3$	**f**	$-CH_2C_6H_4$(-Cl, m)
b	$-CH_2CH_3$	**g**	$-CH_2C_6H_4$(-Cl, o)
c	$-C_6H_5$	**h**	$-CH_2C_6H_4$($-CH_3$, p)
d	$-CH_2C_6H_5$	**i**	$-CH_2C_6H_4$($-CH_3$,m)
e	$-CH_2C_6H_4$(-Cl, p)	**j**	$-CH_2C_6H_4$($-CH_3$, o)

Scheme 1. Pathway for the formation of the 3H-1,2,4-triazol-3-ones.

field are increased with the polarity of reactants. Such an explanation of microwave effects is supported by calculations suggesting a relation between microwave irradiation and the polarity of the transition state,[23] so we can say that in our reactions specific microwave effects occur when the reaction mixture is melting.

Encouraged by these findings, we next investigated the optimum reaction condition for the synthesis of 3*H*-1,2,4-triazol-3-ones (**2a–j**) under conventional conditions and a monomodal microwave oven. For conventional conditions, the reaction occurred in an oil bath for 5 h at 170 °C. For a Discover monomodal microwave oven, mixture was irradiated in closed vessels with pressure control at 150 °C for 3 min (hold time) at 300 W maximum power.

By comparision of data, it is obvious that the microwave irradiation protocol resulted in much faster reactions and significantly greater yields (Table 1) than the thermal heating process.

Here, we report our further investigations concerning the reduction of the carbonyl group in the molecule, which have been carried out to produce a corresponding hydroxyl group that possesses asymmetric carbon atoms under microwave irradiation as well as conventional methods. However, there was no reduction of carbonyl in the triazole ring but only a reduction of carbonyl in the substitute group bounding the N-4 nitrogen atom. Thus, in a conventional experiment, we obtained reductive products **3a–j** in the presence of an ion exchange solid (Amberlyst-15 H^+) in the aprotic solvent tetrahydrofuran (THF). Amberlyst-15 (H^+) is an effective material for reduction of hindered and unreactive ketones.[24] However, we obtained **3a–j** in the presence of alumina under microwave irradiation in the absence of solvent (Scheme 2).

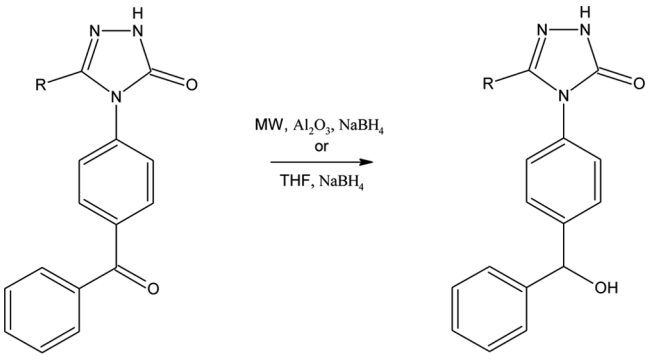
Varma and Saini[25] demonstrated the reduction of the carbonyl group in a solid state under microwave irradiation. Here, we synthesized **3a–j** in a monomode microwave synthesizer for 2 min at 300 W maximum power with high yield (Table 2).

A comparison of the spectral data gave some information as to the nature of the products. In this context, a comparison of the infrared (IR) spectral data clearly indicates the formation of compounds **3a–j** by the disappearance of the C=O band at

Table 1. Comparison of yields under microwave irradiation and conventional heating (for compounds **2a–j**)

	Yield (%)	
Compound	Oil bath[a]	Microwave[b]
2a	48	78
2b	56	81
2c	54	75
2d	54	85
2e	64	88
2f	58	76
2g	53	83
2h	67	77
2i	59	91
2j	63	70

[a]5 h at 170 °C.
[b]3 min at 150 °C.



Scheme 2. Pathway for the reduction reaction of the carbonyl group.

about 1649–1668 cm^{-1} in compounds **2a–j** and the appearance of the OH band at about 3375–3439 cm^{-1} and C—O band at about 1013–1059 cm^{-1} in compounds **3a–j.** In addition, in the ^1H NMR spectrum of **3a–j** revealed for OH group doublet signals at about 5.91–6.08 ppm in the dimethylsulfoxide (DMSO-d_6) and broad singlet signal at about 2.88–3.38 ppm in the $CDCl_3$ and revealed for CH group doublet signals at about 5.70–5.77 ppm in the DMSO-d_6 and singlet signals at about 5.80–5.86 ppm in the $CDCl_3$. The ^{13}C NMR spectrum of **3a–j** shows a signal that indicates the appearance of CH groups at about 73.52–75.81 ppm and the disappearance of the C=O group at about 194.84–195.69 ppm in compounds **2a–j**.

Antibacterial Activities

While antibacterial, antituberculotic, and antifungal activity were shown on some tested compounds, some of compounds did not show any antimicrobial

Table 2. Comparison of yields under microwave irradiation and conventional heating (for compounds **3a–j**)

	Yield (%)	
Compound	THF[a]	Microwave[b]
3a	45	72
3b	58	75
3c	56	80
3d	52	68
3e	54	75
3f	56	65
3g	47	70
3h	36	63
3i	41	78
3j	42	81

[a]12 h at rt.
[b]2 min at 150 °C.

Table 3. Antimicrobial activity of the compounds (μg/ml)

	Microorganism and minimal inhibition concentration								
Compound	Ec	Yp	Pa	Sa	Ef	Bc	Ms	Ca	Sa
2a	—	—	—	—	—	—	—	—	—
2b	—	—	—	—	—	—	—	—	—
2c	—	—	—	—	—	—	—	—	—
2d	—	—	—	—	—	—	—	250	125
2e	—	—	—	—	—	—	—	—	—
2f	—	—	—	—	—	—	—	—	—
2g	—	—	—	—	—	—	—	—	—
2h	—	—	—	—	—	—	—	—	—
2i	—	—	—	—	—	—	15.6	31.3	31.3
2j	—	—	—	—	—	—	—	—	—
3a	—	—	—	—	—	—	—	—	—
3b	—	—	—	—	—	—	—	—	—
3c	—	—	—	125	125	62.5	125	—	—
3d	—	—	—	—	—	—	—	—	—
3e	—	—	—	—	—	—	—	—	—
3f	—	—	—	—	—	—	—	—	—
3g	—	—	—	62.5	62.5	62.5	31.3	—	—
3h	—	—	—	125	125	125	15,6	—	—
3i	—	—	—	250	250	250	62,5	—	—
3j	—	—	—	250	250	250	62.5	—	—
Amp.	2	32	>128	2	2	<1			
Strep.							4		
Flu.								<8	<8

Notes. Ec, *E. coli* ATCC 25922; Yp, *Y. pseudotuberculosis* ATCC 911; Pa, *P. aeruginosa* ATCC 43288; Sa, *S. aureus* ATCC 25923; Ef, *E. faecalis* ATCC 29212; Bc, *B. cereus* 702 Roma; Ms, *M. smegmatis* ATCC607; Ca, *C. albicans* ATCC 60193; *S. cerevisiae* RSKK 251; Amp., ampicillin; Strep., streptomycin; Flu., fluconazole; —, no activity.

activity. Compounds **2i, 3c, 3g–3j** demonstrated antitubercolitic activity (*M. smegmatis*) in 15.6–250 μg/ml concentration. Compound **2d** exhibited antimicrobial activity against only yeast (*C. albicans*, *S. cerevisiae*) fungals. Compounds **3c** and **3g–3j** exhibited antimicrobial activity against Gram-positive *M. smegmatis* in 15–250 μg/ml concentration. The results are shown in Table 3.

CONCLUSION

We have developed a novel and efficient approach for the synthesis of some 3*H*-1,2,4-triazol-3-ones and reduction of carbonyl group in these molecules under microwave irradiation in the absence of solvent. The important advantages of this procedure include (a) operational simplicity (ease of setup and workup), (b) safe and environmentally benign solvent-free procedure (eliminating toxic organic solvents as reaction medium), (c) good yield of the products with high purity, (d) mild reaction conditions, (e) good selectivity, (f) general applicability, accommodating a variety of substitution patterns, and (g) effective antibacterial activities (Table 3) for the compounds **3a–j**.[26]

EXPERIMENTAL

Chemistry

Melting points were determined in open capillaries on a Büchi digital melting-point apparatus and were uncorrected. Infrared (IR) spectra were recorded in KBr pellets on a Perkin–Elmer 100 Fourier transform (FT)-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian 400 spectrometer using $CDCl_3$ and DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts are given in parts per million, and coupling constants J are in hertz. Elemental analyses were performed on a Carlo Erba 1106 CHN analyzer. A monomode CEM-Discover microwave was used in the standard configuration as delivered, including proprietary software. All experiments were carried out in microwave process vials (30 mL) with control of the temperature by IR detection temperature sensor. The temperature was computer monitored and maintained by discrete modulation of delivered microwave power. After completion of the reaction, the vial was cooled to 60 °C by air jet cooling.

General Procedure for the Synthesis of Compounds 2a–j Under Conventional Conditions

A mixture of the corresponding (*N*′-ethoxycarbonyl)-4-alkyl(aryl)hydrazonic acid ethyl ester (**1a–j**) (0.01 mol) and p-aminobenzophenone (0.01 mol) was heated in an oil bath for 5 h (monitored by TLC, ethylacetate–hexane, 3:1) at 170 °C. The crystals formed on cooling were recrystallized from ethyl acetate–petroleum ether (3:1) to give pure **2a–j**.

General Procedure for the Synthesis of Compounds 2a–j in a Monomode Microwave Synthesizer

A mixture of the corresponding (*N*′-ethoxycarbonyl)-4-alkyl(aryl)hydrazonic acid ethyl ester (**1a–j**) (0.01 mol) and p-aminobenzophenone (0.01 mol) was irradiated in closed vessels with pressure control at 150 °C for 3 min (hold time) at 300 W maximum power. After the completion of the reaction (monitored by TLC, AcOEt/hexane, 3:1) the crystals formed on cooling were recrystallized from ethyl acetate–petroleum ether (3:1) to give pure **2a–j**.

General Procedure for the Synthesis of Compounds 3a–j Under Conventional Condition

A mixture of the **2a–j** (0.01 mol), $NaBH_4$ (0.03 mol), and amberlyst-15 (H^+) (5 g) was stirred at room temperature for 12 h in dry tetrahydrofurane (100 mL) (monitored by TLC, ethylacetate–hexane, 3:1). The reaction mixture was filtered. The solvent was removed under reduced pressure. The residue was recrystallized from ethyl acetate–petroleum ether (3:1) to give pure **3a–j**.

General Procedure for the Synthesis of Compounds 3a–j in a Monomode Microwave Synthesizer

A mixture of **2a–j** (0.01 mol), $NaBH_4$ (0.03 mol) and neutral alumina (9.5 g) was added in a pyrex open vessel (30 mL) and microwave irradiated at 150 °C for

2 min (hold time) at 300 W maximum power. Completion of the reaction was indicated by TLC (ethylacetate–hexane, 3:1). The reaction mass was eluted with ethanol and 25 mL of water was added and heated for 10 min. The solvent was removed under reduced pressure. The residue was recrystallized from ethyl acetate–petroleum ether (3:1) to give pure **3a–j**.

MICROBIOLOGY

All test microorganisms were obtained from the Hifzissihha Institute of Refik Saydam (Ankara, Turkey) and were as follows: *Escherichia coli* (*E. coli*) ATCC35218, *Yersinia pseudotuberculosis (Y. pseudotuberculosis*) ATCC911, *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC43288, *Enterococcus faecalis* (*E. faecalis*) ATCC29212, *Staphylococcus aureus* (*S. aureus*) ATCC25923, *Bacillus cereus* (*B. cereus)* 709 Roma, *Mycobacterium smegmatis* (*M. smegmatis*) ATCC607, *Candida albicans* (*C. albicans*) ATCC60193, and *Saccharomyces cerevisiae* (*S. cerevisia*) RSKK 251. All the newly synthesized compounds were weighed and dissolved in dimethylsulfoxide (DMSO) to prepare extract stock solution of 10.000 μg/ml.

The antimicrobial effects of the substances were tested quantitatively in respective broth media by using double microdilution, and the minimal inhibition concentration (MIC) values (μg/ml) were determined.[27] The antibacterial and antifungal assays were performed in Mueller-Hinton broth (MH) (Difco, Detroit, MI) at pH 7.3 and buffered yeast nitrogen base (Difco, Detroit, MI) at pH 7.0, respectively. The microdilution test plates were incubated for 18–24 h at 35 °C. Brain heart infusion broth (BHI) (Difco, Detriot, MI) was used for *M. smegmatis* and incubated for 48–72 h at 35 °C.[28] The MIC was defined as the lowest concentration that showed no growth. Ampicillin (10.000 μg g/ml), streptomycin 10.000 μg g/ml, and fluconazole (2.000 μg g/ml) were used as standard antibacterial and antifungal drugs, respectively. Dimethylsulfoxide with dilution of 1:10 was used as solvent control.

SUPPLEMENTARY INFORMATION

Full experimental details for all experiments are given in the Supplementary Information, available online.

ACKNOWLEDGMENT

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