

Mild and ecofriendly tandem synthesis of 1,2,4-triazolo [4,3-*a*]pyrimidines in aqueous medium

Anshu Dandia*^a, Pritima Sarawgi^a, Kapil Arya^b, and Sarita Khaturia^a

^aDepartment of Chemistry, University of Rajasthan, Jaipur 302004, INDIA

^bIndian Oil Corporation Limited, Faridabad, India

E-mail: dranshudandia@yahoo.co.in

Abstract

A rapid, efficient, clean and environmentally benign exclusive synthesis of 1,2,4-triazolo[4,3-*a*]pyrimidines from the reaction of amino triazole, carbonyl compounds and alkene-nitrile derivatives has been developed in an aqueous medium in an excellent yields using microwaves or ultrasonic waves. The results are compared with conventional heating. Structural assignments are based on spectroscopic data (IR, ¹HNMR, ¹³CNMR, mass spectra). Further the product structure is confirmed by the single-crystal X-ray molecular structure of 7'-amino-8'*H*-spiro [cyclohexane-1,5'-[1,2,4] triazolo [4,3-*a*] pyrimidine]-6'-carbonitrile (**4g**).

Keywords: Microwave irradiation, aqueous medium, triazolopyrimidines

Introduction

The synthesis of heterocycles has become the cornerstone of synthetic organic chemistry. Exploitation of these heterocycles should allow the synthetic chemist to rapidly discover methodology for the preparation of complex molecules in a shorter time scale. Among alternatives, water is very benign. The use of water as a solvent for organic transformations offers green chemistry benefits¹ and has been utilized in combination with microwave irradiation, which is widely used to enable and expedite the synthesis of diverse heterocycles. Microwave irradiation, has been shown not only to reduce reaction times but often to provide higher yields of the desired products as compared to traditional heating methods². Furthermore, multicomponent coupling reactions³ have received significant research in this context and their utility in preparing libraries to screen for functional molecules is well appreciated⁴⁻⁵. Therefore, they constitute a superior tool for diversity-oriented synthesis.

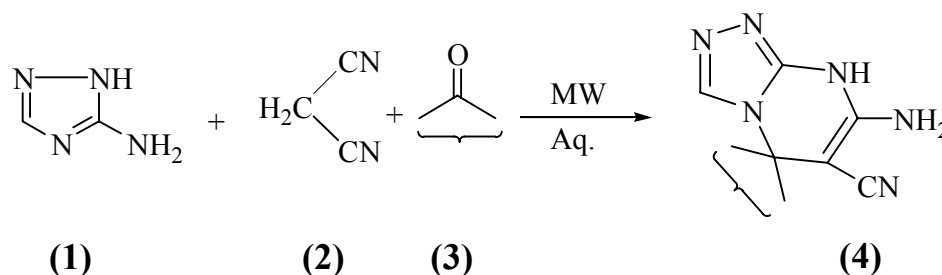
Among the nitrogen containing heterocycles, triazolopyrimidines represent a pharmaceutically important class of compounds because of their diverse range of biological activities, such as anti-tumor⁶, cytotoxicity⁷, therapeutic potentiality⁸, potent and selective ATP site directed inhibition of

the EGF-receptor protein tyrosine kinase⁹ and cardiovascular¹⁰ activities. In addition, they have been found in DNA-interactive drugs¹¹ and as useful building blocks in the synthesis of herbicidal drugs, e.g. *Metosulam*, *Flumetsulam*, *Azafenidin*, *Diclosulam*, *Penoxsulam*, *Floransulan*, *Cloransulam* etc.

For the preparation of complex molecules, large efforts have been directed towards the synthetic manipulation of triazolopyrimidines. As a result, a number of reports have appeared which usually require drastic conditions, long reaction times and complex synthetic pathways and often react in organic solvents¹²⁻¹⁶, which are least desirable commercially. Thus, developing efficient, selective and ecofriendly synthetic methods for applications in complex organic preparations is the ultimate goal of several research group including ours. Also, because of environmental concerns and increased restrictions on the use of hazardous organic solvents, it has recently become of significant interest to develop reactions in water, which is an environmentally benign protocol.

To the best of our knowledge the one pot tandem synthesis of triazolopyrimidines in an aqueous medium has not been studied so far¹⁷.

As per our ongoing efforts to synthesize privileged class molecules¹⁸ and our particular interest in the use of the aqueous medium¹⁹ for heterocyclic synthesis, we herein report a convenient and rapid one pot microwave/ ultrasound promoted, economic, ecofriendly methodology for the synthesis of triazolopyrimidines by simple addition of an equimolar mixture of amino triazole **1**, malononitrile **2** and carbonyl compounds **3** in an aqueous medium. We also provide a structural study for compound **4g** by X-ray crystallography.



Scheme 1

Results and Discussion

The multi-component condensation of aminotriazole **1**, active methylene compound **2** and carbonyl compounds **3** afforded the product triazolopyrimidines **4**. To optimize the method, the reaction was studied under different reaction conditions to find the best results. Initially, we examined the reaction in ethanol with triethylamine catalyst under the conventional method and observed that the desired product was formed in low yield. Interestingly, no product was formed

when the reaction was carried out in ethanol in the absence of catalyst under the conventional method, whereas reaction proceeded very smoothly under microwave irradiation without catalyst. Further, all our attempts to improve the yield at elevated temperature and longer reaction times were unsuccessful. To increase the efficiency we decided to perform the reaction under mild conditions in water and observed that the reaction proceeded uneventfully, forming the desired product in good to excellent yields. To further improve the procedure, the reaction was studied also using cetyl trimethyl ammonium bromide as phase transfer catalyst²⁰, and by implementing the vast potential of ultrasound promoted reactions.²¹ For sake of comparison, we have also carried out the reaction in an ultrasonic bath, however, although the reaction required reduced time there was no appreciable increase in yield, hence all other compounds (**4a-4j**) were synthesized in an aqueous medium under microwave irradiation (Table 1).

Table 1. Comparative study for synthesis of 1,2,4-Triazolo (4,3-*a*) pyrimidines [Power =600 watt for water and 360 watt for alcohol]

S. No.	Reaction conditions	Method	Time / Yield (%)		
			4b	4e	4g
1.	Ethanol	Δ	-/-	-/-	-/-
2.	Ethanol + Triethylamine	Δ	12 hrs./68	10 hrs./68	9 hrs./68
3.	Ethanol	MW	4 min./90	3 min./89	2.5 min./91
4.	Ethanol	Ultrasonic bath	3 hrs./87	2 hrs./86	2.5 hrs./89
5.	Water	Δ	8 hrs./80	6 hrs./82	7 hrs./84
6.	Water	MW	8 min./94	10 min./90	9 min./94
7.	Water	Ultrasonic bath	5 hrs./92	4 hrs./92	4 hrs./90
8.	Neat (MCR)	MW	4 min./85	3 min./88	4 min./86
9.	Neat (Oil bath)	Δ	-/-	-/-	-/-
10.	Water/PTC*	MW	4 min./85	4 min./80	5 min./90
11.	Water/PTC*	Ultrasonic bath	2.5 hrs./82	2 hrs./85	3 hrs./86

*= Cetyl trimethyl ammonium bromide is used as phase transfer catalyst.

Encouraged by this result and to understand the generally applicability of this protocol, we have synthesized a variety of triazolopyrimidines. For this purpose different types of aromatic aldehydes containing both electron withdrawing or donating groups, as well as cyclic and aliphatic ketones, were used successfully in good to excellent yields. (**Table 2**)

The multi-component condensation of **1**, **2** and **3** afforded the product triazolo[4,3-*a*] pyrimidines **4**. Formation of product **4** can be explained by involving the intermediacy of alkylidenemalononitrile (indicated by tlc studies). A plausible mechanism for the multi-component reaction of **1**, **2** and **3** is given (Scheme 2) and is confirmed by carrying out the

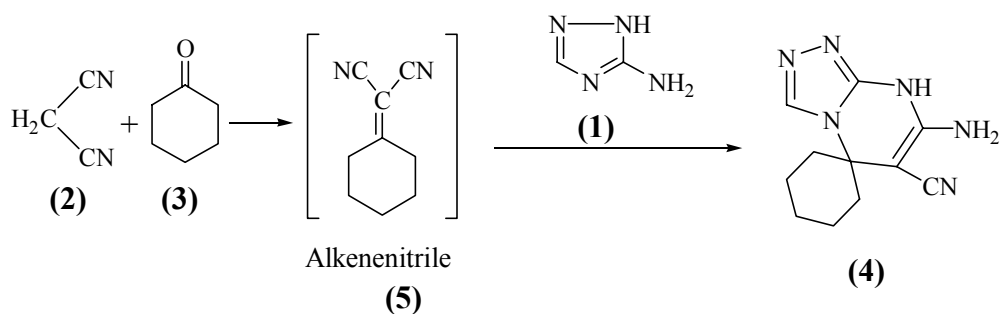
reaction of pre-synthesized alkene-nitrile derivative **5** and isolation of intermediate **5** during the progress of the reaction.

Table 2. Physical data of synthesized compounds (**4a-4j**)

Entry	Carbonyl compounds	Time (min.)	Temp. (°c)	M.P. (°c)	Yield (%)	Rf
4a	Benzaldehyde	8	96	172	82	.78
4b	p-Anisic aldehyde	8	94	115 ^a	94	.82
4c	o-Nitrobenzaldehyde	8	92	168	88	.81
4d	m-Nitrobenzaldehyde	7	95	260	90	.82
4e	p-Chlorobenzaldehyde	10	96	157	90	.83
4f	Cyclopentanone	11	94	310	78	.85
4g	Cyclohexanone	9	98	340	94	.81
4h	α -Tetralone	13	96	280	72	.84
4i	Acetophenone	12	95	168	88	.75
4j	p-Methoxyacetophenone	11	93	143	86	.78

a = Reference 22

The structure assigned for the reaction product is established from analytical and spectral data. The ¹HNMR spectrum of **4g** indicated the presence of a single triazole signal at δ 9.69 ppm shifted to lower field by almost δ 1.5 ppm compared to the single triazole signal in the parent aminotriazole. Consequently the 1,2,4-triazolo[4,3-a]pyrimidine **4** was assigned to this reaction product which is also observed by earlier workers²³⁻²⁴. The ¹HNMR spectra of **4g** showed signals of methylene protons in the cyclohexane ring at δ 1.27-1.35 (m, 2H, CH₂), 1.52-1.65 (m, 4H, CH₂), 1.73-1.98 (m, 2H, CH₂), 2.06-2.30 (m, 2H, CH₂), 5.80 (s, 2H, NH₂), 7.26 (s, 1H, NH) and 9.69 (s, 1H, CH, triazolic proton) ppm. In the ¹³CNMR spectra of **4g** the absence of the signal at 164.25 (C=O, cyclohexanone ring) further confirmed the proposed structure.



Scheme 2. Reaction mechanism for the synthesis of triazolo [4,3-a] pyrimidine (**4g**).

The IR spectra of **4a-j** displayed characteristic absorptions in the region 3485-3210 (NH₂ & NH), 2240-2180 (C≡N) and 1605-1630 cm⁻¹ (C=N). Absence of C=O at 1740 cm⁻¹ further confirmed the formation of **4**.

In the mass spectrum of **4g**, the molecular ion peak was observed at m/z 230 ([M⁺], 70%) corresponding to its molecular weight along with base peak at m/z 154 (100%).

Further, X-ray crystallographic analysis of one representative compound 7'-amino-8'H-spiro [cyclohexane-1,5'-[1,2,4] triazolo [4,3-*a*] pyrimidine]-6'-carbonitrile (**4g**), confirms the proposed structure for **4**.

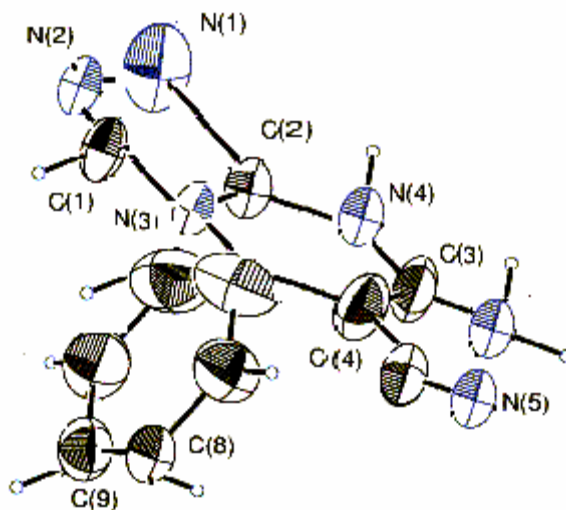


Figure 1. Molecular structure of 7'-AMINO-8'H-SPIRO [CYCLOHEXANE-1,5'-[1,2,4] TRIAZOLO [4,3-*a*] PYRIMIDINE]-6'-CARBONITRILE (**4g**).

Conclusions

In conclusion, an efficient synthesis of triazolo[4,3-*a*]pyrimidines, an important class of building blocks in herbicidal drugs and pharmaceuticals, has been developed *via* a multi-component condensation reaction under microwave irradiation conditions in an aqueous medium. The simplicity of this short procedure and enhanced yields render this method particularly attractive for the rapid synthesis of triazolo[4,3-*a*]pyrimidines.

Experimental Section

General Procedure. Melting points were determined on a Toshniwal apparatus and were uncorrected. The purity of compounds was checked on thin layers of silica gel in various non-aqueous solvent systems, for e.g. benzene: ethylacetate (9:1), benzene: dichloromethane (8:2). IR spectra (KBr) were recorded on FT IR spectrophotometer model 8400 S Shimadzu as nujol mull using KBr pellets in the range of 4000-400 cm^{-1} and ^1H , ^{13}C NMR spectra were recorded in DMSO- d_6 using Jeol FX 90Q (89.55MHz) and Bruker DPX-300 spectrophotometers using TMS as internal reference. Mass spectra were recorded on Kratos 50 mass spectrometer at 70 eV. The microwave-assisted reactions were carried out in a multimode MW oven (Panasonic-NN-781JF) equipped with inverter technology (generating fixed frequency throughout the required time) for realistic control of the microwave operating at 1000W generating 2450 MHz frequency and ultrasonic bath (Bandelin Sonorex) operating at 230 V generating 33 KHz output frequency. Synthesis of 7'-Amino-8'H-spiro [cyclohexane-1,5'-[1,2,4] triazolo[4,3-a]pyrimidine]-6'-carbonitrile (**4g**). It was synthesized by the following routes.

(A) Conventional method

A solution of 3-amino-1,2,4-triazole (**1**) (0.001mol), malononitrile (**2**) (0.001 mol) and cyclohexanone (**3**) (0.001 mol) in ethanol (25 ml) was refluxed for 5 days. However, no reaction occurred after the intermediate stage. Then the reaction was continued after addition of 4-5 drops of triethylamine, immediately a colour change occurred from yellow to red and progress was monitored by TLC. The reaction mixture was kept overnight at room temperature. The resulting precipitate was filtered, washed with ethanol, dried and recrystallized from ethanol.

(B) Microwave activation method

1. **Neat.** An equimolar mixture (0.001 mol) of **1**, **2** and **3** contained in an open borosil beaker was placed in the microwave oven and irradiated for 4 min (TLC) at 640 w. The reaction mixture was cooled at room temperature to give a solid mass, which was crystallized from ethanol.
2. **Using water.** An equimolar mixture (0.001 mol) of **1**, **2** and **3** in water (8-10 ml) in an open borosil beaker (100 ml) was irradiated inside a microwave oven at 640 watt until completion of reaction (TLC control). The crystalline product started to separate out just after cooling the reaction mixture, which was washed with water and found to be pure by TLC, with no need of further purification. All compounds **4a-4j** were synthesized similarly in comparatively high yields and reduced times using water under microwave irradiation. For analytical and spectral studies the products were recrystallized from ethanol.

(C) Ultrasonic radiation method

An equimolar quantity (0.001 mol) of **1**, **2** and **3** were added in a conical flask in water (10 ml). The mixture was introduced under ultrasonic waves using an ultrasonic bath (operating at 230 V generating 33 KHz output frequencies) for 3 hrs. at room temperature. The product started to

separate out during the course of reaction. The crystalline solid was filtered and found pure on TLC with no need of further recrystallization.

4a. IR (KBr)/cm⁻¹ 3465-3235 (br, NH & NH₂), 2210 (C≡N), 1625 (C=N). ¹HNMR (CDCl₃) δ ppm 4.65 (s, 1H, CH), 6.95 (s, 2H, NH₂*), 6.82-7.72 (m, 5Ar-H), 8.1 (s, 1H, NH*), 8.57 (s, 1H, triazolic proton). ¹³CNMR (CDCl₃) δ ppm 43.6, 68.2, 117.3, 137.8, 146.5, 148.2, 150.1, 154.8, 176.4. Anal. calcd for C₁₂H₁₀N₆: C, 60.50; H, 4.23; N, 35.27. Found C, 60.66; H, 4.24; N, 35.41.

4b. IR (KBr)/cm⁻¹ 3470-3250 (br, NH & NH₂), 2185(C≡N), 1610 (C=N). ¹HNMR (CDCl₃) δ ppm 3.50 (s, 3H, OCH₃), 5.85 (s, 1H, CH), 5.98 (s, 2H, NH₂*), 7.25-8.14 (m, 4Ar-H & s, 1H, NH*), 8.80 (s, 1H, triazolic proton). ¹³CNMR (CDCl₃) δ ppm 44.1, 58.4, 66.3, 118.4, 123.3, 133.3, 147.1, 152.3, 162.5, 179.6. Anal. calcd for C₁₃H₁₂N₆O: C, 58.20; H, 4.51; N, 31.33. Found C, 58.37; H, 4.49; N, 31.20.

4c. IR (KBr)/cm⁻¹ 3445-3210 (br, NH & NH₂), 2225(C≡N), 1635 (C=N), 1575 & 1380 (NO₂). ¹HNMR (CDCl₃) δ ppm 5.89 (s, 1H, CH), 5.95 (s, 2H, NH₂*), 7.30-8.24 (m, 4Ar-H & s, 1H, NH*), 8.90 (s, 1H, triazolic proton). ¹³CNMR (CDCl₃) δ ppm 45.6, 63.3, 119.2, 122.5, 125.5, 132.6, 137.5, 140.9, 151.5, 153.4, 155.1, 180.4. Anal. calcd for C₁₂H₉N₇O₂: C, 50.88; H, 3.20; N, 34.62. Found C, 50.72; H, 3.21; N, 34.77.

4d. IR (KBr)/cm⁻¹ 3440-3215 (br, NH & NH₂), 2215(C≡N), 1630 (C=N), 1575 & 1380 (NO₂). ¹HNMR (CDCl₃) δ ppm 5.79 (s, 1H, CH), 5.90 (s, 2H, NH₂*), 7.35-8.29 (m, 4Ar-H & s, 1H, NH*), 8.95 (s, 1H, triazolic proton). ¹³CNMR (CDCl₃) δ ppm 43.1, 60.9, 118.4, 121.7, 126.5, 131.4, 139.5, 141.8, 152.4, 154.4, 156.1, 178.9. Anal. calcd for C₁₂H₉N₇O₂: C, 50.88; H, 3.20; N, 34.62. Found C, 50.72; H, 3.21; N, 34.77.

4e. IR (KBr)/cm⁻¹ 3470-3240 (br, NH & NH₂), 2220 (C≡N), 1630 (C=N). ¹HNMR (CDCl₃) δ ppm 5.65 (s, 1H, CH), 6.78 (s, 2H, NH₂*), 6.88-7.16 (d, 2Ar-H & s, 1H, NH*) 7.26-7.86 (d, 2Ar-H), 8.57 (s, 1H, triazolic proton). ¹³CNMR (CDCl₃) δ ppm 51.4, 86.2, 122.3, 125.9, 129.8, 139.3, 142.3, 143.4, 147.3, 152.4, 157.2, 159.6, 177.4. Anal. calcd for C₁₂H₉N₆Cl: C, 52.85; H, 3.33; N, 30.82. Found C, 52.99; H, 3.31; N, 30.68.

4f. IR (KBr)/cm⁻¹ 3485-3245 (br, NH & NH₂), 2925-2865 (br, ali. CH), 2230 (C≡N), 1625 (C=N). ¹HNMR (CDCl₃) δ ppm 1.45-1.72 (t, 4H, CH₂), 1.85-1.98 (m, 4H, CH₂), 5.97 (s, 2H, NH₂*), 7.95 (s, 1H, NH*), 9.80 (s, 1H, triazolic proton). ¹³CNMR (CDCl₃) δ ppm 17.5, 37.3, 53.3, 77.6, 119.2, 149.1, 151.2, 172.2. Anal. calcd for C₁₀H₁₂N₆: C, 55.54; H, 5.59; N, 38.86. Found C, 55.37; H, 5.60; N, 38.77.

4g. IR (KBr)/cm⁻¹ 3420-3210 (br, NH & NH₂), 2945-2895 (br, ali. CH), 2210(C≡N), 1620 (C=N). ¹HNMR (CDCl₃) δ ppm 1.27-1.35 (t, 2H, CH₂), 1.52-1.65 (m, 4H, CH₂), 1.73-1.98 (m, 2H, CH₂), 2.06-2.30 (t, 2H, CH₂), 5.80 (s, 2H, NH₂*), 7.26 (s, 1H, NH*), 9.69 (s, 1H, triazolic proton). ¹³CNMR (CDCl₃) δ ppm 20.4, 29.5, 33.4, 37.5, 70.1, 120.1, 153, 155.1, 173.6. MS [m/z]: 230(M⁺), 154, 136. Anal. calcd for C₁₁H₁₄N₆: C, 57.38; H, 6.13; N, 36.50. Found C, 57.54; H, 6.12; N, 36.29.

4h. IR (KBr)/cm⁻¹ 3475-3245 (br, NH & NH₂), 2925-2870 (br, ali. CH), 2240 (C≡N), 1605 (C=N). ¹HNMR (CDCl₃) δ ppm 1.50-1.62 (m, 2H, CH₂), 1.98-2.04 (t, 2H, CH₂), 2.15-2.48 (t,

2H, CH₂), 5.87 (s, 2H, NH₂*), 7.05 (t, 1H), 7.15 (t, 1H), 7.35 (d, 1H, J=2Hz), 7.66 (d, 1H, J=8Hz), 7.95 (s, 1H, NH*), 8.79 (s, 1H triazolic proton). ¹³CNMR (CDCl₃) δ ppm 25.4, 32.5, 39.4, 41.5, 70.1, 120.1, 153, 155.1, 173.6. Anal. calcd for C₁₅H₁₄N₆: C, 64.73; H, 5.07; N, 30.20. Found C, 64.53; H, 5.06; N, 30.35.

4i. IR (KBr)/cm⁻¹ 3475-3240 (br, NH & NH₂), 2945-2895 (br, ali. CH), 2180 (C≡N), 1620 (C=N). ¹HNMR (CDCl₃) δ ppm 2.01 (s, 3H, CH₃), 5.85 (s, 2H, NH₂*), 7.40-8.20 (m, 5Ar-H & s, 1H, NH*), 8.75 (s, 1H, triazolic proton). ¹³CNMR (CDCl₃) δ ppm 23.3, 45.2, 63.1, 119.3, 122.3, 129.4, 133.3, 139.3, 147.1, 152.3, 178.7. Anal. calcd for C₁₃H₁₂N₆: C, 61.89; H, 4.79; N, 33.31. Found C, 61.70; H, 4.81; N, 33.16.

4j. IR (KBr)/cm⁻¹ 3460-3250 (br, NH & NH₂), 3050-2995 (br, ali. CH), 2280 (C≡N), 1610 (C=N). ¹HNMR (CDCl₃) δ ppm 2.15 (s, 3H, CH₃), 3.95 (s, 3H, OCH₃), 5.92 (s, 2H, NH₂*), 7.15-7.61 (d, 2Ar-H), 7.90-8.41 (d, 2Ar-H, s, 1H, NH*), 8.98 (s, 1H, triazolic proton). ¹³CNMR (CDCl₃) δ ppm 25.1, 44.1, 59.9, 66.3, 118.4, 123.3, 127.5, 131.2, 138.3, 149.1, 153.3, 179.6. Anal. calcd for C₁₄H₁₄N₆O: C, 59.56; H, 5.00; N, 29.77. Found C, 59.74; H, 4.98; N, 29.62.

Presence and position of NH and NH₂ protons are confirmed by deuterium exchange.

Acknowledgements

We wish to thank to the CSIR (No 01(1907)/03/EMR-II) and U.G.C. New Delhi for financial support is gratefully acknowledged. One of us (P. S.) is thankful to CSIR for the award of Senior Research Fellowship. We are also thankful to RSIC, CDRI, Lucknow for the elemental and spectral analyses. We are also thankful to Indian oil corporation limited, Faridabad, for X-ray facility.

References

- (a) Aplander, K.; Hidestøl, O.; Katebzadeh K.; Lindstorm, U. M. *Green Chem.* **2006**, *8*, 22. (b) Liu, R.; Dong, C.; Liang X.; Hu, X. *J. Org. Chem.* **2005**, *70*, 729. (c) Staver, G.; Zupam, M.; Jerez M.; Staber, S. *Org. Letters* **2004**, *6* (26), 4973. (d) Kavala, V.; Samal A. K.; Patel, B. K. *Arkivoc* **2005**, (i), 20; (e) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881.
- (a) Loupy, A. *Microwaves in Organic synthesis*; Wiley-VCH: Weinheim, 2006. (b) Kappe C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005. (c) Hoz, A. De La; Diaz-Ortiz A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164. (d) Dai, W. M.; Wang X.; Ma, C. *Tetrahedron* **2005**, *61*, 6879. (e) Hayes, B. L. *Aldrichim. Acta* **2004**, *37*, 66. (f) Nuchter, M.; Ondruschka, B.; Bonrath W.; Gum, A. *Green chemistry* **2004**, *6*, 128. (g) Varma, R. S. *Green Chem.* **1999**, *43*. (h) Perreux L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.

3. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123.
4. Kappe, C. O.; Stadler, A. *Method. Enzym.* **2003**, *369*, 197.
5. Dax, S. L.; Mc Nally J. J.; Yougman, M. A. *Curr. Med. Chem.* **1999**, *6*, 255.
6. Navarro, J. A. R.; Salas, J. M.; Romero, M. A.; Vilaplana R.; Faure, R. *J. Med. Chem.* **1998**, *41*, 332.
7. Magan, R.; Marin, C.; Salas, J. M.; Perez M. B.; Rosales, M. J. Men Instaswaldo Cruz, *Rio de Janeiro*, **2004**, *99* (6), 651.
8. Magan, R.; Marin, C.; Rosales M.J.; Salas, J.M. *Pharmacology* **2005**, *73*, 41.
9. Traxler, P. M.; Furet, P.; Mett, H.; Buchdunger, E.; Meyer, T.; Lydon, N. *J. Med. Chem.*, **1996**, *39*, 2285.
10. Rusinov, V. L.; Yu, A.; Petrov, Pilicheva, T. L.; Chupakhin, O. N.; Kovalev G. V.; Komina, E. R. *Khimiko-Farmatsevticheskii Zhurnal*, **1986**, *20*, 178.
11. Lauria, A.; Diana, P.; Barraja, P.; Montalbano, A.; Cirrinicione, G.; Dattolo G.; Almerico, A.M. *Tetrahedron* **2002**, *58*, 9723.
12. Kuznetsova, O. A.; Filyakova, V. I.; Pashkevich K. I.; Ulomskii, E. S. *Russian Chemical Bulletin, International Edition* **2003**, *52* (5), 1190.
13. (a) Dawood, K. M.; Farag A. M.; Kandeel, Z. E. *J. Chem. Res. (S)* **1999**, 88. (b) Al-Zaydi, K. M.; Al-Shiekh M. A. A; Hafez, E. A. A. *J. Chem. Res. (S)* **2000**, 13.
14. Pryadina, M. V.; Burgart, Ya. V.; Saloutin, V. I.; Kodess, M. I.; Vlomskii, E. N.; Rusinov, V. L. *Russian Journal of Org. Chem*, **2004**, *40*, 902.
15. Lipson, V. V.; Desenko, S. M.; Borodina V. V.; Shirobokova, M. G. *Chemistry of Heterocyclic Compd.* **2005**, *41*, 216.
16. Eld, F. A.; Abdel-Wahab, A. H. F.; El-Hag Ali G. A. M.; Khafagy, M. M. *Acta Pharm.* **2004**, *54*, 13.
17. (a) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095. (b) Lindstorm, U. M. *Chem. Rev.* **2002**, *102*, 2751.
18. (a) Dandia, A.; Singh, R.; Sarawgi P.; Khaturia, S. *Chinese Journal of Chemistry* **2006**, *23*, 1. (b) Dandia, A.; Singh R.; Khaturia, S. *Bioorg. and Med. Chem.* **2006**, *14*, 1303. (c) Dandia, A.; Singh, R.; Sarawgi, P. *Org. Prep. Proceed and Int.* **2005**, *37*, 397. (d) Dandia, A.; Sati, M.; Arya, K.; Sarawgi, P.; Loupy, A. *Arkivoc* **2005**, (i), 105. (e) Dandia, A.; Arya, K.; Sati M.; Gautam, S. *Tetrahedron* **2004**, *60*, 5253. (f) Dandia, A.; Singh R.; Sarawgi, P. *J. Fluorine Chem.* **2004**, *125*, 1835. (g) Dandia, A.; Sati, M.; Arya K.; Loupy, A. *Green Chem.* **2002**, *4*, 599. (h) Dandia, A.; Sachdeva, H.; Singh, R. *J. Chem. Res. (S)* **2000**, 272.
19. (a) Dandia, A.; Arya K.; Sarawgi, P. *J. Indian Chem. Soc.* **2003**, *80*, 1183. (b) Dandia, A.; Sati, M.; Arya, K.; Sarawgi, P. *Journal of Fluorine Chem.* **2004**, *125*, 1273. (c) Dandia, A.; Sati, M.; Arya, K. *Synth. Commun.* **2004**, *34*(6), 1141.
20. Jin, T. S.; Wang, A. Q.; Wang, X.; Zhang, J. S.; Li, T. S. *Synlett* **2004**, *5*, 871.
21. (a) Cravotto, G.; Cintas, P. *Chem. Soc. Rev.* **2006**, *35*, 180. (b) Rajagopal, R.; Srinivasan, K. V. *Ultrason. Sonochem.* **2003**, *10*, 41. (c) Villagra'n, C.; Banks, C. E.; Pitner, W. R.; Hardacre, C.; Compton, R. G. *Ultrason. Sonochem.* **2005**, *12*, 423.

22. Mohamed Kamal Ahmed, I. *Indian J. Chem.* **1988**, 27B(5), 478.
23. Al-Zaydi, K. M.; Borik R. M.; Elnagdi, M. H. *Molecules* **2003**, 8, 910.
24. Ahmed. E. Kh. *Phosphorus, Sulfur and Silicon* **2002**, 177, 1323.