Facile Regioselective Green Synthesis of Triazolo [4,3-a] Pyrimidines in Aqueous Medium

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Abstract: Regioselectivity is investigated in multi-component reaction of amino triazole, carbonyl compounds and α-cyano esters derivative and exclusive synthesis of triazolopyrimidines is developed in aqueous medium in excellent yields in shorter period using microwaves or ultrasonic waves. Path and mechanism of the reaction has also been discussed. The operational simplicity, environmental friendly conditions, regioselective formation of target product, high yield in significantly very short reaction time, are major benefits.

Keywords: α-Cyano acrylates, microwave irradiations, ultrasound, aqueous medium, triazolopyrimidines.

INTRODUCTION

1,2,4-Triazole system is a structural unit of many drugs that have antimycotic activity, e.g., *Fluconazole*, *Itraconazole*, *Voriconzole*, *Tricyclazole*, *Furconazole*, *Hexaconazole*, *Tetraconazole*, *Quinconazole*, *Penconazole* [1-2], herbicidal activity, e.g., *Lucarbazone*, *Bencarbazone* e.g., and Virucidal activity, e.g., *Ribavirin*.

Further, the importance of triazolopyrimidines is well recognized in the field of medicinal chemistry because these heterocycles have a structure similar to that of purine and adenine, their fused ring system differing in having the pyrimidine nitrogen atom in a bridgehead position [3-5]. Triazolo pyrimidines are useful building blocks in the synthesis of herbicidal drugs, e.g. *Metosulam*, *Flumetsulam*, *Azafenidin*, *Diclosulam*, *Penoxsulam*, *Floransulan*, and *Cloransulam* etc.

Recently, C.M. Richardson *et al.* described the triazolopyrimidines as novel CDK2 inhibitors [6]. Beside these triazolopyrimidines are also useful as potential anticancer [7], antibronchoconstrictor [8], antiviral [9], diuretic [10], antibacterial [11] and antifungal [12] agents.

For the preparation of the complex molecules much efforts have been directed towards the synthetic manipulation of triazolopyrimidines. A number of reports dealing with the preparation of these system have appeared, which, however, usually require drastic conditions, long reaction times and complex synthetic pathways and often require volatile organic solvents [13-21]. Thus new route for the synthesis of these molecules have attracted considerable attention in search for a rapid entry to these heterocycles.

In recent years, microwave-assisted reactions are well established and have gained popularity [22]. The beneficial effects of microwave irradiation are finding an increased role in multiple kilogram scale in fine chemical and drugs [23], especially in cases when usual methods require forcing conditions or prolonged reaction times. The use of ultrasounds in organic transformations is now well known to enhance, in some cases, reaction rates and yield/selectivity of reactions and in several cases facilitates organic transformation at ambient conditions which otherwise require drastic conditions of temperature and pressure [24].

The search for alternative reaction media to replace volatile, flammable and often toxic solvents commonly used in organic synthetic procedures is an important objective of the development of green chemical processes. From both the environmental and economic points of view, using aqueous media to perform organic reactions has attracted intense interest, since water is the most environmentally acceptable, safe and inexpensive solvent [25]. In addition, using water as the solvent generally means easier workup because most organic compounds are lipophilic and are easily separated from aqueous media.

On the other hand, the utility of multi-component reactions (MCRs) involving domino process with at least three different simple substrates has emerged as a powerful strategy [26]. This methodology allows molecular complexity and diversity to be created by the facile formation of several new covalent bonds in a one-pot transformation quite closely approaching the concept of an ideal synthesis and is particularly well adapted for combinatorial synthesis [27].

In continuation to our general interest on the economic and environmentally benign synthesis of biodynamic heterocycles [28] and particular interest on use of aqueous medium [29] for heterocyclic synthesis, we report herein for the first time the microwave/ ultrasound promoted, economic, ecofriendly, and facile multi-component regioselective synthesis of triazolopyrimidines by simple addition of an equimolar mixture of amino triazole **1**, ethyl cyanoacetate **2** and carbonyl compound **3** in aqueous medium under microwaves/ultrasonic waves (Scheme **1**).

RESULT AND DISCUSSION

The reaction was studied under different reaction conditions to find out the role of substituents, giving the products

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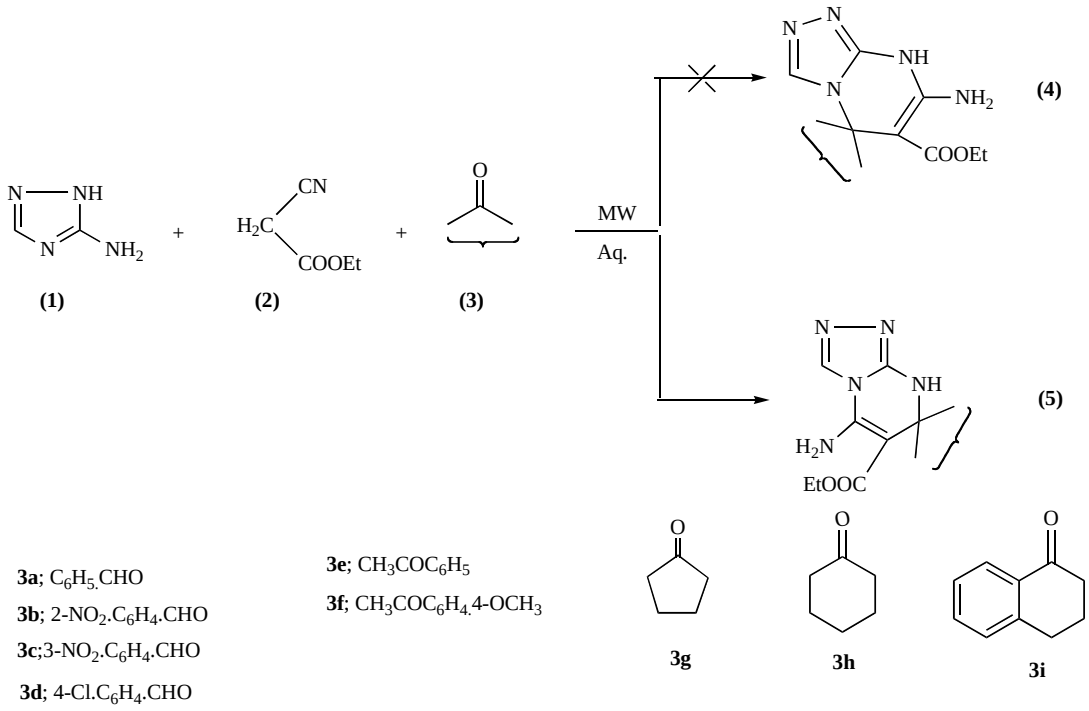
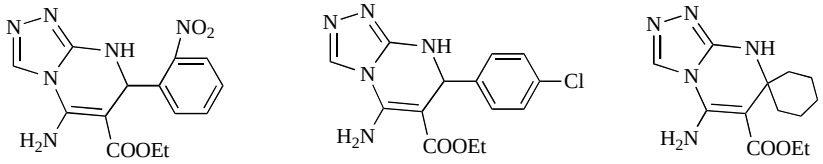


Scheme 1.

Table 1. Comparative Study for Synthesis of Triazolopyrimidines [Power =600 Watt for Water and 360 Watt for Ethanol]



Entry	Reaction conditions	Method	Temp.[#] (°C)	Time / Yield (%)		
				5b	5d	5h
i.	Ethanol	Δ	Reflux	Intermediate **6b**	Intermediate **6d**	Intermediate **6h**
ii.	Ethanol + Triethylamine	Δ	Reflux	12 hrs./65	10 hrs./68	9 hrs./62
iii.	Ethanol	MW	78	4 min./87	5 min./91	3.5 min./88
iv.	Ethanol	US	r.t	3 hrs./86	2 hrs./89	2.5 hrs./85
v.	Water	Δ	Reflux	8 hrs./80	6 hrs./88	7 hrs./84
vi.	Water	MW	95	6 min./94	8 min./92	10 min./96
vii.	Water	US	r.t	5 hrs./92	4 hrs./92	4 hrs./90
viii.	Neat (MCR)	MW	110	4 min./85	3 min./88	4 min./86
ix.	Water/PTC**	MW	96	4 min./85	5 min./80	7 min./90
x.	Water/PTC**	US	r.t.	2.5 hrs./82	2 hrs./85	3 hrs./83
xi.	α-Cyano acrylates► + 1 (Ethanol)	MW	78	4+4* min./86	3+4 min./80	4+5 min./82
xii.	α-Cyano acrylates + 1 (Water)	MW	95	5+4 min./88	3+5 min./90	4+6 min./92
xiii.	Anil ►►+ 2 (Ethanol)	MW	78	5+4 min./86	5+4 min./80	4+7 min./82
xiv.	Anil + 2 (Water)	MW	95	5+4 min./86	2.5+5 min./88	3+6 min./90

*4+4 indicates, first irradiation for 4 min gives intermediate (detected by TLC) and then further irradiation for 4 min after adding 3-aminotriazole.
**Cetyl trimethyl ammonium bromide is used as phase transfer catalyst.
► α-Cyano acrylates synthesized in situ by reaction of ethyl cyanoacetate (**2**) + carbonyl compound (**3**).
►► Anil synthesized in situ by reaction of 2-aminotriazole (**1**) + carbonyl compound (**3**).
[#]The final temperature is measured at the end of microwave irradiation by introducing a glass thermometer in the reaction mixture in the beaker.

in higher yields with operational simplicity. In the present work, we studied the synthesis of **5b**, **5d** and **5h** taking different parameters as shown in Table **1**.

From the results obtained as shown in Table **1**, it is clear that the MCR of (**1**), (**2**) and (**3**) occurred successfully in ethanol without using any catalyst under microwave and ultrasound bath (entry iii and iv). However, intermediate **6** was formed when the reaction was carried out conventionally in ethanol and in absence of catalyst (entry i). The reaction was also performed under neat condition in absence of any solvent and catalyst under microwaves but the product required further purification and recrystallization with suitable solvents giving comparatively lower yield (entry viii). A very good result was obtained in aqueous medium both under microwaves and ultrasonic waves giving the pure crystalline product upon post reaction cooling, while in case of microwaves comparatively high yield (92-94%) was achieved in few minutes.

To further improve the procedure, reaction was also studied using cetyl trimethyl ammonium bromide as phase transfer catalyst (entry ix and x) but no change in yields was observed, although reaction time was reduced slightly. The present protocol simplified the synthesis of triazolopyrimidines into a one-pot fashion under aqueous media using microwaves. Therefore, the current procedure is more facile and friendly to environment.

The present reaction was also studied alternatively by the step-wise synthesis which involves the reaction of α-cyano acrylates **6** with amino-triazole **1** and reaction of anil **9** with ethyl cyanoacetate **2** in ethanol and water (entry xi-xiv). The results showed the formation of identical products as formed in MCR reaction.

In order to check the general applicability for the synthesis of triazolopyrimidines, benzaldehyde and other aromatic aldehydes containing both electron withdrawing or donating group as well as cyclic ketones were used successfully to give the corresponding triazolopyrimidines in good to excellent yields Table **2**.

The multi-component condensation of amino triazole (**1**), active methylene compound (**2**) and carbonyl compounds (**3d**) shows high degree of regioselectivity to give a product of molecular formula $C_{14}H_{14}ClN_5O_2$. Two possible isomeric structures **4** and **5** were proposed, as both the amino function and ring nitrogen in aminotriazole are active sites of nucleophilic attack on α,β-unsaturated nitriles. The products were identified in all cases as structure **5** based on the chemical and spectral data.

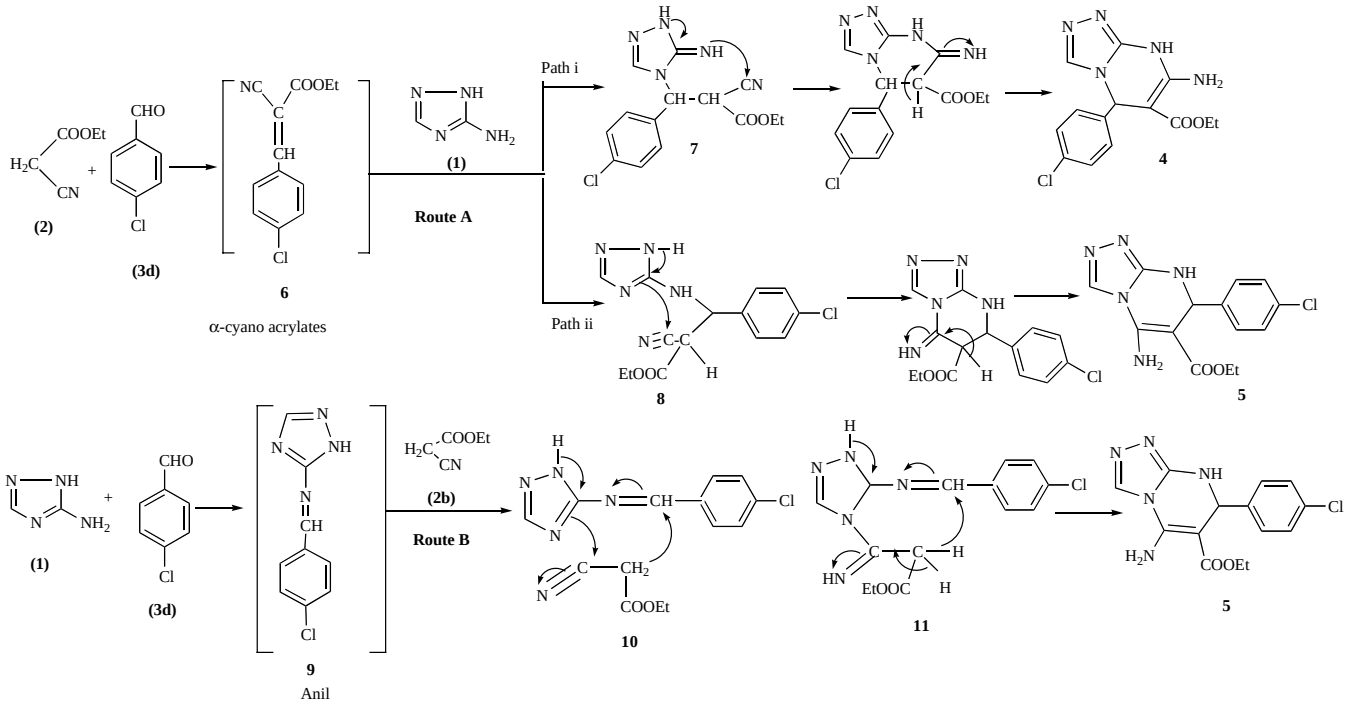
The TLC monitoring of the reaction studies during the progress of reaction indicated that intermediacy of alkene-nitrile (**6**), which may result in the formation of either product **4** or **5** involving either attack of NH_2 or imino ring nitrogen. It is difficult to distinguish these two isomers on the basis of spectral studies.

To confirm the pathway we have carried out the reaction of the pre-synthesized alkene-nitrile with 2-aminotriazole (route-A) or the reaction of anil with ethylcyanoacetate (route B), where in all cases the identical product (**5**) was

Table 2. Experimental, Physical and Analytical Data of Synthesized Compounds (5a-5i)

Compd	Time (min.)	Temp. (°C)	M.P. (°C)	Yield (%)	Rf[a]	Analysis calcd (found) %		
						C	H	N
5a	6	98	129-131	92	.81	58.94 (58.73)	5.30 (5.28)	24.55 (24.47)
5b	6	95	124-126	94	.82	50.91 (50.70)	4.27 (4.29)	25.44 (25.36)
5c	8	94	115-117	94	.87	50.91 (50.71)	4.27 (4.25)	25.44 (25.52)
5d	8	95	168-170	92	.75	52.59 (52.79)	4.41 (4.43)	21.90 (21.96)
5e	11	93	142-145	86	.78	60.19 (60.00)	5.72 (5.74)	23.40 (23.47)
5f	13	96	240-242	93	.82	58.35 (58.55)	5.81 (5.85)	21.26 (21.20)
5g	9	92	228-230	92	.74	54.74 (54.54)	6.51 (6.48)	26.60 (26.68)
5h	10	94	340-342	96	.78	56.30 (56.51)	6.91 (6.93)	25.25 (25.17)
5i	12	92	254-256	93	.92	62.37 (62.60)	6.47 (6.40)	21.39 (21.20

[a]Using solvent system benzene : ethyl acetate (8:2).



Scheme 2. Postulated mechanism for the Synthesis of triazolo [4,3-a] pyrimidine.

obtained (Scheme **2**). Thus, even in case of alkene nitrile the product obtained results from the initial attack of the amino group followed by cyclization at N-4 centre instead of N-2 centre as reported earlier by O. A. Kuznetsova [13].

The IR spectra of **5a-5i** displayed characteristic absorption in the region 3470-3240 (symmetric and asymmetric stretching) of (NH_2 & NH), 2310-2175 (C≡N) and 1605-1630 cm^{-1} (C=N). The ^{1}HNMR spectra of **5d** showed signals at δ 1.70-1.78 (t, 3H, CH_3, J=6Hz), 4.20-4.35 (q, 2H, CH_2, J=6Hz), 4.62 (s, 1H, CH), 6.78 (s, 2H, NH_2), 6.88-7.16 (d, 2Ar-H) 7.26-7.86 (d, 2Ar-H), 7.92 (1H, triazolic proton), 8.57 (s, 1H, NH) ppm. The presence and position of NH and NH_2 protons are confirmed by deuterium exchange. In the mass spectrum of **5d**, the molecular ion peak was observed at m/z 319 ([M^+], 70%) corresponding to its molecular weight along with base peak at 165.

EXPERIMENTAL

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: ethyl acetate (9:1), benzene: dichloromethane (8:2). IR spectra (KBr) were recorded on a Magna FT IR–550 spectrophotometer and ^{1}H NMR and ^{13}C NMR spectra was recorded on a Bruker DRX-300 using $CDCl_3$ at 300.15 and 75. 47 respectively. TMS was used as internal reference. Mass spectrum of representative compound was recorded on a Kratos 50 mass spectrometer at 70 eV. The 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.

GENERAL PROCEDURE

Synthesis of Ethyl 5-amino-7-(4-chlorophenyl)-7,8-dihydro[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylate (**5d**).

It has been synthesized by different ways.

(A) Conventional Method

A solution of 3-amino-1,2,4-triazole (**1**) (0.01 mol), ethyl cyanoacetate (**2**) (0.01 mol) and p-chlorobenzaldehyde (**3d**) (0.01mol) in ethanol (25 ml) was refluxed for 5 days. However, no reaction occurred after 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 is 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

(i) Using Water

A equimolar mixture of **1**, **2** and **3d** (.01mol) in water (8-10 ml) in open borosil beaker covered with petridish (100 ml) was irradiated intermittently inside a microwave oven at 640 watt till the 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 process.

(ii) Neat

An equimolar mixture (0.01 mol) of **1**, **2** and **3d** contained in an open borosil beaker was placed in the microwave oven and irradiated for 3 min (TLC) at 640 w. The reaction mixture was cooled at room temperature to give solid mass, which was crystallized from ethanol.

(iii) Ethanol / MW:

An equimolar (.01m) quantity of **1**,**2** and **3d** were placed in a beaker and the minimum quantity of ethanol, sufficient to make slurry was added. The mixture was placed in the MW oven and irradiated at power output 360 watts intermittently for 4-5 min (TLC). The product started to separate out immediately after cooling the reaction mixture to room temperature (or in some cases during the course of reaction). The crystalline solid that separated out was filtered and found to be pure on TLC with no need of further recrystallization.

(C) Ultrasonic Radiation

Equimolar quantity of **1**, **2** and **3d** were added in a conical flask in water (10 ml). The mixture was introduced under ultrasonic waves using ultrasonic bath (operating at 230 V generating 33 KHz output frequency) for 4 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.

All compounds listed in Table **2** were synthesized similarly in comparatively high yields and reduced times using water under microwave irradiation.

CONCLUSION

We have developed a simple, economic and eco-friendly highly efficient synthetic strategy for exclusive synthesis of triazolopyrimidines using inexpensive and commercially

Table 3. Spectral Data of Synthesized Compounds (5a- 5i)

Compd	IR (cm^{-1})	^{1}HNMR (δ, ppm)	^{13}CNMR (δ, ppm)
5a	3465-3235 (br, NH & NH_2), 1745 (C=O), 1625 (C=N), 1115 cm^{-1} (C-O)	1.70-1.88 (t, 3H, CH_3, J=6.1Hz), 4.10-4.18 (q, 2H, CH_2, J=6.1Hz), 4.65 (s, 1H, CH), 6.95 (s, 2H, NH_2*), 6.82-7.72 (m, 5Ar-H), 8.10 (s, 1H, triazolic proton) & 8.57 (s, 1H, NH*)	13.2 (CH_2-$\underline{C}H_3$), 52.6 ($\underline{C}$-7), 58.9 ($\underline{C}H_2$-CH_3), 88.2 ($\underline{C}$-6), 122.3-143.4 (aromatic carbons), 150.3, 152.1 (two ring C=N), 160.1 ($\underline{C}$-5) & 168.2 ($\underline{C}$=O)
5b	3485-3235 (br, NH & NH_2), 1730 (C=O), 1630 (C=N), 1570 & 1385 (NO_2), 1095 cm^{-1} (C-O)	1.73-1.78 (t, 3H, CH_3, J=6.3Hz), 4.20-4.25 (q, 2H, CH_2, J=6.3Hz), 4.73 (s, 1H, CH), 6.90 (s, 2H, NH_2*), 6.89-7.62 (m, 4Ar-H), 8.50 (s, 1H triazolic proton) & 8.97 (s, 1H, NH*)	13.5 (CH_2-$\underline{C}H_3$), 42.8 ($\underline{C}$-7), 56.6 ($\underline{C}H_2$-CH_3), 87.3 ($\underline{C}$-6), 121.5-141.2 (aromatic carbons), 151.3, 152.9 (two ring C=N) 161.3 ($\underline{C}$-5) & 166.2 ($\underline{C}$=O)
5c	3475-3245 (br, NH & NH_2), 1740 (C=O), 1635 (C=N), 1575 & 1380 (NO_2), 1075 cm^{-1} (C-O)	1.80-1.88 (t, 3H, CH_3, J=6.2Hz), 4.30-4.35 (q, 2H, CH_2, J=6.2Hz), 4.52 (s, 1H, CH), 6.70 (s, 2H, NH_2*, 6.88-7.66 (m, 4Ar-H), 8.20 (s, 1H triazolic proton) & 8.77 (s, 1H, NH*)	12.7 (CH_2-$\underline{C}H_3$), 48.6 ($\underline{C}$-7), 57.3 ($\underline{C}H_2$-CH_3), 88.3 ($\underline{C}$-6), 120.5-141.3 (aromatic carbons), 152.3, 153.6 (two ring C=N), 161.4 ($\underline{C}$-5) & 166.4 ($\underline{C}$=O)
5d	3470-3240 (br, NH & NH_2), 2920-2880 (br, ali. CH), 1735 (C=O), 1630 (C=N), 1130 cm^{-1} (C-O)	1.70-1.78 (t, 3H, CH_3, J=6Hz), 4.20-4.35 (q, 2H, CH_2, J=6Hz), 4.62 (s, 1H, CH), 6.78 (s, 2H, NH_2*), 6.88-7.16 (d, 2Ar-H) 7.26-7.86 (d, 2Ar-H), 7.92 (s, 1H, triazolic proton), 8.57 (s, 1H, NH*)	13.9 (CH_2-$\underline{C}H_3$), 55.4 ($\underline{C}$-7), 60.2 ($\underline{C}H_2$-CH_3), 86.2 ($\underline{C}$-6), 122.3-139.3 (aromatic carbons), 152.6, 153.2 (two ring C=N), 152.4 ($\underline{C}$-5) & 167.2 ($\underline{C}$=O)
5e	3440-3220 (br, NH & NH_2), 2925-2875 (br, ali. CH), 1715 (C=O), 1620 (C=N), 1150 cm^{-1} (C-O)	1.72-1.75 (t, 3H, CH_3, J=6.4Hz), 2.02 (s, 3H, CH_3), 4.22-4.31 (q, 2H, CH_2, J=6.4Hz), 6.70 (s, 2H, NH_2*), 7.88-8.21(m, 5Ar-H & 1H triazolic proton), 8.78 (s, 1H, NH*)	12.8 (CH_2-$\underline{C}H_3$), 28.6 ($\underline{C}H_3$), 52.3 ($\underline{C}$-7), 58.4 ($\underline{C}H_2$-CH_3), 85.4 ($\underline{C}$-6), 125.2-140.3 (aromatic carbons), 150.2, 153.1 (two ring C=N), 160.2 ($\underline{C}$-5) & 167.1 ($\underline{C}$=O)
5f	3435-3215 (br, NH & NH_2), 2935-2885 (br, ali. CH), 1720 (C=O), 1615 (C=N), 1130 cm^{-1} (C-O)	1.71-1.74 (t, 3H, CH_3, J=6.3Hz), 2.05 (s, 3H, CH_3), 3.59 (s, 3H, OCH_3), 4.25-4.33 (q, 2H, CH_2, J=6.3Hz), 6.70 (s, 2H, NH_2*), 6.78-6.88 (d, 2Ar-H), 6.96-6.88 (d, 2Ar-H), 8.01(1H triazolic proton), 8.78 (s, 1H, NH*)	14.6 (CH_2-$\underline{C}H_3$), 26.4 ($\underline{C}H_3$), 54.1 ($\underline{C}$-7), 54.6 ($O\underline{C}H_3$), 55.2 ($\underline{C}H_2$-CH_3), 87.4 ($\underline{C}$-6), 126.8-153.6 (aromatic carbons), 153.1, 154.1 (two ring C=N), 161.1 ($\underline{C}$-5) & 169.3 ($\underline{C}$=O)
5g	3485-3245 (br, NH & NH_2), 2925-2865 (br, ali. CH), 1740 (C=O), 1625 (C=N), 1090 cm^{-1} (C-O)	1.42-1.45 (t, 3H, CH_3, J=6Hz), 1.45-1.72 (t, 4H, CH_2), 1.85-1.98 (m, 4H, CH_2), 4.25-4.45 (q, 2H, CH_2, J=6Hz), 5.97 (s, 2H, NH_2*), 7.95 (s, 1H, triazolic proton), 9.80 (s, 1H, NH*)	12.4 (CH_2-$\underline{C}H_3$), 17.5 ($2\underline{C}H_2$, cyclo pantane ring), 37.3 ($2\underline{C}H_2$, cyclo pantane ring), 53.3 (spiro carbon), 57.3 ($\underline{C}H_2$-CH_3), 97.6 ($\underline{C}$-6), 152.3, 154.1 (two ring C=N), 162.2 ($\underline{C}$-5) & 168.4 ($\underline{C}$=O)
5h	3465-3240 (br, NH & NH_2), 2935-2875 (br, ali. CH), 1760 (C=O), 1645(C=N), 1070 cm^{-1} (C-O)	1.22-1.46 (t, 3H, CH_3, J=6Hz), 1.60-1.75 (t, 4H, CH_2), 1.92-2.09 (m, 2H, CH_2), 2.21-2.54 (t, 4H, CH_2), 3.99-4.35 (q, 2H, CH_2, J=6Hz), 6.55 (s, 2H, NH_2*), 7.92 (s, 1H, triazolic proton), 9.70 (s, 1H, NH*)	13.9 (CH_2-$\underline{C}H_3$), 21.2 ($2\underline{C}H_2$, cyclo hexane ring), 29.3 ($\underline{C}H_2$, cyclohexane ring), 35.1 ($2\underline{C}H_2$, cyclohexane ring), 48.1 (spiro carbon), 61.1 ($\underline{C}H_2$-CH_3), 93.4 ($\underline{C}$-6),), 151.3, 153.1 (two ring C=N), 161.7 ($\underline{C}$-5) & 167.2 ($\underline{C}$=O)
5i	3475-3245 (br, NH & NH_2), 2925-2870 (br, ali. CH), 1740 (C=O), 1605 (C=N), 1140 cm^{-1} (C-O)	1.50-1.62 (m, 2H, CH_2), 1.65-1.78 (t, 3H, CH_3, J=6Hz), 1.98-2.04 (t, 2H, CH_2), 2.15-2.48 (t, 2H, CH_2), 4.20-4.32 (q, 2H, CH_2, J=6Hz), 5.87 (s, 2H, NH_2*), 7.05 (t, 1H,), 7.15 (t, 1H), 7.35 (d, 1H, J=2Hz), 7.66 (d, 1H, J=8Hz), 7.95 (s, 1H triazolic proton) & 8.79 (s, 1H, NH*)	-

*Presence and position of NH and NH_2 protons are confirmed by deuterium exchange.

available starting material. For reason of economy and pollution, solvent free methods are of great interest in order to modernize classical procedure making them more clean, safe and easy to perform. This is a one-pot procedure in aqueous media, which not only preserves the simplicity but also consistently gives the corresponding product in good to excellent yields.

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REFERENCES

[1] The Merck index, 12th ed, Merck Co. Inc. Whitehouse station, **1996**.
[2] Haber, J. *Present status and perspective on antimycotics with systematic effects*, *Casopis Lekaru Ceskych* (Praha) **2001**, *140*, 596.
[3] Fischer, G.*Z. Chem.*, **1990**, *30*, 305.
[4] Fischer G. *Adv. Heterocycl. Chem.*,**1993**, *57*, 81.
[5] Elashry, E.S.H.; Rashed, N. *Adv. Heterocycl. Chem.*, **1999**, *73*, 127.
[6] (a) Richardson, C.M.; Williamson, D.S.; Parratt, M.J.; Borgognoni, J.; Cansfield, A.D.; Dokurno, P.; Francis, G.L.; Howes, R.; Moore, J.D.; Murray, J.B.; Robertson, A; Surgenor A.E.; Torrance, C.J. *Bioorg. Med. Chem. Lett*., **2006**, *16*(5), 1353; (b) Zaki, Y. H.; Ahmad, S.A; Hussein, A.M.; Abdelhamid, A.O. *Phosphorus Sulfur Silicon*, **2006**, *181*(4), 825.
[7] Badawey, E.-S.A.M. *J. Heterocycl. Chem*., **1996**, *33*(2), 229.
[8] Davies, G.E. *J. Pharm. Pharmacol.*, **1973**, *25*(9), 681.
[9] Brdar, B.; Japelj, M.; Kobe, J. *Biochem. Pharmacol.*, **1979**, *28*(10), 1683.
[10] Eisa, H.M.; El-Ashmawy, M.B.; Tayel, M.M.; El-Magd, S.A.; El. Kashef. *Boll. Chim. Farm.*, **1996**, *135*(10), 585.
[11] Prakash, O.; Bhardwaj, V.; Kumar, R.; Tyagi, P.; Aneja, K.R. *Eur. J. Med. Chem.*, **2004**, *39* (12), 1073.
[12] Moawad, E.B.; Yousif, M.Y.; Metwally, M.A. *Pharmazie*, **1989**, *44* (12), 820.
[13] Kuznetsova, O.A.; Filyakova, V.I.; Pashkevich, K.I.; Ulomskii, E.N. *Russ. Chem. Bull. Int. Ed.*, **2003**, *52* (5), 1190.
[14] (a) Dawood, K.M.; Farag, A.M.; Kandeel, Z.E. *J. Chem. Res.*, **1999**, *88*, 537; (b) Al-Zaydi, K.M.; Al-Shiekh, M.A.A.; Hafez, E.A.A. *J. Chem. Res.*, **2000**, *2000*, 13.
[15] Pryadina, M.V.; Burgart, Ya. V.; Saloutin, V.I.; Kodess, M.I.; Vlomskii, E.N.; Rusinov, V.L. *Russ. J. Org. Chem.*, **2004**, *40* (6), 902.
[16] Lipson, V.V.; Desenko, S.M.; Borodina, V.V.; Shirobokova, M.G. *Chem. Heterocycl. Compd*., **2005**, *41* (2), 216.
[17] Eld, F.A.; Abdel-Wahab, A.H.F.; El-Hag Ali G.A.M.; Khafagy, M.M. *Acta Pharm.*, **2004**, *54*, 13.
[18] Al-Zaydi, K.M.; Borik, R.M.; Elnagdi, M.H. *Molecules*, **2003**, *8*, 910.
[19] Ahmed. E.Kh. *Phosphorus Sulfur and Silicon*, **2002**, *177*, 1323.
[20] Agrody, A.M.EI.; EI-Latif M.S. Abd.; EI-Hady, N. A.; Fakery, A.H.; Bedair, A.H. *Molecules*, **2001**, *6*, 519.
[21] Abdelhamid, A.I.; Abdel-Wahab, B.A.M.; Al-Atoom, A.A. *Phosphorus Sulpur Silicon*, **2004**, *179*, 601.
[23] Wiesbrock, F.; Ulrich, S.S. *Chem. Today*, **2006**, *24*, 30.
[22] (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) De La Hoz, A.; 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 Chem*., **2004**, *6*, 128; (g) Varma, R.S. *Green Chem*., **1999**, *1*, 43; (h) Perreux, L.; Loupy, A. *Tetrahedron*, **2001**, *57*, 9199.
[24] (a) Luche, J.L. *Synthetic Organic Sonochemistry*, Plenum Press, New York, **1998**; (b) Gholap, A.R.; Venkatesan, K.; Daniel, T.; Lahoti, R.J.; Srinivasan, K.V. *Green Chem*., **2003**, *5*, 693.
[25] (a) Aplander, K.; Hidestal, O.; Katebzadeh, K.; Lindstorm, U.M. *Green Chem*., **2006**, *8*, 22-24; (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. Lett.*, **2004**, *6* (26), 4973; (d) Li, C.-J. *Chem. Rev*., **1993**, *93*, 2023; (e) Lindstrom, U.M. *Chem. Rev*., **2002**, *102*, 2751.
[26] Armstrong, R.W.; Combs, A.P.; Tempest, P.A.; Brown, S.D.; Keating, T. A. *Acc. Chem. Res*., **1996**, *29*, 123.
[27] (a) Kappe, C.O.; Stadler, A. *Method. Enzym*., **2003**, *369*, 197; (b) Dax, S.L.; Mc Nally J.J.; Yougman, M.A. *Curr. Med. Chem*., **1999**, *6*, 255.
[28] (a) Dandia, A.; Arya, K. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 114; (b) Dandia, A.; Singh, R; Khaturia, S. *J. Fluorine Chem*., **2007**, *128*, 524; (c) Dandia, A.; Singh, R.; Khaturia, S. *Bioorg. Med. Chem*., **2006**, *14*, 1303; (d) Dandia, A.; Singh, R.; Sarawgi, P. O*rg. Prep. Proced. Int*., **2005**, *37*(4), 397; (e) Dandia, A.; Sati, M.; Arya, K.; Sarawgi, P.; Loupy, A. *Arkivoc*, **2005**, *(i)*, 105; (f) Dandia, A.; Arya, K.; Sati M.; Gautam, S. *Tetrahedron*, **2004**, *60*, 5253; (g) Dandia, A.; Singh, R. ; Sarawgi, P. *J. Fluorine Chem*., **2004**, *125*, 1835; (h) Dandia, A.; Sati, M.; Arya K.; Loupy, A. *Green Chem*., **2002**, *4*, 599; (i) Dandia, A.; Sachdeva, H.; Singh, R. *J. Chem. Res*., **2000**, *2000*, 272.
[29] (a) Dandia, A.; Arya, K.; Sarawgi, P. *J. Indian Chem. Soc.*, **2003**, *80*, 1183; (b) Dandia, A.; Arya, K.; Sati, M.; Sarawgi, P. *J. Fluorine Chem*. **2004**, *125*, 1273; (c) Dandia, A.; Arya, K.; Sati, M. *Synth. Commun*., **2004**, *34*(6), 1141; (d) Dandia, A.; Sarawgi, P.; Binghamb, A.L.; Drakec, J.E.; Hursthouseb, M.B.; Light, M.E.; Ratnani, R. *J. Chem. Res.*, **2007**, *2007*, 155; (e) Dandia, A.; Khaturia, S.; Jain, A.K. *Phosphorus Sulfur Silicon*, **2007**, *182*, 2529.