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Process optimization and eco-friendly/greener synthesis of some n-aryl/heteryl acetoacetamides

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ABSTRACT
N-aryl/heteryl acetoacetamides are the intermediates used in the synthesis of various heterocyclic compounds like 1,4-dihydropyridines, pyrimidines etc. Three different substituted N-aryl/heteryl acetoacetamide derivatives (I-III) have been prepared from the reaction of ethylacetoacetate and three different aryl/heteryl primary amines under solvent free conditions using potassium *tert*-butoxide as catalyst. The reactions were carried out by two different methods (*viz.*, Conventional and Microwave irradiation) and they are simple, eco-friendly and economical. All reactions were processed for optimization with different ratios of aryl/heteryl amine and ethylacetoacetate like1:1,1:1.2,1:1.4,1:1.6,1:1.8,1:2 and a comparison was made between the percentage yields with each ratio. Highest percentage yield was observed with 1:1.8 ratio for I & II and 1:1.6 ratio for III in both the methods. However, the microwave irradiation method was found to be superior to the conventional method. The newly synthesized compounds have been purified by recrystallization and characterized by physical and spectral data.

***Key Words*:** Ethylacetoacetate, potassium *tert*-butoxide, optimization, microwave irradiation, amine, catalyst.

INTRODUCTION

N-aryl/heteryl acetoacetamides are intermediate compounds used in the synthesis of various heterocyclics exhibiting a wide range of pharmacological activities (Chang *et al.*, 2001). In particular, they play key role as intermediates in the synthesis of pyridines and pyrimidines (Dyachenko, 2005; Habashi *et al.*, 1986; Lebed *et al.*, 2012; Kumar *et al.*, 2009; Riad *et al.*, 1989; Sadek *et al.*, 2011; Viale *et al.*, 2011; Yadav *et al.*, 2003; Yadav *et al.*, 2011). They are prepared by the two component reaction of alkyl acetoacetate and different aromatic /hetero aromatic amines (Desai *et al.*, 2001). Reaction of acetoacetamides with various aldehydes in presence of ammonia source yield different derivatives of pyridines and pyrimidines having different pharmacological activities like antibacterial, antitubercular (Sirisha *et al.*, 2011), anticancer (Sirisha *et al.*, 2010), antioxidant (Velena *et al.*, 1999) etc. The present study deals with a new and better protocol to prepare some N-aryl/heteryl acetoacetamides (I-III). Solvent free conventional and microwave irradiation methods using potassium *tert*-butoxide as catalyst were employed for the synthesis of N-aryl/heteryl acetoacetamides. The reactions are simple, eco-friendly and cost effective. They have been optimized by both the methods. The parameters of interest were the concentration of reactants and time of reaction.

MATERIALS AND METHODS

Materials

Chemicals used in synthetic work were p-toluidine, p-chloroaniline, 2-aminopyridine, ethylacetoacetate, potassium *tert* butoxide. They were purchased from SD Fine Chem Limited, Mumbai and Sigma Aldrich, Mumbai. All the solvents used were of analytical grade and were obtained from E. Merck, Mumbai and SD Fine Chem Limited, Mumbai.

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Methods

Melting points were determined in open capillaries using Toshniwal electrical melting point apparatus (Toshniwal Instruments, Amjer, India) and are uncorrected. IR spectra were recorded on a Bruker FTIR spectrometer in KBr discs. ^{1}H-NMR spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard on a Bruker 80 MHz FT-NMR (300 MHz) spectrometer (Bruker Bioscience, USA) and the chemical shifts are reported as **δ** (ppm). Mass spectra were recorded on a GC-MS QP-1100 Shimadzu instrument (70 eV; Shimadzu). A domestic LG Little Chef microwave oven (LG, India) was used for microwave irradiation. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F254 aluminum plates (Merck, Germany).

General procedure for synthesis

Conventional method

A mixture of an appropriate amine and ethyl acetoacetate in different ratios i.e., 1:1, 1:1.2, 1:1.4, 1:1.6, 1:1.8, 1:2 and a catalytic amount of potassium *tert*-butoxide was taken into a 250 mL RB flask. The reaction mixture was heated under reflux for 1–10 h. The residue was cooled and triturated with dry ether. The product was filtered and washed with small portions of dry ether. Purification was effected by recrystallization from aqueous ethanol to obtain a colorless crystalline solid.

Microwave method

A mixture of an appropriate amine and ethyl acetoacetate in different ratios i.e., 1:1, 1:1.2, 1:1.4, 1:1.6, 1:1.8, 1:2 and a catalytic amount of potassium tert-butoxide was taken into a 250 mL Pyrex beaker with an inverted glass funnel and irradiated in a domestic microwave oven for 3–7 min with 30s pulses at 480-640W while monitoring the progress of the reaction by TLC. On completion of the reaction, the reaction mixture was cooled and triturated with ice-cold ether. The product separated was filtered, washed with small portions of ice cold ether and dried.

Table 1: Physical data of N-aryl/heterylacetoacetamides.

Code	R	Molecular formula	Molecular weight	Melting point (°C)
I	4-Chlorophenyl	$C_{10}H_{10}ClNO_2$	211.64	115-118
II	2-Pyridyl	$C_9H_{10}N_2O_2$	178.19	114-116
III	4-Methyl phenyl	$C_{11}H_{13}NO_2$	191.23	78-80

Table 2: Reaction optimization data for N-(4-Chlorophenyl)-acetoacetamide (I).

4-Chloroaniline: Ethylacetoacetate	Time		% Yield	
	Conventional heating	MW irradiation at 640W	Conventional heating	MW irradiation
1:1	1hr	3mins	16	44
1:1.2	2hrs	3.5mins	17	47
1:1.4	3.5hrs	4mins	42	53
1:1.6	5hrs	4mins	46	54.8
1:1.8	6hrs	6mins	51	56
1:2	8hrs	7mins	14	10

Table 3: Reaction optimization data for N-(pyridin-2-yl)-acetoacetamide (II).

2-Aminopyridine: Ethylacetoacetate	Time		% Yield	
	Conventional heating	MW irradiation at 480W	Conventional heating	MW irradiation
1:1	1hr	4mins	7.4	13.6
1:1.2	3.5hrs	4mins	8.6	18.7
1:1.4	4.5hrs	4mins	36	41
1:1.6	7hrs	5mins	38	44
1:1.8	10hrs	6mins	41	46
1:2	4hrs	7mins	7.3	No yield

Table 4: Reaction optimization data for N-(4-methyl phenyl)-acetoacetamide (III).

4-Toluidine: Ethylacetoacetate	Time		%yield	
	Conventional heating	MW irradiation at 640W	Conventional heating	MW irradiation
1:1	5hr	4mins	9.4	13.2
1:1.2	6hrs	5mins	1.5	19.2
1:1.4	7hrs	5mins	2.5	51.36
1:1.6	7hrs	5mins	12.4	61.2
1:1.8	7hrs	6mins	9.94	40.9
1:2	6hrs	7mins	10.5	38.3

Table 5: Spectral characterization data of N-aryl/heteryl acetoacetamides (I-III).

Compound (Molecular formula)	IR (KBr)ν(cm^{-1})	^{1}HNMR (CDCl$_3$) δ (ppm)	MS m/z (%)	Anal. calcd. (%)
N-(4-Chlorophenyl) acetoacetamide (I) $C_{10}H_{10}ClNO_2$	3260(N-H), 1645(C=O), 1514,1316(C=N), 1091 (C-Cl)	2.28(s,3H,-COCH$_3$), 3.24(s,2H,-COCH$_2$CO), 7.06-7.80(m,4H, Ar-H), 9.76 (s, 1H, CONH)	211[M+], 212(11), 213[M+2], 214(3),176, 43(100)	C(56.75);H(4.76); N(6.62).Found: C(56.7);H(4.8); N(6.58)
N-(2-Pyridyl) acetoacetamide (II) $C_9H_{10}N_2O_2$	3236(N-H), 1660(C=O), 1154, 779, 705	2.33(s,3H,-CH$_3$), 3.62(s, 2H, -CH$_2$),7.62-7.70(dd,1H,H$_4$-pyridyl), 8.10-8.29 (m,3H, H$_3$, H$_5$&H$_6$-pyridyl),9.48 (s,1H,CONH)	178(42)[M+], 163(22),135(12), 121(37),106(21), 93(32)	C(60.65);H(5.65); N(15.71).Found: C(60.62);H(5.61); N(15.68)
N-(4-Methylphenyl) acetoacetamide (III) $C_{11}H_{13}NO_2$	3293(N-H), 1657(C=O), 1162,1001, 818, 786	2.29 (s, 6H, 2x CH$_3$), 3.54 (s, 2H, -CH$_2$), 7.09-7.11 (d, 2H,Ar-H$_3$ &H$_5$), 7.39-7.40 (d, 2H,Ar-H$_2$ &H$_6$), 8.98 (s, 1H, CO-NH)	191(26)[M$^+$],148(3), 133(73),120(10), 107(76),91(9), 77(53),65(17), 43(100)	C(69.10);H(6.80); N(7.32).Found: C(69.12);H(6.83); N(7.35)

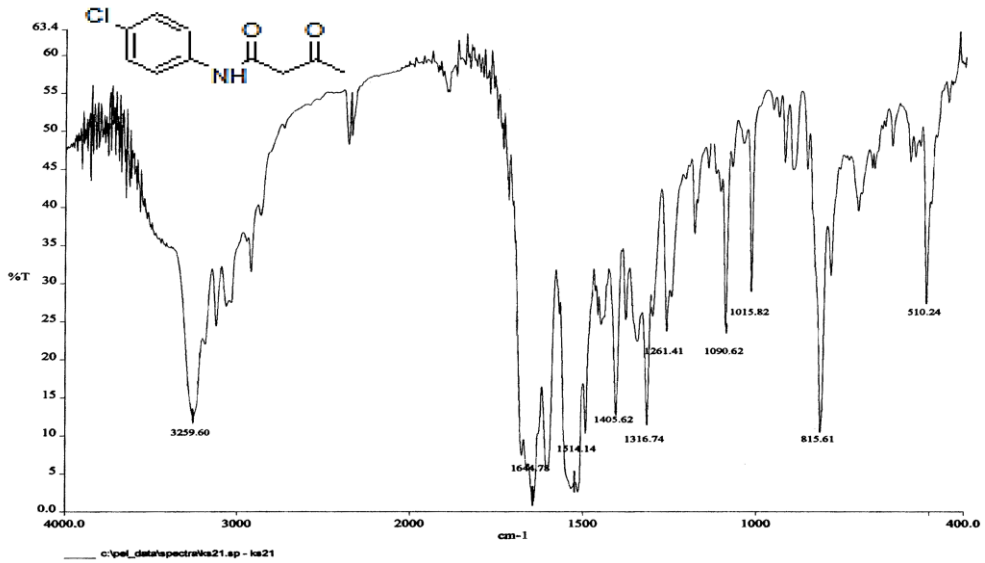


Figure 1: IR Spectrum of N-(4-chlorophenyl)acetoacetamide (I).

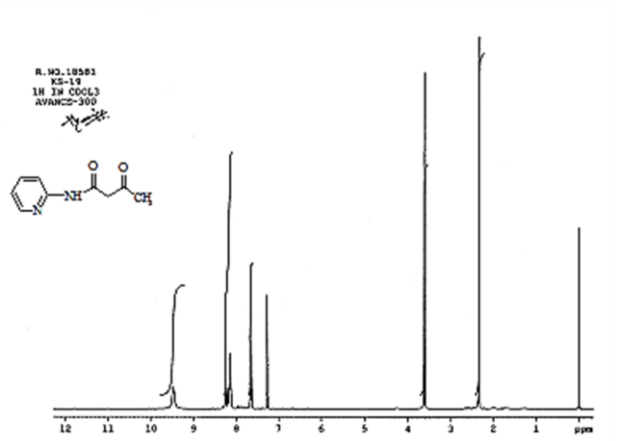
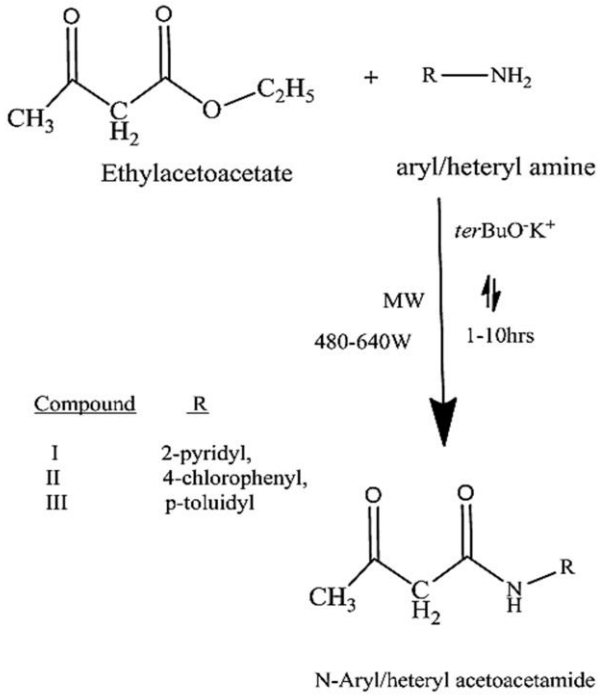


Figure 2: ^{1}H NMR Spectrum of N-(2-pyridyl)acetoacetamide (II).



Scheme 1: Synthesis of N-aryl/heteryl acetoacetamides.

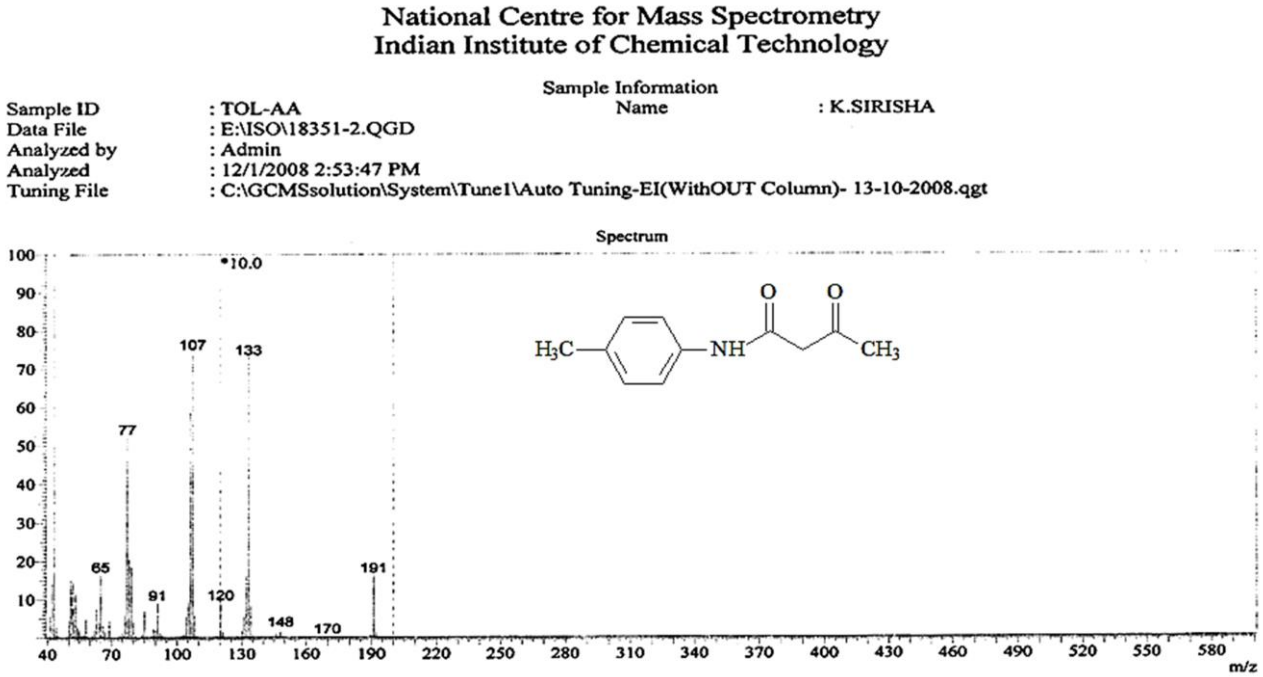


Figure 3: Mass Spectrum of N-(4-methylphenyl)acetoacetamide (III).

Purification by recrystallization from aqueous ethanol afforded a colorless crystalline solid.

RESULTS AND DISCUSSION

N-aryl/heteryl acetoacetamides (I-III) were synthesized from the reaction of three different aryl/heteryl primary amines and ethylacetoacetate in the presence of a trace of catalyst, potassium *tert*-butoxide under solvent free conditions by conventional and microwave irradiation methods (Scheme-1). The reactants were subjected to reflux for 1 to 10h by conventional method while they were irradiated at 480-640W for 3-7min by microwave method to yield compounds I-III. The results are presented in tables 1-4.

Aryl/ heteryl amines and ethylacetoacetate were taken in various ratios like 1:1, 1:1.2, 1:1.4, 1:1.6, 1:1.8, 1:2 i.e., the concentration of ethylacetoacetate was gradually enhanced keeping the aryl/heteryl amines concentration constant. The percentage yield of N-substituted acetoacetamides was found to increase with increasing concentration of ethylacetoacetate considerably up to 1:1.6 [for N-(4-methyl phenyl) acetoacetamide (III)] and up to 1:1.8 [for N-(4-chloro phenyl) and N-(pyridin-2-yl) acetoacetamides (I&II)], beyond which it decreased. Further the reaction times mentioned in the tables 2-4 illustrate the fact that for each ratio of amine and ethylacetoacetate there was no further progress in the reaction beyond the specified time. However, with an increase in the concentration of ethylacetoacetate the reaction times and the percentage yield were found to increase in all the three N-substituted acetoacetamides. Amongst both the methods employed, the microwave irradiation method was found to be superior as it resulted in pure compounds in high yields within less time (3-7min). This is more clearly evident in case of N-(4-methyl phenyl) acetoacetamide (III). The structures of the newly synthesized compounds were confirmed from physical and spectral (IR, ^{1}H-NMR, Mass) data (table 5 and figure 1-3).

CONCLUSION

A new green synthetic methodology has been developed to generate N-substituted acetoacetamides using potassium *tert*-butoxide as catalyst. The reactions were simple, economic and eco-friendly. Optimization of the reaction conditions using appropriate amine and ethyl acetoacetate revealed that an excess of ethyl acetoacetate resulted in improved yields with high purity. The reaction protocol involving Microwave irradiation was found to be superior to the Conventional heating and give highly encouraging results.

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REFERENCES

Chang, J.Y., Kim, B. J., Park, C.R., Han, M.J., Kim, T.J., Yun, H. (2001). Synthesis and polymerization mechanism of bisacetoacetamides. Journal of Polymer Science, Part A: Polymer Chemistry, 39: 1456–1462. [DOI]

Desai, B., Sureja, D., Naliapara, Y., Shah, A., Saxena, A.K. (2001). Synthesis and QSAR Studies of 4-Substituted phenyl-2,6-dimethyl-3,5-bis-N-(substituted phenyl)carbamoyl-1,4-dihydropyridines as potential antitubercular agents. Bioorg. Med. Chem. 9: 1993-1998. [DOI]

Dyachenko, V. D. (2005). Synthesis of Ammonium 5-Arylcarbamoyl-4-heteryl-6-methyl-3-cyano-1,4-dihydropyridine-2-thiolates and 4-Heteryl-5-carbamoyl-6-methyl-3-cyano-1,4-dihydropyridine-2-selenolates. Russian Journal of General Chemistry, 75: 447-456. [DOI]

Habashi, A., Ibraheim, N.S., Mohareb, R.M., Fahmy, S.M. (1986). Reactions with Acetoacetanilide: New approaches for the Synthesis of Polyfunctionally Substituted Pyridine Derivatives. Liebigs Annalen der Chemie, 1986: 1632–1638. [DOI]

Lebed, P. S., Mozgovaya, N. G., Manoilenko, O.V., Tolmachova, V.S., Vovk, M.V. (2012). Synthesis of 1-substituted 5-acetyl (ethoxycarbonyl)-2,3-dihydropyrazolo-[3,4-b]pyridin-3-ones. Chemistry of Heterocyclic Compounds, 48: 1058-1063. [DOI]

Kumar, P, Sankar, B. R., Nasir Baig G., R.B., Chandrashekaran, S. (2009). Novel Biginelli dihydropyrimidines with potential anticancer activity: A parallel synthesis and CoMSIA study. European Journal of Medicinal Chemistry, 44: 4192-4198. [DOI]

Riad, B.Y., Abdelhamid, A.O., Khalifa, F.A., Saleh, Y.E. (1989). Reactions with acetoacetanilide: Synthesis and antibacterial activity of some new pyran, pyrano[2,3-c]pyrazole and pyrano[2,3-c]-pyridine derivatives, Archives of Pharmacal Research, 12: 201-206. [DOI]

Sadek, B., Fahelelbom, K.M.S., Morusciag, L., Elz, S. (2011). Synthesis and Calcium Channel Blocking Activity of 1, 4-Dihydropyridine Derivatives Containing Ester Substitute and Phenyl Carbamoyl Group. American Journal of Applied Sciences 8: 303-309. [DOI]

Sirisha, K., Bikshapathi, G., Achaiah, G., Reddy, V. M. (2011). Synthesis, antibacterial and antimycobacterial activities of some new 4-aryl/heteroaryl-2,6-dimethyl-3,5-bis-N-(aryl)-carbamoyl-1,4-dihydropyridines. European Journal of Medicinal Chemistry, 46: 1564-1571. [DOI]

Sirisha, K., Achaiah, G., Reddy, V. M. (2010). Facile Synthesis and Antibacterial, Antitubercular, and Anticancer Activities of Novel 1,4-Dihydropyridines, Arch. Pharm. Chem. Life Sci., 343: 342 – 352. [DOI]

Velena, A., Zilbers, J., Duburs, G. (1999) Derivatives of 1,4-dihydropyridines as modulators of ascorbate-induced lipid peroxidation and high-amplitude swelling of mitochondria, caused by ascorbate, sodium linoleate and sodium pyrophosphate. Cell Biochem. Funct., 17: 237-252. [DOI]

Viale, M., Cordazzo, C., de Totero, D., Budriesi, R., Rosano, C., Leoni, A., Ioan, P., Aiello, C., Croce, M., Andreani, A., Rambaldi, M., Russo, P., Chiarini, A., Spinelli, D. (2011). Inhibition of MDR1 activity and induction of apoptosis by analogues of nifedipine and diltiazem: an in vitro analysis. Invest New Drugs, 29:98–109. [DOI]

Yadav, J. S., Reddy, B. V. S., Basak, A. K., Narsaiah, A. V. (2003). Three-component coupling reactions in ionic liquids: an improved protocol for the synthesis of 1,4-dihydropyridines. Green Chem, 5: 60-63. [DOI]

Yadav, D.K., Patel, R., Srivastava, V.P., Watal, G., Yadav, L.D.S. (2011). LiBr as an Efficient Catalyst for One-pot Synthesis of Hantzsch 1,4-Dihydropyridines under Mild Conditions. Chin. J. Chem, 29: 118-122. [DOI]