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Microwave Synthesis and Characterisation of Some Cycl [3, 2, 2] Azine Derivatives

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Abstract: ***The synthesis and characterisation of few cycl[3.2.2]azine systems are described. They were obtained in moderate yields by microwave technique from 2-picoline, dimethyl acetylenedicarboxylate and phenacyl bromides in presence of a base. Antibacterial activity and fluorescence behaviour of these compounds are also described.***

Keywords: Cycl[3, 2, 2]azine, Green chemistry, Antibacterial activity, Fluorescence

1. Introduction

The indolizine ring system found in natural products is an important structural skeleton in pharmaceutics because of their interesting biological properties [1]-[3]. Synthetic indolizines have found wide spread applications in drug designing, biological and pharmaceutical research fields [4]-[7]. Several reports are available showing the potential of indolizine derivatives as antimicrobial agent [8]. The cycl[3.2.2.]azine systems are tricyclic aromatic heterocycles with nitrogen as the central atom common to three rings and they are widely accepted due to their interesting physical and chemical properties[9]-[10]. Among cyclazine derivatives, tricyclic fused imidazo[1, 2-*a*]pyridines bridged between the C(3) and C(5) positions would be of particular interest because an imidazo[1, 2-*a*]pyridine ring system has popularly been utilized as a pharrmacophore for therapeutic drugs[11]-[13] and as biochemical fluorescent marker[14] due to its strong fluorescence[15]. The important characteristic feature of the cycl[3.2.2] azine is in the fact that the central nitrogen atom is nonbasic, indicating its pi-electrons are completely involved in the aromatic pi-electron system..

The synthesis of cyclazine derivatives has been actively investigated and many synthetic strategies for producing cyclazine derivatives have been described in the literature [16]-[19]. However, in many cases extended reaction times, elevated temp conditions, and environmentally hazardous organic solvents were used. The synthesis of cycl[3, 2, 2]azine in aqueous medium under microwave condition was also reported[20].The present work is a microwave mediated multi-component reactions (MCRs) which constitute an attractive synthetic strategy for rapid and efficient reaction, enhanced reaction rates, cleaner products in a simple way. In continuation of our work for the synthesis of N-heterocycles under microwave condition [21] cycl[3, 2, 2]azine derivatives have been synthesised using 2-methyl pyridine, phenacyl bromide derivatives and DMAD in presence of alumina in moderate yields.

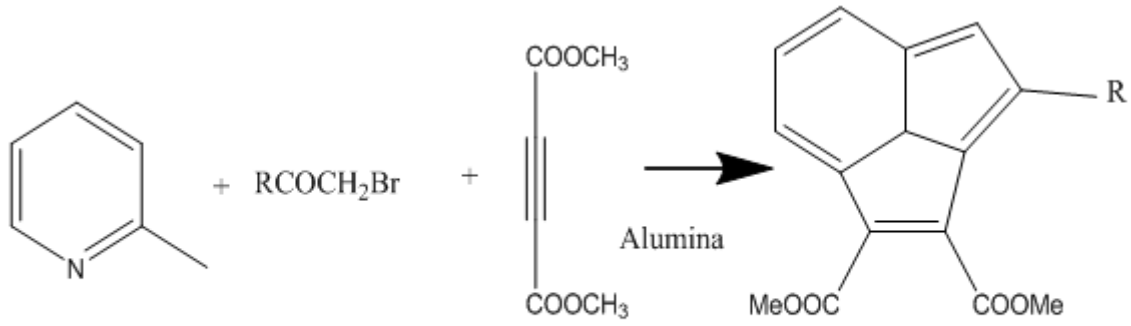
2. Materials and Methods

Melting points were determined with a Metler melting point apparatus and are uncorrected. All reactions were carried out in a commercially available microwave oven (Samsung M183DN) operating at 300W. IR spectra were recorded on a Jasco FT/IR -4100 spectrometer using KBr. Mass spectra were recorded with a Waters-3100 spectrometer. ^{1}H NMR spectra were measured in DMSO at room temperature on Brucker Avance III 400MHz spectrometer. Elemental analyses were conducted on the Elementarvario EL III instrument. All fluorescence measurements were recorded on Jaz Ocean Optics spectrofluorometer. Thin layer chromatography was carried out on aluminium foil coated with silica gel60 F254 (Merck) and column chromatography on silica gel; 70-230 mesh (Merck). UV-visible absorption spectra were studied using Evolution -201 spectrophotometer. All reagents were obtained from commercial sources and used without further purification.

2.1. Procedure

R= **a)**C_6H_5, **b)** $C_6H_5NO_2$ **c)** C_6H_5Cl, **d)** C_6H_5OMe, **e)** C_6H_5Me, **f)** C_6H_5OH, **g)** C_6H_5Br, **h)** C_6H_5F

To a mixture of 1mmol (0.12mL) 2-picoline (1), 1.2mmol (240mg) phenacyl bromide(2) and 1.5mmol(0.18mL) DMAD(3) were added and mixed with 1mmol (153mg)alumina in an Erlenmeyer flask and is fitted with a bent tube. The other end of the bent tube is connected to a receiver. The reaction mixture was irradiated for 2 minutes at 300W with intermittent irradiation for 30 seconds (reaction monitored by TLC). The viscous mass obtained was cooled to room temperature and the products were further purified by column chromatography using n-hexane/EtOAc, (9:1v/v). The products were recrystallized from methanol.



1 2 3 4

Scheme 1: Microwave synthesis of cycl[3, 2, 2]azine derivatives (**4a-h)**

3. Results and Discussion

The cyclazine derivatives (4a-h) synthesised were analysed for IR.UV, ^{1}HNMR, ^{13}C NMR and mass spectral techniques. The cycl[3.2.2]azine products (4a-h) were obtained within 2–5 min in 20–80% yield. The analytical parameters are represented in Table 1.

Table 1: Analytical parameters of the synthesised compounds

Compound	*Yield (%)*	*M.P (^{0}C)*	*M^{+} from mass spectra*	*Molecular formula*
4a	37	140	333	$C_{20}H_{15}NO_4$
4b	78	138	378	$C_{20}H_{14}N_2O_6$
4c	46	153	367.5	$C_{20}H_{14}NO_4Cl$
4d	23	113	363	$C_{21}H_{17}NO_5$
4e	39	97	347	$C_{21}H_{17}NO_4$
4f	36	111	349	$C_{20}H_{15}NO_5$
4g	49	123	411	$C_{20}H_{14}NO_4Br$
4h	42	93	352	$C_{20}H_{14}NO_4F$

It was observed that substrates bearing an electron releasing group at the para position of the aromatic ring (2b) facilitated the enhancement in yields of the products, whereas electron deficient (2d) gave lower yields. The three-component reactions in the absence of solvent were found time consuming when carried out under thermal conditions (1–24 h) in comparison to microwave heating wherein the reactions were very rapid (2–5 min).

3.1. Fluorescence Activity

All the products obtained were found to be fluorescent active and further studies were conducted. In presence of metal ions, methoxy cycl[3, 2, 2]azine derivative exhibited a quenching effect (Figure 1).

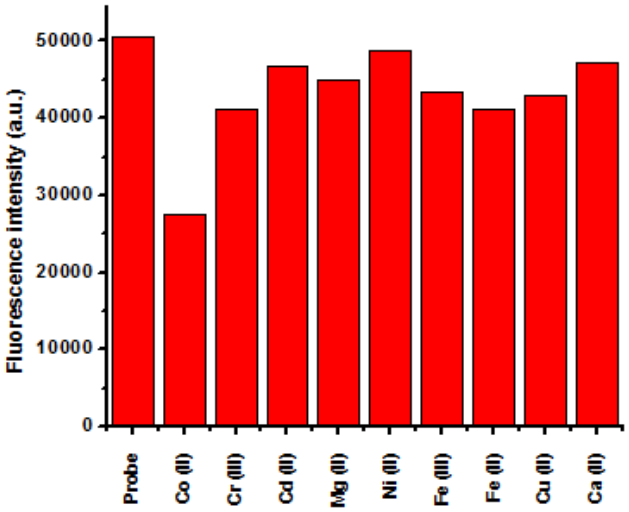


Figure 1: Fluorescence quenching effect of methoxycycl[3, 2, 2]azine derivative in presence of various metal ions

It was found that methoxy cyclazine derivative can be employed as a fluorophore for developing Co^{2+}ion sensor [22].

3.2. Antibacterial Activity

The activity was measured against 10 pathogenic microorganisms. The antibacterial activity of the compounds were studied against *Bacillus cereus, Bacillus pumilus, Bacillus Maculans, Escherichia coli, Klebsiella pneumonia, Proteus vulgaris, Clostridium perfringens, Pseudomonas aeruginosa, Salmonella typhimurium* and *Staphylococcus aureus*. Pure ampicillin was taken as positive control. Antibacterial activity studies of the synthesised derivatives revealed that hydroxy and chloro derivatives showed pronounced antibacterial activity. The bromo and fluoro derivatives showed activity for certain microorganisms only (Table 2).

Table 2: Antibacterial activity studies of cycl[3, 2, 2]azine derivatives

	Antibacterial activity of samples 4(a-h)							
Microorganism	Me	OH	Cl	OMe	NO_2	H	Br	F
B. cereus		++	+				++	
B. pumilus		++	++					++
B. maculans		+	+				+	+
Staphylococcus aureus		++	++		+			+
Salmonella typhimurium	+	++	++	+	+	+		++
E. coli		+	+				+	
Proteus vulgaris		++	+					+
Clostridium perfringens		+					++	++
Klebsiella pneumoniae		++	+					+
Pseudomonas aeruginosa		+	+				++	

4a)**2-Phenyl-4, 5-dicarbmethoxycycl[3.2.2]azine** yellow needles;Yield:37% ;mp 140 ^{0}C**;** Elemental Analysis for $C_{20}H_{15}NO_4$; Calculated: C 72.68; H 3.75; N 3.6 Found: C 70.54; H 3.19; N 3.66; IR (KBr cm^{-1}): 2924, 2853, 1723, 1705, 1617, 1487, 1256, 1209, 1169, 1117, 1067, 760, 401; ^{1}H NMR (DMSO): 7.93–8.42 (4H, m), 7.43–7.52 (5H, m), 5.12 (3H, s), 3.57 (3H, s); ^{13}C NMR :190.3, 165.6, 164.3(2C), 163.8, 158.4, 145.6, 138.4, 138.3, 130.7, 127.2, 124.6, 124.1, 123.4, 89.6, 66.4, 54.3., 53.4, 52.7, 50.8; Mass m/z : 333 [M+].

4b)**2-Nitrophenyl-4, 5 dicarbmethoxycycl[3.2.2]azine** yellow powder; Yield: 78% ;mp 138^{0}C;.Elemental Analysis for$C_{20}H_{14}N_2O_6$;Calculated:C57.15;H2.35;N8.9Found:C56.87; H2.49;N7.13;IR(KBrcm^1):2924, 1733, 1698, 1610, 1545, 1356, 1176, 1097, 772, 406;^{1}HNMR(DMSO):7.80(2H, d, J=7.3Hz), 6.32(1H),.7.57(1H, m), 7.11(1H, m), 3.51 (3H, s); ^{13}C NMR :190.1, 166.7(2C), 163.7, 145.9, 138.7, 138.5(2C), 124.4, 124.3 (2C), 123.4, 89.6, 89.1, 66.5, 54.1, 53.1, 52.2, 51.5(2C);Mass m/z : 378 [M+].

4c)**2-Chlorophenyl-4, 5-dicarbmethoxy-cycl[3.2.2]azine** yellow needles; Yield: 46%; mp 153^{0}C.; Elemental AnalysisfOr$C_{20}H_{14}NO_4Cl$;Calculated:C60.21;H4.32;N7.57Fo und:C57.64;H3.33;N7.13;IR(KBrcm1):2924, 1740, 1698, 1610, 1505, 1256, 1176, 1097, 772, 432;^{1}H, NMR(DMSO):7.67(2H, d, J=7.1Hz), 7.42(1H).7.45(1H, m), 6.34(1H, t), 7.21(1H, m), 3.49(3H, s);^{13}CNMR:190.2, 166.9(2C), 162.2, 159.0, 154.1, 145.2, 143.6, 129.7(2C), 125.5, 124.6 (2C), 123.6, 89.1, 66.5, 54.1, 53.4, 53.2, 52.5(2C); Mass m/z : 367.5 [M+].

4d)**2-Methoxyphenyl-4, 5-dicarbmethoxy cycl[3.2.2]azine** yellow needles; Yield: 23%; mp 113^{0}C; Elemental Analysis for $C_{21}H_{17}NO_5$; Calculated: C 62.42; H 3.56; N 6.78 Found: C 61.36; H 3.09; N 6.54; IR(KBrcm^{-1}):2924, 1738, 1698, 1610, 1505, 1250, 1176, 1097, 772, 436;^{1}HNMR(DMSO):7.67(2H, d, J=7.3Hz), 6.42(1H, d).7.45(1H, m), 6.34(1H, t), 7.21(1H, m), 3.50(3H, s);^{13}CNMR:190.1, 166.3, 163.9(2C), 154.2, 146.0, 145.4, 138.1, 136.1, 135.6, 127.7(2C), 125.9 (2C), 125.4, 87.6, 67.9, 54.5, 53.5(2C) ; Mass m/z : 363 [M+].

4e)**2-Methylphenyl-4, 5-dicarbmethoxy-cycl[3.2.2]azine** yellow needles; Yield: 39%; mp 97^{0}C; Elemental Analysis for $C_{21}H_{17}NO_4$ Calculated: C 56.78; H 4.23; N 4.98 Found: C 58.45; H 3.67; N 4.06; IR (KBrcm^{-1}):2924, 2919, 1740, 1698, 1610, 1505, 1256, 1176, 1097, 772, 405;^{1}HNMR(DMSO):7.68(2H, d.J=7.1Hz),.7.67(1H, m), 6.32(1H, t), 7.23(1H, m);^{13}CNMR:190.0, 166.7, 162.9(2C), 150.1, 147.0, 146.8, 136.1, 132.2, 131.1, 124.5(2C), 123.6 (2C), 124.2, 87.6, 68.1, 66.2, 52.5, 20.2 ;Mass m/z : 347 [M+].

4f)**2-Hydroxyphenyl-4, 5- dicarbmethoxycycl[3.2.2]azine** yellowneedles;Yield:36%;mp111^{0}C;Elemental Analysis for $C_{20}H_{15}NO_5$ Calculated: C 60.56; H 3.24; N 1.89 Found: C 59.06;H3.83;N2.21;IR(KBrcm^{-1}):3431, 2924, 1727, 1698, 1610, 1505, 1256, 1176, 1097, 772, 415;^{1}HNMR(DMSO):7.64(2H, d, J=7.2Hz), 8.52(1H).7.32(1H, m), 6.42(1H, t), 7.45(1H, m);^{13}CNMR:190.2, 166.4, 161.9(2C), 154.2, 148.0, 146.9, 38.4, 134.1, 130.6, 126.7(2C), 125.2 (2C), 125.8, 88.4, 66.1, 56.2, 51.5(2C); Mass m/z : 349 [M+].

4g)**2-Bromophenyl-4, 5-dicarbmethoxy-cycl[3.2.2]azine** yellowneedles;Yield:49%;mp123^{0}C;Elemental Analysis for $C_{20}H_{14}NO_4Br$; Calculated: C 71.42; H 4.76 N 3.43 Found: C 74.54; H 4.24; N 3.13;IR(KBrcm^{-1}):2825, 1733, 1674, 1520, 1578, 1134, 1098, 1021, 807, 716;.^{1}H, NMR(DMSO):7.65(2H, d.J=7.2Hz), 8.22(1H).7.41(1H, m), 6.21(1H, t), 7.17(1H, m);^{13}CNMR:190.1, 166.9(2C), 154.2, 146.2, 145.0, 144.6, 143.6, 132.7, 130.1, 127.7(2C), 125.3(2C), 89.7, 66.1, 64.1, 55.2, 54.5(2C); Mass m/z : 411 [M+].

4h)**2-Fluorophenyl-4, 5-dicarbmethoxy-cycl[3.2.2]azine** yellow needles; Yield: 42%; mp 93^{0}C Elemental Anal. for $C_{20}H_{14}NO_4F$;Calculated:C 73.22; H 4.02; N 3.13 Found: C 74.14 ; H 3.74; N 3.87; IR (KBr cm-^{1}):2951, 1737, 1545, 1513, 1478, 1227, 1167, 432;^{1}HNMR(DMSO):7.66(2H, J=7.1Hz), 7.47(1H, m), 6.14(1H, t), 7.05(1H, m);^{13}CNMR190.2, 166.6, 163.2, 156.9(2C), 154.8, 151.0, 153.6, 130.6, 124.9, 124.7(2C), 123.3(2C), 122.6, 89.1, 93.2, 54.4, 53.3(2C); Mass m/z: 352 [M+]

4. Conclusions

An efficient and convenient method for the synthesis of cyclazines in the absence of solvents and metal catalysts is described. A variety of cyclazine derivatives can be synthesised in moderate yields using this solvent free approach. All the synthesised derivatives were fluorescent and can be applied in sensor development. The biological importances of these classes of compounds are also interesting.

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