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Microwave-accelerated preparation of N- alkyl 2- ketomethyl quinoline Derivatives

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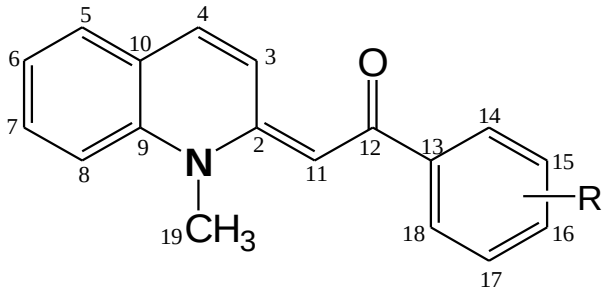
Abstract:
A series of N- alkyl 2- ketomethylquinoline derivatives were synthesis by reaction of benzoyl chloride derivatives with N- methyl quinaldine iodide in the presence of triethyl amine under microwave irradiation. Enaminone form of the product study by spectroscopy method. The result revealed the N- alkyl 2- ketomethylquinoline the fixed enaminone tautomer.

Key words: N- alkyl 2- ketomethylquinoline, Enaminone, triethyl amine, microwave irradiation, Solvent-free conditions.

Introduction
2- ketomethylquinoline contain the -N-C=C-C=O system in their structure and are classified as enaminone [1]. Although methyl derivatives of ketimino tautomers of 2- ketomethylquinoline were recently obtained [2] only unsubstituted N- alkyl 2- ketomethylquinoline the fixed enaminone tautomer [3-7]. It can be prepared by successive treating of 1- 2- dimethyl quinolinum iodide with triethyl amine, benzoyl chloride and hydrochloric acid. Other methods of its synthesis include reaction of 1- methyl quinolinium iodide with benzoyl chloride in the presence of aqueous solution of sodium hydroxide [8] or reaction of 1- methyl quinolinium- 2- sulfonate with benzoylaceton, followed by reflux of the

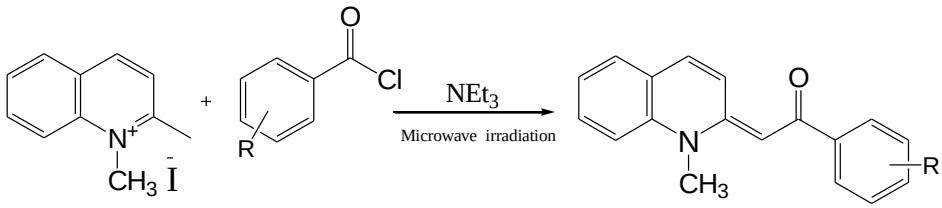
reaction mixture with hydrochloric acid[7] or reaction of 2,2- diethoxy- 1,2- dihydro- 1 -methylquinoline with acetophenone. [9] .Enaminone are important organic intermediate and biologically active substances[10-11]. Their structure was studied by various NMR , IR and UV techniques. In this paper we prepared N- alkyl 2- ketomethyl quinoline derivatives by facile method in the presence of triethyl amine under microwave irradiation and investigation enaminone form in this compound.(Scheme 1).



Scheme 1.structure of N- alkyl 2- ketomethylquinoline

Results And Discussion

for synthesis of N- alkyl 2- ketomethylquinoline(see Table 1). Compared with the heating method, the reaction time using microwave irradiation is sharply decreased from 3-5h to 5-10 min. In conclusion, the reported method is an interesting, easy and novel method, high yields of the products, ease of work-up conditions and low cost make the above method preferable to other existing methods. (Scheme 2).



(1) (2) (3)

Scheme 2. Preparation of N- alkyl 2- ketomethylquinoline under microwave irradiation

Table 1. Preparation of several N- alkyl 2- ketomethylquinoline under microwave irradiation

Compound	R	Yield(%)	Mp(^{0}C)	Mp(^{0}C)
1	H	85	212-215	213-214[4-8]
2	2-Me	52	115-117	114-116[8]
3	4-Me	70	156-157	155-156[8]
4	4-OMe	48	89-90	90-92[8]
5	2-Br	30	145-147	146-148[8]
6	4-Br	35	179-180	180-182[8]
7	4-NO_2	43	212-215	213-214[8]

1) (2E)-2-(1-methylquinolin-2(1H)-ylidene)-1-phenylethanone:
MW: 261.32, MF: $C_{18}H_{15}NO$, Uv/λ max =414-432.5-455, IR(KBr): ύ (cm^{-1})= 1442 , 1511 , 1555,1635 ,^{1}H NMR($CDCl_3$) :δ(ppm)=3.52(CH_3),5.95(=CH),9.2(dd, J=9.5 Hz, H_3), 7.22(d, J=6.7 Hz, H_4) 6.53(dt, J=6.7 Hz, H_6) 7.15(d, J=6.7 Hz, H_7)7.25-7.46(H_5,H_8),7.92-7.86(H_{14},H_{18}), 7.41-7.34(H_{15},H_{17}), 7.54(H_{16}),^{13}C NMR ($CDCl_3$) : δ(ppm) =43(CH_3), 85.2(=CH),154.2(C_2),110.1(C_3),125.9(C_4),127.2(C_5), 117.1(C_6) 128.8(C_7)113.4(C_8),137.9(C_9) 126.8(C_{10})185.1(C=O) 143.6(C_{13})127(C_{14},C_{18}), 128(C_{15},C_{17}), 134.6(C_{16})

2) (2E)-2-(1-methylquinolin-2(1H)-ylidene)-1-o-tolylethanone:
MW: 275, MF: $C_{19}H_{17}NO$, Uv/λ max =414-432.5-456, IR(KBr): ύ (cm^{-1})= 1442,1510,1557,1632,^{1}H NMR($CDCl_3$) :δ(ppm)=2.3(CH_3),3.4(CH_3),5.57(=CH), 9.1(dd, J=9.5 Hz, H_3), 7.15(d, J=6.7 Hz, H_4) 6.5 (dt, J=6.7 Hz, H_6) 7.09(d, J=6.7 Hz, H_7)7.15-7.37 (H_5,H_8), 7.25(H_{15}), 7.42(H_{16}) 7.26(H_{17}) 7.69(H_{18}), ^{13}C NMR ($CDCl_3$) : δ(ppm) =19.6(CH_3),43(CH_3), 85.1(=CH), 153.7(C_2),109.2 (C_3),124.6(C_4), 126.3(C_5),116.2(C_6) 127.6(C_7)112.9(C_8),137.5(C_9) 125.1(C_{10})184.3(C=O) 139.8(C_{13})139.5(C_{14}) 129.6(C_{15}), 134.5 (C_{16}), 126.3(C_{17}), 129.8(C_{18}).

3) (2E)-2-(1-methylquinolin-2(1H)-ylidene)-1-p-tolylethanone:
MW: 275, MF: $C_{19}H_{17}NO$, Uv/λ max =414-433.5-456, IR(KBr): ύ (cm^{-1})= 1441,1509,1556,1631,^{1}H NMR($CDCl_3$) :δ(ppm)=2.3(CH_3),3.4(CH_3),5.57(=CH), 9.1(dd, J=9.5 Hz, H_3), 7.18(d, J=6.7 Hz, H_4) 6.65 (dt, J=6.7 Hz, H_6) 7.1(d, J=6.7 Hz, H_7)7.18-7.43 (H_5,H_8), 7.69 (H_{14},H_{18}), 7.25 (H_{15},H_{17}), ^{13}C NMR ($CDCl_3$) : δ(ppm) =24.3(CH_3),43(CH_3), 85.1(=CH),154.1(C_2),110.1(C_3),125.6(C_4),126.9(C_5),116.8(C_6)128.4(C_7)113.2(C_8),137.6(C_9) 126.5(C_{10})184.8(C=O)139.4(C_{13})129.6(C_{14},C_{18}), 129.8(C_{15},C_{17}), 144.2 (C_{16})

4) (2E)-1-(4-methoxyphenyl)-2-(1-methylquinolin-2(1H)-ylidene)ethanone:
MW: 291, MF: $C_{19}H_{17}NO_2$, Uv/λ max =414-433.5-457, IR(KBr): ύ (cm^{-1})= 1442 , 1509 ,1556 -1634 ,^{1}H NMR($CDCl_3$) :δ(ppm)=3.72(OCH_3),3.5(CH_3),5.6(=CH), 9.15(dd, J=9.5 Hz, H_3), 7.2(d, J=6.7 Hz, H_4) 6.7 (dt, J=6.7 Hz, H_6) 7.15(d, J=6.7 Hz, H_7)7.2-7.5 (H_5,H_8), 7.75 (H_{14},H_{18}), 7.1 (H_{15},H_{17}), ^{13}C NMR ($CDCl_3$): δ(ppm), 55.9(OCH_3), 43.6(CH_3), 85.6(=CH),154.8(C_2),110.4(C_3),125.8(C_4),127.3(C_5),117.5(C_6),128.6(C_7)113.9(C_8),137.8 (C_9) 126.9(C_{10})185.4(C=O) 133.6(C_{13}) 129.3(C_{14},C_{18}), 115.8 (C_{15},C_{17}), 166.5(C_{16}).

5) (2E)-1-(2-bromophenyl)-2-(1-methylquinolin-2(1H)-ylidene)ethanone:
MW: 340.2, MF: $C_{18}H_{14}NOBr$, Uv/λ max = 414-434-457.5, IR(KBr): ύ (cm^{-1})= 1441, 1508, 1555, 1634, ^{1}H NMR($CDCl_3$) :δ(ppm)= 3.4(CH_3),5.57(=CH), 9.2(dd, J=9.5 Hz, H_3), 7.2(d, J=6.7 Hz, H_4) 6.55 (dt, J=6.7 Hz, H_6) 7.1(d, J=6.7 Hz, H_7)7.2-7.4 (H_5,H_8), 7.62(H_{15}),

7.43(H_{16}) 7.39(H_{17}) 7.7(H_{18}), ^{13}C NMR ($CDCl_3$) : δ(ppm) =43.2(CH_3), 85.8(=CH),153.9(C_2),109.7(C_3),124.8(C_4),126.7(C_5),116.6(C_6)127.8(C_7)113.1(C_8),137.7(C_9) 125.8(C_{10})185.6(C=O) 138.3(C_{13})122.4(C_{14}) 132.2(C_{15}), 136.8(C_{16}), 128.3(C_{17}), 132.1(C_{18})

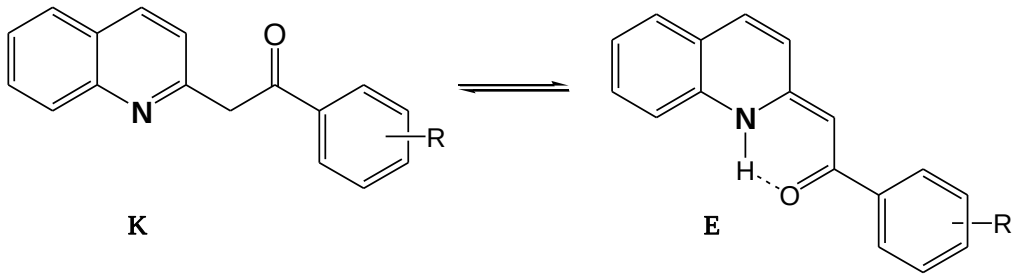
6) (2E)-1-(4-bromophenyl)-2-(1-methylquinolin-2(1H)-ylidene)ethanone

MW: 340.2, MF: $C_{18}H_{14}NOBr$, Uv/λ max =414-434.5-458, IR(KBr): ύ (cm^{-1})=1442, 1509, 1556 , 1631, ^1H NMR($CDCl_3$) :δ(ppm)= 3.45(CH_3),5.59(=CH), 9.15(dd, J=9.5 Hz, H_3), 7.2(d, J=6.7 Hz, H_4) 6.8 (dt, J=6.7 Hz, H_6) 7.3(d, J=6.7 Hz, H_7)7.2-7.45 (H_5,H_8), 7.7 (H_{14},H_{18}), 7.62 (H_{15},H_{17}), ^{13}C NMR ($CDCl_3$) : δ(ppm) =43.6(CH_3), 85.7(=CH), 154.3 (C_2),110.5(C_3),125.9(C_4),127.3(C_5),116.9(C_6),128.7(C_7)113.6(C_8),137.8(C_9)126.9(C_{10})18 5.1(C=O) 136.9(C_{13})132.1(C_{14},C_{18}), 132.2(C_{15},C_{17}), 128.9(C_{16}).

7) (2E)-2-(1-methylquinolin-2(1H)-ylidene)-1-(4-nitrophenyl)ethanone:

MW: 306, MF: $C_{18}H_{14}N_2O_3$, Uv/λ max =452-468, IR(KBr): ύ(cm^{-1})=1327-1424-1526-1634, ^1H NMR($CDCl_3$) :δ(ppm)= 3.55(CH_3),5.63(=CH), 9.2(dd, J=9.5 Hz, H_3), 7.25(d, J=6.7 Hz, H_4) 6.9 (dt, J=6.7 Hz, H_6) 7.45(d, J=6.7 Hz, H_7)7.3-7.5 (H_5,H_8), 8.1 (H_{14},H_{18}), 8.4 (H_{15},H_{17}), ^{13}C NMR ($CDCl_3$) : δ(ppm) =43.9(CH_3), 85.8(=CH), 154.6 (C_2),110.9 (C_3),126.3(C_4),127.8(C_5),117.1(C_6), 129.5(C_7), 113.9(C_8), 138.6(C_9) 127.4(C_{10}), 189.7(C=O) 144.2(C_{13}), 130.8(C_{14},C_{18}), 121.6(C_{15},C_{17}), 154.2(C_{16}).

Compound **1-7** are expected to be helpful in studies of tautomeric equiliberia in 2 -ketomethylquinoline(Scheme 3).



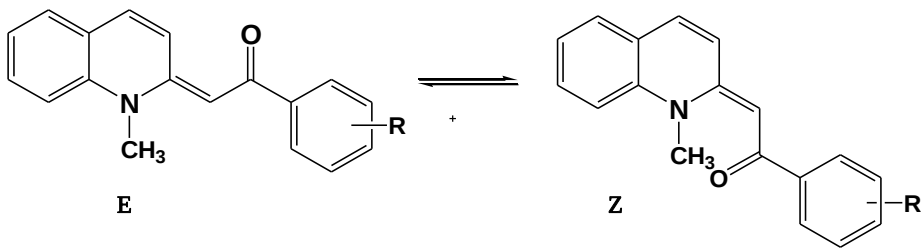
Scheme 3. tautomeric equiliberia in 2- ketomethylquinoline

In **Table 2** the UV-VIS spectra of tautomeric mixture of **K** and **E** were compared to those of respective N- alkyl 2- ketomethylquinoline **1-7**. As it can be seen those spectra are very similar to each other which means that the minor ketimino (**K**) from 2-ketomethylquinoline do not absorb in the visible region.

Table 2. data spectroscopy of N- alkyl 2- ketomethylquinoline

R	λ_{max}(nm) 1-7 K E ⇌		ύc=o
H	414-432.5-455	413-430-457	1635
2-Me	414-432.5-456	413-432-455	1630
4-Me	414-433-456	411.5-433-455.5	1631
4-OMe	414-433.5-457	413-433.5-460.5	1634
2-Br	414-434-457.5	413-433-459.5	1634
4-Br	414-434.5-458	412.5-433.5-459	1631
4-NO_2	452-468	--------	1634

N- alkyl 2- ketomethylquinolines (solution in $CDCl_3$) has the **E** configuration. This was also proved by UV-VIS (solution in ethanol) and IR (solution in chloroform) spectra. The aim of the present paper is to test if the substituted N- alkyl 2- ketomethyl quinoline can be used as models for tautomeric studies of 2- ketomethyl quinoline both in solution and in solide state. More ever substituent effect on the obtained spectral was also studied to see how substitution affects the molecular geometry of those compounds (Scheme 4).



Scheme 4. tautomeric equiliberia in N- alkyl 2- ketomethylquinoline

Full conjugation in N- alkyl 2- ketomethylquinoline requires their molecules to be planer. However, due to steric interaction of N-methyl and carbonyl groups with H8 and H3,respectively, planarity of the Z molecule is notpossible [7]. Downfield shift of the H3 signal in N- alkyl 2- ketomethylquinoline (δ= 8.9–9:1 ppm),as compared to the shift of H3 for enaminone tautomers of 2- ketomethylquinoline (δ= 6.76–6.87 ppm), is a result of the proximity of the carbonyl group and H3 [12]. The chemical shifts of other protons in the spectra of N- alkyl 2- ketomethylquinoline are equal to 7.35, 5.85, and 3.51ppm for H8, H11, and H19, respectively. Chemical shifts of H8, H11, C2 and C3 for compounds **1–7** are comparable to those of respective 2- ketomethylquinoline. N-Methylation of the latter compounds causes an upfield effect of C12 (Δδ= 2:39–3:83 ppm). And downfield effect of C8 signals (Δδ=3:43–3:84 ppm). Chemical shifts of carbon atoms in the spectra of N-

alkyl 2- ketomethylquinoline **1–7** are equal to 153.47–154.60, 110.1–110.7, 113.27–113.82, 126.58–126.86, 85.47–85.48, 184.20–187.62 and 43.03–43.48 ppm for C2, C3, C8, C10, C11, C12 and C19, respectively. Values of the proton–proton spin–spin coupling constants are very helpful to distinguish between different tautomers. It was found that the ^{3}J(H3,H4)s for the enaminone tautomeric form of 2- ketomethylquinoline equal to 9.1–9.2 Hz [12], are higher as compared to those for their ketimino (,8.5 Hz) [5] and enolimino forms (8.0–8.2 Hz) [4]. The respective constants for N-methylated enaminone tautomers are even higher (9.7–9.8 Hz). In conclusion, in this special case N-alkyl 2- ketomethylquinoline are not directly suitable models to be used in estimating the tautomeric equilibria of their unmethylated congeners due to their configurational dissimilarity in solution.

Experimental

In a typical procedure,chemical reagent was purchased from Merck chemical company. ^{1}H and ^{13}C NMR spectra were recorded ($CDCl_3$, CD_3CN AND DMSO-d_6 solvent) by a Bruker DRX-500 Avance spectrometer at 400.1 and 125.8 MHz, respectively, with tetramethylsilane (TMS) as an internal reference. A Magna-550 Nicolet recorded IR spectra. Solide compound reported in this paper gave satisfactory C, H, N microanalyses with a Perkin-Elmer Model 240 analyzer. Melting point obtained with an electrothermal micromelting point apparatus is uncorrected.

General synthesis of N- alkyl 2- ketomethylquinoline derivatives

Quinaldine methyl iodide prepared with reaction 2- methylquinoline (1mmol) and iodo methan for 3h. the reaction mixture diluted with 2- propanol . quinaldine methiodide (1mmol) reaction with benzoyl chloride(2mmol) in the presence of triethyl amine ($20cm^3$) with a catalytic amount of 2,6- dimethyl amino pyridine by microwave in domestic microwave oven(sam-sung RE 555 TCW). The reaction mixture was cooled ,diluted with chloroform and extract with solvent and washed with saturated $NaHCO_3$ and dried. The solvent was removed and the product which was obtained as a brown oil was purified by flash chromatography on silica. Recrystaisation from ethyl acetate light petroleum bp(40-60^0) after removing insoluble material by filteration gave yellow needles.

Acknowledgements

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