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Simple Synthesis of α-Oxime Derivatives of 2-Ketomethyl Quinolines under Mild and Heterogeneous Conditions

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2-Ketomethyl quinolines are converted to their α-oximinoketone derivatives in quantitative yields using sodium nitrite in the presence of silica sulfuric acid as nitrosating agent under mild and heterogeneous conditions.

Key Words: Quinolines, α-oximinoketones, heterogeneous catalysis, nitrosation.

Introduction

There are a large number of pharmaceuticals containing an oximino group attached to a variable structure, frequently a heterocyclic one.[1−3] Some oxime derivatives present a fungitoxic and herbicide effect,[4−6] or act as growth regulators for plants.[7] Some α-oximinoketones are known to be important intermediates for the synthesis of aminoacids,[8] nitrosopyrazoles,[9] 2-vinylimidazoles,[10] and so on. Moreover, 2-substituted quinolines are incorporated in many biologically active compounds and natural products. Numerous natural products, including prominent alkaloids such as quinine, belong to the category of quinoline alkaloids.[11−13]

Nitrosation chemistry has been a fruitful area for mechanistic organic and biological chemists,[14−16] and efforts have been made to combine both the synthetic and mechanistic aspects of nitrosation or transnitrosation.[17−18] The most general reagent for nitrosation is nitrous acid, generated from sodium nitrite and mineral acid in water or in a mixture of alcohol and water as solvent.[19,20] Other nitrosating agents such as alkyl nitrites,[21−23] nitrosyl salts,[24−28] dinitrogentetroxide,[29] Fremy's salt,[30] bis(triphenylphosphine)nitrogen (1+) nitrite,[31] *N*-haloamides and sodium nitrite under phase-transfer conditions,[32] alkyl thionitrite and thionitrate,[33] and oxyhyponitrite[34] have been used. This study aimed to overcome the limitations and drawbacks of the reported methods such as tedious work-up, low yields and selectivity; and to replace labor-extensive trial and error improvements with a rational design. Moreover, constraining a reaction to the surface of a solid habitually allows the use of milder conditions and increases its reactivity.[35]

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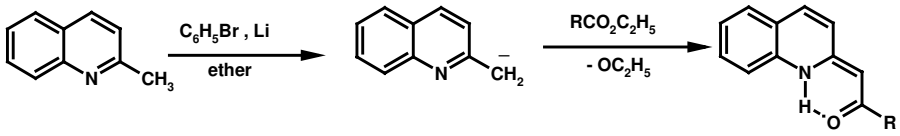
Experimental

Chemicals were purchased from Merck (Germany) and were used without further purification. ^{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 500.1 and 125.8 MHz, respectively, with tetramethylsilane (TMS) as an internal reference. A Magna-550 Nicolet recorded IR spectra. Mass spectra were recorded by a Qp1100Ex Shimadzu spectrometer. Melting points were measured on an Electerothermal micro melting point apparatus and are uncorrected. Elemental analyses for C, H and N were performed using a Perkin-Elmer Model 240 analyzer.

The 2-ketomethyl quinoline (1 mmol), sodium nitrite (3 mmol), and silica sulfuric acid (0.3 g) in dichloromethane (10 mL) were vigorously stirred at 0 °C. The progress of the reaction was followed by TLC. The reaction went to completion after 0.5-1 h. After the completion of the reaction, the mixture was dissolved in dichloromethane (20 mL), filtered and washed with dichloromethane (20 mL). Then the solvent was evaporated and the α-oximinoketone was obtained.

Results

2-Ketomethylquinolines (**1**) are important component in organic chemistry because of the applications of these compounds in heterocyclic synthesis and chemical transformations.[36−41] (Scheme 1).



1

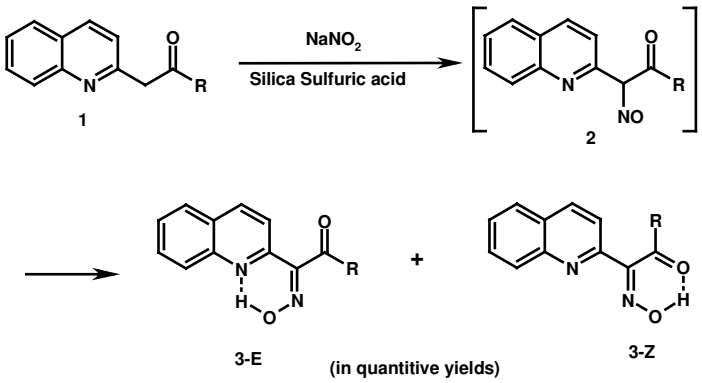
Scheme 1

2-Ketomethylquinolines (**1**) are nitrosated using sodium nitrite in the presence of silica sulfuric acid in dichloromethane and then initially formed nitroso compounds (**2**) are converted to the corresponding α-oximinoketones (**3**) under the reaction conditions (Scheme 2). The nitrosation reactions are carried out under mild and completely heterogeneous conditions at room temperature and give quantitative yields.

Discussion

The reported nitrosation reaction can be simply carried out by placing sodium nitrite and silica sulfuric acid and dicholoromethane as the inert solvent in a reaction vessel and efficient stirring the resultant heterogeneous mixture at room temperature for 0.5-1 h. The initial nitroso compounds are immediately converted to the corresponding α-oximinoketones under the reaction conditions, and, by simple filtration and evaporation of the solvent, the product can be isolated. This new system generates NO^+ in situ, and thus acts as a N_2O_4 equivalent.

The initial oxime products were converted to the corresponding α-oximinokethones immediately and the products can be isolated by simple filtration and evaporation of the solvent. The results and reaction conditions are given in the Table. Although the nitroso coupling also occurs in the absence of silica modified sulfuric acid, the reaction time is very long with lower yield. Therefore, we think that the silica modified sulfuric acid acts as a reaction medium, providing a heterogeneous effective surface area for in situ generation of HNO_2 in low concentrations. It also makes work-up easy.



3	R
a	C_6H_5
b	4-CH_3-C_6H_4
c	4-CH_3O-C_6H_4
d	$C(CH_3)_3$
e	CH_3
f	4-C_5H_4N

Scheme 2

Table

% Yield in heterogeneous reaction	% Yield in homogeneous reaction	R	**3**	Entry
99.9	75.0	C_6H_5	a	**1**
99.9	73.0	4-CH_3-C_6H_4	b	**2**
93.0	82.0	4-CH_3O-C_6H_4	c	**3**
99.9	85.0	$C(CH_3)_3$	d	**4**
99.9	99.9	CH_3	e	**5**
99.9	99.0	4-C_5H_4N	f	**6**

The structures **3a-f** were assigned to the isolated products on the basis of their elemental analyses and their high-field ^{1}H and ^{13}C NMR, IR, and mass spectral data. TLC, ^{1}H and ^{13}C NMR showed 2 isomers of oximes (*E*, *Z*). Partial assignment of the ^{1}H and ^{13}C resonances is given in the experimental section.

In conclusion, the low cost and the availability of the reagents, the easy and clean work-up, and the high yield make this an attractive method for organic synthesis.

1-Phenyl-2-quinolin-2-ylethane-1,2-dione 2-oxime (**3a**, $C_{17}H_{12}N_2O_2$)

Yellow powder; mp 156-158 °C; IR (KBr): υ = 3600-2200, 1640, 1590, 1495 cm^{-1}.

Major isomer (*E*): ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 7.45 (t, *J*= 7.8 Hz, CH), 7.50 (d, *J*= 7.5 Hz, 2CH), 7.62 (t, *J*= 7.3 Hz, CH), 7.69 (t, *J*= 7.9 Hz, CH), 7.82 (dt, *J* = 8.0 and *J*= 0.9 Hz, CH), 7.88 (t, *J* = 8.0 Hz, CH), 7.99 (d, *J* = 8.4 Hz, CH), 8.08 (d, *J* = 8.4 Hz, CH), 8.13 (d, *J* = 7.9 Hz, CH), 8.36 (d, *J* = 8.7 Hz, CH), 18.25 (br. s, OH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 151.25 (C=NOH), 193.82 (C=O) ppm.

Minor isomer (*Z*): ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 7.47 (t, *J*= 7.8 Hz, CH), 7.52 (d, *J*= 7.5 Hz, 2CH), 7.58 (t, *J*= 7.2 Hz, CH), 7.71 (t, *J*= 7.9 Hz, CH), 7.77 (d, *J*= 8.0 Hz, CH), 7.84 (dt, *J* = 8.0 Hz and *J*= 0.9 Hz, CH), 7.90 (t, *J* = 8.0 Hz, CH), 8.09 (d, *J* = 8.3 Hz, CH), 8.14 (d, *J* = 7.9 Hz, CH), 8.39 (d, *J* =

8.7 Hz, CH), 18.25 (br. s, OH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 151.58 (C=NOH), 191.24 (C=O) ppm; MS: m/z (%) = 276 (M^+, 22), 231 (62), 171 (100), 154 (20), 128 (20), 105 (64), 77 (76), 51 (28).

1-(4-Methylphenyl)-2-quinolin-2-ylethane-1,2-dione 2-oxime (**3b**, $C_{18}H_{14}N_2O_2$)

Orange powder; mp 173-175 °C; IR (KBr): υ = 3600-2200, 1676, 1595, 1480 cm^{-1}.

Major isomer (*E*): ^{1}H NMR (500.1 MHz, CD_3CN): δ = 2.41 (s, CH_3), 7.35 (d, J = 8.0 Hz, 2CH), 7.59 (dt, J = 7.9 Hz and J = 0.9 Hz, CH), 7.68 (dt, J = 8.1 Hz and J = 1.0 Hz, CH), 7.71 (d, J = 8.4 Hz, CH), 7.83 (d, J = 8.1 Hz, 2CH), 7.94 (d, J = 8.7 Hz, CH), 8.10 (d, J = 8.7 Hz, CH), 8.33 (d, J = 8.7 Hz, CH), 9.83 (br. s, OH) ppm; ^{13}C NMR (125.8 MHz, CD_3CN): δ = 21.75 (CH_3), 153.43 (C=NOH), 194.51(C=O) ppm.

Minor isomer (*Z*): ^{1}H NMR (500.1 MHz, CD_3CN): δ = 2.43 (s, CH_3), 7.36 (d, J = 8.0 Hz, 2CH), 7.69 (dt, J = 7.9 Hz and J = 1.0 Hz, CH), 7.72 (d, J = 8.4 Hz, CH), 7.84 (d, J = 8.0 Hz, 2CH), 7.95 (t, J = 8.7 Hz, CH), 8.00 (d, J = 8.2 Hz, CH), 8.06 (d, J = 8.4 Hz, CH), 8.48 (d, J = 8.6 Hz, CH), 9.83 (br. s, OH) ppm; ^{13}C NMR (125.8 MHz, CD_3CN): δ = 21.80 (CH_3), 154.65 (C=NOH), 196.54 (C=O); MS: m/z (%) = 290 (M^+, 19), 245 (86), 171 (84), 154 (43), 128 (31), 119 (100), 91 (98), 65 (71).

1-(4-Methoxy phenyl)-2-quinolin-2-ylethane-1,2-dione 2-oxime (**3c**, $C_{18}H_{14}N_2O_3$)

Orange powder; mp 83-85 °C; IR (KBr): υ = 3600-2200, 1680, 1600, 1450 cm^{-1}.

Major isomer (*E*): ^{1}H NMR (500.1 MHz, $CDCl_3$ + DMSO-d_6): δ = 3.85 (s, OCH_3), 6.95 (d, J = 8.7 Hz, 2CH), 7.53 (t, J = 7.4 Hz, CH), 7.63 (t, J= 7.6 Hz, CH), 7.79 (d, J = 8.0 Hz, CH), 7.93 (d, J = 8.4 Hz, CH), 7.97 (d, J = 8.7 Hz, 2CH), 8.00 (d, J = 8.6 Hz, CH), 8.14 (d, J = 8.6 Hz, CH), 9.25 (br. s, OH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$ + DMSO-d_6): δ = 55.12 (OCH_3), 151.44 (C=NOH), 191.95 (C=O) ppm.

Minor isomer (*Z*): ^{1}H NMR (500.1 MHz, $CDCl_3$ + DMSO-d_6): δ = 3.89 (s, OCH_3), 6.98 (d, J = 8.7 Hz, 2CH), 7.54 (t, J = 7.4 Hz, CH), 7.75 (d, J = 7.7 Hz, CH), 7.82 (t, J = 8.4 Hz, CH), 7.89 (d, J = 8.1 Hz, CH), 7.99 (d, J = 8.7 Hz, 2CH), 8.06 (d, J = 8.6 Hz, CH), 8.15 (d, J = 8.6 Hz, CH), 9.25 (br. s, OH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$ + DMSO-d_6): δ = 55.20 (OCH_3), 152.25 (C=NOH), 197.68 (C=O) ppm; MS: m/z (%) = 306 (M^+, 25), 261 (73), 171 (77), 155 (35), 135 (100), 128 (22), 107 (20), 92 (38), 51 (18).

3,3-Dimethyl-1-quinolin-2-ylbutane-1,2-dione 1-oxime (**3d**, $C_{15}H_{16}N_2O_2$)

Ivory powder; mp 134-136 °C; IR (KBr): υ = 3600-220, 1685, 1595, 1490 cm^{-1}.

Major isomer (*E*): ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.42 [s, $C(CH_3)_3$], 7.50 (d, J= 8.7 Hz, CH), 7.68 (t, J = 7.5 Hz, CH), 7.82 (t, J = 8.1 Hz, CH), 7.87 (d, J= 8.1 Hz, CH), 8.07 (d, J= 8.5 Hz, CH), 8.33 (d, J= 8.7 Hz, CH), 17.5 (br. s, OH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 27.38 [$C(CH_3)_3$], 45.29 [$C(CH_3)_3$], 150.46 (C=NOH), 205.45 (C=O) ppm.

Minor isomer (*Z*): ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.35 [s, $C(CH_3)_3$], 7.49 (d, J= 8.7 Hz, CH), 7.56 (t, J= 7.5 Hz, CH), 7.70 (t, J = 8.1 Hz, CH), 7.91 (d, J = 8.4 Hz, CH), 8.00 (d, J = 8.6 Hz, CH), 8.12 (d, J= 8.5 Hz, CH), 17.5 (br. s, OH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 26.55 [$C(CH_3)_3$], 43.19 [$C(CH_3)_3$], 149.40 (C=NOH), 212.54 (C=O) ppm; MS: m/z (%) = 257 (M^++1, 75), 239 (10), 171 (89), 155 (81), 128 (39), 101 (12), 57 (100), 41 (60).

1-Quinolin-2-ylpropane-1,2-dione 1-oxime (**3e**, $C_{12}H_{10}N_2O_2$)

White powder; mp 140-142 °C; IR (KBr): υ = 3400-2300, 1689, 1564, 1500 cm^{-1}.

Major isomer (*E*): ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.60 (s, CH_3), 7.68 (t, J = 7.4 Hz, CH), 7.82 (t, J = 7.6 Hz, CH), 7.89 (d, J= 8.0 Hz, CH), 8.06 (d, J= 8.4 Hz, CH), 8.31 (d, J= 8.8 Hz, CH), 8.39 (d, J= 8.8 Hz, CH), 18.25 (br.s, OH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 28.26 (CH_3), 150.74 (C=NOH), 199.06 (C=O) ppm; MS: m/z (%) = 214 (M^+, 33), 171 (63), 154 (85), 128 (100), 114 (40), 101 (47), 77 (30) 43 (62).

1-Pyridin-4-yl-2-quinolin-2-ylethane-1,2-dione 2-oxime (**3f**, $C_{16}H_{11}N_3O_2$)

Ivory powder; mp 172-174 °C; IR (KBr): υ = 3600-2200, 1700, 1676, 1630, 1580, 1495, 990 cm^{-1}.

Major isomer (*E*): ^{1}H NMR (500.1 MHz, $CDCl_3$ and DMSO-d_6): δ = 7.50 (t, J = 7.4 Hz, CH), 7.60 (t, J = 7.9 Hz, CH), 7.77 (d, J =8.0 Hz, CH), 7.84 (m, CH), 7.91 (d, J= 8.1 Hz, CH), 8.06 (m, CH), 8.13 (d, J = 8.5 Hz, CH), 8.43 (d, J =8.7 Hz, CH), 8.80 (br., 2CH), 12.00 (br. s, OH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$ and DMSO-d_6):g = 151.60 (C=NOH), 190.23 (C=O) ppm.

Minor isomer (*Z*): ^{1}H NMR (500.1 MHz, $CDCl_3$ and DMSO-d_6): δ = 7.55 (t, J =7.4 Hz, CH), 7.71 (t, J = 7.5 Hz, CH), 7.81 (d, J = 7.9 Hz, CH), 7.83-8.60 (m, CH), 7.86 (d, J = 8.0 Hz, CH), 7.93 (d, J= 8.1 Hz, CH), 8.08 (m, 2CH), 8.81 (br., 2CH), 12.00 (br. s, OH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$ and DMSO-d_6): δ = 150.95 (C=NOH), 194.10 (C=O) ppm; MS: m/z (%) = 277 (M^+, 37), 232 (48), 171 (100), 154 (58), 128 (37), 106 (45), 78 (72), 51 (64).

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