SYNTHESIS AND NMR SPECTRA OF 2-METHYL-2-QUINOLIN-2-YL-PROPIOPHENONES

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Abstract: Twelve 2-methyl-2-quinolin-2-yl-propiophenones were obtained by treating 2-(1-cyano-1-methylethyl)quinoline with phenylmagnesium bromides. IR and ^{1}H, ^{13}C and ^{15}N NMR spectra were recorded for these fixed ketimino tautomers of 2-phenacylquinolines. X-Ray diffraction studies show that the molecule of *p*-methoxy derivative is strongly twisted.

Introduction

Comparison between experimental data obtained for mixture of tautomers and for its separated congeners is a very helpful method to study tautomerism [1]. This requires the so-called fixed tautomers, usually alkyl derivatives of tautomeric forms, to be used [2]. For 2-phenacyl derivatives of pyridine and quinoline, which reveal interesting ketimino-enamino-enol tautomerism [3], such fixed enamino and enol forms were prepared [4,5] but their stable ketimino derivatives, Het-CMe_2-COAr (Het = 2-pyridyl or 2-quinolyl) are not known. Since deprotonation of highly hindered 2-alkylpyridines, *e.g.* 2-isopropylpyridine, followed by its aroylation proceeds with great difficulty [5-7], that procedure is useless in preparation of desired ketones. On the other hand, it is known that *tert*alkyl-aryl ketones may be obtained by consecutive alkylation of acetophenones [8]. Similar method was used to transform 3-phenacylpyridine to its dimethyl derivative [9]. When

testing different preparative methods, we found the classic Grignard reaction between 2-(1-cyano-1-methylethyl)quinoline and phenyl magnesium halides to be effective procedure for preparation 2-methyl-2-quinolin-2-yl-propiophenones.

Experimental

Melting points are uncorrected. Satisfactory microanalyses (± 0.30 % for C, H and N) were obtained for all compounds. IR and UV-vis spectra were recorded for compounds **1** - **12** dissolved in chloroform on a VECTOR 22 (Bruker) and CARY 3E (Varian) spectrophotometers, respectively. Details of the NMR and X-ray determinations are available elsewhere [10,11].

Conditions applied in transformation of 2-ethylpyridine to 2-*iso*propylpyridine (PhLi/MeI) [6] were used in the attempted preparation of 2-methyl-2-quinolin-2-yl-propiophenone from 2-quinolin-2-yl-propiophenone. Starting materials were recovered in reaction of isopropyl-phenyl ketone with sodium hydride followed by addition of 2-bromopyridine.

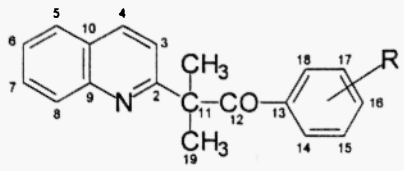
Quinoline 1-oxide was obtained in 83 % yield by oxidation of quinoline with urea-hydrogen peroxide complex [12] according to ref. [13]. It was then treated with α,α'-azo-isobutyronitrile (Fluka) to give 2-(1-cyano-1-methylethyl)quinoline, bp. 134-137°C/1 mm Hg in 35 % yield [14].

2-Methyl-2-quinolin-2-yl-propiophenones (1 - 12). Solution of 8.83 g (0.045 mol) of 2-(1-cyano-1-methylethyl)quinoline in 40 mL of dry ether was added to a stirred solution of 0.07 mol of phenylmagnesium bromide in 40 mL of dry ether at the rate allowing reaction mixture to boil. It was refluxed for additional 3h, cooled and poured onto mixture of 250 g of cracked ice and 25 mL of concentrated hydrochloric acid. The water layer was alkalized with ammonia, extracted with ether and dried with solid potassium carbonate. The residue obtained after evaporation of ether was distilled in vacuum. The crude products obtained by the *vacuum* distillation were purified by column chromatography [silica gel (230-400 mesh), hexane/ethyl acetate (9:1)], crystallization from the mixture of hexane and ethyl acetate (9:1) or repeated *vacuum* distillation. The yields, boiling and melting points, and spectral data for the obtained ketones are given in Table 1.

Results and Discussion

Experiment shows that attempted methylation of 2-quinolin-2-yl-propiophenone gave a complex mixture of products. Reaction of isopropyl-phenyl ketone with sodium hydride followed by addition of 2-bromopyridine was also ineffective in preparation of 2-methyl-2-quinolin-2-yl-propiophenones. On the other hand, the classic Grignard reaction between 2-(1-cyano-1-methyl-

Table 1. Reaction yields and some physical data for compounds **1** - **12**



No	R	Yield[a] (%)	Bp. [°C/mm Hg][b]	Mp. [°C] or Bp. [°C/mm Hg][c]	$\nu_{C=O}$ [cm^{-1}]	δ_{15N} [ppm][d]
1	4-CF_3	53	166-185/1	84-86	1683.6	-76.4
2	3-CF_3	52	176-178/1	176-8/1	1684.7	-76.4
3	3-Cl	88	204-206/1	67-69	1682.5	-77.1
4	3-F	85	188-191/1	60-62	1682.2	-76.7
5	4-Br	54	201-212/1	78-80	1680.2	-77.3
6	4-Cl	57	190-201/1	84-86	1678.7	-77.3
7	3-OMe	55	211-214/1	212-214/1	1676.3	-77.5
8	4-F	61	195-198/0.5	193-195/1	1678.6	-77.2
9	H	82	185-193/3	56-58	1676.2	-77.7
10	3-Me	52	175-188/1	76-78	1675.6	-78.2
11	4-Me	70	165-170/2	105-107	1674.4	-78.1
12	4-OMe	76	190-211/2	142-143	1668.7	-78.4

[a] After purification by distillation, column chromatography and repeated vacuum distillation or crystallization; [b c] Before and after purification by the column chromatography, respectively; [d] In $CDCl_3$ with respect to external CH_3NO_2.

Table 2. ^1H NMR chemical shifts (δ, from internal TMS) of compounds **1** - **12** measured for solutions in $CDCl_3$

No	H3	H4	H5	H6	H7	H8	H14	H15	H16	H17	H18	H19	H(R)
1	7.32	8.11	7.80	7.54	7.72	8.08	7.65	7.45	-	7.45	7.65	1.79	-
2	7.32	8.10[a]	7.78	7.53	7.71	8.02	b	-	8.08[a]	7.25	7.60	1.79	-
3	7.30	8.07	7.76	7.50	7.68	8.05	7.75	-	7.25	7.01	7.30	1.76	-
4	7.31	8.05	7.74	7.47	7.65	8.09	7.42	-	6.97	7.06	7.29	1.81	-
5	7.27	8.06	7.77	7.52	7.70	8.09	7.45	7.31	-	7.31	7.45	1.79	-
6	7.27	8.05	7.76	7.50	7.69	8.10	7.54	7.13	-	7.13	7.54	1.79	-
7	7.27	7.99	7.71	7.45	7.65	8.11	c	-	6.84	7.01	7.11	1.83	3.53
8	7.26	8.04	7.75	7.49	7.69	8.11	7.64	6.83	-	6.83	7.64	1.81	-
9	7.28	8.04	7.76	7.51	7.71	8.13	7.80	7.17	7.31	7.17	7.80	1.82	-
10	7.27	8.04	7.77	7.52	7.72	8.12	7.54	-	7.14	7.00	7.21	1.79	2.22
11	7.25	8.00	7.72	7.49	7.69	8.14	7.54	6.96	-	6.96	7.54	1.82	2.21
12	7.22	7.99	7.73	7.48	7.68	8.13	7.63	6.64	-	6.64	7.63	1.80	3.65

[a] Signals of H4 and H16 can be exchanged; [b] Overlapped by signal of H7; [c] Overlapped by signal of H3.

Table 3. ^{13}C NMR chemical shifts (δ, from internal TMS) of compounds **1 - 12** measured for solutions in $CDCl_3$[a]

No	C2	C12	C13	C14	C15	C16	C17	C18	C19	C(R)
1[b]	163.51	201.60	138.96	129.92	125.04	133.02[c]	125.04	129.92	26.49	118.89
2	163.49	201.09	137.61	126.05	129.85	128.90	128.47	132.71	26.52	118.64
3	163.52	200.95	137.49	129.62	134.24	131.54	129.07	127.61	26.52	-
4[d]	163.57	200.80	137.92	116.24	162.34	118.53	129.37	125.27	26.45	-
5	163.74	201.24	136.66	131.27[e]	131.24[e]	127.94	131.24[e]	131.27[e]	26.64	-
6	163.73	200.95	134.02	131.11	128.19	138.02	128.19	131.11	26.56	-
7	163.91	201.73	136.96	113.90	158.98	118.23	128.70	122.06	26.50	55.07
8[f]	163.85	200.55	131.97	132.28	114.92	164.48	114.92	132.28	26.60	-
9	164.03	202.34	135.81	129.65	127.91	131.70	127.91	129.65	26.76	-
10	164.17	202.73	135.91	130.28	137.81	132.56	127.72	126.95	26.75	21.26
11	164.19	201.69	133.00	129.82	128.56	142.29	128.56	129.82	26.67	21.26
12	164.39	201.09	128.27	132.02	113.08	162.21	113.08	132.02	26.52	54.98

[a] Substituent chemical shift [in ppm]: C3 [118.74-119.53], C4 [136.45-137.10], C5 [127.24-127.47], C6 [126.09-126.71], C7 [129.26-129.70], C8 [129.20-129.60], C9 [147.53-147.81], C10 [126.40-126.82], C11 [54.71-55.04]; [b] J(F,Cn) = 32 and 4 Hz for n = 16 and 15, respectively; [c] Quartet, ^2J(F,C16) = 33 Hz; [d] J(F,Cn) = -311, 22, 21, 8, 6 and 2 Hz for n = 15, 14, 16, 17, 13 and 18, respectively; [e] Signals of C14(17) and C15(18) can be exchanged; [f] J(F,Cn) = -254, 22, 9 and 3 Hz for n = 16, 15, 14 and 13, respectively.

ethyl)quinoline, 2-Qui-CMe_2CN, and (substituted) phenyl magnesium bromides, R-C_6H_4-MgX, gave compounds **1 - 12** (this method was earlier found successful in preparation of α-benzoyl-cumene, Ph-CMe_2-COPh [15]). Both $\nu_{C=O}$ and $\delta_{^{15}N}$ values (Table 1) increase for more electron-donor substituents but linear correlations of $\nu_{C=O}$ and $\delta_{^{15}N}$ *vs* σ substituent constants are of rather

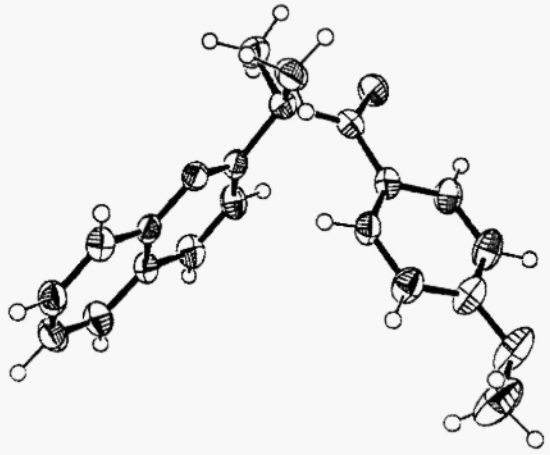


Figure. X-Ray structure (ORTEP-III plot) of compound **12**

Table 4. Bond lengths and bond and dihedral angles for compound **12**

Bond lengths [pm]		Bond and dihedral angles [deg]	
N1-C2	131.6	C9N1C2	118.4
C2-C3	142.3	N1C2C3	122.4
C3-C4	135.4	N1C2C11	118.3
C2-C11	152.2	C2C11C12	112.2
C11-C12	154.0	C11C12O	119.2
C12-O	122.0	C11C12C13	121.4
C12-C13	149.1	N1C2C11C12	136.4
C3-H3	99.2	C2C11C12O	129.3
C4-H4	97.5	C19C11C12C13	170.0
C11-C19	153.8	C11C12C13C14	180.0

low quality. ^{1}H and ^{13}C NMR spectral data presented in Tables 2 and 3 support the structures of compounds **1** - **12**. The obtained quinoline ketones can be treated as the fixed ketimino tautomers of 2-phenacyl-quinolines unless their conformation is not much different from that of respective tautomeric form. It seems interesting that ^{15}N chemical shifts for **1** - **12** are comparable to those of 2-phenacylquinolines (ketimine tautomeric form) [11]. The X-ray structure of quinoline ketone **12** is shown in the Figure (see also Table 4). It can be seen that the molecule is strongly twisted around C2-C11 and C11-C12 bonds. Since 2-phenacylquinolines appear in ketimino form in the solid state, their geometry cannot be compared to that of compound **12**. The chloroform solutions of compounds **1** - **12** do not absorb above 330 nm which is also typical of the ketimino form of 2-phenacylquinolines [3]. Thus, from that point of view, compounds **1** - **12** resemble the ketimine tautomers of 2-phenacylquinolines.

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