Reaction of Schiff Bases with Acryl Esters [1]. Synthesis of 2-Oxo- and 4-Oxotetrahydropyridines

José Barluenga*, Laudina Muñiz, Fernando López,
Francisco Palacios and Vicente Gotor

Departamento de Química Orgánica, Facultad de Ciencias,
Universidad de Oviedo, Oviedo, Spain

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Ketimines react with acryl esters in the presence of aluminium chloride to afford 2-oxo- and 4-oxotetrahydropyridines. The heterocycles obtained are isolated depending on the structure of the ester and the polarity of the solvent.

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The reaction of *C*- and *N*-alkylation of Schiff bases has been studied in great detail. However, it is difficult to predict the regiospecificity of these processes in spite of the existence of a great deal of information especially concerning the behavior of ketimines towards electron deficient olefins and acetylenes [2].

Ketimines react with electron deficient olefins [3], acyl chlorides [4] and phenylisocyanates [5] leading exclusively to the *C*-alkylation products. The silylation of metalled imines [6] affords mixtures of the corresponding *C*- and *N*-silyl derivatives. On the other hand, the reaction with electron deficient acetylenes [7,8], trimethylsilyltriflate [9] and electrophilic olefins [10] only gives *N*-alkylation compounds.

The existence of an amine-enamine tautomerism [11] in Schiff bases accounts for the above results. It has been suggested that in solution a part of the imine exists in the enamine form [8b] and Albrecht [12] proposed that the concentration of enamine in the equilibria increases with the polarity of the solvent.

In previous communications we have described the reactivity of the C_α-H bond in ketimines towards acrylesters [1], diethyl fumarate [13] and acrylamides [14] under aluminum chloride catalysis. We wish now to report our exhaustive study on the reactivity of ketimines with acrylesters in the presence of aluminum chloride.

Results and Discussion.

The reaction of **1** with methyl acrylate **2** (R^5, R^6 = H) or methyl crotonoate **2** (R^5 = CH_3, R^6 = H) and aluminum chloride at room temperature in benzene or dioxane as the solvent leads exclusively to 4-oxotetrahydropyridines **6**. In

Table 1

^{13}C-NMR Spectral Data for 2-oxotetrahydropyridines [a]

Product	2-C	3-C	4-C	5-C	6-C
5a	173.76	36.22	28.05	109.71	142.71
5b	172.83	35.84	35.29	115.32	139.41
5c	173.04	35.93	35.37	115.13	136.81
5d	169.66	40.52	37.72	114.57	142.94
5f	169.59	40.41	37.57	114.25	143.88
5g	168.70	43.90	39.50	117.29	141.34
6a	52.94	35.88	192.39	106.29	161.43
6b	52.29	35.99	192.62	110.41	158.61
6c	52.02	34.83	191.07	104.78	160.52
6d	52.37	35.90	192.50	109.89	158.99
6e	52.93	35.75	192.13	106.05	159.88
6g	58.26	42.07	191.61	105.86	159.47
6h	58.35	42.14	191.57	105.50	159.84
6j	56.17	41.19	190.51	108.27	155.98
6n	59.33	39.35	195.41	105.30	160.73
6o	57.58	34.96	194.31	108.08	145.42
6p	58.55	38.90	195.24	108.43	158.06
6q	59.25	39.22	195.25	105.44	160.27

[a] δ from internal TMS.

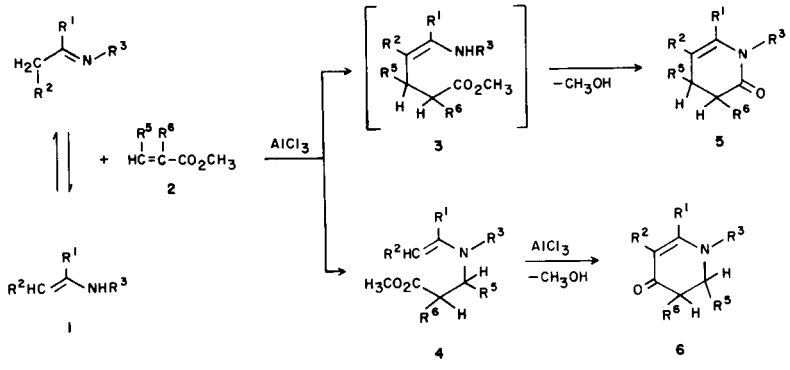

Table 2

Yields and Melting Points for 2-Oxo and 4-Oxotetrahydropyridines

Product	R^1	R^2	R^3	R^5	R^6	Yield %	Mp (°C)
5a	C_6H_5	H	C_6H_5	H	CH_3	55	139-140
5b	C_6H_5	CH_3	C_6H_5	H	CH_3	60	106-107
5c	C_6H_5	CH_3	p-$CH_3C_6H_4$	H	CH_3	52	130-131
5d	C_6H_5	H	C_6H_5	C_6H_5	H	30	118-119
5e	C_6H_5	CH_3	C_6H_5	C_6H_5	H	25	99-100
5f	C_6H_5	H	p-$CH_3C_6H_4$	C_6H_5	H	23	144-145
5g	C_6H_5	CH_3	p-$CH_3C_6H_4$	C_6H_5	H	22	99-100
6a	C_6H_5	H	C_6H_5	H	H	85	141-142
6b	C_6H_5	CH_3	C_6H_5	H	H	85	144-145
6c	C_6H_5	H	p-$CH_3C_6H_4$	H	H	81	108-109
6d	p-ClC_6H_4	H	C_6H_5	H	H	89	124-125
6e	C_6H_5	H	C_6H_5	CH_3	H	71	98-99
6f	C_6H_5	H	p-$CH_3C_6H_4$	CH_3	H	72	106-107
6g	C_6H_5	CH_3	C_6H_5	CH_3	H	69	119-120
6h	p-ClC_6H_4	H	C_6H_5	CH_3	H	76	117-118
6i	C_6H_5	H	C_6H_5	H	CH_3	58	108-109
6j	C_6H_5	H	p-$CH_3C_6H_4$	H	CH_3	52	111-112
6k	C_6H_5	CH_3	C_6H_5	H	CH_3	57	82-84
6l	p-ClC_6H_4	H	C_6H_5	H	CH_3	59	101-102

Table 3

Compound	Formula	Molecular weight	Analysis Found (Calcd.) C	H	N	IR ν max (Nujol)/cm^{-1}	^{1}H-NMR (δ from TMS)
5a	$C_{18}H_{17}NO$	263.18	82.37 (82.14)	6.33 (6.45)	5.34 (5.32)	1690 (CO)	1.30 (d, 3H, $J_{CH_3,3}$ = 6.0), 2.10-3.10 (m, H_{4a},H_{4e},H_3), 5.50 (dd, H_5, $J_{5,4a}$ = 5.9, $J_{5,4e}$ = 11.9), 6.80-7.30 (m, HAr)
5b	$C_{19}H_{19}NO$	277.19	82.43 (82.32)	6.73 (6.85)	4.99 (5.05)	1680 (CO)	1.30 (d, 3H, $J_{CH_3,3}$ = 6.0), 1.70 (s, 3H), 2.30-3.00 (m, H_{4a},-H_{4e},H_3), 6.82-7.30 (m, HAr)
5c	$C_{20}H_{21}NO$	291.20	82.39 (82.48)	7.22 (7.21)	4.79 (4.80)	1700 (CO)	1.30 (d, 3H, $J_{CH_3,3}$ = 6.0), 1.73 (s, 3H), 2.13 (s, 3H), 2.30-3.00 (m, H_{4a},H_{4b},H_3), 6.70-7.13 (m, HAr)
5d	$C_{23}H_{19}NO$	325.23	84.87 (84.93)	5.76 (5.84)	4.27 (4.30)	1700 (CO)	2.90-3.10 (m, H_a,H_e, $J_{3a,4}$ = 9.2, $J_{3e,4}$ = 6.3), 3.95 (m, H_4, $J_{4,5}$ = 4.8), 5.80 (d, H_5), 6.90-7.40 (m, HAr)
5e	$C_{24}H_{21}NO$	339.24	84.88 (84.96)	6.17 (6.19)	4.11 (4.12)	1690 (CO)	1.70 (s, 3H), 2.70-3.60 (m, H_{3a},H_{3e},H_4), 6.70-7.50 (m, HAr)
5f	$C_{24}H_{21}NO$	339.24	84.85 (84.96)	6.10 (6.19)	4.09 (4.12)	1700 (CO)	2.20 (s, 3H), 2.90-3.15 (m, H_{3a}, H_{3e}, $J_{3a,4}$ = 9.2, $J_{3e,4}$ 6.3), 4.00 (m, H_4, $J_{4,5}$ = 4.9), 5.75 (d, H_5), 7.00-7.50 (m, HAr)
5g	$C_{25}H_{23}NO$	353.25	84.89 (84.99)	6.49 (6.51)	3.92 (3.96)	1690 (CO)	1.70 (s, 3H), 2.15 (s, 3H), 2.80-3.75 (m, H_{3a},H_{3e},H_4), 6.90-7.50 (m, HAr)
6a	$C_{17}H_{15}NO$	249.17	81.93 (81.94)	6.03 (6.01)	5.68 (5.61)	1640 (CO)	2.60 (t, 2H, J = 7.8), 4.18 (t, 2H, J = 7.8), 5.48 (s, H), 6.78-7.29 (m, HAr)
6b	$C_{18}H_{17}NO$	263.18	82.35 (82.14)	6.39 (6.45)	5.28 (5.32)	1630 (CO)	1.70 (s, 3H), 2.70 (t, 3H, J = 7.1), 4.14 (t, 2H, J = 7.1), 6.70-7.33 (m, HAr)
6c	$C_{18}H_{17}NO$	263.18	82.24 (82.14)	6.39 (6.45)	5.27 (5.32)	1640 (CO)	2.25 (s, 3H), 2.60 (t, 2H, J = 7.5), 4.10 (t, 2H, J = 7.5), 5.50 (s, H), 6.70-7.40 (m, HAr)
6d	$C_{17}H_{14}NOCl$	283.62	71.97 (71.98)	4.89 (4.93)	4.98 (4.93)	1660 (CO)	2.60 (t, 2H, J = 7.5), 4.20 (t, 2H, J = 7.5), 5.50 (s, H), 6.74-7.40 (m, HAr)
6e	$C_{18}H_{17}NO$	263.18	82.34 (82.14)	6.39 (6.45)	5.36 (5.32)	1630 (CO)	1.60 (d, 3H), 2.28 (m, H_a, $J_{3a,2}$ = 2.3, $J_{3a,3e}$ = 15.5, $J_{3a,5}$ = 0.8), 3.06 (m, H_e, $J_{3e,2}$ = 5.2, $J_{3e,3a}$ = 15.5), 4.30 (m, H_2, $J_{2,3a}$ = 2.3, $J_{2,3e}$ = 5.2, J_{2,CH_3} = 6.0), 5.50 (d, H_5, $J_{5,3a}$ = 0.8), 6.84-7.30 (m, HAr)

Table 3, continued

Compound	Formula	Molecular weight	Analysis Found (Calcd.) C	H	N	IR ν max (Nujol)/cm^{-1}	^{1}H-NMR (δ from TMS)
6f	$C_{19}H_{19}NO$	277.19	82.38 (82.32)	6.89 (6.85)	5.07 (5.05)	1680 (CO)	1.50 (d, 3H), 2.15 (s, 3H), 2.50 (m, H_a, $J_{3a,2}$ = 2.3, $J_{3a,3e}$ = 15.5, $J_{3a,5}$ = 0.8), 3.05 (m, H_e, $J_{3e,2}$ = 5.2, $J_{3e,3a}$ = 15.5), 4.25 (m, H_2, $J_{2,3a}$ = 2.3, $J_{2,3e}$ = 5.2, J_{2,CH_3} = 6.0), 5.50 (d, H_5, $J_{5,3a}$ = 0.8), 6.70-7.50 (m, HAr)
6g [a]	$C_{19}H_{19}NO$	277.19	82.32 (82.32)	6.79 (6.85)	5.12 (5.05)	1630 (CO)	1.55 (d, 3H), 1.80 (s, 3H), 2.40 (m, H_a, $J_{3a,2}$ = 2.3, $J_{3a,3e}$ = 15.5, $J_{3a,5}$ = 0.8), 3.06 (m, H_e, $J_{3e,2}$ = 6.2, $J_{3e,3a}$ = 15.5), 4.15 (m, H_2, $J_{2,3a}$ = 2.5, $J_{2,3e}$ = 5.4, J_{2,CH_3} = 6.0), 6.75-7.5 (m, HAr)
6h	$C_{18}H_{16}NOCl$	297.63	72.44 (72.73)	5.26 (5.37)	4.57 (4.70)	1650 (CO)	1.60 (d, 3H), 2.25 (m, H_a, $J_{3a,2}$ = 2.3, $J_{3a,3e}$ = 15.5, $J_{3a,5}$ = 0.8), 3.05 (m, H_e, $J_{3e,2}$ = 5.2, $J_{3e,3a}$ = 15.5), 4.30 (m, H_2, $J_{2,3a}$ = 2.3, $J_{2,3e}$ = 5.2, J_{2,CH_3} = 6.0), 5.50 (d, H_5, $J_{5,3a}$ = 0.8), 6.85-7.30 (m, HAr)
6i	$C_{18}H_{17}NO$	263.18	82.25 (82.14)	6.39 (6.45)	5.38 (5.32)	1640 (CO)	1.20 (d, 3H), 2.70 (m, H_3, J_{3,CH_3} = 6.0), 3.90 (q, H_a, $J_{2a,2e}$ = 12.5, $J_{2a,3}$ = 9.5), 4.15 (q, H_e, $J_{2e,2a}$ = 12.5, $J_{2e,3}$ = 5.5), 5.50 (s, H), 6.70-7.40 (m, HAr)
6j	$C_{19}H_{19}NO$	277.19	82.22 (82.32)	6.75 (6.85)	5.09 (5.05)	1650 (CO)	1.20 (d, 3H, J_{3,CH_3} = 6.0), 2.20 (s, 3H), 2.65 (m, H_3), 3.80 (q, H_a, $J_{2a,2e}$ = 12.5, $J_{2a,3}$ = 9.5), 4.10 (q, H_e, $J_{2e,2a}$ = 12.5, $J_{2e,3}$ = 5.5), 5.45 (s, H), 6.70-7.40 (m, HAr)
6k	$C_{19}H_{19}NO$	277.19	82.37 (82.32)	6.68 (6.85)	4.98 (5.05)	1640 (CO)	1.30 (d, 3H, J_{3,CH_3} = 6.0), 1.60 (s, 3H), 2.70 (m, H_3), 3.80 (q, H_a, $J_{2a,2e}$ = 12.5, $J_{2a,3}$ = 9.5), 4.05 (q, H_e, $J_{2e,2a}$ = 12.5, $J_{2e,3}$ = 5.6), 7.00-7.30 (m, HAr)
6l	$C_{18}H_{16}NOCl$	297.63	72.85 (72.63)	5.39 (5.37)	4.62 (4.70)	1640 (CO)	1.20 (d, 3H, J_{3,CH_3} = 6.0), 2.70 (m, H_3), 3.90 (q, H_a, $J_{2a,3}$ = 9.6, $J_{2a,2e}$ = 12.5), 4.10 (q, H_e, $J_{2e,2a}$ = 12.5, $J_{2e,3}$ = 5.5), 5.50 (s, H_5), 6.80-7.30 (m, HAr)

[a] m/e: 291 (M^+).

Table 4

π-Charge Density Values for Acrylic Esters

Methyl acrylate	48 me
Methyl crotonoate	47 me
Methyl methacrylate	47 me
Methyl cinnamate	37 me
Methyl maleate	34 me

a first instance, the structure **5** could not be excluded for the reaction products so, even after careful examination of the ir and ^{1}H-nmr spectra (Table 3). However, the structure **6** can be fully established by the ^{13}C-nmr spectral data of the compounds and especially by the 190 δ ppm resonance value found for the conjugated carbonyl carbon which exclude the presence of an amide carbonyl [15], (Tables 1, 3).

The *N*-alkyl intermediate **4** is isolated when the reaction of **1** with methyl acrylate and aluminum chloride is carried out at 0° in dimethylene dichloride as solvent. The heterocyclization of **4** to **6** is catalyzed by aluminum chloride and proceeds at room temperature in nearly quantitative yield.

On the other hand, heterocycles **5** are obtained from methyl cinnamate **2** (R^5 = C_6H_5, R^6 = H). In this case the reaction only takes place at 80° and yields decrease to 30%. The compounds type **6** could not be isolated even when the reaction conditions were modified by the use of solvents of different polarity. The ^{13}C-nmr spectra of the compounds **5** display the expected absorption centered at about 170 ppm in concordance with the existence of an amide carbonyl.

Both heterocycles **5** and **6** are obtained from methyl methacrylate **2** (R^6 = H, R^7 = CH_3) depending on the solvent. Compounds **5** are isolated in solvents of moderate polarity, *i.e.* dioxane, but when the reactions are carried out in benzene only 4-oxotetrahydropyridines **6** are obtained. Spectral data to allow complete characterization of the products are summarized in Tables 1 and 3.

From the above results we deduce that the substituents on the acrylester skeleta besides the polarity of the solvent conduct the process to the synthesis of 2-oxo- **5** or 4-oxotetrahydropyridines **6**. The formation of these compounds could be explained through the monoaddition intermediates **3** and **4** which proceed from the *C*- or *N*-alkylation of the starting ketimine **1** respectively.

Unsubstituted acrylesters (methyl acrylate) or those carrying electron donor groups with little steric demand on the β-carbon (*i.e.* methyl cortonoate) react by the enamine

N-H bond. On the contrary, the *C*-alkylation reaction is promoted by the existence of bulky electron-withdrawing substitutes on the β-position (methyl cinnamate). Similar *C*-alkylations were found in the reaction of ketimines with ethyl maleate and fumarate [13]. The behavior of methyl methacrylate is borderline between the two reaction pathways and, hence, the solvent plays the key role on the course of the heterocycle formation.

In a kinetic study, Friedman *et al.* [16] have established a scale of reactivities of a series of methyl-substituted acryl esters towards glycine. They found that methyl acrylate reacts 15 times as fast as methyl crotonoate and this 314 times as fast as methyl methacrylate. However, attempts to relate the reactivity of these esters with that of methyl cinnamate were unsuccessful because of the relatively low reactivity of the β-aryl substituted esters [17].

Our results lead to a reactivity order: methyl acrylate > crotonoate > methacrylate ≫ cinnamate, which is in good agreement with the Friedman's data.

The regioselectivity observed is in concordance with the predictions by the HSAB principle [18]. Acryl esters are soft acids and their softness increases from the acrylate to cinnamate. This is consistent with the calculated values for the π-charge densities at $C\beta$ in the corresponding acrylic esters [19].

On the other hand, the ketimine system is an ambident nucleophile in which the C_α is a base softer than the enamine nitrogen atom [20]. We have found that ketimines react with soft acrylic esters, *i.e.* methyl cinnamate and dialkyl fumarate, through their C_α carbon. On the contrary, towards less soft esters, *i.e.* methyl acrylate and crotonoate, the reaction takes place at the nitrogen site in the enamine form. The charge densities of methyl methacrylate and methyl crotonoate have similar values, but kinetic data show that the methyl methacrylate reacts more slowly and it could be classified in a middle position in the HSAB scale. The influence of the solvent on the reactivity of methyl acrylate correlates well with this classification.

In conclusion, we describe a simple method for the synthesis of 2-oxo and 4-oxotetrahydropyridines. The utility of the process is based on both the good yields obtained and the application of these types of dihydropyridines as fungicides and herbicides [21].

EXPERIMENTAL

Melting points are uncorrected, ir spectra were recorded on a Pye-Unicam SP-1000 instrument. The ^{1}H-nmr spectra were recorded on a Varian Em-390 spectrometer and a Varian FT-80 spectrometer in deuteriochloroform, with tetramethylsilane as an internal lock. The ^{13}C-nmr spectra were also recorded on a Varian FT-80 spectrometer using the same internal lock.

Preparation of Methyl 3-*N*-Phenyl-*N*-(1-phenyl-1-propenyl)propanoate **4**.

To a stirred solution of **1** (10 mmoles) in methylene dichloride, 10 mmoles of aluminum chloride were added under an argon atmosphere. The temperature was kept at 0° during 20 hours. After this time the resulting solution was poured into ice-cooled 2*N* sulfuric acid (200 ml), extracted with ether, and the organic layer dried over anhydrous sodium sulphate. The extract was evaporated and distilled under high vacuum (10^{-3} Torr) yielding **4** (2.4 g), which was recrystallized from hexane/chloroform 6:1, mp 76°; ir: ν C=O 1760 cm^{-1}; ^{1}H-nmr δ ppm 1.51 (d, -CH_3), 2.55 (t, 2-CH_2), 3.55 (s, -OCH_3), 3.67 (t, 3-CH_2), 5.95 (c, =CH), 6.51-7.24 (m, 10H Ar).

Conversion of methyl 3-*N*-phenyl-*N*-(1-phenyl-1-propenyl)propanoate **4** into 5-methyl-1,6-diphenyl-4-oxo-1,2,3,4-tetrahydropyridine **6b** was performed according to the following procedure.

Aluminum chloride (5 mmoles) was added to a solution of **4** (5 mmoles) in benzene under argon atmosphere. After two hours at room temperature the mixture was acidified with ice-cooled 2*N* sulfuric acid (100 ml) and extracted with ether. The extract was dried with anhydrous sodium sulphate, solvent removed under reduced pressure and the residue obtained recrystallized from hexane/chloroform 6:1 (1.1 g). Data for this product are given in Tables 2 and 3.

Preparation of 4-Oxotetrahydropyridines **6**. Reaction of **1** with Methyl Acrylate or Methyl Crotonoate. General Procedure.

Aluminum chloride (1.4 g, 10 mmoles) was added to a solution of **1** in benzene or dioxane under an argon atmosphere. The flask was cooled during the addition. After the addition was completed, methyl acrylate (10 mmoles) or methyl crotonoate was added. The mixture was stirred at room temperature for 2 hours, acidified with ice-cooled 2*N* sulphuric acid (200 ml) and extracted with ether. The extract was dried with anhydrous sodium sulphate, solvent removed under reduced pressure and the residual crude product recrystallized from hexane/chloroform 6:1. Data for the products are given in Tables 2 and 3.

Synthesis of 2-Oxo and 4-Oxotetrahydropyridines. Reaction of **1** with Methyl Methacrylate. General Procedure.

Reactions were carried out in benzene or dioxane solution respectively following the above described procedure.

Synthesis of 2-oxotetrahydropyridines **5**. Reaction of **1** with Methyl Cinnamate. General Procedure.

To a stirred solution of **1** (10 mmoles) in benzene, aluminum chloride was added under argon atmosphere cooling the flask during the addition. At the end, methyl cinnamate (10 mmoles) was added. The mixture was heated at 80° during 8 hours and then was hydrolyzed with ice-cooled 2*N* sulfuric acid with anhydrous sodium sulphate, the solvent removed under reduced pressure and the residue recrystallized from hexane/chloroform 6:1. Data for the products are given in Tables 1, 2 and 3.

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