Reaction of Schiff Bases with Acrylamides. Synthesis of 2-Oxotetrahydropyridines

José Barluenga, Laudina Muñiz, Francisco Palacios and Vicente Gotor

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

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Ketimines react with acrylamide and methacrylamide in the presence of aluminium chloride to afford 2-oxotetrahydropyridines by a *C*-alkylation pathway.

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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 even though there is in existence a great deal of information specifically on the behavior of ketimines towards electron deficient olefins and acetylenes (1).

In earlier papers (2) we have reported on the utilization of the reaction of Schiff bases with different electrophilic olefins under acid catalysis for the synthesis of heterocycles. We now wish to report on the reaction of ketimines with acrylamide and methacrylamide in the presence of aluminium chloride.

Acrylamides act as the acceptor in Michael additions under basic catalysis (3). For this reason it appeared to be of interest to study the aluminium chloride promoted reactivity of these compounds with ketimines in order to determine whether their behavior is analogous to that observed in other electron deficient olefins (2).

Table 1

2-Oxotetrahydropyridines **4** and **6** from Ketimines **1** and Acrylamides **2**

Product	R^1	R^2	R^4	Yield (a)	MP°C
4a	C_6H_5	H	H	74	158-159
4b	C_6H_5	CH_3	H	72	127-128
4c	C_6H_5	C_2H_5	H	69	109-110
4d	*p*(Cl)C_6H_4	CH_3	H	78	149-150
4e	-$(CH_2)_4$-		H	72	144-145
4f	C_6H_5	H	CH_3	60	129-130
4g	C_6H_5	CH_3	CH_3	62	125-126
4h	-$(CH_2)_4$-		CH_3	61	100-101
6a	C_6H_5	H	H	92	106-107
6b	C_6H_5	CH_3	H	91	104-105
6h	C_6H_5	H	CH_3	90	71- 72

(a) Yields are given for Ketimines **1** in which $R^3 = C_6H_5$.

Ketimines **1** react with acrylamide and methacrylamide **2** and aluminium chloride in dioxane solution at 70° to afford exclusively non *N*-substituted-2-oxotetrahydropyridines **4** in good yields (Table 1). On the contrary, the heterocyclation does not proceed with *N*-phenylacrylamide since it polymerizes by the action of a Lewis acid.

Heterocycles **4** lead to the *N*-acetyl derivatives **6** by reaction with acetyl chloride and *N,N*-diethylaniline at 80°. The structure proposed for compounds **4** is fully consistent with their spectral data and elemental analyses. The ir-spectrum of **4** shows typical absorptions at 3300 (ν NH) and 1690 (ν C=O) cm^{-1}. The most significant data are those obtained from the ^{13}C-nmr spectra which display the five expected ring-carbon absorptions centered at about δ 170 (C=O), 136 (C-6), 101 (C-5), 29 (C-3), 19 (C-4) for all compounds (Table 2).

The formation of the heterocycles **4** can be explained through the mono-addition intermediate **3** which would result from the *C*-alkylation of the starting ketimine **1**. *N*-Substituted dihydropyridones **5** could not be obtained (Scheme).

The existence of the imino-enamino tautomerism in Schiff bases has been suggested by numerous authors (4) to account for the *C*- and *N*-alkylation for these compounds. The site of the alkylation has been shown to depend upon the nature of the alkylating agent (5). In the reaction of **1** with methylacrylate (2a), we found that 4-oxo-

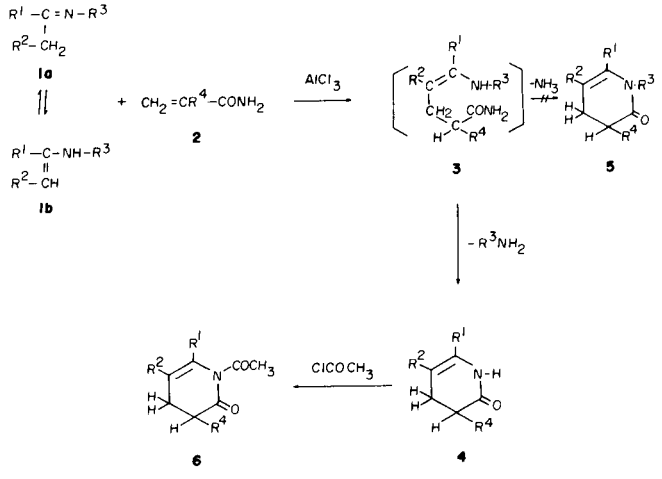

Table 2

^{13}C-NMR Spectral Data for 2-Oxotetrahydropyridines **4** and **6**

Product	2-C	3-C	4-C	5-C	6-C	
4a	171.5 (s)	30.2 (t)	20.7 (t)	102.1 (d)	137.4 (s)	
4b	170.2 (s)	30.1 (t)	27.5 (t)	109.8 (s)	135.6 (s)	
4f	174.4 (s)	34.6 (d)	29.0 (t)	101.6 (d)	135.4 (s)	
4g	173.2 (s)	36.0 (d)	34.5 (t)	109.7 (s)	135.6 (s)	
6b	172.0 (s)	34.1 (t)	27.2 (t)	123.7 (s)	136.3 (s)	173.2 (s, C=O)

Table 3

Microanalytical, IR and ^{1}H-NMR Spectral Data for 2-Oxotetrahydropyridines **4** and **6**

Compound	Formula	Molecular weight	Analysis Found (Calcd.) C	H	N	ν max (Nujol)/cm^{-1}	^{1}H-NMR (δ from TMS)
4a	$C_{11}H_{11}NO$	173.11	76.51 (76.31)	6.37 (6.35)	8.12 (8.08)	1690 (CO) 3200 (NH)	2.55 (d. t, 3H), 5.50 (m, H), 7.30-8.00 (m, HAr, NH)
4b	$C_{12}H_{13}NO$	187.11	77.22 (77.02)	7.04 (6.94)	7.39 (7.48)	1690 (CO) 3210 (NH)	1.75 (s, 3H), 2.20-2.60 (m, 4H), 7.00-7.50 (m, HAr, NH)
4c	$C_{13}H_{15}NO$	201.13	77.42 (77.62)	7.29 (7.45)	6.94 (6.96)	1690 (CO) 3200 (NH)	1.00 (t, 3H), 2.10 (q, 2H), 2.35-2.50 (m, 3H), 7.00-7.50 (m, HAr, NH)
4d	$C_{12}H_{12}NOCl$	221.57	65.14 (65.04)	5.37 (5.41)	6.33 (6.81)	1670 (CO) 3160 (NH)	1.70 (s, 3H), 2.30-2.70 (m, 4H), 7.10-7.50 (m, HAr, NH)
4e	$C_9H_{13}NO$	151.09	71.59 (71.54)	8.58 (8.60)	9.30 (9.26)	1680 (CO) 3190 (NH)	1.40-2.60 (m 12H), 8.40 (m, NH)
4f	$C_{12}H_{13}NO$	187.11	77.22 (77.02)	6.85 (6.94)	7.45 (7.48)	1670 (CO) 3180 (NH)	1.20 (d, 3H), 2.10-2.70 (m, 3H), 5.40 (m, H), 7.20-7.60 (m, HAr), 7.90 (m, NH)
4g	$C_{13}H_{15}NO$	201.13	77.72 (77.62)	7.39 (7.45)	6.88 (6.96)	1690 (CO) 3260 (NH)	1.25 (d, 3H), 1.80 (s, 3H), 2.10-2.80 (m, 3H), 6.90-7.50 (m, HAr, NH)
4h	$C_{10}H_{15}NO$	165.10	72.77 (72.74)	9.17 (9.08)	8.57 (8.47)	1680 (CO) 3200 (NH)	1.20 (d, 3H), 1.30-2.30 (m, 11H), 7.90 (m, NH)
6a	$C_{13}H_{13}NO_2$	215.13	72.67 (72.57)	6.14 (6.04)	6.45 (6.50)	1710 (CO)	2.20-2.80 (m, 6H), 5.60 (dd, H), 7.10-7.50 (m, HAr)
6b	$C_{14}H_{15}NO_2$	229.14	73.26 (73.37)	6.45 (6.54)	6.09 (6.11)	1710 (CO)	2.20 (s, 3H), 2.60-3.20 (m, 6H), 7.50-8.00 (m, HAr)
6h	$C_{14}H_{15}NO_2$	229.14	73.33 (73.37)	6.59 (6.54)	6.21 (6.11)	1720 (CO)	1.60 (d, 3H), 2.45-3.15 (m, 6H), 6.15 (dd, H), 7.50-7.80 (m, HAr)

tetrahydropyridines were obtained through the formation of the corresponding adduct of *N*-alkylation. On the contrary, other unsaturated esters such as methyl cinnamate led to 2-oxotetrahydropyridines **5** which resulted from the intermediate product of *C*-alkylation (6).

The reaction of **1** with acrylamide and methacrylamide gave rise to the unequivocal formation of *N*-nonsubstituted 2-oxotetrahydropyridines **4**. For its simplicity and high yields, the procedure described in this paper should be the method of choice for the synthesis of heterocycles **4**. On

the other hand, these compounds could be interesting intermediates for the preparation of nitrogen containing natural products.

EXPERIMENTAL

The melting points are uncorrected. The infrared spectra were obtained with a Pye-Unicam SP-1000 spectrophotometer. 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 2-Oxotetrahydropyridines **4**. General Procedure.

Aluminium chloride, (1.4 g, 10 mmoles) was added to a solution of **1** (10 mmoles) in dioxane under an argon atmosphere. The reaction flask was cooled during the addition. Then acrylamide (0.7g, 10 mmoles) was added (methacrylamide 0.8 g). The mixture was heating at 90° for 6 hours and slowly poured into ice-cooled 2*N*- sulfuric acid (200 ml). The resulting mixture was extracted with ether, and the organic layer dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo*. The residual solid was recrystallized from hexane/chloroform (5:1). Data for the products are given in Tables, 1, 2 and 3.

Synthesis of 1-Acetyl-2-oxotetrahydropyridines **6**. Reaction of **4** with Acetyl Chloride. General Procedure.

To a stirred solution of **4** (10 mmoles) in *N,N*-dimethylaniline, was added 10 mmoles of acetyl chloride. The mixture was heated at 80° during 8 hours and then was hydrolyzed with 2*N* sulfuric acid (200 ml) and extracted with ether. The organic layer was dried with anhydrous sodium sulphate and the solvent removed under reduced pressure. The residual solid was recrystallized from hexane. Data for products are given in the table.

REFERENCES AND NOTES

(1) Th. Wagner-Jauregg, *Synthesis*, 349 (1979).

(2a) V. Gómez-Aranda, J. Barluenga and V. Gotor, *Tetrahedron Letters*, 977 (1974); (b) J. Barluenga, F. Palacios, S. Fustero and V. Gotor, *Synthesis*, 200 (1981).

(3) H. A. Bruson, U. S. Patent 2,370,142; *Chem. Abstr.*, **39**, 3544 (1945); D. Elad and D. Ginsburg, *J. Chem. Soc.*, 4137 (1953); T. Minomiya, T. Naito, S. Higuchi and T. Mori, *J. Chem. Soc., Chem. Commun.*, 457 (1971).

(4) H. Albrecht and R. D. Kalas, *Ann. Chem.*, 102 (1979) and literature cited therein.

(5) Y. Nomura, T. Bando, Y. Takeuchi and S. Tamoda, *Tetrahedron Letters*, 3453 (1979).

(6) 2-Oxotetrahydropyridines are obtained in the reaction of **1** with methyl methacrylate, but the course of the process can be modified to the preparation of 4-oxotetrahydropyridines if the solvents are properly chosen; unpublished results.