

Arylhydrazones and Methyl Acrylate

J. Barluenga*, F. Palacios, S. Viña and V. Gotor

Departamento de Química Orgánica, Facultad de Química, Universidad de Oviedo,
33071 Oviedo, Spain

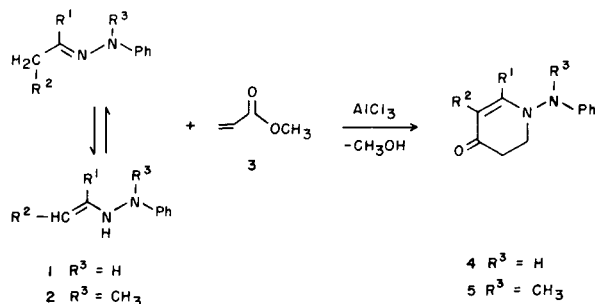
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Arylhydrazones react with methyl acrylate in the presence of aluminium chloride to afford amino substituted 4-oxo-1,2,3,4-tetrahydropyridines.

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4-Oxo-tetrahydropyridines are found in lupine alkaloids [1] and act as key intermediates in the formal synthesis of (\pm)ipalbidine [2]. Some methods of synthesis of these compounds have been recently reported starting from heterocycles [3] as well as from acyclic precursors such as Schiff bases [4,5].

In earlier papers [6] we have reported on the utilization of ketimines for the synthesis of heterocycles. Other iminic derivatives, *e.g.* hydrazones [7], can be also suitable starting material to construct heterocycles. The results obtained with Schiff bases and acrylate esters [5], affording, depending on the nature of the ester, 2-oxo- or 4-oxo-tetrahydropyridines prompted us to revise the reaction of arylhydrazones with methyl acrylate [8].



Phenylhydrazones derived from enolizable ketones **1** react with methyl acrylate **3** in the presence of aluminium chloride at room temperature in benzene to afford **4** (Table 1). The structure is fully consistent with that of 4-oxo-tetrahydropyridines showing a singlet in the region of 190 ppm in ^{13}C nmr attributed to the conjugated carbonyl carbon [3-5] (Table 2).

This result can be explained in terms of addition of the NH of the enehydrazone to methyl acrylate followed by cyclocondensation and loss of methanol. It is known that hydrazones [9] are ambident synthons and they can react at either carbon or nitrogen; moreover the existence of a hydrazone-enehydrazone tautomerie has been discovered in the last decade [10] on *N*-aryl-*N*-methylhydrazones from β -ketoesters.

Despite cycloaddition of *N,N*-disubstituted enhydrazines involving the NH and the C β recently reported [11], no similar reactions are known in the case of *N*-substituted hydrazones. For this reason and to rationalize the mentioned results, we carried out the reaction of *N*-methyl-*N*-phenylhydrazones **2** with **3** in the presence of aluminium chloride and obtain similar derivatives as with **1**; thus *N*-Methyl-*N*-phenylamino-4-oxo-tetrahydropyridines **5** were formed. Structure **5** was alternatively synthesized by lithiation of **4** followed by addition of methyl iodide.

To the best of our knowledge, the reported synthesis of

Table 1

Yields, Melting points and Microanalytical Data for 4-oxo-tetrahydropyridines **4** and **5**

Product	R ¹	R ²	R ³	Yield (%)	Mp (°C)	Formula	Molecular weight	Analysis C,H,N Found (Calcd.)		
4a	C ₆ H ₅	H	H	78	186-187	C ₁₇ H ₁₆ N ₂ O	264.3	77.55	6.04	10.41
								77.25	6.10	10.60
4b	C ₆ H ₅	C ₂ H ₅	H	81	158-159	C ₁₉ H ₂₀ N ₂ O	292.4	77.92	6.73	9.44
								78.04	6.89	9.58
								78.40	7.05	9.08
4c	C ₆ H ₅	C ₃ H ₇	H	79	127-128	C ₂₀ H ₂₂ N ₂ O	306.4	78.65	7.05	9.08
								78.40	7.23	9.15
4d	CH ₃	C ₆ H ₅	H	83	176-177	C ₁₈ H ₁₈ N ₂ O	278.3	77.82	6.50	9.88
								77.67	6.51	10.07
5a	C ₆ H ₅	H	CH ₃	70	140-141	C ₁₈ H ₁₈ N ₂ O	278.3	77.79	6.45	9.99
								77.67	6.51	10.07
5b	C ₆ H ₅	CH ₃	CH ₃	72	134-135	C ₁₉ H ₂₀ N ₂ O	292.4	77.96	6.78	9.39
								78.04	6.89	9.58
5d	CH ₃	C ₆ H ₅	CH ₃	79	133-134	C ₁₉ H ₂₀ N ₂ O	292.4	77.89	6.75	9.48
								78.04	6.89	9.58

Table 2
Spectral Data for 4-Oxo-tetrahydropyridines **4** and **5**

Compound	IR/nujol ν (cm ⁻¹)	¹ H-NMR (Deuteriochloroform δ (ppm))	¹³ C-NMR (Deuteriochloroform δ (ppm))
4a	3230(NH) 1650(CO)	2.77 (t, CH ₂ CO), 3.73 (t, CH ₂ N), 5.25 (s, CH), 5.7 (s, NH), 6.7-7.3 (m, ArH)	191.9 (C-4), 167.1 (C-6), 103.4 (C-5), 50.6 (C-2), 36.4 (C-3), 145.9, 113.0, 129.4, 120.7, 134.8, 127.9, 127.2, 129.4 (C-Ar)
4b	3240(NH) 1650(CO)	0.85 (t, CH ₃), 2.0 (q, CH ₂), 2.7 (t, CH ₂ CO), 3.7 (t, CH ₂ N), 5.5 (s, NH), 6.6-7.3 (m, ArH)	190.9 (C-4), 163.7 (C-6), 96.1 (C-5), 51.1 (C-2), 37.05 (C-3), 19.7 (CH ₃), 15.9 (CH ₂), 146.5, 112.8, 129.1, 120.5, 134.6, 128.0, 127.2, 128.3 (C-Ar)
4c	3240(NH) 1650(CO)	0.6 (t, CH ₃), 1.3 (m, CH ₂), 1.8 (t, CH ₂), 2.7 (t, CH ₂ CO), 3.7 (t, CH ₂ N), 5.4 (s, NH), 6.6-7.3 (m, ArH)	191.6 (C-4), 163.8 (C-6), 113.3 (C-5), 51.0 (C-2), 37.0 (C-3), 28.4 (CH ₃), 23.3 (CH ₂), 13.9 (CH ₃), 146.4, 112.8, 129.1, 120.4, 134.5, 127.9, 127.2, 128.2 (C-Ar)
4d [a]	3270(NH) 1660(CO)	1.9 (s, CH ₃), 2.7 (t, CH ₂ CO), 3.7 (t, CH ₂ N), 5.9 (s, NH), 6.7-7.3 (m, ArH)	189.1 (C-4), 163.9 (C-6), 113.7 (C-5), 49.6 (C-2), 37.0 (C-3), 17.7 (CH ₃), 146.0, 112.7, 129.0, 120.7, 136.7, 129.4, 131.4, 126.4 (C-Ar)
5a	1670(CO)	2.65 (m, CH ₂ CO), 2.8 (s, CH ₃ N), 3.6 (m, CH ₂ N), 5.3 (s, CH), 6.7-7.5 (m, ArH)	191.5 (C-4), 166.0 (C-6), 104.4 (C-5), 45.1 (C-2), 36.2 (C-3), 36.4 (CH ₃), 146.6, 112.9, 129.5, 119.8, 136.2, 126.8, 128.0, 129.5 (C-Ar)
5b	1660(CO)	1.45 (s, CH ₃), 2.65 (m, CH ₂ CO), 2.78 (s, CH ₃ N), 3.5 (m, CH ₂ N), 6.7-7.4 (m, ArH)	191.5 (C-4), 162.9 (C-6), 108.5 (C-5), 44.8 (C-2), 36.3 (C-3), 36.8 (CH ₃ N), 12.0 (CH ₃), 147.7, 112.9, 129.1, 119.8, 134.9, 126.9, 127.8, 128.3 (C-Ar)
5d [b]	1650(CO)	1.9 (s, CH ₃), 2.7 (m, CH ₂ CO), 3.01 (s, CH ₃ N), 3.45 (m, CH ₂ N), 6.6-7.7 (m, ArH)	188.5 (C-4), 161.5 (C-6), 114.0 (C-5), 44.1 (C-2), 36.5 (C-3), 36.8 (CH ₃ N), 17.0 (CH ₃), 147.2, 112.7, 129.4, 120.8, 136.5, 127.7, 129.4, 126.2 (C-Ar)

[a] m/e 278. [b] m/e 292.

N-substituted-4-oxotetrahydropyridines has been accomplished for the first time. These compounds are potential building blocks for the construction of alkaloid skeletons.

EXPERIMENTAL

Melting points are uncorrected. Microanalysis were performed on a Perkin Elmer Model 240 Instrument. The ir spectra were recorded on a Pye-Unicam SP-1000. The ¹H nmr spectra were recorded on a Varian FT-80 Spectrometer in deuterio-chloroform, with tetramethyl silane as an internal lock. The ¹³C nmr spectra were also recorded on a Varian FT-80 Spectrometer using the same internal lock.

Preparation of 4-Oxo-1,2,3,4-tetrahydropyridines **4** and **5**.

Aluminium chloride (1.4 g, 10 mmoles) was added to a solution of the arylhydrazones **1** or **2** and methyl acrylate in benzene under an argon atmosphere. The flask was cooled during the addition. After the addition was completed, the reaction mixture was stirred for 1 hour at room temperature, acidified with ice-cooled 2*N* sulphuric acid 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 1 and 2.

Conversion of **4d** into **5d**.

To a solution of methyl lithium (10 mmoles) at 0°, 10 mmoles of **4d** dissolved in 30 ml of THF was added. The reaction was stirred during 1 hour and then 10 mmoles of methyl iodide was added. After 2 hours,

aqueous work-up followed by extraction with ether, drying (sodium sulfate) and *in vacuo* solvent evaporation, a solid was obtained (2.8 g, 96%), which was recrystallized from hexane-chloroform (6:1), mp 133-134°.

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