Pergamon

Tetrahedron Letters, Vol. 37, No. 42, pp. 7653-7656, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01703-0

The Effect of Lithium Iodide on the Acid-Promoted Cyclization of 4-[(1-Indolylcarbonyl)methyl]-1,4-dihydropyridines

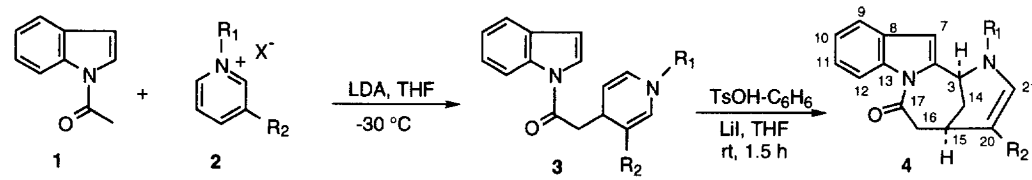
M.-Lluïsa Bennasar, Juan-Miguel Jiménez, Bilal A. Sufi, and Joan Bosch

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona,
08028-Barcelona, Spain

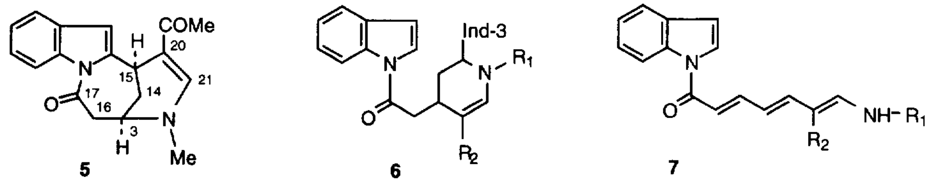
Abstract: 1,4-Dihydropyridines **3** resulting from the addition of the enolate derived from 1-acetylindole (**1**) to pyridinium salts **2** do not undergo cyclization under the usual acidic conditions, but do satisfactorily cyclize to the tetracyclic derivatives **4** by treatment with TsOH in the presence of lithium iodide. Copyright © 1996 Elsevier Science Ltd

The nucleophilic addition of indole-containing enolates to *N*-alkylpyridinium salts, followed by elaboration of the resulting 1,4-dihydropyridines (in most cases by acid-promoted cyclization) constitutes a general and versatile method for the synthesis of indole alkaloids.[1] Although this methodology has proved to be exceptionally useful, providing access to a number of alkaloids belonging to different structural types, some important aspects, such as the factors controlling the regioselectivity of the nucleophilic attack, still remain unclear. In fact, we have previously demonstrated that the regioselectivity observed in the process depends on the method used for the trapping of the initially formed mixture of 1,2- and 1,4-dihydropyridines and that the absence of a specific cyclized product is not indicative of the absence of the corresponding dihydropyridine precursor because, under acidic conditions, dihydropyridines can undergo decomposition or fragmentation into the starting products.[2]

In the context of our studies on the synthesis of alkaloids of the akagerine group[3] we have been involved in the above nucleophilic addition–acid cyclization sequence starting from 1-acetylindole (**1**). However, when the enolate derived from **1** (LDA, THF, -70 °C) was allowed to react with a variety of pyridinium salts **2a-f** (Scheme 1) and then with acid, the expected tetracycles **4**, which had been envisaged as synthetic precursors of akagerine, were not detected. Instead, in the series **a**, tetracycle **5**[4] and tetrahydropyridine **6a**[5] were isolated in 21% and 5-15% yields, respectively.[6] Although the formation of tetracycles coming from cyclization of a 1,2-dihydropyridine has previously been observed in related nucleophilic addition-cyclization processes,[7] the formation of **6a** is more surprising. It indicates that the expected γ-attack on the pyridinium salt does occur, but also that the dihydropyridinium cation formed by protonation of the resulting 1,4-dihydropyridine **3a**, instead of undergoing cyclization, is intermolecularly



	R_1	R_2	X (only for 2)	Yield of 3	Yield of 4
a	Me	COMe	I	24%	25%
b	Bn	COMe	Cl	15%	15%
c	Bn	$CH{=}CHCO_2Me$	Cl	22%	50%
d	CH_2CH_2OAc	COMe	Br	15%	25%
e	CH_2CH_2OAc	$CH{=}CHCO_2Me$	Br	20%	25%
f	CH_2CH_2SPh	$CH{=}CHCO_2Me$	Br	20%	40%



Scheme 1

trapped by the indole present in the mixture (probably formed by a Claisen-type base-catalyzed condensation of **1**). In the other series (**b-f**), complex mixtures were formed, from which only the starting acetylindole was identified.

The failure of the formation of tetracycles **4** could be attributed either to an inefficient generation of the required 1,4-dihydropyridines **3** or to the failure of the cyclization step. However, after column chromatography of the crude mixtures resulting from interaction of **1**·enolate with pyridinium salts **2a-f,** the respective 1,4-dihydropyridines **3a-f** (Table 1)[6] could be isolated in the yields shown in Scheme 1. Unsaturated amines **7b** (30%) and **7d** (15%), formed by ring-opening of the corresponding 1,2-dihydropyridines, were also isolated.[8] As could be expected from the above results, pure 1,4-dihydropyridines **3a-f** were reluctant to undergo cyclization to the corresponding tetracycles **4** when treated with acid under the usual experimental conditions ($HCl\text{-}C_6H_6$ or $TsOH\text{-}C_6H_6$, rt) for this ring closure.

In some experiments, instead of pyridinium bromides **2d** and **2e**, we used the corresponding iodides. Surprisingly, in these cases, after the one-pot nucleophilic addition-acid treatment, tetrahydropyridines **6d** and **6e**, derived from the respective 1,4-dihydropyridines **3d** and **3e**, were isolated in approximately 10% yield. The different course of the reactions involving pyridinium iodides, leading to tetrahydropyridines **6a**, **6d**, and **6e**, prompted us to study the acid-promoted cyclization of the isolated 1,4-dihydropyridines **3** *in the presence of lithium iodide* (1.7 eq). Under these conditions, tetracycles **4a-f** (Table 1)[6] were obtained in the yields given in Scheme 1.

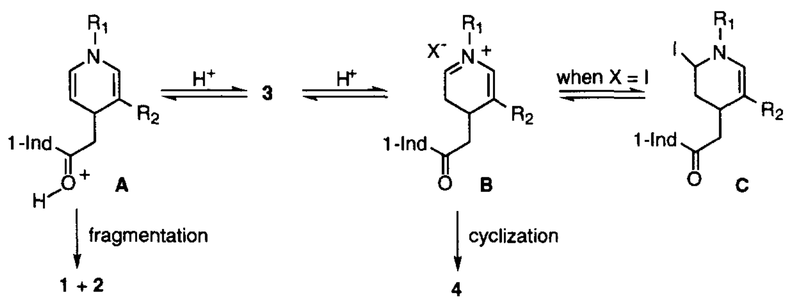
A plausible mechanism that rationalizes the effect of iodide ions on the acid-promoted cyclization of 1,4-dihydropyridines **3** is depicted in Scheme 2. Two equilibria from dihydropyridines **3** under acidic conditions are possible: fragmentation into the starting products **1** and **2** through intermediate **A**, and

Table 1. Significant ^{13}C-NMR Chemical Shifts of Dihydropyridines 3 and Tetracycles 4[a,b]

	C-3	C-14	C-15	C-16	C-17	C-20	C-21	R_1	R_2
3a	128.7	108.0	29.6	44.7	169.7	111.0	144.3	41.3	24.2, 194.3
3b	128.1	108.3	29.8	44.5	169.7	111.6	143.7	57.8[c]	24.3, 195.0
3c	128.9	107.3	29.3	42.5	169.5	108.6	145.3	57.2[c]	105.4, 140.0[d]
3d	127.7	108.2	29.4	44.3	169.6	111.6	143.4	52.8, 62.4[e]	24.2, 194.9
3e	128.7	107.5	28.9	42.4	169.8	108.9	145.3	52.6, 62.6[e]	105.5, 139.6[d]
3f	128.3	107.3	29.2	42.3	169.5	108.4	145.2	34.0, 52.8[f]	105.4, 139.5[d]
4a	55.7	31.0	23.8	46.3	173.4	110.1	146.6	41.0	23.6, 192.3
4b	52.3	31.2	24.2	46.3	173.4	110.4	146.5	56.7[c]	23.8, 192.6
4c	52.4	31.5	25.5	45.5	172.2	106.1	145.7	56.2[c]	104.5, 143.4[d]
4d	53.8	31.6	24.0	46.2	173.3	110.8	145.8	51.3, 61.0[e]	23.8, 192.4
4e	53.6	31.4	25.4	45.4	172.1	106.6	145.4	50.8, 61.0[e]	104.8, 142.7[d]
4f	53.9	31.3	25.5	45.5	172.0	106.5	145.5	33.1, 51.4[f]	104.6, 142.5[d]

[a] Biogenetic numbering as depicted in Scheme 1· [b] In ppm relative to TMS. Measured in $CDCl_3$ solution at 75 MHz. [c] For the Ph group (average values): 126.9, 127.8, 128.9, and 136.4. [d] For the CO_2Me group (average values): 51.0 and 168.5. [e] For the OAc group (average values): 20.6 and 170.5. [f] For the SPh group (average values): 126.7, 129.1, 129.8, and 134.3.

protonation to give dihydropyridinium ion **B**. As cyclization of **B** to **4** is a slow process due to the deactivation exerted by the *N*-acyl group, in absence of iodide anions the fragmentative way is the only operating process. The presence of iodide anions (X = I) would remove the dihydropyridinium ion **B** from the unproductive equilibria that interconnect **3** with the starting product, thus favouring cyclization to **4**.



Scheme 2

Acknowledgment. Financial support from the DGICYT, Spain (project PB94-0214) is gratefully acknowledged. Thanks are also due to the "Comissionat per a Universitats i Recerca", Generalitat de Catalunya, for Grant SGR95-0428. We thank Professor Ernest Wenkert (University of California-San Diego) for his helpful suggestions.

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3. Massiot, G.; Delaude, C. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1988; Vol. 34, Chapter 5.
4. **5**: mp 215-217 °C (ether-acetone); ^{1}H-NMR ($CDCl_3$, 200 MHz) 2.03 (s, 3H, MeCO), 2.20 (m, 1H, 14-H), 2.40 (dt, J = 13.5 and 2 Hz, 1H, 14-H), 2.93 (dd, J = 14.3 and 2.4 Hz, 1H, 16-H), 3.22 (s, 3H, NMe), 3.44 (dd, J = 14.3 and 1.7 Hz, 1H, 16-H), 3.67 (m, 1H, 3-H), 4.67 (dt, J = 5.2 and 2 Hz, 1H, 15-H), 6.68 (s, 1H, 7-H), 7.18 (s, 1H, 21-H), 7.10-7.30 (m, 3H, indole), 7.43 (dd, J = 7.3 and 2 Hz, 1H, 9-H), 8.01 (dm, J = 8 Hz, 1H, 12-H); ^{13}C-NMR 24.0 (MeCO), 28.4 (C-15), 30.0 (C-14), 41.5 (NMe), 44.4 (C-16), 51.6 (C-3), 110.0 (C-20), 110.5 (C-7), 114.5 (C-12), 120.2 (C-9), 123.0 (C-10), 124.0 (C-11), 129.0 (C-8), 137.5 (C-2), 139.4 (C-13), 146.2 (C-21), 171.1, 191.3 (CO).
5. **6a**: ^{1}H-NMR ($CDCl_3$, 200 MHz) 2.25 (s, 3H, MeCO), 2.30 (masked, 1H, pyr 3-H), 2.60 (t, J = 11 Hz, 1H, pyr 3-H), 2.80 (s, 3H, NMe), 3.50 (m, 3H), 4.70 (dd, J = 11 and 4 Hz, 1H, pyr 2-H), 6.65 (d, J = 2 Hz, 1H, indole 3-H), 7.05-7.65 (m, 8H, indole), 8.45 (d, J = 2 Hz, 1H, indole 2-H), 8.50 (dm, J = 8 Hz, 1H, indole 7-H), 8.60 (br s, 1H, NH); ^{13}C-NMR 23.8 (MeCO), 28.7 (pyr C-4), 32.1 (pyr C-3), 40.8 (NMe), 41.8 (CH_2CO), 50.7 (pyr C-2), 109.2 (indole C-3), 111.2 (pyr C-5), 111.7 (indole' C-7), 113.5 (indole' C-3), 116.5 (indole C-7), 119.0 (indole' C-4), 119.7 (indole' C-5), 120.6 (indole C-4), 122.6 (indole' C-6), 123.6 (indole C-5, indole' C-2), 124.6 (indole C-2), 125.5 (indole' C-3a), 127.0 (indole C-6), 130.6 (indole C-3a), 135.4 (indole' C-7a), 136.8 (indole C-7a), 150.5 (pyr C-6), 171.3, 192.9 (CO).
6. All new compounds gave satisfactory spectral, analytical and/or HRMS data. All yields are from material purified by column chromatography.
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8. For related ring-openings, see: (a) Wenkert, E.; Angell, E. C.; Drexler, J.; Moeller, P. D. R.; Pyrek, J. S.; Shi, Y.-J.; Sultana, M.; Vankar, Y. D. *J. Org. Chem.* **1986**, *51*, 2995-3000. (b) Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 1156-1168. See also reference 7a.

(*Received in UK* 18 *July* 1996; *accepted* 30 *August* 1996)