Reduction of *N*-Acyl-2,3-dihydro-4-pyridones to *N*-Acyl-4-piperidones Using Zinc/Acetic Acid

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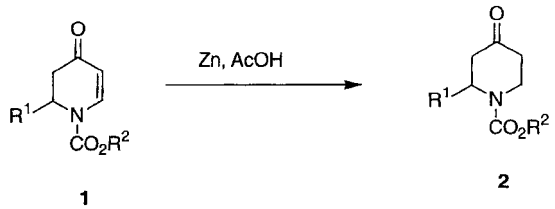
Substituted 4-piperidones are important synthetic intermediates for the preparation of various alkaloids and pharmaceuticals.[1] Derivatives of 4-piperidones have been found to exhibit antidepressant,[2] antiarrhythmic,[3] antithrombogenic,[4] spasmolytic,[5] tranquilizing,[6] and blood cholesterol lowering[6] activities. Due to their medicinal potential, syntheses of substituted 4-piperidones have been of current interest.[1] As part of a program directed at studying the synthesis and synthetic utility of 1-acyl-2,3-dihydropyridones (**1**), we examined various reductions of **1** to provide the corresponding 4-piperidones **2** (Scheme 1). Conjugate reduction of dihydropyridones of the type **1** have generally been carried out using L- or K-Selectrides,[7] as catalytic hydrogenation often leads to over reduction.[8] Although the Selectride reduction is effective in most cases, the reagent is expensive, competing 1,2-reduction can occur,[9] and purification of large scale reaction products can be tedious. Since dissolving metal reductions, i.e., lithium/ammonia, of related enaminones have been reported to give β-amino ketones in good yield,[10] we decided to investigate a mild reduction of dihydropyridones **1** using zinc in acetic acid.

The *N*-acyldihydropyridones **1** were prepared by the addition of Grignard reagents to 1-acylpyridinium salts using literature procedures.[11] In most cases, the reduction could be carried out using inexpensive zinc dust (−325 mesh) at room temperature to provide excellent yields of the corresponding piperidones **2** (see Table 1). Trace impurities present in the metal do not influence the reaction since ultrapure zinc powder (99.999%) gives identical results.[12] The reduction of dihydropyridone **1f** to give piperidone **2f** demonstrates the chemoselectivity and mildness of this procedure. The bicyclic carbamate **3**[13] was also reduced in excellent yield to give indolizidinone **4** (Scheme 2).

In contrast, when reduction of **3** was carried out using catalytic hydrogenation over palladium on carbon, over-reduction to alcohol **5** could not be prevented.

This simple, inexpensive, and mild procedure should be amenable to the large scale preparation of various

Scheme 1



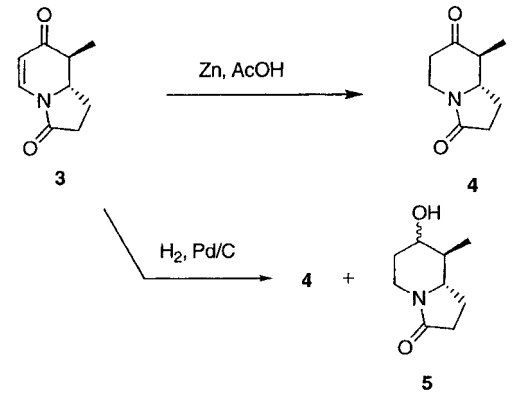
1 **2**

Table 1. Reduction of 1 to 2 Using Zn/AcOH

entry[a]	R^1	R^2	product	conditions	yield[d](%)
1	vinyl	Bn	**2a**	a[b]	94
2	Me	Ph	**2b**	a, b[c]	95, 93
3	Ph	Ph	**2c**	a, b	95, 95
4	Ph	Bn	**2d**	a, b	94, 95
5	$PhCH_2CH_2$	Bn	**2e**	a,b	92, 92
6	$EtO_2CCH{=}CH(CH_2)_3$	Ph	**2f**	b	91

[a] The reactions were performed on a 0.1 to 1.0-mmol scale. [b]Experimental method A. [c] Experimental method B. [d]Yield of purified product obtained from radial preparative-layer chromatography.

Scheme 2



3 **4** **4** + **5**

(1) (a) Wang, C.-L.; Wuorola, M. A. *Org. Prep. Proceed. Int.* **1992**, *24*, 585−621. (b) Grishina, G. V.; Gaidarova, E. L.; Zefirov, N. S. *Chem. Heterocycl. Compd.* **1994**, *30*, 1401−1426. (c) Angle, S. R.; Breitenbucher, J. G. In *Studies in Natural Products Chemistry; Stereoselective Synthesis*, Atta-ur-Rahman, Ed.; Elsevier: New York, 1995; vol. 16, Part J, pp 453−502.

(2) Champseix, A. A.; Lefur, G. R. Eur. Pat. 12,643; *Chem. Abstr.* **1981**, *94*, 15175.

(3) Samczuk, S.; Hermans, H. K. F. Ger. Pat. 2,642,856; *Chem. Abstr.* **1977**, *87*, 53094.

(4) Ciba-Geigy, Fr. Pat. 2,437,405; *Chem. Abstr.* **1981**, *94*, 83739.

(5) Abignente, E.; Biniecka-Picazio, M. *Acta Pol. Pharm.* **1977**, *34*, 241.

(6) Nalanishi, M.; Shiraki, M.; Kobayakawa, T.; Kobayashi, R. Jpn. Pat. 74-03987; *Chem. Abstr.* **1974**, *81*, 12085.

(7) (a) Comins, D. L.; Williams, A. L. *Tetrahedron Lett.* **2000**, *41*, 2839. (b) Huang, S.; Comins, D. L. *Chem. Commun.* **2000**, 569. (c) Comins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035 and references therein.

(8) (a) Ma, D.; Sun, H. *Org. Lett.* **2000**, *2*, 2503. (b) Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, 2261.

(9) (a) Comins, D. L.; Libby, A. H.; Al-awar, R. S.; Foti, C. J. *J. Org. Chem.* **1999**, *64*, 2184 and references therein. (b) Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444.

(10) (a) Ramesh, N. G. Klunder, A. J. H.; Zwanenburg, B. *J. Org. Chem.* **1999**, *64*, 3635 and references therein.

(11) (a) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549. (b) Comins, D. L.; Joseph, S. P.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 793.

(12) A trace amount of lead in zinc powder has been demonstrated to promote certain reductions; see: (a) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668. (b) Hansen, M. M.; Grutsch, J. L. *Org. Process Res. Dev.* **1997**, *1*, 168.

(13) (a) Comins, D. L.; Stolze, D. A.; Thakker, P.; McArdle, C. L. *Tetrahedron Lett.* **1998**, *39*, 5693. (b) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *J. Org. Chem.* **1993**, *58*, 7732.

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racemic or enantiopure[14] 4-piperidones of the type **2**, or indolizidinones such as **4**.

Experimental Section

Typical Experimental Procedure for the Reduction of Dihydropyridones 1. Method A. A solution of dihydropyridone **1** (1 mmol) in 10 mL of glacial acetic acid was stirred vigorously as zinc dust (15 mmol) was added in one portion. The mixture was stirred at room temperature for 36 h, filtered through Celite, and concentrated under reduced pressure. Purification using radial PLC (10% EtOAc/hexane) gave the desired piperidone in 91−95% yield as a clear oil.

Method B. A solution of the dihydropyridone (1 mmol) in 10 mL of acetic acid is stirred vigorously as zinc dust (15 mmol) is added in one portion. The mixture is refluxed from 12 to 20 h until the reaction is complete by TLC (10% EtOAc/hexane). The reaction mixture was filtered through Celite and concentrated under reduced pressure. Purification of the residue by radial PLC (10% EtOAc/hexane) gave the resulting piperidone in 91−95% yield as a clear oil.

(8*R*,9*S*)-8-Methyl-5,6-hexahydroindolizidine-3,7-dione (4). To a stirred solution of **3** (176.7 mg, 1.07 mmol) dissolved in 53 mL of glacial acetic acid was added zinc dust (1.049 g, 16 mmol). The suspension was brought to reflux and stirred for 15 h. The mixture was cooled to room temperature and filtered through a silica plug with CH_2Cl_2. The solution was concentrated to give a white solid which was purified by column chromatography (100% EtOAc) to give 165.5 mg (93%) of **4** as a white solid: mp 115−116 °C; $[\alpha]^{23}_D$ −19.8 (*c* 0.45, MeOH; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (ddd, 1 H, J = 13.3 Hz, 6.8 Hz, 2.1 Hz), 3.42 (m, 1 H), 3.02 (td, 1 H, J = 12.3 Hz, 4.6 Hz), 2.65−2.22 (m, 6 H), 1.85 (m, 1 H), 1.10 (d, 3 H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 173.8, 63.0, 51.9, 40.1, 38.9, 30.1, 24.5, 9.8; IR (thin film, NaCl) 2970, 2930, 2873, 1685, 1448, 1416, 1360, 1267 cm^{-1}; HRMS calcd for $C_9H_{13}NO_2$ 167.0946 (M^+), found 167.0952.

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Supporting Information Available: Spectroscopic data for **2a**−**f**, ^{13}C NMR spectra of **2a**−**f** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For the asymmetric synthesis of *N*-acyldihydropyridones **2**, see (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719. (b) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1994**, *35*, 7343. (c) Comins, D. L.; Guerra-Weltzien, L. *Tetrahedron Lett.* **1996**, *37*, 3807.