A Convenient Synthesis of α-Acylamino Alcohols from Azlactones

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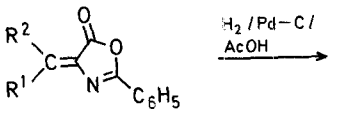
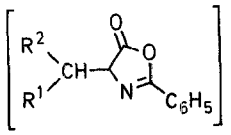
Unsaturated azlactones **1** furnish a convenient starting point for the synthesis of a variety of compounds such as α-acylamino acids, α-keto acids, and α-amino acids[1]. We wish to add α-acylamino alcohols **3** to this list.



1

H_2 / Pd–C / AcOH



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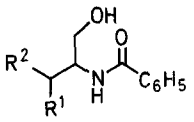

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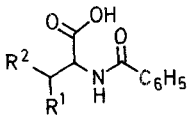

4

1,3	R^1	R^2
a	H_3CO–C$_6$H$_4$–	H
b	C$_6$H$_5$–	H
c	H_3C	H_3C

Table. *Compounds* **3a–c** *prepared*

Product	Yield [%]	m.p. [°C]	Molecular formula	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
3a	50	104–106°	$C_{17}H_{19}NO_3$[a] (285.1)	2.91 (d, 2H, J = 7.1 Hz); 3.3 (br. s, 1H); 3.66 (dd, 1H, J = 11.6 Hz, 5.0 Hz); 3.76 (dd, 1H, J = 11.6 Hz, 3.8 Hz); 4.3 (m, 1H); 6.57 (d, 1H, J = 7.5 Hz); 6.83 (d, 2H, J = 8.7 Hz); 7.17 (d, 2H, J = 8.7 Hz); 7.36 (t, 2H, J = 7.3 Hz); 7.47 (t, 1H, J = 7.3 Hz); 7.66 (d, 2H, J = 8.4 Hz)
3b	60	133–134°	$C_{16}H_{17}NO_2$[b] (255.3)	2.99 (d, 2H, J = 7.2 Hz); 3.69 (dd, 1H, J = 11.2 Hz, 5.0 Hz); 3.76 (dd, 1H, J = 11.2 Hz, 3.7 Hz); 4.36 (m, 1H); 6.5 (br. d, 1H, J = 7.5 Hz); 7.25–7.55 (m, 8H); 7.67 (d, 2H, J = 8.4 Hz)
3c	60	75–77°	$C_{12}H_{17}NO_2$[b] (207.3)	0.91 (d, 6H, J = 6.7 Hz); 1.95 (oct, 1H, J = 7.0 Hz); 3.68 (d, 2H, J = 3.6 Hz); 3.86 (m, 1H); 4.49 (br. s, 1H); 7.20 (d, 1H, J = 9.0 Hz); 7.29 (t, 2H, J = 8.0 Hz); 7.39 (t, 1H, J = 7.6 Hz); 7.75 (d, 2H, J = 8.4 Hz)

[a] M.S.: m/e = 285.140 (M^+); calc. for M^+: 285.144.
[b] *Satisfactory microanalyses obtained:* $C \pm 0.40$, $H \pm 0.30$, $N \pm 0.16$.

As a model for a step in a synthesis of the antitumor agent deoxybouvardin[2], we hydrogenated unsaturated azlactone **1a** with palladium on charcoal (10%) in acetic acid in the hope of obtaining racemic tyrosine *O*-methyl ether via reduction of the olefin and imine followed by hydrogenolysis of the benzyl ester and benzylamine[3,4]. Instead, the major product (50%) was *N*-[2-hydroxy-1-(4-methoxybenzyl)-ethyl]-benzamide (**3a**). Apparently, the lactone carbonyl group of **2a** is reduced faster than the imine group, and the resulting lactol opens to give the α-acylamino aldehyde, which is reduced to the α-acylamino alcohol **3a**. The hydrogenation of the unsaturated azlactone **1a** to azlactone **2a** is precedented, but, in the past, sufficient water was present to hydrolyze **2a** to the α-acylamino acid **4** before further reduction could occur[5].

The analogous phenylalanine and valine derivatives **3b** and **3c**, respectively, were prepared similarly in 60% yields. Thus, α-acylamino alcohols **3** can be readily prepared in two steps from aldehydes or ketones and hippuric acid via azlactones **1**. Compounds **3a** and **3c** are being tested by the National Cancer Institute.

^{1}*H*-N.M.R. spectra were run at 250 MHz and ^{13}C-N.M.R. spectra at 62.9 MHz on a Bruker WM 250 spectrometer. Mass spectra were run on a Varian MAT 311A spectrometer.

Alcohols 3; General Procedure:
Azlactones **1** (1.5 g) in dry acetic acid (50 ml) containing palladium on charcoal (1.2 g, 10%) are shaken for 10 h under hydrogen (3 atm). Filtration, evaporation at room temperature, and chromatography over silica gel with hexane/ethyl acetate (6 : 4) gives compounds **3** in 50–60% yield.

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