J. Sci. Soc. Thailand, **8 (1982)** 167 - 169

THE PICTET-SPENGLER REACTION OF ARYLGLYOXALS: A CONVENIENT SYNTHESIS OF 1-AROYL-1,2,3,4-TETRAHYDROISOQUINOLINES

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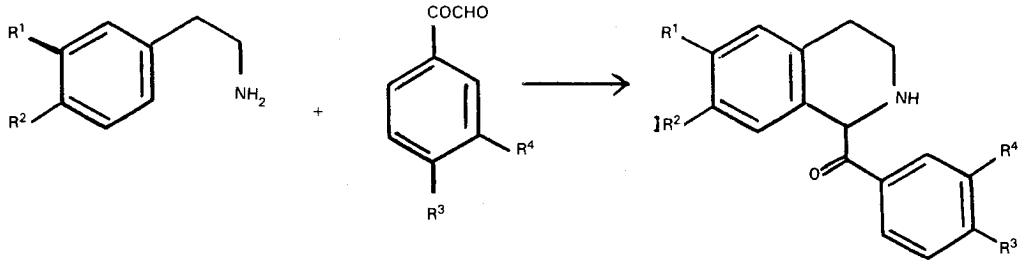
(Received 23 May 1982)

Abstract

The Pictet-Spengler reaction of arylglyoxals with 2-arylethylamines afforded the corresponding 1-aroyl-1,2,3,4-tetrahydro-isoquinolines in moderate yields.

In connection with our interest in the synthesis of isoquinoline alkaloids, we required a number of 1-aroyl-1,2,3,4-tetrahydroisoquinolines. As a search in the literature revealed very little mention of synthesis of these compounds, we sought to develop a direct and convenient route to these compounds. The Pictet-Spengler reaction[1], extensively used for the synthesis of 1,2,3,4-tetrahydroisoquinolines, seemed to be the method of choice. We reasoned that the arylglyoxals, which are easily accessible by selenium dioxide oxidation of the corresponding acetophenones[2], should readily afford the required 1-aroyl-1,2,3,4-tetrahydroisoquinolines under the Pictet-Spengler reaction conditions. In this connection, it is surprising that the use of arylglyoxals in the Pictet-Spengler reaction has hitherto not been investigated although pyruvic acid derivatives and glyoxylic acid derivatives have been employed[3,4].



	R^1	R^2
(1):	H	H
(2):	OMe	OMe
(3):	$O-CH_2-O$	

	R^3	R^4
(4):	H	H
(5):	OMe	H
(6):	OMe	OMe
(7):	Cl	H
(8):	Me	H

	R^1	R^2	R^3	R^4
(9):	OMe	OMe	H	H
(10):	OMe	OMe	OMe	H
(11):	OMe	OMe	OMe	OMe
(12):	OMe	OMe	Cl	H
(13):	$O-CH_2-O$		OMe	H
(14):	$O-CH_2-O$		Cl	H
(15):	$O-CH_2-O$		Me	H

The reaction between the commercially available 2-(3,4-dimethoxyphenyl)-ethylamine and phenylglyoxal was studied under various experimental conditions. After much experimentation, it was found that refluxing with 3*N* or 5.5*N* aqueous hydrochloric acid gave the desired 1-aroyl-1,2,3,4-tetrahydroisoquinolines in moderate yields (see Table). It was also found that 100% formic acid and 90% formic acid were less effective than aqueous hydrochloric acid while glacial acetic acid, *p*-toluenesulphonic acid and trifluoroacetic acid were completely ineffective. As expected the unactivated 2-phenylethylamine failed to react under any of these conditions. The 1-aroyl-1,2,3,4-tetrahydroisoquinolines were relatively unstable substances and were best handled as the oxalate salts.

Table: Synthesis of 1-aroyl-1,2,3,4-tetrahydroisoquinolines

Amine	Arylglyoxal	Acid	Product	% Yield of oxalate	m.p. of oxalate	N.m.r. spectral data (δ)
(1)	(4)	3*N* HCl	none			
(2)	(4)	3*N* HCl	(9)	75	155–157°	see text
(2)	(5)	3*N* HCl	(10)	54	149–151°	8.00(d, J=9 Hz, 2H), 7.23(s, 1H), 6.90(d, J=9 Hz, 2H), 6.90(s, 1H), 6.70(s, 1H), 4.07–3.50(m, 2H), 3.93 (s, 3H), 3.87(s, 3H), 3.77 (s, 3H), 2.74(t, J=7 Hz, 2H).
(2)	(6)	3*N* HCl	(11)	29	181–184° (free base)	7.63 - 7.35(m, 2H), 7.23(s, 1H), 6.95 - 6.65(m, 3H), 4.10 - 3.50(m, 2H), 3.97(s, 9H), 3.77(s, 3H), 2.77 (t, J=7 Hz, 2H).
(2)	(7)	5.5*N* HCl	(12)	41	130–132° (free base)	7.97(d, J=9 Hz, 2H), 7.40(d, J= 9 Hz, 2H), 7.21(s, 1H), 6.90(s, 1H), 6.70(s, 1H), 4.10 - 3.50(m, 2H), 3.90(s, 3H), 3.80(s, 3H), 2.77(t, J=7 Hz, 2H).
(3)	(5)	5.5*N* HCl	(13)	25	189–191°	8.00(d, J=9 Hz, 2H), 7.23(s, 1H), 6.90(d, J=9 Hz, 2H), 6.90(s, 1H), 5.90(s, 2H), 4.05 - 3.50(m, 2H), 3.87(s, 3H), 2.73(t, J=7 Hz, 2H).
(3)	(7)	5.5*N* HCl	(14)	30	170–172°	7.97(d, J=8 Hz, 2H), 7.40(d, J= 8 Hz, 2H), 7.23(s, 1H), 6.83(s, 1H), 6.70(s, 1H), 5.93(s, 2H), 3.90 (t, J=7 Hz, 2H), 2.73(t, J=7 Hz, 2H).
(3)	(8)	5.5*N* HCl	(15)	31	172–173°	7.87(d, J=8 Hz, 2H), 7.20(s, 1H), 7.20(d, J=8 Hz, 2H), 6.77(s, 1H), 6.67(s, 1H), 5.90(s, 2H), 3.87(t, J=7 Hz, 2H), 2.73(t, J=7 Hz, 2H), 2.40(s, 3H).
(2)	(4)	90% HCO_2H	(9)	44	155–157°	
(2)	(4)	100% HCO_2H	(9)	30	155–157°	
(2)	(4)	CH_3CO_2H	none			
(2)	(4)	CF_3CO_2H	none			
(2)	(4)	*p*-toluene-sulphonic acid	none			

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Ultraviolet spectra were measured with a Shimadzu UV-240 spectrophotometer and infrared spectra were measured with a Jasco IRA-1 spectrophotometer. Nuclear magnetic resonance spectra were measured in deuterochloroform solutions with a Varian EM360A spectrometer operating at 60 MHz and tetramethylsilane was used as an internal reference.

The synthesis of 1-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline is representative of the procedure employed.

A mixture of 2-(3,4-dimethoxyphenyl) ethylamine (5.1 g) and phenylglyoxal hydrate (5.0 g) in 3*N* hydrochloric acid (150 ml) was refluxed for 5 hours; then the cooled reaction mixture was poured into ice-water (200 ml), basified with 3*N* sodium hydroxide, and extracted with chloroform (3 × 200 ml). The chloroform extracts were washed with water (2 × 100 ml) and saturated sodium chloride (2 × 100 ml) and then dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave an oil (7.8 g) which was dissolved in tetrahydrofuran (25 ml) and then added to a solution of oxalic acid (3.7 g) in tetrahydrofuran (10 ml). The yellow oxalate salt was filtered and recrystallised from ethanol-chloroform to give yellow crystals (7.2 g; 75%), m.p. 155-157°C. The oxalate salt on treatment with chloroform and aqueous sodium carbonate gave 1-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline as a pale yellow oil, λ_{max}^{MeOH} nm(log ε): 233(4.58), 256sh(4.40) and 318(3.98); ν_{max}(neat): 3360 cm^{-1}(NH), 1670 cm^{-1}(C=O); n.m.r. spectrum δ($CDCl_3$): 8.15-7.75(m, 2H, H_2, and $H_{6'}$), 7.60-7.30 (m, 3H, $H_{3'}$, $H_{4'}$ and $H_{5'}$), 7.23(s, 1H, H_1), 6.87(s, 1H, H_1), 6.70(s, 1H, H_6), 4.10-3.50 (m, 2H, $ArCH_2CH_2N$), signals partially obscured by methoxy signals, 3.90(s, 3H, OCH_3), 3.75(s, 3H, OCH_3), 2.77(t, J = 7 Hz, 2H, $ArCH_2$).

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บทคัดย่อ

ปฏิกิริยาพิคเทต-สเปงเกลอร์ระหว่างสารประเภทเอริลไกลออกซาลกับ 2-เอริลเอธิลเอมีนให้สารประเภท 1-เอโรอิล-1,2,3,4-เตตระไฮโดรไอโซควิโนลีนในปริมาณผลผลิตปานกลาง