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IMPROVED METHODS FOR THE SYNTHESIS OF N-ACYLTETRAHYDROISOQUINOLINES

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ABSTRACT: One-pot procedures for the synthesis of N-acyltetrahydroisoquinolines have been developed from 2-phenylethylamines, acyl chlorides or carboxylic acids and aldehydes.

The intramolecular α-amidoalkylation reaction of N-acylphenylethylamines 3 with aldehydes 4 is a modified Pictet-Spengler cyclization leading to 2-acyltetrahydroisoquinolines 7. The reaction was successfully used for the synthesis of 2-formyl and 2-arylsulfonyltetrahydroisoquinolines[1,2] as well as for some N-acetyltetrahydroisoquinolines.[3]

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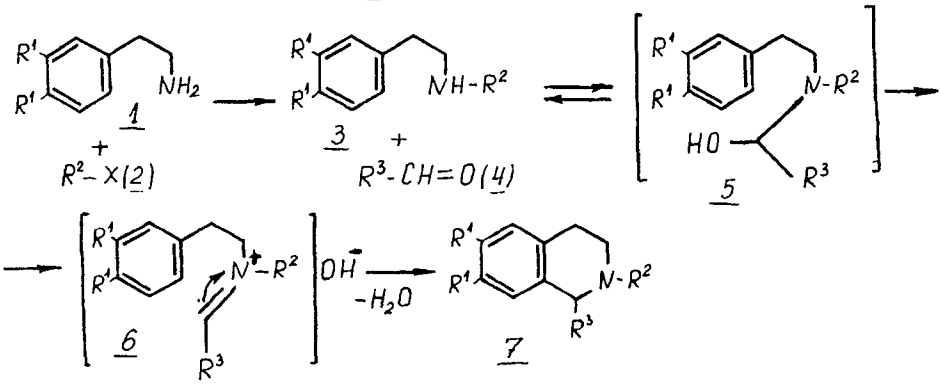
The accepted mechanism for the reaction included the formation of carbinolamide type intermediates 5 from the starting amides 3 and aldehydes 4 and their cyclization to N-acyltetrahydroisoquinolines 7 through an N-acyliminium ion 6.



The carbinolamides 5 are more reactive then Pictet-Spengler's carbinolamine intermediates 5 (R=H or alkyl) and the cyclization is successful to less reactive aromatic systems. The main synthetic problem with this reaction is the formation of the carbinolamides 5 which is not a favoured one and can be overcome by carring it as one pot reaction. The relative rate of the reaction is strongly dependant on the amide and the carbonyl components used. NH-acidity of the amide 3 probably is an important factor for the formation of intermediates 5, while the acidic media will influence their transformation to the more electrophylic N-acyliminium ions 6.

We investigated the dependance of the cyclization reaction from NH-acidity of the starting amide by carrying out the reaction of paraformaldehyde with different N-acylphenylethylamines 3 in a refluxed toluene for 3 h. The yields of the obtained N-acyltetrahydroisoquinolines 7 (Table, Method A) show that the decreasing of NH-acidity of the amide from 3a to 3j lead to a lower yields. Next, we carried out the same reaction in the presence of a catalytic amount of p-toluenesulfonic acid monohydrate (Table, Method B). The better yields of 7a-j lead to the assumption that the rate determining process of the reaction is the formation of N-acyliminium ions 6 and it can be favourized by the presence of protonic acids.

The above investigations enabled us to develop an one-pot procedure for the synthesis of N-acyltetrahydroisoquinolines 7 starting the reaction from 2-(3,4-dimethoxyphenyl)ethylamine 1 (R^1=OMe). The amine was converted to the amide 3 with the corresponding acyl chloride in a refluxed toluene, then paraformaldehyde is added and the reaction mixture is refluxed for 4 h (Table, Method C).

Finally it was shown that 2-acetyltetrahydroisoquinolines 7 can be obtained in an one-pot the procedure starting the reaction from equivalent amounts of 2-(3,4-dimethoxyphenyl)ethylamine 1, carboxylic acid 2

Table 2-Acyltetrahydroisoquinolines 7[5,6]

7	R^1	R^2	R^3	Yields (%) by methods:				m.p.
				A	B	C	D	(°C)
a	MeO	$C_6H_5SO_2$	H	77	86	85	-	146-8
b	MeO	$(EtO)_2P(O)$	H	72	90	88	-	69-70
c	MeO	CHO	H	67	78	75	-	129-30
d	MeO	$COOCH_3$	H	65	75	70	-	oil
e	MeO	$COCHCl_2$	H	65	80	77	75	128
f	MeO	$COCH_2Cl$	H	62	80	75	74	124
g	MeO	C_6H_5CO	H	59	77	73	70	80-2
h	MeO	CH_3CO	H	52	70	68	63	94-5
i	MeO	C_6H_5NHCO	H	51	70	50	-	150-2
j	MeO	$(CH_3)_2NCO$	H	49	70	69	-	89-90
k	H	$COCHCl_2$	H	-	88	-	-	86-7
l	H	$COCH_2Cl$	H	-	83	-	-	63-4
m	H	$COCH_2OCH_3$	H	-	73	-	-	oil
n	MeO	$COCH_2Cl_2$	C_6H_5	-	79	-	-	187-9
o	MeO	$COCF_3$	C_6H_5	-	70	-	-	136-7
p	MeO	$COCH_2Cl$	$4\text{-}O_2N\text{-}C_6H_4$	-	88	-	-	176-7
q	MeO	$COCH_2OCH_3$	$4\text{-}O_2N\text{-}C_6H_4$	-	70	-	-	141-3

(X=COOH) and paraformaldehyde in the presence of $SOCl_2$ or PCl_3 in a refluxed toluene for 6h (Table, Method D). However, the reaction of nonactivated in the aromatic ring amides 3 with paraformaldehyde proceeds sluggishly at the conditions of Method A and Method B. Stronger acidic media as a mixture of H_2SO_4-AcOH (25%) is required to give N-acetyltetrahydroisoquinolines (Table, 7k-m).

Aromatic aldehydes 4 can also be used for the cyclization reaction. Benzaldehyde and 4-nitrobenzaldehyde react with activated amides 3 in a mixture of H_2SO_4-AcOH (25%) at room temperature for 10 days to the corresponding N-acetyltetrahydroisoqunolones (Table, 7n-q).

EXPERIMENTAL

N-Acyltetrahydroisoquinolines 7a-j;General Procedures:

Method A: A mixture of N-acyl-(3,4-dimethoxyphenyl)-ethylamine 3 (10 mmol) and paraformaldehyde (15 mmol) in toluene (20mL) was refluxed for 3 h. The solvent is distilled at reduced pressure and the residue was purified by recrystallization or by passing through a column of silica gel and eluted out with a mixtures of petroleum ether/Et_2O (1:1) and Et_2O .

Method B: A mixture of N-acyl-(3,4-dimethoxyphenyl)-ethylamine 3 (10 mmol), paraformaldehyde (15 mmol) and

p-toluenesulfonic acid monohydrate (50 mg) in toluene (20 mL) was refluxed for 3 h. Water (50 mL) was added to the cooled mixture and the organic layer was again washed with 20% aq. Na_2CO_3 (2x20 mL) and dried (Na_2SO_4). The solvent was removed at reduced pressure and the product was purified as described above.

Method C: 2-(3,4-Dimethoxyphenyl)ethylamine (1.81g, 10 mmol) in toluene (20 mL) was heated to reflux and then acyl chloride (for 7c, 98% HCOOH) (10 mmol) in toluene (5 mL) was added dropwise. Paraformaldehyde (15 mmol) was added at once and the mixture was stirred at reflux for 4 h. Then the mixture was worked up as described above.

Method D: A solution of 2-(3,4-dimethoxyphenyl)-ethylamine (10 mmol) and carboxylic acid (12 mmol) in toluene (25 mL) was heated to reflux. A solution of $SOCl_2$ (12 mmol) in toluene (5 mL) was added dropwise to the stirred mixture and after 15 min was added paraformaldehyde (15 mmol) at once, then was refluxed for 6 h. The mixture was worked up as above.

N-acyltetrahydroisoquinolines 7k-m;General Procedure: N-Acetylphenylethylamine 3 (10 mmol) and paraform-aldehyde (11 mmol) were dissolved in a mixture of conc.H_2SO_4-AcOH (20 mL, 2:8) at r.t. and the solution was stirred for 48 h. The solution was poured on crushed ice (100 g) and extracted with $CHCl_3$ (3x2(

mL). The extract was washed with 20% aq. Na_2CO_3 (2x30 mL) and dried (Na_2SO_4). The solvent was distilled and the products were purified by recrystallization (Et_2O/MeOH, 5:1).

1-Phenyl-2-acyltetrahydroisoquinolines 7n-q:General Procedure:

N-Acetyl-(3,4-dimethoxyphenyl)ethylamine 3 (5 mmol) and benzaldehyde or 4-nitrobenzaldehyde (5 mmol) were dissolved in a mixture of conc.H_2SO_4-AcOH (20 mL, 2:8) at r.t. and the solution was allowed to stay for 10 days. The reaction mixture was worked up as described above.

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5. Compounds 7a-h and 7j-m were compared by their spectral data with the previously reported in references 2 and 4.
6. The ^{1}H-NMR spectra for 7i and 7n-q were recorded on a Perkin-Elmer R-24B spectrometer in $CDCI_3$

(TMS) and are as follows: 7i 2.79(t,2H,J=9),3.52 (t,2H,J=9),3.70(s,3H),3.75(s,3H),4.52(s,2H),6.52 (s,1H),6.58(s,1H),6.80-7.35(m,5H)); 7n 2.85(t,2H, J=11),3.30(t,2H,J=11),3.82(s,3H),3.90(s,3H), 6.38 (s,1H),6.48(s,1H),6.65(s,1H),6.78(s,1H),7.00-7.25 (m,5H);7o 2.85(t,2H,J=11),3.30(t,2H,J=11),3.64 (s,3H),3.80(s,3H),6.58(s,1H),6.64(s,1H), 6.78 (s,1H),7.12-7.30(m,5H);7p 2.85(t,2H,J=10), 3.25 (t,2H,J=10),3.72(s,3H),3.85(s,3H),4.10(s,2H), 6.38(s,1H),6.60(s,1H),6.70(s,1H),7.29 (d,2H, J=16),8.00 (d,2H,J=16); 7q 2.85(t,2H,J=12),3.25 (t,2H,J=12),3.40(s,3H), 3.82(s,3H),3.90(s,3H), 4.20(s,2H),6.48(s,1H),6.65(s,1H),6.78 (s,1H), 7.48(d,2H,J=10),8.02(d,2H,J=10).

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