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Application of the Intermolecular α-Amido-alkylation Reaction for the Synthesis of Tertiary Amides and 1-Substituted 2-Acyltetrahydroiso-Quinolines. Synthesis of (±)-Carnegine

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APPLICATION OF THE INTERMOLECULAR α-AMIDOALKYLATION REACTION FOR THE SYNTHESIS OF TERTIARY AMIDES AND 1-SUBSTITUTED 2-ACYLTETRAHYDROISOQUINOLINES. SYNTHESIS OF (±)- CARNEGINE.

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ABSTRACT: Adducts **4** of Schiff bases and 3,4-dihydroisoquinolines with acyl chlorides react with Grignard reagents **5** in an intermolecular α-amidoalkylation reaction to the corresponding tertiary amides or 1-substituted 2-acyltetrahydroisoquinolines.

Adducts **4** of imines and acyl chlorides as reactive electrophilic reagents have been successfully used in the intra and intermolecular α -amidoalkylation reaction for the synthesis of different N-heterocyclic compounds.[1-5]

Now we wish to report our investigations on the intermolecular α -amidoalkylation reaction of adducts **4** from imines **1** or **2** and acyl chlorides with Grignard reagents. The reaction allows the synthesis of the difficultly accessible tertiary amides, some of them known as herbicides,[6]

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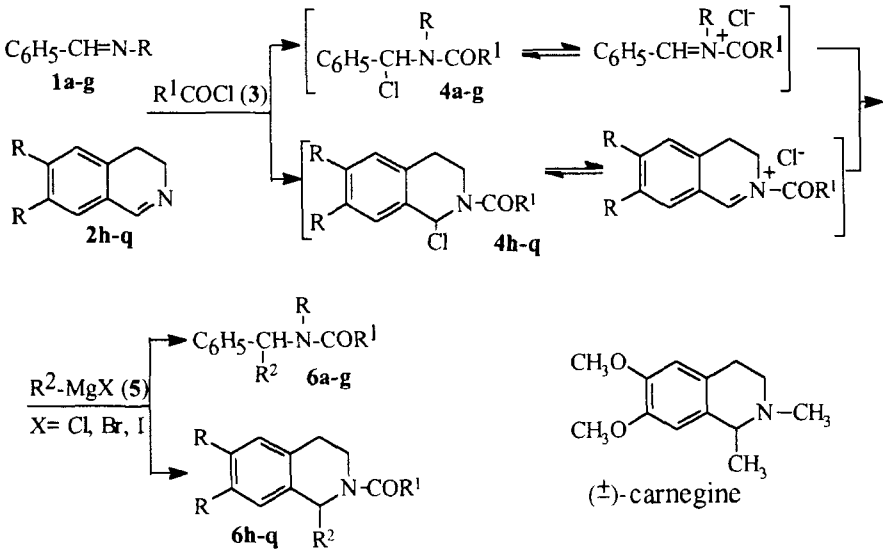
and 1-alkyl, 1-phenyl or 1-benzyltetrahydroisoquinoline derivatives which are found in many alkaloids as the main structural element.[7,8]

Their synthesis by Bischler-Napieralski or Pictet-Spengler reactions is often not successful, especially when the used amides or imines of 2-phenyl-ethylamine are not activated by electrondonating groups in the aromatic ring.[9,10]



The Grignard reagents **5** were prepared as usual in diethyl ether or tetrahydrofuran. The adducts **4** were obtained from the imines **1** or **2** and acyl chlorides **3** in a small amount of dichloromethane since they were not soluble in the above solvents. The mixture was stirred for 30 min to 1 h at room temperature and then added to the solution of the obtained Grignard reagent.

The reaction of adducts **4a-g** from Schiff bases **1** and acyl chlorides **3** with Grignard reagents **5** proceeds at a room temperature to the corresponding tertiary amides in moderate yields (Table 1,**6a-g**). The adducts of 3,4-dihydroisoquinolines **2** and acyl chlorides **3** also react with Grignard

Table1 Amides **6a-g** and 2-acyltetrahydroisoquinolines **6h-q**

Product	R	R^1	R^2	Yield(%)	Mp (°C)
6a	C_6H_5	OEt	$C_6H_5CH_2$	40	75
6b	C_6H_5	OEt	Me	52	oil
6c	C_6H_5	OEt	i-Pr	50	oil
6d	C_6H_5	Me	Me	88	oil
6e	C_6H_5	Me	$C_6H_5CH_2$	60	82-83
6f	C_6H_5	C_6H_5	Me	35	oil
6g	$C_6H_5(CH_2)_2$	OEt	Me	50	oil
6h	H	OEt	Me	68	oil
6i	H	OEt	Et	73	oil
6j	H	OEt	i-Pr	60	oil
6k	H	OEt	C_6H_5	50	oil
6l	H	OEt	$C_6H_5CH_2$	85	oil
6m	H	Me	$C_6H_5CH_2$	38	76-78
6n	H	C_6H_5	$C_6H_5CH_2$	76	oil
6o	MeO	OEt	Me	58	72-73
6p	MeO	OEt	$C_6H_5CH_2$	40	118-120
6q	MeO	C_6H_5	$C_6H_5CH_2$	35	127-128

Table 2 Spectral data of **6a-q**

Product	^{1}H-NMR ($CDCl_3$/TMS), J(Hz)	MS(70eV) m/z(M^+)
6a	1.10(t,3H,J=6),3.26(t,2H,J=7),4.02(q,2H,J=7),5.71 (t,1H,J=8),6.40-6.55(m,3H),6.82(d,1H,J=2),7.10 (s,5H),7.12(s,5H),7.44(d,1H,J=2)	345 ($C_{23}H_{23}NO_2$)
6b	1.12(t,3H,J=7), 1.25 and 1.42(d,d,3H,J=7),4.00(q,2H, J=6),5.66(q,1H,J=7),6.53-6.72(m,3H),7.03(d,1H,J=2), 7.10(s,5H),7.18(d,1H,J=2)	269 ($C_{17}H_{19}NO_2$)
6c	0.76 and 1.31(d,d,6H,J=6),1.12(t,3H,J=6),2.25-2.50, (m,1H),4.04(q,2H,J=7),4.87 and 5.02(d,d,1H,J=2), 6.45-6.70(m,2H), 6.80-7.15(m,8H)	297 ($C_{19}H_{23}NO_2$)
6d	1.39(d,3H,J=7),1.72(s,3H),6.16(q,1H,J=7), 7.05(s,6H),7.10-7.30(m,4H)	239 ($C_{16}H_{17}NO$)
6e	1.64(s,3H),3.15(d,2H,J=8),6.27(t,1H,J=8), 7.06(s,15H)	315 ($C_{22}H_{21}NO$)
6f	1.47(d,3H,J=8),6.25(q,1H,J=7),6.40-6.53 (m,2H),6.80-7.07(m,8H),7.12(s,5H)	301 ($C_{21}H_{19}NO$)
6g	1.32(t,3H,J=6),1.48(d,3H,J=7),2.25-2.75(m,2H),2.97-3.18(m,2H),4.14(q,2H,J=7), 5.42(q,1H,J=7),6.72-6.92(m,3H),7.02(d,1H,J=2),7.08(d,1H,J=2),7.16(s,5H)	297 ($C_{19}H_{23}NO_2$)
6h	1.25(t,3H,J=7),1.42(d,3H,J=7),2.65-2.87(m,2H),3.02-3.40(m,2H),4.14(q,2H,J=7),5.00-5.30(m,1H),7.05(s,4H)	219 ($C_{13}H_{17}NO_2$)
6i	0.95(t,3H,J=7),1.25(t,3H,J=7),1.51-1.95(m,2H),2.67-	233

Table 2 Continued

	2.92(m,2H),3.25-3.67(m,2H),4.07(q,2H,J=6), 4.80-5.08(m,1H),6.98(s,3H),7.06(d,1H,J=4)	($C_{14}H_{19}NO_2$)
6j	0.92(d,6H,J=6),1.25(t,3H,J=7),1.75-2.12 (m,1H),2.81(t,2H,J=7),3.17-3.67(m,2H),4.10(q,2H, J=6),4.67(t,1H,J=8),6.95(s,3H),7.04(d,1H,J=4)	247 ($C_{15}H_{21}NO_2$)
6k	1.27(t,3H,J=7),2.65-2.97(m,2H),3.05-3.40(m,2H), 4.17(q,2H,J=7),6.32(s,1H),7.07(s,1H),7.17(s,6H), 7.19(s,2H)	282 ($C_{18}H_{19}NO_2$)
6l	1.20(t,3H,J=7),2.60-2.85(m,2H),3.03(d,2H,J=7),3.45 (q,2H,J=7),3.97(m,2H),5.32(t,1H,J=8), 7.00-7.24(m,9H)	295 ($C_{19}H_{21}NO_2$)
6m	1.49 and 2.11(s,s,3H),2.65-3.00(m,2H),3.11(d,2H,J=6), 3.54(t,2H,J=6),4.85 and 5.75(t,t,1H,J=6), 7.16-7.24(m,9H)	265 ($C_{18}H_{19}NO$)
6n	2.55-2.77(m,2H),3.05-3.28(m,2H),3.40(d,2H,J=7), 5.92(t,1H,J=7),6.51(d,1H,J=6),6.79(d,1H,J=6), 7.00-7.25(m,12H)	327 ($C_{23}H_{21}NO$)
6o	1.22(t,3H,J=7),1.38(d,3H,J=6),2.55-2.77(m,2H), 2.92-3.42(m,2H),3.75(s,6H),4.05(q,2H,J=7), 5.04(q,1H,J=6),6.40(s,2H)	279 ($C_{15}H_{21}NO_4$)
6p	1.10 and 1.25(t,t,3H,J=7),2.60-2.80(m,2H),2.92-3.12 (m,2H),3.57(d,2H,J=9),3.80(s,6H),4.04(q,2H,J=7), 5.12(t,1H,J=6),6.22(s,1H),6.53(s,1H),7.00-7.20(m,5H)	355 ($C_{21}H_{25}NO_4$)

(continued)

Table 2 Continued

6q	2.50-2.74(m,2H),2.80-3.00(m,2H),3.20(d,2H,J=7), 3.63(s,3H),3.81(s,3H),4.65-4.92(m,1H), 6.27(s,1H),6.51(s,1H),7.20(s,10H)	387 ($C_{25}H_{25}NO_3$)

reagents to 1-alkyl 1-phenyl and 1-benzyl 2-acyltetrahydroisoquinolines in moderate to good yields (Table 1, **6h-q**) when the reaction was carried out at room temperature,then at reflux. The spectral data of **6** are given in Table 2.

An extension of this procedure to include the reaction of 3,4-dihydro-isoquinolines with Grignard reagents failed to give the expected 1-substituted tetrahydroisoquinolines.

1-Methyl-2-ethoxycarbonyl-6,7-dimethoxytetrahydroisoquinoline **6o** was converted to the alkaloid (±)-carnegine[12,13] in a very good yield by reduction with $LiAlH_4$ in Et_2O after reflux for 4h.

EXPERIMENTAL

Tertiary amides (6a-g);Typical Procedure: To a solution of azomethine (3 mmol) in 3mL dry dichloromethane was added acyl chloride (3 mmol) and the mixture was stirred for 30min at r.t. The solution was added portionwise to a freshly prepared Grignard reagent (6 mmol) from the corresponding RX and Mg in 10 mL dry Et_2O and the reaction mixture was stirred for 30 min at r.t. 10% aq.HCl (10mL) was added and the mixture extracted with $CHCl_3$ (3x20mL). The combined extracts were dried (Na_2SO_4) and the solvents

removed by distillation. The crude products were purified by column chromatography on neutral Al_2O_3 using hexane and p.ether as eluents.

1-Alkyl, 1-benzyl 2-acyltetrahydroisoquinolines (6h-q);Typical Procedure: 3,4-Dihydroisoquinoline (2mmol) and acyl chloride (2mmol) were mixed in 3 mL dry dichloromethane and stirred for 1 h at room temperature. The solution was added portionwise to a freshly prepared Grignard reagent (4 mmol) from the corresponding RX and Mg in 10 mL dry Et_2O. The reaction mixture was stirred for 30 min at room temperature, then refluxed for 1 h and allowed to cool. 10% aq.HCl (10mL) was added and the mixture extracted with $CHCl_3$ (3x10mL). The combined extracts were dried (Na_2SO_4) and concentrated. The crude products were purifified by column chromatograpy on neutral Al_2O_3 using p.ether, Et_2O or their mixtures as eluents.

(±)-Carnegine: 1-Methyl-2-ethoxycarbonyl-6,7-dimethoxytetrahydro-isoquinoline **6o** (0.2g, 0.64 mmol) was added to a cooled suspension of $LiAlH_4$ (0.2g) in dry Et_2O (20mL) and the reaction mixture was stirred at reflux for 4 h. The mixture was treated with H_2O (0.5 mL), 15% NaOH (0.5 mL), stirred for 15 min, and filtered. The organic extract was washed (1N NaOH, water), dried (Na_2SO_4) and concentrated to give the product as an oil (0.15g; 93%); HCl.salt mp 210-211°C (from MeOH). ^1H NMR ($CDCl_3$/TMS),δ: 1.36(d,2H,J=6), 2.42(s,3H), 2.60-2.77(m,2H), 2.80-3.08(m,1H),3.30-3.60(m,2H), 3.75(s,6H), 6.40(s,1H), 6.43(s,1H).

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