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REDUCTIVE FORMYLATION OF ISOQUINOLINE DERIVATIVES WITH FORMAMIDE AND SYNTHESIS OF 2-FORMYLTETRAHYDROISOQUINOLINES

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Abstract: Reductive formylation of isoquinoline derivatives as 3,4-dihydroisoquinolines **1**, enamines and enamides of tetrahydroisoquinoline **2** and the reaction of 2-(2-acylphenyl)ethylamides **3** with formamide afforded the corresponding N-formyltetrahydroisoquinolines **4** and N-acyltetrahydroisoquinolines **5**.

Formamide has been widely used in Leuckart-Wallach reactions for reductive amination of carbonyl compounds and different reaction mechanisms have been discussed over the years.[1a-e] Incidentally, it has been also used for reductive formylation of some heterocycles as methylpyridines, methylquinolines and methylisoquinolines.[2]

2-Formyltetrahydroisoquinolines are known as alkaloids,[3] they are useful for synthesis of other tetrahydroisoquinolines and can also be reduced to 2-methyltetrahydroisoquinolines or hydrolyzed to N-nor derivatives.[4] A few years ago, we reported the synthesis of 1- and 1,3-substituted 2-formyltetrahydroisoquinolines from 2-phenylethylformamides and aldehydes in the presence of acids.[5,6]

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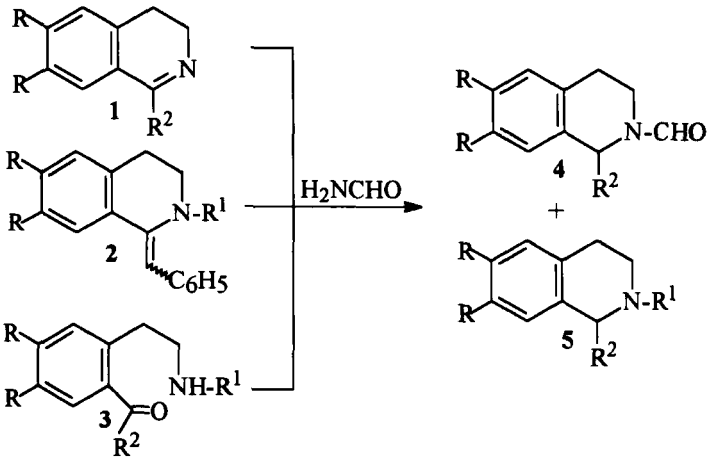
The application of the method for preparation of 1-benzyl- or 1-phenylethyl-2-formyltetrahydroisoquinolines however led to unsatisfactory results because of the instability of the used aldehydes in acidic media.

Now we report the results of our investigations on the reductive formylation of 3,4-dihydroisoquinolines **1**, enamines and enamides of tetrahydroisoquinoline **2** with formamide as well as on the reaction of 2-(2-acylphenyl)ethylamides **3** with formamide.



The starting isoquinoline derivatives **1** and **2** were prepared by a method recently reported.[7] It was found that 3,4-dihydroisoquinolines **1** undergo reductive formylation with formamide to the corresponding 2-formyltetrahydroisoquinolines **4** in good yields by heating the reaction mixture at 180°C for 1-2 h (Table 1, **4a-e**). The yields of **4** improved in some cases when the reaction was carried out in a mixture of formamide and 98% HCOOH (3v:1v) - e.g. **4c** was obtained in a yield of 93% at reflux for 2 h. Enamine **2a** was reduced at the same reaction conditions to 1,2-dibenzyltetrahydroisoquinoline **5a** (Table 1). The reaction of enamine **2a** showed that the reaction of 3,4-dihydroisoquinolines **1** with formamide probably proceeded with the reduction of C=N bond and then with the N-formylation of the obtained tetrahydroisoquinoline.

Enamides of tetrahydroisoquinoline **2b-d** (Table 1) reacted with formamide with reduction of C=C bond and transamidation of N-atom, depending on the nature of N-acyl group. When N-acyl group of **2** is not a good leaving group (Table 1, **2d**), the transamidation was not completed and 1-benzyl-2-carboxyethyl-6,7-dimethoxytetrahydroisoquinoline **5d** was also obtained.

Recently we reported a method for synthesis of 3-oxo-2,3-dihydroisoquinolines from the reaction of ethyl 2-(2-acylphenyl)ethylamides and formamides.[8] Now we extended our investigations on the reaction of 2-(2-acylphenyl) ethylamides **3** with formamide. It was found that the reaction of **3** with formamide in the presence 98% HCOOH (3v:1v) at reflux for 3 h leads predominantly to N-formyltetrahydroisoquinolines **4** (Table 2). Again, when the N-acyl group of **3** was a not good leaving group, the transamidation was not completed and led to a mixture of N-formyltetrahydroisoquinolines **4** and N-acyltetrahydroisoquinolines **5** (Table 2, **5e,f**).

Table 1.

Entry	R	R^1	R^2	Yield [%]		React.
				4	**5**	cond. [h]
1a	H	-	H	75[a]	-	1
1b	MeO	-	H	70[a]	-	1
1c	MeO	-	Me	67[a]	-	2
1d	MeO	-	C_6H_5	93[a]	-	2
1e	MeO	-	$C_6H_5CH_2$	72	-	1
2a	MeO	$C_6H_5CH_2$	$C_6H_5CH_2$	-	72[b]	1
2b	MeO	COMe	$C_6H_5CH_2$	76	-	2
2c	MeO	COC_6H_5	$C_6H_5CH_2$	56	-	1
2d	MeO	COOEt	$C_6H_5CH_2$	38	46[c]	1

[a]mp and spectral data are given in ref. 5; [b]mp and spectral data are given in ref. 7.
[c]mp and spectral data are given in ref. 9.

Table 2.

Entry*	R	R^1	R^2	Yield [%]	
				4[a]	5
3a	MeO	COMe	Me	71	-
3b	MeO	COC_6H_5	Me	86	-
3c	MeO	$CONH_2$	Me	94	-
3d	MeO	COC_6H_5	$C_6H_5CH_2$	88	-
3e	MeO	COOEt	Me	18	33[a]
3f	MeO	COOEt	$C_6H_5CH_2$	42	45[b]

[a]mp and spectral data are given in ref. 5; [b]mp and spectral data are given in ref. 9.

The reductive formylation with formamide was carried out also with some N-heterocyclic compounds. The reactions of pyridine, indole, imidazole, and pyrazine with formamide or its mixtures with 98% HCOOH led to unchanged starting compounds at different reaction conditions. The reaction of quinoline with formamide for 4 h at 180°C led to N-formyltetrahydroquinoline in a yield of 40%. When the same reaction was carried out in a mixture of H_2NCHO/HCOOH (3v:1v) at reflux for 2 h, the yield of the same product increased to 67%.

The reaction of isoquinoline with formamide in the presence of HCOOH (3v:1v) for 3 h at reflux afforded N-formyltetrahydroisoquinoline in 70% yield. However, two products- N-formyltetrahydroisoquinoline (21%) and N-formyl-1,2-dihydroisoquinoline (7%) were obtained, when the same reaction was carried out only in formamide for 4 h at 180°C.

The efforts to extend the reductive formylation with formamide or its mixtures with HCOOH to some other imines as N-benzylideneaniline, at different reaction conditions, led to N-phenylformamide and N-benzylformamide.

Mp and spectral data of the obtained new compounds are given in the experimental part. ^{1}H-NMR were measured on a Tesla BS 587A 80 MHz spectrometer in $CDCl_3$ (TMS) in δ, ppm and MS spectra were recorded on a JMS-D300 spectrometer.

EXPERIMENTAL

Reductive formylation of 3,4-dihydroisoquinolines 1, enamines and enamides of tetrahydroisoquinoline 2; Typical procedure: The corresponding isoquinoline (Table 1, **1a-e, 2a-d**) (2 mmol) in formamide (3 mL) was stirred at 180°C for the time given. The solution was cooled to room temperature, then water (50 mL) was added and the mixture was extracted with $CHCl_3$ (3x30 mL). The combined extract was dried (Na_2SO_4) and the solvent was evaporated under vacuum. The products (Table 1, **4** and **5**) were purified by recrystallization (MeOH or MeOH/Et_2O) or separated by column chromatography on neutral Al_2O_3 using Et_2O and $CHCl_3$ as eluents.

1-Benzyl-2-formyl-6,7-dimethoxytetrahydroisoquinoline (Table 1, **4e** from **1b** and **4b-d** from **2a-d**): mp 129-130°C; ^{1}H-NMR: 2.70-2.88(m,2H), 3.10(d,2H,J=8), 3.60 (s,3H), 3.83(s,3H), 3.85(t,2H,J=4), 5.50(t,1H,J=8), 6.25 (s,1H), 6.53(s,1H), 7.00-7.28(m,5H), 7.55 and 8.05(s,s, 1H); MS (M^+): 311 ($C_{19}H_{21}NO_3$, 311.4)

Reaction of 2-(2-acylphenyl)ethylamides 3 with formamide: A solution of 2-(2-acylphenyl)ethylamides **3**[8] (2 mmol) in a mixture of formamide (6 mL) and 98% HCOOH (2 mL) was reflux for 3 h and then was worked up as above. The products were purified by recrystallization (MeOH or MeOH/Et_2O) or separated by column chromatography on neutral Al_2O_3 using Et_2O and $CHCl_3$ as eluents (Table 2, **4a-d** and **5e,f**).

1-Methyl-2-carboxyethyl-6,7-dimethoxytetrahydroisoquinoline (Table 2, **5e**): mp 72-74°C; ^{1}H-NMR: 1.26(t,1H,J=6), 1.45(d,3H,J=6), 2.55-2.85(m,2H), 3.15-3.36(m,2H), 3.85(s,6H), 4.15(q,2H,J=6), 5.00-5.25(m,1H), 6.55(s,2H); MS (M^+): 279 ($C_{15}H_{21}NO_4$, 279.3).

Reductive formylation of quinoline and isoquinoline: Quinoline or isoquinoline (2 mmol) in a solution of formamide/98% HCOOH (6:2 mL) were reflux for 2 h and the reaction mixtures were worked up as above. The products were purified by column chromatography on neutral Al_2O_3, using Et_2O as eluent.

1-Formyltetrahydroquinoline: oil, ^{1}H-NMR: 1.75-2.15(m,2H), 2.70(t,2H,J=8), 3.82 (t,2H,J=8), 7.12(s,4H), 8.65(s,1H); MS (M^+): 161 ($C_{10}H_{11}NO$, 161.2).

The reaction of isoquinoline (3 mmol) with formamide (9 mL) for 4 h at 180°C afforded two products after working up as above. They were separated by PTLC and identified as 2-formyltetrahydroisoquinoline (21%) and 2-formyl-1,2-dihydroisoquinoline (7%).

2-Formyl-1,2-dihydroisoquinoline: oil, ^{1}H-NMR: 4.75(s,2H), 5.80(d,1H,J=8), 6.55 (d,1H,J=8), 6.90-7.20(m,4H), 8.25(s,1H); IR($CHCl_3$): 1635 cm^{-1}(C=C), 1687 cm^{-1} (CO); MS (M^+): 159 ($C_{10}H_9NO$, 159.2).

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