Hydroamination of Carbonyl Compounds with Oximes

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Abstract -N-alkyl(cycloalkyl)benzylamines, p-fluorobenzylamines, (1-phenylethyl)amines, [1-(p-fluorophenyl)ethyl]amines were synthesized by hydroamination of aldehydes and ketones with oximes.

Derivatives of benzylamine and (1-phenylethyl)amine have found wide application in industry, pharmacology, and agriculture. In this connection there has been active search for new synthetic routes to these compounds and work on improvement of known synthetic procedures. In particular, research into reductive amination of alcohols, ketones, and aldehydes with ammonia, amines, nitro compounds, and nitriles has been continued [1].

In the present work we report on a new catalytic method of synthesis of *N*-alkylated benzylamines and (1-phenylethyl)amines by hydroamination of aliphatic aldehydes and ketones with benzaldehyde, *p*-fluorobenzaldehyde, acetophenone, and *p*-acetophenone oximes. The method is based on the earlier developed procedure of hydroamination of aliphatic aldehydes with benzaldehyde oxime [2] and involves passing of the aldehyde and oxime in a (1.2-1.5):1 molar ratio over a heated heterogeneous catalysts in a flow apparatus under hydrogen pressure.

Hydroamination of carbonyl-containing compounds with various oximes is a process comprising a number of consecutive conjugated reactions similar in essence to reactions attendant on hydroamination with nitriles [3].

First the oxime is reduced to a primary amine on hydrogenating centers of the catalyst. Further on the primaty amine can take part in several reactions. For successful reaction in the required direction, the condensation of the primary amine with carbonylcontaining reagent to form an imine is the most important. The following stage is the reduction of the C=N bond on hydrogenating centers of the catalyst to form the final reaction product, a secondary amine.

The possible side reactions are the Beckmann rearrangement of oximes (especially when highly acidic catalysts are used) and their hydrolysis to carbonyl compounds. The latter can serve as an additional source of symmetrical secondary amines.

The major direction of the hydroamination of aldehydes and ketones with benzaldehyde and p-fluorobenzaldehyde oximes (I, II) is the synthesis of secondary amines III–XXIV.

The isolated reaction by-products [*N*,*N*-dialkylbenzylamines **XXV**–**XVII**, *N*,*N*-dialkyl(*p*-fluorobenzyl)amines **XXIX**–**XXXI**, dibenzylamine (**XXXII**), bis(*p*-fluorobenzyl)amine (**XXXIII**), benzyl alcohol, and toluene] are mostly formed by the following reactions: hydrolysis of oximes, deamination of primary amines, and alkylation of amines.

The optimal conditions providing the highest yield of the target secondary amines are as follows: 210°C, $p(H_2)$ 1 MPa, v 0.3 h⁻¹, and aldehyde: oxime molar ratio 1.5:1.

Table 1 presents the results of the hydroamination of aliphatic aldehydes with oximes **I** and **II**. As seen, the reaction route depends on the structure of the starting aldehyde.



I, **II**, **R** = H (**I**), F (**II**); **III**–**XXII**, **R** = H, **R**' = H, **R**'' = CH₃ (**III**), C₂H₅ (**IV**), C₃H₇ (**V**), (CH₃)₂CH (**VI**), C₄H₉ (**VII**), (CH₃)₂CHCH₂ (**VIII**); **R** = H, **R**' = CH₃, **R**'' = CH₃ (**IX**), C₂H₅ (**X**), C₃H₇ (**XI**), C₄H₉ (**XII**); **R** = H, **R**' = C₂H₅, **R**'' = C₂H₅ (**XIII**); **R** = F, **R**' = H, **R**'' = CH₃ (**XIV**), C₂H₅ (**XV**), C₃H₇ (**XVI**), (CH₃)₂CH (**XVII**); **R** = F, **R**' = CH₃, **R**''' = C₃(**XVIII**), C₂H₅ (**XVI**), (CH₃)₂CH (**XVIII**); **R** = F, **R**' = CH₃, **R**''' = CH₃ (**XVIII**), C₂H₅ (**XIX**), C₃H₇ (**XXI**), C₄H₉ (**XXII**); **R** = F, **R**' = CH₃ (**XXII**), **XXIII**, **XXIV**, *n* = 2 (**XXIII**), 3 (**XXIV**).

Branched aldehydes are less reactive and form no tertiary amines.

The optimal conditions for th hydroamination of ketones are as follows: 220° C, $p(H_2)$ 1.5 MPa,

 $v \ 0.25 \ h^{-1}$, oxime: ketone molar ratio 1:1.5 (Table 2). With acyclic ketones, certain amounts (3–5%) of dicycloalkylamines were found among reaction products, along with dibenzylamine.

$$R \xrightarrow{CH_3} R \xrightarrow{R'R''CO} R \xrightarrow{CH_3} R \xrightarrow{CH_3} R \xrightarrow{CH_3} R$$

$$XXXIV, XXXV XXV XXVI-XLV$$

 $\begin{array}{l} R = H, \ R' = H, \ R'' = CH_3 \ (\textbf{XXXVI}), \ C_2H_5 \ (\textbf{XXXVII}), \ C_3H_7 \ (\textbf{XXXVIII}), \ (CH_3)_2CH \ (\textbf{XXXIX}); \ R = F, \ R' = H, \ R'' = CH_3 \ (\textbf{XL}), \ C_2H_5 \ (\textbf{XLI}), \ C_3H_7 \ (\textbf{XLII}), \ (CH_3)_2CH \ (\textbf{XLIII}); \ R = H, \ R' = CH_3 \ (\textbf{XLIV}), \ C_2H_5 \ (\textbf{XLIV}). \end{array}$

R in RCHO		Total yield of						
	III–VIII, XIV–XVII	XXV–XXVIII, XXIX–XXXI	XXXII, XXXIII	annies, 70				
Oxime I								
CH ₃	48 (III)	17 (XXV)	15 (XXXII)	80				
$C_2 H_5$	66 (IV)	10 (XXVI)	12 (XXXII)	88				
$\tilde{C_3H_7}$	65 (V)	7 (XXVII)	14 (XXXII)	86				
$C_4 H_9$	60 (VII)	4 (XXVIII)	18 (XXXII)	82				
$(CH_3)_2CH$	45 (VI)	_	17 (XXXII)	62				
(CH ₃) ₂ CHCH ₂	48 (VIII)	_	18 (XXXII)	56				
Oxime II								
CH ₃	45 (XIV)	17 (XXIX)	10 (XXXIII)	72				
$C_2 H_5$	56 (XV)	11 (XXX)	8 (XXXIII)	75				
$\tilde{C_3H_7}$	54 (XVI)	7 (XXXI)	11 (XXXIII)	72				
(CH ₃) ₂ CH	43 (XVII)	_	15 (XXXIII)	58				

Table 1. Products and yields of hydroamination of aliphatic aldehydes with oximes I and II^a

^a 210°C, *p*(H₂) 1 MPa, *v* 0.3 h⁻¹, oxime: aldehyde molar ratio 1:1.5, catalyst 36% Cu/MgO. Here and hereinafter, the yields of amines per taken oxime are given.

Table 2. Products and yields of hydroamination of aldehydes and ketones with oximes I, II, XXXIV, and XXXV^a

R' and R" in R'R"CO	Oxime		Amine		Yield, %	
CH ₃ , CH ₃	I	II	IX	X	61	54
CH_3, C_2H_5	Ι	II	Χ	XIX	52	46
CH_3, C_3H_7	Ι	II	XI	XX	48	45
CH_3, C_4H_9	Ι	II	XII	XXI	38	36
C_2H_5, C_2H_5	Ι	II	XIII	XXII	45	50
$cyclo-C_4H_8$	Ι	_	XXIII	-	37	_
$cyclo-C_5H_{10}$	Ι	_	XXIV	-	46	_
H, CH ₃	XXXIV	XXXV	XXXVI	XL	47	43
H, $C_2 H_5$	XXXIV	XXXV	XXXVII	XLI	56	50
H, $\tilde{C_3H_7}$	XXXIV	XXXV	XXXVIII	XLII	51	47
H, $(CH_3)_2CH$	XXXIV	XXXV	XXXIX	XLIII	42	37
CH_3, CH_3	XXXIV	_	XLIV	-	39	_
CH_3, C_2H_5	XXXIV	_	XLV	_	36	_

^a 210-220°C, p(H₂) 1-1.5 MPa, v 0.25 h⁻¹, oxime:aldehyde(ketone) molar ratio 1:1.5, catalyst 36% Cu/MgO.

With acetophenone and *p*-fluoroacetophenone oximes (**XXXIV**, **XXXV**) as aminating agents we prepared a series of aromatic amines with the amino group in the side chain (compounds **XXXVI–XLV**; Table 2).

With oxime **XXXIV**, the following by-products were found: ethylbenzene (**XLVI**), (1-phenylethyl)-amine (**XLVII**), and 1-phenylethanol (**XLVIII**). The

effect of the temperature in the hydroamination of propanal with oxime **XXXIV** was studied to show that the increase of the temperature from 210 to 230°C decreases the yield of propyl(1-phenylethyl)amine (**XXXVII**) from 56 to 43%; therewith, the yield of ethylbenzene (**XLVI**) increases from 23 to 41%. This hydrocarbon is formed by partial hydrogenolysis of amine **XXXVII** and deoxygenation of acetophenone **XLIX**.



It is known [4] that the products of incomplete reduction of oximes, imines, in the course of reduction can be hydrolyzed by the reaction water to carbonyl compounds. The same was observed in our case. Part of acetophenone **XLIX** formed was reduced to 1-phenylethanol (**XLVIII**) only, and the latter was found among the reaction products. It should be noted that the degree of the deoxygenation of product **XLIX** to form ethylbenzene (**XLVI**) is much higher on an "acidic" catalyst (15% Cu/Al₂O₃) than on lithium hydroxide-promoted or copper–magnesium catalysts.

The highest yields of butyl(1-phenylethyl)amine (**XXXVIII**) on the hydroamination of butanal with acetophenone oxime (**XXXIV**) were obtained on the catalysts 15% Cu/Al₂O₃ + 6% LiOH (45%) and 36% Cu/MgO (51%); therewith, the yields of ethylbenzene (**XLVI**) were 36 and 23%, respectively. The lowest activity and selectivity were shown by the copper–aluminum oxide catalysts without lithium hydroxide additives. With this catalyst, the yield of ethylbenzene (**XLVI**) was the highest (36%).

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Table 3. Characteristics of synthesized amines

Comp. no.	bp, °C (<i>p</i> , mm)	n ²⁰ _D	mp, °C (hydrochloride)
III	60–64 (6)	1.5008	181–183
IV	72–74 (4)	1.5058	184–185
V	78–81 (2)	1.4982	215-217
VI	69–71 (3)	1.4952	175–177
VII	83-86 (3)	1.4985	237-239
VIII	120–121 (5)	1.4995	110-112
IX	64–66 (4)	1.5031	195–196
X	87-88 (5)	1.5028	143–145
XI	120–121 (5)	1.4995	110-112
XIV	56–58 (3)	1.4942	203-205
XV	51–53 (2)	1.4920	194–196
XVI	70–74 (2)	1.4881	246-248
XVII	70–71 (3)	1.4858	207-209
XVIII	58–61 (4)	1.4882	179–181
XIX	70–72 (4)	1.4884	168–170
XX	77–79 (4)	1.4845	153–155
XXI	87–90 (5)	1.4833	156–157
XXII	76–80 (4)	1.4888	144–146
XXIII	114–116 (6)	1.5280	220-222
XXIV	127–128 (5)	1.5285	252-254
XXXVI	89–92 (11)	1.5100	—
XXXVII	96–99 (12)	1.5028	—
XXXVIII	104–106 (12)	1.4934	—
XL	53–54 (4)	1.4858	110-112
XLI	69–71 (3)	1.4868	146–148
XLII	71–74 (2)	1.4828	135–137
XLIII	66–68 (3)	1.4802	187–189
XLIV	196–197 (760)	1.4958	-
XLV	214–216 (760)	1.4914	_

It should be noted that, unlike what is observed with hydroamination of aldehydes and ketones with other oximes, such as benzaldehyde and cyclic ketone oximes [5], in the case in hand no symmetrical secondary amines formed as a result of the possible reaction of oxime **XXXIV** and its hydrolysis product acetophenone **XLIX**. The lack of these secondary amines is probably explained by the steric hindrances produced by phenyl substituents at the carbonyl group and the nitrogen atom.

Table 2 presents the results of the hydroamination with oximes **XXXIV** and **XXXV** with aldehydes and ketones on the catalyst 36% Cu/MgO in optimal conditions. As seen from Table 2, the yields of secondary amines decrease as the molecular weight of the starting aldehyde and ketone increases. With oxime **XXXV**, we obtained previously unknown fluorinated amines.

Table 3 lists the principal characteristics of the synthesized secondary amines.

EXPERIMENTAL

Analysis of products and reaction monitoring were performed by GLC on an LKhM-8MD chromatograph on a column (2000 × 2 mm) packed with Chromosorb W (60–80 mesh) modified with 5% KOH, on Apieson K (12%). The IR spectra were measured on a Nicolet Protege-460 Fourier IR spectrometer. The ¹H NMR spectra were recorded on Tesla BS–567A (100 MHz) or Bruker AC-300 (300 MHz) spectrometers for 2–5% solutions in DMSO- d_6 , internal reference TMS. The mass spectra were obtained on a Hewlett–Packard 5890/5972 GC–MS system, ionizing energy 70 eV, column HP-5MS.

Catalyst 15% Cu/Al₂O₃. A weighed sample of copper(II) formate (15% per metal) was dissolved in distilled water with heating (80°C). Aluminum oxide of A-1 brand preliminary calcined at 400°C for 3 h was added to the resulting solution, and the mixture was left to stand for 4 h. After that the water was let to evaporate in air under continuous stirring. The anhydrous sample was calcined at 400°C for 2 h in a muffle oven. The catalyst was sieved, collecting a 2–4-mm fraction.

Catalyst 15% Cu/Al₂O₃ + 6% LiOH. A weighed sample of lithium hydroxide (6% per ready catalyst) was dissolved in distilled water, and calcined sample of the 15% Cu/Al2O3 catalyst was added to the resulting solution. The subsequent workup was performed as described above. Catalysts with other active component ratios were prepared in a similar way.

Catalyst 36% Cu/MgO. The speciation of the catalyst is as follows: 59% Cu(OH)₂+36% (MgOH)₂+ 0.5% NaNO₃ + 4.5% H₂O. A 50% solution of copper(II) nitrate, 141 g, was prepared and added with stirring to a solution of 80 g of magnesium nitrate in 1070 ml of distilled water. The final concentration of the salts should be about 8%. For precipitation, ~1400 g of 12% NaOH was prepared. The process was performed in a reactor equipped with a stirrer. The reactor was charged with 925 ml of distilled water, and the salt and alkali solutions were fed simultaneously with stirring. The alkali was fed in such a rate that the pH of the solution was maintained at 8. A pasty material precipitated on settling and was separated, washed with water to remove sodium nitrate and alkali, and dried at 120–150°C for about 4 h. The dried product was ground, wetted with water, formed in granules 3 mm in diameter and 5 mm in length, and dried. The bulk weight of the ready catalyst was 0.68–0.75 g/cm³.

Benzyl(propyl)amine (IV). A stainless-steel reactor 20 mm in diameter was charged with 20 cm³ of the catalyst 36% Cu/MgO (15% Cu/Al₂O₃ + 6% LiOH) which was reduced in hydrogen at 350°C for 3 h. A solution of 60 g of oxime I in 43 g of propanal was passed at a volume rate of 0.3 h⁻¹ through the catalyst bed at 210°C and a hydrogen pressure of 1 MPa. Reaction products were treated with dilute (1:3) hydrochloric acid. The hydrogen chloride solution was treated with ten volumes of diethyl ether to remove neutral reaction products and then made weakly alkaline with 15% KOH, after which amines were extracted with diethyl ether. The ethereal layer was dried with K_2CO_3 , the solvent was removed, and the residue was distilled in a vacuum to obtain 49 g (66% per taken oxime) of the target reaction product. IR spectrum, cm⁻¹: 3320, 3005, 3032, 3068, 2815, 2878, 2962, 1600, 1494.

Benzyl(2-methylpropyl)amine (VI) was prepared in a similar way using a solution of 60 g of oxime **I** in 54 g of 2-methylpropanal. Vacuum distillation gave 37 g (45%) of amine **VI**. IR spectrum, cm⁻¹: 3330, 3070, 3045, 3010, 2960, 2930, 2875, 2820, 1610, 1510, 1385, 1364. ¹H NMR spectrum (CDCl₃), δ , ppm: 7.19 m (5H, Ar–H), 3.73 s, 2.39 d (2H, PhCH₂), 1.69 m (1H, CH), 0.90 d (6H, 2Me).

Amines **III–VIII**, **IX–XXIV** were prepared in a similar way. The mass spectra contain molecular ion peaks with relative intensities of about 30% and the following ion peaks (m/z): 120 [C₆H₅CH₂NHCH₂]⁺, 106 [C₆H₅CHNH₂]⁺, 91 [C₇H₇]⁺, 77 [C₆H₅]⁺, 78 [C₆H₆]⁺, 79 [C₆H₇]⁺, 65 [C₅H₅].

p-Fluorobenzyl(isopropyl)amine (XVIII) was prepared in a similar way using a solution of 70 g of oxime II in 44 g of acetone. Vacuum distillation gave 45 g (54%) of amine **XVIII**. IR spectrum, cm⁻¹: 3324, 3070, 3040, 3005, 2962, 2932, 2876, 2865, 1605, 1512, 1222, 826. ¹H NMR spectrum (CDCl₃), δ , ppm: 7.40 m (2H, Ar–H), 7.00 t (2H, Ar–H), 3.75 s (2H, PhCH₂), 2.85 m (1H, CH), 1.10 d (6H, 2Me).

Amines **XIV**–**XVII**, **XIX**–**XXII** were prepared in a similar way. Their mass spectra contain $[C_7H_6F]^+$ ion peaks at m/z 109.

Ethyl[1-(*p*-fluorophenyl)ethyl]amine (XL) was prepared in a similar way using a solution of 77 g of oxime II in 34 g of acetaldehyde. Yield 36 g (43%). ¹H NMR spectrum (CDCl₃), δ , ppm: 7.30 m (2H, Ar–H), 6.90 t (2H, Ar–H), 3.69 m (CHMe), 2.43 q (2H, CH₂Me), 1.45 d, 1.01 t (3H, CH₂Me).

Amines **XXXVI–XLV**, **XLI–XLIII** were prepared in a similar way. Their mass spectra contain $[C_7H_6F]^+$ ion peaks at m/z 109.

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