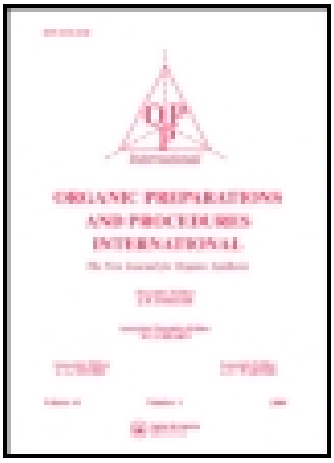

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INVESTIGATION OF THE ALKYLATION OF AROMATIC AND HYDROAROMATIC ALDOXIMES WITH HALOHYDRINS

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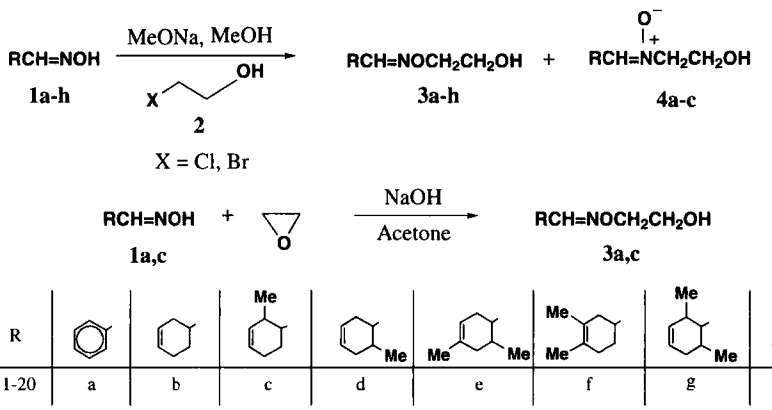
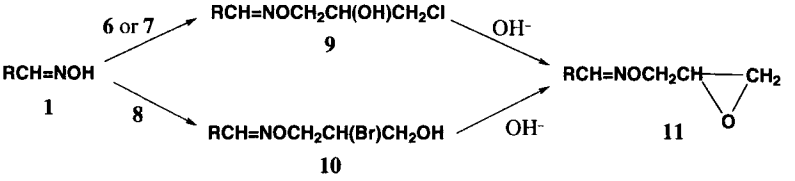
O- or N-Alkyl derivatives of oximes have been reported to exhibit physiological[1,2] and biological[3,4] activity, are employed as antibiotics,[5] antihistamines[6] and are useful as starting materials[7] in pharmaceutical industry. A literature survey showed that although the alkylation of aldoximes and ketoximes with alkyl halides have been widely investigated, the alkylation with monohalo and dihalohydrins has been limited.[8-10] The alkylation of oximes with alkyl halides yields a mixture of O-alkyl or N-alkyl derivatives (nitrones) in the presence of base,[11] while other reports[8,9] indicate that only O-derivatives are formed under same conditions. We now describe the preparation of various oxime derivatives from alkylation of aromatic and hydroaromatic aldoximes with halohydrins under basic conditions.

Alkylation of oximes with 2-chloro- and 2-bromoethanol, gave either O-alkyl or N-alkyl derivatives, while treatment of oximes with 1,3-dichloro-2-propanol, 1-chloro-3-bromo-2-propanol and 2,3-dibromopropanol yielded halohydrins that were easily converted into corresponding epoxides under basic conditions. Amino alcohols and dioxolanes were sythesized by reacting the obtained epoxides with amines and acetone respectively.

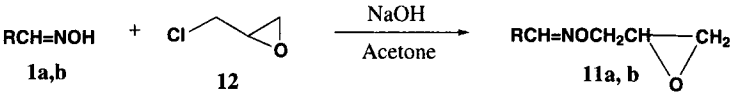
The required oximes were prepared *via* modification of literature procedures[10] from benzaldehyde, 2-furfuraldehyde, D^3-tetrahydrobenzaldehyde and the mono- and dimethyl derivatives of D^3-tetrahydrobenzaldehyde. In the presence of basic catalysts, alkylation with monohalohydrins in protic solvents yielded O-alkyloximes **3a-h** along with the nitrones as minor by-products; they were separated by fractional distillation under reduced pressure. Only the O-alkyl oximes **(3a and 3c)** were formed in aprotic solvents, such as acetone. The structure of **3a,c** was established by spectroscopic analysis and confirmed by synthesis from **1a,c** with ethylene oxide.



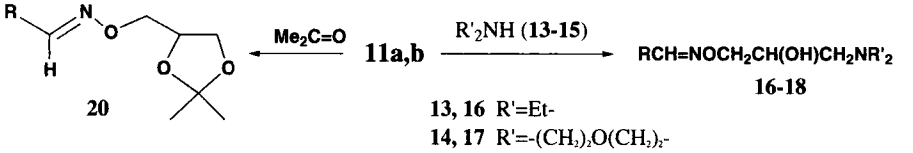
Oximes **1a,b,d,h** reacted easily with 1,3-dichloro-2-propanol (**6**), 1-chloro-3-bromo-2-propanol (**7**) and 2,3-dibromopropanol (**8**) to give the corresponding O-alkyl derivatives of oximes **9** and **10** exclusively in 67-73% yield.

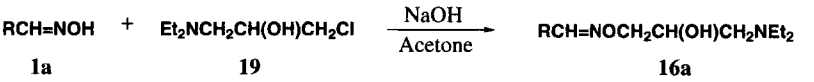


Compounds **9a,b,h** and **10a,b,d** were converted to corresponding glycidic ethers **11** in 82-85% yield by heating in the presence of base. **11a,b** were also prepared by reaction of oximes **1a,b** with *epi*-chlorohydrin (**12**) in aprotic solvents.



Ring opening of epoxides **11a,b** with diethylamine (**13**), morpholine (**14**), and piperidine (**15**) afforded amino alcohols **16a,b** as liquids, **17a,b** and **18a,b** as their HCl salts in good yields, while dioxolanes **20a,b** were formed with acetone in the presence of $BF_3 \cdot Et_2O$. Compound **16a** was also prepared from the reaction of **1a** with **19**.





The structure of all compounds synthesized was confirmed by microanalyses, IR, ^{1}H NMR and chemical methods (Tables 1 and 2).

Table 1. Physical Data of the Newly Synthesized Compounds

Comp.	Yield (%)	bp. (mp.) (°C/mmHg) (T/°C)	n_4^{20}	Elemental Analyses (Found)			
				C	H	Cl (Br)	N
3a	65	132/0.5	1.5632	65.44(65.72)	6.72(6.78)	-	8.48(8.72)
3b	68	118/1	1.5020	63.90(63.72)	8.87(8.68)	-	8.28(8.04)
3c	64	120/1	1.4920	65.57(65.38)	9.29(9.18)	-	7.65(7.72)
3d	66	110/1.5	1.4972	65.57(65.36)	9.29(9.22)	-	7.65(7.55)
3e	73	126/1.5	1.4965	67.00(67.25)	9.64(9.52)	-	7.11(7.40)
3f	71	130/2.5	1.5050	67.00(67.28)	9.64(9.44)	-	7.11(7.18)
3g	76	122/0.5	1.4935	67.00(66.78)	9.64(9.56)	-	7.11(6.88)
3h	62	114/1	1.5980	54.15(54.34)	5.96(5.86)	-	8.98(8.74)
4a	3.5	168/0.5	1.5880	65.44(65.16)	6.71(6.64)	-	8.48(8.76)
4b	3.8	158/0.5	1.5416	63.90(63.72)	8.87(8.78)	-	8.28(8.54)
4c	3.4	167/0.5	1.5492	65.57(65.38)	9.29(9.18)	-	7.65(7.54)
9a	68	148/0.5	1.5785	56.21(56.02)	5.62(5.56)	16.62(16.34)	6.56(6.42)
9b	65	138/1.5	1.5630	54.92(54.70)	7.78(7.68)	16.43(15.94)	6.41(6.14)
9h	72	121/0.5	1.5998	51.20(50.97)	5.33(5.18)	18.66(18.42)	7.46(7.22)
10a	73	154/1	1.5995	46.51(46.33)	4.65(4.62)	31.05(32.72)	5.42(5.14)
10b	70	143/0.5	1.5875	45.80(45.58)	6.11(6.10)	30.53(30.14)	5.34(5.04)
10d	67	146/1.5	1.5570	47.82(47.58)	6.52(6.47)	29.05(28.71)	5.07(4.95)
11a	85	132/2	1.5595	67.79(67.62)	6.26(6.24)	-	7.91(7.65)
11b	82	110/2	1.4986	66.27(66.48)	8.34(8.12)	-	7.73(7.45)
11d	84	118/1.5	1.4905	67.66(67.54	8.72(8.68)	-	7.17(6.96)
11h	80	98/0.5	1.5848	57.48(57.22)	5.38(5.28)	-	8.38(8.08)
16a	92	196/0.5	1.5290	67.17(67.32)	8.68(8.78)	-	11.19(11.32)
16b	84	159/1	1.5010	66.14(65.89)	10.23(10.12)	-	11.02(10.78)
17a	82	(109-000)[a]	-	49.85(49.62)	6.53(6.48)	21.06(20.84)	8.30(8.22)
17b	79	(142-000)[a]	-	49.26(49.03)	7.62(7.54)	20.82(20.56)	8.21(7.92)
18a	86	(92-000)[a]	-	53.73(53.52)	7.16(7.04)	21.19(20.86)	8.58(8.40)
18b	82	(194-000)[a]	-	53.10(52.86)	8.59(8.32)	20.94(20.44)	8.25(8.04)
20a	58	145/3	1.5280	53.10(52.86)	8.59(8.49)	-	8.25(8.04)
20b	56	120/1	1.4935	49.26(49.10)	7.62(7.54)	-	8.21(7.92)

a) Mps.

Table 2. Spectroscopic Data of the Newly Synthesized Compounds

Compd	IR (ν_{max} / cm^{-1})				^1H NMR (δ_H / ppm)
	C=N	N-O	OH	Other	
3a	1675	970	1050 3500	-	2.55 (1H, s, OH), 3.70 (2H, t, CH_2O), 4.25 (2H, t, OCH_2), 6.60 (1H, d, HC=N anti), 7.25 (1H, d, HC=N syn), 7.50 (Ar)
3b	1675	990	1040 3450	-	1.8 (2H, m, CH_2), 2.5 (4H, d, CH_2), 3.20 (1H, s, OH), 3.75 (2H, t, CH_2O), 4.20 (2H, t, OCH_2), 5.60 (s, HC=CH, J=10.5), 6.65 (1H, HC=N, anti), 7.35 (1H, d, HC=N, syn)
3c	1680	995	1050 3500	-	0.95 (3H, d, CH_3), 1.2-2.2 (4H, m, CH_2), 3.35 (1H, s, OH), 3.85 (2H, m, CH_2O), 4.15 (2H, m, OCH_2), 5.60 (d, HC=CH, J=10.5), 6.65 (t, HC=N, anti), 7.45 (t, HC=N, syn), 8.65 (1H, N=CH)
3d	1690	930	1075 3450	-	0.93 (3H, d, CH_3), 1.25-2.30 (4H, m, CH_2), 3.30 (1H, s, OH), 3.62 (2H, t, CH_2O), 4.15 (2H, t, OCH_2), 5.62 (d, HC=CH, J=10.5), 6.60 (t, HC=N, anti), 7.42 (t, HC=N, syn)
3e	1670	925	1085 3500	-	0.92 (3H, d, CH_3), 1.60 (3H, s, CH_3), 1.15-1.75 (4H, m, CH_2), 2.05 (1H, s, OH), 3.85 (2H, m, CH_2O), 4.15 (2H, m, OCH_2), 6.65 (t, HC=N, anti), 7.40 (t, HC=N, syn)
3f	1680	975	1080 3450	-	1.30 (3H, s, CH_3), 1.70 (3H, s, CH_3), 2.25 (1H, s, OH), 2.35 (2H, m, CH_2), 3.20 (4H, m, CH_2), 3.85 (2H, m, CH_2O), 4.15 (2H, m, OCH_2), 6.60 (d, HC=N, anti), 7.35 (d, HC=N, syn)
3g	1685	980	1075 3400	-	0.90 (6H, d, CH_3), 1.85-2.10 (2H, m, CH_2), 1.65 (1H, s, OH), 3.80 (2H, q, OCH_2), 4.15 (2H, q, CH_2O), 5.35 (s, HC=CH, J=10.5), 6.60 (t, HC=N, anti), 7.35 (t, HC=N, syn)
3h	1695	975	1080 3500	-	4.70 (1H, d, CH), 5.65 (1H, t, CH), 6.40 (1H, br, CH), 2.05 (1H, s, OH), 3.85 (2H, q, OCH_2), 4.15 (2H, t, CH_2O), 6.60 (br, HC=N, anti), 7.35 (br, HC=N, syn)
4a	1660	-	1070 3500	1180[a]	2.38 (1H, s, OH), 3.65 (2H, t, CH_2O), 4.20 (2H, t, N-CH_2), 7.10 (1H, q, HC=N, anti), 7.50 (Ar)
4b	1680	-	1080 3450	1185[a]	1.85 (2H, m, CH_2), 2.52 (4H, d, CH_2), 3.25 (1H, s, OH), 3.60 (2H, t, CH_2O), 4.15 (2H, t, N-CH_2), 5.65 (s, HC=CH), 7.10 (q, HC=N, anti)
4c	1690	980	1040 3500	750[b]	0.91 (3H, d, CH_3), 1.25-2.30 (4H, m, CH_2), 3.30 (1H, s, OH), 3.62 (2H, t, CH_2O), 4.15 (2H, t, N-CH_2), 5.60 (d, HC=CH), 7.10 (q, HC=N, anti)

Table 2. Continued...

Compd	IR (ν_{max} / cm^{-1})				^1H NMR (δ_H / ppm)
	C=N	N-O	OH	Other	
9a	1690	940	1050 3450	780[b]	3.15 (1H, br, OH), 3.55 (2H, d, CH_2O), 4.20 (2H, t, OCH_2), 3.92 (1H, m, CH), 6.60 (d, HC=N, anti), 7.30 (t, HC=N, syn), 7.15-7.60 (Ar)
9b	1685	965	1050 3400	720[b]	1.20-2.55 (6H, m, CH_2), 3.20 (1H, br, OH), 3.85 (1H, m, CH), 3.55 (2H, d, CH_2), 5.65 (s, HC=CH), 6.55 (d, HC=N, anti), 7.25 (t, HC=N, syn)
9h	1690	980	1040 3500	730[b]	4.85 (1H, d, CH), 5.80 (1H, t, CH), 6.40 (1H, br, CH), 4.25 (2H, d, OCH_2), 3.95 (1H, m, CH), 3.65 (2H, d, CH_2), 3.15 (1H, br, OH), 6.62 (d, HC=N, anti), 7.35 (t, HC=N, syn)
10a	1695	985	1055 3450	740[b]	2.20 (1H, s, OH), 3.85 (2H, d, OCH_2), 3.10 (2H, d, CH_2O), 7.20-7.60 (Ar), 3.65 (1H, m, CH), 6.65 (d, HC=N, anti), 7.35 (t, HC=N, syn)
10b	1675	970	1040 3400	730[b]	1.6-2.35 (6H, m, CH_2), 2.15 (1H, s, OH), 3.14 (2H, t, CH_2O), 3.7-4.2 (2H, m, OCH_2), 5.6 (s, HC=CH, J=10.5), 3.60 (1H, m, CH), 6.15 (q, HC=N, anti), 7.40 (br, HC=N, syn)
10d	1685	955	-	850[c] 1250[c]	0.95 (3H, d, CH_3), 1.20-2.30 (4H, m, CH_2), 5.60 (d, HC=CH), 3.45 (2H, m, CH_2O), 4.15 (2H, d, OCH_2), 3.62 (1H, m, CH),2.25 (1H, s, OH), 6.62 (q, HC=N, anti), 7.25 (t, HC=N, syn)
11a	1675	990	-	855[c] 1260[c]	3.85 (2H, d, OCH_2), 2.90 (1H, m, H-epoxy), 2.65 (2H, d, CH_2-epoxy), 6.60 (d, HC=N, anti),
11b	1680	970	-	1250[c]	7.40 (t, HC=N, syn)3.90 (2H, d, OCH_2), 2.85 (1H, m, H-epoxy), 2.60 (2H, d, CH_2-epoxy), 6.65 (d, HC=N, anti), 7.40 (t, HC=N, syn)
11d	1670	927	3500	-	3.85 (2H, d, OCH_2), 2.95 (1H, m, H-epoxy), 2.65 (2H, d, CH_2-epoxy), 6.60 (d, HC=N, anti), 7.40 (t, HC=N, syn)
11h	1680	985	-	750[c] 1260[c]	3.80 (2H, d, OCH_2), 2.85 (1H, m, H-epoxy), 2.70 (2H, d, CH_2-epoxy), 6.60 (d, HC=N, anti), 7.40 (t, HC=N, syn)
16a	1667	975	3400	-	1.2 (6H, d, CH_3), 2.6 (4H, q, CH_2), 3.1 (2H, d, CH_2-N), 3.9 (1H, m, CH), 3.15 (1H, br, OH), 4.10 (2H, d, OCH_2), 6.65 (d, HC=N, anti), 7.35 (t, HC=N, syn)
16b	1685	990	3350	-	1.15 (6H, d, CH_3), 2.5 (4H, m, CH_2), 3.0 (2H, d, CH_2-N), 3.8 (1H, m, CH), 3.10 (1H, br, OH), 4.00 (2H, t, OCH_2), 6.60 (d, HC=N, anti), 7.25 (t, HC=N, syn)

Table 2. Continued...

Compd	IR (ν_{max} / cm^{-1})				^{1}H NMR (δ_H / ppm)
	C=N	N-O	OH	Other	
17a	1690	975	3450	-	2.7-3.0 (4H, m, CH_2), 3.4-3.7 (4H, m, CH_2), 3.2 (2H, d, CH_2-N), 3.9 (1H, m, CH), 3.25 (1H, br, OH), 4.15 (2H, d, OCH_2),6.50 (d, HC=N, anti), 7.25 (t, HC=N, syn)
17b	1665	980	-	-	2.6-3.0 (4H, m, CH_2), 3.3-3.6 (4H, m, CH_2), 3.0 (2H, d, CH_2-N), 3.7 (1H, m, CH), 3.15 (1H, br, OH), 3.85 (2H, d, OCH_2), 6.55 (d, HC=N, anti), 7.20 (t, HC=N, syn)
18a	1675	980	3350	-	1.3-1.7 (6H, m, CH_2), 2.5-2.9 (4H, m, CH_2), 2.9 (2H, d, CH_2-N), 3.85 (1H, m, CH), 3.15 (1H, br, OH), 3.95 (2H, d, OCH_2), 6.55 (d, HC=N, anti), 7.25 (t, HC=N, syn)
18b	1695	970	3300	-	1.4-1.7 (6H, m, CH_2), 2.4-2.8 (4H, m, CH_2), 3.1 (2H, d, CH_2-N), 3.9 (1H, m, CH), 3.2 (1H, br, OH), 3.90 (2H, d, OCH_2), 6.65 (d, HC=N, anti), 7.30 (t, HC=N, syn)
20a	1690	945	-	-	1.45 (3H, s, CH_3), 1.47 (3H, s, CH_3), 3.9 (2H, d, CH_2),4.2 (1H, m, CH), 3.80 (2H, d, OCH_2), 6.55 (d, HC=N, anti), 7.30 (t, HC=N, syn)
20b	1690	945	-	-	1.42 (3H, s, CH_3), 1.45 (3H, s, CH_3), 4.0 (2H, d, CH_2), 4.3 (1H, m, CH), 3.75 (2H, d, OCH_2), 6.60 (d, HC=N, anti), 7.35 (t, HC=N, syn)

a) C-N. b) C-halide. c) epoxy.

EXPERIMENTAL SECTION

Infrared spectra were recorded on a Pye Unicam SP1025 spectrometer. ^{1}H nmr spectra were recorded on a Varian T100-A spectrometer at 100 MHz. All spectra used tetramethylsilane as the internal standard, and were run in deuterated chloroform. Elemental analyses were obtained using a Carlo Erba 1106 automatic elemental analyses instrument. Melting points were recorded on an Electrothermal digital melting point apparatus, and are uncorrected. Thin layer chromatography was carried out on Merck 5735 Kieselgel 60 F_{254} fluorescent plates.

Synthesis of Oximes. General Procedure.- Hydroxylamine hydrochloride (0.5 mol) and Na_2CO_3 (0.5 mol) in 100 mL of benzene were stirred at 60° for 45 min. The aldehyde (0.5 mol) was then added dropwise and stirring was continued at 80° for 4-5 hrs, after which time organic phase was separated from salt by filtration and neutralized with 2M acetic acid. The separated organic phase was dried over $MgSO_4$ and solvent evaporated in *vacuo*. The residue was fractionally distilled under reduced pressure to give **1a-h**.

Alkylation of Oximes with 2-Chloro- and 2-Bromoethanol. General Procedure.- To a solution of sodium ethoxide prepared by dissolving sodium (5.75 g, 0.25 mol) in 75 mL of dry EtOH, the oxime (0.25 mol) was added at r.t. and the mixture was stirred at 30-40° for 20 min. Then the halohydrin **(2)** (0.25 mol) was added to the solution and stirred at the same temperature. The reaction mixture was allowed to stand overnight and the organic phase was separated from the salt. Half of the solvent was evaporated and water was added. The mixture was extracted first with diethyl ether (3x50 mL) and second with chloroform (3x50 mL). Ethereal phase was dried over Na_2SO_4, and the solvent was evaporated in *vacuo*. Fractional distillation of the residue under reduced pressure gave **3a-h**. Compounds **4a-c** were obtained from the chloroform extract following the same procedure.

Synthesis of 3a and 3c.- A mixture of benzaldoxime **(1a)** (0.1 mol) or D^3-tetrahydrobenzaldoxime **(1c)** and NaOH (5N, 12 mL) in acetone (45 mL) was stirred at 40-45° for 5 hrs. Ethylene oxide gas was passed through the solution, after increasing the temperature up to 60-65°. The solution was neutralized with 2M acetic acid, extracted with diethyl ether. The solvent was dried over Na_2SO_4, evaporated in vacuo and finally the residue was fractionally distilled to give **3a** and **3c** in aproximately 60% yields.

Alkylation of Oximes with Dihalohydrins. General Procedure.- A mixture of aldoxime (0.25 mol) and NaOH (5N, 28.5 mL) in acetone (65 mL) was stirred at 40-45° for an hour. After the mixture was heated to 60-65°, **6, 7** or **8** were added and stirred for 3 hrs. The solution was neutralized with 2M acetic acid, extracted with ether (3x50 mL) before the extraction with chloroform (3x50 mL) and the extracts were dried over $MgSO_4$. **9a,b,h** and **10a,b,d** were obtained from ethereal phase after evaporation of the solvent and subsequent fractionally distillation. None of the products was obtained from chloroform extracts.

Synthesis of 11a,b,d,h. General Procedure.- Compounds **9a,b,h** (0.25 mol) or **10a,b,d** (0.25 mol) and NaOH pellets (0.30 mol) in Et_2O (65 mL) were refluxed for 5 hrs. The organic phase was separated from the precipitated salt, washed with distilled water until the solution become neutral and dried over Na_2SO_4. After evaporation of the solvent in *vacuo*, the residue was fractionally distilled under reduced pressure to afford compounds **11a,b,d,h**.

Synthesis of 11a,b.- Compounds **1a** or **1b** (0.25 mol) and NaOH (5N, 28.5 mL) in acetone (75 mL) were stirred at 45° for 40 min. and **12** (0.25 mol) was added. The reaction mixture was heated up to 60-65° and stirred for 3 hrs, after which time the solution was neutralized with 2M acetic acid, extracted with diethyl ether and dried over Na_2SO_4. After evaporation of the solvent in *vacuo*, the residue was fractionally distilled under reduced pressure to afford **11a** in a 65% or **11b** in a 70% yield.

Synthesis of 16a,b , 17a,b and 18a,b. General Procedure.- Compounds **11a** or **11b** (0.18 mol), the amine (0.25 mol) and 5-6 drops of distilled water were heated at 75-80° with stirring for 6-7 hrs. After evaporation of excess amine, **16a,b** was fractionally distilled under reduced pressure, while **17a,b** and **18a,b** was obtained as the HCl salts.

Synthesis of 16a.- A mixture of **1a** (0.05 mol) and NaOH (5N, 20 mL) in acetone (25 mL) were stirred at 40° for 40 min. After the reaction mixture was heated to 65° with stirring, **19** (0.05 mol) was

introduced and stirring was continued for 5 hrs. The solution was neutralized with 2M acetic acid, extracted with Et_2O and the organic phase was dried over Na_2SO_4. Evaporation of the solvent which was followed by fractional distillation, gave **16a** in a 65% yield.

Synthesis of 20a,b.- To a solution of **11a** or **11b** (0.025 mol) in acetone, 4-5 drops of $BF_3 \cdot Et_2O$ was added at 0°. The reaction mixture was allowed to warm to room temperature and stirred for 7-8 hrs. After evaporation of excess acetone, the residue was fractionally distilled to afford compounds **20a** or **20b**.

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