The Claisen rearrangement in the aminophenol series

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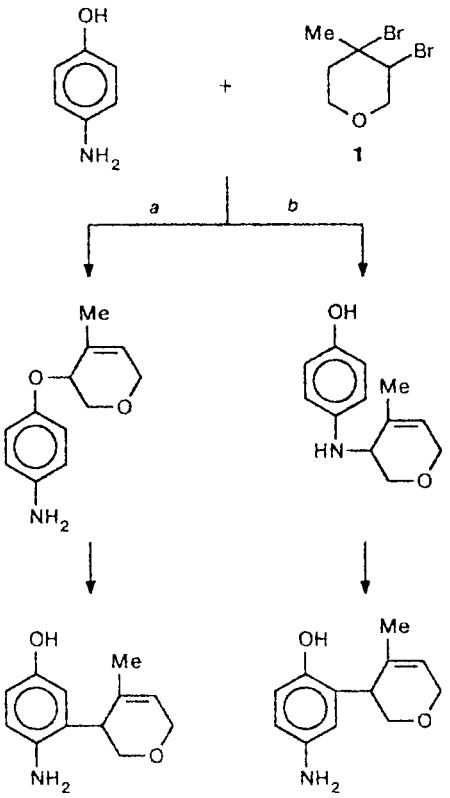
Novel compounds, dihydropyranylaminophenols, were synthesized by condensation of 3,4-dibromo-4-methyltetrahydropyran with aminophenols followed by the Claisen rearrangement of *O*- and *N*-substituted products.

Key words: Claisen rearrangement, condensation, aminophenols, *N*-dihydropyranylaminophenols, isomerization, dihydropyranyloxyanilines.

The Claisen reaction is one of the convenient methods for the synthesis of derivatives of amines and phenols. The classic variant of this reaction is a thermal rearrangement of allyl aryl ethers into allylic phenols.[1] The number of works that study the Claisen isomerization of aromatic compounds with a migrating heterocyclic radical is limited. These works deal with either the phenol[2] or amine series[3,4] and do not describe this reaction for aminophenols. However, the condensation of aminophenols with 3,4-dibromo-4-methyltetrahydropyran (**1**) followed by isomerization of the reaction products is of interest because the presence of two reaction centers (the OH and NH_2 groups) allows the reaction to follow two pathways, thus predetermining the mechanism of the consequent Claisen rearrangement and the chemical structure of resulting compounds (Scheme 1).

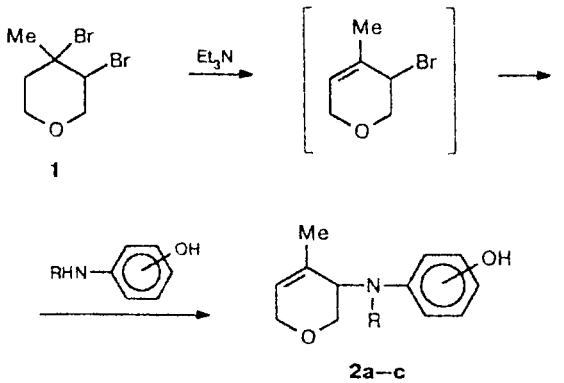
Scheme 1



The reaction of dihydropyrans involving the hydroxy group of aminophenols (provided that the amino group is protected) with subsequent migration of the radical to the aromatic ring has been carried out for both low- and high-molecular phenols,[5,6] and the Claisen amino-rearrangement has been studied for low-molecular aminopyrans.[7] In the present work, we attempted to carry out condensation of aminophenols with 3,4-dibromo-4-methyltetrahydropyran (**1**) on both the NH_2 and OH group (pathways *a* or *b*) with subsequent Claisen rearrangement of the reaction products.

The reaction of aminophenols with dibromide **1** on the amino group (pathway *a*) was carried out in triethylamine as the solvent.

Scheme 2



2a–c

a: 2-OH, R = H; **b:** 4-OH, R = H; **c:** 4-OH, R = Ph

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The reaction follows Scheme 2 and proceeds through an intermediate product, probably, 5-bromo-4-methyl-5,6-dihydro-2*H*-pyran formed upon elimination of HBr. Subsequent nucleophilic substitution of the mobile allylic bromine atom yields compounds **2a—c**, products of the reaction of aminophenols on the amino group (Table 1).

The structures of compounds **2a—c** obtained were proved by combination of spectroscopic methods and elemental analysis. The IR spectra of **2a,b** exhibit an absorption band at 3396—3364 cm^{-1} characteristic of the N—H stretching vibrations; while tertiary amine **2c** does not absorb in this range.

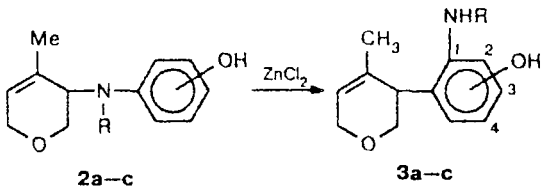
Unlike dihydropyran ethers, which characteristically rearrange with heating (170 °C) in a strong base into dihydropyranylphenols,[8] compounds **2a—c** are isomerized only in the presence of catalytic amounts of Lewis acids, in particular $ZnCl_2$, at 120 °C to give isomerization products in 81—85% yield (Scheme 3).

The pyranyl radical migrates exclusively to the vacant *ortho*-position with respect to the amino group to give *o*-pyranylaminophenols **3a—c**. The IR spectra of compounds **3a,b** exhibit two absorption bands of a primary amino group (ν_{as}(N—H) 3480—3470 cm^{-1} and ν_s(N—H) 3400—3390 cm^{-1}), and the IR spectrum of

Table 1. The physicochemical characteristics and data from elemental analysis of the compounds synthesized

Compound	Yield (%)	B.p./°C (*p*/Torr) [M.p./°C]	Found / Calculated (%) C	H	N	Molecular formula	n_D^{20}	^{1}H NMR (δ)
2a	86	141(3)	70.58 / 70.24	7.54 / 7.32	7.13 / 6.82	$C_{12}H_{15}NO_2$	1.4565	1.86 (s, 3 H, CH_3), 3.60—4.44 (m, 7 H, CH_2OCH_2, CH, OH, NH), 5.62 (m, 1 H, CH=C), 6.51—7.00 (m, 4 H, Ph)
2b	83	139(5)	70.69 / 70.24	7.49 / 7.32	6.99 / 6.82	$C_{12}H_{15}NO_2$	1.4403	1.57 (s, 3 H, CH_3), 3.51—4.40 (m, 7 H, CH_2OCH_2, CH, OH, NH), 5.60 (m, 1 H, CH=C), 6.50—7.01 (m, 4 H, Ph)
2c	81	149(6)	77.01 / 76.86	6.95 / 6.81	5.13 / 4.98	$C_{18}H_{19}NO_2$	1.4678	1.58 (s, 3 H, CH_3), 3.50—4.40 (m, 6 H, CH_2OCH_2, CH, OH), 5.45 (m, 1 H, CH=C), 7.33 (m, 3 H, Ph)
3a	85	145(4)	70.03 / 70.24	7.46 / 7.32	7.04 / 6.82	$C_{12}H_{15}NO_2$	1.4681	1.63 (s, 3 H, CH_3), 3.62—4.34 (m, 7 H, CH_2OCH_2, CH, OH, NH_2), 5.74 (m, 1 H, CH=C), 7.33 (m, 3 H, Ph)
3b	81	140(3)	70.62 / 70.24	7.21 / 7.32	7.13 / 6.82	$C_{12}H_{15}NO_2$	1.4520	1.51 (s, 3 H, CH_3), 3.51—4.40 (m, 8 H, CH_2OCH_2, CH, OH, NH_2), 5.12 (s, 1 H, CH=C), 6.50—7.01 (m, 3 H, Ph)
3c	84	153(5)	77.15 / 76.86	6.89 / 6.81	5.20 / 4.98	$C_{18}H_{19}NO_2$	1.4754	1.57 (s, 3 H, CH_3), 3.61—4.30 (m, 7 H, CH_2OCH_2, CH, OH, NH), 5.53 (m, 1 H, CH=C), 6.51—7.11 (m, 8 H, Ph)
4a	43	[91—93]	70.39 / 70.24	7.48 / 7.32	7.16 / 6.82	$C_{12}H_{15}NO_2$	—	1.89 (s, 3 H, CH_3), 3.65—4.52 (m, 5 H, CH_2OCH_2, O—CH—C), 5.77 (s, C, H, CH=C), 6.54—7.06 (m, 4 H, Ph)
4b	48	[120—122]	70.40 / 70.24	7.45 / 7.32	6.66 / 6.82	$C_{12}H_{15}NO_2$	—	1.87 (s, 3 H, CH_3), 3.34 (s, 2 H, NH_2), 3.90 (m, 5 H, CH_2OCH_2, O—CH—C), 5.72 (s, H, CH=C), 6.71—6.83 (m, 4 H, Ph)
4c	59	[100—102]	77.05 / 76.86	6.70 / 6.81	5.17 / 4.98	$C_{18}H_{19}NO_2$	—	1.91 (s, 3 H, CH_3), 3.75—4.48 (m, 6 H, CH_2OCH_2, O—CH—C, NH), 5.79 (s, H, CH=C), 6.88—7.30 (m, Ph)
5a	89	142(6)	70.43 / 70.24	7.15 / 7.32	7.03 / 6.82	$C_{12}H_{15}NO_2$	1.4699	1.51 (s, 3 H, CH_3), 2.25 (s, H, O—CH—C), 3.51—4.41 (m, 5 H, CH_2OCH_2, NH), 5.22 (s, H, CH=C), 6.51—6.54 (m, 3 H, Ph), 8.81 (s, H, OH)
5b	87	138(5)	70.50 / 70.24	7.49 / 7.32	6.61 / 6.82	$C_{12}H_{15}NO_2$	1.4505	1.80 (s, 3 H, CH_3), 2.83 (s, H, O—CH—C), 3.18 (s, 2 H, NH_2), 3.72—4.35 (m, 4 H, CH_2OCH_2), 5.60 (s, H, CH=C), 6.50—6.66 (m, 3 H, Ph), 7.29 (s, H, OH)
5c	84	155(7)	77.02 / 76.86	6.88 / 6.81	5.11 / 4.98	$C_{18}H_{19}NO_2$	1.4800	1.63 (s, 3 H, CH_3), 4.25—4.42 (m, 4 H, CH_2OCH_2), 5.16 (s, H, OH), 5.64 (s, H, CH=C), 6.33—7.40 (m, 8 H, Ph)

Scheme 3

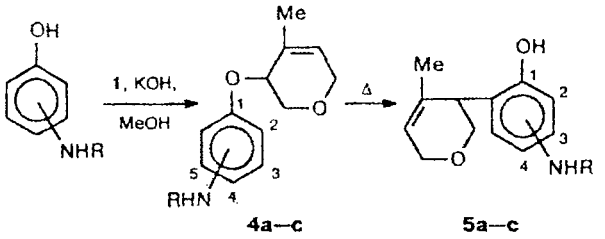


2a—c **3a—c**

a: 2-OH, R = H; **b**: 4-OH, R = H; **c**: 4-OH, R = Ph

compound **3c** exhibits a band characteristic of secondary amine.

Pathway *b* (Scheme 1), *i.e.*, condensation of dibromide **1** with aminophenol on the OH group, occurs in the presence of strong bases (KOH in MeOH)



4a—c **5a—c**

a: 2-NHR, R = H; **b**: 4-NHR, R = H; **c**: 4-NHR, R = Ph

Note that if aminophenols are condensed with dibromide **1** in the presence of Et_3N as a base to give mostly an *N*-substituted product (Scheme 2), the reaction in the presence of KOH yields both *O*-ethers and *N*-substituted compounds in the ratio 2 : 1. The isomeric products were separated by column chromatography.

Thus, we studied the condensation of 3,4-dibromo-4-methyltetrahydropyran (**1**) with aminophenols followed by Claisen rearrangement of *O*- and *N*-substituted products and determined the conditions under which either the hydroxy or amino group is mainly involved in the process. The condensation of dibromide **1** with aminophenols on the NH_2 group yields [*N*-(4-methyl-5,6-dihydro-2*H*-pyran-5-yl)amino]phenols (**2a—c**), while that involving the OH group gives, along with (4-methyl-5,6-dihydro-3*H*-pyran-5-yloxy)anilines **4a—c**, *N*-substituted compounds **2a—c**. Taking into account that the allylic fragment of the *O*- and *N*-substituted compounds of the dihydropyran series, involved in the Claisen rearrangement, is allyl-symmetrical, the structure of this fragment is retained in rearrangement products **3a—c** and **5a—c**.

Experimental

IR spectra were recorded on a Specord MK-80 spectrometer. ^1H NMR spectra were recorded on a Bruker AM-350 (100 MHz) spectrometer with HMDS as the internal standard (in all cases, solutions in CCl_4 were used).

The yields and physical and spectral properties of all compounds obtained are given in Table 1.

Synthesis of [*N*-(4-methyl-5,6-dihydro-2*H*-pyran-5-yl)-amino]phenols 2a—c (general procedure). Dibromide **1** (0.025 mol), aminophenol (0.025 mol), and Et_3N (10.5 mL) were placed in a flask equipped with a reflux condenser capped with a calcium chloride tube, a thermometer, and a stirrer. The reaction mixture was vigorously stirred at 90 °C for 18 h and then cooled. The precipitate of $Et_3N \cdot HBr$ that formed was filtered off, the filtrate was diluted with 50 mL of water, and the product was extracted with ether. The extract was dried with $MgSO_4$, and the solvent was removed. The product was purified by column chromatography (silica gel L 60/100 μm, benzene—propan-2-ol (4 : 1) as the eluent), R_f 0.54 (**2a**); 0.38 (**2b**); 0.50 (**2c**).

Synthesis of (4-methyl-5,6-dihydro-2*H*-pyran-5-yl)aminophenols (3a—c). Anhydrous zinc chloride ($5 \cdot 10^{-4}$ mol) in 16.5 mL of nitrobenzene was added to [*N*-(4-methyl-5,6-dihydro-2*H*-pyran-5-yl)amino]phenol (**2a—c**) ($5 \cdot 10^{-3}$ mol) in 1 mL of dioxane. The reaction mixture was stirred at 120 °C for 28 h and then cooled. $ZnCl_2$ was filtered off, and the solvents were removed. The products were purified by column chromatography (toluene—propan-2-ol (4 : 1) as the eluent), R_f 0.48 (**3a**); 0.30 (**3b**); 0.28 (**3c**).

Synthesis of (4-methyl-5,6-dihydro-2*H*-pyran-5-yloxy)anilines (4a—c). Dibromide **1** (0.03 mol) and aminophenol (0.03 mol) dissolved in 13.4 mL (0.15 mol) of ethyl methyl ketone were placed in a flask equipped with a stirrer, a reflux condenser, and a dropping funnel. A solution of KOH (0.09 mol) in 10 mL of MeOH was added dropwise with vigorous stirring. The reaction mixture was refluxed for 1.0—1.5 h. The precipitate that formed was filtered off, the solvent was removed, and the products were purified by column chromatography (hexane—acetone (4 : 1) as the eluent), R_f 0.33 (**4a**); 0.57 (**4b**); 0.59 (**4c**).

Synthesis of 2-(4-methyl-5,6-dihydro-2*H*-pyran-5-yl)-aminophenols (5a—c). Compounds **4a—c** (0.012 mol) and *N*,*N*-diethylaniline (0.06 mol) were placed in a flask equipped with a reflux condenser. The reaction mixture was thermostatically controlled at 170 °C for 5 h (to complete conversion of the initial *O*-ether). The solvent was removed, and the products were isolated from the residue by column chromatography (hexane—acetone (4 : 1) as the eluent), R_f 0.32 (**5a**); 0.28 (**5b**); 0.14 (**5c**).

References

1. *Organic Reactions*, Ed. R. Adams, New York, 1994, vol. 2, 531 pp.
2. R. Z. Biglova, V. P. Malinskaya, G. E. Zaikov, and K. S. Minsker, *Polymer Degradation and Stability*, 1996, **51**, 251.
3. I. Makisumi, *Tetrahedron Lett.*, 1996, 6413.
4. I. B. Abdrakhmanov, G. B. Shabaeva, E. V. Tal'vinskii, L. A. Biktimirova, A. A. Fatykhov, and G. A. Tolstikov, *Zh. Org. Khim.*, 1985, **21**, 829 [*J. Org. Chem.*, 1985, **21** (Engl. Transl.)].
5. U. G. Ibatullin, Kh. F. Sagitdinova, G. R. Talipova, and M. G. Safarov, *Khim. Geterotsikl. Soedin.*, 1985, 315 [*Chem. Heterocycl. Compd.*, 1985 (Engl. Transl.)]
6. R. Z. Biglova, V. P. Malinskaya, Kh. F. Sagitdinova, and K. S. Minsker, *Vysokomol. Soedin., Ser. A*, 1995, **37**, 1474 [*Polym. Sci.*, 1995, **37A** (Engl. Transl.)]
7. I. B. Abdrakhmanov, A. G. Mustafin, G. A. Tolstikov, L. V. Spirikhin, and L. M. Khalilov, *Izv. Akad. Nauk, Ser. Khim.*, 1987, 613 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, (Engl. Transl.)]
8. R. Z. Biglova, V. P. Malinskaya, G. E. Zaikov, and K. S. Minsker, *Mendeleev Commun.*, 1993, 234.

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