INVESTIGATION OF REACTIONS INVOLVING DESTABILIZED GLYCOSYLIUM ION INTERMEDIATES

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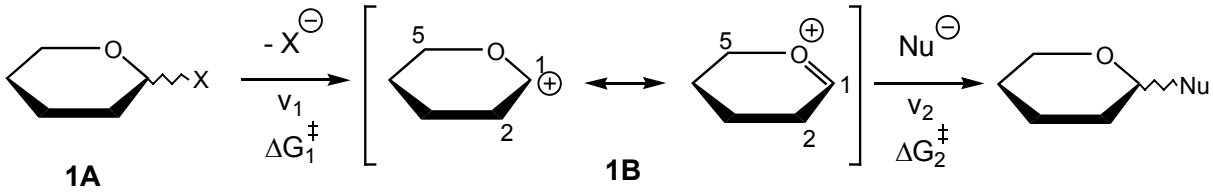
1. Background and Aims of the Dissertation

Nucleophilic substitutions are one of the most important reactions occurring at the anomeric center of carbohydrate derivatives. In the transition state of unimolecular substitutions, the anomeric center has a positive charge and the intermediate is called glycosyl carbenium ion (**1B**, Scheme 1).



X: leaving group

Scheme 1.

Nucleophilic substitutions, employing various nucleophiles, can provide easy routes for the synthesis of *O*-, *N*-, *S*- and *C*-glycosyl derivatives. Glycosyl donors can be of different reactivity depending on the leaving ability of the X-group ($\Delta G_1^{\ddagger}$), but in case of a given nucleophile (Nu) it is probably reasonable to consider the rate of the second step (v_2) to be independent of any factors except the energy-level of the intermediate glycosyl carbenium ion. The energy-level of this intermediate is influenced mainly by the electron withdrawing or donating character of the substituents close to the anomeric center (i.e. at C-1, C-2 and C-5). A special case of this influence include the type and number of *O*-protecting groups of the saccharide (cf. “armed” and “disarmed” glycosyl donorsQUOTE).

Our goal was to shadow the influence of the C-1 substituents on the reactivity of C-1 substituted glycosyl donors and on the outcome of their reactions. Each of the investigated substituents (CN, $CONH_2$, COOMe) are *Z*-type (electron withdrawing). We also wanted to know, whether the difference in reactivity was accompanied by different reaction pathways in order to show a uniform picture of the influence of this kind of substituents at the anomeric center.

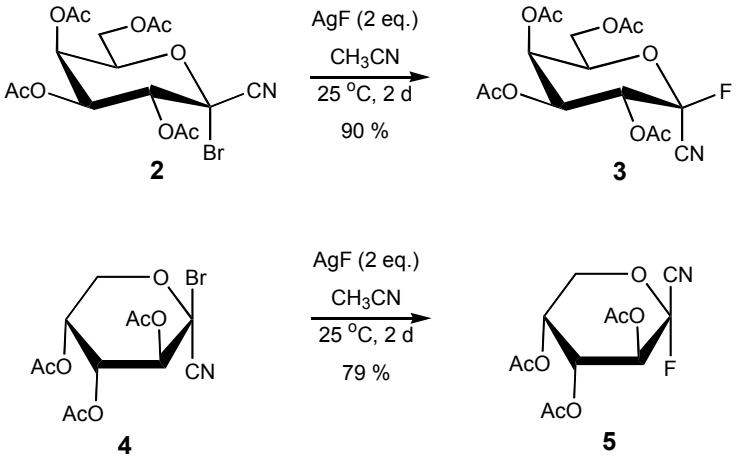
2. Applied Methods

During our research we have applied the macro-, semimicro- and micro methods of the modern preparative organic chemistry. Reactions were monitored by thin-layer chromatography. The isolation and purification of the products were carried out by crystallization or by column chromatography. Products were identified by classical (elemental analysis, melting point and optical rotation measurement) and modern analytical methods (^{1}H-,^{13}C NMR).

3. Results

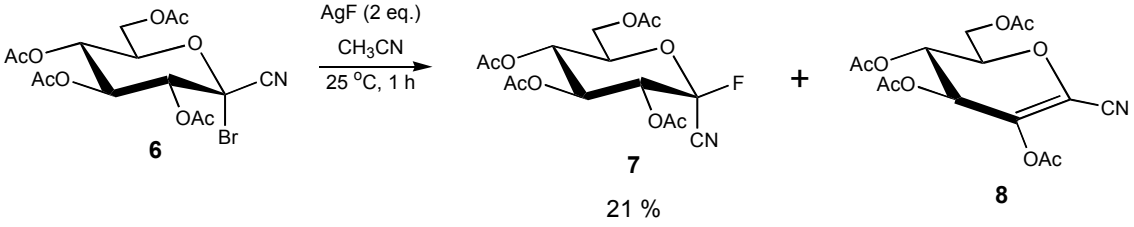
3.1. Synthesis of C-1 Substituted Glycosyl Fluoride Derivatives

Contrary to the behavior of the unsubstituted glycosyl halides known from the literature, the reaction of per-*O*-acetyl-1-cyanoglycopyranosyl halides (**2**, **4**, **6**, **9** and **12**) with silver fluoride in acetonitrile (Helferich conditions), irrespective of the anomeric configuration of the starting glycosyl halide, furnished inversion product in each case (Scheme 2, 3 and 4). We explained this difference by the change in the strength of the C-1–halogen bond and the stability of the glycosyl carbenium ion that necessitates a push-pull pathway and excludes the intermediacy of a glycosylium ion.



2 **3** **4** **5**

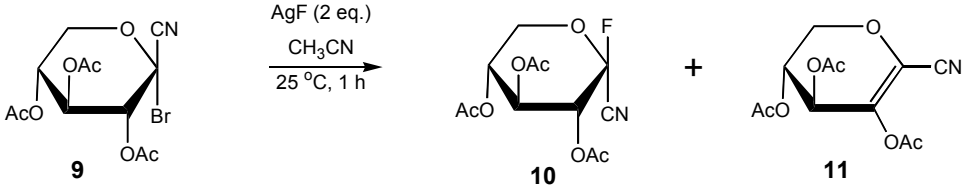
Scheme 2.



6 **7** **8**

21 %

Ratio of products from ^{1}H NMR of the crude product: 1 : 1



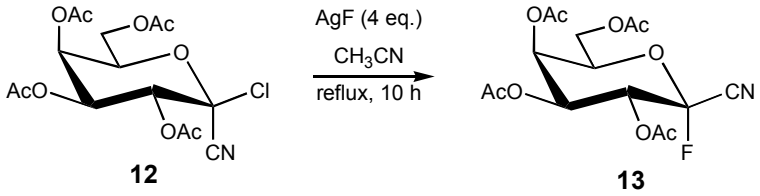
9 **10** **11**

11 %

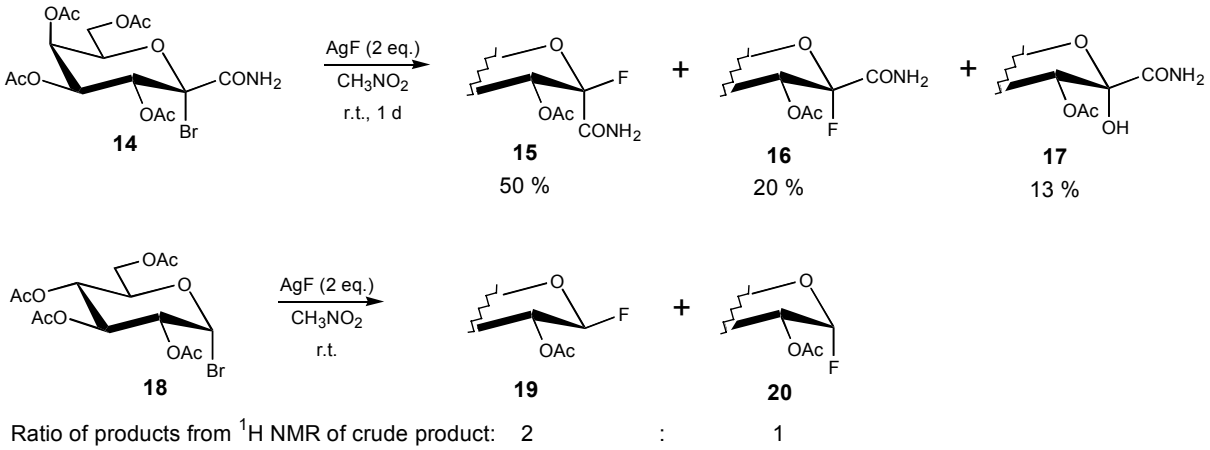
Ratio of products from ^{1}H NMR of the crude product: 3 : 1

Scheme 3.

In case of D-*gluco* and D-*xylo* configuration the 2-acetoxy D-glycal derivatives **8** and **11** appeared as side products (Scheme 3). The absence of side products and longer reaction time observed with the other two sugars (Scheme 2) are explained by the steric influence of the *axial* 4-*O*-acetoxy group.



Scheme 4.



Scheme 5.
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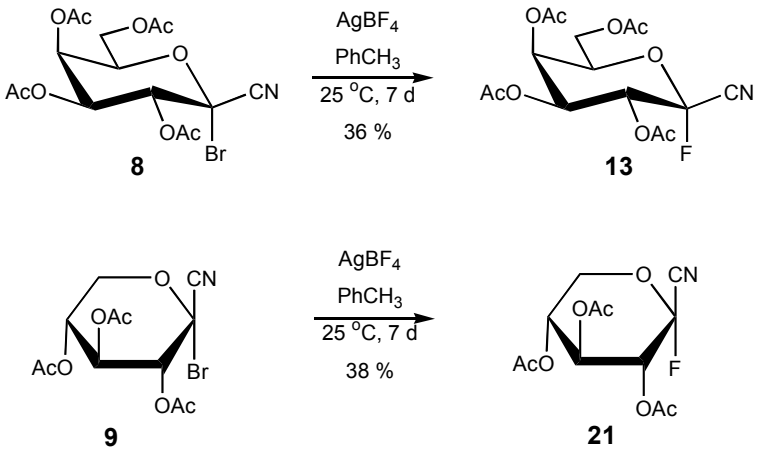
The presence of the less strongly electron withdrawing carbamoyl group (–$CONH_2$), however, did not alter the fluoro-substitution reaction. Thus, despite the fact that the reaction had to be carried out in a solvent other than acetonitrile, it proceeded similarly to that of the unsubstituted analogs and gave a mixture of the two anomeric fluorides (Scheme 5).

In the D-*gluco* and D-*xylo* configuration, we have attempted and successfully accomplished the preparation of the thermodynamically more stable glycosyl fluoride derivatives directly from the more easily available glycosyl bromide derivatives (Scheme 6). We used the method published by Irishawa et al.QUOTE The method employs silver tetrafluoroborate which is believed to anomerize the glycosyl fluorides.QUOTE



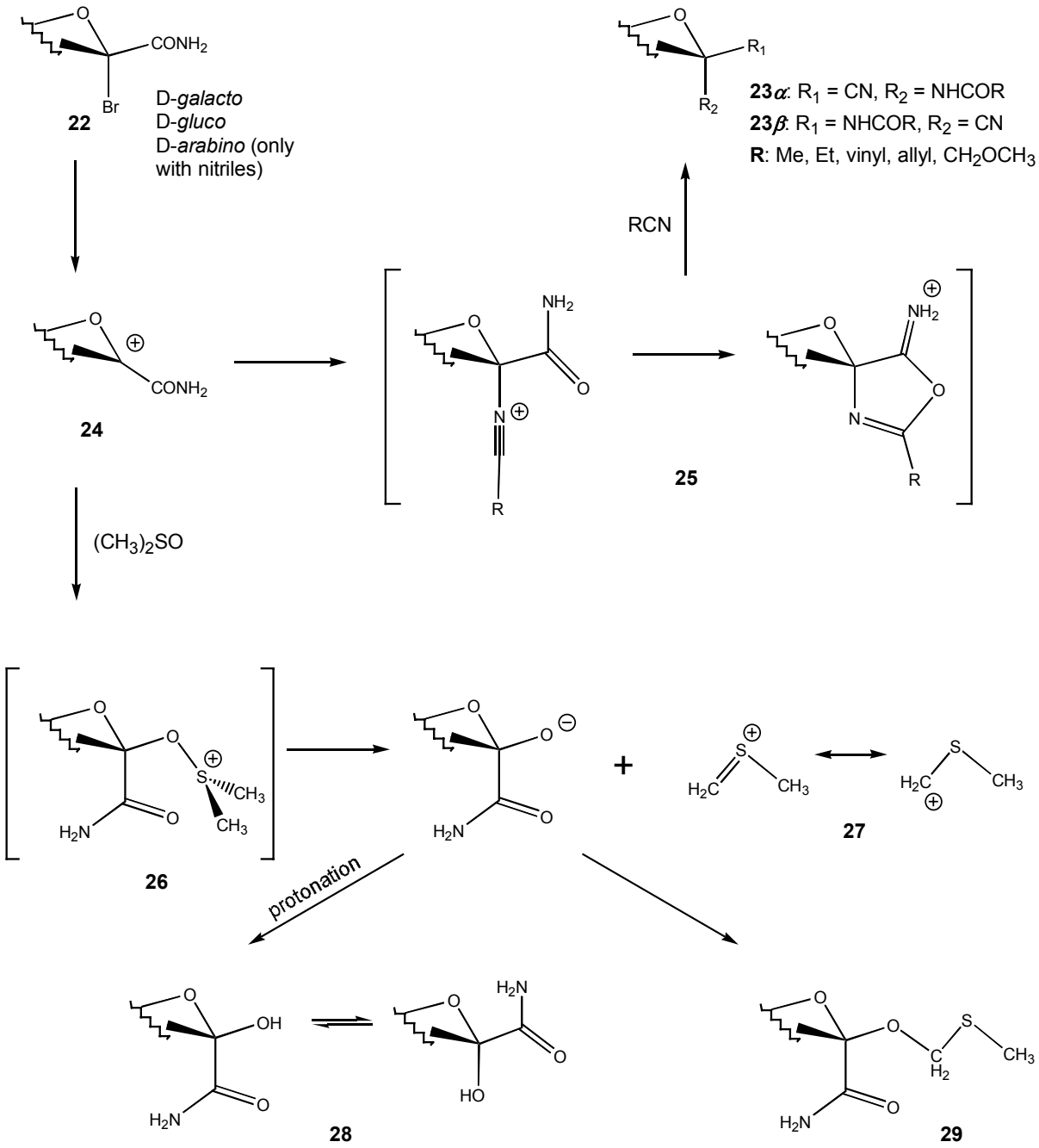
Scheme 6.

3.2. Solvent Incorporation Reactions

The glycosylium ion (**24**, Scheme 7), which is formed from the carbamoyl-substituted glycosyl bromides (**22**), was found to react with various types of nucleophilic solvents. The reaction with nitriles furnishes *N*-acyl-1-cyano-α-D-glycopyranosylamines (see Table 1).

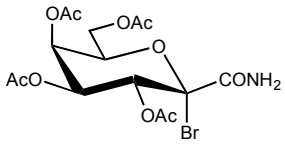
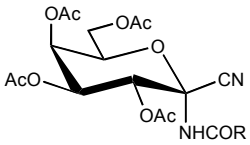
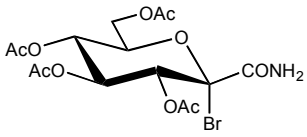
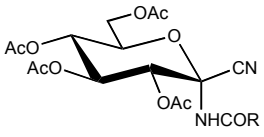
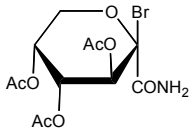
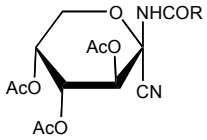
The stereoselectivity of the former reaction, in the presence of a silver-salt promoter, is probably controlled by the fast kinetic formation and intramolecular dehydration of α-glycosyl-nitrilium ions (**25**).QUOTEQUOTE This reaction may form a basis for an effective and stereoselective synthesis leading to novel derivatives of anomeric α-aminoacids. We have systematically examined the reaction by applying different promoters, changing the structure and the excess of the nitrile and variation of temperature in order to determine its scope and limitations. It was found that in the presence of $HgBr_2$ the reaction could be carried out using 5-10 equiv. nitrile without considerable amount of side-products (a selection of experiments is seen in Table 2). The stereoselectivity of the reaction is, however, changed in these conditions and the other anomeric amide (**23**β) becomes the major product.

The carbamoyl group does not participate in the reaction with dimethyl sulfoxide; the sulfur-centered cation (**26**) formed in the first step is stabilized by the well-known Pummerer-type rearrangement. The main products of these reactions are the 1-OH derivatives (**28**), the methylthiomethyl-glycosides (**29**) are isolated in 11 and 15 % yield in D-*gluco* and D-*galacto* configuration, respectively. The reaction is stereoselective since only β-glycosides are formed.


CONH2
Br
22
D-galacto
D-gluco
D-arabino (only with nitriles)
24
(CH3)2SO
RCN
23α: R1 = CN, R2 = NHCOR
23β: R1 = NHCOR, R2 = CN
R: Me, Et, vinyl, allyl, CH2OCH3
25
26
27
protonation
28
29

Scheme 7.

Table 1.

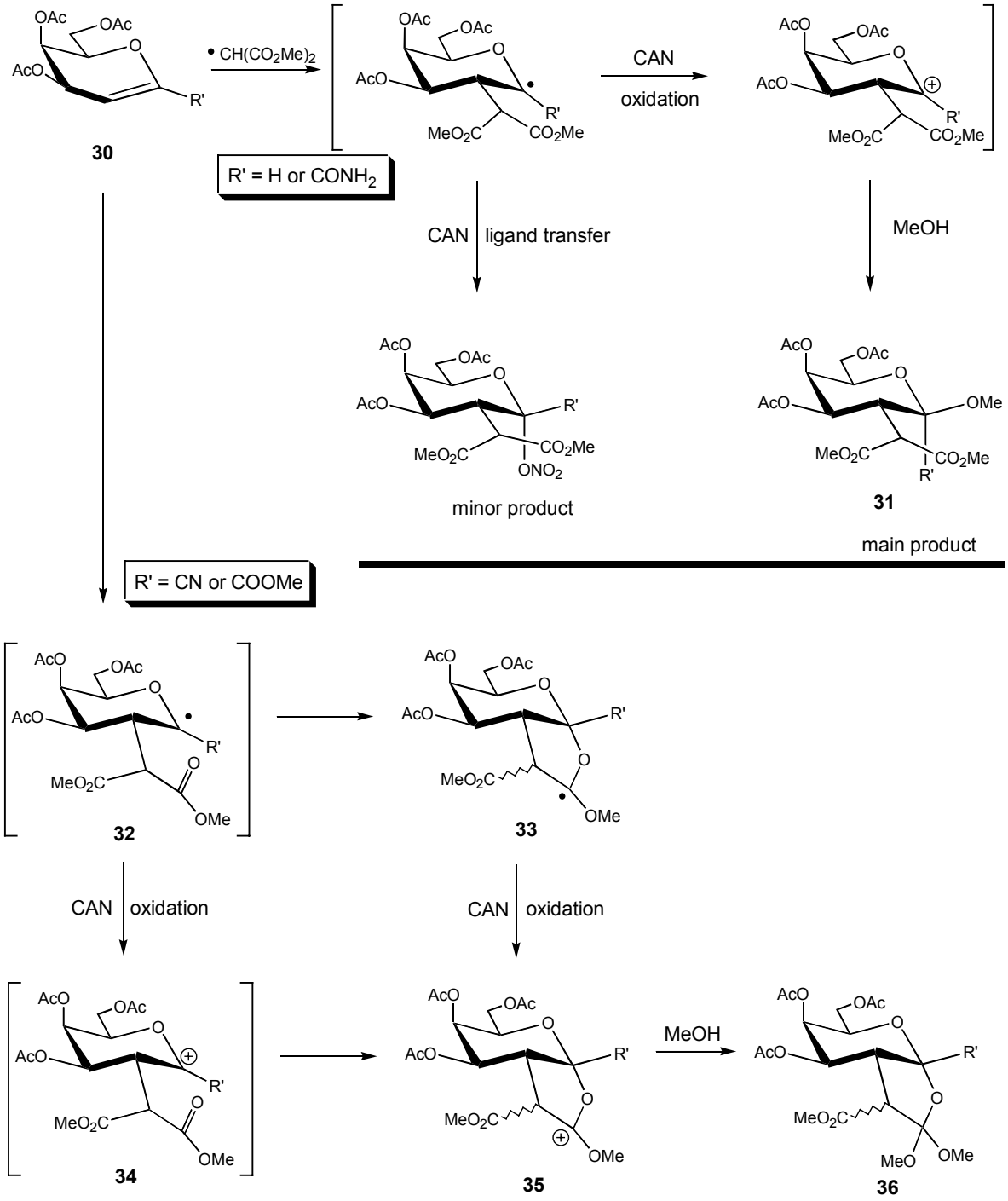
Starting Sugar	AgX	*R*-CN	Yield (%)	Product
	Ag_2CO_3	CH_3	76	
	AgF	CH_3	70[a]	
	Ag_2CO_3	CH_3CH_2	74	
	Ag_2CO_3	CH_2=CH	57	
	Ag_2CO_3	CH_2=CH-CH_2	62	
	Ag_2CO_3	CH_3OCH_2	24	
	AgF	CH_3	36	
	Ag_2CO_3	CH_3CH_2	53	
	Ag_2CO_3	CH_3	41	
	Ag_2CO_3	CH_2=CH	43	

[a] Side-product: *C*-(2,3,4,6-tetra-*O*-acetyl-1-fluoro-α-D-galactopyranosyl)formamide (~3 %)

EMBED**Table 2.**

Exp. No.	solvent	promoter	CH_3CN (eq.)	Temp. (°C)	α:β ratio (^{1}H NMR)
1	CH_3CN	$HgBr_2$	as solvent	25	67:33
2	CH_3NO_2	$HgBr_2$	10	25	36:64
3	CH_3NO_2	$HgBr_2$	5	25	35:65
4	CH_3NO_2	$HgBr_2$	1.5	25	–[a]
5	CH_3NO_2	$HgBr_2$/$Hg(CN)_2$	5	25	89:11
6	CH_3NO_2	$Hg(CN)_2$	5	25	90:10
7	CH_3NO_2	$HgBr_2$/$ZnBr_2$	5	25	19:81
8	CH_3NO_2	$HgCl_2$	5	25	–[b]
9	CH_3CN	$HgBr_2$	as solvent	-30	57:43
10	CH_3NO_2	$HgBr_2$	5	50	83:17

[a] Several by products [b] Main product: 1-Cl derivative



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Scheme 8.

3.3. Addition of Oxidatively Generated Malonyl Radical to Glycals

The last investigated reaction seems to be extraneous to the reactions examined so far. This reaction is published by Linker et al. who describe a method for the generation of malonyl radicals by an oxidative pathway and the addition of these free radicals to D-glycals (Scheme 4, R' = H).QUOTEQUOTE The reaction is carried out in methanol the oxidizing

agent being CAN. The main product is the methyl glycoside (**31**) substituted with a malonyl side-chain at the C-2 position.

We have accomplished the reaction with three different C-1 substituted D-galactals (**30**, R'= CN, $CONH_2$, COOMe), but our products were similar only in one case (R' = $CONH_2$). In the other two cases (R' = CN, COOMe), orthoesters (**36**) are obtained as the major products of the reaction. This anomalous behavior was explained by the stronger electron withdrawing character of these latter groups as compared to the carbamoyl group. The oxidation of the stabile capto-dative free radical (**32**, R' = CN, COOMe) yielding the destabilized glycosylium ion (**34**) is probably much slower than in case of the unsubstituted or the carbamoyl-substituted derivatives because of the increased free-energy difference between the radical (**32**) and the carbocation (**34**) mentioned above.

The longer half-life and perhaps the more appropriate energy-level of the SOMO of this radical may favor free-radical cyclization (**32** → **33**, R' = CN, COOMe). Another possibility that the unusually low energy-level of the LUMO of the glycosylium ion facilitates the intramolecular carbonyl addition (**34** → **35**).

3.4. Classification of the Investigated Substituents

It can be concluded from the outcome of the reactions dealt with in this dissertation that the electron withdrawing character of the substituent at C-1 can considerably influence nucleophilic substitutions and other reactions supposing the intermediacy of glycosylium ions.

The three investigated substituents can be classified according to their behavior in these reactions as follows. The carbamoyl group is placed in the first class. It has no or little influence on the reactions because of its electron withdrawing character; on the other hand, it can specifically change the way of certain reactions due to its nucleophilic oxygen. These latter reactions are very weakly investigated up to now. The other class contains the cyano group and the ester group. These substituents, because of their strongly electron withdrawing character, cause substantial differences in the chemical behavior which is seen in (a) the decreased reactivity and (b) manifestation of other reaction mechanisms.

4. Potential Utilization of the New Observations

The experimental observations presented in this dissertation can help one to understand the differences in reactivity between the unsubstituted anomeric center and the one bearing an electron-withdrawing substituent. In this way experiments can be schemed more successfully and the anomalous behavior can be explained more easily during the research of the chemistry of these and similar molecules.

The new carbohydrate derivatives can be tested as potential glycosidase inhibitors in order to obtain useful tools for the study of these enzymes or the therapy of certain diseases connected to their activity.

5. Közlemények, előadások (Publications)

Közlemények (Papers)

1) **Viktor Gyóllai**, László Somsák, Zoltán Györgydeák
Preparation of Acetylated 1-Fluoroglycopyranosyl Cyanides
Tetrahedron **1998** (54) 13267-13276

2) **Viktor Gyóllai**, László Somsák, László Szilágyi
N-(1-Cyano-D-glycosyl)amides – Novel Anomeric α-Amino-acid Derivatives
Tetrahedron Lett. **1999** (40) 3969-3972

3) László Somsák, László Kovács, **Viktor Gyóllai**, Erzsébet Ősz
Novel glycosylidene-spiro-heterocycles from unprecedented solvent incorporation in Koenigs-Knorr-like reactions of C-(1-bromo-1-deoxy-β-D-glycopyranosyl) formamides
Chem.Commun. **1999**, 591-592

4) **Viktor Gyóllai**, Dirk Schanzenbach, László Somsák and Torsten Linker
Addition of Malonyl Radicals to Glycals with C-1 Acceptor Groups: Remarkable Influence of the Substituents on the Product Distribution.
Chem.Commun. **2002**, 1294-1295

Előadások, poszterek (Oral and poster presentations)

5) László Somsák, **Viktor Gyóllai**, Zoltán Györgydeák
1-Fluoroglycopyranosyl Cyanides as Potential Glycosidase Inhibitors
Annual Meeting of the Carbohydrate Committee, Hungarian Academy of Sciences, Mátrafüred, Hungary, 1997

6) **Viktor Gyóllai**, László Kovács, László Somsák
Unprecedented solvent participation in Koenigs-Knorr-like reactions
Annual Meeting of the Carbohydrate Committee, Hungarian Academy of Sciences, Mátrafüred, Hungary, 1998

7) **Viktor Gyóllai**, László Somsák
Novel Anomeric α-Amino Acid Derivatives
12th Int. Conf. Org. Synth., Venezia, Italy, 1998, OC-04

8) László Somsák, **Viktor Gyóllai**, Zoltán Györgydeák
1-Fluoro-glycopyranosyl Cyanides as Potential Glycosidase Inhibitors
12th Int. Conf. Org. Synth., Venezia, Italy, 1998, P A-110

9) László Somsák, Erzsébet Ősz, László Kovács, **Viktor Gyóllai**, Marietta Tóth, László Szilágyi
Glycosylidene Spiro-heterocycles: New Glycomimetics (in Hungarian)
Annual Meeting of the Committee on Heterocyclic Chemistry, Hungarian Academy of Sciences, Balatonszemes, Hungary, 1999

10) László Kovács, **Viktor Gyóllai**, László Somsák
Syntheses of Glycopyranosylidene Spiro-dioxolanes and anomeric *α*-amino acid derivatives from *C*-(1-Bromo-1-deoxy-D-glycopyranosyl)formamides via solvent participation in Koenigs-Knorr type reactions (in Hungarian)
Biannual Conference of the Hungarian Chemists' Association, Eger, Hungary, 1999

11) **Viktor Gyóllai**, László Kovács, László Somsák
Glycopyranosylidene-spiro-dioxolanes and anomeric *α*-amino acid derivatives from solvent incorporation in Koenigs-Knorr-like reactions of *C*-(1-bromo-1-deoxy-D-glycopyranosyl) formamides
10th European Carbohydrate Symposium, Galway, Ireland, 1999. PA076

12) **Viktor Gyóllai**
Reaction of C-1 Substituted Glycals with Malonyl Radical (in Hungarian)
21st Lecturers' Days in Chemistry, Szeged, Hungary, 1999

13) **Viktor Gyóllai**, László Kovács, László Somsák
Addition of oxidatively generated malonyl radicals to acylated pyranoid 1-cyano- and 1-carbamoyl-D-glycals
Annual Meeting of the Carbohydrate Committee, Hungarian Academy of Sciences, Mátrafüred, Hungary, 2000

14) **Viktor Gyóllai**, Torsten Linker, László Somsák
Reaction of C-1 Substituted Glycals with Malonyl Radical
20th Int. Carbohydr. Symp., Hamburg, Germany, 2000, B-255

15) **Viktor Gyóllai**, László Somsák
Further Studies of Ritter-reactions with 1-Carboxamido-glycosylium Ions
Annual Meeting of the Carbohydrate Committee, Hungarian Academy of Sciences, Mátrafüred, Hungary, 2001

16) **Viktor Gyóllai**, László Somsák
Synthesis of *N*-acyl-(1-cyanoglycopyranosyl)amines via Ritter-reaction, Stereochemical Examination of the Reaction (in Hungarian)
Biannual Conference of the Hungarian Chemists' Association, Hajdúszoboszló, Hungary, 2001, P-28