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NEW CATALYSTS FOR THE GLYCOSYL TRANSFER WITH O-GLYCOSYL TRICHLOROACETIMIDATES[1]

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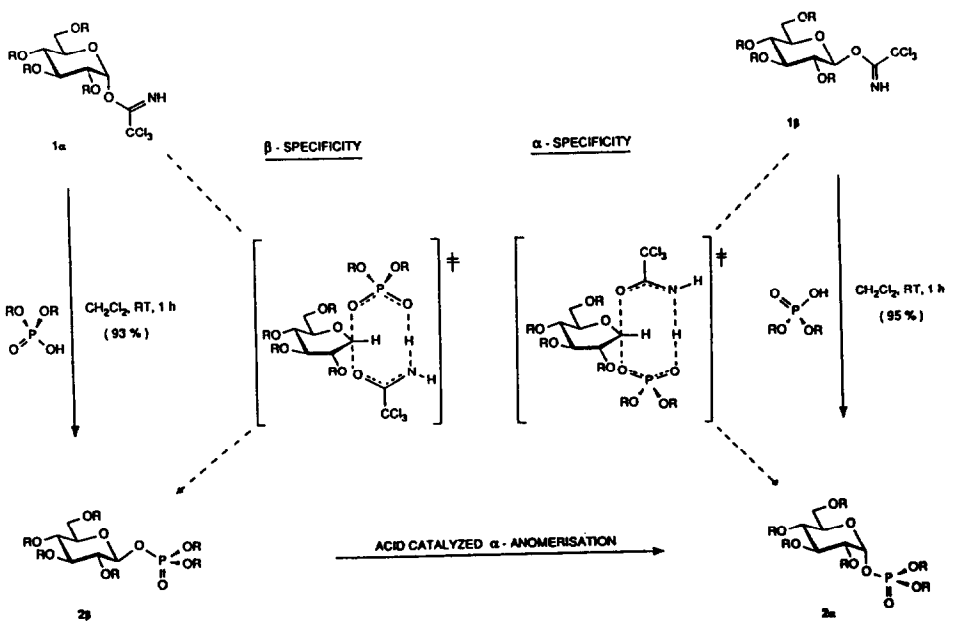
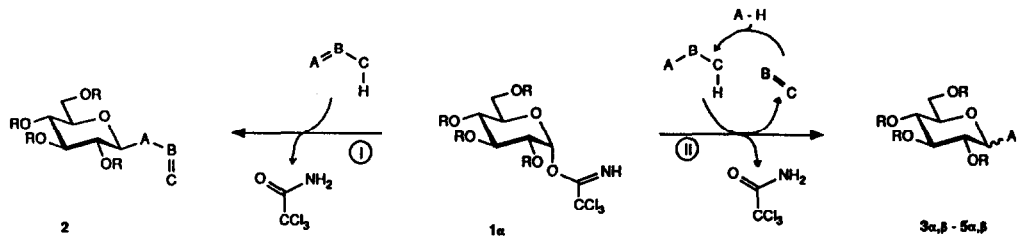
Abstract: O-Glycosyl trichloroacetimidates transfer the glycosyl moiety to phosphate esters and related A=B-C-H systems highly diastereoselectively. A cyclic transition state for this reaction is also supported by conformational studies. Investigations to possibly generate A-B-C-H type intermediates with alcohol acceptors A-H require a catalyst B=C which reversibly binds A-H. Thus, carbonyl compounds were investigated exhibiting excellent results for chloral as catalyst.

The reaction of α-trichloroacetimidate 1α with dibenzyl phosphate afforded without addition of any acid catalyst exclusively the β-glycosyl phosphate 2β (Scheme 1)[2-4].



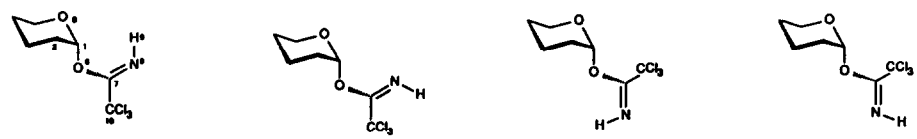
Scheme 1 (R = Benzyl)

Correspondingly, from β-trichloroacetimidate 1β and dibenzyl phosphate the α-glycosyl phosphate 2α was obtained[2,3]. Under acid conditions the β-anomer can be readily converted into the thermodynamically more stable α-anomer 2α[2,3]. From this finding it was deduced that structurally related A=B-C-H systems should exhibit a corresponding diastereoselectivity (Scheme 2, route Ⓘ).



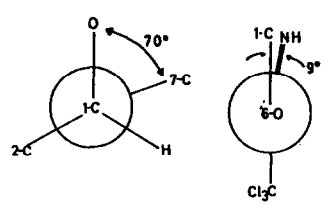
Scheme 2

MM2 and MNDO CALCULATIONS OF α - TRICHLOROACETIMIDATE CONFORMERS



	A	B	C	D
MM2 [kcal, relative]*	0	+1.37	+8.69	+12.43
MNDO [kcal, relative]**	0	+0.12	+4.84	+10.49

CONFORMER B	∢ (0-1-6-7)	∢ (1-6-7-8)
MM2	70° ±1°	9° ±1°
MNDO	81.3°	19.8°



* STERIC ENERGY (PARAMETERS FROM N.L. ALLINGER, 10.3.89)
** HEAT OF FORMATION

Scheme 3

Indeed, this was observed for carboxylic acids[2,5], monoalkyl sulfates[6], and the weakly acidic α-pyridone[7], thus supporting transition states for the α- and β-specificity, respectively, as indicated in Scheme 1, where protonation of the trichloroacetimidate nitrogen and concomitant oxygen attack at the anomeric center play an important role for the ease of the reaction and the high diastereocontrol.

MM2[8] and MNDO calculations on the basic structure of the α-trichloroacetimidate exhibit ground state conformational preference for conformers A and B (Scheme 3).Their rapid interconversion favors the generation of the cyclic transition states as drawn in Scheme 1[9]. The calculated dihedral angles indicate that this transition state consisting of eight atoms will be not planar. Presumably a chairlike transition state with two long bonds representing the O---C---O and N---H---O connections is adopted.

If this bimolecular reaction course can be enforced on glycoside bond formation with alcohols as glycosyl acceptors, possibly mild reaction conditions and high diastereoselectivities are gained. However, as indicated in Scheme 2 (route (II)), generation of an intermediate A-B-C-H (or A-B=C-H) system is required. Thus, a catalyst B=C (or B≡C) has to be found (i) which binds the glycosyl acceptor A-H (corresponding to the alcohol) to form the A-B-C-H adduct, (ii) which then displays the acidity required for the proton transfer to the trichloroacetimidate nitrogen, and (iii) exhibits glycosyl acceptor property at center A leading to reversible and rapid regeneration of the catalyst.

For the catalyst B=C our attention turned to carbonyl compounds known to favor adduct formation. Thus, experiments with anhydrous hexafluoroacetone and **1α** were undertaken[7]. However, they failed presumably due to irreversible adduct formation. Surprisingly, not even the trichloroacetimidate **1α** was affected. Therefore, we turned to cyclopentanone, which is only slightly activated for alcohol addition due to relieve of ring strain. Obviously, catalysis of **1α** reaction with cyclohexanol and glucoside **6**, respectively, in refluxing toluene is observed (Table 1, entries 1 and 2).

Table 1: Reaction of **1α** with different alcohol acceptors in presence of catalyst B=C

Entry	B=C	(eq.)[a]	Acceptor A-H (1.5 eq)[a]	Reaction Conditions Solvent	Temp. [°C]	Time [h]	Products Compound	Yield [%][b]	β:α-Ratio
1		(1.0)	Cyclohexanol	Toluene	110	12	**3**	59	1:1
2	"		**6**	Toluene	110	8	**4**	11	1:1
3		(1.0)	Cyclohexanol	Toluene	110	7	**3**	79	1:1
4	"	(1.0)	**6**	Toluene	110	8	**4**	72	1:1
5	"	(1.0)	**6**	CH_3CN	80	5	**4**	89	2:1
6	CCl_3-CHO	(1.0)	**6**	CH_3CN	80	3	**4**	91	3:1
7	"	(1.0)	**6**	"	RT	2	**4**	94	5:1
8	"	(0.3)	**6**	"	RT	1	**4**	91	4:1
9	"	(0.1)	**6**	"	RT	10	**4**	76	6:1
10	"	(1.0)	**6**	"	- 10	3	**4**	83	14:1
11	"	(1.0)	**6**	"	- 20	3	**4**	84	>19:1
12	"	(1.0)	**6**	"	- 40	18	**4**	79	only β
13	"	(1.0)	**7**	"	RT	6	**5**	79	7:1

[a] Related to 1 equivalent of donor **1α**

[b] Isolated product

However, better results were obtained for the more activated cyclobutanone (entries 3-5), providing the glycosides 3[12] and 4[13] in very good yields and, in refluxing acetonitrile as solvent, even the expected β-product in 2:1 excess. The low diastereoselectivity could be due either to uncontrolled reaction of the A-B-C-H adduct at higher temperature or to an alternative reaction course in which reaction of the trichloroacetimidate **1α** with the carbonyl compound takes place first, then resulting in uncontrolled glycosyl transfer.

Obviously, a better catalyst was required. Thus far, chloral seems to fulfill the demands outlined above quite nicely (Table 1, entries 6-13). The temperature, solvent, and catalyst concentration effects concerning reaction rate, yield, and diastereoselectivity are quite dramatic. Thus, from the primary alcohol acceptor **6** the β-connected disaccharide **4β** can be obtained in acetonitrile at lower temperatures in a clean and highly diastereoselective reaction. Also disaccharide 7[10], having a secondary alcohol acceptor group, provides the β-connected trisaccharide **5β**[14] in high yield (entry 13). The fact that chloral does not affect the glycosyl donor **1α** in the absence of the acceptor and that trichloroacetamide-chloral adducts are not observed in these reactions, is support for the envisaged reaction course which could have bearing also for the borontrifluoride catalyzed reactions[3] and for the enzymatic glycosyl transfer with nucleoside mono- and diphosphate leaving groups[11].

REFERENCES AND FOOTNOTES

1. Glycosylimidates, Part 45.- This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.- For part 44, see Toepfer, A.; Schmidt R.R. *Carbohydr. Res.*, submitted.
2. Schmidt, R.R.; Stumpp, M. *Liebigs Ann. Chem.* **1984**, 680; Stumpp, M. Dissertation, Universität Konstanz, **1985**.
3. Schmidt, R.R. *Angew. Chem.* 98, **1986**, 213; *Angew. Chem., Int. Ed. Engl.* 25 (**1986**) 212; *Pure Appl. Chem.* 61, **1989**, 423.
4. Hoch, M.; Heinz, E.; Schmidt, R.R. *Carbohydr. Res.* 191, **1989**, 21.
5. Schmidt, R.R.; Michel, J. *Angew. Chem.* 92, **1980**, 763; *Angew. Chem., Int. Ed. Engl.* 19, **1980**, 731.
6. Regele, C. unpublished results, Universität Konstanz, 1989.
7. Gaden, H. Dissertation in preparation.
8. We are grateful to Professor N.L. Allinger for estimating some unpublished parameters required for the MM2 calculations.
9. This structural type has not only importance in the association of carboxylic acids and N-alkyl amides but also in bifunctional catalysis, for instance, in the mutarotation of glucose: Swain, C.G.; Brown, J.F. *J. Am. Chem. Soc.* 74, **1952**, 2534.
10. Bommer, R.; Schmidt, R.R. *Liebigs Ann. Chem.*, in print.
11. Sinnott, M.L. in Page, M.I.; Williams, A. (Eds), Enzyme Mechanisms, The Royal Chemical Society, Burlington House, London, **1987**, pp. 259 and ref.
12. The O-acetyl derivatives, obtained via O-debenzylation of the anomers of **3** and subsequent O-acetylation, have ^{1}H-NMR data in agreement with published values: Matsui, M; Okada, M. *Chem.Pharm.Bull* 18, **1970**, 2129.
13. The anomers of **4** were already reported: Schmidt, R.R.; Reichrath, M.; Moering, U. *J.Carbohydr.Chem.* 3, **1984**, 67; Eby, R.; Schuerch, C. *Carbohydr. Res.* 34, **1974**, 79.
14. ^{1}H NMR data (400 MHz, $CDCl_3$) of **5β**:δ = 7.56-7.13 (m, 45H, 9Ph), 5.20 (d, J = 10.5 Hz, 1H, C*H*-Ph), 4.96-4.45 (m, 18H), 4.38 (d, $J_{1'',2''}$ = 7.6 Hz, 1H, 1''-H), 4.34 (d, J = 12.2 Hz, 1H, C*H*-Ph), 4.20 (d, J = 3.4 Hz, 1H), 4.00 (dd, J = 9.2 Hz, 1 H), 3.88-3.23 (m, 15H), 2.94 (bs, 1H, 4'-H), 1.46, 1.44 (2s, 6H, 2Me).

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