ACTIVATION OF TRICHLOROACETIMIDATES USING MONTMORILLONITE AS CATALYST IN GLYCOSIDATION AND BENZYLATION REACTIONS

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ABSTRACT

ACTIVATION OF TRICHLOROACETIMIDATES USING MONTMORILLONITE AS CATALYST IN GLYCOSIDATION AND BENZYLATION REACTIONS. Glycosidations using glycosyl trichloroacetimidates as donors has been conducted effectively using strong acidic montmorillonite K10 as catalyst. The reactions were carried out at -20°C within 2 min by adding the montmorillonite K10 as catalyst.The desired disaccharides were formed in high yields (≥ 90%) with the selectivity of $\alpha:\beta$ = 1:4.5 in dichloroethane, 1:1.8 in ether, and 1:20.0 in acetonitrile as solvents. Benzylation of hydroxyl functions of glycosyl donors with the corresponding benzyltrichloroacetimidate was also affected by the same catalyst in 50% yield, even though the reaction conditions have not yet been optimized.

ABSTRAK

PENGAKTIFAN TRIKLOROASETIMIDAT MENGGUNAKAN MONTMORILLONITE SEBAGAI KATALIS DALAM REAKSI GLIKOSIDASI DAN BENZILASI. Telah dilakukan reaksi glikosidasi menggunakan glikosil trikloroasetimidat sebagai donor. Reaksi dilakukan pada suhu -20°C dalam waktu < 2 menit dengan menambahkan asam kuat montmorillonite K10 sebagai katalis asam. Produk disakarida diperoleh dengan rendemen yang tinggi (≥ 90%) dengan selektivitas $\alpha:\beta$ = 1:4,5 dalam pelarut dikloroetana, 1:1,8 dalam pelarut eter, dan 1:20,0 dalam pelarut asetonitril. Dengan katalis yang sama benzilasi menggunakan benziltrikloroasetimidat juga efektif terjadi pada gugus hidroksi senyawa glikosil donor, dengan rendemen 50%, meskipun kondisi reaksi belum dioptimalkan.

INTRODUCTION

Glycosidation and protection of functional groups are important in carbohydrate chemistry. One of the classical method in glycoside synthesis is the Koenigs - Knorr reaction or Helferich procedure, which is the reaction of a glycosyl halide with a compound containing an unprotected hydroxyl group in the presence of silver salt or a mercury-containing compound (usually mercury(II) cyanide) as catalyst (Scheme 1) [1]. However, these methods are not satisfactorily convenient, because glycosyl bromide is unstable, and the catalyst used is very toxic. In the 1980s, the use of glycosyl trichloroacetimidates became

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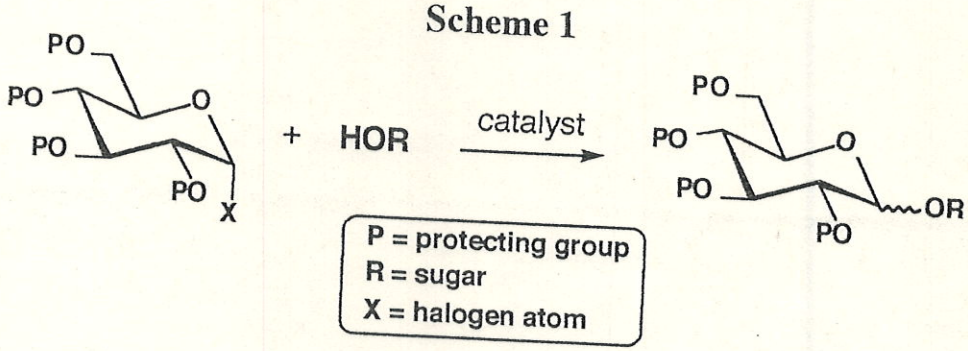
popular, these compounds have been proved to be efficient as glycosyl donors for carbohydrate synthesis, and they can be obtained readily as stable compounds through the reaction of trichloroacetonitrile with sugar components having free 1-hydroxyl functions in the presence of a mild base. They exhibit a high glycosyl transfer potential through activation by a homogeneous acid catalyst, such as trimethylsilyl triflouromethanesulfonate or $BF_3 \cdot Et_2O$ [2, 3].

Recently, strong acidic montmorillonite clays are already available for organic synthesis as heterogeneous acid catalysts [4, 5]. The use of montmorillonites often afford much better results than those of homogeneous acid catalysts. The experimental procedure is quite simple with regard to treatment and removal of the catalyst because of the non-hygroscopic and insoluble properties of solid montmorillonites. In this study, commercial acidic montmorillonite K10 was used instead of trimethylsilyl triflouromethanesulfonate or $BF_3 \cdot Et_2O$ to activating trichloroacetimidates for either glycosidation or benzylation reactions. It is expected that the use of montmorillonite as an acid catalyst will make glycosidation method more convenient.

Scheme 1



MATERIALS AND METHODS

Materials. The starting materials consisted of: **A**. glycosyl trichloroacetimidate (α:β = 8:1), which was prepared from D-glucose through the Schmidt's procedure [3]; **B**. glycosyl acceptor prepared according to Hasuoka's procedure [6]; **C**. pivaloylaminobenzyl trichloroacetimidate prepared according to Fukase's procedure [7]; **D**. glycosyl donor

prepared according to Winarno's procedure [8]. The anhydrous solvents used (dichloroethane, ether, and acetonitrile) were prepared from redistilled solvents, which were distilled again after reflux for 2 hours with the addition of Na or CaH_2. Chloroform and acetone were used for extraction and eluent of column chromatography. Molecular sieves 4A (Wako) and montmorillonite K10 (Aldrich & Fluka) were dried at 350°C for 5 hours before use. HPTLC Kieselgel 60 F_{254} (E. Merck) was used for TLC, and Kieselgel 60 (0,040-0,063 mm) was used for column chromatography.

Equipment. The equipment used were distillation apparatus, reaction flask equipped with magnetic stirrer and cooler connected to a balloon containing nitrogen, rotary evaporator with vacuum line, column chromatography equipped with fraction collector, JEOL JNM-EX270 NMR spectrometer, and JMS-SX102 mass spectrometer.

Glycosidation. To the solution of methyl 2,3,4-tribenzylglucopyranoside (**B**) (175 mg, 255 μmol) in anhydrous dichloromethane or dichloroethane or acetonitrile (5 ml) was added molecular sieves 4A (200 mg), then the solution mixture was cooled at -20°C and stirred for 5 min. To this solution were added 2,3,4,6-tetrabenzylglucopyranoside trichloroacetimidate (**A**) (60 mg, 170 μmol) and montmorillonite K10 (= 50 mg, except in CH_3CN = 500 mg), then the solution was stirred until the starting material **B** disappeared. The reaction kinetic was monitored using TLC (eluent chloroform/acetone : 20/1, R_f of **B** = 0.37, R_f of the product **P** = 0.52). After removal of the catalyst and drying agent by filtration, the filtrate was concentrated under reduced pressure. Then the product was purified by medium pressure silica gel column chromatography (silica gel =15 g, eluent : chloroform/acetone = 50/1). Confirmation of the product was done by measuring it's NMR and mass spectra.

Benzylation. To the solution of allyl 3-*O*-[(*R*)-3-benzyloxytetradecanoyl]-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (**D**) (50 mg, 76 μmol) in anhydrous dichloroethane (5 ml) was added molecular sieves 4A (50 mg) and stirred under nitrogen atmosphere at room temperature for 5 min. Then *p*-pivaloylaminobenzyl

trichloroacetimidate (**C**) (53.5 mg, 152 μmol) and montmorillonite K10 (25 mg) were added respectively and the reaction mixture was stirred for additional 5 min (the stirring of the reaction mixture until 15 min did not increase the product, checked by TLC). After removing the insoluble material by filtration, the filtrate was concentrated under reduced pressure. Isolation of the product was carried out using medium pressure silica gel column chromatography (silica gel = 20 g, eluent : chloroform/acetone = 50/1), which gave a white crystal of product **E**. Further elusion with chloroform/acetone = 20/1, gave the starting material **D**.

RESULTS AND DISCUSSIONS

The β-glycoside was obtained preferentially in dichloroethane (Scheme 2; Table 1). The formation of the α-anomer increased slightly in ether as expected from the known solvent effect, but the α-orienting effect was not sufficient.

Scheme 2

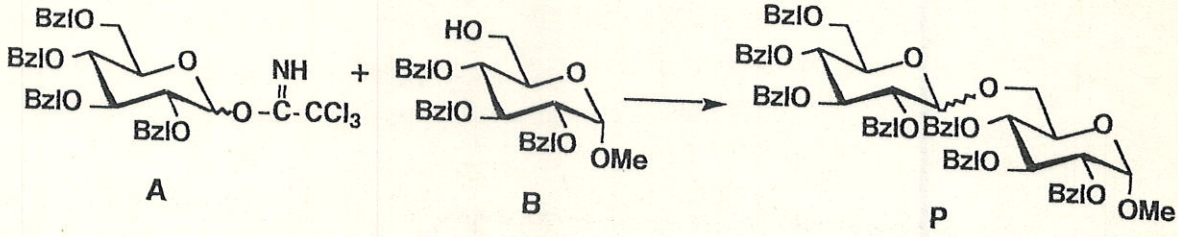
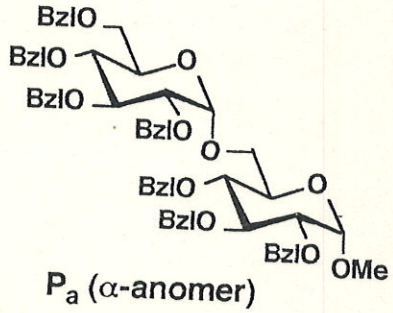


Table 1. Glycosidation of glycosyl donor **A** to glycosyl acceptor **B**

Solvent	**A / B**	K10 / **B** (mg/mmol)	Temperature (°C)	Time (min)	Yield **P** (%)	Selectivity (α : β)
$(CH_2Cl)_2$	1.5	300	-20	< 2	92	1 : 4.5
ether	1.5	300	-20	< 2	96	1 : 1.8
CH_3CN	1.5	3000	-20	< 2	90	1 : 20.0

Therefore, β-anomer was still the major product. In acetonitrile, much larger quantities of montmorillonite K10 was required for promoting the glycosidation than that in the solvents mentioned earlier. The reaction, however, also proceeded rapidly to give disaccharide **P** in good yields with high β-selectivity due to well documented solvent effect of acetonitrile via the α-nitrilium kinetic intermediates as proposed by VANKAR *et al.* [2].

Since the separation of a and β-anomers of product disaccharide **P** by silica gel column chromatography was difficult, the separation was first done using preparative TLC (5 mm, 20 x 20 cm; eluent : chloroform/acetone = 30/1). Although the spots obtained still overlapped, a small part of a and β-anomers could be isolated, then measured by NMR spectrometer. The ^{1}HNMR data (270 MHz, $CDCl_3$) of α and β-anomers of disaccharides produced are as follows :



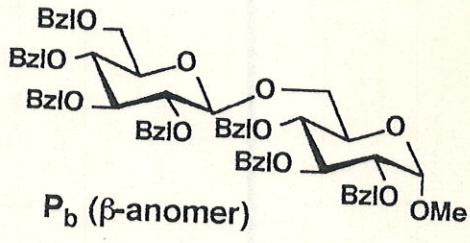
P_a (α-anomer)

δ=4,61 (d, 1H, $J_{1,2}$=3,50 Hz, H-1)

4,35 (d, 1H, $J_{1',2'}$=7,94 Hz, H-1')

3,44-3,55 (2H, m, H-2, H-2')

3,32 (s, 3H, OCH_3)



P_b (β-anomer)

δ=4,98 (d, 1H, $J_{1',2}$=3.36 Hz, H-1')

4,44 (d, 1H, $J_{1,2}$=4,10 Hz, H-1)

3,43 (dd, 1H, $J_{2,1}$=4,10, J2,3=9,46 Hz, H-2)

3,55 (dd, 1H, $J_{2',1'}$=3,66, J2',3'=9,1 Hz, H-2')

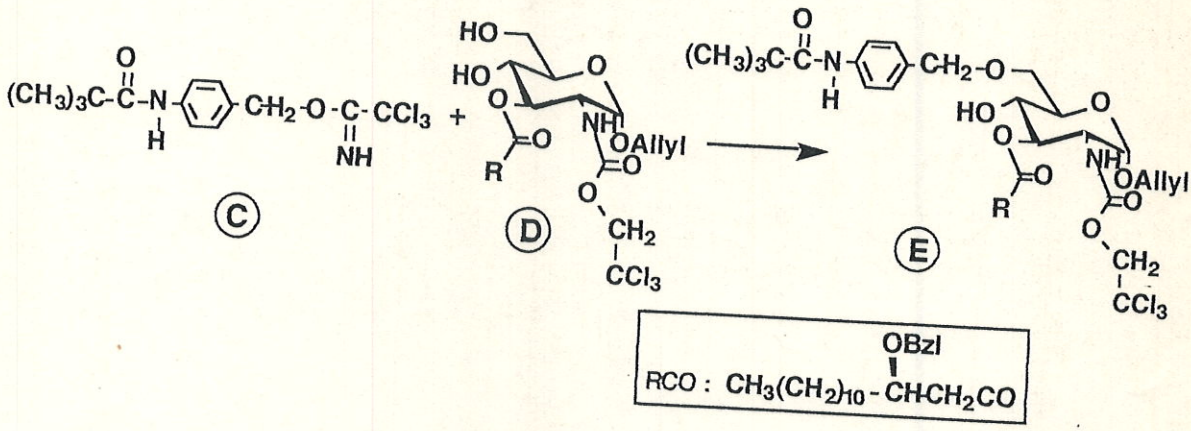
3,35 (s, 3H, OCH_3)

Furthermore, the determination of α/β ratio was done by comparing the proton signal of OCH_3 of α-form (δ = 3.32 ppm, singlet) and β-form (δ = 3.35 ppm, singlet) in NMR spectra of the mixture of product **P**.

Montmorillonite K10 was also effective for promoting the benzylation of hydroxyl functions using benzyl trichloroacetimidates. The reaction of *p*-pivaloylaminobenzyl

trichloroacetimidate (**C**) with the allyl 3-*O*-[(*R*)-3-benzyloxytetradecanoyl]-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside (**D**) was carried out using 2 equivalent of **C** based on **D** in dichloroethane at room temperature to give compound **E** in 50% yield with 45% recovery of starting material **D**, though the reaction conditions have not yet been optimized (Scheme 3). Although there is free hydroxyl function at 4-position, *p*-pivaloylaminobenzyl group was selectively introduced to the 6-position of **D** , because the primary 6-hydroxyl function has much higher reactivity than the secondary one at 4-position. Besides, the fatty acids group at 3-position also made more hindrance.

Scheme 3



CONCLUSION

The use of montmorillonite K10 as catalyst is versatile and convenient for promoting the reaction of trichloroacetoimidates with regard to high reaction rate under mild conditions and good yields. Moreover, the experimental procedure is operationally much simpler than those using conventional homogeneous catalysts such as $BF_3{\cdot}Et_2O$ or trimethylsilyl trifluoro-methanesulfonate.

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