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N-Glycosylation Reactions in the Solid to Solid State

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Abstract: *The solid to solid state reactions of glycopyranosyl bromide and silylated uracil or thymine in the presence of silver trifluoroacetate provided glycopyranosyl uracil or thymine with an excellent stereoselectivity.*

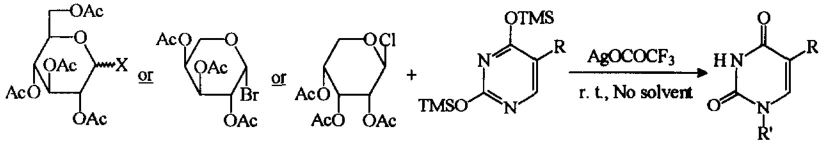
Most studies of chemical reactions are concerned with the behavior of liquid or gaseous systems. Toda et al. have demonstrated, however, that not only photochemical reactions, but also ground state organic reactions take place efficiently in the solid to solid state. Organic reactions[1] such as Baeyer-Villiger oxidation,[2] $NaBH_4$ reduction,[3] pinacol rearrangement,[4] Grignard,[5] Reformatsky,[6] Wittig,[7] aldol reactions[8] and oxidative coupling of β-naphthol,[9] proceed even more efficiently and selectively in the solid to solid state than those in solution.

Among various procedures for the synthesis of pyrimidine nucleoside, glycosylation reaction by Hilbert-Johnson is the simplest one with wide application.[10] This reaction is encumbered, however, by the formation of not only α, β-anomeric mixture, but also the *N*-3-substituted glycosyl pyrimidines.[11]

We tested the *N*-glycosylation reaction of glycopyranosyl bromide to further explore and develop the solid to solid state synthetic methodologies, and found that it is a viable alternative to the existing fusion procedure with an enhancement in the selectivity, which is described in this report.

After grinding of the glycosyl halide **1** and silver trifluoroacetate with mortar and pestle for 5 min under a N_2 atmosphere in a glove box, silylated pyrimidines **2** was added to the solid mixture and the resulting heterogenous mixture was further ground in a ball mill for 2 days.

The results of *N*-glycosylation reactions obtained from the comparison experiments of the fusion method and the present method are summarized in Table 1. The yield of the *N*-glycosylated product was 20-42%, which was comparable with the result obtained by the fusion method.[12] The distinction between the two reactions is in their stereoselectivity. The solid to solid reaction gave only one anomer, while the fusion method afforded an anomeric mixture.



1
a ; X = α-Br
b ; X = β-Cl

1c

1d

2
a ; R = H
b ; R = CH_3

3
a ; R = H
b ; R = CH_3
c ; R' = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl
d ; R' = 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl
e ; R' = 2,3,4-tri-*O*-acetyl-β-D-ribopyranosyl

Table 1. *N*-Glycosylation reaction in the solid to solid state

Substrate	Reactant	Method[a]	Product[b]	Yield(%)[c]	α:β[d]	$[\alpha]^{20}_{D}$[e]	mp(°C)
1a	2a	solid	3a-c	42	β	-13(c = 1.1)	147-148[f]
	2a	fusion	mixture	43	1 : 4		
	2b	solid	3b-c	42	β	-29(c = 1.8)	153[g]
	2b	fusion	mixture	43	1 : 4		
1b	2b	solid	3b-c	20	β	-29(c = 1.8)	153-154
	2b	fusion	mixture	32	1 : 9		
1c	2a	solid	3a-d	28	α	+13.3(c = 1.32)	108-110
	2a	fusion	mixture	32	10 : 1		
	2b	solid	3b-d	28	α	+64.8(c = 10.8)	108-110
	2b	fusion	mixture	35	10 : 1		
1d	2b	solid	3b-e	20	β	+5.7(c = 0.55)	126-128
	2b	fusion	mixture	32	1 : 2.4		

[a]Fusion was performed by melting the reaction mixture in the absence of $AgOCOCF_3$ for 30 min at 130-140 °C in vacuo.[12] [b]All products gave satisfactory ^1H- and ^{13}C-NMR spectra. [c]Isolated yield by recrystallization. [d]The configuration of the anomer was confirmed by δ and J values of the anomeric proton and by comparison of the spectral data with those of published data.[13] [e]$[\alpha]^{20}_{D}$ were measured in $CHCl_3$ with JASCO DIP-370. [f]lit. 149-151 °C.[12] [g]lit. 154.5-155.5 °C.[12]

A typical experimental procedure is as follows; A mixture of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.82 g, 2 mmol) and silver trifluoroacetate (1 g, 4.5 mmol) was ground with mortar and pestle at room temperature for 5 min under a N_2 atomosphere in a glove box. Then the silylated uracil (0.77 g, 3 mmol) was added to the mixture, which was further ground in a ball mill for 2 days. After quenching the reaction by the addition of water, $CHCl_3$ was added and the mixture was filtered. Extraction with $CHCl_3$ and evaporation of the solvents gave a single crude product which was recrystalized from ether-hexane (3 : 1) to afford 0.43 g (42%) of crystalline product. mp 147-148 °C.

In conclusion, the solid to solid state reaction, though the yields of nucleoside product are only modest, could serve as a simple and efficient method for glycopyranosyl nucleoside synthesis with high stereoselectivity under mild conditions. An extension of this method to glycoside synthesis is currently under study in our laboratory.

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