An Efficacious *C*-Glucosidation of β-Ketoesters and Ketones *via* Enamines

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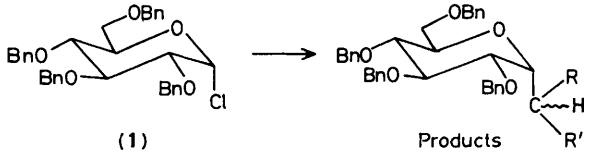
A route for the synthesis of α-*C*-glucosides of β-keto esters and ketones through the reaction of the corresponding enamines with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride activated by silver(I) trifluoromethanesulphonate is described.

A number of methods have been reported for the production of *C*-glycosides, many of which possess significant biological activity[1]. The reported methods include *inter alia* the coupling of unprotected or protected C-1 functionalized carbohydrate precursors with different nucleophiles such as allylsilane and silyl enol ethers and silyl ketenes, metallated heterocycles, or activated aromatic hydrocarbons.[2] More complex aryl and heteroaryl *C*-glycosides have recently been obtained by dipolar cycloaddition reactions of nitrile oxides to allyl substituted aromatic compounds.[3] Our interest in the syn-

Table 1. Synthesis of *C*-glucosyl derivatives from (**1**).

Reaction	Nucleophile	R	R′	Yield[a]/%
1	$Me(C_4H_8N)C{=}CHCO_2Me$	CO_2Me	COMe[b]	85
2	$Et(C_4H_8N)C{=}CHCO_2Me$	CO_2Me	COEt[c]	80
3	$MeOCH_2(C_4H_8N)C{=}CHCO_2Me$	CO_2Me	$COCH_2OMe$[d]	85
4	$Ph(C_5H_{10}N)C{=}CH_2$	H	COPh[e]	85
5	$Ph(Me_2N)C{=}CH_2$	H	COPh[e]	85
6	$p\text{-}ClC_6H_4(C_5H_{10}N)C{=}CH_2$	H	$COC_6H_4Cl\text{-}p$[e]	83
7	$Bu^t(C_5H_{10}N)C{=}CH_2$	H	COBu[te]	40

[a] Yields refer to pure isolated [flash column chromatography (silica gel) and crystallized] products. [b] Mixture of epimers (9:1); the major one showed m.p. 75—76 °C; $[\alpha]_D^{20}$ 95°; ^{1}H n.m.r. δ 4.94, H-1, $J_{1,2}$ 4.9 Hz; the minor one showed m.p. 67—68 °C; $[\alpha]_D^{20}$ 91°; ^{1}H n.m.r. δ 4.95, H-1, $J_{1,2}$ 5 Hz. [c] Mixture of epimers (3:2); the major one showed m.p. 83—84 °C; $[\alpha]_D^{20}$ 108°; ^{1}H n.m.r. δ 4.98, H-1, $J_{1,2}$ 4.8 Hz; the minor one showed m.p. 85—86 °C; $[\alpha]_D^{20}$ 89°; ^{1}H n.m.r. δ 4.99, H-1, $J_{1,2}$ 4 Hz. [d] Inseparable mixture of epimers (3:2); m.p. 55—63 °C; $[\alpha]_D^{20}$ 77°; the major one showed a signal at δ 5.00, H-1, $J_{1,2}$ 5 Hz; the minor one showed a signal at δ 4.87, H-1, $J_{1,2}$ 4.5 Hz. [e] See ref. 8.



Scheme 1. Bn = benzyl. The reaction with ethyl acetoacetate (reaction 1) is representative. To a solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**1**) (1 g) and methyl 3-pyrrolidinylcrotonate (0.9 g) in anhydrous dichloromethane (50 ml) containing pulverized molecular sieves (3 Å), silver(I) triflate (0.690 g) was added at room temperature in the dark. After 10 min stirring, the mixture was treated with saturated sodium chloride solution (20 ml) and stirred for 15 min. Filtration, flash chromatography and usual work up afforded the two epimeric products cited in Table 1.

thesis of carminic acid, an anthraquinone *C*-glucoside[4,5] and in its analogues as potential antitumour agents,[6] prompted us to devise the synthesis of *C*-glucosides of β-keto esters as possible precursors of appropriately substituted vinylketene acetals which have been shown to be useful for the construction of complex polycyclic quinones *via* Diels–Alder cycloadditions.[7]

Since we were unable to obtain successful results in the *C*-glucosidation of β-keto esters by the reaction of silyl enol derivatives of acetoacetic ester or of its analogues, according to the procedures reported by us and by others for similar derivatives of ketones or esters, we tried to reach our goal by the use of enamine derivatives of β-keto esters. Even though it is considered that enamines are weaker nucleophiles than silyl enol ethers, experimental results have shown that enamines represent the only efficacious nucleophiles for introducing a glucosidic portion into a β-keto ester and that this is possible using 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**1**) activated by silver(I) trifluoromethanesulphonate (triflate),[8] see Scheme 1 and Table 1.†

The *C*-glucoside bond formed by this route always takes the α-configuration, contrasting with the mixture of epimers formed at the glucosidate carbon of the keto esters.‡ In the case of the products reported in reactions 1 and 2, the epimers are separable by flash chromatography (f.c.) but are both equilibrated to the starting mixture ratio in a few minutes by treatment with a saturated solution of potassium carbonate in methanol. In the case of reaction 3, the mixture of epimers was inseparable (by h.p.l.c. and f.c.) but its composition could be determined by ^{1}H n.m.r. spectroscopy.

In order to evaluate the usefulness of this route we also studied some enamines of ketones (reactions 4—7) and observed that the reaction proceeds with yields comparable with those observed for silyl ethers.[8] By contrast, the enamine of acetylacetone fails to yield any *C*-glucosidic compound. In conclusion, this route represents the first route for obtaining *C*-glucosides from β-keto esters and a new method for obtaining α-*C*-glucosides from ketones.

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† New compounds gave satisfactory analytical and spectral data.

‡ Based on ^{1}H n.m.r. evidence.

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