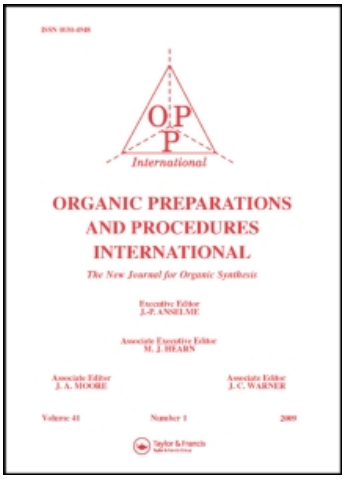

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

IMPROVED METHOD FOR THE ESTERIFICATION OF SUGAR ACETALS WITH DICYCLOHEXYLCARBODIIMIDE

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To cite this Article Perrone, Clarissa C. , Costa, Paulo R. R. and Ferreira, Vítor F.(1999) 'IMPROVED METHOD FOR THE ESTERIFICATION OF SUGAR ACETALS WITH DICYCLOHEXYLCARBODIIMIDE', Organic Preparations and Procedures International, 31: 6, 689 — 692
To link to this Article: DOI: 10.1080/00304949909355350
URL: http://dx.doi.org/10.1080/00304949909355350

ORGANIC PREPARATIONS AND PROCEDURES INT., 31 (6), 689-704 (1999)

OPPI BRIEFS

IMPROVED METHOD FOR THE ESTERIFICATION OF SUGAR ACETALS WITH DICYCLOHEXYLCARBODIIMIDE

Submitted by (09/09/99)

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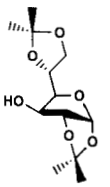
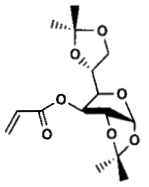
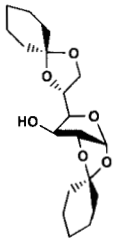
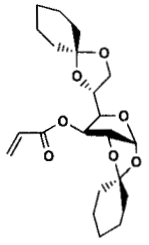
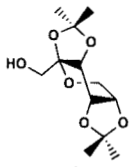
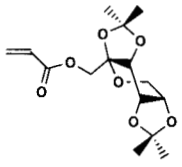
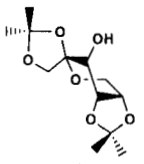
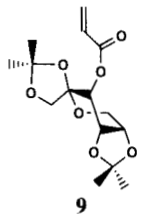
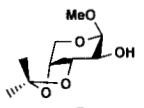
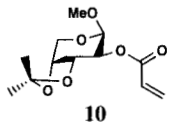
In connection with the preparation of chiral auxiliaries from sugar derivatives for asymmetric Diels-Alder reactions,[1] the synthesis of acrylic esters of sugar acetals was of interest. Although a number of esterification methods are known, most require either the presence of strong acids or the application of heat. The utilization of a mild procedure such as direct room temperature esterification in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) was thus of considerable interest; however, the yields obtained in our labs employing the typical procedure described in the literature[2] were very low (Table).

The mechanism for the reaction of carbodiimides with monocarboxylic acids suggested by Khorana[3] explains its bi-directional course through the competition between the formation of an acid anhydride (the desired intermediate) and the formation of a N-acylurea, both derived from the very active O-acylisourea formed in the first step of the reaction. The rate of the reaction and the ratio of the products obtained are affected by a whole range of factors, among them the strength of the acid and the nucleophilicity of its anion.[4] The greater the strength of the acid used, the greater is the reaction rate and the higher is the yield of anhydride and lower that of N-acylurea.

TABLE Esterification of Sugar Acetals

Entry	Sugar Derivative	Product	Yield (%)	lit. Yield[2] (%)
1	 **1**	 **6**	80	33
2	 **2**	 **7**	88	23
3	 **3**	 **8**	74	28
4	 **4**	 **9**	76	36
5	 **5**	 **10**	61	11

As the reaction exhibits first-order kinetics both in the acid and in the carbodiimide, attempts to use an excess of the carboxylic acid failed. However, we were able to improve the yields (Table) through periodical additions of both reagents, until the complete consumption of the substrate alcohol. Our modified procedure for the preparation of compound **10** (entry 5 in the Table) for example, proved to be more efficient than either the esterification with DCC/carboxylic acid or the classical acyl chloride esterification method.[5]

EXPERIMENTAL SECTION

IR spectra were obtained on a Nicolet Magna-750 (FT-IR) spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini-200 spectrometer. Chemical shifts are expressed in d (ppm) downfield from TMS as internal standard. Mass spectra were determined at 70 eV on an Auto Spec (VG) high-resolution spectrometer. Elemental analyses were obtained on a Carlo Erba 1104 apparatus. The starting sugar derivatives **1-5** were prepared by methods described in the literature.[6]

General Procedure for Esterification.- A solution of the appropriate carboxylic acid (10 mmol), N,N-dicyclohexylcarbodiimide (11 mmol), the sugar acetal (11 mmol) and dimethylaminopyridine (1 mmol) in dichloromethane (100 mL) was stirred for 12 h at room temperature. The reaction was monitored by TLC and additional portions of carboxylic acid (5 mmol) and DCC (5.5 mmol) in dichloromethane (10 mL) were added until the complete consumption of the starting sugar, as shown by TLC (generally, one or two additions were necessary). The mixture was filtered and the filtrate washed with water (3 x 100 mL), 5% acetic acid solution (3 x 100 mL) and again with water (3 x 100 mL), then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to yield the crude product, which was purified by column chromatography over silica gel using a gradient of hexane and ethyl acetate as eluent.

3-*O*-Acryloyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (6).-White crystalline solid, mp. 75-76°; IR (neat): 1720 (C=O) 1620 (CH=CH_2) and 1380 cm^{-1} (gem-dimethyl); ^{1}H NMR ($CDCl_3$): d 1.37 (s, 6H, $2CH_3$), 1.46 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 4.00-4.20 (m, 2H, H-6 and H-6'), 4.20-4.40 (m, 2H, H-4 and H-5), 4.57 (d, $J_{1,2}$ = 4.8, 1H, H-2), 5.35 (d, $J_{3,4}$ = 2.4, 1H, H-3), 5.93 (d, $J_{1,2}$ = 4.8, 1H, H-1), 5.96 (dd, J_{gem} = 1.2, J_{cis} = 9.7, 1H, olefin-CH_2), 6.17 (dd, J_{cis} = 9.7, J_{trans} = 18.1, 1H, olefin-CH) and 6.49 (dd, J_{gem} = 1.2, J_{trans} = 18.1, 1H, olefin-CH_2); HREIMS: Calcd for $C_{14}H_{19}O_7$ (M^+-15) (299.113078). Found: 299.112791.

Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.05. Found: C, 57.29; H, 7.06

3-*O*-Acryloyl-1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (7).- Colorless oil; IR (neat): 1725 (C=O) and 1625 (CH=CH_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): d 1.20-1.80 (m, 20H, cyclohexylidene ring), 3.96-4.16 (m, 2H, H-6), 4.16-4.32 (m, 2H, H-4 and H-5), 4.54 (d, $J_{1,2}$ = 4.1, 1H, H-2), 5.41 (d, $J_{3,4}$ = 2.7, 1H, H-3), 5.90 (dd, J_{gem} = 1.4, J_{cis} = 10.8, 1H, olefin-CH_2), 5.92 (d, $J_{1,2}$ = 4.1, 1H, H-1), 6.15 (dd, J_{cis} = 10.8, J_{trans} = 16.2, 1H, olefin-CH) and 6.47 (dd, J_{gem} = 1.4, J_{trans} = 16.2, 1H, olefin-CH_2); HREIMS: Calcd for $C_{18}H_{23}O_7$ (M^+-43) (351.144378). Found: 351.144856.

Anal. Calcd for $C_{21}H_{30}O_7$: C, 63.94; H, 7.66. Found: C, 63.97; H, 7.64

1-*O*-Acryloyl-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (8).- Light yellow oil; IR (neat): 1730 (C=O), 1630 (CH=CH_2) and 1380 cm^{-1} (gem-dimethyl); ^{1}H NMR ($CDCl_3$): d 1.37 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.81 (dd, $J_{5,6}$ = 1.9, $J_{6,6'}$ = 15.5, 1H, H-6), 3.96 (dd, $J_{6,6'}$ = 15.5, 1H, H-6'), 4.17 (d, $J_{1,1'}$ = 14.0, 1H, H-1), 4,28 (dd, $J_{4,5}$ = 9.7, $J_{5,6}$ = 1.9, 1H, H-5), 4.39 (d, $J_{3,4}$ = 2.9, 1H, H-3), 4.55 (d, $J_{1,1'}$ = 14.0, 1H, H-1'), 4.65 (dd, $J_{3,4}$ = 2.9, $J_{4,5}$ = 9.7, 1H, H-4), 5.90 (dd, J_{gem} = 1.9, J_{cis} = 10.4, 1H, olefin-CH_2), 6.20 (dd, J_{cis} = 10.4, J_{trans} = 17.9, 1H, olefin-CH) and 6.50 (dd, J_{gem} = 1.9, J_{trans} = 17.9, 1H, olefin-CH_2); HREIMS: Calcd for $C_{14}H_{19}O_7$ (M^+-15) (299.113078).

Found: 299.112952.

Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.05. Found: C, 57.36; H, 7.04.

3-*O*-Acryloyl-1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (9).- Colorless oil; IR (neat): 1730 (C=O), 1630 ($CH=CH_2$) and 1380 cm^{-1} (gem-dimethyl); ^1H NMR ($CDCl_3$): d 1.36 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 3.84 (d, $J_{1,1'}$ = 9.3, 1H, H-1), 3.97 (d, $J_{1,1'}$ = 9.3, 1H, H-1'), 4.10-4.20 (m, 2H, H-6 and H-6'), 4.20-4.30 (m, 1H, H-5), 4.34 (dd, $J_{3,4}$ = 7.7, $J_{4,5}$ = 5.4, 1H, H-4), 5.20 (d, $J_{3,4}$ = 7.7, 1H, H-3), 5.92 (dd, J_{gem} = 1.5, J_{cis} = 10.0, 1H, olefin-CH_2), 6.17 (dd, J_{cis} = 10.0, J_{trans} = 17.8, 1H, olefin-CH) and 6.49 (dd, J_{gem} = 1.5, J_{trans} = 17.8, 1H, olefin-CH_2); HREIMS: Calcd for $C_{14}H_{19}O_7$ (M^+-15) (299.113078). Found: 299.111743.

Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.05. Found: C, 57.39; H, 7.07

Methyl-2-*O*-acryloyl-3,4-*O*-isopropylidene-β-D-arabinopyranoside (10).- White solid, mp. 78°, lit.[5] 78-79°; IR (neat): 1720 (C=O) 1630 ($CH=CH_2$) and 1380 cm^{-1} (gem-dimethyl); ^1H NMR ($CDCl_3$): d 1.37 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 3.38 (s, 3H, OCH_3), 3.94 (dd, $J_{4,5}$ = 3.3, $J_{5,5'}$ = 13.9, 1H, H-5), 4.05 (dd, $J_{4,5'}$ = 0.8, $J_{5,5'}$ = 13.9, 1H, H-5'), 4.20-4.50 (m, 2H, H-3 and H-4), 4.86 (d, $J_{1,2}$ = 3.3, 1H, H-1), 4.99 (dd, $J_{1,2}$ = 3.3, $J_{2,3}$ = 8.2, 1H, H-2), 5.90 (dd, J_{gem} = 1.6, J_{cis} = 10.7, 1H, olefin-CH_2), 6.15 (dd, J_{cis} = 10.7, J_{trans} = 16.4, 1H, olefin-CH) and 6.49 (dd, J_{gem} = 1.6, J_{trans} = 16.4, 1H, olefin-CH_2).

Acknowledgements.- The authors wish to thank Dr. Bernd Kammerer from Tübingen University, Germany, for providing the elemental analyses.

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