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A SIMPLE PREPARATION OF 2-(ACYLAMINO)-2-DEOXY-3,4:5,6-DI-*O*-ISOPROPYLIDENE-*aldehydo*-D-GLUCOSE DIMETHYL AND DIBENZYL ACETAL*

AKIRA HASEGAWA AND MAKOTO KISO
Department of Agricultural Chemistry, Gifu University, Kakamigahara, Gifu 504 (Japan)
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ABSTRACT

When treated with a large excess of 2,2-dimethoxypropane or 2,2-dibenzyloxypropane in 1,4-dioxane solution in the presence of *p*-toluenesulfonic acid, 2-acetamido-2-deoxy-D-glucose and 2-(benzyloxycarbonylamino)-2-deoxy-D-glucose yield the corresponding 3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl or dibenzyl acetal in good yield.

INTRODUCTION

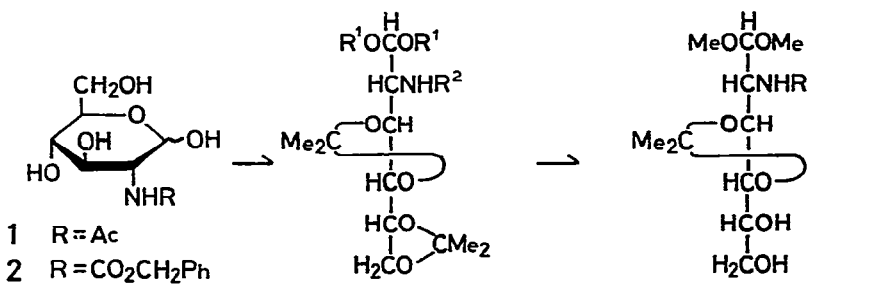
In the course of studies involving the use of 2-(acylamino)-2-deoxyaldohexoses as intermediates in synthesis, our work[1–9] has shown that, for some aldoses, 2,2-dialkoxypropane–*N*,*N*-dimethylformamide–*p*-toluenesulfonic acid is a unique acetonating agent that may give unexpected, and potentially useful, products on changing such reaction conditions as the temperature, the reaction time, and the ratios of the acid, the 2,2-dialkoxypropane, and *N*,*N*-dimethylformamide. We now describe a highly contrasting result that provides a simple preparation of 2-(acylamino)-2-deoxy-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl and dibenzyl acetals, obtained when the 2,2-dialkoxypropane in 1,4-dioxane solution (instead of *N*,*N*-dimethylformamide) in the presence of *p*-toluenesulfonic acid was employed at 60–70°.

RESULTS AND DISCUSSION

Treatment of 2-acetamido-2-deoxy-D-glucose (**1**) with a large excess of 2,2-dimethoxypropane in dry 1,4-dioxane in the presence of *p*-toluenesulfonic acid for 2 h at 68–70° gave 2-acetamido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal[9] (**3**; 67.5%) as the main product, together with a small proportion of methyl 2-acetamido-2-deoxy-5,6-*O*-isopropylidene-β-D-glucofuranoside[3] (**9**). The result shows that the dimethyl acetal is mainly formed when 1,4-dioxane is used as the solvent instead of *N*,*N*-dimethylformamide; on the other hand, when

treated with 2,2-dialkoxypropane in *N*,*N*-dimethylformamide under similar conditions, 2-(acylamino)-2-deoxyaldohexoses afforded the corresponding 5,6-*O*-isopropylidene-β-hexofuranosides[3-5] as the main product. The method provides a facile preparation of the 1,1-diacetals of 2-(acylamino)-2-deoxyaldohexoses. A possible mechanism for the reaction will be described later. Hydrolytic removal of the 5,6-*O*-isopropylidene group in **3** under mild conditions gave crystalline monoisopropylidene dimethyl acetal derivative **7** in quantitative yield; in the n.m.r. spectrum of a solution of **7** in dimethyl sulfoxide-d_6, H-1 appeared as a doublet at δ 4.35 (7.0 Hz) (ref. 10), the OH-6 proton as a triplet due to coupling with H-6,6′ at δ 4.43 (5.2 Hz), and the OH-5 proton as a doublet at δ 4.65 (4.6 Hz), and other data were consistent with structure **7**. The assignment of the OH protons was confirmed by D_2O treatment.

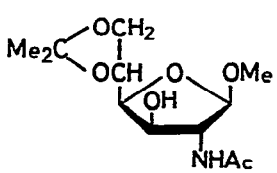
Treatment of 2-(benzyloxycarbonylamino)-2-deoxy-D-glucose (**2**) with the 2,2-dimethoxypropane reagent at 60–65° gave 2-(benzyloxycarbonylamino)-2-deoxy-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (**4**) in 69% yield after column chromatography. Spectral observations showed the product to be a dimethyl acetal having a free benzyloxycarbonylamino group and two isopropylidene groups, and the H-1 signal appeared as a doublet at δ 4.35 ($J_{1,2}$ 5.2 Hz)—all suggestive of structure **4**. Removal of the 5,6-*O*-isopropylidene group of **4** was accomplished by heating at 40° with 80% aqueous acetic acid, to give, in almost quantitative yield, a syrupy diol (**8**); in the n.m.r. spectrum of **8** in dimethyl sulfoxide-d_6, the OH-6 proton appeared as a triplet, due to couplings with H-6 and H-6′, at δ 4.45 (5.6 Hz), the OH-5 proton as a doublet at δ 4.70 (5.0 Hz), and the other data were in harmony with structure **8**. On the other hand, when treated with 2,2-dibenzyloxypropane[11]



1 R=Ac
2 R=CO_2CH_2Ph

3 R^1=Me, R^2=Ac
4 R^1=Me, R^2=CO_2CH_2Ph
5 R^1=CH_2Ph, R^2=Ac
6 R^1=CH_2Ph, R^2=CO_2CH_2Ph

7 R=Ac
8 R=CO_2CH_2Ph



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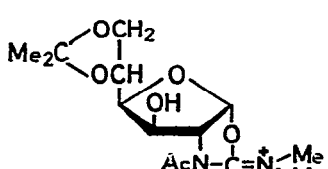

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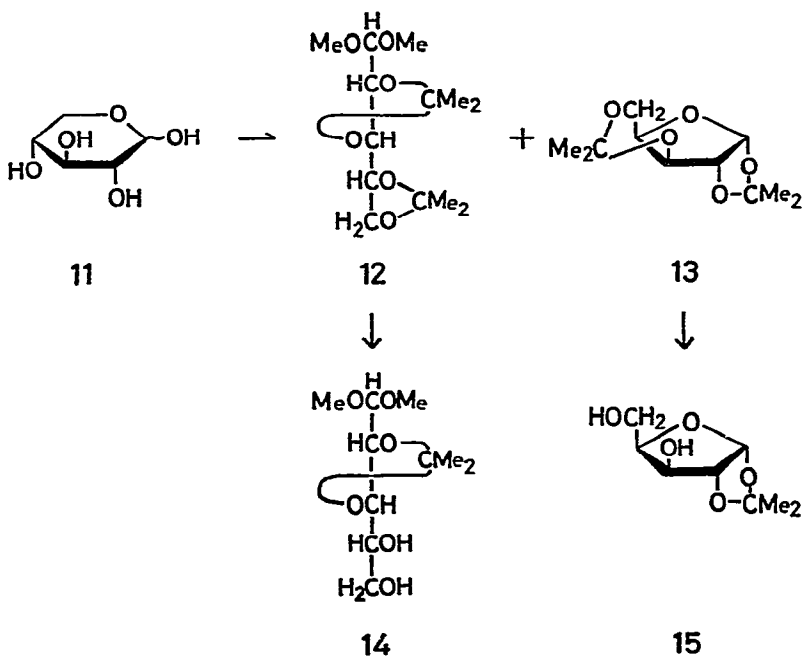
in the presence of *p*-toluenesulfonic acid for 2 h at 60–65°, 2-acetamido-2-deoxy-D-glucose (**1**) or 2-(benzyloxycarbonylamino)-2-deoxy-D-glucose (**2**) respectively gave 2-acetamido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dibenzyl acetal (**5**; 66%) and 2-(benzyloxycarbonylamino)-2-deoxy-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dibenzyl acetal (**6**, 79%). All of the spectral features were consistent with structures **5** and **6**, respectively.

However, treatment of D-xylose (**11**) with the 2,2-dimethoxypropane reagent for 2 h at 65–68° gave in good yield a mixture (**12**, **13**) showing a single spot in t.l.c.; each compound bears two isopropylidene groups. Mild hydrolysis of the mixture yielded two monoisopropylidene derivatives, **14** and **15**. The n.m.r. spectrum of **14** showed the presence of an isopropylidene group at δ 1.44 (s, 6 H), two *O*-methyl groups at δ 3.45 (s, 6 H), two hydroxyl groups, and H-1 as a doublet (due to coupling with H-2) at δ 4.38 (5.6 Hz), and these data were consistent with structure **14**, whereas the n.m.r. spectrum of **15** revealed an isopropylidene group, and an anomeric proton at δ 5.96 (3.0 Hz); the specific rotation and melting point of **15** were identical with those reported[12] for **15**.



11 **12** **13**

14 **15**

Although the present investigation has been restricted to a very limited number of aldoses, it appears that 1,4-dioxane or dibenzyloxypropane employed as the solvent gives results that are, in general, qualitatively different from those earlier noted[1–9] when the reagent was used in *N*,*N*-dimethylformamide. It is considered that furanose structures are much more frequently encountered under the drastic conditions employed, or in such solvents as *N*,*N*-dimethylformamide[13,14] and dimethyl sulfo-

xide[15,16], and the main route of glycoside formation may involve the attack of a methoxyl or benzyloxyl group on a possible intermediate (**10**) formed by *N,N*-dimethylformamide in the course of the reaction. However, when 1,4-dioxane is used as the solvent, such an intermediate is not formed, and the products described here are obtained, *via* the furanoid and aldehyde forms, by stepwise acetalation.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto micro melting-point apparatus, and are uncorrected. Specific rotations were determined with a Yanagimoto OR-50 polarimeter, and i.r. spectra were recorded with a Jasco IRA-spectrophotometer. N.m.r. spectra were recorded at 90 MHz with a Hitachi R-22 spectrometer. Preparative chromatography was performed on 300-mesh silica gel (Waco Co) with the solvent systems specified. 1,4-Dioxane was distilled, and dried over sodium metal. Evaporations were conducted *in vacuo*.

*2-Acetamido-2-deoxy-3,4:5,6-di-*O*-isopropylidene*-aldehydo-D-*glucose dimethyl acetal* (**3**). — A suspension of 2-acetamido-2-deoxy-D-glucose (**1**; 1.0 g) in 1,4-dioxane (10 mL) was stirred at 68–70°, while 2,2-dimethoxypropane (4 mL) and *p*-toluenesulfonic acid monohydrate (150 mg) were added; stirring was continued for 2 h at 70°. The mixture was cooled, and treated with Amberlite IRA-410 (OH^-) ion-exchange resin to remove the acid; the resin was filtered off and washed with 1,4-dioxane. The filtrate and washings were combined, and evaporated to a syrup that was chromatographed on a column of silica gel (30 g) with (*a*) 100:1 and (*b*) 70:1 chloroform–methanol. Eluant *a* gave 2-acetamido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (**3**) (1.06 g, 67.5%), m.p. 57°, $[\alpha]_D^{25}$ +5.0° (*c* 1.0, methanol) {lit.[9] m.p. 55–57°, $[\alpha]_D^{21}$ +5.0° (methanol)}, and eluant *b* afforded methyl 2-acetamido-2-deoxy-5,6-*O*-isopropylidene-*β*-D-glucofuranoside[3] (**9**) (155 mg, 12.5%).

*2-(Benzyloxycarbonylamino)-2-deoxy-3,4:5,6-di-*O*-isopropylidene*-aldehydo-D-*glucose dimethyl acetal* (**4**). — A solution of **2** (1.0 g) in 1,4-dioxane (10 mL) was heated at 60–65° and stirred while 2,2-dimethoxypropane (3 mL) and *p*-toluenesulfonic acid monohydrate (150 mg) were added. The mixture was stirred for 2 h at 60–65°, cooled, and freed of the acid by addition of Amberlite IRA-410 (OH^-) ion-exchange resin. The suspension was filtered, and the filtrate evaporated, to give a syrup which was chromatographed on a column of silica gel (30 g) with chloroform and then 200:1 chloroform–methanol. The latter eluate afforded 960 mg (68.6%) of **4** as a syrup, $[\alpha]_D^{25}$ +13.6° (*c* 0.7, methanol); ν_{max}^{film} 3420 (OH), 3310 (NH), 1720 and 1500 (amide), 870 and 840 (Me_2C), and 745 and 690 cm^{-1} (Ph); n.m.r. data (in chloroform-*d*): δ 1.27 (s, 9 H, Me_2C), 1.40 (s, 3 H, Me_2C), 3.27, 3.30 (2 s, 6 H, 2 MeO), 3.45–4.27 (m, 6 H, H-2–H-6'), 4.35 (d, 1 H, $J_{1,2}$ 5.2 Hz, H-1), 5.06 (s, 2 H, benzyl methylene), 5.22 (d, 1 H, $J_{2,NH}$ 8.0 Hz), and 7.21 (s, 5 H, Ph).

Anal. Calc. for $C_{22}H_{33}NO_8$: C, 60.12; H, 7.57; N, 3.19. Found: C, 60.33; H, 7.60; N, 3.03.

*2-Acetamido-2-deoxy-3,4:5,6-di-*O*-isopropylidene*-aldehydo-D-*glucose dibenzyl*

acetal (**5**). — A suspension of **1** (1.0 g) in 2,2-dibenzyloxypropane[11] (10 mL) was stirred at 60–65° while *p*-toluenesulfonic acid monohydrate (150 mg) was added; stirring was continued for 2 h at 60–65°. The product was chromatographed on a column of silica gel (50 g), with chloroform as the eluant, to give compound **5** (1.48 g, 65.5%) as a syrup, $[\alpha]_D^{25}$ +32.5° (*c* 0.76, methanol); ν_{max}^{film} 3260 (NH), 1650 and 1520 (amide), 870 and 835 (Me_2C), and 730 and 680 cm^{-1} (Ph); n.m.r. data (in chloroform-*d*): δ 1.33, 1.44 (2 s, 6 H, Me_2C), 1.36 (s, 6 H, Me_2C), 1.97 (s, 3 H, AcN), 3.55–4.13 (m, 6 H, H-2–H-6'), 4.32 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.60–4.71 (m, 4 H, 2 benzyl methylene), 5.84 (d, 1 H, $J_{2,NH}$ 8.0 Hz, NH), and 7.31 and 7.32 (2 s, 10 H, 2 Ph).

Anal. Calc. for $C_{28}H_{37}NO_7$: C, 67.31; H, 7.46; N, 2.80. Found: C, 67.08; H, 7.39; N, 2.78.

2-(Benzyloxycarbonylamino)-2-deoxy-3,4:5,6-di-O-isopropylidene-aldehydo-D-*glucose dibenzyl acetal* (**6**). — A suspension of **2** (1.0 g) in 2,2-dibenzyloxypropane (10 mL) was stirred at 60–65° while *p*-toluenesulfonic acid monohydrate (150 mg) was added; stirring was continued for 2 h at 65°. The product, purified by chromatography on a column of silica gel (50 g) with chloroform, was obtained as a syrup: wt. 1.48 g (79%), $[\alpha]_D^{25}$ +23° (*c* 1.1, methanol); ν_{max}^{film} 3320 (NH), 1720 and 1520 (amide), 870 and 835 (Me_2C), and 720 and 680 cm^{-1} (Ph); n.m.r. data (in chloroform-*d*): δ 1.33 (s, 6 H, Me_2C), 1.34, 1.44 (2 s, 6 H, Me_2C), 3.60–4.15 (m, 6 H, H-2–H-6'), 4.33 (d, 1 H, $J_{1,2}$ 7.0 Hz, H-1), 4.44–5.25 (m, 6 H, 3 benzyl methylene), 7.28 (s, 5 H, Ph), and 7.31 (s, 10 H, 2 Ph).

Anal. Calc. for $C_{34}H_{41}NO_8$: C, 69.01; H, 6.98; N, 2.37. Found: C, 69.15; H, 6.93; N, 2.21.

2-Acetamido-2-deoxy-3,4-O-isopropylidene-aldehydo-D-*glucose dimethyl acetal* (**7**). — A solution of **3** (300 mg) in 80% aqueous acetic acid (10 mL) was heated for 1.5 h at 40°; it was then evaporated at 40° to a syrup which was chromatographed on a column of silica gel (10 g) with (*a*) chloroform, (*b*) 50:1, and (*c*) 30:1 chloroform–methanol. Eluant *c* gave **7** (260 mg, 98%) as needles, m.p. 110–111°, $[\alpha]_D^{25}$ +5.8° (*c* 0.4, methanol); ν_{max}^{Nujol} 3450–3350 (OH), 3230 (NH), 1640 and 1540 (amide), and 860 cm^{-1} (Me_2C); n.m.r. data (in dimethyl sulfoxide-d_6): δ 1.29, 1.31 (2 s, 6 H, Me_2C), 1.91 (s, 3 H, AcN), 3.20, 3.31 (2 s, 6 H, 2 OMe), 3.40–4.21 (m, 6 H, H-2–H-6'), 4.35 (d, 1 H, $J_{1,2}$ 7.0 Hz, H-1), 4.43 (t, 1 H, $J_{6,OH} = J_{6',OH} = 5.2$ Hz, OH-6), 4.65 (d, 1 H, $J_{5,OH}$ 4.6 Hz, OH-5), and 7.17 (d, 1 H, $J_{2,NH}$ 8.4 Hz, NH).

Anal. Calc. for $C_{13}H_{25}NO_7$: C, 50.80; H, 9.51; N, 4.56. Found: C, 50.59; H, 9.46; N, 4.38.

2-(Benzyloxycarbonylamino)-2-deoxy-3,4-O-isopropylidene-aldehydo-D-*glucose dimethyl acetal* (**8**). — A solution of **4** (200 mg) in 80% aqueous acetic acid (10 mL) was heated for 1.5 h at 40° and then evaporated at 40°. The residue was purified by chromatography on a column of silica gel (10 g) with (*a*) 200:1 and (*b*) 70:1 chloroform–methanol. Eluant *b* gave 168 mg (92%) of **8** as a syrup; $[\alpha]_D^{25}$ +8.8° (*c* 0.5, methanol); ν_{max}^{film} 3450–3280 (OH, NH), 1690 and 1510 (amide), 870 (Me_2C), and 730 and 680 cm^{-1} (Ph); n.m.r. data (in dimethyl sulfoxide-d_6): δ 1.29 (s, 6 H, Me_2C),

3.22, 3.30 (2 s, 6 H, 2 MeO), 3.43–4.23 (m, 6 H, H-2–H-6'), 4.33 (d, 1 H, $J_{1,2}$ 7.0 Hz, H-1), 4.45 (near t, 1 H, $J_{6,OH} = J_{6',OH} = 5.6$ Hz, OH-6), 4.70 (d, 1 H, $J_{5,OH}$ 5.0 Hz, OH-5), 5.04 (s, 2 H, benzyl methylene), 6.87 (d, 1 H, $J_{2,NH}$ 9.5 Hz, NH), and 7.32 (s, 5 H, Ph).

Anal. Calc. for $C_{19}H_{29}NO_8$: C, 57.13; H, 7.32; N, 3.51. Found: C, 57.20; H, 7.38; N, 3.63.

2,3-O-Isopropylidene-aldehydo-D-*xylose dimethyl acetal* (**14**) *and 1,2-O-isopropylidene-α-D-xylofuranose* (**15**). — To a stirred solution of **11** (1.0 g) in 1,4-dioxane (10 mL) at 65° were added 2,2-dimethoxypropane (4 mL) and *p*-toluenesulfonic acid monohydrate (150 mg). The mixture was stirred for 2 h at 65–68° and then treated with Amberlite IRA-410 (OH^-) ion-exchange resin to remove the acid; the resin was filtered off, and washed with methanol. The filtrate and washings were combined and evaporated, and the syrupy residue was chromatographed on a column of silica gel (15 g) with chloroform, to give a mixture (1.4 g) of **12** and **13** showing a single spot in t.l.c. A solution of the mixture (400 mg) in 80% aqueous acetic acid (20 mL) was heated for 1 h at 40°; it was then evaporated at 40° to a syrup which was chromatographed on a column of silica gel (15 g) with (*a*) 100:1 and (*b*) 70:1 chloroform–methanol. Eluant *a* gave **14** (210 mg) as a syrup; $[\alpha]_D^{25}$ −19° (*c* 0.42, methanol); n.m.r. data (in chloroform-*d*): δ 1.44 (s, 6 H, Me_2C), 2.29–2.72 (2 H, 2 OH), 3.45 (s, 6 H, 2 MeO), 3.73–4.23 (m, 5 H, H-2–H-5'), and 4.38 (d, 1 H, $J_{1,2}$ 5.6 Hz, H-1).

Anal. Calc. for $C_{10}H_{20}O_6$: C, 50.83; H, 8.53. Found: C, 50.69; H, 8.45.

Eluant *b* yielded **15** as needles, wt. 105 mg, m.p. 42–44° (lit.[12] 41–43°), $[\alpha]_D^{25}$ −23° (*c* 0.7, methanol) (lit.[12] −19°); n.m.r. data (in chloroform-*d*): δ (before D_2O treatment) 1.32, 1.48 (2 s, 6 H, Me_2C), 3.03 (near t, 1 H, $J_{5,OH} = J_{5',OH} = 5.0$ Hz, OH-5), 3.98–4.35 (m, 5 H, H-3–H-5', OH-3), 4.51 (d, 1 H, $J_{1,2}$ 3.0 Hz, $J_{2,3}$ 0 Hz, H-2), and 5.96 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1); (after D_2O treatment) 1.32, 1.48 (2 s, 6 H, Me_2C), 3.98–4.10 (m, 2 H, H-5,5'), 4.18 (m, 1 H, H-4), 4.30 (d, 1 H, $J_{3,4}$ 2.4 Hz, $J_{2,3}$ 0 Hz, H-3), 4.51 (d, 1 H, $J_{1,2}$ 3.0 Hz, $J_{2,3}$ 0 Hz, H-2), and 5.96 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1).

REFERENCES

1 A. HASEGAWA, E. TANAHASHI, AND M. KISO, *Carbohydr. Res.*, 79 (1980) 255–264.
2 A. HASEGAWA AND H. G. FLETCHER, JR., *Carbohydr. Res.*, 29 (1973) 209–222.
3 A. HASEGAWA AND H. G. FLETCHER, JR., *Carbohydr. Res.*, 29 (1973) 223–237.
4 A. HASEGAWA, T. SAKURAI, AND N. HASEGAWA, *Carbohydr. Res.*, 45 (1975) 19–27.
5 A. HASEGAWA, N. ARITAKE, AND M. KISO, *Carbohydr. Res.*, 52 (1976) 137–149.
6 M. KISO AND A. HASEGAWA, *Carbohydr. Res.*, 52 (1976) 87–94.
7 M. KISO AND A. HASEGAWA, *Carbohydr. Res.*, 52 (1976) 95–101.
8 A. HASEGAWA AND M. KISO, *Carbohydr. Res.*, 59 (1977) c17–c19.
9 A. HASEGAWA AND M. KISO, *Carbohydr. Res.*, 63 (1978) 91–98.
10 J. D. STEVENS, *Carbohydr. Res.*, 45 (1975) 143–150.
11 A. B. BORKOVEC, *J. Org. Chem.*, 26 (1961) 4866–4868.
12 O. SVANBERG AND K. SJÖBERG, *Ber.*, 56 (1923) 863–869.
13 R. KUHN, H. TRISCHMANN, AND I. LÖW, *Angew. Chem.*, 67 (1955) 32.
14 R. KUHN AND H. GRASSNER, *Justus Liebigs Ann. Chem.*, 610 (1957) 122–131.
15 W. MACKIE AND A. S. PERLIN, *Can. J. Chem.*, 44 (1966) 2039–2049.
16 A. S. PERLIN, *Can. J. Chem.*, 44 (1966) 539–550.