Synthesis of Acyclic Sugar Oxazoles

By Stephen J. Eitelman, Richard H. Hall,* and Amor Jordaan
(*National Chemical Research Laboratory, South African Council for Scientific and Industrial Research, Pretoria* 0001, *Republic of South Africa*)

Summary The reaction of protected aldonic acid lactones with ethyl isocyanoacetate and base in aprotic medium gives either α-(formylamino)acrylic ester derivatives or acyclic sugar oxazole derivatives, where base-catalysed elimination reactions can be suppressed.

Ethyl isocyanoacetate (EIA) reacts with aldehydes and ketones in strongly basic and aprotic medium to give α-(formylamino)acrylic esters (formylaminomethylenation),[1] but attempts to apply the reaction to γ-butyrolactone were unsuccessful.[2] However, the formylaminomethylenation of 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone gave acrylic esters in 63% yield (12:1, *E*:*Z*-isomers).[2] As the reaction represents a route to *C*-glycosyl compounds[3] and specifically to carbon–carbon linked *C*-glycosyl α-amino acids,[2,4] the scope of the reaction is being explored, and we report on the effects of the nature of the lactone and the reaction conditions on the course of the reaction.

Formylaminomethylenation of 2,3:5,6-di-*O*-isopropylidene-D-allono-1,4-lactone ($EtO_2C{\cdot}CH_2NC$, KH, tetrahydrofuran, −10 °C) gave, as expected, the (*E*)-compound (**1**)† (59%), a syrup, $[\alpha]_D^{20}$ −241°, and its (*Z*)-isomer (**2**) (2%), a syrup, $[\alpha]_D^{21}$ −124°, but a major by-product, compound (**6**) (10%) was also obtained as a syrup, $[\alpha]_D^{20}$ +51°. Further, when the reaction was applied to 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone,[5] compound (**8**) (50%), a syrup, $[\alpha]_D^{20}$ +28°, was obtained as the major product and an intensive search of reaction products showed that no acrylic esters, analogous to (**1**) and (**2**), had been produced.

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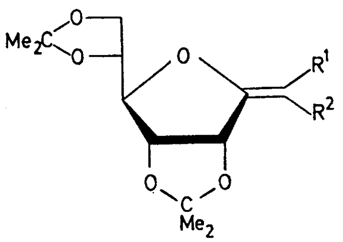
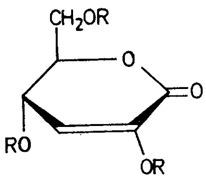
† All new compounds were chromatographically homogeneous and had satisfactory analytical and spectral properties. Optical rotations were measured for solution in chloroform (c 1·0 ± 0·3%).

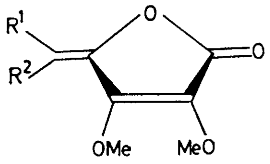


(1) $R^1 = CO_2Et$, $R^2 = NHCHO$

(2) $R^1 = NHCHO$, $R^2 = CO_2Et$

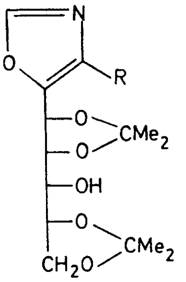


(3) $R = CH_2Ph$

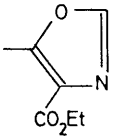


(4) $R^1 = CH_2OH$, $R^2 = H$

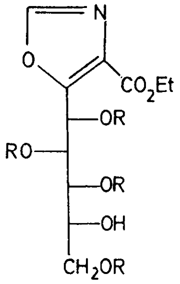
(5) $R^1 = H$, $R^2 = CH_2OH$



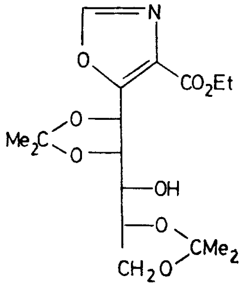
(6) R =



(7) $R = CO_2Et$

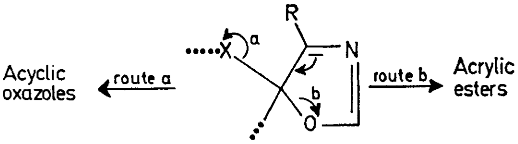


(8) $R = CH_2Ph$



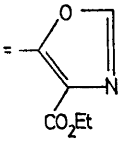
(9)

The reaction of 2,3:5,6-di-*O*-isopropylidene-D-allono-1,4-lactone with EIA, and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) as base instead of potassium hydride gave compound (**7**) (56%), a syrup, $[\alpha]_D^{20}$ +48°, as the major product and the acrylic esters (**1**) and (**2**) were not detected. The reagents were added at 25 °C as there was no appreciable change in the product mixture when the reaction was carried out at lower temperatures. Similar treatment of 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone gave the oxazole (**9**) (49%), a syrup, $[\alpha]_D^{20}$ −48°.



(10) $R = CO_2Et$, X = C or O

(11) R =



, X = C or O

With DBN as base, 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone did not give the oxazole (**8**) and the only product obtained in appreciable yield (20%) was the lactone (**3**), a syrup, $[\alpha]_D^{22}$ +52°, which presumably is formed by β-elimination.[6] Similarly, the reaction with 5,6-*O*-isopropylidene-2,3-di-*O*-methyl-L-ascorbic acid[7] gave the lactone (**4**) and its 4-(*E*)-isomer (**5**) [differentiation between the two isomers, m.p. 79·5–81 °C (69%) and m.p. 36–38 °C (7%), was not possible], by elimination of acetone. The same products were obtained in lower yield (*ca.* 30%) with KH as base.

The reaction of EIA with carbonyl compounds in basic and aprotic medium involves[1] a spiro-intermediate (**10**) or (**11**) [(**11**) arises from the reaction of the product of self-condensation[8] of EIA with the carbonyl compound]. The results indicate that whereas with aldehydes and ketones the intermediate (**10**) or (**11**) (X = C) opens to form a 'pentadienyl anion,' which on protonation gives the acrylic esters (route b), with lactones the intermediate (**10**) or (**11**) (X = O) can also open to form an alkoxide, which on protonation gives the acyclic oxazole (route a). The reaction is further complicated by base-induced elimination reactions and such reactions depend on the relative acidities of the α-protons of EIA and the lactone ring protons.

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[3] For recent examples see: G. Just and S. Kim, *Tetrahedron Letters*, 1976, 1063; S. De Bernardo and M. Weigele, *J. Org. Chem.*, 1976, **41**, 287; F. G. De Las Heras, C. K. Chu, S. Y-K. Tam, R. S. Klein, K. A. Watanabe, and J. J. Fox, *J. Heterocyclic Chem.*, 1976, **13**, 175; J. G. Buchanan, A. R. Edgar, M. J. Power, and G. C. Williams, *Carbohydrate Res.*, 1975, **45**, 312; G. Trummlitz, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.*, 1975, **40**, 3352; T. Huynh-Dinh, A. Kolb, C. Gouyette, J. Igolen, and S. Tran-Dinh, *ibid.*, p. 2825.

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