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[4+2] CYCLOADDITION REACTION OF BIS (TRICHLOROETHYL) AZODICARBOXYLATE AND GLYCALS: PREPARATION OF A C1-C1 2-AMINO DISACCHARIDE

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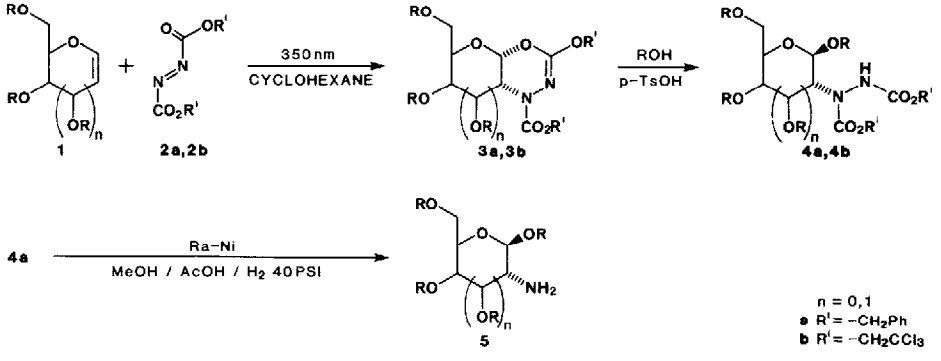
SUMMARY: *Bis (trichloroethyl) azodicarboxylate is an efficient diene in the [4+2] cycloaddition reaction with glycals. It offers several advantages over the previously described dibenzyl azodicarboxylate (DBAD) which was used to prepare 2-amino glycosides.*

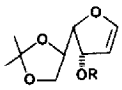
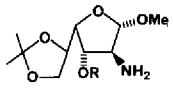
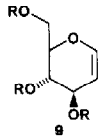
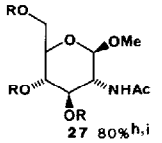
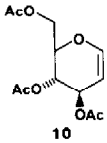
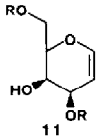
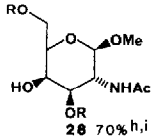
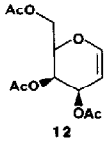
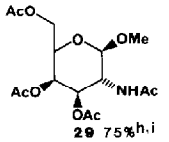
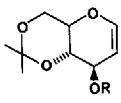
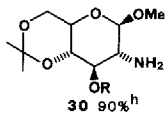
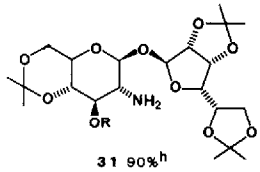
We have recently disclosed the usefulness of the [4+2] cycloaddition reaction between dialkyl azodicarboxylates and glycals (**1**) in the preparation of 2-amino glycosides[1-3]. At that time dibenzyl azodicarboxylate (DBAD) (**2a**) was used to conduct the cycloaddition reaction since the adducts could be efficiently converted to 2-amino glycosides (Scheme 1). However, under the standard experimental conditions, i.e. irradiation at 350 nm in cyclohexane, no formation of cycloadduct was detected when triacetyl glucal (TAG) was the substrate, even after several weeks. It was subsequently found that the poor reactivity of TAG toward DBAD is due to the C-3 acetoxy group[3]. Presumably, the presence of an electron withdrawing group at C-3 lowers the energy of the HOMO of the vinyl ether affecting its overlap with the LUMO of the azo compound. It was therefore reasoned that azo compounds bearing electron withdrawing groups should be more reactive toward glycals than DBAD due to the lowering of the LUMO energy.

SCHEME 1



This indeed proved to be the case for bis(trichloroethyl) azodicarboxylate (BTCEAD, **2b**)[4] which adds to glycals at significantly higher rates than DBAD. The reaction was evaluated on several glycals (**8** - **13**) and very good yields of the corresponding adducts (**14** - **19**) were obtained using 1.5 equiv. of BTCEAD (c.f. 5 equiv. for DBAD) (Table 1). The difference in reactivity between DBAD

TABLE 1

GLYCAL	ADDUCT[a,b]	GLYCOSIDE	AMINE
 **8**	**14** 73%[c] 18 hr (18 hr)	**20** 95%[f]	 **26** 65%[h]
 **9**	**15** 80%[c] 1.5 days (3–4 days)	**21** 88%[f]	 **27** 80%[h,i]
 **10**	**16** 76%[d] 2 weeks (no reaction) 2/3 Top/Bottom	—	—
 **11**	**17** 78%[c] 1 day (2–3 days)	**22** 75%[f]	 **28** 70%[h,i]
 **12**	**18** 85%[e] 1.5 weeks (no reaction)	**23** 97%[f]	 **29** 75%[h,i]
 **13**	**19** 80%[c] 5 days (1 week) 15/1 Top/Bottom	**24** 90%[f]	 **30** 90%[h]
R = t-BuMe$_2$Si		**25** 60–68%[g]	 **31** 90%[h]

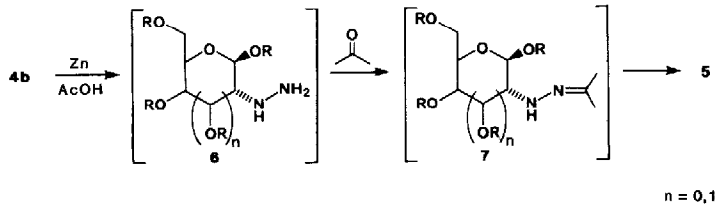
a) ALL NEW COMPOUNDS CITED IN THIS COMMUNICATION GAVE SATISFACTORY ELEMENTAL ANALYSIS OR HIGH RESOLUTION MASS SPECTRUM b) NUMBERS IN BRACKETS REFER TO THE TIME REQUIRED TO AFFORD THE CYCLOADDITION REACTION WITH 5 EQUIV. OF DBAD. c) BTCEAD 1.5 EQUIV./ CYCLOHEXANE / CH_2Cl_2/ 350 nm. d) BTCEAD 1.5 EQUIV./ FOLLOWED BY 1.5 EQUIV. AFTER ONE WEEK./ CYCLOHEXANE / CH_2Cl_2/ 350 nm. e) BTCEAD 1.5 EQUIV./ FOLLOWED BY 0.3 EQUIV. AFTER ONE WEEK / CYCLOHEXANE CH_2Cl_2 / 350 nm f) CH_2Cl_2 / MeOH (3/1) / p-TsOH (0.5 mg)/ RT/ 1–2 MIN. g) L-DIACETONIDE MANNOSE / $BF_3 \cdot Et_2O$ 1.5 EQUIV. / MOLECULAR SIEVE 4 Å / CH_2Cl_2 / −78°C (45 min) → −15°C (10 min). h) Zn THREE FOLD EXCESS BY WEIGHT / AcOH (45 min) → ACETONE (1 hr) / RT. i) Ac_2O / Py / RT.

and BTCEAD is most obvious in the case of 3-acyl glycals. The reaction did take place with TAG (**10**), albeit at a lower rate than the corresponding 3-silyloxy cases, to give in good yield a 3:2 diastereomeric mixture of adducts. With triacetyl galactal[5] (**12**) as substrate a single cycloadduct (**18**) was obtained in good yield[6].

As with the DBAD series, treatment of the adducts with a catalytic amount of p.TsOH in methanol gave the corresponding methyl glycosides (**20** - **24**) in good yields. In addition, the adducts underwent ring opening by other alcohols as found in the dibenzyl cases[2]. Here however, another advantage to BTCEAD became apparent. While no great success was obtained with the dibenzyl adducts in the preparation of C1- C1 disaccharides, the BTCEAD adducts could be converted to these structurally complex disaccharides. The disaccharide **25** was efficiently prepared by treating a CH_2Cl_2 solution of the dihydrooxadiazine **19** and L-diisopropylidene mannose with $BF_3 \cdot Et_2O$ (-78° to -15°C) . To our knowledge, this is the first synthesis of a C1- C1 disaccharide with an amino group at C-2.

Once the reactivity of the adducts toward various alcohols was established, we then focused our attention on the transformation of the hydrazides (**4b**) to the amines (**5**). Catalytic hydrogenation (Ra-Ni, 40 PSI) gave the amines in only very low yields . However, treatment with zinc dust in acetic acid, converted the hydrazides to the hydrazines (**6**)[7] (Scheme 2), instead of the desired amines. Interestingly, the addition of acetone to the reaction mixture generated the amines in high yields. By monitoring the reaction (TLC, ^{1}H-NMR), it was observed that the production of the amine proceeds via the hydrazone (**7**)[8,9]. Therefore, the 2-hydrazido glycosides (**20** to **25**) prepared by the method described herein can be converted to their corresponding 2-amino glycosides (**26** - **31**) under mild conditions. Obviously, these reduction conditions offer an alternative to those used for the dibenzyl cases that will be compatible with functional groups that are susceptible to Ra-Ni.

SCHEME 2



In conclusion, BTCEAD is a good alternative to DBAD as a reagent to perform the [4+2] cycloaddition reaction on glycals, particularly when an acyl group is attached at C-3. The adducts can be converted to 2-amino glycosides by glycosylation with alcohols, followed by reduction with zinc in acetic acid/acetone mixture. In addition, these adducts offer an entry into C1-C1 disaccharides not available from the dibenzyl series. Theoretical aspects on this [4+2] cycloaddition reaction will be reported in due course.

ACKNOWLEDGEMENT: The authors wish to thank Dr Bernstein for recording the ^{1}H-NMR spectrum and to have performed NOE experiment on compound **31**.

References and footnotes

1. Fitzsimmons, B. J.; Leblanc, Y.; Rokach, J. *J. Am.Chem. Soc.* **1987**, 109, 285-285

2. Fitzsimmons, B. J.; Leblanc, Y.; Ling, C.W.; Rokach, J. *J. Am. Chem. Soc.* **1988**, 110, 5229-5231.

3. Leblanc, Y.; Fitzsimmons, B.J.; Springer, J. P.; Rokach, J. *J.Am.Chem. Soc.* **1989**, 111, 0000-0000.

4. Mackay, D.; Pilger, C.W.; Wong, L. L. *J.Org. Chem.* **1973**, 38, 2043-2049.
Also available from Aldrich and co.

5. Available from Toronto Research Chemical Inc.

6. A solution of the galactal **126** and BTCEAD (3 g, 1.5 equiv.) in cyclohexane (24 ml) and CH_2Cl_2 (5 5 ml) was irradiated at 350 nm in a Rayonnet apparatus for a week when additional reagent (0.5 g, 0.3 equiv.) was added. After a futher 4 days of irradiation, the mixture was chromatographed to afford the adduct **18** (2.4 g, 85%).

7. The R-NH-NHAc was isolated in 75% yield by reduction of the glycoside **22** with zinc dust followed by acetylation.

8. Shapiro, D.; Abramovitch, R. A. *J. Am. Chem. Soc.* **1955**, 77, 6690-6691

9. Typical procedure for the reduction of hydrazides to amines: To a solution of the glycoside **21** (250 mg, 0.28 mmol) in glacial acetic acid (2 ml), zinc dust (750 mg) was added portionwise over 5 min. The resulting mixture was stirred 45 min at rt and acetone (200 ul) was then added. After 1 hr, the tlc (60% ether in hexane) showed complete conversion of the hydrazone to the amine. CH_2Cl_2 was then added and the resulting mixture filtered through a pad of celite. The solvents were removed on high vacuum pump and excess of acetic anhydride and pyridine were added to give, after purification by flash chromatography, the amide **27** (150 mg, 0.23 mmol, 80%).

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