Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 417–421

TETRAHEDRON: *ASYMMETRY*

Efficient conditions for the synthesis of *C*-glycosylidene derivatives: a direct and stereoselective route to *C*-glycosyl compounds†

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Received 9 December 1999; accepted 13 December 1999

Abstract

Efficient conditions for the synthesis of *C*-glycosylidene compounds from lactones based on Wittig reactions of cyanomethyl triphenylphosphoranylidene involving microwave heating are described: subsequent stereoselective reduction of the anomeric olefins gave the corresponding *C*-glycosides in good yields with high stereocontrol.

1. Introduction

Wittig olefination is one of the most employed reactions for the transformation of a carbonyl group of ketones and aldehydes into an olefin.[1] Many functionalized Wittig reagents,[2] including sugar-containing ones, are now available,[3] and allow the construction of complex structures with high efficiency. Nevertheless, this olefination is essentially limited to the above-mentioned carbonyl groups and only a few examples of the Wittig olefination of esters, amides or anhydrides have been reported.[4] Moreover, these non-classical Wittig olefinations often refer to intramolecular reactions.[5] We have recently investigated the reactivity of lactones and some esters in the Wittig olefination. We put particular emphasis on sugar-derived lactones because the resulting *C*-glycosylidenes are of special interest as carbohydrate mimics,[6,7] and in the synthesis of *C*-glycosyl compounds. We showed that dichloromethylenation of ester carbonyl groups is possible with triphenylphosphine and carbon tetrachloride in refluxing THF.[8] More recently, we successfully investigated the reaction of stabilized phosphoranes with some sugar lactones,[9,10] thus providing a direct entry to *C*-glycosylidene compounds (Scheme 1).[11,12] This reaction

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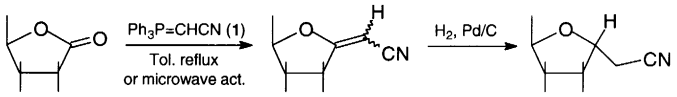
† Dedicated to Professor Pierre Sinaÿ on the occasion of his 62nd birthday.

0957-4166/00/$ - see front matter
PII: S0957-4166(99)00586-8

is usually performed in toluene at 140°C in a sealed vessel.[13] Although these rather harsh conditions can be easily reached, more simple ones would be of interest.



Scheme 1.

2. Results and discussion

We have now investigated the reaction of cyanomethyl triphenylphosphorane **1**, which is readily prepared by treatment of the commercially available corresponding phosphonium chloride under basic conditions.[14] The phosphorane is sufficiently stable to be stored for weeks. Its reactivity is greater than that of the corresponding ester[9a] so the reaction with lactones can be carried out in refluxing toluene. Preliminary investigations, conducted on the D-gulonolactone derivative **2**, showed that the reaction needed at least 4 equivalents of phosphorane to go to completion, the use of 2 equivalents leaving some unchanged starting material. Of note is also the poor stability of the phosphorane under our previous conditions (toluene, 130°C).

Different lactones **2**, **4**, **6**, **8**, **10**, **12**, **14**, **17** and **19** were submitted to these reaction conditions and gave good to excellent yields of the expected olefins (Fig. 1). It should be mentioned that the *E*:*Z* mixture was essentially 1:1 in most cases. All reactions needed at least 16 h to go to completion.[15] The reaction worked equally well with γ- and δ-lactones. It is also important to note that in the case of lactone **17** the *E*:*Z* 1:1 mixture was formed, whereas with the carbomethoxy triphenylphosphorane only the *Z*-isomer was formed.[10] No interference with acetal-protecting groups was observed as expected. Moreover, the acetate-protecting group (Table 1, entries 7 and 8) did not interfere under these conditions, in contrast with the dichloro-olefination reaction where acetates were also olefinated.[8b]

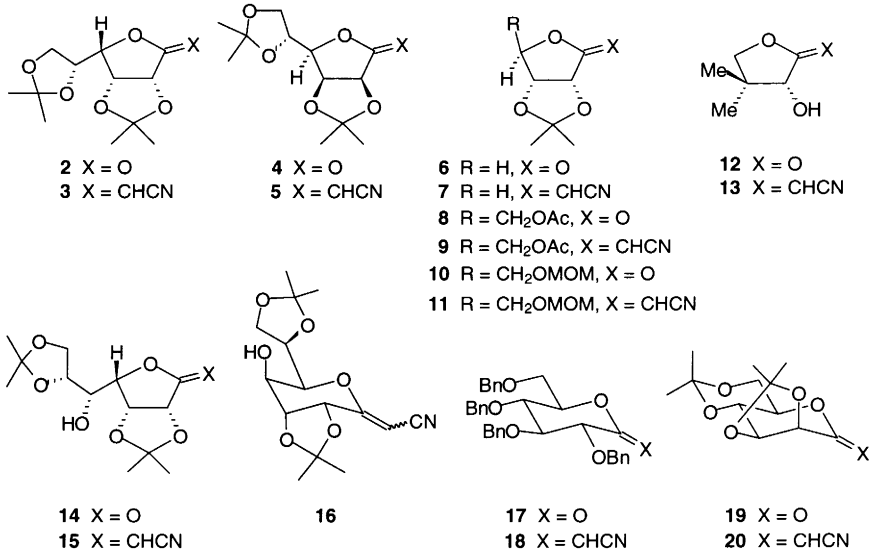


Fig. 1.

In the search for milder conditions our attention turned to the use of microwave activation. This technique, rarely employed in organic chemistry until recently, has great potential for many different

Table 1
Wittig olefination of lactones

Entry	Starting lactone	Conditions	Product	Yield (%)	*E/Z*[a)]
1	**2**	Toluene, reflux 24 h	**3**	96	3.5:1
2	**2**	Microwave activation, 4 min	**3**	98	1.7:1
3	**4**	Toluene, reflux 24 h	**5**	76	1.7:1
4	**4**	Microwave activation, 4 min	**5**	98	1.2:1
5	**6**	Toluene reflux 24 h	**7**	83	1:1
6	**6**	Microwave activation, 4 min	**7**	86	1.1:1
7	**8**	Toluene, reflux 48 h	**9**	69	1:1.8
8	**8**	Microwave activation, 4 min	**9**	85	1:1.8
9	**10**	Toluene, reflux 72 h	**11**	96	1.1:1
10	**10**	Microwave activation, 4 min	**11**	88	1:1.8
11	**12**	Toluene, reflux 24 h	**13**	64	1.9:1
12	**12**	Microwave activation, 4 min	**13**	96	1:1.2
13	**14**	Toluene, reflux 16 h	**15, 16**	98	1:1
14	**17**	Toluene, reflux 16 h	**18**	91	2.8:1
15	**17**	Microwave activation, 6 min	**18**	90	1.8:1
16	**19**	Toluene, reflux 24 h	**20**	86	1.3:1
17	**19**	Microwave activation, 8 min	**20**	89	1.1:1

a) Ratio determined from ^{1}H nmr spectrum see ref. 9a.

reactions.[16] In our case a dramatic improvement was observed when going from standard heating to microwave activation, particularly in terms of reaction time.[17] Thus, as shown in Table 1, reactions were now performed in less than 10 min with the use of a standard microwave oven. Although the *E*:*Z* ratio was in some cases different from that observed in the purely thermal reaction, there was no major improvement in this regard.

Finally, we investigated the reaction of two partially-protected lactones with phosphorane **1**. The glucoheptonolactone **14** was treated according to the heating conditions and gave an excellent 98% yield of two olefins, each being an *E*:*Z* mixture. The expected olefin **15** was formed in 48% yield (*E*:*Z*, 1:1) and was accompanied by the rearranged product **16** (*E*:*Z*, 2:1). The formation of this product can be explained by the 1,4 addition of the free OH group of **15** on the double bond followed by opening of the five-membered ring to form the less constrained pyranoside **16**.

The hydrogenation of the *C*-glycosylidene compounds obtained above was next examined. Reduction of the double bond of some representatives (**3**, **5**, **7**, **9**, **11**, **13** and **20**) (Fig. 2) by catalytic hydrogenation over 10% Pd/C under a hydrogen atmosphere produced the expected *C*-glycosyl derivatives essentially as single isomers with a 3,4 *cis*-relationship (*C*-glycoside numbering).[18] A strong directing effect of the acetal group was observed as in the reduction of dichloro-olefins.[19] All reactions gave excellent yields as shown in Table 2 except for olefins **18**, which obviously underwent simultaneous debenzylation. Unexpectedly, removal of all benzyl-protecting groups could not be achieved so that an intractable mixture of compounds was obtained.[20]

Given the versatility of the cyano group as an amide, ester and aldehyde group surrogate, the above

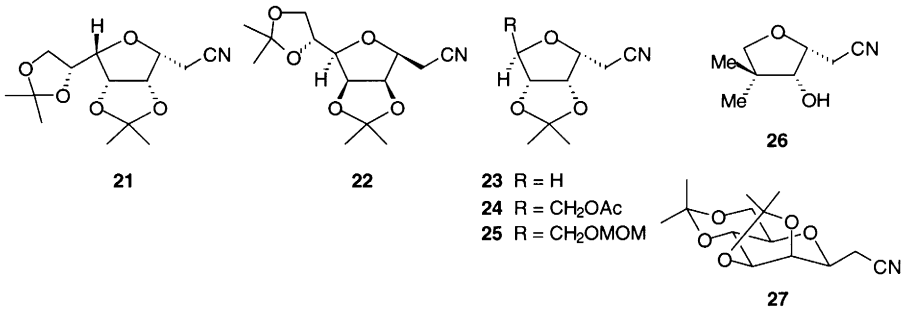


Fig. 2.

Table 2
Catalytic hydrogenation of *C*-glycosylidene compounds

Entry	Starting olefin	Product	Yield (%)
1	**3**	**21**	73
2	**5**	**22**	71
3	**7**	**23**	86
4	**9**	**24**	89
5	**11**	**25**	92
6	**13**	**26**	75
7	**20**	**27**	62

olefination using thermal conditions or microwave activation constitutes an efficient and versatile route to new *C*-glycosylidene nitriles which can be reduced to the corresponding *C*-glycosyl compounds with complete stereocontrol at the anomeric centre. The use of carbohydrate-derived phosphoranes[3] in the Wittig olefination of lactones under these conditions should open the way to new disaccharidic mimics and this is under current study in our laboratories.

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