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Selective *N*-Debenzylation of Benzylamino Derivatives of 1,6-Anhydro-β-D-hexopyranoses

Jiri Kroutil,* Tomas Trnka, and Miloslav Cerny

Department of Organic Chemistry, Charles University, Albertov 6, 128 43 Prague 2, Czech Republic

kroutil@natur.cuni.cz.

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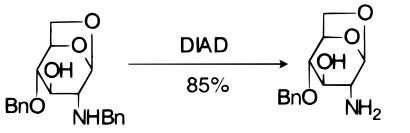
ABSTRACT



When the series of 2-, 3-, and 4-(benzylamino)-2-, 3-, and 4-deoxy derivatives of 1,6-anhydro-β-D-hexopyranoses in the D-*gluco*, D-*lyxo*, and D-*arabino* configurations were reacted with diisopropyl azodicarboxylate, *N*-benzyl groups were selectively cleaved in the presence of *O*-benzyl groups. The yields ranged from 51 to 97%. The debenzylation of some aliphatic benzylamines is also discussed.

The benzyl group is frequently used as a protecting group for amino, hydroxyl and thiol groups,[1] especially in carbohydrate chemistry. Its high chemical stability toward many reagents used for modifying sugar skeletons along with the existence of relatively easy methods for its introduction and mild conditions for its deprotection are the main reasons for its dominance over other protecting groups. However, in many cases it is very difficult to selectively remove one benzyl group in the presence of others.[2] One possible solution to this problem is hydrogenation under various conditions, as the reactivity order of *N*-benzyl and *O*-benzyl groups toward hydrogenation is dependent upon pH and solvent. Often though, this selectivity is too low to obtain reasonable reaction yields. The development of new methods for selective debenzylation is, therefore, still a challenge.

In this letter, we present a procedure for the *N*-debenzylation of various secondary benzylamines derived from the 1,6-anhydro-β-D-hexopyranose skeleton (Figure 1) by reaction with diisopropyl azodicarboxylate (DIAD).

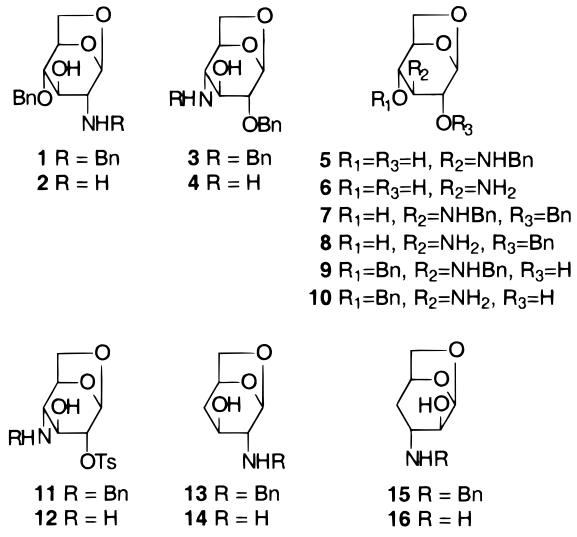


Figure 1. The benzylamino derivatives of 1,6-anhydro-β-D-hexopyranoses used for the reaction with diisopropyl azodicarboxylate (Bn = benzyl and Ts = *p*-toluenesulfonyl).

Esters of azodicarboxylic acid are known to be dealkylating agents for amines. The reaction of an amine with dialkyl azodicarboxylates is complex and the actual product depends

† e-mail: trnka@natur.cuni.cz.
‡ e-mail: mila@natur.cuni.cz.

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on the type of amine used. Aliphatic primary amines give amides [3,4,5] while aromatic amines (e.g., aniline[5,6] or toluidine[7]) lead to a triazane adduct, **I** (Figure 2), or form ring substitution products (e.g., 2,5-dimethylaniline[3]).

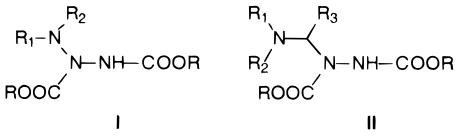

Figure 2. Proposed structures (**I** and **II**) for the reaction product of an amine with dialkyl azodicarboxylates.

Secondary amines form either an amide (e.g., piperidine and dimethylamine[8]) or adducts with triazane structure **I**,[9,10] or the structure **II** [4] (Figure 2). These adducts produce aldehydes and dealkylated primary amines upon acidic hydrolysis.[4,5]

Tertiary amines react with dialkyl azodicarboxylates to form adducts of structure **II**,[8] which are hydrolyzed by dilute hydrochloric acid to give dealkylated secondary amines. The yields range from good to high (73−91%). Thus, the dealkylation of tertiary amines with dialkyl azodicarboxylates is a feasible synthetic procedure, whereas no successful utilization of this method for secondary amines has previously been reported.

When 1,6-anhydro-4-*O*-benzyl-2-(benzylamino)-2-deoxy-β-D-glucopyranose **1** was reacted with DIAD in toluene, the debenzylated amine **2**, benzaldehyde, and diisopropyl hydrazinodicarboxylate (DIHD) were formed. [11] GC-MS analysis of the reaction mixture showed that benzaldehyde and DIHD were formed in approximately equal amounts. After hydrolysis of DIHD, 2-amino-1,6-anhydro-4-*O*-benzyl-2-deoxy-β-D-glucopyranose **2** was isolated in 81% yield. Similarly other *N*-benzylamino derivatives **3**, **5**, **7**, **9**, **11**, **13**, and **15** were treated with DIAD to obtain the corresponding *N*-debenzylated amines **4**, **6**, **8**, **10**, **12**, **14**, and **16**. No other products were formed. The results are summarized in Table 1.

Table 1. Reactants, Products and Reaction Conditions for the Reaction of Benzylamines with Diisopropyl Azodicarboxylate

no.	reactant	product	method[11]	temp °C	time	yield[a]%
1	1	2	A	reflux	2 h	81
2			B	55	48 h	85
3			B	reflux	2 h	84
4			*b*	55	64 h	60
5	3	4	A	reflux	2 h	75
6			B	50	48 h	67
7	5	6	A	reflux	10.5 h	58
8			B	50	64 h	51
9	7	8	B	50	64 h	59
10	9	10	A	reflux	12 h	60
11			B	50	64 h	62
12	11	12	B[c]	55	4 d	97
13	13	14	A	rt	2 d	89
14	15	16	A	rt	7 d	55
15	17	18	A	rt	14 d	52[d]
16			B	55	–	*e*
17	19	20	B	50	7 d	62
18	21	–	A	rt	–	*e*
19			B	reflux	–	*e*
20	22	–	B	reflux	–	*f*

[a] Isolated yields. [b] The reaction was conducted in a pyridine−water (50:1) mixture. [c] Reaction mixture was chromatographed on silica gel (toluene−acetone 2:1 mixture) in order to separate DIHD. [d] In addition 12% of the reactant was isolated by chromatography on silica gel (toluene−acetone 2:1 mixture). [e] Decomposition of benzylamine. [f] Starting material was recovered. All prepared compounds were characterized.

The rate of reaction with DIAD was affected by the choice of solvent and temperature. The presence of HCl in the reaction mixture (reported as a necessary component[12]) is not critical for successful debenzylation. However, in the case of compound **1**, HCl greatly accelerates the reaction (compare entries 2 and 4 in Table 1).

We did not prove the presence of adducts **I** or **II** in the reaction mixture by either NMR (^{1}H and ^{13}C) or by the IR spectral characteristics listed in refs 8−10. The attempts to isolate these adducts by varying the reaction conditions failed. Nevertheless, there is indirect evidence that the reaction involves attack at the nitrogen atom of the benzylamino group: The reaction proceeds slowly with benzylamines **5**, **7**, and **9** where steric interactions between the 1,6-anhydro bridge and the C-3 benzylamino group are likely to diminish the accessibility of the nitrogen atom toward attack by DIAD.

When aliphatic benzylamines **17**, **19**, **21,** and **22** (Figure 3) were treated with DIAD, the results were much less satisfactory and the course of the reaction often depended upon the solvent and the structure of the benzylamine. Generally the reaction was quite slow in toluene at room temperature, whereas heating in a mixture of pyridine and

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(11) Typical experimental procedure for *N*-debenzylation with DIAD: **Method A** (in toluene). To a solution of benzylamine **1** (1 mmol, 340 mg) in toluene (5 mL) was added DIAD (220 μL, 1.1 equiv), and the mixture was stirred at the given temperature until TLC showed no starting material. The mixture was concentrated in vacuo, and the resulting oil was treated with 5% NaOH in water−ethanol (in order to hydrolyze the DIHD) for several days at room temperature. After evaporation of ethanol and dilution with an equal volume of water, the debenzylated amine **2** was extracted with dichloromethane (repeatedly) and crystallized from a mixture of ethanol−ether−light petroleum ether. **Method B** (in pyridine−concentrated HCl mixture). A solution of benzylamine **1** (1 mmol, 340 mg), concentrated HCl (ca. 35%, 0.1 mL), and DIAD (220 μL, 1.1 equiv) in pyridine (5 mL) was heated to the given temperature until benzylamine disappeared. After evaporation of the solvent, the reaction mixture was treated following the same procedure as in method A.

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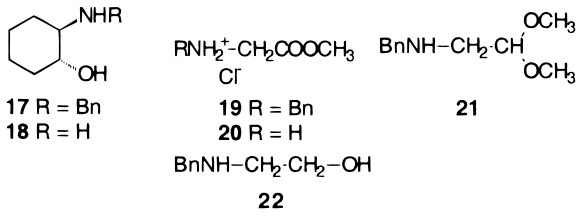

Figure 3. Aliphatic benzylamines used for the reaction with diisopropyl azodicarboxylate (Bn = benzyl).

concentrated HCl led to either complete decomposition or recovery of the starting benzylamine. While simple *(N*-benzylamino*)*ethanol **22** did not react with DIAD at all, racemic *trans*-2-(benzyl amino)cyclohexanol **17** gave the corresponding amine in 52% yield in toluene, but was totally decomposed in the pyridine−concentrated HCl mixture.

Similar results were obtained for *N*-benzyl-2,2-dimethoxyethylamine **21** which has an acetal moiety and should mimic the 1,6-anhydro-β-D-hexopyranose derivative **1**.

The difference in reactivity toward DIAD between the sugar derivatives and the aliphatic benzylamines is perplexing. One alternate mechanism for the dealkylation of tertiary amines containing a CHCHN moiety has been reported.[13] This mechanism proceeds via an enamine intermediate and requires 2 equiv of dialkyl azodicarboxylate. However, since all of the studied benzylamines except methyl *N*-benzylglycinate **19** contain a CHCHN moiety, this mechanism could only account for the differences between **19** and the other aliphatic amines. Therefore, the reason that the 1,6-anhydro-β-D-hexopyranoses are *N*-debenzylated cleanly by DIAD while the aliphatic benzylamines are not is probably due to the considerably limited steric flexibility of the sugar skeleton rather than to the existence of a competing mechanism.

The described procedure for *N*-debenzylation tolerates the presence of other types of benzyl groups (*O*-benzyl) as well as other functional groups in the molecule (free hydroxyl and *O*-tosyl group). Toluene is the recommended reaction solvent because it gave satisfactory yields of debenzylation for most of the investigated benzylamino derivatives.

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