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A convenient method for the alkylation of sulfamides using alkyl bromides and Mitsunobu betaine

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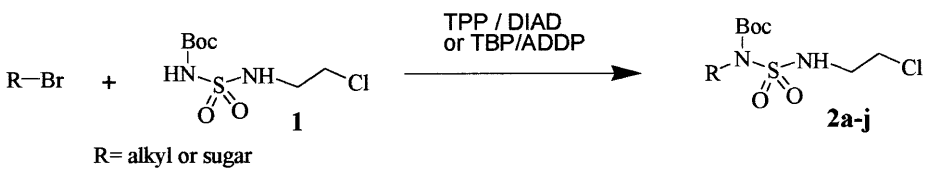
Abstract—The alkylation of *N*-Boc-*N*′-(2-chloroethyl)sulfamide **1** by electron-deficient alkyl bromides using the Mitsunobu reagent as mild base is described. This method was also applied to the *N*-glycosylation of various carbohydrates and was anomerically selective.

In our ongoing research on the synthesis of alkylating agents such as *N*-chloroethylnitrososulfamide (CENS) compounds,[1] we focused our attention on the synthesis of a new generation of sugar-derived compounds. The key step in the preparation of such compounds is the alkylation of *N*-Boc-*N*′-(2-chloroethylsulfamide) **1**. This was followed by the selective removal of the Boc group on molecule **2**, and then by nitrosation to afford CENS in good overall yields.

To promote efficiently the *N*-alkylation reaction, we first used a classical *N*-alkylation method using a mineral base such as potassium or sodium carbonate in an heterogeneous medium. In each case, we obtained the desired products in less than 10% yield (data not shown). These disappointing results led us to investigate another approach in condensing various bromosugars on **1** using a Mitsunobu redox couple (Scheme 1).

We first applied the reaction to different alkyl bromides in which the bromine atom is bonded to electron-deficient carbon (experiments on inactivated alkyl bromides were unsuccessful). The reaction proceeds under mild and neutral conditions. Mitsunobu betaine[2] generated in situ from the phosphine and the azodicarboxylate plays the role of a base which is sufficiently strong to deprotonate the NH of the sulfamide prior to alkylation. Two different redox couples have been tested: (a) tri-*n*-butylphosphine (TBP) and 1,1′-(azodicarbonyl)-dipiperidine and (b) triphenylphosphine (TPP) and diisopropylazodicarboxylate (DIAD). The former (using 1.5 equiv. of each) appears to be superior to the latter (using 3 equiv. of each). Table 1 summarizes the results.[3]

The synthesis was carried out in THF for the TPP/DIAD couple, and in benzene for the TBP/ADDP couple. A standard sequence of reagent additions was used. Thus compound **1** (1 equiv.), the phosphine and alkyl bromide (1 equiv.) were dissolved in the appropriate solvent. After addition of DIAD or ADDP, the mixture was allowed to stand at room temperature overnight. The mixture was poured into water, and extracted with methylene chloride. The combined organic layers were dried over anhydrous Na_2SO_4, and



Scheme 1.

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concentrated in vacuo. The resulting residue was then purified by chromatography on silica gel. The different products were obtained in moderate to good yields. The structures of all new compounds were confirmed by the usual spectroscopic analysis.[4]

We then applied the method to the glycosylation reaction (Table 1). Thus the reaction of tetra-*O*-acetyl-α-D-glycopyranosyl bromide with *N*-Boc-*N'*-(2-chloroethyl)sulfamide using Mitsunobu reagents afforded selectively and exclusively the β anomer product in good or moderate yield with anomeric carbon–nitrogen bond forming (entries 2f–2j). The reaction, applied to pyranoses (entries 2f–2h) and to furanose (entries 2i and 2j), demonstrates the potential of our approach.

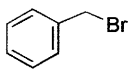
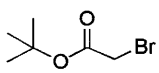
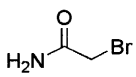
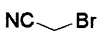
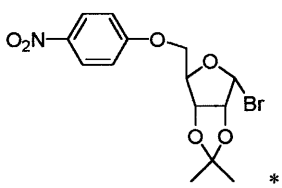
Our method compares favorably with the Mitsunobu reaction applied to sugars with anomeric hydroxyl functions. Its usefulness with such compounds is limited owing to the formation of various ratios of anomeric products. In fact few applications of the Mitsunobu reaction to glycoside bond formation have been reported in the literature.[5–9]

The present approach to *N*-glycoside synthesis is a mild and viable procedure which circumvents the need for deprotection of the anomeric position, and is compatible with various protecting groups (entry 2j).

In conclusion, we have achieved a convenient and interesting method involving the addition of *N*-Boc sulfamide to various alkyl bromide derivatives under Mitsunobu conditions. This approach provides an excellent entry into the selective synthesis of *N*-β-glycosyl compounds starting from halogeno sugar.

We note that our mild Mitsunobu base might be useful in the synthesis of secondary amines.[10] Work aimed at the development of this methodology is currently underway and will be reported in due course.

Table 1. Reaction of **1** with alkyl bromide under Mitsunobu conditions using two different redox couples

entry	R-Br	TPP / DIAD	TBP / ADDP
2a		37%	86%
2b		41%	88%
2c		37%	60%
2d		20%	45%
2e		32%	56%
2f	α-acetobromoglucose	35% β-anomer	60% β-anomer
2g	α-acetobromogalactose	23% β-anomer	44% β-anomer
2h	α-acetobromorhamnose	10% β-anomer	45% β-anomer
2i	α-acetobromoribose	21% β-anomer	42% β-anomer
2j	 *	20% β-anomer	40% β-anomer

*This compound was synthesized as described in Ref. 11.

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4. ^{1}H NMR data (250 MHz, $CDCl_3$, δ, ppm) of the different compounds synthesized **2a**: 7.4 (5H, m, H*arom.*), 5.7 (1H, t, N*H*, $J=6$ Hz), 4.9 (2H, s, ΦCH_2), 3.5 (2H, t, $ClCH_2$, $J=6$ Hz), 3.1 (2H, q, $NHCH_2$, $J=6$ Hz), 1.5 (9H, s, Boc). **2b**: 5.8 (2H, m, CH_2=C*H* and N*H*), 5.3 (2H, m, CH_2=CH), 4.3 (2H, d, CH_2=CH-CH_2, $J=6$ Hz), 3.7 (2H, t, $ClCH_2$, $J=6$ Hz), 3.3 (2H, q, $NHCH_2$, $J=6$ Hz), 1.5 (9H, s, Boc). **2c**: 5.8 (1H, t, N*H*, $J=6$ Hz), 4.3 (2H, s, $COCH_2$), 3.8 (2H, t, $ClCH_2$, $J=6$ Hz), 3.6 (2H, q, $NHCH_2$, $J=6$ Hz), 1.6 (18H, m, Boc and *t*Bu). **2d**: 6 (1H, t, N*H*, $J=6$ Hz), 5.8 (2H, br. d, $CONH_2$, $J=8$ Hz), 4.4 (2H, s, $COCH_2$), 3.7 (2H, t, $ClCH_2$, $J=6$ Hz), 3.6 (2H, q, $NHCH_2$, $J=6$ Hz), 1.5 (9H, s, Boc). **2e**: 5.8 (1H, s, N*H*), 4.6 (2H, s, $NCCH_2$), 3.7 (2H, t, $ClCH_2$, $J=6$ Hz), 3.5 (2H, q, $NHCH_2$, $J=6$ Hz), 1.6 (9H, s, Boc). **2f**: 5.9 (1H, m, N*H*), 5.8 (1H, t, H_2, $J=9.3$ Hz), 5.3 (1H, d, H_1, $J=9.3$ Hz), 5.15 (1H, t, H_3, $J=9.5$ Hz), 5 (1H, t, H_4, $J=9.9$ Hz), 4.15 (2H, m, H_6, $H_{6'}$), 3.7 (1H, m, H_5), 3.6 (2H, m, CH_2Cl), 3.3 (2H, m, CH_2NH), 1.9–2 (12H, 4s, CH_3CO), 1.55 (9H, s, Boc). **2g**: 5.85 (2H, m, H_2, N*H*); 5.4 (1H, d, H_4, $J=3$ Hz), 5.25 (1H, d, H_1, $J=9.4$ Hz), 5 (1H, dd, H_3, $J=10.1$ Hz, $J=3.4$ Hz), 4.15 (2H, d, H_6, $H_{6'}$, $J=6.5$ Hz), 3.95 (1H, t, H_5, $J=6.5$ Hz), 3.55 (2H, m, CH_2Cl), 3.3 (2H, m, CH_2NH), 1.95–2.1 (12H, 4s, CH_3CO), 1.55 (9H, s, Boc). **2h**: 6.05 (1H, dd, H_2, $J=9.8$ Hz, $J=3.54$ Hz), 5.9 (1H, s, H_1), 5.85 (2H, t, N*H*, $J=3.6$ Hz), 5.45 (1H, t, H_3, $J=3$ Hz), 4.8 (1H, t, H_4, $J=2.95$ Hz), 4.3 (1H, ddd, H_5, $J=9.7$ Hz, $J=7$ Hz, $J=2.4$ Hz), 3.7 (2H, m, CH_2Cl), 3.4 (2H, m, CH_2NH), 2–2.2 (9H, 3s, CH_3CO), 1.6 (9H, s, Boc), 1.45 (3H, d, CH_3, $J=7$ Hz). **2i**: 5.7 (1H, d, H_1, $J=3.3$ Hz), 5.6 (2H, m, H_2, N*H*), 5.25 (1H, t, H_3, $J=7.2$ Hz), 4.3 (1H, dd, H_5, $J=12.1$ Hz, $J=3.3$ Hz), 4.1 (1H, dd, $H_{5'}$, $J=12.1$ Hz, $J=5.7$ Hz), 4 (1H, m, H_4), 3.6 (2H, t, CH_2Cl, $J=5.7$ Hz), 3.4 (2H, q, CH_2NH, $J=7.1$ Hz), 2 (9H, m, CH_3CO), 1.5 (9H, s, Boc). **2j**: 8.35 (2H, d, H*arom.*, $J=6.8$ Hz), 8.2 (2H, d, H*arom.*, $J=6.8$ Hz), 6.2 (1H, d, H_1, $J=5.5$ Hz), 5.6 (1H, t, N*H*, $J=6.25$ Hz), 4.9 (3H, m, H_2, H_3, H_4), 4.5 (2H, m, H_5, $H_{5'}$), 3.7 (2H, m, CH_2Cl), 3.35 (2H, m, CH_2NH), 1.65 (3H, s, C-CH_3), 1.6 (9H, s, Boc), 1.35 (3H, s, C-CH_3).
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