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The 2-(2-Chloroacetoxyethyl)benzoyl Group - Stable to Hydrogenolysis and Cleavable beside other Acyl Groups

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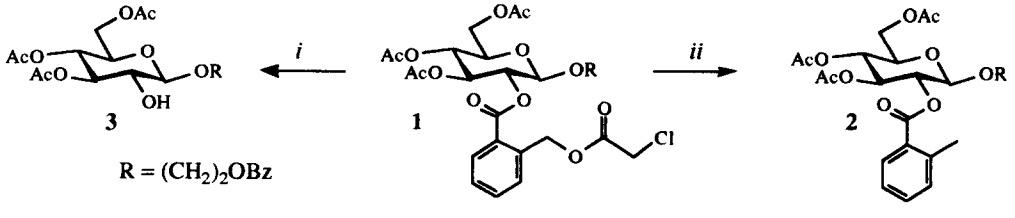
Abstract: The 2-(2-chloroacetoxyethyl)benzoyl (CAEB) group is prepared from isochromane in 4 steps and used as a temporary protecting group for carbohydrates. The CAEB group functions as a neighboring active, 1,2-*trans*-directing blocking group for glycosyl donors. It does not show transesterification to less reactive nucleophiles and is stable toward hydrogenolysis. CAEB can be cleaved off with thiourea and without effecting other acyl groups. It is suited for orthogonal protection strategies in combination with acetyl, benzoyl, benzyl and benzylidene groups in saccharide synthesis.

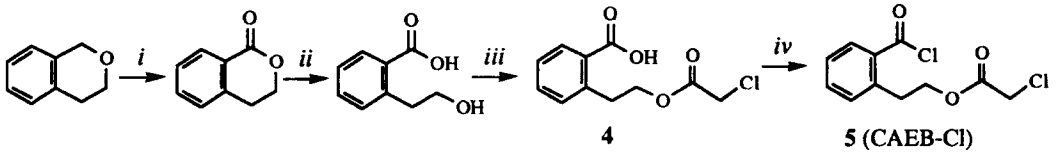
The proper choice of blocking groups and protection strategies is often the most crucial step in planning saccharide syntheses. It has to be considered that commonly used blocking groups such as acyl and benzyl can modulate the reactivity of glycosyl donors and acceptors and strongly affect the diastereoselectivity of a given glycosylation reaction (*i.e.* the anomeric outcome of the coupling step). In general, an acyl group (acetyl or benzoyl) at position 2 of a glycosyl donor will lead predominantly *via* neighboring group participation to the corresponding 1,2-*trans*-glycosidic linkage. Therefore, it appears to be highly desirable to have such neighboring active acyl groups available for this position that can be selectively cleaved without affecting other acyl groups present in the glycosyl donor. Temporary protecting groups that fulfill these requirements are for example chloroacetyl[1] and levulinoyl[2]. Both groups are 1,2-*trans*-directing and can be selectively cleaved off. However, as was previously shown, the latter are not always suitable as blocking groups for position 2 of glycosyl donors. When less reactive nucleophiles were used, extensive transesterification can occur[1,3]. Therefore, we recently developed the 2-(chloroacetoxymethyl)benzoyl (CAMB) group[4] that functioned as a 1,2-*trans*-directing group, did not show any transesterification during glycosylation and could be selectively cleaved with thiourea. A major drawback of the CAMB group was, however, its instability toward hydrogenolysis and thus, its incompatibility with benzyl groups. For example, treatment of the 2-*O*-CAMB-protected glucose derivative **1**[4a] under conditions typical for the removal of benzyl groups gave the 2-*O*-(2-methylbenzoyl)-blocked glucose **2** that could not be further transformed to the corresponding 2-OH compound **3**[4a] (Scheme 1).



Scheme 1. *i:* Ref. 4a, 3 eq. thiourea, MeOH/CH_2Cl_2, 50° C, 16 h (88%); *ii:* cat. Pd-C, ethyl acetate/AcOH, H_2, rt, 16 h (88%).

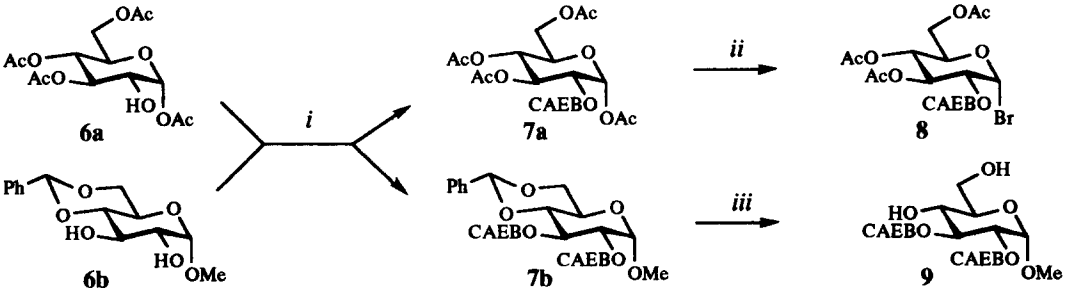
In order to construct a novel blocking group which combines all features of the CAMB group with the desired applicability of benzyl-protection we developed the 2-(2-chloroacetoxyethyl)benzoyl chloride (CAEB-Cl) group **5**. The latter should be stable toward hydrogenolysis since a cleavable benzylic position is now eliminated but should still allow the selective deblocking *via* intramolecular lactonisation to dihydroisocoumarin. Therefore, CAEB should allow an orthogonal protection strategy for carbohydrates in combination with acetyl or benzoyl and benzyl groups.

CAEB-Cl (**5**) was easily prepared from isochromane (scheme 2), oxidation[5] of which afforded first dihydroisocoumarin. Next, the latter was converted into 2-(2-hydroxyethyl)benzoic acid[6] chloroacetylation of which gave the benzoic acid derivative **4**[7a] that was finally converted into CAEB-Cl[7b] (**5**).



Scheme 2. *i:* Ref. 5a, pyridinium chlorochromate (79%) or Ref. 5b, SeO_2 (100%); *ii:* Ref., NaOH (97%); *iii:* chloroacetyl chloride, 2-methoxypyridine, DMF, -30° C, 3.5 h (72%); *iv:* $SOCl_2$, rt, 24 h (100%).

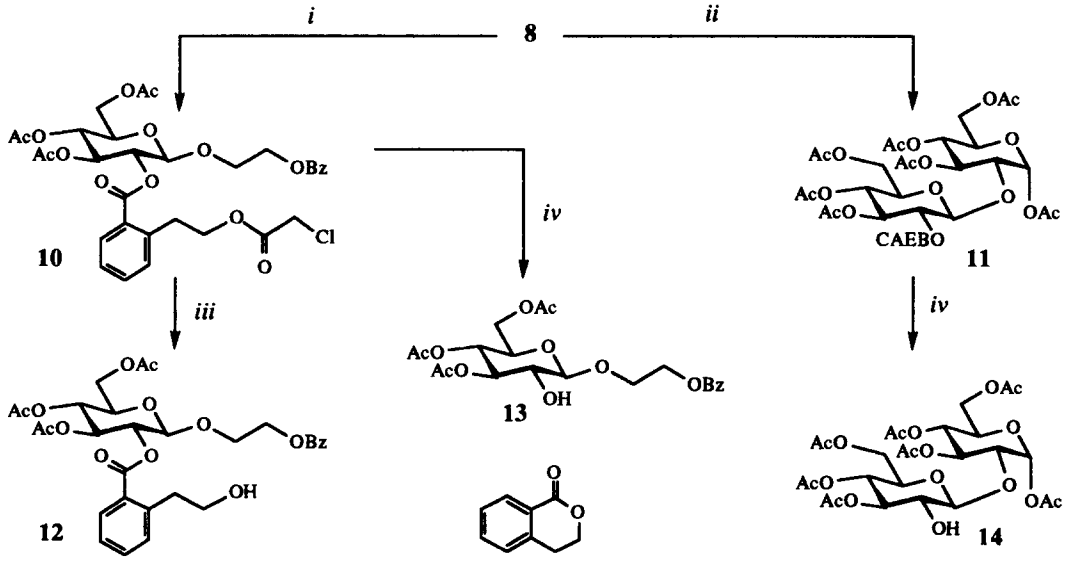
The CAEB group may be introduced as outlined in scheme 3 for glucose derivatives **6** either *via* benzoic acid derivative **4** or chloride **5**[8a]. The 2-*O*-CAEB-protected derivative **7a** can further be converted into the corresponding glucosyl bromide **8**[8b]. Here, the tendency to give substitution of the chloroacetyl group by bromide as was observed for the CAMB group[4a] was less pronounced since CAEB did not bear a benzylic chloroacetate. Furthermore, as demonstrated for the conversion **7b**→**9**, the CAEB group was indeed stable under conditions typical for the removal of benzyl and benzylidene groups and thus, excellently suited for the above outlined orthogonal protection strategies.



Scheme 3. *i:* A: **5**, pyridine, CH_2Cl_2, rt, 72 h (91% **7a**, 67% **7b**); B: **4**, DCC, cat. DMAP, CH_2Cl_2, rt, 24 h (76% **7a**, 62% **7b**); *ii:* HBr/AcOH, CH_2Cl_2, rt, 0.5 h (93%); *iii:* cat. Pd-C, ethyl acetate/AcOH, H_2, rt, 16 h (90%).

The CAEB-protected glucosyl bromide **8** reacted under promotion of silver trifluoromethanesulfonate with 2-benzoyloxyethanol, previously used as a rather unreactive nucleophil in order to test possible transesterification[4a] to give the β-glycoside **10** in 75% yield. No transesterification occurred. Similarly, **8** was coupled to **6a** to give the β-(1→2)-linked disaccharide **11** in good yield. Problems arose when **10** was treated with thiourea in order to cleave off the CAEB group at position 2. It was previously observed for CAMB protected glycosides that the chloroacetyl group was split off fast and lactonisation of the remaining *O*-(2-

hydroxymethyl)benzoyl moiety to phthalide was rather slow[4a]. For the CAEB derivative **10**, also a fast cleavage of the chloroacetyl group was observed on TLC. However, lactonisation of the formed *O*-2-(2-hydroxyethyl)-benzoyl moiety to dihydroisocoumarin did not occur spontaneously. Thus, compound **12** (45%) was isolated. Similar problems have been recently encountered during hydrogenolytic cleavage of 2-(2-benzyloxyethyl)-benzoates, the 2-(2-hydroxyethyl)benzoyl intermediate of which had to be treated with *tert*-butanolate in order to induce lactonisation[5b]. Basic conditions, however, had to be excluded in our case since acetyl group migration was expected. Good conditions for the removal of the CAEB group[9] were treatment of **10** with thiourea in DMF until complete formation of **12** (TLC) followed by the addition of *p*-toluenesulfonic acid which induced lactonisation and afforded **13** and dihydroisocoumarin in 83% overall yield. No acetyl migration was observed. Similarly, disaccharide **11** was thus converted into the 2' unprotected sophorobiose derivative **14** (scheme 4).



Scheme 4. *i:* $HO(CH_2)_2OBz$, AgOTf, collidine, CH_2Cl_2, -30° C (75%); *ii:* **6a**, AgOTf, collidine, CH_2Cl_2, -30° C (71%); *iii:* 3 eq. thiourea, MeOH, 50° C, 16 h (45%); *iv:* 1) 3 eq. thiourea, DMF, 55° C, 8-17 h; 2) TosOH, 120 h (83% **13**, 68% **14**).

In summary, the herein described CAEB protecting group should evolve into a good alternative to the CAMB group and similarly conditioned temporary blocking groups like chloroacetyl and levulinoyl since it opens up effective orthogonal protecting strategies in combination with acetyl, benzoyl, benzyl and benzylidene groups. Especially, when attached to position 2 of a glycosyl donor the CAEB group allows 1,2-*trans*-selective glycosylations without transesterification.

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7. All new compounds gave satisfactory elemental analyses. (a) Synthesis of **4**: a solution of 2-(2-hydroxyethyl)benzoic acid[6] (13.02 g) in DMF (190 ml) was added at -30° C over 2.5 h to a solution of chloroacetyl chloride (17.53 g) and 2-methoxypyridine (17.3 g) in DMF (190 ml). The mixture was warmed to rt during 1 h, poured into 15% icecold aq. HCl solution (400 ml) and extracted with CH_2Cl_2 (5 x 100 ml). The combined extracts were washed with aq. HCl solution, dried and concentrated. The residue was crystallised from 2/1 *n*-hexane/$CHCl_3$ (550 ml) to afford **4** (12.65 g, 72%), m.p. 108-109° C. (b) Synthesis of **5**: a suspension of **4** (7.17 g) in $SOCl_2$ (25 ml) was stirred at rt for 24 h whereupon a clear solution was obtained. The solution was concentrated to give **5** (7.7 g, 100%) as an oil that slowly crystallised, m.p. 19° C; ^1H NMR ($CDCl_3$): δ = 8.24 (dd, 1H, H^{Ar}), 7.58 (dt, 1H, H^{Ar}), 7.44 (dt, 1H, H^{Ar}), 7.34 (dd, 1H, H^{Ar}), 4.42 (t, 2H, J = 6.5 Hz, CH_2O), 4.03 (s, 2H, CH_2Cl), 3.29 (t, 2H, J = 6.5 Hz, $ArCH_2$); ^{13}C NMR ($CDCl_3$): δ = 168.5 (COCl), 167.1 ($COCH_2Cl$), 139.8, 134.3, 134.1, 133.0, 132.1, 127.6 (C^{Ar}), 65.8 (CH_2O), 40.8 (CH_2Cl), 33.4 ($ArCH_2$).
8. All new compounds gave satisfactory elemental analyses. (a) Synthesis of **7a**: A) pyridine (0.5 ml) was added at rt to a solution of **5** (1.89 g) and **6a** (Helferich, B.; Zirner, J., *Chem. Ber.*, **1962**, *95*, 2604-2611; 1.3 g) in CH_2Cl_2 (20 ml), the mixture was stirred for 72 h and poured into 15% aq. HCl solution. The organic layer was separated, dried and concentrated. Chromatography (5/1 CCl_4/acetone) of the residue afforded **7a** (3.4 g, 91%), $[\alpha]_D^{20}$ = +98.6 (*c* = 1.0, $CHCl_3$); B) DCC (0.32 g) was added at rt to a solution of **4** (0.45 g), **6a** (0.5 g) and a catalytic amount of DMAP in CH_2Cl_2 (10 ml) and the mixture was stirred for 24 h. The mixture was filtered, the filtrate washed with H_2O, 5% aq. AcOH solution and H_2O and dried. Concentration and chromatography afforded **7a** (0.64 g, 76%). (b) Synthesis of **8**: 30% HBr in AcOH (4 ml) was added at rt to a solution of **7a** (2.34 g) in CH_2Cl_2 (4 ml), the mixture was stirred for 0.5 h, diluted with CH_2Cl_2 and poured into H_2O. The organic layer was separated, washed with aq. $NaHCO_3$ solution and dried. Concentration of the solution and chromatography (10/1 CCl_4/acetone) of the residue afforded **8** (2.26 g, 93%), $[\alpha]_D^{20}$ = +140.1 (*c* = 1.0, $CHCl_3$).
9. In a typical procedure for the cleavage of the CAEB group, a solution of **10** (203.1 mg) and thiourea (45.7 mg) in DMF (10 ml) was stirred at 55° C for 8 h. A catalytic amount of TosOH was added and stirring was continued at 55° C for 120 h. The mixture was diluted with CH_2Cl_2, washed with aq. $NaHCO_3$ solution dried and concentrated. Chromatography (5/1 CCl_4/acetone) of the residue afforded **13** (112.5 mg, 83%); $[\alpha]_D^{20}$ = +5.2 (*c* = 1.0, $CHCl_3$).

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