DMAP-promoted racemization-free deacylation of carboxthioimide† adducts: carboxthioimide as a versatile carboxy protecting group

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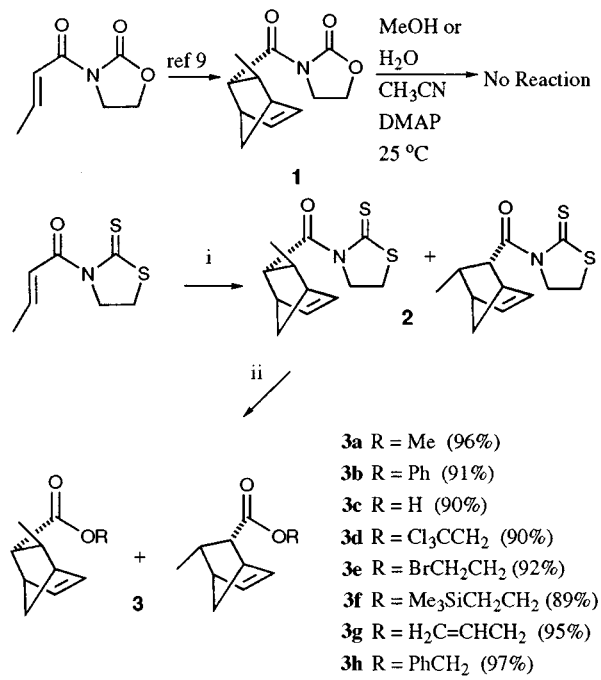
The DMAP-promoted deacylation of carboxthioimide adducts can be directed to form either acid or various ester protecting groups with no detectable levels of epimerization.

The development of protecting groups of carboxy functionality which are stable under the usual reaction conditions and which can be activated by a specific reagent for nucleophilic deacylation under very mild conditions has been a challenging undertaking. Oxazolidinone-derived carboximides[1–4] as well as oxazolidinethione- and thiazolidinethione-based carboxthioimides[5,6] have proven to be valuable carboxy-protecting groups for the construction of enantiomerically pure substances. While, traditionally, the use of basic reagents ($LiOCH_2Ph$, BrMgOMe, LiOH, LiOOH, K_2CO_3/MeOH)[6,7] for the nucleophilic cleavage of imide the thioimide adducts has been the method of choice for removing the auxiliary from substances, progress in nucleophilic catalyst-promoted imide and thioimide deacylation with oxygen nucleophiles like H_2O, alcohols and phenol remains far less developed. Effecting such nucleophilic acyl substitution may have the advantage of (i) controlling the nucleophilic cleavage without causing racemization of the newly created stereocenters, (ii) promoting further useful transformations of the initial adducts without influencing the pendent functional groups, and (iii) enhancing synthetic efficiency by direct conversion of the initial adducts to various ester protecting groups. The tremendous impact of DMAP[8] in catalyzing the acylation of alcohols suggested the feasibility of DMAP as a catalyst to effect transesterification or hydrolysis of imides and thioimides. Here we report protocols whereby the thioimide transesterification promoted by DMAP can be directed to form either acid or various ester protecting groups with no detectable levels of epimerization.

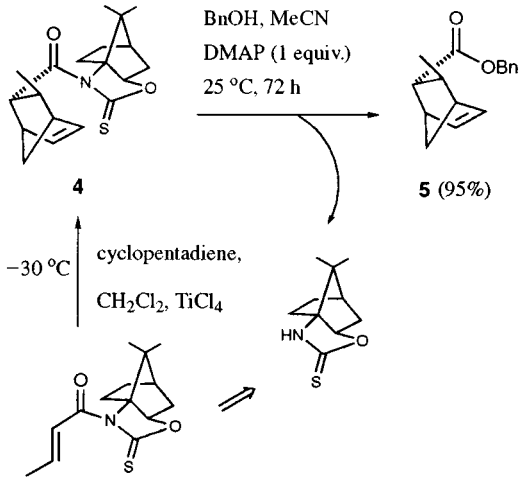
The reactions of crotonyloxazolidinone-derived Diels–Alder adduct **1** with MeOH and H_2O were chosen to test the feasibility of the DMAP-promoted oxazolidinone deacylation (Scheme 1). In view of the well-documented excellent shelf lives of *N*-acyloxazolidinones,[9] we were not surprised to observe no detectable methanolysis and hydrolysis at the exocyclic carbonyl center. Believing a more polarizable auxiliary might facilitate nucleophilic attack, we turned to the deacylation of carboxthioimide derived adducts. Initial work centered on the deacylation of the Diels–Alder adduct **2** derived from the unsaturated *N*-acylthiazolidine-2-thione (*cf.* Scheme 1) which has been shown to exhibit enhanced dienophilic reactivity in a copper(II)-catalyzed asymmetric cycloaddition.[10] The requisite thioimide adduct **2** was available by treating crotonylthiazolidienethione with excess cyclopentadiene (5–10 equiv.) and 1.2 equiv. of $ZnCl_2$ in CH_2Cl_2 at 0 °C. Treatment of thioimide **2** with 1.5 equiv. of MeOH in MeCN with 20 mol% DMAP at room temperature gave the methyl ester **3a** in 96% yield along with a 93% recovery of the auxiliary (Scheme 1). The DMAP-promoted thiazolidinethione deacylation exhibited good generality. Thus, switching the nucleophile from MeOH to PhOH had little effect. The same conditions effected transesterification of **2** to afford phenyl ester **3b** in 91% yield. Similarly, DMAP (1.1 equiv.) promoted hydrolysis of **2** with H_2O as the nucleophile afforded the acid **3c**. The broad scope of the transesterification is illustrated by the tolerance of β-substituents on ethanol. Thus deacylation of **2** with 2,2,2-trichloroethanol under the same conditions gave the corresponding β-substituted ethyl ester protecting group. A labile alcohol, 2-bromoethanol, also proved to be a satisfactory nucleophile under our standard conditions in the presence of the DMAP catalyst. Trimethylsilylethanol gave similar results, albeit in a somewhat slower reaction. After 24 h, an 89% yield of 2-(trimethylsilyl)ethyl ester **3f** was obtained.‡ The utility of allyl and benzyl esters as useful carboxy-protecting groups led to our examination of allyl and benzyl alcohols, which participated equally well, giving the corresponding esters **3g** and **3h** in excellent yield (≥95%).[11] Steric hindrance plays a role; in contrast to the above, *tert*-butyl alcohol failed to react with thioimide adduct **2** under the above conditions.

The suitability of these mild conditions for oxazolidinethione deacylation is illustrated by the additional examples provided below. Camphor-based *N*-acyloxazolidinethiones such as Diels–Alder cycloadduct **4** and aldol adduct **6**[5] were utilized to test the feasibility of DMAP-promoted nucleophilic cleavage. The DMAP-promoted transesterification of cycloadduct **4**, which was prepared from the $TiCl_4$-mediated Diels–Alder reaction of camphor-based crotonyloxazolidinethione with cyclopentadiene, with benzyl alcohol proceeded more slowly



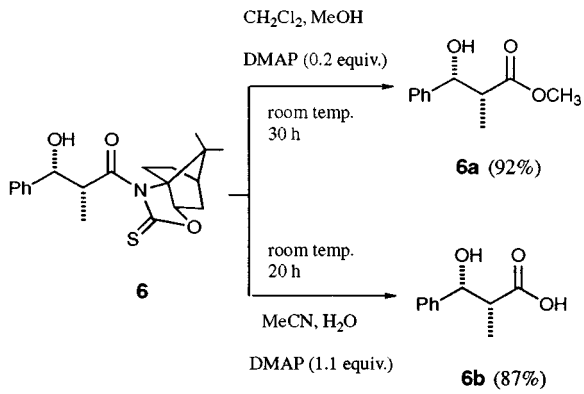
Scheme 1 *Reagents and conditions*: i, $ZnCl_2$, cyclopentadiene, CH_2Cl_2 0 °C; ii, ROH or H_2O, DMAP (0.2–1.1 equiv.), MeCN, room temp., 4–24 h.

† General IUPAC name: 3-acyl-1,3-thiazolidine-2-thione.



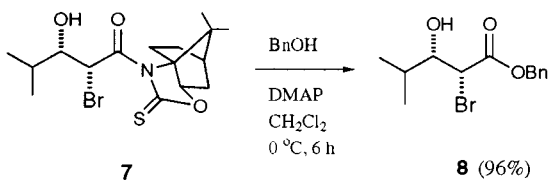
Scheme 2

but still in excellent yield (Scheme 2). After 72 h, the transesterification product **5**, $[\alpha]_D^{25}$ +129.3 (*c* 0.9, CH_2Cl_2),[9] was obtained in 95% with no detectable levels of epimerization. Using the above standard conditions, both hydrolysis and methanolysis of aldol adduct **6** were easily effected without racemization of either center (Scheme 3). The acid **6a**, $[\alpha]_D^{25}$ +13.6 (*c* 1.1, CH_2Cl_2), and ester **6b**, $[\alpha]_D^{25}$ +22.5 (*c* 1.4, CH_2Cl_2),[2] were obtained in 87 and 92% yield, respectively.



Scheme 3

In conjunction with a program directed toward the asymmetric synthesis of β-hydroxy-α-amino acids, a key intermediate toward biologically active peptides and β- and γ-lactam antibiotics,[12] we were particularly interested in bromohydrin substrates.[13] To demonstrate the utility of this protocol, we examined the transesterification of bromohydrin aldol **7**,[14] which by virtue of the ease of bromide displacement demands very mild methods. In the DMAP (0.2 equiv.) catalyzed transesterification ($PhCH_2OH$) of bromohydrin **7** at 0 °C, epoxide formation was completely suppressed and benzyl β-hydroxy-α-amino ester **8** was isolated in 96% yield with no apparent loss of stereochemistry (Scheme 4).‡ This result is in directed contrast to the BnOLi deacylation conditions for



Scheme 4

oxazolidinone bromohydrins, in which benzyl α,β-epoxy esters are formed.[3]

In conclusion, we have demonstrated that carboxthioimides are very versatile and useful carboxy-protecting groups. Significantly, the thioimide transesterification *via* DMAP catalysis provides the acids or various ester protecting groups without danger of racemization. The successful control of oxazolidinethione deacylation *vs.* cyclization of nucleophiles with bromohydrin aldol adducts illustrates the power of our newly developed DMAP-promoted nucleophilic cleavage. Further details in this area will be forthcoming.

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Notes and references

‡ *Selected data* for **3f**: δ_H(400 MHz, $CDCl_3$) 6.22 (dd, *J* 5.6, 3.2, 1H, C*H*=CH), 5.96 (dd, *J* 5.6, 2.8, 1H, C*H*=CH), 4.07 (m, 2H, OCH_2CH_2), 3.06 (m, 1H, *H*CC=C), 2.43 (m, 1H, C=CC*H*), 2.31 (dd, *J* 4.0, 4.0, 1H, *H*CC=O), 1.79 (m, 1H, *H*CCH_3), 1.37–1.52 (m, 2H, H_2CCH), 1.14 (d, *J* 7.2, 3H, $CHCH_3$), 0.92 [m, 2H, $CH_2CH_2Si(CH_3)_3$], 0.01 [s, 9H, $Si(CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 174.97, 138.59, 133.21, 62.31, 52.60, 48.79, 45.96, 45.90, 37.71, 20.96, 17.30, −1.50 (HRMS: calc. for $C_{14}H_{24}O_2Si$, 252.1546. Found 252.1545. Calc. for $C_{14}H_{24}O_2Si$: C, 66.62; H, 9.58. Found: C, 66.40; H, 9.69%). For **8**: δ_H(400 MHz, $CDCl_3$) 7.35 (br s, 5H, C_6H_5), 5.20 (2d, *J* 12.0, 2H, $C_6H_5CH_2$), 4.47 (d, *J* 3.6, 1H, CHC*H*Br), 3.53 (dd, *J* 7.2, 3.6, 1 H, CHC*H*CHBr), 1.87 (br s, 1H, O*H*), 1.78 (app. octet, *J* 7.2, 1H, $(CH_3)_2CHCH$), 1.00 (d, *J* 6.8, 3H, CH_3CHCH_3), 0.91 (d, *J* 6.8, 3H, CH_3CHCH_3); δ_C(100 MHz, $CDCl_3$) 169.18, 134.67, 128.60, 128.48, 128.25, 75.91, 67.94, 51.07, 31.61, 18.90, 17.60; $[\alpha]_D^{25}$ +15.5 (*c* 0.9, CH_2Cl_2) (HRMS: calc. for $C_{13}H_{17}O_3Br$, 300.0361. Found, 300.0355. Calc. for $C_{13}H_{17}O_3Br$: C, 51.82; H, 5.69. Found: C, 51.80; H, 5.65%).

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